Pediatric Asthma: Improving Management to Reduce Cost of Care

MICHAEL MELLON, MD, and BHASH PARASURAMAN, PhD

ABSTRACT

BACKGROUND: The economic burden of pediatric asthma is substantial, with national annual health care costs of \$3 billion. Successful clinical management of asthma in children has the potential to decrease this burden by lowering the disproportionate costs of hospitalization and acute care for pediatric asthma patients.

RESULTS: Based on increased understanding of the pathogenesis of asthma, revised guidelines were published by the National Institutes of Health in 1997 (with an update in 2002) and by the American Academy of Allergy, Asthma, and Immunology in 1999 to assist in the diagnosis and management of pediatric asthma. These guidelines emphasize the role of inflammation in asthma and recommend treatment of the underlying inflammatory process. Despite increased knowledge regarding the pathogenesis of the disease and the availability of effective anti-inflammatory agents, particularly inhaled corticosteroids, the prevalence of asthma and disease-related morbidity continues to remain high in children.

CONCLUSION: Asthma interventions that include the use of guideline-recommended inhaled corticosteroid therapy and patient and caregiver education in asthma management may help to reduce asthma morbidity in children and decrease the substantial costs of pediatric asthma.

KEYWORDS: Asthma, Pediatric, Morbidity, Inhaled corticosteroids, Cost-effectiveness

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An estimated 6.3 million children in the United States had asthma in 2001.¹ Despite the availability of effective controller medications, the annual rate of pediatric hospital admissions for asthma remains high.²⁻⁴ In an analysis of population-based data from California acute-care hospitals, asthma was ranked as the primary cause of hospitalization in children aged 1 to 5 years and the third cause of hospitalization in children aged 6 to 12 years.² In 1999, the hospitalization rate was 55.4 admissions per 10,000 population among children aged 0 to 4 years and 21.5 admissions per 10,000 population among children aged 5 to 14 years (Figure 1).⁵ The emergency department visit rates also were high for these age groups.

The disproportionate share of costs for hospitalization and unscheduled emergency care of children with asthma is largely responsible for the significant economic burden of pediatric asthma.⁶ The national annual health care cost for pediatric asthma is approaching \$3 billion, of which direct treatment costs account for approximately \$2 billion and indirect costs \$1 billion.⁷ An analysis of the per capita impact of pediatric asthma on health care utilization and total costs, based on 1987 National Medical Expenditure Survey data, demonstrated that children with asthma had more inpatient hospital days (0.23 versus 0.11 per year), required 65% more nonurgent outpatient

FIGURE 1 Estimated Annual Rates of Hospitalization for Asthma in the United States From 1980 to 1999, Stratified by Age

Source: Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma—United States, 1980-1999. *MMWR Surveill Summ.* 2002;51:1-13.⁵

FIGURE 2 Distribution of Direct Asthma Costs in Children Aged (A) 0 to 4 Years and (B) 5 to 17 Years, in 1994 Dollars

Source: Smith DH, Malone DC, Lawson KA, et al. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med.* 1997;156:787-93.⁹

clinic visits, filled 2.8 times more prescriptions, and incurred 88% higher medical expenses than those without asthma.⁸ Analysis of the 1987 data inflated to 1994 dollars showed that hospitalizations accounted for the greatest proportion of direct costs in children aged 0 to 4 years (\$586.2 million) and 5 to 17 years (\$286.2 million) (Figure 2).⁹ A more recent analysis of cost estimates for 1994 showed similarly high costs for hospitalization of children younger than 18 years (\$514.3 million).¹⁰ Emergency department visits comprised approximately 7% to 19% of total direct costs for patients younger than 18 years,^{4,9,10} with costs estimated at \$228.7 million in 1994.¹⁰

Pediatric asthma results in 14 million missed school days each year.¹ Considerable indirect costs are therefore incurred as a result of workdays lost by caregivers of children with asthma.⁴ In 1994, children aged 5 to 17 years missed 11.8 million school days.¹⁰ These missed days cost an estimated \$956.7 million for caretakers' time lost from work and housekeeping.¹¹ For 1998, these costs were projected at \$1.1 billion.¹¹

Missed school days and increased hospitalizations and emergency care for children with asthma suggest poor disease management. Although hospital length of stay and emergency department visits decreased from 1985 to 1994, the costs for these services increased over the same time period.¹⁰ The use of hospital services contributes to higher costs for asthma management than does appropriate physician and pharmaceutical care.^{6,9} Guidelines for health care management in patients with asthma have been developed,^{12,13} and adherence to these standards decreases hospitalization costs.¹⁴ The guidelines outline steps for early recognition of children with asthma and appropriate intervention with pharmacologic agents and health education.

Improving Care to Reduce Costs

Because hospitalizations account for a large proportion of direct costs of pediatric asthma (74% and 34% of direct costs in children aged 0 to 4 years and 5 to 17 years, respectively),⁹ measures aimed at improving care to reduce hospital use would significantly decrease the overall costs of pediatric asthma. These strategies include accurate diagnosis and assessment of disease severity, appropriate pharmacologic intervention and follow-up, and programs designed to teach patients and their parents to monitor and manage asthma. Furthermore, patients must be taught to understand and accept the importance of adhering to prescribed therapy and avoiding possible precipitating factors to minimize acute episodes.

