

Achieving control of asthma in preschoolers

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The cases

Billy, who is 2 years old, presents to the physician's office with his fourth episode of wheezing in the past 18 months. He was admitted to hospital at 6 months of age with bronchiolitis caused by respiratory syncytial virus. At 9 months, he was seen in the local emergency department with a cold complicated by wheezing and severe cough. He was discharged home with salbutamol, to be given by metered-dose inhaler and valved holding chamber, and a 7-day course of amoxicillin. He had a similar episode resulting in another emergency department visit 2 months later, and his community physician advised the family to administer beclomethasone–hydrofluoroalkane 100 µg twice daily for 2 weeks for subsequent upper respiratory tract infections. Despite these measures, Billy has had 4 more colds complicated by wheezing, cough and dyspnea. During 2 of these episodes, "bronchitis" was diagnosed, and he was given azithromycin. His wheezing typically improves for 2 hours after he receives salbutamol. Between colds, he has no symptoms. He has no other medical problems, and his growth is normal. Billy was born at term, but was small for his gestational age. His mother had smoked 10 cigarettes per day through the pregnancy. His parents have 3 questions: Does Billy have asthma? How can they help him to handle colds better? Will he outgrow this condition?

Chantal, who is 4 years old, first experienced wheezing in association with colds at 11 months of age. By 3 years of age, she had a nighttime cough even between colds and played for shorter periods than the other children in her preschool because sustained activity led to wheezing and dyspnea. Asthma was diagnosed, and fluticasone 125 µg twice daily by spacer was prescribed, along with salbutamol as needed. However, Chantal's parents were worried about adverse effects and administered the medications only when she was especially unwell. During the past year, Chantal has visited the emergency department and received prednisone twice, but she has never been admitted to hospital. She has eczema, and both parents have hay fever. Her parents want to know whether it is safe to give her inhaled corticosteroids over a long period of time.

Key points

- A child's pattern of asthma may help to predict whether the child will "outgrow" the condition.
- Inhaled steroids are the controller medication of choice for children.
- To be effective, inhaled steroids must be given regularly, for at least a season at a time, not just during asthma attacks.
- Leukotriene receptor antagonists may be useful for asthma triggered by colds.
- Most children who are seen in the emergency department can be given bronchodilator therapy with a metered-dose inhaler and valved spacer.

Asthma is the most common chronic disease among children,¹ affecting 10% to 15% of children.^{2,3} Asthma is a major reason for pediatric admissions to hospital^{3,4} and visits to the emergency department.⁵ Inadequate control of asthma, as defined by previous Canadian Asthma Consensus Guidelines,⁶ is present in 26% to 45% of children with asthma,^{7,8} which suggests that previous guidelines have still not been fully incorporated into Canadian clinical practice.^{9,10}

Since publication of the 2003 version of the Canadian Pediatric Asthma Consensus Guidelines,¹¹ important new information has emerged from randomized controlled trials, particularly with regard to treatment with inhaled corticosteroids and use of add-on controller therapies. Further information has become available about the classification of asthma in preschool-aged children through large studies¹²⁻¹⁴

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and during the planning of a large randomized trial.¹⁵ Diagnosis is more challenging in young children than in adults, because conventional pulmonary function testing is unavailable for young patients. Although the medications used to treat asthma in children are generally the same as those used for adults, there are important differences between children and adults in terms of types of asthma and symptom patterns. In addition, there appear to be differences in the most effective strategies for each group.

Several national and international asthma guidelines, including those of the Global Initiative for Asthma¹⁶ and organizations in the United States,¹⁷ the United Kingdom,¹⁸ New Zealand¹⁹ and Australia,²⁰ also discuss pediatric asthma and have been recently updated. Important similarities and differences between our recommendations and these guidelines from other countries will be highlighted in the text.

Sources of information

Literature searches were performed to retrieve relevant articles on randomized controlled trials of asthma therapy in children published since the 2003 Canadian Pediatric Asthma Consensus Guidelines (updated to December 2004).¹¹ We used a structured literature search, originally developed by the Cochrane Collaboration Airways Group, to search its asthma registry, and pairs of authors independently graded the suitability of each article, resolving areas of disagreement by discussion. The following search strategy was employed: (child* or paediat* or pediat* or infan* or toddler* or bab* or young* or preschool* or “pre school*” or pre-school* or newborn* or “new born*” or new-born* or neo-nat* or neonat*) and ((steroid* or corticosteroid* or glucocorticoid* or “adrenal cortex hormone*” or budesonide or Pulmicort or fluticasone or Flixotide or Flovent or ciclesonide or Alvesco or triamcinolone or Kenalog or beclomethasone or Becotide or flunisolide or Aerobid or Symbicort or Seretide) or (leukotriene* or leucotriene* or anti-leukotriene or anti-leucotriene or montelukast or Singulair or zafirlukast or Accolate)) (*n* = 436 records). In addition, we performed hand searches of journal articles identified by PubMed searches in the areas of intermittent asthma, persistent asthma in preschoolers and emergency treatment. In many of these topic areas, large, well-conducted randomized controlled trials are not available, but we included the best available articles.

We based our grades of evidence and levels of recommendations, determined by consensus, on those of the Canadian Task Force on Preventive Health Care,²¹ as described previously.²²

Diagnosis and patterns of asthma

For children under 6 years of age, for whom conventional pulmonary function testing is not feasible, the diagnosis of asthma is based on a typical pattern of symptoms (cough with wheezing or dyspnea that typically varies in severity over time), response to therapy (either immediately after administration of a bronchodilator or, perhaps more importantly, over time after initiation of anti-inflammatory therapy) and absence of “warning signs” that suggest an alternative diag-

nosis (Table 1).¹¹ Primary care data suggest that asthma can be diagnosed accurately with basic clinical information in 85% of children.²³

