Archives of Disease in Childhood 1992; **67**: 240–248

SPECIAL REPORT

Asthma: a follow up statement from an international paediatric asthma consensus group

The first consensus report,[1] which was the result of a meeting held in December 1988 of a small group of paediatric chest physicians from 17 countries, has had a major impact on paediatric asthma management. The document has been used in many countries as a basis for management protocols, and it has been translated into several languages. In the last two years there have been many new questions but no dramatic advances in either the understanding of the condition or its management. However it was felt appropriate to review the consensus statement in the light of the experience gained in its application throughout the world.

The second meeting, held in July 1991, achieved the same notable accord, this time from 34 delegates representing 22 countries. Several textural adjustments were made and with the involvement of primary care physicians the protocols can be viewed as a complete strategy for the management of children with asthma.

The need for a consensus

Some have questioned the validity of a consensus statement on the management of asthma.[2] Clearly there are many publications in the literature outlining very appropriate management strategies and a consensus statement might be seen as a challenge to experts who have suggested alternative protocols. There has been concern that management which deviated from the consensus recommendations might be viewed unfavourably in legal proceedings, but this is not our intention. However, it must be recognised that consistent delivery of effective and safe care is in the best interests of children with asthma. This is difficult to achieve because of the plethora of conflicting publications on asthma. The prevalence and severity of asthma are increasing, while our understanding of the basic pathology remains incomplete.[3] There are increasing concerns about many of the pharmacotherapies at our disposal, as yet no new drugs have found a place in the management of childhood asthma. The lack of hard data in many areas of management justifies the need for guidelines. The consensus publication is not a set of didactic rules but is intended to aid physicians who are unable to wade through the vast literature of confusing information about virtually every aspect of the condition.

The definition of asthma

The vague definition outlined in the first document has not been changed. This definition was based on a pragmatic approach that asthma was a condition in which episodic wheeze and/or cough occurred in a clinical setting where asthma was likely and other, rarer conditions had been excluded. There has been a strong feeling by some that the concept of eosinophil mediated airway inflammation should be incorporated into the definition.[4]

As we have no information on the pathology in the airway of all but the most severe childhood asthmatics it was not included. However, the need to introduce prophylactic treatment at a very early stage remains a firm recommendation. While this might be seen as synonymous with anti-inflammatory treatment even this has yet to be established.

Community care

A large proportion of children with asthma are managed without recourse to specialised care.[5] There are no absolute criteria for specialist referral, and health systems around the world vary considerably, making general statements about who should care for patients unhelpful. Clinicians must recognise that there are special circumstances which should lower the threshold for referral. Thus the consensus strategies indicate what is required for the patients' effective management rather than who should provide the care. Referral becomes a progressively increasing priority with increasing severity and is mandatory at any stage once the requisite standard of care cannot be met. Communication

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between physicians managing children with asthma has sometimes left much to be desired, leading to conflicting recommendations being made by different doctors about the same patients. Implicit in all the recommendations is the idea that there should be effective communication between doctors and far better medical education for undergraduates and postgraduates. Educational strategies should be evolved for nurses, physiotherapists, and other allied health professionals. Nursery and school personnel require specific additional help in understanding how to handle asthma as it might arise in the school environment.

Diagnosis

The first consensus statement presented two diagnostic algorithms based on the ability of children of different ages to perform simple lung function tests. These have now been combined into one (fig 1). Lung function testing is available at any age but will only be possible in special centres for infants and young children. Furthermore, the younger the child the more likely it is that there may be an alternative underlying cause for recurrent cough and wheeze. Thus there is a greater likelihood that infants will require referral for diagnostic investigation.

The diagnostic scheme starts with a full clinical history and physical examination. Some features strongly support a diagnosis of asthma such as the periodicity of symptoms, nocturnal attacks, seasonal variations, and symptoms produced by allergen exposure or exertion. Associated atopy either in the patient or the family will also support the diagnosis. Under such circumstances a trial of antiasthma treatment can be commenced. In children old enough to perform lung function tests, the response to treatment should be monitored by frequent measurements of peak flow and certainly measurements before and after administration of a bronchodilator. In most cases of asthma where the diagnosis is clear and there is

