Asthma in Childhood

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KEYWORDS

• Asthma • Pediatrics • Management

Asthma is the most common chronic disease in childhood, with a prevalence of 10% to 30%.[1] Many of the current recommendations for management of asthma in children are based on studies in the adult asthmatic population, and there is a paucity of published pediatric data. The available literature can be divided into two main age groups, children younger than 12 years, and those aged 12 years and older (adults and adolescents). Although adult and adolescent asthma are comparable, adult asthma is different from pediatric asthma (age < 12 years) in many important ways, and consequently it may not be appropriate to extrapolate adult evidence to pediatric management. This article reviews the available pediatric evidence and provides evidence-based recommendations for management, based on recent American Thoracic Society grading recommendations (**Table 1**).[2] A number of guidelines exist for asthma management, but for consistency this article refers primarily to the National Asthma Council guidelines, recently updated and published in Australia.[3] Management of asthma is divided into the management of acute exacerbations (**Tables 1–5**) and interval management (**Tables 6–10**).

DIAGNOSIS AND MISDIAGNOSIS

Wheeze and dyspnea, with or without cough, are the core symptoms of asthma, but because these individual respiratory symptoms are common in children, asthma frequently is misdiagnosed. Parents may misinterpret other respiratory sounds, such as stridor and rattle, as wheeze. The relationship between cough and asthma also is complex.[4] Isolated persistent cough is rarely asthma. A number of important differential diagnoses exist and should be considered (see **Table 2**)[3,5] if other features of asthma are not present or if an inappropriate response to treatment is seen. A more detailed discussion of each of these conditions is beyond the scope of this article.

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Table 1
The American Thoracic Society grading recommendations

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong recommendation: High-quality evidence	Benefits clearly outweigh harms and burdens or vice versa	Consistent evidence from well-performed randomized, controlled trials or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation: Moderate-quality evidence	Benefits clearly outweigh harms and burdens or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flows, indirect or imprecise), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation: Low-quality evidence	Benefits clearly outweigh harms and burdens or vice versa	Evidence for at least one critical outcome from observational studies, from randomized, controlled trials with serious flaws, or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to charge the estimate.
Strong recommendation: Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens or vice versa	Evidence for a least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.
Weak recommendation: High-quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed randomized, controlled trials or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances, patient characteristics, or societal values. Further research is very unlikely to change our confidence in the estimate of effect.

Weak recommendation: Moderate-quality evidence	Benefits closely balanced with harms and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results. methodologic flaws, indirect or imprecise), or unusually strong evidence from unbiased observational studies	Alternative approaches are likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation: Low-quality evidence	Uncertainty in the estimates of benefits harms, and burdens; benefits may be closely balanced with harms and burdens	Evidence for at least one critical outcome from observations studies, from randomized, controlled trials with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation: Very low quality evidence	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

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Table 2
Important differential diagnoses in pediatric asthma

Condition	Characteristics
Transient infant wheezing (eg, recurrent bronchiolitis)	Onset in infancy No associated atopy Associated with maternal smoking
Cystic fibrosis	Recurrent wheeze and failure to thrive
Primary ciliary dyskinesia	Associated recurrent otitis media and sinusitis Initial oxygen requirement postnatally Situs inversus in 50%
Chronic bronchitis (viral or bacterial)	Persistent moist cough in combination with wheeze Purulent sputum suggests bacterial cause
Structural abnormality (eg, tracheomalacia, bronchomalacia)	Onset usually from or shortly after birth but occasionally later
Vocal cord dysfunction	High-pitched inspiratory stridor and dyspnea May be spontaneous or exercise induced Blunting of inspiratory volume loop on spirometry
Inhaled foreign body	Sudden onset Differential air entry or wheeze on examination
Cardiac failure	Associated with congenital or acquired heart disease (eg, dilated cardiomyopathy after viral infection)
Eosinophilic lung disorders including allergic bronchopulmonary aspergillosis	Skin prick test positivity to *Aspergillus fumigatus* Raised serum IgE Infiltrates on chest radiograph
Anxiety causing hyperventilation	No wheeze audible Spirometry at the time of symptoms may help distinguish
Exertional dyspnea	No respiratory symptoms other than with exercise Exercise testing may distinguish
Milk aspiration/cough during feeds	Symptomatic particularly with liquids Associated with developmental delay

Data from National Asthma Council Australia. Asthma management handbook. 2006. Available at: www.nationalasthma.org.au; and Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. Pediatrics 2007;120:855–64.

MANAGEMENT OF ACUTE ASTHMA

Assessing Severity

Assessment of severity (see **Table 3**) determines subsequent treatment. The evidence and grading of the approach and options of managing acute asthma are summarized in **Table 4**. Treatment of acute asthma is based on the underlying pathophysiology, attempting to reverse bronchoconstriction, airway inflammation, and mucus production.

Oxygen

If a patient is in acute distress, oxygen (to maintain oxygen saturations $\geq$ 95%) and a short-acting beta-2 agonist (SABA) should be given immediately. Subsequent salbutamol administration may precipitate further desaturation via pulmonary vasodilatation in areas of poorly ventilated lung. The value of initial oxygen saturation as a predictor of

Table 3
Initial assessment of acute asthma

Symptom	Mild	Moderate	Severe or Life-Threatening[a]
Confused/drowsy	No	No	Agitated *or* altered consciousness
Oximetry on presentation (Sao_2)	94%	94%–90%	Less than 90%
Talks in	Sentences	Phrases	Words *or* unable to speak
Pulse rate	Less than 100 beats/min	100–200 beats /min	More than 200 beats/min
Central cyanosis	Absent	Absent	Likely to be present
Wheeze intensity	Variable	Moderate to loud	Often quiet
PEF[b]	More than 60% predicted or personal best	40%–60% predicted or personal best	Less than 40% predicted or personal best *or* unable to perform
FEV_1	More than 60% predicted	40%–60% predicted	Less than 40% predicted *or* unable to perform

[a] Any of these features indicates that the episode is severe. The absence of any feature does not exclude a severe attack.
[b] Children under 7 years old are unlikely to perform PEF or spirometry reliably during an acute episode. These tests usually are not used in the assessment of acute asthma in children.
From National Asthma Council Australia. Asthma management handbook. 2006. Available at: www.nationalasthma.org.au; with permission.

subsequent hospitalization remains controversial.[6,7] Intensity of wheeze is a poor predictor.

Beta-2 Agonists

Selective beta-2 agonists (salbutamol) have been the mainstay of acute asthma management since the late 1970s. Frequency of administration is determined by the severity of the exacerbation (see **Table 5**). Continuous use of SABA has been shown to be more effective than intermittent regimens in severe exacerbations[8] and to reduce hospitalization (RR, 0.64; 95% confidence interval [CI], 0.5–0.9), resulting in a modest improvement in lung function at 2 to 3 hours. This benefit was not seen in mild or moderate asthma. Only one of the eight relatively small randomized, control trials (RCTs) included was pediatric[9] (n = 70, age 2–18 years) and studied children who had moderate to severe asthma. It found no difference in hospitalization rates or time spent in the emergency department. Excluded from the analysis was an RCT in a more severe pediatric asthma cohort (n = 17) admitted to intensive care, which demonstrated a benefit in clinical status and hospital stay.[10] A meta-analysis of 25 RCTs, including 21 pediatric studies and more than 2000 children,[11] demonstrated that in acute asthma spacers were as effective as nebulizers in limiting hospitalization rates and reducing the time spent in emergency department (−0.47 hours; 95% CI, −0.58 to −0.37). The role of spacers in life-threatening asthma has yet to be investigated.