Both parents and health care professionals may confuse wheezing with noisy breathing caused by retained upper airway secretions that the child has not learned to swallow or is unable to swallow; such noisy breathing is especially common in infants²⁴ and children with severe developmental delay. In patients with mild asthma-like symptoms, it may be challenging to differentiate cough or congestion typical of a viral cold from mild asthma; in such patients, a trial of therapy is often helpful. Excess production of mucus is a key component of airway obstruction in asthma. Plugging with mucus can cause crackles or radiographic evidence of atelectasis. In patients with viral respiratory tract infection and fever, these findings often lead to an incorrect diagnosis of “bronchitis” or pneumonia. The most common cause of recurrent “bronchitis” or pneumonia in children is underappreciated asthma,²⁵ which may be the underlying cause of “recurrent pneumonia” in up to 92% of pediatric cases.²⁶

Currently available asthma therapies are highly effective, and a lack of response to appropriately dosed therapy should prompt a search for suboptimal adherence to therapy, improper inhaler technique or a different diagnosis.¹¹ The Australian asthma guidelines stress the importance of ruling out other diagnoses when wet cough is the main symptom and when shortness of breath or wheezing is absent, particularly in indigenous children,²⁰ in whom other diagnoses, such as bronchiectasis, are relatively common. Bronchiectasis also appears to be more common among First Nations and Inuit Canadian children, particularly if there is a history of severe infection of the lower respiratory tract early in life.^{27,28}

Although the principles for diagnosing asthma have not changed since the previous guidelines, the importance of

Table 1: Other diagnoses to consider in young children with asthma-like symptoms

| Clinical finding | Potential diagnosis |
|--|--|
| Failure to thrive, steatorrhea | Cystic fibrosis |
| Frequent, persistent or unusual infections | Immunodeficiency |
| Chronic rhinitis and severe recurrent otitis media, with or without situs inversus | Primary ciliary dyskinesia |
| Severe regurgitation or vomiting | Gastroesophageal reflux |
| Persistent wheezing | Fixed obstructive lesion of the airway (e.g., vascular ring, hilar adenopathy, aspirated foreign body) |
| Heart murmur or known congenital heart disease | Wheezing caused by congestive heart failure |
| Noisy breathing caused by retained upper airway secretions, aspiration | Swallowing disorder (particularly if the child has an underlying neurologic disorder or developmental delay) |

classifying preschool asthma on the basis of pattern of symptoms and association with atopy and outcome has become increasingly evident. About half of children never wheeze during the first 3 years of life. About 20% of children have early transient wheezing in the first 3 years of life, and 15% to 20% begin wheezing after 3 years of age. Another group of children (14%–16%) will have persistent wheezing that starts before the age of 3 years and is still present at age 6.^{12,14} Large population-based studies have suggested that about two-thirds of children with wheezing in the first 3 years of life will no longer have wheezing by 6 years of age.¹² These data suggest 2 principal types of asthma in young children: early transient wheezing and persistent asthma. The Modified Asthma Predictive Index,¹⁵ which has been validated in several independent populations,^{13,29} may help to identify those young children at highest risk for persistent asthma (Box 1).

Transient asthma induced by viral infections typically starts in the first 3 years of life. Children with this pattern usually have no symptoms between colds, do not have atopic disease (e.g., have no eczema or allergic rhinitis) and have no first-degree relatives with asthma. This type of asthma may be related to the presence of smaller-than-normal airways at birth, possibly associated with in utero exposure to maternal smoking. The symptoms often abate by 6 years of age with growth of the airways.¹² Although transient, intermittent asthma has traditionally been considered a mild condition, some children have severe episodes of intermittent asthma, precipitated by colds and resulting in multiple visits to the emergency department or admissions to hospital.¹⁷ The risk factors for severe intermittent asthma, other than prior severe episodes,³⁰ have not been clearly identified, although one recent study indicated that some children with severe intermittent asthma may have atopic disease.³¹

Chronic or persistent asthma may begin either before or after 3 years of age. Children with chronic asthma have exacerbations caused by colds, as well as by exposure to allergens or irritants. These children almost always exhibit symptoms between major exacerbations, such as nighttime cough or cough, wheeze or excessive dyspnea with exercise, with the symptoms fluctuating over time. They also tend to have allergies and other atopic diseases, such as eczema or allergic rhinitis, and often have a family history of atopy. These children are less likely to “outgrow” their asthma.¹²

The recommendation to differentiate between transient and intermittent wheezing is also included in the British,¹⁸ Australian²⁰ and New Zealand¹⁹ asthma guidelines. The British guidelines suggest more detailed investigations and referral to a specialist for children who have symptoms but a low probability of asthma.¹⁸ The latest US guidelines recognize that intermittent asthma is not necessarily mild.¹⁷

Management of intermittent asthma

Although intermittent therapy with conventional doses of inhaled corticosteroids remains common practice in Canada, this practice was discouraged in the previous Canadian guidelines.¹¹ A more recent well-designed study has confirmed the

Box 1: Modified Asthma Predictive Index*†

- Wheezing on at least 4 occasions during the first 3 years of life, at least 1 episode of which was observed by a physician
- Combined with at least 1 of the following major risk factors:
 - Parental history of asthma
 - Physician-diagnosed atopic dermatitis
 - Allergic sensitization to at least 1 aeroallergen (e.g., house dust mite, cockroach, dog, cat, mould, grass, tree)
- OR combined with at least 2 of the following minor risk factors:
 - Wheezing unrelated to colds
 - Allergic sensitization to milk, eggs or peanuts
 - Blood eosinophils above 4%

*Adapted, with permission, from Guilbert et al.¹⁵

†A positive result indicates a child who is at the highest risk of persistent asthma.

ineffectiveness of the intermittent approach.³² Novel studies have suggested that therapy with leukotriene receptor antagonists, administered regularly or intermittently, may be effective in children with intermittent asthma.^{33,34}

Bronchodilators

All children with asthma must have access to an inhaled rapid-acting bronchodilator, such as salbutamol. Their families must receive asthma education and a written action plan, and the child must have regular follow-up. Because coordination in children is poor, those using a metered-dose inhaler should use a valved holding chamber. By 5 or 6 years of age, many children can use a dry powder inhaler, which has the advantages of portability and lower cost (no need to purchase a holding chamber). Wet nebulizer therapy is rarely necessary.¹¹