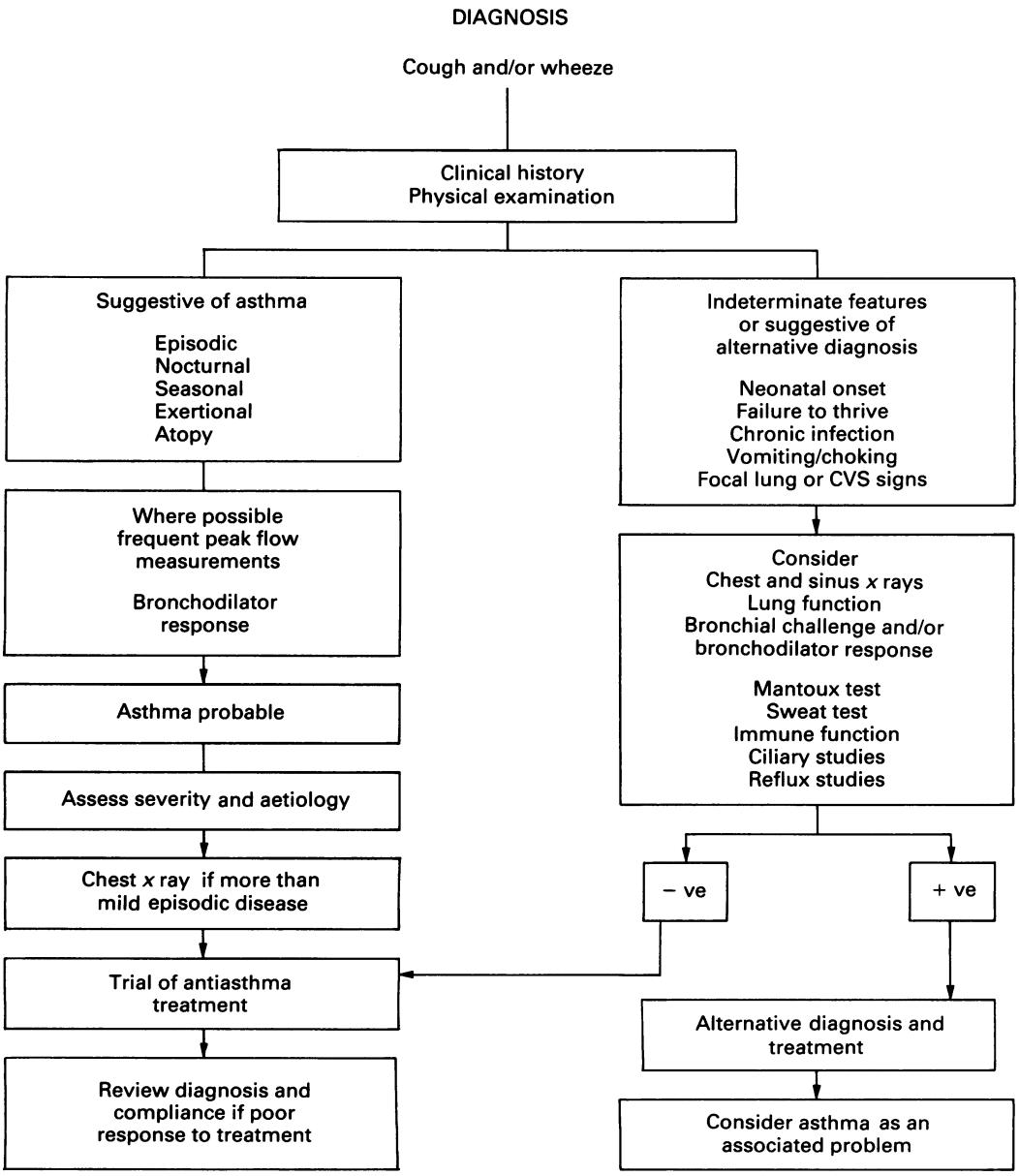

Figure 1 Diagnostic algorithm for asthma (CVS=cardiovascular system).

an excellent response to treatment, there may be no need for further investigation. However, in all other cases a chest radiograph should be performed to exclude any unexpected alternative pathology. If a response to treatment is poor the diagnosis should be reviewed and the compliance checked before progressing to more potent treatment.