Table 4
Grading of evidence and recommendations for acute asthma management in children

Medication	Recommendation	Grading of Recommendation (Based on Evidence of Benefit)	Quality of Supporting Evidence
SABA	Recommended as first-line bronchodilator	Strong	High
Anticholinergics	Multiple doses beneficial in severe asthma	Strong	Moderate
Corticosteroids			
Inhaled	May be an alternative in mild asthma. High dose required if given.	Strong	Moderate
Oral	Beneficial in acute asthma not responding to SABA	Strong	High
Intravenous salbutamol	Beneficial in severe or life-threatening asthma	Strong	Moderate
Intravenous aminophylline	Alternative to IV salbutamol in severe or life-threatening asthma	Strong	Moderate
Magnesium sulfate			
Inhaled	Unclear role in severe asthma	Weak	Moderate
Intravenous	Beneficial in severe or life-threatening asthma	Strong	High
Heliox	May have a role in medication delivery but insufficient evidence to recommend currently	Weak	Moderate
Noninvasive ventilation	May have a role in life-threatening asthma to prevent intubation	Weak	Low
Leukotriene receptor antagonists	May have a role in mild to moderate acute asthma but further studies are required	Weak	Low
Antibiotics	No indication for routine use	Weak	Low
Education	Recommended but little evidence for improved outcome	Weak	High
Physiotherapy	May be of benefit in resolving stage of hypersecretory asthma	Weak	Low
Spacers	Spacer delivery of inhaled medications is recommended for all but life-threatening acute asthma	Strong	High

Anticholinergic Agents

Anticholinergic agents (ipratropium bromide, atropine sulfate) produce a weaker bronchodilation response with a slower onset of action (30–90 minutes versus 5–15 minutes)[12] but, by relieving cholinergic bronchomotor tone and secretions, have a beneficial effect when added to beta-agonist therapy in acute asthma. Meta-analysis of eight high-quality pediatric RCTs demonstrated that a single dose of an anticholinergic agent was insufficient to reduce hospital admission rate for any grade of severity (although in severe attacks persisting to 120 minutes, a benefit in lung function was seen).[13] In severe exacerbations in school-age children, multiple doses reduced hospital admission rates by 25% (number needed to treat [NNT], 7; 95% CI, 5–20) and additional bronchodilator use by 19%. No benefit was seen for mild attacks. The suggested benefit in moderate acute asthma may be skewed by the response in the severe subset and is insufficient to allow recommendation. There is a paucity of studies in children of preschool age.

The role of anticholinergics in wheezy children under the age of 2 years, excluding those who have bronchiolitis and chronic lung disease of prematurity, remains questionable. Parental preference and improvement in some (eg, clinical scores at 24 hours, additional treatment) but not all outcomes (eg, respiratory rate, need for oxygen supplementation, hospital stay), when given with or without beta-agonist, are not sufficient to recommend the use of an anticholinergic agent in this population.[14]

Corticosteroids

Although bronchoconstriction is best targeted with beta-2 agonists, the airway edema and secretions that accompany an acute exacerbation respond to systemic corticosteroid therapy. Considerable research effort has concentrated on the best route of administration, timing, and dose of corticosteroid. Corticosteroids are recommended for asthma exacerbations that are incompletely responsive to inhaled beta-agonists.

Doubling the dose of inhaled corticosteroids (ICS) at the onset of an exacerbation is ineffective in improving lung function and controlling symptoms (n = 28, age 6–14 years).[15] A review of published pediatric studies concluded that ICS given at high doses (eg, 1600 μg/d of budesonide) seem to have a modest benefit compared with placebo but are inferior to oral corticosteroids (OCS) in preventing hospitalization in more severe attacks.[16] The most commonly used OCS is prednisolone, often chosen because of its palatability[17] rather than because of comparative OCS data. Only one pediatric RCT has examined differing doses of prednisolone, in a mild to moderate severity cohort, and found no difference between 0.5, 1.0, and 2.0 mg/kg/d.[18] Meta-analysis of adult RCT data in severe asthma has shown no benefit from higher doses of corticosteroids, although these trials primarily examined intravenous (IV) administration.[19] At present, the recommended dose of oral prednisolone is 1 mg/kg every 12 to 24 hours (maximum dose, 50 mg) depending on progress.[20] The optimal duration of treatment also is unclear. A single dose of OCS on admission has failed to show consistent benefit.[21,22] A recent pediatric RCT comparing 3- and 5-day courses demonstrated equivalent efficacy.[23] Currently a 3-day course is recommended, lengthened to 5 days in more severe exacerbations.[20]

Early administration of OCS, within the first hour of arrival, has been shown to reduce admission rates in children (three RCTs; OR, 0.24; 95% CI, 0.11–0.53).[24] To date, however, parent-initiated OCS has not been demonstrated to improve outcomes, as evaluated by unscheduled medical visits,[25] but further trials are required to establish firm recommendations. OCS in children are as effective as parenteral dosing,[26] are more cost effective, and are more convenient but rely on the child's

Table 5
Initial management of children who have acute asthma

Treatment	Mild Episode	Moderate Episode	Severe or Life-Threatening Episode
Hospital admission necessary	Probably not required	Probably required	Yes Consider intensive care
Supplementary oxygen	Probably not required	May be required. Monitor Sao_2	Required. Monitor Sao_2. Arterial blood gases may be required.
Salbutamol (100 μg per puff)[a]	4–6 puffs (children < 6 years) or 8–12 puffs (children ≥ 6 years). Review in 20 minutes	6 puffs (children < 6 years) or 12 puffs (children ≥ 6 years) If initial response is inadequate, repeat at 20-minute intervals for two further doses; then give every 1–4 hours.	6 puffs (children < 6 years) or 12 puffs (children ≥ 6 years) every 20 minutes for three doses in first hour. If episode is life threatening, use continuous nebulized salbutamol. If no response, bolus IV salbutamol (15 μg/kg) over 10 minutes, then 1 μg/kg/min thereafter.
Ipratropium (20 μg per puff)	Not necessary	Optional	2 puffs (children < 6 years) or 4 puffs (children ≥ 6 years) every 20 minutes for three doses in first hour or use nebulized ipratropium
Systemic corticosteroids	Yes (consider)	Oral prednisolone (1 mg/kg daily for up to 3 days)	Oral prednisolone (1 mg/kg/dose) daily for up to 5 days Methylprednisolone IV (1 mg/kg) every 6 hours on day 1, every 12 hours on day 2, then daily

Magnesium	No	No	Magnesium sulfate 50% 0.1 mL/kg (50 mg/kg) IV over 20 minutes, then 0.06 mL/kg/h (30 mg/kg/h): target serum 1.5–2.5 mmol/L
Aminophylline	No	No	Only in intensive care: loading dose: 10 mg/kg; maintenance: 1.1 mg/kg/h if < 9 years or 0.7 mg/kg/h if ≥ 9 years
Chest radiograph	Not necessary unless focal signs present	Not necessary unless focal signs present	Necessary if no response to initial therapy or pneumothorax is suspected
Observations	Observe for 20 minutes after dose	Observe for 1 hour after last dose	Arrange for admission to hospital

[a] In children who have severe acute asthma that does not respond to initial treatment with inhaled SABA, bolus IV salbutamol (15 μg/kg) is effective and can avoid the need for continuous IV salbutamol and ICU admission.