Inhaled corticosteroids

Few studies have evaluated regular treatment with inhaled corticosteroids for children with intermittent asthma. One Cochrane review found no evidence to suggest that a low daily dose of inhaled corticosteroids was beneficial.³⁵ However, there were methodologic limitations in the 2 studies included in the review.^{36,37} The 2003 Canadian Pediatric Asthma Consensus Guidelines specified, on the basis of expert consensus, that inhaled corticosteroids, administered regularly, were effective for children with intermittent asthma.^{6,11} Since then, in a 2-year study of 285 toddlers at risk for asthma (on the basis of the Modified Asthma Predictive Index¹⁵ [Box 1]), most of whom probably had intermittent asthma, regular therapy with fluticasone 100 µg twice daily improved asthma control but did not prevent the development of asthma, as determined during a subsequent year of observation.³⁸ An additional large study examining early introduction of fluticasone also showed that therapy did not alter prognosis.³⁹

Earlier studies examining the intermittent use of inhaled corticosteroids in children with intermittent asthma reported some improvements in symptoms, but not in the prevention of more severe exacerbations or progression to persistent

asthma.^{32,40,41} A Cochrane review published after the 2003 Canadian guidelines concluded that the available evidence was inconclusive with regard to parent-initiated oral corticosteroid therapy for the management of intermittent wheezing in children.⁴²

The guidelines of the Global Initiative for Asthma noted a continuing lack of high-level evidence demonstrating the clinical benefits of inhaled or systemic corticosteroids for intermittent viral-induced wheeze.¹⁶ The US guidelines did not discuss intermittent use of inhaled corticosteroids, but recommended treating patients with intermittent asthma who are at high risk with continuous inhaled corticosteroids;¹⁷ this would roughly correspond to our definition of children with severe episodes of intermittent asthma. The guidelines of the Global Initiative for Asthma also noted that inhaled corticosteroids do not induce remission of asthma and that symptoms generally return once treatment is stopped.¹⁶ Similarly, the US guidelines noted that inhaled corticosteroids do not appear to alter outcome but are important for controlling symptoms.¹⁷ Inhaled corticosteroids may be particularly helpful for children with recurrent wheezing and a positive Modified Asthma Predictive Index¹⁵ (Box 1).

Leukotriene receptor antagonists

Several recent studies have examined the effectiveness of the leukotriene receptor antagonist montelukast in children with intermittent asthma. Regular therapy with montelukast for 12 months significantly reduced the rate of asthma exacerbations in preschool children with intermittent asthma. However, the treatment did not significantly reduce prednisone use⁴³ and hence the clinical relevance of the reduction in exacerbations was not clear. In a large novel study involving children 2 to 14 years of age with intermittent asthma, administering montelukast from the onset of upper respiratory tract infections for a minimum of 7 days significantly reduced unscheduled health care visits, daytime and nighttime symptoms, days off from school or child care, and parents' time off from work, although there was no significant reduction in duration of episodes, use of prednisolone or admission to hospital.³³ A Canadian study evaluated administration of montelukast for 6 weeks in September and October,³⁴ when rates of asthma exacerbations peak in Canada (probably because older children return to school and there is rapid spread of respiratory viruses among students).⁴⁴ Montelukast added to usual therapy in children 2 to 14 years of age, about two-thirds of whom had previous prescriptions for inhaled corticosteroids, reduced the number of days with worse asthma symptoms by 53%. However, in preschool children, the effect was significant only among boys.³⁴

The use of montelukast by children with viral-associated wheezing was not discussed in the New Zealand asthma guidelines,¹⁹ but was supported in the guidelines of the Global Initiative for Asthma.¹⁶ The Australian²⁰ and British¹⁸ guidelines discussed the use of sodium cromoglycate and nedocromil sodium in children with frequent, intermittent asthma. We do not discuss these agents, as nonsteroidal anti-inflammatory asthma medications other than montelukast are now used only infrequently in Canada.

Outcome of the first case (Billy)

Billy receives a diagnosis of severe intermittent asthma, which warrants regular controller therapy. Billy's result on the Modified Asthma Predictive Index is negative, and the family is told that he has about a two-thirds chance of eventually "outgrowing" his asthma, probably by the time he reaches school age. Regular therapy with beclomethasone-hydrofluoroalkane 100 µg twice daily by valved holding chamber and salbutamol as needed are prescribed for Billy. Although Billy has 5 colds over the subsequent 5-month period, none result in asthma-related symptoms; his beclomethasone dose is therefore halved. Billy experiences no difficulties with colds for another 4 months, and the beclomethasone-hydrofluoroalkane is discontinued.

Management of persistent asthma

Since publication of the 2003 Canadian guidelines, newer, high-quality studies have reaffirmed the effectiveness of regular therapy with inhaled corticosteroids for young children with persistent asthma and have suggested a role for newer inhaled corticosteroids, which may also be even safer.

Environmental control

Given the close association of persistent asthma with atopy, management of persistent asthma in children should always start with environmental control, including, as for all children, avoidance of exposure to cigarette smoke.⁶ Appropriate allergy skin testing will help to direct a patient-specific approach to environmental control. Control of asthma should be specifically assessed and documented during every clinical visit (Table 2).⁶ The guidelines of the Global Initiative for Asthma also emphasized the importance of evaluating control and attempting to achieve excellent control (i.e., no symptoms or manifestations of disease).¹⁶ A recent study suggested that parental reports may overestimate the degree of asthma control.⁷ As such, the physi-

Table 2: Minimum criteria for acceptable control of asthma in preschoolers*

| Criterion† | Definition of control |
|------------------------------------|---|
| Daytime symptoms | < 4 days per week |
| Nighttime symptoms | < 1 night/week |
| Physical activity | Normal |
| Use of rapid-acting bronchodilator | < 4 times per week (unless before exercise only‡) |
| Exacerbations | Mild, infrequent (no more than once a year) |
| School, preschool or child care | None missed |

*Adapted from Canadian Pediatric Asthma Consensus Guidelines.¹¹

†Direct questioning at every office visit should be used to assess each criterion. Questioning should also specifically determine triggers of the child's asthma, adherence with therapy, inhaler technique and any concerns of the child or the family. Treatment should aim to establish the best possible control while minimizing toxic effects of drugs.