Patients who have a productive cough or apparently recurrent chest infections, a neonatal onset of symptoms, associated failure to thrive, vomiting and choking with respiratory symptoms or focal lung signs, require further investigation. This will include a chest radiograph and lung function measurements before and after treatment. Radiographs of the sinuses, sweat test, tests for immunodeficiency, reflux studies, Mantoux test, ciliary studies, and possibly bronchoscopy may be required. Allergy tests are an aid to diagnosis and are necessary before sensible environmental control measurements can be recommended.

In older children the use of simple lung function tests such as peak flow measurements to record variability over short periods of time, or basic spirometry and responses either to challenge with histamine, metacholine, exercise, cold air or allergen, are worthwhile in diagnosis. In those with subnormal lung function, response to a bronchodilator is equally appropriate.

Assessment of severity

Whereas it is difficult to divide asthma into mild, moderate, and severe categories, no better subdivision exists at present. Categorisation is based on frequency, chronicity, and severity of asthma symptoms. Where possible, lung function measurements will permit a more objective assessment. The response to treatment following the therapeutic algorithms must also be taken into account in the final judgment on the severity. We do, however, need more effective markers of disease activity. Indices such as allergic status, based on skin tests, total IgE and IgE antibodies, bronchial hyperresponsiveness, and the detection of circulating inflammatory markers such as specific cytokines do not yet have a place in routine severity assessment. In adults, increasingly, bronchoalveolar lavage and bronchial biopsies are being performed and the results may well provide information on the severity of disease and indeed on the effectiveness of antiasthma treatment.[6] No information exists to suggest that any of these data can yet be used clinically and research in these areas must be extended.

Mild asthma may be classified as low grade symptoms that do not intefere with sleep and lifestyle, or episodes of cough and wheeze occurring less than once per month. All such episodes should be responsive to bronchodilators taken no more frequently than two or three times per week. Moderate asthma is either discrete attacks occurring no more frequently than once a week or more chronic symptoms not affecting growth or development, in which case sodium cromoglycate prophylaxis is indicated. Patients with severe attacks requiring oral or intravenous steroids or troublesome wheezing on most days or nights are less likely to respond to sodium cromoglycate and will often require inhaled steroids. There are a few patients who fall outside these categories: in particular, patients who have very infrequent but severe or life threatening attacks with completely normal lung function and no symptoms between episodes. This type of patient remains very difficult to manage.

Aims of managment

The goal of treatment should be to allow children to be involved with normal activity, including full participation in exercise and sport. There should not be excessive school absences. Symptoms should not occur by either day or night. Lung function should be normalised with no excess of diurnal variation in peak expiratory flow rate. There should be little need to use relieving doses of β-agonists, preferably less than once every two or three days, and no exacerbations of disease. Adverse side effects of treatment must be avoided, particularly in relation to growth and development. Failure to achieve these goals is indicative of a need to change the treatment.

Co-management: the partnership

Management of asthma is an overall strategy and not just the writing of a prescription. It should not be only patient initiated and involving crisis management but proactive with doctor initiated routine consultation. It has become fashionable to talk about patient self management. However, we should not be asking patients to look after themselves but to manage themselves in partnership with their health professionals.[7] It should be appreciated that day to day management of asthma falls upon the patient and the family and not upon the physician. We, therefore, need to tailor the educational packages and co-management programmes to the individual patient and family. The involvement of appropriately trained practice nurses or physiotherapists in this strategy is particularly important. The objectives are to help the patients and parents as far as possible to develop a complete understanding of the condition, its treatment, and the way to respond to any changes in clinical state. The programme begins immediately the diagnosis has been made, and involves a team approach.

Patients should understand the use of inhaled drugs and peak flow meters, the difference between medications for relief of symptoms and those to prevent episodes. Action plans should be evolved that include instruction on the signs that indicate worsening of asthma and what changes in treatment should be initiated at such times. Thus the four elements of co-management are (i) understanding the condition, (ii) monitoring symptoms, peak flow, and drug usage, (iii) a prearranged action plan, and (iv) written guidelines. A patient diary utilising a traffic signal notation has been found useful in the United States, Australia, and the United Kingdom. Written materials produced by various professional and lay organisations,

computer programs, videos, special holidays, and organised sports activities may be of value. Further work is still required to evaluate many of the education materials currently being produced, although some programs have been found to be safe and effective in clinical trials.[8] Ultimately nothing can replace the interaction between patient, family, and health professionals, particularly in addressing psychosocial factors which may make effective disease control difficult.