A randomized controlled study reported by Greineder et al. demonstrated a 75% reduction in hospitalizations ($P < 0.05$) among children aged 1 to 15 years with asthma who participated in a comprehensive asthma outreach program.¹⁵ The program was focused on ensuring that patients kept scheduled pediatric appointments, monitored their asthma, and took maintenance medications. Reduced hospitalizations, along with significant reductions in emergency department use (57%, $P < 0.05$) and out-of-health-plan use including referrals, home care, and durable medical equipment (71%, $P < 0.001$), contributed to an estimated direct savings of \$7.69 to \$11.67 for every dollar spent on the intervention.

Diagnosis of Asthma in Infants and Children

Difficulty in diagnosing asthma in children leads to frequent underdiagnosis, resulting in many cases of undertreatment.¹² The diagnosis is particularly difficult because the 2 most com-

FIGURE 3 NAEPP: Stepwise Approach for Managing Asthma in Infants and Young Children (Aged ≤5 Years)

Step 1 Mild Intermittent		Step 2 Mild Persistent		Step 3 Moderate Persistent		Step 4 Severe Persistent	
Symptoms: Daytime: ≤2 days/week Nighttime: ≤2 nights/month		Symptoms: Daytime: >2x/week but <1x/day Nighttime: >2 nights/month		Symptoms: Daytime: daily Nighttime: >1 night/week		Symptoms: Daytime: continual Nighttime: frequent	
No daily medication needed		Preferred treatment: <ul style="list-style-type: none"> • Low-dose ICS* (with nebulizer, MDI† with holding chamber with or without face mask, or DPI)‡ Alternative treatment: <ul style="list-style-type: none"> • Cromolyn (nebulizer is preferred or MDI with holding chamber) • LTRA§ 		Preferred treatments: <ul style="list-style-type: none"> • Low-dose ICS + LABA¶ • Medium-dose ICS Alternative treatments: <ul style="list-style-type: none"> • Low-dose ICS + either LTRA or theophylline If needed: <ul style="list-style-type: none"> • Preferred: medium-dose ICS + LABA • Alternative: medium-dose ICS + either LTRA or theophylline 		Preferred treatment: <ul style="list-style-type: none"> • High-dose ICS + LABA If needed: <ul style="list-style-type: none"> • High-dose ICS + LABA + corticosteroid tablets or syrup long-term (2 mg/kg/day, generally do not exceed 60 mg/day) 	

Quick Relief (all severities of asthma)

- Bronchodilator as needed for symptoms—short-acting inhaled β_2 -agonists by nebulizer or face mask and spacer/holding chamber are preferred, with oral β_2 -agonists as an alternative.
- With viral respiratory infection use a bronchodilator every 4 to 6 hours up to 24 hours (no more than once every 6 weeks); consider systemic corticosteroids for severe exacerbations or a patient history of severe exacerbations.
- Use of short-acting β_2 -agonists >2 times/week for intermittent asthma may indicate the need to initiate long-term controller therapy, and daily or increasing use in persistent asthma may indicate the need to increase control therapy.

* ICS = inhaled corticosteroid.

§ LTRA = leukotriene receptor antagonist.

† MDI = metered-dose inhaler.

¶ LABA = long-acting β_2 -agonist.

‡ DPI = dry-powder inhaler.

Source: National Asthma Education and Prevention Program. Expert panel report: Guidelines for the diagnosis and management of asthma. Update on selected topics—2002. *J Allergy Clin Immunol.* 2002; 110(suppl 5):S141-S219.¹³

mon symptoms of asthma in children—cough and wheeze—are encountered in many other childhood illnesses.¹⁶ Among children aged 5 years or younger, diagnosis is complicated by the challenge in obtaining objective measurements of lung function.¹² Although spirometry generally is recommended for diagnostic purposes in adults, children cannot reliably perform these tests due to the mechanics involved.^{12,17} Thus, in younger children, the diagnosis must be based on symptoms, history, and physical examination.^{12,17}

Not all children who wheeze during infancy will develop persistent asthma, thus it is important to be able to distinguish these infants with transient wheeze from those with early-onset asthma. Data suggest that wheeze will subside by the age of 6 years in at least 60% of children who wheeze with viral infections in early life.¹⁸ A predictive index for persistent asthma in children (Table 1) has been developed to help determine which young children with wheeze will go on to develop persistent disease.¹⁹

Asthma severity must be accurately assessed to evaluate

treatment options and provide optimal disease management. Disease severity is based on symptoms in preschool children (Figure 3) and on symptoms and pulmonary function in older children who are capable of performing pulmonary function tests (Figure 4). According to a national survey that included parents of 721 children with asthma, based upon symptoms, 54% of children were classified with mild intermittent asthma, 21% with mild persistent asthma, 14% with moderate persistent asthma, and 12% with severe persistent disease.²⁰

Pharmacotherapy

Asthma is well established as a chronic inflammatory disease that results from a complex interaction among inflammatory, airway epithelial, and endothelial cells.²¹ Persistent asthma is most effectively controlled by daily anti-inflammatory therapy. Although leukotriene modifiers and other long-term control medications are available, corticosteroids are considered the most potent and consistently effective anti-inflammatory medications available.^{12,13} Recent long-term studies have established a robust safety profile for inhaled corticosteroids (ICSs).²² They have long been an important and often life-saving therapy for patients with severe asthma. However, the long-term use of systemically administered corticosteroids in

children is associated with adverse effects such as adrenal suppression, skin and bone changes, and growth impairment.²³