‡Preschool children rarely participate in organized sports for which pretreatment with a rapid-acting bronchodilator can be planned.

cian’s assessment may benefit from asking the child directly about symptoms, as well as specifically determining the occurrence of previous severe exacerbations.

Inhaled corticosteroids

The most recent Canadian Pediatric Asthma Consensus Guidelines stated that inhaled corticosteroids are the anti-inflammatory drug of choice for persistent asthma.¹¹ Conventional doses of inhaled corticosteroids have an onset of action within 1–6 weeks, and regular therapy is therefore essential for therapeutic benefit.⁴⁵ Recent studies have continued to demonstrate the efficacy of inhaled corticosteroids for young children with chronic symptoms. Bisgaard and colleagues⁴⁶ found that fluticasone 100 µg, given twice daily to preschool children, reduced the frequency of mild or severe exacerbations (defined in terms of use of prednisone, visits to the emergency department and admission to hospital), symptoms and need for bronchodilators significantly more than use of inhaled sodium cromoglycate. In another recent study, fluticasone 100 µg twice daily reduced exacerbations by half, relative to placebo.⁴⁷ Ciclesonide, a new inhaled corticosteroid, given at doses of 100 or 200 µg once daily, significantly improved symptoms and pulmonary function and reduced bronchodilator use among children 4 years of age and older.⁴⁸ All currently available inhaled corticosteroids appear to have similar efficacy. Approximate dose equivalences are provided in Table 3.⁴⁵

Studies of older individuals have shown that the common practice of doubling the dose of inhaled corticosteroid during exacerbations is ineffective,^{49,50} and this is likely true for preschool children as well. During a severe exacerbation, the most effective therapy to prevent a visit to the emergency department⁵¹ or admission to hospital⁵² is a short course of prednisone (see the section “Emergency management of asthma: systemic corticosteroids” in this article). With good control, severe exacerbations should be infrequent.¹¹

The main limitation of inhaled corticosteroids in clinical practice is concern about toxicity. Fortunately, the toxicity of low to moderate doses of inhaled corticosteroids (Table 3)⁴⁵ in young children appears minimal, although the data are somewhat contradictory. Nebulized budesonide at doses of up to 1000 µg daily for 12 weeks had no significant effect on adrenocorticotropic hormone stimulation tests in infants 6–12 months of age.⁵³ Fluticasone 100 µg twice daily for 12 weeks caused little change in urinary excretion of cortisol and no significant change in rate of linear growth.⁵⁴ Conversely, in a large recent study of children 2–3 years of age at risk for asthma, fluticasone 100 µg twice daily for 2 years significantly reduced the mean increase in height by 1.1 cm at 24 months, with some catch-up growth apparently occurring after cessation of the inhaled corticosteroids.³⁸ However, in school-aged children, ciclesonide 200 µg

daily for 1 year had no effect on linear growth velocity.⁵⁵ Furthermore, ciclesonide 100 or 200 µg once daily had no effect on urinary cortisol or adrenocorticotropic hormone stimulation tests in children 4 years and older.⁴⁸

High doses of inhaled corticosteroid — particularly doses equivalent to more than 500 µg per day of fluticasone — have been associated with symptomatic adrenal suppression and hypoglycemia, as well as reduced growth velocity.⁵⁶ The growth of children who are receiving inhaled corticosteroids should be monitored at every clinical visit. For this purpose, a pediatric growth chart should be used (e.g., growth charts of the Centers for Disease Control and Prevention, available at www.cdc.gov/nchs/about/major/nhanes/growthcharts/charts.htm). Re-evaluation of the dose of inhaled corticosteroid or addition of a second controller agent (see “Augmentation and add-on therapies,” below), or both, should be considered if growth is 1–2 cm less than expected per year^{57,58} or if growth drops by more than a major percentile on the growth chart. Children who are receiving high doses of inhaled corticosteroids should be referred to an asthma specialist, and consideration should be given to monitoring adrenal function by measuring the fasting morning serum cortisol level. The Australian asthma guidelines noted that the administration of inhaled corticosteroids at or above 200 µg of beclomethasone–hydrofluoroalkane daily or equivalent (i.e., equivalent to 200 µg of fluticasone) “may be associated with systemic side-effects.”²⁰

Starting doses of inhaled corticosteroids are similar to initial doses for older children and adults (Table 3). The dose need not be scaled down because of body size.⁶ The Australian asthma guidelines did not specify dosing for inhaled corticosteroids in pediatric asthma.²⁰ The guidelines of the Global Initiative for Asthma stated that daily doses of budesonide 400 µg (or equivalent) or less result in near-maximal

Table 3: Starting doses for inhaled corticosteroids for asthma therapy in children in Canada*

| Medication and inhaler device | Minimum age licensed for use in Canada | Low to moderate dose | High dose† |
|--|--|------------------------|-----------------------------|
| Beclomethasone–hydrofluoroalkane by metered-dose inhaler and spacer | 5 yr | 100–150 µg twice daily | 200 µg twice daily |
| Budesonide by dry powder inhaler | 6 yr‡ | 200 µg twice daily | 400 µg twice daily |
| Budesonide by wet nebulizer‡ | 3 mo | 250–500 µg twice daily | 1000 µg twice daily |
| Fluticasone by metered-dose inhaler and spacer or dry powder inhaler | 12 mo‡ | 100–125 µg twice daily | 250 µg twice daily |
| Ciclesonide by metered-dose inhaler and spacer | 6 yr | 100–200 µg once daily | 400 µg once or twice daily§ |

*Adapted from the Canadian asthma consensus report (1999).⁴⁵

†It is preferable to administer high-dose inhaled corticosteroids (or budesonide by nebulizer) in consultation with an asthma expert.