Environmental control

The role of allergy in asthma management remains one of the more contentious areas. It is widely accepted that the presence of allergy is an important prognostic feature, predicting a more chronic problem. There is also little dispute that allergy is important both in the genesis of the condition and in provocation of symptoms when it is established.[9 10] However, many deny the value of making a specific allergy diagnosis because this has little impact on the management of the condition.

Everyone accepts that environmental tobacco smoke exposure is associated with an increase of symptoms and there is no doubt that this exposure should be avoided at all costs.[11] Reducing house dust mite exposure remains extremely difficult, though there are good controlled trials which have now shown that if mite levels can be significantly reduced symptoms also improve.[12] This, unfortunately, is still not practical in many circumstances. The removal of pets from the home where pet allergy has been established is also important, though it may take many months for the dander to disappear from the dust after removal of the animal.[13] It is possible that the introduction of environmental control in susceptible infants before asthma has developed may become the most effective preventive protocol.[10]

Immunotherapy

Immunotherapy has been established to be superior to placebo in many controlled trials.[14] However, comparison of this treatment with pharmacotherapy in proper controlled studies remains necessary to establish the role of immunotherapy in the management of asthma. There are considerable national variations in attitudes to this treatment and the controversies will only be resolved when larger and more carefully controlled studies are performed. It should only be used when a clear unavoidable allergic trigger has been identified. The treatment should only be initiated by specialists with standardised, characterised extracts. It would appear to be most beneficial in patients with seasonal rhinoconjunctivitis and mild asthma.

Pharmacology

The first consensus document presented four therapeutic algorithms for different ages. These have been simplified and combined into one (fig 2). Thus mild asthma is treated with intermittent β_2-adrenergic agonists, preferably used by inhalation. Once such treatment is required more than three times a week in episodic asthma or where a more severe attack has occurred, there should be a very low threshold for introducing sodium cromoglycate. This should be administered three or four times daily and given a trial of at least six weeks before considering alternative therapeutic agents. Once control is achieved it may be possible to reduce the dose frequency to twice daily. Sodium cromoglycate remains the safest compound developed for the management of asthma and no concerns have ever been raised about side effects. If sodium cromoglycate fails to control the condition and bronchodilators are still required more frequently than three times a week, inhaled corticosteroids should be started. Only the occasional child will require both prophylactic drugs together and compliance is more likely to be maintained if a single prophylactic compound is used.

Inhaled corticosteroids are usually effective in low doses (beclomethasone and budesonide 400 μg/day), though in severe cases higher doses may be necessary. At low doses there is relative sparing from side effects on the hypothalamic-pituitary-adrenocortical axis and growth, but with increasing doses the frequency of side effects also increases.[15]

Side effects may be reduced by the use of a spacer device with metered dose inhaler, which enhances lung deposition while lessening oropharyngeal deposition and systemic absorption.[16 17] After one to two months of inhaled corticosteroids to achieve optimal lung function, it may be possible to reduce slowly the dose to the minimum which maintains good control.

The use of regular inhaled β-agonists more than three times daily has been implicated as a factor contributing to asthma morbidity and deaths.[18] Though not proved, it is prudent where possible to minimise the use of regular β-agonists. However, when moderate doses of inhaled steroid (>600 μg/day) of beclomethasone or budesonide) have failed to control asthma, it may be necessary to consider the use of regular β-agonist treatment including long acting compounds such as salmeterol or formoterol.[19 20] Alternatives may be the use of oral slow release xanthines or inhaled ipratropium bromide.

In very severe disease it will be necessary to increase the dose of inhaled corticosteroid and even to use oral corticosteroids. Under such circumstances the potential dangers of uncontrolled asthma are far greater than any possible side effects that might be produced by the medications. The algorithm demonstrates a progressive increase in treatment with increasing severity of asthma. Some centres recommended an initial 'blitz' approach to achieve maximum response then drawing back to the minimum required to retain this level of function. As yet this can only be recommended for severe asthma.