ICSs were developed to maximize local anti-inflammatory effects in the lungs and to minimize unwanted systemic effects. The potential for ICSs to produce clinically significant systemic adverse effects is limited. In general, ICS doses of 400 mg/day or less in children do not appear to affect adrenal function.²⁴ Short-term growth velocity may be affected initially by ICSs, but clinical studies evaluating long-term growth in children suggest that final adult height is not adversely affected.^{22,25}

A randomized controlled trial of 1,041 children aged 5 through 12 years with mild-to-moderate persistent asthma found that 4 to 6 years of treatment with inhaled budesonide was superior in many clinical outcomes to either nedocromil or placebo but caused a small, transient reduction in growth velocity that was apparent mostly within the first year of treatment.²² At treatment end, bone age and projected final height in children treated with budesonide and nedocromil were similar to

placebo. A paper published coincidentally by Agertoft and Pedersen involving 211 children who had achieved final adult height included 142 children treated with budesonide (mean daily dose, 412 µg) for a mean of 9.2 years. In this paper, the authors concluded that long-term treatment with budesonide is not associated with reduction in normal height in adulthood.²⁵ To minimize the potential for unwanted systemic effects, it is important to monitor growth in children receiving ICS therapy and to step down to the minimum effective dose.¹²

The National Institutes of Health guidelines for the prevention and management of asthma provide specific recommendations for safe and effective use of ICSs in children.^{12,13} Asthma treatment recommendations for children aged 5 years or younger (Figure 3) differ slightly from those for adults and children aged 5 years or older (Figure 4). ICSs are recommended as the preferred treatment for infants and children of any age with mild persistent asthma, and they are recommended along with long-acting β_2 -agonists for all patients with moderate or severe persistent asthma and as an additional preferred treatment (at a medium dose) for children aged 5 years or younger with moderate persistent disease.¹³ In patients with intermittent asthma, as-needed use of short-acting β_2 -agonists (SABAs) is recommended.

Differences in physiochemical and pharmacokinetic properties exist among corticosteroids. However, all of the currently available agents have demonstrated efficacy in the treatment of asthma in various age groups of children.²³ Use of these agents has been associated with improved pulmonary function, decreased symptoms, and reduced airway hyperresponsiveness.²³

Several ICS products are available for the management of childhood asthma. In the United States, the pressurized metered-dose inhaler (pMDI) formulations of triamcinolone acetonide, beclomethasone dipropionate, and fluticasone and the dry-powder inhaler formulation of budesonide are approved by the U.S. Food and Drug Administration and available for use in children older than 6 years.²⁶ One dry-powder inhaler formulation of fluticasone is approved and available for use in children as young as 4 years.

FIGURE 4 NAEPP: Stepwise Approach for Managing Asthma in Children Aged >5 Years

Step 1 Mild Intermittent		Step 2 Mild Persistent		Step 3 Moderate Persistent		Step 4 Severe Persistent	
Symptoms: Daytime: ≤ 2 days/week Nighttime: ≤ 2 nights/month PEF* or FEV ₁ † $\geq 80\%$ PEF variability $< 20\%$		Symptoms: Daytime: $< 2 \times$ /week but $< 1 \times$ /day Nighttime: > 2 nights/month PEF or FEV ₁ $\geq 80\%$ PEF variability $< 20\%$		Symptoms: Daytime: daily Nighttime: > 1 night/week PEF or FEV ₁ $> 60\%$ – $< 80\%$ PEF variability $> 30\%$		Symptoms: Daytime: continual Nighttime: frequent PEF or FEV ₁ $\leq 60\%$ PEF variability $> 30\%$	
No daily medication needed. A course of systemic corticosteroids is recommended for severe exacerbations		Preferred treatment: • Low-dose ICS‡ Alternative treatment: • Cromolyn • LTM§ • Nedocromil • Sustained-release theophylline		Preferred treatments: • Low- to medium-dose ICS + LABA¶ Alternative treatments: • Increase ICS within medium dose range • Low- to medium-dose ICS + either LTM or theophylline If needed: • Preferred: Increase ICS within medium dose range + add LABA • Alternative: Increase ICS within medium dose range + add either LTM or theophylline		Preferred treatment: • High-dose ICS + LABA If needed: • High-dose ICS + LABA + corticosteroid tablets or syrup long-term (2 mg/kg/day, generally do not exceed 60 mg/day)	

Quick Relief (all severities of asthma)

- Two to four puffs short-acting inhaled β_2 -agonists as needed for symptoms; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed.
- Course of systemic corticosteroids may be needed.
- Use of short-acting β_2 -agonists > 2 times/week for intermittent asthma may indicate the need to initiate long-term controller therapy, and daily or increasing use in persistent asthma may indicate the need to increase control therapy.

* PEF = peak expiratory flow.

§ LTM = leukotriene modifier.

† FEV₁ = forced expiratory volume in 1 second.

// LABA = long-acting β_2 -agonist.

‡ ICS = inhaled corticosteroid.

Source: National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics-2002. *J Allergy Clin Immunol.* 2002; 110(suppl 5):S141-S219.¹³

Budesonide inhalation suspension (Pulmicort Respules), a nebulized corticosteroid formulation, is the only ICS product approved for children younger than 4 years and available for children as young as 1 year.