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Table 6
Assessment of severity of interval asthma

Severity Level	Daytime Symptoms Between Exacerbations	Night-Time Symptoms Between Exacerbations	Exacerbations	PEF or FEV_1[a]	PEF Variability[b]
Infrequent intermittent	None	None	Brief, mild Occur < every 4–6 weeks	> 80% predicted	< 20%
Frequent intermittent	None	None	> Two per month	At least 80% predicted	< 20%
Mild persistent	More than once per week but not every day	More than twice per month but not every week	May affect activity and sleep	At least 80% predicted	20%–30%
Moderate persistent	Daily	More than once per week	At least twice per week; restrict activity or affect sleep	60%–80% predicted	> 30%
Severe persistent	Continual	Frequent	Frequent; restrict activity	≤ 60% predicted	> 30%

An individual's asthma pattern (infrequent intermittent, frequent intermittent, mild persistent, or severe persistent) is determined by the level in the table that corresponds to the most severe feature present. Other features associated with that pattern need not be present.

[a] Predicted values are based on age, sex, and height.

[b] Difference between morning and evening values.

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Table 7
Assessment of asthma control

	Level of Control		
Parameters	**Good**	**Fair**	**Poor**
Daytime symptoms	None	< 3 days/wk	≥ 3 days/wk
Night-time symptoms	Not wakened	≤ 1 night/wk	> 1 night/wk
Physical activity	Normal	Normal	Restricted
Exacerbations	None	Mild, infrequent	Moderate, severe frequent
Missed school/work because of asthma	None	None	Any
Reliever use[a]	None	< 3 doses/wk	≥ 3 doses/wk
[b]FEV_1 [b]FEV_1/FVC	Normal	≥ 90% personal best	< 90% personal best
[b]PEF	Normal	≥ 90% personal best	< 90% personal best

[a] Does not include one dose per day for prevention of exercise-induced symptoms.

[b] Applicable to adults and older children. Lung function parameters are not appropriate measures of asthma control in younger children.

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tolerating and retaining the dose. IV corticosteroids should be used in patients who are unlikely to tolerate OCS (ie, children experiencing severe exacerbation). Benefit is seen by 4 to 6 hours.[24] A single dose of oral or intramuscular (IM) dexamethasone (0.6 mg/kg to a maximum of 15–18 mg) was comparable to a 5-day course of oral prednisolone (2 mg/kg/d) in three pediatric RCTs (total n = 324),[27,28,29] although systemic side effects may be more common with IM long-acting corticosteroids.[17] OCS also have been shown to reduce relapse rates,[24] although this meta-analysis included only one pediatric RCT.[30] High-dose ICS regimens on discharge from hospital have shown efficacy similar to OCS but are not as cost effective.[31]

Intravenous Bronchodilators

First-line IV bronchodilator therapy in severe acute asthma not improving with inhaled beta-agonist and OCS therapy remains controversial. Guidelines recommend IV salbutamol as the first-line agent; it is preferred because of its better safety profile, but the lack of clear evidence has led to the continuing widespread use of aminophylline.[32]

Intravenous salbutamol

IV salbutamol has been shown to improve clinical outcome in comparison with placebo in individual pediatric RCTs both as an infusion[33] and as a bolus of 15 μg/kg.[34,35] Although an attempted meta-analysis of the adult and pediatric data failed to demonstrate improvement,[36] the conclusions of this meta-analysis have been criticized.[37]

Intravenous aminophylline

Meta-analysis of seven pediatric RCTs (n = 380 patients, mean age 5–9 years) in severe acute asthma demonstrated improvements in lung function and clinical symptoms with IV aminophylline infusion,[38] but the analysis is affected significantly by the results of the largest RCT (n = 179), the only RCT to show benefit.[39] A recent pediatric RCT (n = 44) directly comparing aminophylline and salbutamol (an IV salbutamol bolus of 15 μg/kg versus IV aminophylline infusion) demonstrated no difference in efficacy in the first 2 hours of treatment[37] but found a 30% reduction in hospital stay in the aminophylline group. Repeat IV aminophylline boluses have demonstrated no additional benefit over standard treatment (n = 60, age 2–5 years).[40]

Magnesium sulfate

Magnesium is a potential therapeutic agent in asthma because of its bronchodilating effect on smooth muscle cells[41] and reduction of the neutrophilic burst associated with inflammation.[42] In a meta-analysis of five pediatric RCTs (n = 182, age 1–18 years), IV magnesium sulfate decreased hospitalizations (OR, 0.29; 95% CI, 0.14–0.59; NNT, 4; 95% CI, 3–8) and improved pulmonary function and symptom scores, despite variation in dosage (25–75 mg/kg).[43] Another predominantly adult meta-analysis that included two pediatric RCTs (n = 78 subject age 1–18 years in a total of 665 subjects) confirmed its safe and beneficial role in severe acute asthma.[44] Meta-analysis of trials of inhaled magnesium sulfate, including two pediatric RCTs (n = 102), demonstrated significant improvements in lung function only in severe acute asthma and no difference in hospitalization.[45] The comparative benefit of bolus IV salbutamol and bolus IV magnesium sulfate is yet to be established.

Other Therapies

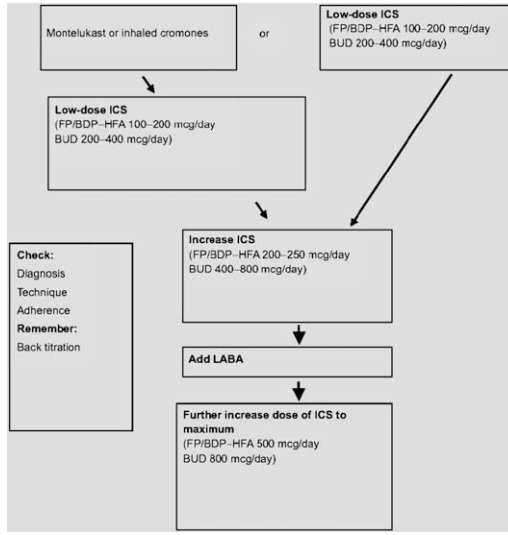
Heliox (helium/oxygen mixture) has lower gas density and higher viscosity, decreasing flow resistance and enhancing airway penetration. A meta-analysis including three pediatric RCTs demonstrated a potential benefit for heliox as a stand-alone therapy in severe acute asthma, but sample sizes were small.[46] In a recent pediatric RCT

Table 8
Table of grading of evidence and recommendations for interval asthma management in children