Inhalation or delivery systems

A single management protocol is now proposed, but it must be adapted for children of different ages, based on their ability to use particular

delivery systems (table). More than 50% of children receiving inhalation treatment with a conventional metered dose inhaler have little or no benefit from the prescribed medication because of poor inhalation techniques.[21] Thus the conventional devices cannot be normally recommended for children unless the prescription is accompanied by repeated, thorough, and

Inhalation or delivery systems

Age (years)	*Inhalation delivery system*	*Relieving treatment*	*Preventative treatment*
<2	Nebuliser and air compressor	Salbutamol Terbutaline	Sodium cromoglycate
	Valved spacer and face mask	Ipratropium bromide	Budesonide
2–4	Metered dose inhaler with valved spacer:		
	Nebuhaler (Astra)		Sodium cromoglycate
	Volumatic (Allen and Hanburys)	As above	
	Aerochamber (Forest Pharm Inc)		Inhaled steroids
	FISONair (Fisons)		
	Nebuliser for acute episodes		
5–8	Powder inhalers:		
	Spinhaler (Fisons)	—	Sodium cromoglycate
	Diskhaler (Allen and Hanburys)	Salbutamol	Beclomethasone
	Rotahaler (Allen and Hanburys)	Salbutamol	Beclomethasone
	Turbohaler (Turbuhaler, Astra)	Terbutaline	Budesonide
	Metered dose inhaler with valved spacer	For acute attacks instead of nebuliser	High dose inhaled steroids
>8	Autohaler (Riker; 3M)	Salbutamol	Sodium cromoglycate
	Metered dose inhaler *with training* or powder inhalers	All of the above	