‡The youngest children able to use a dry powder inhaler are generally 4–5 years of age.¹¹

§Ciclesonide is usually used once daily except in cases of more severe disease.

benefits for most patients 5 years of age and younger.¹⁶ Once good asthma control has been achieved (Table 2), it is reasonable to reduce the dose of inhaled corticosteroid by about 50% at each follow-up visit; such visits are ideally scheduled every 2–3 months, with the child likely to have had further exposure to triggers in the periods between appointments.¹¹ If control worsens, the previous dose should be resumed. If control is maintained, further reductions in dose can be recommended. If no symptoms occur after 3–6 months of therapy with low doses of inhaled corticosteroids, the physician may consider attempting to stop the medication.¹¹

Leukotriene receptor antagonists

Older data indicated that the leukotriene receptor antagonist montelukast, at a dose of 4 mg daily, significantly reduced daytime symptoms, nighttime cough, need for β_2 -agonist rescue therapy and need for oral corticosteroids among children 2–5 years of age.⁵⁹ A recent small study involving toddlers 10 to 26 months of age also found that montelukast significantly improved lung function, airway inflammation (as measured by exhaled nitric oxide) and symptom scores.⁶⁰ This medication has the advantages of oral administration and rapid action, with 1-day onset of action and establishment of maximal effect in 3 weeks, as well as a low risk of adverse effects. Recent studies have suggested that in older children with persistent asthma, inhaled corticosteroids are more effective than leukotriene receptor antagonists.^{61,62} If control with leukotriene receptor antagonists is inadequate, an inhaled corticosteroid should probably be substituted or added in younger children as well. In a recent study of somewhat older children (6–17 years of age), more patients responded to fluticasone than to montelukast, although a substantial minority responded to both; the response to fluticasone was particularly likely among children with stronger evidence of atopy.⁶³

Recent asthma guidelines from the United Kingdom noted strong evidence to support the use of leukotriene receptor antagonists for children under 5 years of age.¹⁸ The US guidelines also stated that there is evidence to support the use of montelukast or sodium cromoglycate in children under 5 years of age, noting that either of these drugs could be used if an inhaled corticosteroid, the drug of choice, cannot be prescribed or is refused by the family.¹⁷

The second case continued (Chantal)

Chantal's family agrees to have her continue taking fluticasone 125 μ g twice daily on a long-term basis, and they appreciate the improvement in control of her asthma. Unfortunately, after her grandmother moves to a residence for seniors, the family agrees to look after her dog, even though skin prick tests have indicated that Chantal is allergic to cats and dogs. Chantal begins awakening with nighttime cough about 3 nights per week and has to drop her preschool gymnastics program because of dyspnea on exertion.

Augmentation and add-on therapies

Unfortunately, since publication of the most recent pediatric guidelines, no high-quality data on the role of long-

acting β_2 -agonists in pediatric asthma have been published. One large study, which probably included few preschool children, focused on strategies for the use of combination inhalers with long-acting β_2 -agonist and inhaled corticosteroid, rather than on the efficacy of the long-acting bronchodilator component.⁶⁴

When asthma control remains poor despite a low or moderate dose of inhaled corticosteroids, the first step is to assess compliance, given that families often stop maintenance therapy between asthma exacerbations.^{34,65} The physician should also look for comorbidities such as allergic rhinitis or sinusitis and should consider the possibility of new exposure or sensitization to allergens.⁶ If there are no such confounding factors, the dose of inhaled corticosteroid should be increased or a second controller medication added: either a leukotriene receptor antagonist or a long-acting β_2 -agonist.⁶ For preschool children, older research indicated that the therapeutic benefits of leukotriene receptor antagonist monotherapy, such as a reduction in symptoms and in the need for rescue therapy with oral steroids, also occur when a leukotriene receptor antagonist is added to an inhaled corticosteroid.⁵⁹

Long-acting β_2 -agonists

The long-acting β_2 -agonist salmeterol is approved in Canada as an add-on agent to inhaled corticosteroids in children 4 years of age or older. However, very few published studies have examined long-acting β_2 -agonists in prepubertal children, and all published pediatric studies have included children 7 years of age and older. These data are equivocal about the benefits of adding a long-acting β_2 -agonist, and a systematic review found no evidence that adding a long-acting β_2 -agonist to inhaled corticosteroids reduced exacerbations in children.⁶⁶ In one study of children 4 to 11 years of age, budesonide and formoterol improved pulmonary function more than budesonide alone, although both treatments had similar effects on other asthma outcomes.⁶⁷ Among children 7 to 11 years of age, adding montelukast to budesonide reduced airway inflammation, as assessed by measurement of exhaled nitric oxide, more than adding formoterol did.⁶⁸

A large study examined the use of a combination inhaler containing the inhaled corticosteroid budesonide and the rapid-acting, long-acting β_2 -agonist formoterol, for children as young as 4 years of age.⁶⁴ The patients were randomly assigned to receive a fixed dose of the combination inhaler for maintenance therapy plus a short-acting reliever, maintenance therapy with the combination inhaler plus additional doses of the combination inhaler for relief, or a higher dose of inhaled corticosteroid alone plus a short-acting reliever. Using the combination inhaler for regular maintenance and relief reduced the likelihood of exacerbations. Thus, using this inhaler in this fashion may improve outcomes in children.

Given the dearth of studies of long-acting β_2 -agonists in the preschool age group, these medications should probably be reserved for patients with more severe disease, such as those whose asthma is unresponsive to high doses of inhaled corticosteroids (Table 3) or moderate or high doses of inhaled

corticosteroids and a leukotriene receptor antagonist. Careful monitoring of response and adverse effects is required for children who are treated with long-acting β_2 -agonists.

