

Third International Pediatric Consensus Statement on the Management of Childhood Asthma

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INTRODUCTION

The Third Pediatric Asthma Consensus Group met in Sao Paulo, Brazil, for 2 days on March 20/21, 1995. There were 42 participants representing 23 countries from around the world. All were pediatricians with a special interest in pulmonology or allergy and clinical immunology. The primary aim set by the participants was to develop clinically sound and practical guidelines for the management of childhood asthma that could be implemented in different health care systems with a reasonable chance of achieving compliance. While research and unresolved issues were discussed, it was agreed that the guidelines should be based on best established practice and expert opinion, backed up by recently published data, wherever possible. Concern was expressed by all participants about the inappropriate extrapolation of observations from adults with asthma to wheezing in young children, and also from older asthmatic children to wheezing infants. This was particularly relevant to the discussions on definition and pharmacotherapy.

DEFINITION

Whether or not a precise definition of childhood asthma can be developed depends on the reason why it is being sought. Despite improved understanding of the pathology, physiology, immunology, clinical factors, and genetics of asthma in childhood, we still do not know the basic mechanisms underlying the development of the disease. We have no information about immunopathology in the airways in infancy. Furthermore, many infants and toddlers who wheeze with upper respiratory tract infec-

tions do not subsequently develop asthma.¹ The definition of asthma has varied depending on the purposes for which it was being sought.

Epidemiologists tend to use the symptom of wheeze alone, as it is assumed that most such individuals have asthma. However, as has been demonstrated in a number of prospective cohort studies in infancy this is not necessarily the case.¹ *The clinician* usually incorporates the presence of persistent cough and wheeze, particularly at night and precipitated by standard triggers such as allergens, exercise, or infection. Associations with allergic disorders (allergic rhinitis, atopic dermatitis, and food allergy) are usually also sought. *The immunologist* uses an objective evaluation of atopy, including skin prick tests, measurements of total serum IgE and allergen-specific IgE antibodies, eosinophil activation proteins such as ECP, and a number of other markers that reflect immunopathology. These include sIL-2R, sICAM, and relative levels of IFN- γ and IL-4 released from stimulated T lymphocytes.²

Overlap among asthma, other diseases causing airway inflammation, and atopic disorders, as well as technical difficulties and cost, preclude the clinical use of the latter tests at present. *The physiologist* defines asthma in relation to airflow limitation (induced or spontaneous), which is reversible either spontaneously or with treatment.³ *The pathologist* defines it in terms of inflammation and cellular infiltrates of mast cells, T lymphocytes, and eosinophils. Indeed, the latter cellular infiltration has led to a pathological description of asthma as "eosinophilic bronchitis."⁴

Value of a Definition

While defining asthma is an interesting intellectual exercise, its only value for the practicing physician is to give a prognosis and to select and predict response to therapy. In infancy, it has to be admitted that we have only limited information about underlying pathophysiology. Thus, the definition must remain: Recurrent wheezing and/or persistent coughing in a setting where asthma is likely and other rarer conditions have been excluded.⁵ With increasing age, particularly beyond 3 years, the diagnosis of asthma becomes progressively more definitive and beyond 6 years of age, the NHLBI⁶ definition can be accepted. This incorporates the concept of asthma as primarily a disease of airway inflammation in which eosinophils and mast cells are prominent, producing recurrent episodes of cough and wheeze, often associated with increased bronchial hyperresponsiveness and reversible airflow limitation.

PREDICTION OF OUTCOME

The sensitivity and specificity of any measurements to predict outcome in the infant wheezer have yet to be established. A host of cohort studies^{1,7-11} have deter-

Abbreviations

CFC	Chlorofluoro carbon
ECP	Eosinophil cationic protein
EIA	Exercise-induced asthma
EPX	Eosinophil protein X (previously known as eosinophil-derived neurotoxin)
FEV ₁	Forced expiratory volume in 1 s
FEF _{25-75%}	Forced expiratory flow between 25 and 75% of vital capacity
GER	Gastroesophageal reflux
IFN- γ	Interferon-gamma
IgE	Immunoglobulin E
IL-4	Interleukin-4
IPRAF	International Pediatric Respiratory and Allergy Forum
MDI	Metered dose inhaler
NSAID	Non-steroidal anti-inflammatory drug
NHLBI	National Heart, Lung, and Blood Institute
PEF	Peak expiratory flow
sIL-2R	Soluble interleukin-2 receptor
sICAM-1	Soluble intercellular adhesion molecule-1
T lymphocytes	Thymus-dependent lymphocytes
WHO	World Health Organization

mined that many infant wheezers will not continue to have asthma in later childhood and adolescence. The proportion of wheezing infants who do not have continuing problems has been quoted as anything between 45 and 85% depending on the size and type of cohort and the length of follow-up. Elevated serum IgE levels and positive skin prick tests, particularly to house dust mite in infancy,^{12,13} predict persistent wheezing in childhood, but the only predictor of severe disease is pre-existing eczema and a first-degree relative with atopic asthma and/or eczema. Studies are currently in progress to establish the value of markers of allergic inflammation in blood, urine, and bronchoalveolar lavage.^{14–17}

CONTINUING MORBIDITY AND MORTALITY IN CHILDHOOD ASTHMA

Deaths from asthma in childhood are rare.^{18–20} Below the age of 4 they have fallen progressively over the last 20 years,²¹ and in children between 5 and 15 years old, they have been static. Against the background of an increase in the prevalence of disease,²² this suggests that the risk of dying from asthma in childhood has decreased.

Notwithstanding the evidence of avoidable deaths from asthma in adults, it is estimated that in childhood so-called preventable deaths occur rather less frequently when expressed as a percentage of the total. Many occur either totally unexpectedly in individuals who have not had a prior diagnosis of asthma or who have had relatively mild disease by all reasonable assessments.²³ Some occur in poor compliers and those with psychosocial problems, and relatively few are predictable.^{24,25} It is possible that adult asthma deaths are a consequence of poor long-term management in childhood. The burden is on the family physician and pediatrician to identify the child who is at risk of progressively more severe disease that might result in an adult death, and to intervene at a stage when it might be possible to alter the evolution of events. It is likely that delayed diagnosis and undertreatment of severe disease in childhood leads to progressively increasing airflow limitation and increases the risk of death in adulthood.^{9,20} Sustained impairment of function may be associated with psychological problems, scepticism about the value of therapy, and delay in treatment during severe attacks.