Medication	Recommendation	Grading of Recommendation (Based on Evidence of Benefit)	Quality of Supporting Evidence
Cromones (sodium cromoglycate and nedocromil sodium)	Alternative to inhaled corticosteroid in frequent intermittent and mild persistent asthma. May be beneficial in exercise-induced asthma.	Weak	Moderate
Leukotriene receptor antagonists	Beneficial as sole therapy in frequent intermittent or mild persistent asthma. May be beneficial in exercise-induced asthma or allergic rhinitis.	Strong	High
Corticosteroids			
Inhaled corticosteroids	Recommended for persistent asthma	Strong	High
Oral corticosteroids	Severe asthma not responsive to maximal inhaled therapy	Weak	Very weak
Long-acting beta-agonists	Should be considered as an add-on therapy	Weak	Moderate
Steroid-weaning agents			
Immunosuppressive agents	No evidence of efficacy in pediatric patients	Weak	Very low
Intravenous immunoglobulin	Limited role in pediatric asthma. May be beneficial if co-existent immunodeficiency	Weak	Low
Omalizumab	Role in asthma management is not well defined in pediatrics. Expensive	Weak	Moderate

Allergen immunotherapy (subcutaneous)	Potential benefit in children suspected of having allergen-triggered disease, when allergen avoidance has been ineffective or is not possible	Weak	Strong
Macrolides	Some adult data but no evidence of efficacy in pediatric asthma	Weak	Very low
Xanthines	Alternative in mild persistent asthma when inhaled corticosteroids are not available	Weak	Strong
Ketotifen	Alternative in mild persistent asthma when inhaled corticosteroids are not available	Weak	Moderate
Dietary manipulation	Current evidence does not support use in asthma	Weak	Low
Complementary alternative medicine	Current evidence does not support use in asthma	Weak	Low
Allergen avoidance	Some patients may benefit, but there is insufficient evidence to recommend routinely	Weak	High
Prevention strategies			
Primary	Current evidence does not support the use of preventative strategies in asthma	Weak	High
Secondary		Weak	Moderate
Tertiary		Weak	High
Vaccination (influenza and pneumococcus)		Weak	Moderate
Education	Recommended for all asthma patients	Strong	High
Psychotherapy	May be beneficial in a subset of patients	Weak	Moderate

Table 9
Management algorithm for chronic asthma



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(n = 30, age 2–18 years), however, heliox used as a facilitator of aerosol delivery in moderate to severe exacerbations provided significant improvement in clinical scores at 2 to 4 hours and improved discharge rates at 12 hours.[47]

Continuous positive airways pressure often is used in an attempt to avoid intubation and ventilation in exhausted patients who have life-threatening asthma. Its role in asthma remains controversial despite interesting and promising results. Significant improvements in hospitalization rate, discharge from emergency department, pulmonary function, and respiratory rate have been reported by the sole RCT included in a recent adult meta-analysis.[48] There have been no RCTs to date in pediatric populations, although published case reports of benefit exist.[49]

Table 10
Equivalent corticosteroid dosing

	Daily ICS Dose			
Dose Level	**CIC[a]**	**BDP–HFA[b]**	**FP[b]**	**BUD[b]**
Low	80–160 μg	100–200 μg	100–200 μg	200–400 μg
Medium	160–320 μg	200–400 μg	200–400 μg	400–800 μg
High	≥ 320 μg	> 400 μg	> 400 μg	> 800 μg

Abbreviations: BDP-HFA, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FP, fluticasone propionate.

[a] Ex actuator dose.

[b] Ex valve dose.

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Leukotrienes are proinflammatory mediators involved in both early and late asthmatic airway responses to allergen challenge. Leukotriene receptor antagonists (LTRAs) inhibit a part of the asthmatic inflammatory response that is relatively unaffected by OCS[50] and also provide some degree of bronchodilation. Onset of benefit has been shown to occur at 10 minutes with IV administration and within 2 hours with oral administration.[51] An RCT in preschool children demonstrated benefit in respiratory rate and symptoms scores for up to 4 hours and reduced OCS use at 1 hour (20.8% versus 38.5%) in comparison with placebo when LTRAs were given with the first dose of SABA.[52] A short course of LTRAs (given for 7 days or until symptoms had resolved for 48 hours) introduced at the first sign of an asthma exacerbation has been shown to have a beneficial effect in intermittent asthma, with a modest reduction in health care utilization, symptoms, and time off school/work.[53] Although these results are promising, the current evidence is insufficient to recommend the routine use of LTRAs in acute asthma.

There is a paucity of evidence to support the use of antibiotics in the routine management of acute asthma,[54] because most exacerbations are triggered by viral infections. Antibiotics should be reserved for cases in which infection with an antibiotic-responsive organism (bacterial, Mycoplasma) is suspected.

Other Aspects of Treatment

Chest radiographs are indicated only for first presentations of asthma, when there are atypical clinical features (to investigate for important differential diagnoses) or focal signs on examination (collapse, consolidation, or pneumothorax), or when there are severe exacerbations with a lack of response to initial treatment.

The difficulty of performing reproducible spirometry and peak expiratory flow (PEF) in young children means that, despite being listed in severity-assessment guidelines, lung function tests rarely are used during the initial assessment of acute asthma in children.

Arterial blood gases also rarely are used in pediatrics, apart from life-threatening exacerbations.[3] Free-flowing venous blood gases, taken at the time of intravenous cannulation, provide an accurate assessment of PCO_2, which may indicate impending exhaustion if in the normal range (35–45 mm Hg).

Education of parents and children attending the emergency department with acute exacerbations is part of routine management in many centers, although on systematic review an improvement in subsequent emergency department visits, hospitalization, or unscheduled medical reviews was not demonstrated, despite eight pediatric RCTs and large numbers (n = 1407).[55]

Physiotherapy should be avoided in the acute phase of an asthma exacerbation because of the danger of precipitating clinical deterioration[56] but may be of benefit in hypersecretory asthma in the recovery phase once bronchoconstriction has improved.[57]

INTERVAL ASTHMA MANAGEMENT

Assessing Severity

The grading of interval asthma severity and subsequent treatment are based on the clinical features present before commencing treatment (see **Table 6**). This approach, however, does not allow for re-evaluation of severity once treatment has been started, and control then is defined as the extent to which clinical features have been removed by treatment (see **Table 7**). It is important to exclude modifiable factors, such as poor adherence, incorrect inhaler technique, and smoking in adolescents, before this

assessment. Another important consideration is that asthma symptoms are not specific for asthma. The goals of management are a combination of good current control (control of symptoms, no exercise limitation, and normal lung function, if the patient is old enough to perform the test) and minimizing future risk (preventing decline in lung function, preventing future exacerbations, and avoiding medication side effects). The evidence for interval management of asthma is summarized in **Table 8**.

Specific practice points relevant to pediatric asthma management are highlighted in the National Asthma Council guidelines:[3]

- It often is not possible to eradicate transient infant wheeze or intermittent viral-induced wheezing in young children, and dose increases in an attempt to treat this aspect are inappropriate.
- One should avoid inappropriate dose increases made in an attempt to eradicate cough completely.
- Cough should not be used as a marker of control, in the absence of other symptoms.
- Symptoms are as reliable as PEF measurement in the monitoring of asthma control.

PHARMACOLOGIC MANAGEMENT

Preventive Medications

The necessity and choice of preventive medications is determined by the initial severity assessment or the degree of control on the current medication (see **Tables 4** and **5**).