The approach we recommend for the treatment of persistent asthma is similar to that recommended in the New Zealand guidelines¹⁹ and the guidelines of the Global Initiative for Asthma.¹⁶ The British guidelines¹⁸ provided no criteria for introducing add-on therapy for children below 5 years of age, recommended a leukotriene receptor antagonist for add-on therapy for children 2 to 5 years of age and recommended a long-acting β_2 -agonist for children 5 to 12 years of age. For children under 2 years of age needing add-on therapy and for children 2 to 5 years of age with no response to the combination of leukotriene receptor antagonist and inhaled corticosteroid, the British guidelines recommended referral to a specialist.¹⁸ The Australian guidelines indicated that leukotriene receptor antagonists “can be used as sole therapy in children with frequent intermittent or mild persistent asthma.”²⁰ These guidelines also noted, as we do, the lack of evidence supporting the use of long-acting β_2 -agonists in children. Both the Australian²⁰ and British¹⁸ asthma guidelines mentioned theophylline, which we do not discuss because of its infrequent use in children in Canada and the relatively high incidence of adverse effects. The US guidelines¹⁷ suggested that for children with inadequate control of asthma with moderate doses of inhaled corticosteroid, the dose of inhaled corticosteroid should be increased before a second-line agent is added, either a leukotriene receptor antagonist or long-acting β_2 -agonist. Those guidelines also stated that there is inadequate evidence to make good recommendations for children below 5 years of age. For school-aged children, a long-acting β_2 -agonist was recommended for add-on therapy (based on extrapolation of data for adolescents).¹⁷

Monoclonal anti-immunoglobulin E antibody

Omalizumab is a novel monoclonal anti-immunoglobulin E antibody administered every 2 to 4 weeks by subcutaneous injection. For children 6 years of age or older with moderate to severe allergic asthma and serum immunoglobulin E in a relatively narrow range of 70 to 1700 $\mu\text{g/L}$ (30 to 700 IU/mL), this drug is associated with significant improvements in asthma outcomes, including rates of exacerbations.⁶⁹ Omalizumab has not yet been studied in the preschool age group and is licensed in Canada for children 12 years of age and older. The drug is costly and is probably best reserved currently for adolescent patients with very severe allergic asthma.⁷⁰

Box 2: Key historical and clinical red flags indicating rapid deterioration or severe exacerbation

- Previous admission to intensive care unit for asthma
- Excessive use of inhaled bronchodilators before presentation¹⁶
- Already receiving oral corticosteroids for the index episode¹⁶
- Multiple recent visits to the emergency department or multiple recent admissions to hospital for asthma⁷¹
- Poor compliance with maintenance therapy

Emergency management of asthma

The second case continued (Chantal)

Chantal’s family reads on the Internet that inhaled corticosteroids are “addictive” and decide to stop the child’s fluticasone. The next month, while Chantal has a cold, the family visits her aunt, who has 5 cats. Chantal experiences severe dyspnea and wheezing. She is given salbutamol 200 μg every 4 hours, but her condition does not improve, and she is taken to the local emergency department. She is alert and afebrile. Her oxygen saturation is 92% and her respiratory rate 56 breaths per minute. There is an obvious tracheal tug and intercostal retractions, and her air entry is slightly reduced, with biphasic wheezing.

Initial management in the emergency department

Recent studies of management of asthma in the emergency department have focused on objective assessment of the severity of asthma and rapid provision of effective treatment. Care is guided by the clinical evaluation, including a directed history and a physical examination focused on key warning signs of rapid deterioration (Box 2) or severe exacerbation (Box 3) and measurement of oxygen saturation by pulse oximetry. The history should reveal whether inhaled corticosteroids are being used regularly or only during exacerbations. The Preschool Respiratory Assessment Measure⁷¹ (PRAM) has been validated as a responsive index of asthma severity⁷² and is being incorporated into clinical pathways of the emergency departments in several Canadian hospitals (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.071638/DC1).

Chest radiography is appropriate only if the child is severely ill, particularly if another or concurrent diagnosis is strongly suspected, such as pneumonia, lobar atelectasis, pneumomediastinum or pneumothorax.⁷³

Oxygen therapy

Supplemental oxygen therapy should be provided, when necessary, to raise oxygen saturation above 90%.⁷⁴ Arterial partial pressure of carbon dioxide (P_{CO_2}) should be estimated using arterial or arterialized capillary blood samples for children with no response to aggressive treatment, those with an abnormal level of consciousness and those who are in extreme respiratory distress. A recent study reported the estimation of carbon dioxide with an end-tidal carbon dioxide monitor;⁷⁵ however, this technique may be less accurate for patients with ventilation–

Box 3: Physical findings suggestive of severe exacerbation¹⁶

- Breathlessness severe enough to prevent child from talking in sentences or eating properly
- Nasal flaring and marked use of sternocleidomastoid muscles
- Respiratory rate greater than 2 standard deviations above the norm for age
- Markedly decreased entry of air and silent chest
- Excessive anxiety, restlessness or lethargy; inappropriate fatigue

perfusion inequality, as in those with acute asthma.⁷⁶ Most children with acute asthma have a low blood PCO_2 , so a “normal” value of PCO_2 indicates a severe exacerbation.

Bronchodilators

Numerous randomized controlled trials and a recent systematic review⁷⁷ have revealed that administration of bronchodilators by metered-dose inhaler and valved holding chamber has efficacy similar to or greater than that achieved with administration by wet nebulizer in the prevention of hospital admission for children below 5 years of age.^{78,79} Avoiding nebulizers may also help to prevent nosocomial viral infections. Patients (or their parents) should be told to bring their own holding chamber on subsequent visits to the emergency department to allow assessment of the patient’s technique and the condition of the device.

Young children have smaller airways and breathe more through the nose than is the case for older children and adults, and deposition of bronchodilators in the lower airways is therefore less, regardless of the device. As such, relatively large doses of β_2 -agonists are needed.^{80,81} The salbutamol dose range for use with a metered-dose inhaler and valved holding chamber in the emergency department is 400 to 800 μg (4 to 8 puffs) per dose or about 0.3 puffs per kilogram body weight, to a maximum of 8 puffs.⁸² Each puff should be administered separately, to avoid sedimentation of the inhaled particles in the valved holding chamber. Nebulizers are much less efficient, and the comparable dose is 2.5 mg for children weighing less than 15 kg and 5 mg for heavier children.⁸³ These doses should be given every 20 minutes or more to more severely ill children and hourly to patients with less severe disease until the child’s respiratory distress declines.⁸⁴