The paradox in relation to increasing morbidity is that it is related to two mutually exclusive factors: morbidity due to the disease and that due to the prescribed treatment. While at least 50% of children receiving prescriptions for antiasthma drugs have at least one prescription for an inhaled corticosteroid, in the United Kingdom only 15% have sufficiently regular repeat prescriptions so that they might have the opportunity to take it frequently enough to act as a true prophylactic therapy.²⁶ This suggests that 85% have inadequate prophylaxis. On the other

hand, there is evidence of unjustified overprescription of potent high-dose anti-inflammatory prophylaxis for infrequent, episodic asthma.²⁷ This suggests that the problem for persisting high morbidity in childhood asthma rests firmly with the physician.

Previously published guidelines have set unrealistic aims in relation to supposed cure of asthma or prevention of irreversible airway obstruction. There have also been inappropriate extrapolations of treatment practices from adult thoracic physicians, as well as an overemphasis on the use of peak flow meters, which can give spurious information and often interfere with compliance. It is difficult enough to educate a child in the use of inhalation devices without confusing the issue by demanding regular peak flow measurements in mild asthma. Furthermore, guidelines will only be used if information on how they can be implemented within different health-care systems is also given.²⁸

It is important to emphasize that there is no cure for asthma currently. There is scant evidence that an irreversible component to airflow limitation occurs in asthmatics with episodic rather than persistent disease. The use of inhaled corticosteroids in a range of severities of disease in childhood has not made any difference to lung function measured in adult life.²⁹ In a 28-year long longitudinal follow-up of childhood asthma, subjects with mild disease who had not taken inhaled steroids did not show any evidence of deficits in lung function in adulthood.³⁰ Thus the goals of treatment should be to achieve maximum improvement in life style and lung function with minimal side effects of treatment. For the overwhelming majority, it should be possible to normalize life style and optimize growth and development. However, for some this will not be possible. These children may still have symptoms and may require continuous or at least frequent intermittent dosing with short-acting β_2 -agonists to deal with symptoms on exertion and during intercurrent viral infection.³¹

AIMS OF MANAGEMENT

The aims of management should be to:

1. achieve rapid resolution of acute symptoms;
2. employ environmental control where indicated by history and allergy test results;
3. use prophylactic drugs when morbidity of asthma is sufficient to justify their use, taking into account their potential side effects;
4. optimize quality of life with no sleep disturbance and prevent exercise-induced asthma;
5. use delivery devices that are appropriate to the drug and the patient's age.

Critical to this is the proper assessment of severity, which should separate those signs and symptoms relating to long-term morbidity and those relating to acute episodes.

CLINICAL PATTERNS

Long-term morbidity dictates a division of asthma into three groups: infrequent episodic, frequent episodic, and persistent asthma.³²

Infrequent episodic asthma constitutes up to 75% of the childhood asthmatic population and is associated with episodes occurring less than once every 4–6 weeks, minor wheezing after heavy exertion, no interval symptoms, and normal lung function between episodes. Prophylactic therapy is usually not required for such patients.

Frequent episodic asthma constitutes about 20% of the asthma population and is associated with somewhat more frequent attacks and wheeze on moderate exercise, but is prevented by predosing with a β_2 -agonist. Symptoms occur less frequently than once a week, and there is normal or near normal lung function between episodes. Prophylactic treatment is usually necessary.

Persistent asthma affects roughly 5% of children with asthma and is associated with frequent acute episodes, wheezing with minor exertion, and interval symptoms requiring β_2 -agonist drugs more than 3 times a week because of either night wakening or chest tightness in the morning. There is nearly always evidence of airflow limitation between episodes. Prophylactic treatment is mandatory.

MONITORING

Airways

Airway narrowing is the basic physiological abnormality in asthma; it is caused by inflammation and is associated with bronchial hyperresponsiveness.^{2,4,33} It has been suggested that the incidence of airway narrowing in chronic asthma may be much higher than indicated by symptoms or intermittent lung function measurements and that daily or twice daily monitoring of peak flows is necessary to evaluate severity of disease and response of therapy. Studies in children³⁴ suggest that the assessment of morning peak flow as a percent of the highest value recorded is a useful and clinically relevant monitor of asthma severity.³⁴ However, the Consensus Group was concerned about the indiscriminate prescription of peak flow meters in the 75% of childhood asthmatics with infrequent episodic problems. Such patients derive no benefit from daily peak flow monitoring.³⁵ Indeed, there are situations in which spurious results are obtained, leading to inappropriate increases in therapy on one hand, or dishonest recording of spurious high values in children who actually have more severe disease. Lung function measurements, however, are essential in monitoring recovery from an acute asthmatic episode and in guiding optimal management of those with more severe disease. Some older children with frequent symptoms who are not well controlled can have poor perception of

deterioration and may benefit from peak flow monitoring.³⁶ The development of a simple and inexpensive method of measuring FEF_{25–75%} at home could provide a more specific and sensitive evaluation, particularly in patients who have primarily small airway obstruction.³⁷

Emphasis should be placed on careful clinical assessment by asking key questions, which include the following:

1. sleep disturbance requiring β -agonist therapy, morning cough and chest tightness requiring treatment;
2. breakthrough cough and wheezing with viral infection;
3. the number of acute episodes;
4. whether short-acting β -agonists are used regularly or intermittently; how frequently the inhalers are renewed.

It was felt that such assessments should occur at least twice a year in association with a consultation and the use of spirometry. If FEV₁ and flow-volume loops are normal, with β_2 -agonist requirement being less than 3 doses a week and no sleep disturbance or limitation of exercise tolerance, then no indication to use peak flow monitoring exists.