Medication Delivery Needs in Pediatric Asthma

Optimal delivery of asthma medications to infants and children can be challenging. Inhaled therapy is preferred over systemic therapy to reduce the potential for systemic effects and to deliver higher drug concentrations directly to the airways.⁷ However, poor inhaler technique is common^{27,28} and often leads to the failure of inhaled medication in children.²⁹

Common errors demonstrated by children include failure to coordinate actuation and inhalation, and inhalation through the nose after actuation into the mouth.^{27,28} To ensure optimal delivery of inhaled medication, delivery devices should meet the

TABLE 1 Predictive Indices for Asthma in Children*

Major Criteria	Minor Criteria
<ul style="list-style-type: none"> • Parent with a history of physician-diagnosed asthma • Physician diagnosis of eczema 	<ul style="list-style-type: none"> • Physician diagnosis of allergic rhinitis • Wheezing apart from colds • $\geq 4\%$ eosinophilia

* Loose index for the prediction of asthma: early wheezer plus ≥ 1 major criterion or 2 minor criteria. Stringent index for the prediction of asthma: early frequent wheezer plus ≥ 1 major criterion or 2 minor criteria.

Adapted with permission from Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med.* 2000;162:1403-06.¹⁹

TABLE 2 Inhalation Devices and Recommended Patient Ages

Device	Age*	Comments
pMDI†	>5 years (<5 years with spacer/holding chamber and face mask for some children)	Child may have difficulty coordinating inhalation. Use with a spacer/holding chamber helps.
Breath-actuated pMDI	>5 years	Child may not be able to generate necessary inspiratory flow. Device does not require the use of holding chamber or spacer.
Dry-powder inhaler	>5 years (can be used in 4 years olds, but delivery is more consistent in those >5 years)	Some devices deliver drug more effectively than a pMDI. Some devices may not work in children with low inspiratory volumes.
Nebulizer	Patients of any age who cannot use a pMDI with spacer/holding chamber or face mask.	Useful in infants and very young children and any child with a moderate-to-severe asthma episode. Delivery method of choice for cromolyn sodium.

* These ages are suggested as guides for making clinical decisions. The physician should tailor treatment to the specific needs and circumstances of the child and family.

† pMDI = pressurized metered-dose inhaler.

Adapted with permission from the American Academy of Allergy, Asthma & Immunology. *Pediatric Asthma: Promoting Best Practice. Guide for Managing Asthma in Children.* Milwaukee, WI: American Academy of Allergy, Asthma & Immunology, Inc.; 1999. (©2002, all rights reserved.)⁷

specific needs of the child,⁷ and instruction should be given in the proper use of these devices.²⁸ Failure to effectively use inhaler devices may directly increase treatment costs.³⁰

Some young children who have difficulty coordinating the actuation and inhalation of pMDIs can effectively use these devices with spacers, holding chambers, or face masks, whereas others may require a nebulizer to properly administer inhaled

therapy (Table 2).⁷ Delivery difficulties observed with the use of pMDIs in infants and young children may result in suboptimal or inappropriate treatment.

A phase-out of chlorofluorocarbon (CFC)-propelled pMDIs, for environmental reasons, and transition to hydrofluoroalkane (HFA)-propelled inhalers is currently taking place. Reformulation of HFA-pMDI medications may affect patient acceptability, and costs of reformulating may be prohibitive for compounds that are not used to a great extent. HFA-beclomethasone (QVAR) is approved for use in children aged 5 years or older. HFA-beclomethasone has been shown to be cost effective compared with the CFC formulation.

In a 12-month, multicenter, randomized, open-label, parallel-group study, Price et al. showed that patients aged 12 years or older with stable asthma had a significantly higher percentage of symptom-free days with HFA-beclomethasone compared with about half the dose of CFC-beclomethasone (42.4% versus 20.0%) and clinically significant improvement in health-related quality of life with the HFA formulation.³¹ Based on the incremental cost per symptom-free day, HFA-beclomethasone appeared to be cost effective compared with CFC-beclomethasone.

Nebulization is a preferred method for delivering inhaled medications to infants and young children who cannot use other delivery devices.⁷ Until recently, cromolyn sodium nebulizer solution was the only nebulized anti-inflammatory medication approved for the long-term control of asthma in U.S. children.

Budesonide inhalation suspension, the only ICS available in the United States in a nebulized formulation, was shown to be more effective than nebulized cromolyn sodium in children aged 2 to 6 years with mild-to-moderate persistent asthma, based on patient outcomes³² and caregiver quality of life.³³ After 52 weeks, children receiving budesonide (mean daily dose, 0.54 to 0.61 mg) demonstrated a significantly lower asthma exacerbation rate compared with cromolyn (mean daily dose, 65.0 to 76.3 mg) (1.23 ± 1.99 versus 2.41 ± 6.13 exacerbations/year) and significantly longer times to first exacerbation (216.63 ± 146.20 versus 147.78 ± 140.77 days) and use of additional long-term asthma medication (320.52 ± 99.59 versus 235.09 ± 140.31) ($P < 0.001$ for all). Caregivers of children treated with budesonide showed significantly less limitation in daily activities and emotional functioning compared with caregivers of cromolyn-treated children ($P < 0.001$ for both).³³