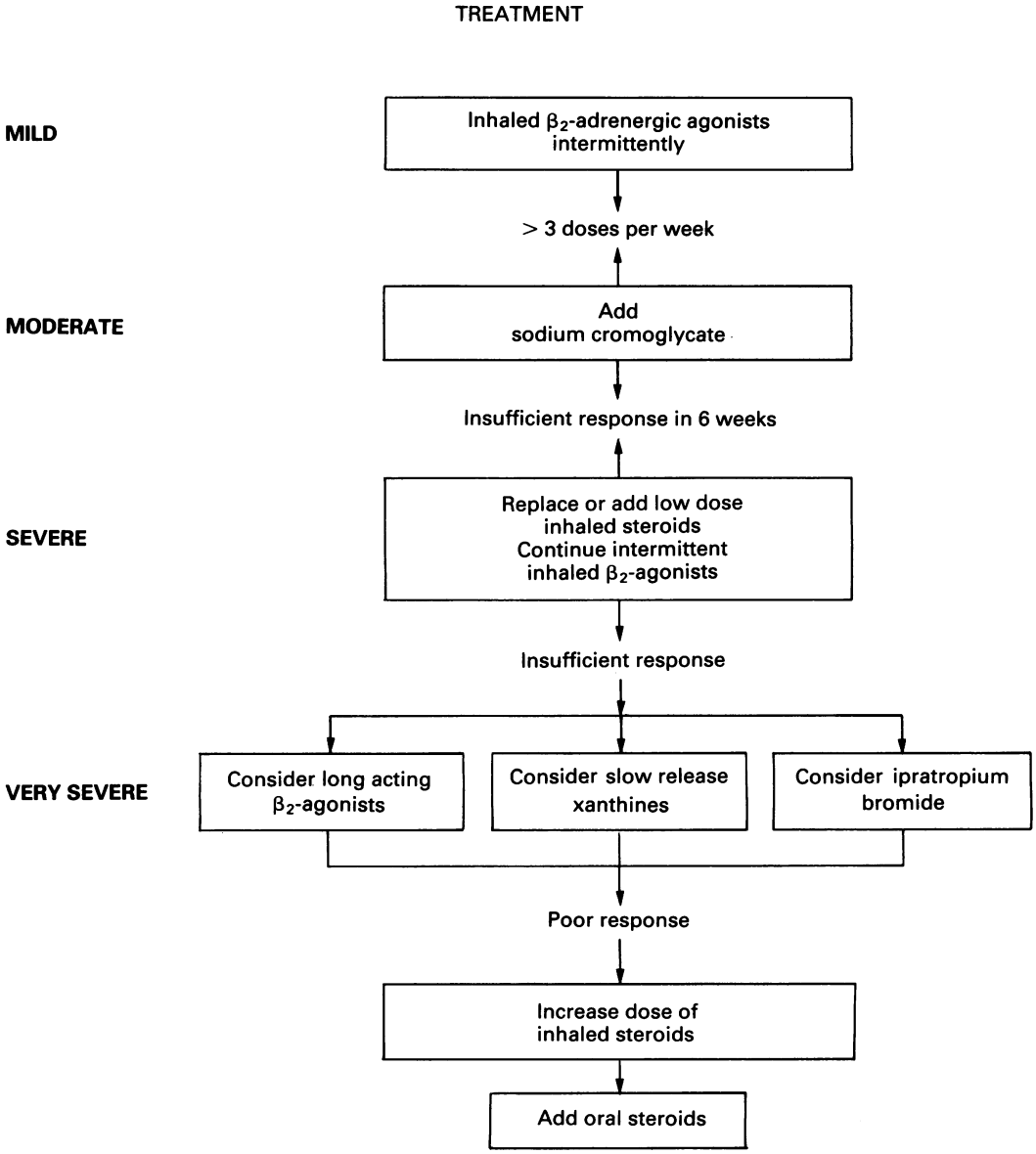

Figure 2 Therapeutic algorithm for asthma. This algorithm involves progression to the next step once control is not maintained and both compliance and inhaler technique are optimal.

correct tuition. The use of breath actuated metered dose inhalers will reduce the amount of tuition time required but this should be reserved for children beyond the age of 7 years.[21] The inclusion of a spacer device with a valve system such as the Nebuhaler (Astra), Volumatic (Allen and Hanburys), FISONair (Fisons), Inspir-ese, or Aerochamber (Forest Pharm Inc) allows children of 2 to 3 years or older to use them after effective training, for all antiasthma medications.[22 23] Some younger infants may be able to use a spacer with face mask.[24] During acute wheezing episodes, young children may not be able to move the valve. In such circumstances only nebulisers will be appropriate. The spacer devices reduce oral deposition and swallowed drug and therefore reduce the systemic effects of inhaled steroids while ensuring a good therapeutic response by increasing drug delivery to the airways.[16 17] A good inspiratory effort is required for dry powder systems but all have slightly different optimal inspiratory flow.[21] Thus the lower age limit for the devices will vary. In general, they are most suitable for school age children onwards.

Though nebulisers are expensive, bulky, inconvenient, time consuming, and inefficient delivery systems they are used extensively. Their use is particularly of value in children who cannot be trained to use any other device. In practice this means either children younger than 2 to 3 years or older children with other difficulties and those prone to severe attacks. There are very few controlled studies of nebuliser treatments in this age group; thus our knowledge of dose requirements and optimal nebuliser systems is rather limited.

Recent studies indicate that it is not justified simply to transfer the dose in mg per kg recommended for older children to the younger age group as their inhalation technique, tidal volume breathing, and anatomy of the upper airways are different.[25] In general, a powerful air compressor capable of a dynamic flow rate of 8–10 l/minute and a volume fill of 4 ml in the nebuliser will produce the best output of respirable particles, particularly when using a suspension such as corticosteroids.[26] More work is required to establish the optimal nebulisation techniques for different treatments. Nebulising units (compressor and nebuliser) should be tested before use and at regular intervals (once every 6–12 months) to ensure that they continue to produce respirable particles.

Other drugs

There are currently no adequate data to justify the addition of any other drugs to the general therapeutic algorithm. However, in special circumstances other compounds may be considered. Ketotifen has been shown in some controlled clinical trials to be of benefit in mild asthma mainly in infancy.[27] As it is orally active it at least has the benefit of being easy to administer. Other potent specific histamine H_1 antagonists may have a similar effect.[28]

Nedocromil sodium is now prescribed for mild to moderate asthma in adults and may find a place in the management strategy for childhood asthma. Trials are awaited with interest. In particular, it will be important to establish whether nedocromil sodium has a place between sodium cromoglycate and inhaled corticosteroids.[29]

Long acting β-agonists have hitherto only been available in oral slow release formulations. These have not found a prominent place in asthma management. Two long acting inhaled β_2-agonists have now been formulated: salmeterol and formoterol. Both are now in clinical use in some countries in adult practice. From a paediatric point of view, formoterol has been more extensively investigated.[20] Initial data suggest that there does not appear to be an increase in bronchial reactivity with these compounds and there is even a suggestion that they might have some anti-inflammatory activity.[30] Until more data are available they can only have a limited place in the protocol. Bambuterol is a third medication in the class of long acting β-agonists. It is a prodrug of terbutaline that can be administered orally and has the potential to produce 24 hour bronchodilatation.[31]