Bronchial Hyperresponsiveness

While bronchial hyperresponsiveness is commonly found in asthma and is increasingly abnormal in severe disease,³³ there is a considerable overlap in results among asthmatics of differing severity and nonasthmatics who have other respiratory problems.³⁸ It was felt that the measurement of the provocation dose or concentration of histamine or metacholine to produce a 20% change in lung function was of little or no value in the diagnosis of disease because of low specificity. Exercise challenge responses while inhaling dry air are, however, more specific and are useful in detecting exercise-induced bronchospasm and to diagnose asthma in children who present with persistent cough alone. There are claims that challenge with indirect agonists might be more specific for asthma, but these are not widely used at present.³⁹

Markers of Airway Inflammation

Bronchoscopy and bronchoalveolar lavage are now being performed in infants and young children for clinical purposes. Where the opportunity arises to obtain lavage in a wheezing infant, the specimens should also be subaliquotted for use in research. This might in time establish whether airway inflammation is truly a feature of all infant wheezers.⁴⁰ However, bronchoscopy and bronchoalveolar lavage are not part of routine clinical practice and should only be used when there is a need to exclude other causes for wheezing, such as tracheo- or bronchomalacia, etc. Sputum induction with hypertonic

saline can be used to examine lower airway secretions for inflammatory cells and their products,⁴¹ but this method is generally only practical in older children.

It is now possible to measure circulating levels of eosinophil activation proteins. Currently the only marketed assay is for ECP. The rigorous sampling requirements, with separation of serum between 1 and 2 h after sampling, renders the test difficult in routine clinical practice. Furthermore, it is not yet established whether measurements will contribute to monitoring. There are conflicting results from studies of the clinical value of ECP monitoring in childhood asthma.^{42,43} It was felt that if a urine measurement, such as EPX, became available it might provide a more robust and useful clinical measurement, but differentiating atopy associated with asthma from hay fever or atopic dermatitis may still be a problem.^{15,16}

Monitoring of Side Effects

It is important to emphasize the need to monitor growth by accurate anthropometry in all children.⁴⁴ This is particularly critical in asthmatic children taking high doses of inhaled or oral corticosteroid. Account must be taken of steroids administered by other routes such as intranasally or applied to the skin. In such circumstances, there may be a need to consider the effect on the hypothalamic-pituitary adrenal axis by measurement of 24-h urinary cortisol⁴⁵ and to monitor the long-term effects on bone density.^{46,47} If moderate- or high-dose theophylline is employed, serum level monitoring is imperative.⁴⁸

Other Modalities

Quality of life assessment has now been applied to asthma in childhood.^{49–51} There was some hope that such assessments might be incorporated into protocols, although more studies are required. It was also agreed that compliance monitoring was important. Indeed, it is probably more important to monitor and improve compliance than to monitor peak flow.

Thus, monitoring of infrequent episodic asthma requires a careful clinical history and examination with targeted questions and spirometry once or twice a year. For more frequent episodic asthma, short periods of peak flow monitoring in addition to interval spirometry will guide therapy, although it is rarely necessary to use peak flow monitoring continuously once disease is controlled. In children with more severe disease, particularly when there is evidence of reduced perception of airflow limitation, peak flow monitoring becomes essential, although this position is not based on any scientific evidence.³⁶

ALLERGY

There is now overwhelming evidence that allergy is a very important prerequisite for the development of

asthma.⁵² At least 75–90% of childhood asthmatics beyond 4–5 years of age have evidence of allergy in both affluent and developing countries. Atopy is a clear risk factor,⁵³ both for the persistence of bronchial hyperresponsiveness and symptoms of asthma.⁵⁴ The presence of atopic eczema predicts more severe disease.⁵⁵ Cross-sectional and longitudinal studies have provided evidence for a quantitative relationship between allergen exposure and sensitization.¹² Higher exposure is also associated with an increase in asthma symptoms in children,⁵⁶ although this relationship is less clear in adults.

Allergen Avoidance

Trials now indicate that allergen avoidance using a range of strategies may result in a reduction in allergen exposure with consequent reductions in bronchial hyperresponsiveness, asthma symptoms, and requirement for antiasthma medications.⁵⁷ Acaricides and allergen denaturants reduce allergen levels, but their clinical efficacy in reducing asthma symptoms is still uncertain and inferior to that of barrier bed covers.⁵⁸ Freezing and exposure to sunlight can also kill mites.⁵⁹ It was appreciated that current strategies for house dust mite avoidance have not been fully evaluated, particularly in relation to cost-benefit ratios by comparison with other therapeutic interventions.⁵⁹ Nevertheless, it was felt that recommendations for environmental avoidance should be made for every wheezing child, whatever their age. Total removal from environmental tobacco smoke exposure is an essential recommendation.^{60–62} It was also felt appropriate to suggest that families should not have pets, particularly cats and dogs.⁶³ Improved ventilation, barrier systems for bedding, and dehumidification were considered to be reasonable recommendations in children with established house mite sensitivity.⁶⁴ This requires an evaluation by a physician experienced in the diagnosis of allergy, in assessment of environmental exposure, and in environmental control.

Concomitant Allergies

It was also emphasized that many asthmatic children have allergic rhinitis, and treatment of the rhinitis could have beneficial effects on asthma.⁶⁵ Children with allergy have a higher incidence of sinusitis, which may in turn trigger asthma. A diagnosis of sinusitis is strongly associated with a diagnosis of asthma and concomitant allergic rhinitis.⁶⁶ Children with allergic rhinitis, sinusitis, and asthma improved their symptoms and concomitant bronchial hyperresponsiveness with appropriate clinical therapy for the upper respiratory tract disease.⁶⁷

In patients with acute allergy to foods, associated asthma is an important risk factor for fatal and near fatal anaphylaxis. Such patients must not only be advised to

avoid the offending foods, but also to carry appropriate inhaled and injectable adrenaline (epinephrine).⁶⁸

Immunotherapy

Immunotherapy as a modality of treatment for asthma was discussed. The European Academy of Allergology and Clinical Immunology recommendation that it should rarely be used under 5 years of age was endorsed.⁶⁹ Furthermore, there is limited indication for its use in older children.⁷⁰ It is most effective when employing high-dose single-allergen therapy, and it should only be administered when an allergen can be identified to be of significant relevance to the child's asthma. It should not be administered when asthma is poorly controlled as it may aggravate the condition. Its most likely role is in seasonal rhinoconjunctivitis, with or without asthma. It seems to be more effective in children than in adults,⁷¹ and meta-analysis has shown that it may provide clinical benefits in asthma,⁷² but more studies are required to define its role in the therapeutic algorithm. Immunotherapy is not a substitute for appropriate environmental control⁷³ or pharmacotherapy.