Nebulized budesonide has been used worldwide for the treatment of persistent asthma. In the United States, its safety and efficacy have been assessed in 3 randomized, double-blind, placebo-controlled trials involving a total of 1,017 children.³⁴⁻³⁶

In children aged 6 months to 8 years with mild persistent asthma, budesonide 0.25, 0.5, and 1.0 mg once daily significantly decreased nighttime and daytime asthma symptoms compared with placebo ($P \leq 0.05$) and reduced use of β_2 -agonist rescue medication ($P \leq 0.038$).³⁴ Similarly, in children aged

6 months to 8 years with moderate persistent asthma, once- or twice-daily budesonide therapy improved nighttime and daytime asthma symptom scores and decreased use of rescue medication compared with placebo.³⁵

Improvements in asthma symptoms were significantly greater compared with placebo in children receiving budesonide inhalation suspension 0.25 and 0.5 mg twice daily and 1.0 mg once daily ($P \leq 0.05$). Improvement was not statistically significant compared with placebo in the 0.25-mg once-daily budesonide treatment group. Compared with placebo, patients in all budesonide treatment groups showed a significantly reduced need for β_2 -agonist use from baseline to treatment end ($P \leq 0.014$).

In children aged 4 to 8 years with corticosteroid-dependent asthma, budesonide inhalation suspension 0.25 mg, 0.50 mg, or 1.0 mg twice daily significantly reduced the use of breakthrough medications ($P \leq 0.032$) and improved nighttime and daytime symptom scores ($P \leq 0.026$) compared with placebo.³⁶ There were no differences in the frequency, severity, or types of adverse events reported in the budesonide inhalation suspension groups compared with the placebo groups in these 3 trials.

■ Early Pharmacologic Intervention

The National Asthma Education and Prevention Program Working Group on the Financing of Asthma Care highlights the importance of early intervention for successful asthma management.⁹ In a study of children and adults aged 15 to 64 years with newly diagnosed asthma, early use of ICSs resulted in greater improvements in objective and subjective variables compared with SABA therapy.³⁷ Notably, improvement in morning peak expiratory flow was 32.8 L/min for budesonide compared with 4.8 L/min for terbutaline ($P < 0.001$). Budesonide also significantly reduced bronchial hyperresponsiveness ($P < 0.001$), asthma symptoms ($P < 0.01$), and use of supplemental β_2 -agonist therapy ($P < 0.01$).

In a continuation of this study, patients who received budesonide therapy at study onset had improved lung function compared with patients who received terbutaline for 2 years before initiating ICSs.³⁸ The authors noted that maintenance therapy usually could be given at a reduced dose. Another study demonstrated that the mean budesonide dose necessary to maintain long-term disease control in children with mild-to-moderate asthma decreased significantly over the course of the study, suggesting that treatment costs also may decrease over time.³⁹

Studies also found that a longer duration of symptoms before treatment was associated with smaller improvements in lung function in both children³⁹ and adults⁴⁰ with mild-to-moderate persistent asthma. Furthermore, treatment with ICSs at least partially reversed basement membrane thickness in adult patients with mild asthma.⁴¹ These findings suggest that early treatment with ICSs may prevent development of chronic airway obstruction.

■ Underuse of Inhaled Corticosteroids

Despite guideline recommendations for ICSs as daily first-line therapy in pediatric asthma, underuse of ICSs is widespread.⁴²⁻⁴⁶ A recent cross-sectional survey of children aged 5 to 17 years enrolled in 2 managed care plans revealed that only 55% of those with moderate and severe persistent asthma used long-term control medication daily.⁴⁷

A second study in a managed care setting demonstrated that less controller medication was dispensed for children aged 3 to 5 years compared with older children.⁴⁸ Furthermore, Yamada et al. reported inadequate medication regimens in a study of 87 children aged 3 to 12 years who were treated for acute asthma in the year before study enrollment.⁴⁴ These studies demonstrate a need for more accurate assessment of disease severity and more frequent use of ICSs consistent with that assessment.

■ Use of Inhaled Corticosteroids Reduces Health Resource Utilization

Underuse of ICSs may contribute to hospitalization and the need for repeated emergency care.⁴⁹ Wennergren et al. showed a gradual decrease over 15 years in the number of hospital days per year and number of admissions for children aged 2 to 18 years that coincided with a continuous increase in the number of children with asthma being treated with ICSs over the same time period.⁵⁰ Other studies demonstrated that ICSs could reduce the risks of hospitalization and emergency department visits in children aged 3 to 15 years⁵¹ and the risk of hospitalization in adults and children,⁵² compared with no controller therapy. Agertoft and Pedersen similarly demonstrated a significant reduction in the number of annual hospitalizations in children with mild-to-moderate persistent asthma treated with inhaled budesonide (0.0041 hospitalizations per child) compared with theophylline, β_2 -agonists, and cromolyn sodium (0.030 hospitalizations per child) ($P < 0.001$).³⁹