Nonsteroidal Agents

Nonsteroidal preventive medications include sodium cromoglycate, nedocromil sodium, and LTRAs. All three are currently recommended as alternatives to ICS for frequent intermittent or mild persistent asthma.[3]

The use of sodium cromoglycate stretches back 35 years but has decreased substantially with the emergence of ICS, and recent systematic reviews (25 RCTs, 17 of which were in a pediatric population) have demonstrated its inferiority to ICS.[58] Its role in asthma remains contentious, however, after initial meta-analyses (24 pediatric RCTs, n = 1024), which concluded that insufficient evidence existed for benefit over placebo, were strongly criticized.[59] Subsequent re-analysis of the data has demonstrated a beneficial effect, particularly in older children who have asthma.[60] Having been withdrawn from the British Thoracic Society guidelines in 2003, it has since been reinstated as ''effective in children aged 5–12,'' but is not named in the corresponding guideline.

Nedocromil sodium is also a cromone, a disodium salt of a pyranoquinolone dicarboxylic acid developed as an anti-inflammatory agent for the treatment of asthma.[61] A recent systematic review of 15 pediatric RCTs (n = 1422) concluded that the benefits in lung function and symptom outcomes suggested by short-term studies was not replicated consistently in longer-term trials. Despite its better side-effect profile, the lack of direct comparison with ICS in RCTs has meant the evidence needed to clarify its position in the treatment of chronic asthma is lacking.[62] This lack of data is in contrast to the adult literature, which shows it to be an effective treatment for asthma.[63]

The role of LTRAs such as montelukast and zafirlukast in interval asthma management is of particular interest in pediatrics because montelukast can be administered as a once-daily oral agent, potentially aiding compliance.[64] In a preschool cohort (age 2–5 years) of 549 children who had predominantly virally induced intermittent asthma, regular LTRA use reduced the rate of exacerbation over a 12-month treatment

period by 31.9% (1.60/year versus 2.34/year) and also reduced the need for ICS.[65] A short course of a LTRA introduced at the first sign of infection also has been shown to have benefit.[53] Regular low-dose ICS is not effective in reducing the exacerbation rate or severity in this asthma subgroup,[66] and parent-initiated OCS does not reduce hospitalization rates in preschoolers.[67] No direct comparison of LTRA and a short-course of high-dose ICS, which may have a beneficial role, has been published to date. Although the published data for zafirlukast in adolescents and adults largely mirror those of montelukast, there is a paucity of data available in pediatric populations.

In persistent asthma, the greatest benefit seems to be in cases of mild severity.[68] Large RCTs in preschool (n = 689)[69] and school-age (n = 336)[70] children have demonstrated benefit in symptoms, SABA and OCS use, and lung function (in those old enough to perform the test). These improvements were not documented for the subgroups that had moderate persistent asthma within these studies. For mild persistent asthma, LTRA offers a clinical alternative to ICS, although ICS has a better effect on lung function parameters.[71] ICS remains the more cost-effective option.[72,73] In moderate persistent asthma, low-dose ICS is superior to LTRA, when the two are compared directly, over a range of outcomes.[72,74,75,76] The clinical characteristics of children more likely to respond to LTRAs are not clearly defined, but children who have more frequent symptoms, increased inflammatory markers, and poorer lung function are more likely to respond to ICS.[75,77] Although a predominantly adult systematic review (only 2 of 27 RCTs were pediatric) found modest improvements (equivalent to increasing the ICS dose) when a LTRA was used as an add-on therapy to ICS,[78] this finding was not replicated in a recent pediatric RCT, which showed a increased exacerbation rate in the add-on group.[76] LTRAs may have a modest steroid-sparing effect.[78] The equivalent data are lacking in pediatrics. A meta-analysis of data concluding that the effect of an add-on LTRA was inferior to that of long-acting beta-agonists (LABA)[79] contained only one pediatric RCT in abstract form, which has been published since then[80] (n = 80 of 6476). No formal comparison pediatric RCTs have been published to date. There is emerging evidence of genetic polymorphisms that may influence the response to LTRAs.[81]

Allergic rhinitis may coexist with asthma. LRTAs are superior to placebo,[82] equivalent to antihistamines,[83] but inferior to nasal ICS in the treatment of allergic rhinitis.[84] A unified approach to treating the airway inflammation of both conditions is recommended. Treatment of allergic rhinitis with nasal corticosteroids also has shown a trend to improved asthma symptoms and forced expiratory volume in 1 second (FEV_1) which did not reach statistical significance (14 RCTs, 3 of which were pediatric).[85] A recent adult RCT of asthmatics who had allergic rhinitis has demonstrated a pronounced benefit of LRTA added to ICS, greater than the benefit achieved by doubling the dose of ICS.[86]

Inhaled Corticosteroids

ICS have formed the cornerstone of modern asthma management. Although not shown to be effective in patients who have episodic virally induced exacerbations,[66] the beneficial effect of ICS in persistent asthma has been established for some time.[87] A number of different ICS have been used, from the first ICS, beclomethasone, to budesonide and, more recently, fluticasone, ciclesonide, and mometasone. (Initial chlorofluorocarbon [CFC]-propelled metered-dose inhalers [MDI] have been reformulated using hydroxyfluoroalkane [HFA] propellant, because of concerns about the environmental impact of CFCs.)

Efficacy

Beclomethasone dipropionate was introduced in 1972. A meta-analysis of eight solely pediatric RCTs (n = 744, age $\geq$ 5 years) and four further RTCs that included children found beclomethasone to be superior to placebo with respect to FEV_1, symptoms, and likelihood of exacerbations when used for at least 4 weeks.[88] Beclomethasone seems to have a flat dose–response curve at higher doses,[89] based on two main RCTs, one of which was pediatric[90] (n = 177, age 6–16 years) comparing 400 μg/d versus 800 μg/d. The overall documented benefits in FEV_1 are small, however, and are of uncertain clinical significance, because there was no benefit in symptoms or exacerbation rate. No differences between the doses were shown in the pediatric trial. Previously reported ability to wean OCS dose with beclomethasone must be interpreted in the context of the time when the RCT was conducted (1970s) and the availability of other treatment options. Subsequent development of a HFA-propelled beclomethasone MDI, with its improved solubility and smaller particle size delivery, has led to improved drug delivery with consequent lower dose requirements.