In contrast, the New Zealand guidelines recommend salbutamol at doses of 6 puffs for children less than 5 years of age and 12 puffs for children 5 years and older,¹⁹ and the Australian guidelines suggest 4 to 6 inhalations for children below 6 years of age and 8 to 12 puffs for those over 6 years of age.²⁰ The British guidelines recommend 2 to 4 puffs repeated every 20 to 30 minutes for children over 2 years of age who are having mild exacerbations and up to 10 puffs for children experiencing severe exacerbations.¹⁸ The US guidelines recommend therapy either by wet nebulizer or by metered-dose inhaler and spacer.¹⁷

Although continuous treatment with inhaled salbutamol has been shown to reduce rates of admission to hospital for adults,⁸⁵ only one pediatric study has been published.⁸⁶ It is difficult to draw meaningful conclusions from this report because of methodologic limitations. The most important adverse effects of β_2 -agonists include hyperactivity, tremor, tachycardia and mild hypokalemia.⁸⁴ These rarely limit therapy, but potassium supplementation may be necessary for children who receive extended bronchodilator therapy in the emergency department or for those who are admitted to hospital or are receiving diuretics. After discharge, the usual dose of salbutamol is 2 puffs (200 μg) every 4 hours, which the family should wean to every 4 hours as needed, as symptoms subside. The caregivers should be instructed to return to the emergency department if bronchodilators are needed more often than every 4 hours.

For children with severe disease, adding 3 consecutive doses of ipratropium to salbutamol therapy improves lung function and decreases rates of admission to hospital.^{87–89} Adverse effects are rare.⁸⁸ Although the optimal dose is unknown, 4 puffs (80 μg) by metered-dose inhaler and valved holding chamber⁹⁰ or 250 μg by nebulizer has been shown to be effective.^{82,88}

Systemic corticosteroids

Systemic corticosteroids lessen symptoms and airway obstruction, improve oxygenation and decrease the likelihood of admission to hospital from the emergency department.⁵² These drugs should therefore be considered part of the initial treatment for all but the mildest asthma exacerbations.⁹¹ Intravenous therapy is indicated only for children with persistent vomiting or very severe disease (score of 8 or more on Preschool Respiratory Assessment Measure [see the section “Initial management in the emergency department” in this article]). Because it takes several hours for the anti-inflammatory action of corticosteroids to take effect, these drugs should be started as soon as possible after the child’s arrival in the emergency department. The recommended dose of oral prednisolone or prednisone is 1–2 mg/kg (maximum 60 mg/dose) given daily for 5 to 7 days.⁵² Tapering is not necessary for short (even 10-day) courses of therapy.⁹² Dexamethasone syrup has a longer physiologic half-life than prednisone, and a 2-day course of this medication, at a dose of 0.15 mg/kg,⁹³ may therefore be just as effective as 5 days of treatment with prednisone. In patients with mild to moderate exacerbations, a single dose of dexamethasone of 0.6 mg/kg may be similarly effective.⁹⁴ Both older and more recent studies have indicated that inhaled corticosteroids are less effective than oral corticosteroids during acute exacerbations in children,^{95,96} and systemic corticosteroids should therefore be used for stabilization.⁹⁷

Additional therapies

Additional therapies are available for severely ill children with no response to standard treatment. Magnesium relaxes smooth-muscle cells,⁹⁸ may reduce neutrophilic inflammation⁹⁹ and is

Box 4: Guidelines for admitting children with asthma to hospital¹⁶

Admission to hospital is required

- Previous admission to an intensive care unit for asthma, unless current attack is mild
- Persistent respiratory distress 4 hours after administration of systemic corticosteroids
- Oxygen saturation < 90% with room air⁷²

Admission to hospital should be considered

- Current excessive use of salbutamol by inhalation, particularly if child is already taking oral corticosteroids and asthma remains poorly controlled
- Several visits to the emergency department for current episode
- Social factors (e.g., concerns about family’s ability to monitor the child, patient living at great distance from hospital, noncompliance with prescribed therapy, chronic poor control of condition)

useful in the treatment of refractory, severe acute asthma in children. Both randomized placebo-controlled trials^{100,101} and a recent systematic review¹⁰² reported that this agent reduces the need for admission to hospital and improves lung function in children with severe acute asthma. Magnesium is given intravenously over 30 minutes. Although the optimal dose is unknown, the most appropriate dosing appears to be 25–75 mg/kg per dose. The clinical response usually occurs within minutes. Given the short half-life of this drug, some patients require repeated infusions. Although it is generally very safe, rare cases of hypotension have occurred. The Global Initiative for Asthma guidelines took a cautious approach and underlined the fact that the infusion of magnesium has not been studied in young children.¹⁶ The use of magnesium by inhalation remains investigational.¹⁰³

New evidence suggests that a helium–oxygen mixture may be beneficial for patients with severe disease,¹⁰⁴ and it can also be used to drive wet nebulizers.¹⁰⁵ It is usually prepared as a mixture of 80% helium and 20% oxygen, although other ratios are also possible. Because the density of helium is about one-third that of air, airway resistance in the presence of turbulent airflow is reduced. Helium–oxygen may be of benefit to patients with severe disease.¹⁰⁴ In one recent study, using helium–oxygen, rather than oxygen, to drive wet nebulizers during continuous salbutamol therapy resulted in greater improvement in respiratory status.¹⁰⁶ This gas mixture may be considered for patients with severe exacerbations poorly responsive to other treatments in centres experienced in its use. Patients requiring therapy with either helium–oxygen or magnesium must be admitted to hospital.

Depending on the severity of the exacerbation, admission to a hospital providing specialized pediatric care or an intensive care unit may be required. Several factors can be used to determine the need for admission (Box 4).