There was complete accord among the consensus members about the declining role of theophyllines. The problems of compliance and effects on behaviour mean that it no longer has anything other than a tertiary role in severe asthmatics already on high doses of inhaled steroids.[32] Nevertheless, recent research has identified that phosphodiesterase can be classified into five different groups. Theophylline is a non-specific phosphodiesterase inhibitor affecting all five subgroups of the enzyme. There are two subgroups that may be important in asthma, type III which is bronchoconstrictor and type IV which is proinflammatory. Thus drugs which specifically inhibits type III and type IV phosphodiesterases may have an important role in the management of asthma in the future. A group of drugs known as the isoquinolines are potent type III and type IV inhibitors and are generating interest in research circles.[33]

Potassium channel activators are another very potent group of bronchodilating drugs.[34] So far, however, the haemodynamic effects have not been disassociated from those of bronchodilatation. The diuretic, frusemide, has been shown to have some bronchodilator and induced asthma blocking effects by inhalation in that it prevents both exercise induced and adenosine induced bronchoconstriction.[35] It is possible that it has a similar mechanism of action to sodium cromoglycate in the airways but this requires further elaboration.

It is too early to say whether the newer inhaled steroids are going to be a significant advance on those already available. There is no place for them in the protocols at present. The role of methotrexate, cyclosporin, oral gold, and other immunomodulatory drugs remains to be established even in adult asthma.[36 37]

Acute severe asthma

The management of acute asthma has undergone some evolutionary changes (fig 3). The importance of oxygen in all cases of acute