Budesonide was introduced in 1980. Systematic review (11 pediatric RCTs, n = 926) demonstrated clear benefit over placebo in mild to moderate persistent asthma.[91] No dose-dependent effect above 100 to 200 μg/d was found for mild persistent asthma (seven pediatric RCTs, n = 726),[92] but an apparent further benefit (4% benefit in predicted FEV_1) in moderate-severe persistent asthma at doses of 800 μg/d has been reported in the only pediatric RCT examining this subgroup.[93] No pediatric RCTs have examined doses above 800 μg/d. A number of guidelines recommend use at the same dosage as CFC beclomethasone, but there is a lack of quality RCT data to support this recommendation (six pediatric RCTs of generally small numbers, with the number of subjects ranging from 10 to 41).[94]

Fluticasone was developed in 1990 and is available as an HFA-MDI and dry powder inhaler (DPI), both alone and in combination with salmeterol. Systematic review (75 RCTs including 8 pediatric RTCs, 5 of which had large sample sizes) has confirmed the benefit of fluticasone in mild to moderate asthma with minimal additional benefit from higher doses.[95] The finding of additional benefit of higher doses and an OCS-sparing effect in severe asthma is based on adolescent and adult data and is not definitive,[96] because no pediatric RCTs examined doses higher than 500 μg/d or included children taking daily OCS. An equivalent or slightly superior effect to budesonide or CFC-beclomethasone at half the dose was demonstrated on systematic review (75 RCTs, 16 pediatric).[97] A newer HFA-beclomethasone aerosol has been recommended at the same dose as fluticasone and was found to be equivalent in an essentially adult meta-analysis.[98] The only pediatric RCT comparison to date (n = 280, age 5–12 years) also has demonstrated equivalent effect.[99]

The two newest ICS are mometasone and ciclesonide. Mometasone is not currently available as an MDI in Australia but has US Food and Drug Administration (FDA) approval for children age 12 years and older. Ciclesonide is licensed in Australia for children 12 years and older and in June 2008 became available for children age 4 years and older, in line with the current FDA approval. Both drugs are approved for once-daily use. Mometasone was introduced in 1999, and evidence from a number of adult studies, some of which included adolescents, suggests a dose-dependent effect up to 400 μg/d in moderate persistent asthma, with no apparent benefit at higher doses.[100,101] An OCS-sparing effect has been documented at doses of 800/1600 μg /d.[102] Once-daily administration seems to be as effective as twice-daily administration at the same total daily dose. The one pediatric RCT to date in 296 children (age 4–11 years) who had mild to moderate persistent asthma showed benefit over

placebo, with equal efficacy of 100 μg once-daily (evening) dosing and 100 μg twice-daily regimens.[103] Ciclesonide is the newest ICS. It has a small particle size with higher lung deposition (52%) and lower oropharyngeal deposition (38%).[104] It is delivered as a prodrug, des-ciclesonide, and is converted to the active drug primarily in the lungs. Initial pediatric RCTs have shown efficacy equal to that of budesonide, at half the budesonide dose, to 320 μg of ciclesonide administered once daily,[105,106] and to equivalent doses of fluticasone.[107] Once-daily dosing seems to be effective.[105,106,108]

Safety

Although ICS remain the treatment of choice for chronic asthma, there are concerns about systemic side effects, such as hypothalamic-pituitary-adrenal axis suppression and effects on linear growth, particularly at higher doses. On meta-analysis, beclomethasone administered at a dose of 200 μg twice daily for 7 to 12 months in mild to moderate persistent asthma has been shown to cause a decrease in linear growth of 1.54 cm/y in children.[109] In the Childhood Asthma Management Plan (CAMP) study, budesonide at doses of 200 to 400 μg/d caused a significant reduction in growth velocity, of 1.0 to 1.5 cm, over 3 to 5 years of treatment.[110] Catch-up growth seems to occur in subsequent years if a lower maintenance dose is used,[111] and final adult height was unaffected in a follow-up of the CAMP cohort.[112] Fluticasone, at half the budesonide and beclomethasone dose, seems to have a comparable safety profile, although firm conclusions are difficult.[97] Adrenal suppression, as detected by urinary cortisol levels, has been demonstrated at 800 to 3200 μg of budesonide,[92] and high doses of fluticasone have been implicated in most (30 of 33) cases of adrenal crisis caused by ICS.[113] Local side effects, such as oral candidiasis, pharyngitis, and hoarse voice can occur with these ICS but generally are not a major issue in children, particularly if the drug is delivered via a spacer, which limits oropharyngeal deposition. Oral candidiasis occurred in approximately 5% of patients taking fluticasone[95] and increased at higher doses.[96] Mometasone seems to have a similar safety profile. The ideal ICS should have high pulmonary deposition and residency time, low systemic bioavailability, and rapid systemic clearance.[114] Ciclesonide with its low oral conversion rate (< 20%), very low systemic bioavailability (< 1%), rapid degradation, high clearance rate, and high plasma protein binding (> 99%) results in negligible systemic levels.[115] No adrenal suppression with ciclesonide has been reported to date, even at high doses, and the rate of local side effects is much better than with fluticasone.[116]

Low-dose ICS have been shown often to provide optimal control for mild persistent asthma and to reduce the risk of severe asthma exacerbations. When commencing ICS therapy, initial low-dose ICS (see **Table 10**) is as effective as an initial high dose and subsequent down titration (23 RCTs, including 5 pediatric and 4 infant RCTs).[117]

Long-Acting Beta-Agonists

LABAs have a mechanism of action similar to that of SABA, but prolonged activation of beta-2 receptors in bronchial smooth muscle results in a prolonged duration of action of up to 12 hours. LABA monotherapy is inferior to ICS in mild to moderate asthma.[118] In addition, no benefit in asthma control was documented when a LABA was added to maintenance ICS in a moderate asthma cohort.[90] (The negative finding in this study may reflect the actual population studied, rather than the intended target population, because the children in the study were controlled as well on low-dose ICS as on a doubled dose of ICS or added LABA.) This lack of response to LABA in children is very different from the response observed in adults;[119,120] in adults, LABA has demonstrated benefits in a number of asthma control measures both in patients being treated with ICS[121] and in

ICS-naïve patients.[122] The apparent increase in exacerbations and lack of protective effect with LABA use in pediatric populations has been well documented.[119,123]

Concern about the safety of LABA has arisen also. Meta-analysis of RCTs with LABA use longer than 3 months has documented an increased risk of severe and life-threatening exacerbations, as well as increased asthma-related deaths, in both adult and pediatric populations.[124] Particular populations identified as being at risk were African Americans and steroid-naïve patients. This concern led the US FDA Pulmonary and Allergy Drugs Advisory Committee to strengthen its warning on all LABAs.[125] Precipitating tachyphylaxis with regular LABA therapy and subsequent lack of response to SABAs during exacerbations is a further concern. Currently, LABA therapy is recommended only as add-on therapy for patients who have moderate persistent asthma and who remain symptomatic despite moderate-dose ICS. The exact recommended dose of ICS above which LABA treatment can be considered in children remains unclear, because of the small number of available pediatric RCTs.[90,121] Until more evidence exists to delineate better the indications for LABA therapy, including the underlying mechanism for the different observed response in children, these recommendations should be followed strictly.

There currently are two choices of combination inhaler: salmeterol/fluticasone available in an MDI and a DPI and eformoterol/ budesonide in an inspiratory flow-driven suspension inhaler. Patient preference for the type of device may influence the physician's decision when evaluating the choice of combination therapy. The fast onset of eformoterol, comparable to that of SABAs, has led to the development of a therapeutic strategy with a single combination medication (eformoterol/budesonide), used as both preventer and reliever medication. This has been demonstrated to reduce exacerbation rates in both adults and children (n = 2760),[126] with pediatric benefit confirmed by subanalysis of the pediatric data (n = 341).[127] Although not yet incorporated into guidelines, this approach remains a promising management strategy that may offer improved compliance and a therapeutic option for adolescents who have difficult-to-control, severe persistent asthma. The drug currently is not approved in Australia for children under age 12 years.