The Childhood Asthma Management Program study demonstrated a 43% lower rate of hospitalization in children treated with budesonide (2.5 hospitalizations per 100 person-years) compared with placebo (4.4 hospitalizations per 100 person-years), whereas there was no significant difference for those treated with nedocromil (4.3 hospitalizations per 100 person-years). In this study, the adjusted annual rates for urgent care visits because of asthma in the budesonide and nedocromil groups were significantly lower (45% and 27%, respectively) than those for the placebo group.²² Finally, in the study by Leflein et al. involving children aged 2 to 6 years with mild-to-moderate persistent asthma, nebulized budesonide inhalation suspension was significantly more effective than cromolyn sodium nebulizer solution. Patients receiving budesonide demonstrated significantly fewer yearly urgent care visits (0.15 versus 0.30), unscheduled physician visits for asthma (2.2 versus 2.8), unscheduled telephone calls to physician offices (4.8 versus 6.3), and days of oral corticosteroid use (6.3 versus 9.3) ($P < 0.01$ for all).³²

TABLE 3 Clinical Studies Reporting Health Care Utilization and Costs With Inhaled Corticosteroid Treatment

Study	Study Design	Length	Enrolled Patients	Treatments	Outcomes	Relative Findings
Murphy (2003) ³³ and Leflein (2002) ³²	R*, OL†, PG‡	52 weeks	426	Budesonide 0.5 mg/day vs. cromolyn 80 mg/day for 8 weeks, with dosage adjustments thereafter	% of patients with hospitalization: ED§ visit: Urgent care visit: Caregiver quality of life:	Similar between groups 8% for budesonide vs. 12% for cromolyn 11% for budesonide vs. 21% for cromolyn Greater improvements in activity limitations, emotional function, and total quality-of-life scores for budesonide
Andersson (2001) ⁵³	R, OL, PG	12 months	138	Budesonide 400 µg/day-800 µg/day vs. cromolyn 60 mg/day	SFDs : Yearly cost:	14% increase with switch to budesonide 24% lower for budesonide
Bisgaard (2001) ⁵⁴	R, DB,¶ PG	12 weeks	237	Fluticasone 100 µg/day and 200 µg/day vs. placebo	GP# visit: Direct cost:	21 for fluticasone 100 µg/day and 15 for 200 µg/day vs. 30 for placebo \$1.73 and \$1.80/patient/day vs. \$2.60/patient/day for placebo
CAMP** (2000) ²²	R, DB, PG	4-6 years	1,041	Budesonide 400 µg/day and nedocromil 16 mg/day vs. placebo	Hospitalization rate: Rate of urgent care visits: Nighttime awakenings:	43% lower for budesonide; not significantly different for nedocromil 45% lower for budesonide; 27% lower for nedocromil Similar between groups
Booth (1996) ⁵⁵	R, OL, PG	8 weeks	305	Fluticasone 100 µg/day vs. cromolyn 80 mg/day	Lack of symptoms in last 3 weeks of study: daytime: Nighttime: Cost-effectiveness:	71% of patients for fluticasone vs. 55% for cromolyn 80% of patients for fluticasone vs. 65% for cromolyn Fluticasone was more than twice as cost effective as cromolyn
Agertoft and Pedersen (1994) ³⁹	Controlled, prospective	3-7 years	278	Budesonide 800 µg/day for 6-8 weeks, with dosage adjustments thereafter; control patients continued regular non-ICS treatment	Hospitalizations:	.0041/patient/year for budesonide vs. .03/patient/year for controls
Connett (1993) ⁵⁶	R, DB, PG	6 months	40	Budesonide 400 µg/day 800 µg/day vs. placebo	SFDs: Cost/SFD: Cost-effectiveness ratio: Missed work days:	Mean 62 for budesonide vs. 38 for placebo £7.17 (U.S. \$13.07) for budesonide vs. £16.16 (U.S. \$29.48) for placebo £6.33 (U.S. -\$11.55) in favor of budesonide Mean 1.9 ± 4.9 for budesonide vs. 2.6 ± 6.0 for placebo
Rutten-van Mölken (1993) ⁵⁷	R, DB, PG	3 years	116	Budesonide 1,200 µg/day vs. placebo, plus SABA††	SFDs: Yearly cost: Missed school days:	212/patient-year for budesonide vs. 174/patient-year for placebo ~43% reduction with addition of budesonide Mean 1.7 day/year for budesonide vs. 3.7 day/year for placebo

* R = randomized.

† OL = open label.

‡ PG = parallel group.

§ ED = emergency department.

// SFDs = symptom-free days.

¶ DB = double-blind.

GP = general practitioner.

** CAMP = Childhood Asthma Management Program.

†† SABA = short-acting β₂-agonist.

■ Economic Value of Inhaled Corticosteroids

The cost-effectiveness of ICS therapy in children has been demonstrated in numerous clinical studies (Table 3). A study from the United Kingdom examined the relative cost-effectiveness of budesonide therapy compared with placebo in 40 children aged 1 to 3 years with symptoms of persistent asthma despite β_2 -agonist therapy.⁵⁶ The study found that budesonide significantly increased the number of symptom-free days compared with placebo (62 versus 38 days/patient, respectively), while lowering the estimated total annual cost of asthma care (£1397.83 versus £1891.43 per patient/year). Although drug costs were higher for children treated with budesonide than for those given placebo (£188.73 versus £47.53 per patient/year, respectively), the additional expense was more than offset by reductions in costs for physician consultations, hospitalizations, and days lost from work or playgroup.