THERAPEUTIC STRATEGIES FOR EARLY INTERVENTION AND PREVENTION

Prevention and early intervention should be a primary aim for all pediatricians treating asthma. However, this should be based on established evidence of efficacy and, indeed, can only be economically viable if it is directed at the high-risk population. At present, inadequate data are available to predict which infants and young children will develop frequent episodic or persistent asthma. Furthermore, there are still no adequate long-term randomized controlled trials of early intervention showing that the disease can be truly prevented or that early intervention can modify the natural history of the disease.³⁰

Interesting data are accumulating on the association between neonatal peripheral blood mononuclear cell responses to allergen and the subsequent development of allergic disease; these data suggest that prediction will be possible in the future.^{74,75} Currently, environmental manipulation, including breast-feeding and avoidance of major food allergens with or without reduction of house dust mite and animal dander exposure, have produced reductions in the prevalence of food allergy, and particularly atopic eczema in infancy.⁷⁶ However, there is conflicting evidence that avoidance strategies have a long-term effect on the prevalence of asthma or, indeed, even on the prevalence of food allergy beyond the age of 2 years.^{77,78} There is evidence that exposure to environmental tobacco smoke, both ante- and postnatally, results in increased symptoms and abnormal lung function, so

avoidance at both of these times is important,⁷⁹ particularly for families with pre-existing atopy. Postnatally, reduction of exposure to major allergens by breast-feeding with maternal avoidance of common dietary allergens (cow's milk/eggs/peanuts), avoiding pet ownership, and reducing house dust mite exposure as much as practicable are reasonable recommendations. However, it was accepted that in many settings such recommendations would be impossible to follow and therefore inappropriate to suggest.

The issue of early intervention with pharmacotherapy is currently based on the premise that delayed introduction of effective asthma prophylaxis results in an irreversible component of airflow limitation.⁸⁰ Current evidence, particularly from the longest longitudinal study ever conducted (in asthmatic children from Melbourne) is that the risk of irreversibility in episodic asthma is very small.^{11,30} Furthermore, there is no evidence that the use of inhaled corticosteroids in any of the groups of asthmatics based on severity has any effect on lung function in mid-adult life.⁷ Under such circumstances, there can be no support for the early use of inhaled corticosteroids in infrequent episodic asthma in the preschool age group. While there are concerns that side effects could outweigh benefits, there is one study showing that 6 months' treatment with beclomethasone 600 µg a day is safe.⁸¹ Thus, in more persistent disease, there should be no hesitation to use inhaled steroids irrespective of age because the risk of complications is minimal.⁸²

The use of antihistamines such as ketotifen has been investigated in children with atopic dermatitis as a strategy to prevent the subsequent development of asthma.⁸³ At present, no data imply that antihistamines should be recommended routinely, but the outcomes of further clinical trials are awaited with interest. There may, however, be an indication to use antihistamines as part of the management of atopic dermatitis and allergic rhinitis. Once an infant with atopic dermatitis has had repeated (more than two or three) significant wheezing illnesses, there is reasonable justification for the early introduction of conventional asthma prophylaxis.

EDUCATION

Inadequate knowledge about asthma and its treatment among physicians⁸⁴ and patients is associated with increased morbidity and mortality from the disease.⁶ Studies have shown that specialist in-patient management of asthma achieves better results than nonspecialist care.⁸⁵ Most physicians do not have an adequate understanding of the changing concepts of asthma and its management. Furthermore, they do not have the practical skills in the use of aerosols and inhaler devices. In many parts of the world, asthma is still underdiagnosed and undertreated.⁶ However, conversely, in some areas overtreatment of

mild and sometimes nonexistent disease is becoming manifest.⁸⁶

There are, therefore, two essential strategies:

1. educate the profession;
2. educational programs for patients, their families, and others involved in the care of the asthmatic child such as school personnel.⁸⁷

Education of Professionals

Publication of consensus guidelines is but the first step in providing educational material for professionals. They must be disseminated by publishing them in major accessible journals in many different languages. Furthermore, the document should be readable and simple to follow. Complex therapeutic guidelines are unlikely to be followed. It is to be hoped that major national and international medical organizations (particularly WHO) will support the initiative and help in its dissemination. However, regional educational and training programs for professionals will need to be developed by local specialists together with their generalist colleagues. The training must include nurses, physiotherapists, pharmacists, and other ancillary medical staff; medical students and junior doctors (residents) require particular attention.⁶

Patients, Families, and School Personnel

It should be appreciated that day-to-day management of asthma falls on the patient, the family, and the school personnel rather than the physician. We therefore need to tailor educational packages and co-management programs to the individual patient and the family. The involvement of appropriately trained nurses in schools and physician practices, as well as physiotherapists, is particularly worthwhile. The objectives are to help the patients and parents as far as possible to develop understanding of the condition, its treatment, and the way to respond to any changes in clinical state. School staff require training in the management of asthma. They must be empowered and supported in the administration of asthma therapy. Children should be allowed to carry their own short-acting β_2 -agonist inhalers in school, and pre-treatment before athletic and other exertional activities should be encouraged.^{6,87}

It is of special importance to ensure that inhaled drugs are taken appropriately. It is also necessary to draw a distinction between those medications that produce symptom relief and those that are used regularly for prophylaxis. In Europe, the use of a color code system on inhalers has been helpful: brown inhalers for prevention and blue ones for relief. In the UCLA ACT program for children,⁸⁸ the red/yellow/green concept was used not only for peak flow monitoring but also for medicines.

The green medicines are to keep everything running smoothly (prevention) and, of course, include the prophylactic drugs for reducing inflammation; yellow medications are for mild increases in symptoms (β -agonists), and red medications are for severe exacerbations (nebulized β -agonists and oral steroids). However, in many countries, these systems have become useless because of the vast number of generic and differently colored drugs appearing on the market. Manufacturers should be aware that the benefits of color coding could have considerable influence on prescribing practices.

Action plans should be evolved to include instructions on signs that indicate worsening of asthma and what changes in treatment should be initiated at such times. Thus, there are four elements to the co-management package:

1. understanding the condition;
2. monitoring symptoms, drug usage, and, if necessary, peak flow;
- 3 a prearranged action plan;
4. written guidelines.

These guidelines should follow the principle of the three Rs: what is (w)ritten, reviewed, and revised.