Discharge planning

The families of patients being discharged from the emergency department should receive, before discharge, education about the therapeutic plan and correct use of the inhaler device. Information on indications that should prompt return to the emergency department and a written action plan should also be provided.¹⁰⁷ One recent study suggested that a single follow-up visit, occurring in the emergency department, for children with a recent visit to the emergency department or admission to hospital may reduce subsequent unscheduled health care visits.¹⁰⁸ Follow-up with a primary care physician within

Box 5: Key messages for achieving control of asthma in preschoolers

Pattern of asthma

- The pattern of asthma in young children (transient or persistent) should be determined, as this pattern can help to predict which children are less likely to “outgrow” their asthma (grade A recommendation; level II-2 evidence).
- Transient asthma induced by viral infections is associated with exacerbations triggered by viral respiratory infections, absence of symptoms between exacerbations and absence of other atopic diseases or family history of atopy. Most children with this pattern “outgrow” their asthma.¹²
- Persistent asthma is associated with exacerbations triggered by viral respiratory infections and exposure to allergens, presence of asthma symptoms between major exacerbations and presence of other atopic diseases and a family history of atopic disease. This pattern is less likely to be “outgrown.”¹²

Management of intermittent asthma

- Intermittent use of inhaled corticosteroids, administered in standard doses, appears ineffective and is therefore not recommended for the treatment of intermittent wheezing (grade E recommendation; level I evidence).
- Regular therapy with inhaled corticosteroids should be used for children with severe or prolonged symptoms and those who have visited the emergency department or been admitted to hospital (grade C recommendation; level III evidence).
- Although inhaled corticosteroids can be used to control asthma symptoms, they do not prevent progression to persistent asthma (grade A recommendation; level I evidence).
- A leukotriene receptor antagonist can be used continuously during the viral season, or at the onset of viral infections, to reduce symptoms and visits to health care providers (grade A recommendation; level I evidence).

Management of persistent asthma

- Inhaled corticosteroids are the anti-inflammatory drugs of choice for the management of persistent asthma and should be administered daily (including between exacerbations) for a minimum of 1 season at a time (grade A recommendation; level I evidence).
- Inhaled corticosteroids are very effective when used optimally; therefore, if such therapy is unsuccessful, the diagnosis of asthma should be questioned or the possibility of a comorbid condition should be considered (grade B recommendation; level II-2 evidence).
- If asthma control remains inadequate with a moderate dose of inhaled corticosteroids, the dose should be increased (grade A recommendation; level I evidence) or a leukotriene receptor antagonist should be added (grade A recommendation; level I evidence).
- There is evidence to support adding a long-acting β_2 -agonist to inhaled corticosteroids for adolescents (grade A recommendation; level II-1 evidence), but there is minimal evidence to support this approach for preschool and school-aged children (grade C recommendation; level III evidence).
- Referral to a pediatric asthma specialist should be considered for patients who require add-on therapy (grade B recommendation; level III evidence).

Management in the emergency department

- A metered-dose inhaler and valved holding chamber should be used for inhaled delivery of medication for almost every child in the emergency department (grade A recommendation; level I evidence).
- Systemic corticosteroids should be started rapidly for patients with moderate or severe asthma exacerbation who are seen in the emergency department (grade A recommendation; level I evidence).
- Published severity scales should be used, as they allow greater objectivity in evaluating the severity of the exacerbation (grade A recommendation; level I evidence).
- Before discharge home, asthma education must be provided. Such education should include instruction in using the inhaler device, signs of an acute exacerbation and appropriate use of preventive therapy to avoid future visits to the emergency department (grade A recommendation; level I evidence).

several days is advisable, and the primary care physician or an asthma specialist (see below) should plan to reassess the level of control and the dose of maintenance therapy about 4 to 8 weeks later.

To prevent further exacerbations, the patient should receive a course of oral corticosteroids (as described above), and regular treatment with inhaled corticosteroids should be either introduced or emphasized (if the patient is not already taking such drugs or they are being used irregularly). If the patient is already receiving regular treatment with inhaled corticosteroids, the maintenance treatment regimen should be reviewed and optimized, as described above.

The indications for referral to a pediatric asthma specialist include recurrent visits to the emergency department or admissions to hospital for asthma within the past year, any admission to an intensive care unit for asthma, recurrent exacerbations or poor control despite attempts by the community physician to optimize therapy, poor adherence with asthma therapy or evidence of inadequate understanding of the therapeutic regimen. In many communities, asthma education programs are available. Such programs offer more intense education and can enhance adherence.

Our suggested management of acute asthma is generally similar to that recommended by the Global Initiative for Asthma¹⁶ and the Australian²⁰ and New Zealand¹⁹ guidelines.

Outcome of the second case (Chantal)

Prednisone is started for Chantal, and she and her family spend 5 hours in the emergency department, during which time salbutamol is given by valved holding chamber every 2 hours. Chantal is then sent home on a 5-day course of prednisone. She is referred to a community asthma education program, where her parents receive detailed information on inhaler technique and the risks and benefits of inhaled corticosteroids. Although they were impressed by the severity of Chantal's exacerbation, the parents cannot be convinced to relocate the family's dog. Fortunately, they do agree to resume regular therapy with inhaled corticosteroids.

Gaps in knowledge

The key messages for the management of asthma in children are presented in Box 5.

More data are urgently needed to evaluate the efficacy of regular therapy with inhaled corticosteroids in young children who have only intermittent asthma. More research is also required to define the effectiveness of long-acting β_2 -agonists in young children and to compare different strategies for the use of long-acting combination inhaler therapy with β_2 -agonist and inhaled corticosteroid. Additional work verifying the efficacy of intermittent therapy with leukotriene receptor antagonists would also be valuable. The key messages presented here do not identify potential differences in the presentation and outcome of asthma that may occur among First Nations and Inuit children, an issue that has already been discussed in the New Zealand guidelines.¹⁹ The British guidelines also discuss other ethnic subgroups who may be at particular risk for increased morbidity and mortality related to asthma.¹⁸

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This article is the last in a 7-part case study series that was developed as a knowledge translation initiative of the Canadian Thoracic Society Asthma Committee. The series aims to educate and inform primary care providers and nonrespiratory specialists about the diagnosis and management of asthma. The key messages presented in the cases are not clinical practice guidelines but are based on a review of the most recent scientific evidence available. Financial support for the publication of this series has been provided, in part, by the Canadian Thoracic Society.

Articles to date in this series

- Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. *CMAJ* 2009. DOI:10.1503/cmaj.080612.
- Kaplan AG, Balter MS, Bell AD, et al. Diagnosis of asthma in adults. *CMAJ* 2009. DOI:10.1503/cmaj.080006.
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