In a Dutch study, Rutten-van Mölken et al. compared the cost-effectiveness of SABA therapy plus an ICS with SABA therapy plus placebo in 116 children aged 7 to 16 years.⁵⁷ Although the addition of an ICS to β_2 -agonist treatment resulted in an increase in treatment cost compared with placebo, the overall impact was a decrease in all other direct health care costs (e.g., antibiotic treatment, outpatient therapy, and hospitalization). When decreases in the indirect costs resulting from parents' lost productivity because of asthma-related school absenteeism were considered in the cost-effectiveness analysis, overall savings were further increased.

The outcomes and cost benefits of introducing ICS therapy to a U.S. Medicaid population were reported in a 2-year claims-based study involving 413 patients, 39% of whom were younger than 16 years.⁵⁸ Patients were monitored for 1 year before and 1 year after the initiation of ICS therapy in the case group. Hospitalizations decreased by 50% and outpatient visits decreased by 26% after initiation of ICSs, but hospitalizations increased 23% and outpatient visits increased by 36% in the control group. After adjusting for confounding variables, patients receiving ICS therapy had monthly health care cost savings of almost 24%.

Health care costs associated with ICS therapy also were assessed in a retrospective, matched-cohort, U.S. study involving ICS (n = 99, 57% younger than 13 years) and noncorticosteroid groups (n = 297, 55% younger than 13 years).⁵⁹ Patients received any combination of asthma medications except ICSs during the first 6 months of the study period. ICS therapy was then initiated in 1 group and continued throughout the 18-month study. Monthly payments for prescriptions increased from \$59 to \$116 in the ICS group and from \$53 to \$55 in the noncorticosteroid group. However, the average monthly payments for medical care decreased to \$28 in the ICS group because of reduced clinic visits, emergency department visits, and hospitalizations, and these costs increased to \$89 in the noncorticosteroid group. Thus, the increased cost of ICS therapy was

offset by the decreased costs of medical care for this population of patients. The authors concluded that ICS therapy improved health care outcomes without increasing the overall cost of care.

Few studies have directly compared the cost-effectiveness of different controller medications in children, and well-controlled cost-effectiveness trials comparing ICS products for the pediatric population have not been conducted.⁶⁰ Indeed, such comparisons can be difficult as the type of delivery device used by the child can affect cost. For example, a European study demonstrated that aggregated medication costs were lower for ICSs delivered via pMDI with Nebuchamber than with either Babyhaler or Aerochamber because of more efficient drug delivery.⁶¹ A significantly lower mean dose of inhaled budesonide also was required when delivered via Turbuhaler compared with Nebuhaler in children with asthma,³⁹ and the lower doses could translate into cost savings. Nevertheless, a recent Swedish study comparing the costs of budesonide and sodium cromoglycate therapy in children aged 5 to 11 years found that budesonide therapy was associated with 24% lower annual costs.⁵³

■ Economic Value of Health Education

A lack of self-management skills by children with asthma or their caregivers contributes to overuse of hospital emergency departments by these children.⁶² Asthma education programs aim to prevent or minimize acute asthma episodes by enhancing self-management behavior, increasing medication compliance, and improving patient-provider communication. Studies have shown these programs to be effective in decreasing asthma morbidity and associated health care costs for both adults and children.⁶³⁻⁶⁷

In a randomized trial of 310 children from low-income families, Clark et al. evaluated the ability of health education to improve asthma self-management.⁶³ Topics discussed in the program included managing an asthma attack, taking medicine, communicating with the physician, and maintaining a healthy home environment. Among children who had been hospitalized in the previous year, those who subsequently received health education had a significantly greater decrease in emergency department visits (-3.84 ± 8.46 versus 0.06 ± 14.24 , $P = 0.04$) and hospitalizations (-1.00 ± 0.33 versus -0.31 ± 1.35 , $P = 0.03$) compared with those in the control group. For enrolled patients, the program saved \$11.22 in emergency department and hospitalization costs for every \$1 spent to deliver health education.

A recent study by Kelly et al. also evaluated the effectiveness of a comprehensive asthma education and outreach program in decreasing emergency department utilization and hospitalization among Medicaid-insured pediatric patients with mild, moderate, or severe persistent asthma.⁶⁴ The intervention was based on National Heart, Lung, and Blood Institute (NHLBI) guidelines and was similar in content to the program of Clark et al. Among children in the intervention group, the number of emergency department visits decreased from 3.6 visits per child

in the year before the intervention to 1.7 visits per child ($P < 0.05$). Hospitalizations decreased from 0.6 to 0.2 ($P < 0.001$), and days in the hospital per child decreased from 2.4 to 0.9 ($P < 0.001$). The average asthma health care charges decreased by \$721 (24%) per child per year in the intervention group, despite the additional cost of subspecialty care in the clinic and salary support for the outreach nurse. Although the cost of outpatient medications was not included in the overall cost analysis, the authors estimated that the savings from decreased hospitalization rates would outweigh the costs related to daily ICS therapy.