Written materials produced by various professional and lay organizations, computer programs, videos, special holidays, organized sports activities, and group training programs may be of value. Further work is required to evaluate many of the educational materials currently being produced, although some programs have been found to be effective in well-conducted studies.⁸⁸ Ultimately, nothing can replace the interaction among the patient, family, physician, and other health professionals, particularly in addressing those psychosocial issues that can adversely effect disease control.

THE MEDIA AND HEALTH SERVICES

It is important to recognize that the media can play a constructive educational role in spreading sensible information about asthma. All too frequently, the media provide confusing and contradictory images of the relative benefits and side effects of various approaches. Opinion

TABLE 1—Requirements of Clinical Services for Childhood Asthma

Training of pediatricians and paramedical personnel
Knowledge of disease mechanisms, signs, symptoms, and treatment
Training and experience in evaluation of:
Spirometry
Atopy
Environment
Skilled in in-patient education and special training in use of inhalers and early recognition and treatment of acute episodes

LONG TERM TREATMENT

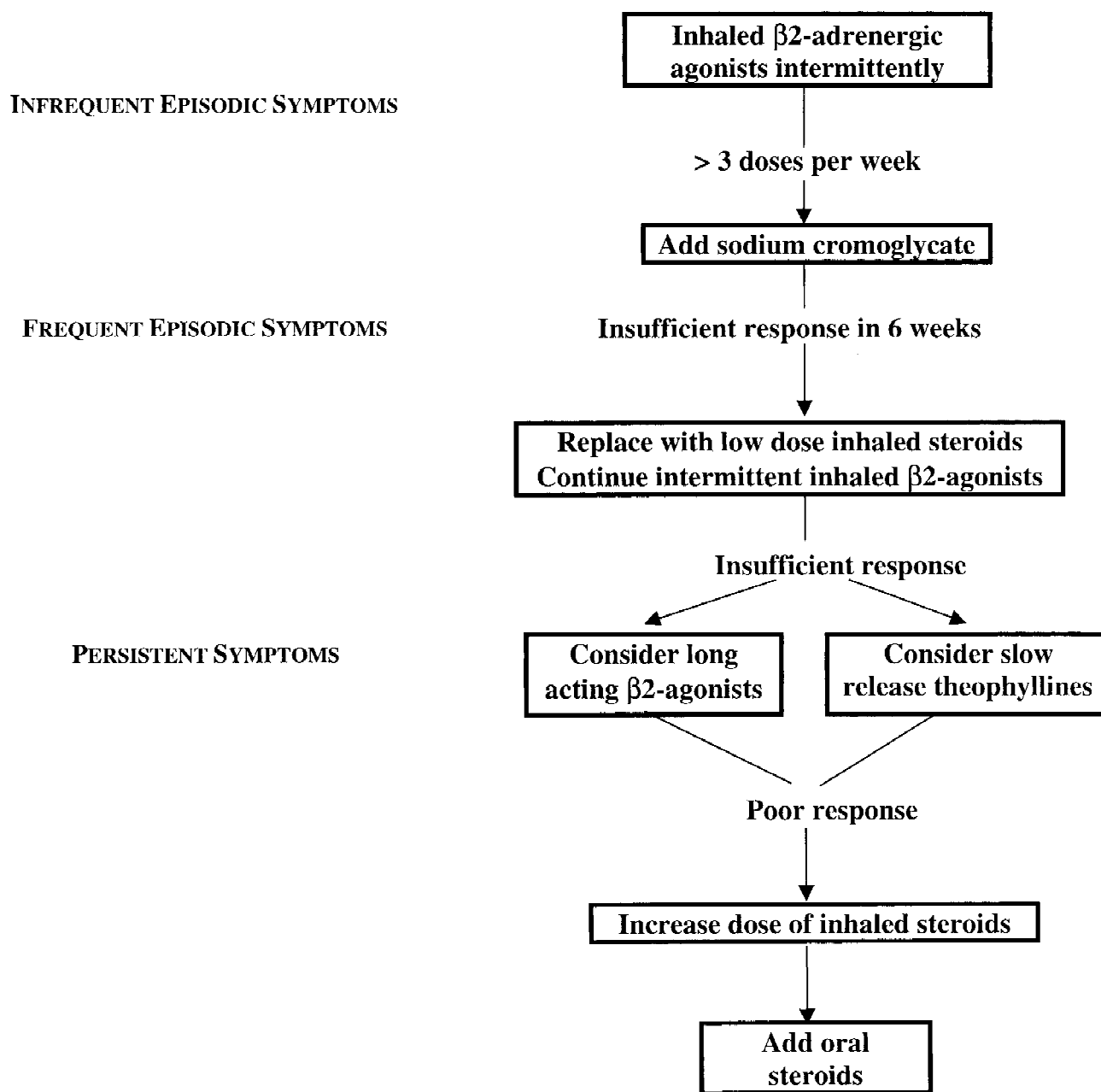


Fig. 1. This algorithm is the gold standard for regions where there are no financial constraints. There are alternative strategies such as the use of theophylline as primary prophylaxis (see text).

leaders must make themselves available to the media to get the appropriate message across to the community.

Asthma is the major cause of morbidity due to chronic disease in childhood,⁵⁵ and it is important that governments should be aware of its importance. Greater resources are required to introduce effective asthma control programs. Particular attention should be paid to ethnic

minorities, who often suffer greater morbidity and mortality from the disease than more affluent social groups.⁸⁹

It was concluded by the Consensus Group that there were two priorities. *One* was to ensure that any physician treating childhood asthma has all the skills to pass on appropriate knowledge to patients, families, and others involved with the child's care (Table 1). *Second*, educa-

tional programs should be evolved to teach inhalation techniques and to focus on early recognition and treatment of acute attacks.