Oral Corticosteroids and Other Immunosuppressive Agents

Five percent to 10% of persons who have severe persistent asthma are not responsive to maximal inhaled therapy[128] and depend on OCS for adequate control. Although some data comparing ICS and OCS dosages in adults are available,[129] equivalent data for the pediatric population are lacking, and the side effects associated with regular OCS are a concern. Potential side effects of regular OCS include osteoporosis, hypertension, and secondary diabetes mellitus. A number of second-line immunosuppressive agents ("steroid-sparing agents") have been evaluated. Attempted systematic reviews of the efficacy of azathioprine,[130] chloroquine,[131] colchicine,[132] cyclosporine,[133] dapsone,[134] methotrexate[135] and gold[136] have been limited by a small number, if any, of acceptable RCTs. No pediatric RCTs have been included. Small but statistically significant decreases in OCS have been demonstrated with gold, methotrexate, and cyclosporine, but the clinical significance of this observed dose response is unclear, especially given the additional side-effect profile of the immunosuppressive drugs themselves. The longest study to date investigating methotrexate, 10 mg weekly for 1 year in adults, reported a 55% reduction in OCS dose (compared with 4% in placebo) but no benefit in bone metabolism.[137]

Immunoglobulins and Omalizumab Therapy

A number of small studies have examined the role of intravenous immunoglobulin (IVIG) as a steroid-sparing agent. The positive results of initial open-label studies

have not been replicated in subsequent RCTs including children,[138,139] and its role in asthma has been restricted. There also are safety concerns: one RCT was terminated prematurely after 3 of 16 patients in the high-dose IVIG arm (2 mg/kg monthly for 7 months) developed aseptic meningitis.[139] IVIG may play a role in a subset patients who have severe asthma with associated specific antibody deficiency,[140] but further research is needed.

Omalizumab is a humanized monoclonal antibody that forms complexes with circulating free IgE and represents a potential therapy for allergic disease. It currently is the only monoclonal antibody approved for asthma treatment and is included at step 5 in the current Global Initiative for Asthma guidelines (2006). Its true role in asthma management remains unclear, however. As an add-on therapy to ICS, omalizumab demonstrated benefits in symptom control and exacerbation rates in persistent asthma of varying severity,[141] but no benefit in exacerbation rate or steroid dose was seen in persons receiving regular OCS therapy. Only one RCT[142] has been conducted to date in children under age 12 years (range, 5–12 years) who had mild to moderate persistent asthma, and the results were similar. Omalizumab is an expensive drug, and its cost effectiveness remains debated.[143,144] Further studies are needed in the pediatric population for better clarification of patients likely to respond. The modest ICS-sparing effect also needs to be compared formally with cheaper alternatives such as the addition of LABA and LTRA.

Allergen Immunotherapy

Allergen immunotherapy is an evolving field, with both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) desensitization now available for common aeroallergens such as pollen, house dust mite (HDM), and cat. Although immunotherapy has been shown to be an effective treatment for insect allergy and allergic rhinitis, its effectiveness and utility in the treatment of asthma are controversial.

On meta-analysis, in comparison with placebo, SCIT led to a reduction in asthma symptoms and use of asthma medication, as well as allergen-specific bronchial hyper-responsiveness, but had no consistent effect on lung function (75 RCTs, including 38 RCTs limited to or including pediatric patients).[145] It remains unclear how SCIT performs against other available therapies; the only comparison RCT, performed in adults, suggests a response inferior to the response to ICS.[146] In a pediatric-specific meta-analysis (nine RCTs including 441 children), SLIT was shown to be effective in reducing asthma scores and reducing the need for rescue medication, but positive findings were confined to SLIT with HDM extract, not in children treated with pollen or grass extract.[147] No directly comparative studies in pediatric asthma have been performed, although SLIT has been reported to be about 50% as efficacious as SCIT for the treatment of allergic rhinitis in adults.[148] Of note, all SCIT and SLIT studies to date included only patients who had mild/moderate asthma and examined monotherapy, not polytherapy with an allergen mixture. Although allergen immunotherapy may provide therapeutic benefit in patients who have an identified extrinsic, clinically unavoidable allergen, the risk of potentially fatal anaphylaxis (although rare) should be considered carefully and discussed with the parents if SCIT is being considered. SLIT has very few reported serious side effects and can be delivered at home. There currently is insufficient evidence to recommend SLIT or SCIT as a standard treatment for pediatric asthma.

Other Anti-Inflammatory Medications

A number of agents with potential anti-inflammatory actions have been identified, including macrolides, xanthines, and ketotifen. Small RCTs of macrolide therapy,

including one pediatric RCT (n = 19),[149] have suggested a beneficial effect, but further studies are necessary to delineate which patients are most likely to benefit.[150] Xanthines (eg, theophylline) have been shown on meta-analysis to improve symptom control and SABA use compared with placebo and seem to be similar in efficacy to sodium cromoglycate but inferior to ICS (n = 2734, 34 pediatric RCTs).[151] Concern regarding a potential negative impact on behavior and concentration has limited its use, although these data are inconclusive; this concern is likely to be less of an issue now that lower doses are being used.[151] Ketotifen, an antihistamine, has been shown to improve asthma control in predominantly atopic, mild to moderate childhood asthma when used alone or in combination with other therapies (meta-analysis of 26 pediatric RCTs).[152] Benefit needs to be weighed against side effects such as sedation and weight gain.

Other Medications

Gastroesophageal reflux is common in asthma[153,154] and often is asymptomatic.[154] Pediatric RCTs of gastroesophageal reflux treatment have documented statistically significant improvements in clinical scores with treatment, but the clinical significance is unclear.[154,155]

Exercise-Induced Asthma

SABA administration before exercise confers significant protection for up to 3 hours.[156] A number of potential preventive therapies also have been shown to be effective for symptoms not adequately controlled with this approach. ICS given for at least 4 weeks were shown on meta-analysis (six RCTs of which four were pediatric, total n = 123, 102 pediatric subjects) to attenuate the fall in FEV_1 associated with exercise.[157] There currently is insufficient evidence to draw conclusions about shorter durations of ICS treatment. Also of note, in a population with mild persistent asthma,[158] there was a pronounced decrease in the exercise-induced fall in FEV_1 with 400 μg/d budesonide compared with 100 μg g/d, suggesting that a higher ICS dose may be needed to negate exercise symptoms despite good control of other symptoms. Nonsteroidal alternatives include sodium cromoglycate, nedocromil sodium, and LTRA. On meta-analysis (n = 280, 60% pediatric), nedocromil sodium has shown a consistent benefit in exercise-induced symptoms in both adults and children age 6 years and older.[159] LRTAs have a beneficial effect in exercise-induced asthma in children, with a significant reduction in FEV_1 fall[160,161,162,163] and onset of action within two doses.[162] Recently a head-to-head comparison between different therapies has been performed in a pediatric RCT (age 6–18 years, n = 80), which confirmed the beneficial effect of regular therapy and suggested that the best protection is offered by montelukast, either alone or in combination with budesonide.[164]

NONPHARMACOLOGIC MANAGEMENT

Dietary

Epidemiologic studies have attempted to explain the increasing prevalence of allergic diseases, especially in developed countries, and have examined a number of possible dietary factors. Attempted meta-analysis of calorie-controlled diets[165] and selenium supplementation[166] was limited by a lack of well-designed RCTs (only one was identified for either condition). Other RTCs, for fish oil supplements,[167] low or excluded salt,[168] tartrazine exclusion,[169] and vitamin C supplementation,[170] included between six and nine RCTs (two or fewer were pediatric) and failed to demonstrate any benefit.