An integral component of this outreach program involved liaison between the patient and provider through monthly contacts with an asthma outreach nurse. The relationship between patients, their families, and their care providers is an important component of health education interventions.¹²

■ Economic Value of Pharmacy-based Intervention

There is great potential for expansion of the pharmacist's role in a multidisciplinary approach to asthma management. Pharmacists can play a greater role in providing information to patients about asthma medications, the importance of medication adherence, and proper medication delivery for optimal disease management. Pharmacists can also contribute to safer and more effective disease management by monitoring medication use and refill intervals and alerting physicians when anti-inflammatory medications are suspected of being underused or quick-relief medications overused.⁶⁸

A transition from purely dispensing medications to working directly with physicians and patients may have a favorable impact on patient disease outcomes and health care utilization.⁶⁹ Numerous studies have demonstrated a positive effect of pharmacist intervention on outcomes in adult patients with chronic diseases, including asthma.⁷⁰⁻⁷⁴ In a 1-year pharmacy-based intervention study carried out in community pharmacies throughout Denmark,⁷⁵ pharmacists counseled patients (aged 16 to 60 years) with asthma and reviewed patient inhaler technique on a monthly basis. Pharmacists also recorded asthma symptoms and lung function and monitored patient diaries.

Compared with patients not receiving intervention, patients in the intervention group demonstrated greater knowledge of asthma and asthma medications ($P < 0.001$), with fewer errors in inhaler technique ($P < 0.001$) and greater improvement in asthma symptom status ($P = 0.004$) and asthma-specific quality of life ($P < 0.001$). During the last 6 months of the study, 3.81 days of sickness were experienced per patient in the intervention group compared with 6.57 days per patient in the control group ($P = 0.078$). Additionally, there were only 4 hospitalizations and 17 asthma clinic visits in the intervention group compared with 11 hospitalizations and 30 clinic visits in the control group.⁷⁵

A similar study conducted in younger asthma patients, aged 6 to 17 years,⁷⁶ demonstrated no significant effect of pharmacy intervention on health or health care utilization. Differences in lung function improvement, asthma severity, and quality of life

were not significantly different based on intervention. Furthermore, there were no differences in the rates of asthma-specific hospitalizations, emergency department visits, or physician visits between patients in the intervention and control groups. The authors noted that the intervention might not have been powerful enough to have a significant effect on pharmacist behavior and patient outcomes and that compliance with the study protocol was low among pharmacists because of patient- and practice-based obstacles.

Pharmacists reported that obstacles to intervention were most frequently patient-based. For example, scheduling interventions was difficult in this young population because of school attendance, and patients lacked motivation to participate, perhaps because they "interpreted their meetings with pharmacists as unwelcome reminders of a medical condition that sets them apart from their peers."

■ Economic Value of Public Health

Numerous public health issues have an impact on asthma burden and subsequent health care costs. It is clear that minority patients and those who are impoverished and living in the inner city suffer higher morbidity and mortality due to asthma.^{77,78} Lack of a primary care provider may contribute significantly to the high asthma morbidity and resource utilization in children from low-income families, who may be more likely to use the emergency department as a source of primary care.

Higgins et al. evaluated the influence of family and provider intervention on asthma costs in 61 pediatric patients with asthma (mean age, 8.4 years) who were treated frequently in the emergency department (mean, 1.36 times per year, with 1.78 mean annual admissions).⁶⁵ These children were assigned to a primary care provider. Both parents and primary care providers received education regarding the NHLBI Guidelines for the Diagnosis and Management of Asthma.

Based on a retrospective review of the medical records, resources used by the patient for a mean of 58.1 months before intervention were compared with resource utilization per patient during the 11.2 months after intervention. Assessments demonstrated that intervention led to decreased health resource utilization and costs (Table 3). Annual cost savings in 1997 dollars after intervention were estimated at \$4,845 per patient. This study shows the value of incorporating patient and provider educational programs into the clinical management of pediatric asthma to reduce morbidity and overall disease costs.

Because health resource use is disproportionately high among disadvantaged populations, treatment interventions might provide greater improvement in asthma outcomes and reduce the need for emergency intervention in these patients.⁶ Multifaceted, inner-city interventions that include patient education and counseling, treatment, and environmental control measures have demonstrated improved asthma control in inner city children, with reduced hospital admissions^{64,78,79} and asthma-related costs.⁶⁴

Exposure to outdoor pollutants has a significant impact on asthma control.^{80,81} The proportion of pediatric asthma costs in the United States attributable to environmental pollutants (i.e., toxic chemicals in the air, water, food, or community) has been estimated at 30%.⁸² Greater relative risk of respiratory-related hospitalizations associated with air pollution in uninsured patients or patients on Medicaid compared with privately insured patients suggests an effect of socioeconomic or health care disparities on this environmental factor.⁸³

Conclusion

From 1985 to 1994, the estimated total cost of illness for pediatric (younger than 17 years) asthma increased from \$2.25 billion (in 1994 dollars) to \$3.17 billion despite a 15.5% decrease in the cost of care per child.¹⁰ This decrease in per-child costs was primarily driven by shorter lengths of hospital stay for children. National trends during this same period show only a 2.8% decrease in the number of hospitalizations (pediatric and adult) for asthma compared with a 15.5% decrease for all causes of hospitalization. Thus, there is a continued need to improve asthma management to reduce the economic burden of pediatric asthma.

It is the responsibility of all health care providers who care for children with asthma to advance the agenda of appropriate education and environmental control. Furthermore, all children should have proper severity classification and, if persistent asthma is diagnosed, should be on a controller agent. Pharmacists are in a unique position to monitor for SABA overuse and to ensure that children with asthma and their caregivers understand the importance of daily use of controller medications, their mechanisms of action, and the proper delivery technique needed for optimal benefit.

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