THERAPEUTIC ALGORITHMS

It was agreed that there was little indication for changing the therapeutic algorithms dramatically⁵ (Fig. 1). While there are some exciting prospects for new drugs, none have yet been proved to have a major role in the management of asthma. Thus, infrequent episodic asthma may be treated with intermittent short-acting β_2 -agonist inhalations alone. There is very little support for the use of oral β -agonists, but it was appreciated that there might be special circumstances when they may be indicated. However, the benefit/side effect profile favors inhaled treatment by a wide margin.⁹⁰

Once β -agonists are used consistently more than 3 times a week, except for predosing before exercise, or when exacerbations occur more frequently than once every 4–6 weeks, there is an indication for prophylaxis. Most of the Consensus participants agreed that the first prophylactic compound to be used should be sodium cromoglycate. The minimum dose would be 10 mg 3–4 times daily. It was noted that in some countries, the only MDI available delivered 1 mg/puff. Under such circumstances, this treatment is unlikely to be effective.⁹¹ Thus, only the nebulizer dose (20 mg/vial) for younger children or powder inhaler (20 mg/capsule) for older children should be used, but if neither is available, low-dose inhaled corticosteroids are recommended. Sodium cromoglycate should be given a therapeutic trial for 6–8 weeks before considering alternative therapies. Once control has been achieved, it is sometimes possible to reduce the dosing frequency to 2–3 times daily.⁹² It is to be emphasized that sodium cromoglycate remains the safest compound developed for the management of asthma, and there has never been any concern about side effects, except occasional cough. This, and its efficacy, dictate its preference as the first-choice prophylactic compound,⁹³ except for children younger than 1 year of age, in whom a prophylactic effect has not been observed. Some participants suggested that low-dose inhaled steroids should be the first prophylactic drug to be used, particularly in noncompliant families and those with more severe disease.

If sodium cromoglycate fails to control symptoms and β -agonists continue to be required more than 3 times a week, inhaled corticosteroids should be substituted. Whether they should be employed initially in a high dose with titration downward while maintaining control or in a low dose with a gradual increase to achieve the same result can only be judged in individual cases. It was felt that in some circumstances, particularly in children with severe disease, it would be appropriate to use high-dose

inhaled steroids as first-line therapy supplemented by a short 3–5 day course of oral corticosteroids to achieve maximum lung function. Gradual reduction in inhaled corticosteroid treatment should follow. However, in most cases, this approach will not be necessary. The goal must be the lowest possible dose of inhaled corticosteroid that is compatible with good disease control. In general, it is preferable to use only one prophylactic compound to have a reasonable chance of achieving good therapeutic compliance. There are few occasions when the use of both sodium cromoglycate and inhaled corticosteroid would produce benefits that outweigh the expense and compliance problems.⁹⁴

Inhaled corticosteroids are usually effective in relatively low doses. At 200 μ g a day of beclomethasone or budesonide, there have never been any reports of long-term side effects.⁹⁵ While posterior subcapsular cataracts are a well-known complication of oral corticosteroid therapy, they do not occur in children with moderate doses of inhaled beclomethasone or budesonide (mean daily dose 750 μ g).⁹⁶ From 400 μ g a day and upward, it is possible to demonstrate a very small systemic effect,^{45,97–100} but only above 800 μ g a day is there likely to be any significant impact on growth, hypothalamic-pituitary-adrenal axis function, or bone density.^{47,95} Systemic effects can be reduced by using a spacer device, which enhances lung deposition while lessening oropharyngeal deposition and systemic absorption.¹⁰¹ Once there is evidence that control of asthma is not possible without potential side effects because of the dose employed, then referral to a specialist is considered essential. Strategies to keep the dose of inhaled corticosteroid manageable include the use of long-acting inhaled β -agonists such as salmeterol and formoterol,^{102–105} or slow-release theophyllines.⁹⁷ However, the commonest cause of apparent inhaled corticosteroid resistance is lack of compliance with inhalations.

To achieve adequate control high doses of inhaled corticosteroids are required in some circumstances.⁹⁵ Such patients should be attending a specialist clinic; additional strategies that might then be employed include the use of alternate-day oral corticosteroids, methotrexate, cyclosporin, troleandomycin, continuous subcutaneous terbutaline infusions, or intravenous immunoglobulin infusions.⁵ However, none have been submitted to large controlled clinical trials in childhood asthma. As this situation arises in only a small minority of patients, it does not impact on the main therapeutic recommendations by the Consensus Group.

OTHER DRUGS

No current data justify the addition of any other drugs to the basic algorithm. However, a number of second-line

and new drugs may be considered in special circumstances.

Ketotifen has been shown in some controlled clinical trials to produce symptom control in infrequent episodic asthma, mainly in infancy.¹⁰⁶ As it is orally active, it at least has the benefit of being easily administered. However, its clinical effect is small in established asthma, and ketotifen has no greater steroid-sparing effect than placebo.¹⁰⁷ Cetirizine has properties that may make it particularly useful in infancy.¹⁰⁸

Nedocromil sodium has been recommended for mild to moderate asthma in adults. A number of trials in childhood asthma have demonstrated it to be superior to placebo.^{109,110} However, no trials have established whether it has any benefits exceeding those of sodium cromoglycate in children, although there are some comparisons in adults,¹¹¹ or whether it has a place in the algorithm between sodium cromoglycate and inhaled corticosteroid. Some trials have investigated its use given twice daily and others 3–4 times daily. This drug could have an advantage if it could be demonstrated to have equivalent efficacy taken twice daily, compared with 4 times a day for sodium cromoglycate. Such trials are now in progress, and results are awaited.

Currently, the long-acting β_2 -agonists salmeterol and formoterol are available in some countries, but the lower age limit at which they are sanctioned for use varies. For the present, it was felt that they should only be used when patients are on moderate doses of inhaled steroids and are still not effectively controlled.^{102,103} Concerns remain that continuous use of the long-acting β -agonist may be associated with effects similar to those that have been observed with frequent dosing of the short-acting β -agonists, namely, an increase in severity of disease and bronchial hyperresponsiveness, which has been demonstrated chiefly in adults.¹¹² However, recent work does not show either deleterious or beneficial effect with the use of regularly scheduled β_2 -agonists in asthma.¹¹³ One recent study in adolescents showed a reduction in the prolonged bronchoprotective effect of salmeterol after 28 days of treatment, despite concomitant inhaled steroids.¹¹⁴

Theophyllines have had a renaissance in the last year or two because of some observed anti-inflammatory effects in low doses.^{115,116} Theophylline may be regarded as an immunomodulator as well as a bronchodilator. This effect is exerted at plasma concentrations that are not associated with undesirable side effects.¹¹⁷ Indeed, in nonaffluent populations with limited access to inhaled drugs, the early introduction of oral theophylline in the therapeutic algorithm could be beneficial to many asthmatic patients, primarily as prophylactic therapy.⁹⁷ There are, however, new developments in specific inhibitors of those phosphodiesterases that may lessen bronchoconstriction and inflammation.¹¹⁸ The Consensus Group dis-

cussed these developments 3 years ago, but as yet they are not therapeutic options. The same can be said of potassium channel activators, which are potent bronchodilators. However, leukotriene antagonists are already being used in clinical practice.¹¹⁹ Studies in children will be awaited with interest as these compounds have anti-inflammatory properties.