Complementary Alternative Medicine

Complementary alternative medicine (CAM) is used commonly in pediatric asthma, with an estimated 50% to 60% of children using CAM at any one time.[171] (Only half of the cohort volunteered this information to their physician.) A lack of high-quality RCTs and heterogeneity of practice has hampered meta-analysis. There currently is no evidence to support the role of acupuncture,[172] homeopathy,[173] manual therapy,[174] or various breathing techniques[175,176] in chronic asthma. A recent RCT of breathing techniques in adults and adolescents who had mild persistent asthma documented impressive reductions in SABA use and ICS dose, although the lack of a true control arm makes it hard to rule out a trial effect.[177] Inspiratory muscle training in adults has demonstrated significant improvement in maximum inspiratory pressure, but the most of the research has been conducted by a single research group, and the clinical significance remains unclear.[178] A number of pediatric studies of physical fitness training in chronic asthmatics have successfully demonstrated improved cardiorespiratory fitness without deterioration in respiratory symptoms,[179] but whether improved fitness translates into better quality of life or lung function remains unclear. This finding, however, reinforces the overall aim of management in pediatric asthma, namely to allow the child to live as normal a life as possible, including full participation in activity.

Allergen Avoidance

Meta-analysis of studies using allergen-avoidance measures, including HDM reduction measures,[180] humidity control,[181] use of ionizers,[182] pet allergen control,[183] non-feather bedding,[184] and speleotherapy,[185] have failed to document any benefit in asthma control.

Asthma Prevention

Asthma prevention can be divided into primary (preventing onset of established risk factors), secondary (preventing development of asthma once established risk factors have developed) and tertiary prevention (care of established asthma and preventing exacerbations).

Potential environmental factors in asthma are supported by marked geographic and temporal variation in asthma prevalence.[1] Initial studies of environmental manipulation were promising, with HDM and food allergen avoidance measures in the first 12 months of life resulting in decreased sensitization and asthma diagnosis persisting until the age of 8 years in a high-risk birth cohort in the Isle of Wight.[186] Subsequent larger, multifaceted studies in Canada and Australia have failed to reproduce these results. The Canadian Childhood Asthma Primary Prevention Study showed a benefit in asthma symptoms but not bronchial hyper-responsiveness at 7 years,[187] whereas the Australian Childhood Asthma Prevention Study failed to show any clinical benefit at 5 years despite a 61% reduction in HDM and successful dietary manipulation.[188] Other current studies at earlier stages have yet to report positive results. The balance of evidence at present does not support the benefit of avoidance of allergens in early life on the subsequent development of asthma.

Breastfeeding currently is recommended for the first 6 months of life. There are a number of advantages to breastfeeding, but its protective role against allergic disease remains controversial. Although studies of formula-fed infants have reported higher rates of allergic disease, evidence does not support a protective effect on allergy and asthma. A recent large RCT in a birth cohort (n = 17,046) documented no protective effect at age 6.5 years of prolonged or exclusive breast feeding.[189] The

link between antenatal and postnatal exposure to environmental tobacco smoke and subsequent increased risk of asthma is well established.[190] No RCTs have been performed to date, but avoidance of environmental tobacco smoke is strongly recommended.

The Early Treatment of the Atopic Child study reported no overall benefit of prolonged cetirizine (H1 receptor antagonist) treatment in infants who had atopic dermatitis at 18-month posttreatment follow-up. Benefit was seen only in sensitized subgroups, persisting to 36 months in grass pollen–sensitized infants but only transiently in those sensitized to HDM.[191] A subsequent study, the Early Prevention of Asthma in Atopic Children study, specifically targeted these subgroups but failed to show any benefit (UCB Pharma SA Belgium, unpublished data).

The rationale for tertiary prevention studies is the observation that a large number of persistent asthma cases start early in life,[192] but the three trials conducted to date, at differing ages or stages of ''asthma development,'' have had disappointing results. Intermittent courses of ICS[193] and maintenance ICS,[194] for varying durations, in infants who had recurrent wheeze demonstrated no difference in asthma prevalence. The Childhood Asthma Management Program examined the effects of prolonged ICS or nedocromil sodium treatment for 4 to 6 years in a large group of school-age (5–12 years) children who had mild to moderate persistent asthma. Although ICS resulted in better symptom control, there was only a mild benefit in bronchial hyper-responsiveness and no effect on lung function outcome at the end of treatment.[110]

Vaccination in asthma may prevent exacerbations and serious complications such as pneumonia. Current guidelines recommend influenza vaccination for all children who have asthma, but there is a lack of pediatric evidence to support this recommendation.[195,196] In practice, vaccine coverage remains low despite the recommendation.[197] Pneumococcal vaccine has yet to demonstrate proven benefit in RCTs[198] but is now part of the routine vaccination schedule in many countries.

Other Aspects of Care

Education is a fundamental part of pediatric asthma management, including specific components of care (eg, training in the optimal use of medications), review of inhaler technique, and understanding of individualized written asthma-management plans. Education in self-management strategies does improve asthma outcomes,[199] including morbidity, but does not seem to improve quality of life.[200] Child-centered education seems to offer greater benefit than caregiver-focused education.[200] Written asthma-management plans, targeting symptom-based management rather than PEF, are effective in reducing exacerbation rates.[201,202] Having health care workers of patients' ethnic groups may be beneficial in improving asthma outcomes.[203] The evidence to support the role of family therapy or other psychologic interventions is limited,[204,205] but it may be a useful adjunct to care in certain children.

Spacers are required to deliver MDI medication effectively to younger children and are recommended to optimize delivery for older children, particularly in preventive therapy and in acute asthma. Small-volume spacers can be used from infancy with facemasks and from age 3 years with mouthpieces. Large-volume spacers can be used from 5 years of age. DPIs can be considered from the age of 6 years; breath-actuated devices are more appropriate from the age of 8 years, depending on the abilities and development of the individual child.[3]

Noninvasive methods to monitor airway inflammation, including exhaled nitric oxide, exhaled breath condensate, and induced sputum eosinophils, have shown benefits in adults.[206] The first pediatric longitudinal studies now have been published. These studies show a benefit in asthma control, and although there is not yet definitive

evidence for incorporating these measures into asthma-management guidelines, these methods are promising tools for future management.[206,207]

SUMMARY

Pediatric asthma is a common condition with a large health care burden. Despite the large number of RCTs and meta-analyses conducted, there is a paucity of pediatric evidence on which to base appropriate management guidelines, and data from adult RCTs should not be extrapolated inappropriately to this younger age group. Consensus guidelines based on a combination of available evidence and expert opinion do exist, however, and these guidelines will continue to evolve as more conclusive pediatric evidence becomes available. Although these guidelines should form the basis of pediatric asthma management, important differential diagnoses and potentially modifiable factors also should be considered before commencing or escalating treatment. Recommendations based on the available pediatric evidence are summarized in **Tables 4** and **8**.

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