OPTIMAL USE OF INHALATION DEVICES

Most important in the delivery of effective therapy to asthmatic children is the optimal use of appropriate inhalation devices. Until recently, oral drugs were used frequently in asthma. With the advent of modern inhalation devices, most children with asthma can be treated and maintained entirely on inhaled therapy. It was appreciated that in some countries, nonavailability of suitable inhalation systems necessitated the continued use of oral therapy. However, particularly for β_2 -sympathomimetic drugs, the rapidity of action and reduction of side effects dictate that inhaled therapy should always be preferred.⁵ In some countries nebulized ipratropium bromide is routinely co-administered with β -agonists to children in acute asthma episodes.^{120,121} Sodium cromoglycate and nedocromil sodium can only be administered in inhaled form to be effective, and inhaled steroids are infinitely preferable to oral formulations because of the relative lack of side effects.

SPACERS

There is now considerable information on optimal use of spacer inhalation devices.^{122,123} Whenever possible, children should be encouraged to inhale an aerosol via a spacer through the mouth, which results in a larger proportion of the medication being deposited in the lungs, while less impacts on the oropharynx.¹²⁴ Spacers are cheap and easy to use; they overcome problems of poor technique and coordination with actuation and inspiration, which occurs using MDIs alone. However, the proportion of drug that reaches the airways varies considerably among spacer devices.¹²⁵ Attaching a face mask to the spacers facilitates their use in very young infants, although this decreases the dose of drug reaching the airways.¹²⁶

NEBULIZERS

Nebulizers with air compressors are bulky and inefficient aerosol delivery systems. With the advent of more efficient spacer systems, the need for nebulizers has greatly diminished. While there is a place for the use of a nebulized β -agonist in acute attacks because this allows the delivery of a large dose, administering the equivalent dose through a valved spacer is at least as good and

probably delivers twice as high a dose to the airways.¹²⁷ It has also been clearly shown that when a face mask is employed, it should be tightly applied around the mouth and nose. If the mask is 1 cm from the face the drug delivery is reduced by 50%, and when it is 2 cm from the face it is reduced by 80%.¹²⁸

While preferring the more efficient newer delivery systems, there are situations in which nebulizers may be necessary. In many countries, the higher dose (5 mg) of sodium cromoglycate MDI is not available, and the use of 1 mg MDI in a valved spacer may be ineffective.⁹¹ Under such circumstances, cromoglycate should be delivered by nebulizer. Similarly, some infants do not accept or do not respond to inhaled corticosteroid delivery through the spacer systems. Under such circumstances, it has been shown that nebulized budesonide (not available in some countries) can be highly effective, provided the nebulizer and air compressor are efficient.^{129,130}

The volume fill in a nebulizer should probably be 4 mL. Thus, the standard 2 mL drug ampoules should be diluted with 2 mL of normal saline. This avoids the progressive increase in osmolality that occurs during the course of nebulization. It is thought that this might be a cause of a paradoxical bronchoconstriction during drug administration.¹³¹

DRY POWDER INHALERS

Dry powder inhalers can be efficient delivery systems for children older than 5 years of age.¹³² The inspiratory flow required to disaggregate the particles needed to allow the powder to be inhaled varies from device to device. In general, powder systems should not be used for children younger than 5 years of age. There may be a problem in high-humidity environments, and high oropharyngeal deposition of drugs may cause problems that cannot be totally prevented by mouth washing. This is of special importance when corticosteroids are inhaled because of the risk of oral candidiasis.

PRESSURIZED METERED DOSE INHALERS

Pressurized MDIs are efficient but require considerable coordination, which precludes their use in young children. However, use of a spacer enables even the youngest patient to use MDIs effectively. For children under the age of 2 years, a small volume (<350 mL) spacer has the theoretical advantage that it can be cleared more readily by infants with a small tidal volume. Indeed, the aerosol delivery to wheezy infants from an MDI through small-volume spacers is effective, and a higher percentage of the total drug is delivered than from a nebulizer.¹³³ Above this age, large-volume spacers have the advantage that they preserve the aerosol cloud more efficiently but have the disadvantage that they are

cumbersome. It has recently been demonstrated that static charge in the spacers can have a considerable effect on aerosol delivery, and this is somewhat unpredictable.^{122,134}

Older children can be trained to use an autohaler, which is triggered automatically to release its metered dose at the onset of inhalation.¹³⁵ Many such devices are appearing and can be of value. The CFC propellants currently used in most MDIs will be slowly phased out over the next decade, as a result of the Montreal Accord. While non-CFC propellants have now been developed, it cannot be assumed that dose-response relationships for drugs will remain the same.¹³⁶ There is a need for extensive re-evaluation of all the standard drugs in the new aerosol devices. It is hoped that studies will be done in children as well as adults, since little work has been published on the current systems for children.

TREATMENT OF ACUTE EPISODES OF ASTHMA

Classification

Acute asthma may be divided into mild, moderate, and severe episodes. *Mild* is associated with cough and audible wheezing without any form of distress, cyanosis, increased respiratory rate, or impairment of activity. Such individuals may have a PEF or FEV₁ above 75% of predicted values, and they can speak in normal sentences between breaths.

A *moderate* acute episode is associated not only with an audible wheeze, but also with use of accessory muscles, a slight increase in respiratory rate, and an inability to walk or utter more than three to five words between breaths. Such individuals may improve with a large dose of inhaled β -agonist, but failure to respond would indicate the need for a short course of oral corticosteroids.

Severe acute episodes are associated with cyanosis, severe distress, lower rib retraction, and poor response to an inhaled β -agonist. Wheeze may not be particularly obvious. Only one to three words of speech will be possible between breaths, and the patient will be chair or bed bound. Such individuals require aggressive high-intensity care with oxygen saturation monitoring, administration of oxygen, high-dose inhaled β -agonists, and oral or intravenous corticosteroids, with or without other treatment depending on response.

Mild Acute Episodes

Such episodes are treated with an inhaled β_2 -agonist using a metered dose aerosol with or without a spacer. This may have to be continued every 4–6 h for 24–36 h. No further action is usually required, but if such episodes

occur more frequently than once every 4–6 weeks, it is necessary to consider prophylactic management.

Moderate Acute Episodes

In such cases, ipratropium bromide may be added to β -agonists or higher doses of β_2 -agonists should be used, either of which may be given by nebulizer.¹²¹ If there is rapid improvement then this management can be continued every 4 h for 24–36 h. However, if there is an incomplete response or a relapse of symptoms within 4 h, then a course of oral corticosteroid should be commenced at home as prednisolone or equivalent, 1–2 mg/kg/day. The β -agonist dosing may be continued as required during this period. If there is no improvement after 3 doses of a β_2 -agonist, then admission to hospital is necessary, and the child should be treated as for a severe acute episode.

Severe Acute Episodes

All children with severe acute episodes require hospitalization and oxygen. Nebulized β_2 -agonist can be administered with oxygen. Corticosteroids are mandatory with either prednisolone orally, if this can be taken, or with intravenous hydrocortisone (4 mg/kg), or methylprednisolone (1 mg/kg), with doses repeated every 4–6 h, particularly in the first 24 h. Frequent or continuously nebulized β_2 -agonist may be administered. However, if this does not achieve rapid improvement, then admission to intensive care is required.¹³⁷ The use of intravenous aminophylline,¹³⁸ intravenous salbutamol, or terbutaline may be appropriate.

The criteria for resorting to mechanical ventilation cannot be easily defined. Current management dictates that arterial blood gases alone are inadequate, as on some occasions it may be appropriate to delay ventilation even with high arterial carbon dioxide tension, if effective treatment is just about to be instituted. However, if there is no favorable response in terms of increased alveolar ventilation, or if exhaustion is setting in, then mechanical ventilation under sedation with neuromuscular blockade should be started. There are occasions when such circumstances might arise even with a relatively low arterial carbon dioxide tension when it is rising rapidly despite maximal treatment.¹³⁹

The period of therapy with oral corticosteroids for acute episodes will be variable and depends on the severity of the attack and the chronicity of the underlying airway inflammation. If treatment is required for longer than 5–10 days, it is advisable to taper the dose slowly. However, if such therapy is used for less than 5 days, there is no need to taper the dose.

SPECIAL CONSIDERATIONS

Aspirin-Induced Asthma

Aspirin and other NSAIDs exacerbate asthma in some adult asthmatics, but rarely in children. Diagnosis can only be established by controlled in-patient challenge in those with a suggestive history.

Gastroesophageal Reflux

GER may provoke asthmatic symptoms. The presence of reflux should be considered in young asthmatic children with recurrent vomiting or regurgitation, acute nocturnal episodes of cough and wheezing, and lack of appropriate response to conventional asthma therapy. The precise role of GER in inciting respiratory symptoms is often difficult to determine, but it seems wise to treat reflux and to observe the effect of such treatment on asthmatic symptoms. The monitoring of esophageal pH for 24 h is generally considered the best way to diagnose the presence and degree of reflux. Therapeutic options include low-density antacid mixtures, gastrointestinal propulsants such as cisapride, H_2 antagonists, and proton pump inhibitors such as omeprazole.¹⁴¹

Exercise-Induced Asthma

Following brief and intense exercise, especially in a cold dry environment, a typical asthma attack will occur in a significant proportion of asthmatic children.³⁹ In some patients EIA is the only manifestation of asthma. The most effective treatment is the inhalation of a short¹⁴² or long-acting β_2 -agonist¹⁴³ before exercising. Other alternatives are: sodium cromoglycate,¹⁴⁴ nedocromil sodium, and inhaled furosemide.¹⁴⁵ Inhaled corticosteroids raise the threshold at which EIA occurs, but they do not totally prevent it. Sports and physical activity should not be avoided in children with EIA. Physical training is also important.¹⁴⁶

Rhinitis and Sinusitis

An increase in asthmatic symptoms has been observed in patients with allergic rhinitis and sinusitis. Although the relationship between upper airway diseases and lower airway function is not well understood, the appropriate management of rhinitis⁶⁵ and sinusitis^{66,67} may help in the control of asthma symptoms and may diminish concomitant bronchial hyperresponsiveness.

Psychological Impact of Childhood Asthma

Psychological factors can influence childhood asthma. However, a complex interaction (not well understood) exists among several factors (genetic, environmental,

physiological, psychosocial, etc.) in the pathogenesis and expression of asthma. The exact contribution of each set of variables to either a specific patient's asthma or to a given attack is beyond our knowledge.¹⁴⁷ Various psychotherapeutic approaches have been shown in controlled studies to be complementary to standard management.¹⁴⁸ Psychological maladjustment does not cause asthma but can trigger exacerbations. Hyperventilation associated with stressful situations may be one trigger of stress-induced asthma.

The Asthmatic Adolescent

Adolescence is a special and confusing time in the life of every developing child. When adolescents are confronted with a chronic illness like asthma, the burden placed upon them and the parents may appear overwhelming.¹⁴⁹ Furthermore, this is the age when the risk of death becomes significant. Adolescent asthmatic patients are a distinct group in whom different approaches to management are required. The health professional caring for an adolescent patient must develop an intelligent and compassionate strategy to help effectively. The importance of regular health checks, smoking, peer pressure, and negotiation in regard to treatment plans should be recognized in this group.¹⁵⁰ Female adolescents may experience a worsening of asthma when menarche occurs. The preponderance of asthma in boys, which is so apparent at a younger age, disappears during adolescence.

Cough

Repeated coughing (especially at night, with exercise, and with viral illness) in the absence of wheeze may be a common symptom of asthma in childhood, but can be different from classical asthma.^{151,152} Sometimes symptoms can be controlled with conventional antiasthma therapy but responses are inconsistent. An episodic "honking" cough can be a feature of a habit spasm related to psychological problems and may co-exist with dysfunctional laryngeal breathing; under such circumstances β_2 -agonists and inhaled corticosteroids are not indicated.¹⁵³

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