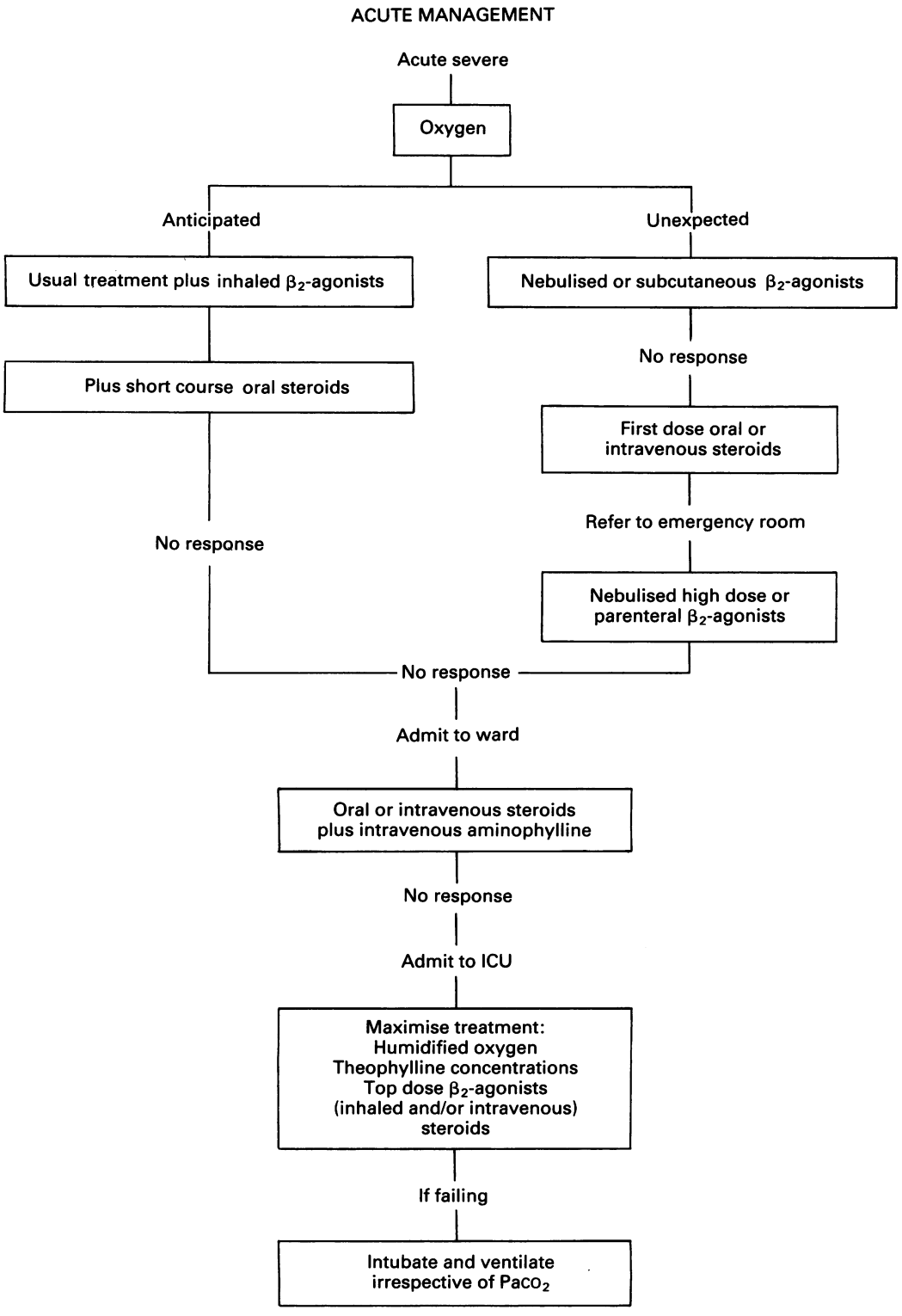

Figure 3 Algorithm for management of acute asthma (ICU=intensive care unit, $PaCO_2$=arterial carbon dioxide tension).

asthma at concentrations that achieve adequate oxygenation requires emphasis, as do the indirect means of measurement of oxygenation and ventilation (for example, pulse oximetry, transcutaneous capnometry) which are now widely available and should be freely used in this setting.[38] Inhaled β-agonists can be used in far higher doses and for longer periods than had been hitherto recommended, including continuous administration of full strength respirator solutions of salbutamol and terbutaline,[39] though this should be done only in a hospital setting.

The criteria for resorting to ventilation cannot be easily defined. At this point there must be serious reservations about the applicability of the Downe's criteria, with their heavy reliance on arterial carbon dioxide tension. Current management dictates that arterial blood gases alone are inadequate: on some occasions it is entirely appropriate to manage patients without ventilation even with a high arterial carbon

dioxide tension, but only if effective treatment is about to be instituted. If there is no beneficial response in terms of increased alveolar ventilation, mechanical ventilation under sedation and neuromuscular blockade should be started. Conversely, there are other occasions when a patient is obviously failing clinically even when the arterial carbon dioxide is relatively low, or when it is still quite low but rising despite maximal treatment having been instituted, and mechanical ventilation is required immediately.[40]

The protocol starts from the use of nebulised β_2-adrenoceptor agonists diluted in normal saline with continuous humidified oxygen. The dose of β-agonists can be repeated frequently, given in multiple breaths of full strength solution, or even given continuously (see above) where appropriate electronic monitoring is available. However, failure to respond to this treatment indicates the need for intravenous salbutamol, or either subcutaneous terbutaline or adrenaline, and oral or intravenous corticosteroids. Appropriate doses of hydrocortisone are 4 mg/kg and prednisolone 1–2 mg/kg, both every six hours. It is no longer appropriate to administer intravenous aminophylline in a home setting but it may be used in hospital in the conventional protocol of a loading dose of 6 mg/kg of aminophylline over 10–20 minutes followed by 1·0 mg/kg/hour continuous infusion, with close monitoring of serum theophylline concentrations in order to keep the values between 10–20 μg/ml.

Clinical trials

As with the previous consensus meeting, more questions than answers were raised in relation to virtually all the areas of management of asthma. There is still a need for basic, well controlled clinical trials. The most important prerequisite is complete characterisation of the population of the patients entered into the trial. Asthma has many forms and studies must involve as homogeneous a population as possible. Thus atopic status, disease severity, age, and physiological variables must, as far as possible, be described. As the disease can be enormously variable long term trials are preferred, covering a period when the patients are most likely to have clinical problems.

The environment will have a strong influence on manifestations and this requires characterisation. Adherence to the treatment during a trial is always difficult to assess, but, with the advent of programmable inhalation devices this may become an important part of the assessment. The mode of inhalation, the characteristics of the delivery system, and the doses delivered must also be standardised.

There are problems in determining outcome. Much of the assessment is based on subjective recording of symptoms but where possible physiological measurements should also be made. Twice daily peak flow measurements are usually employed but their value has been limited. Recently, diary card assessment of some symptoms has been shown to be unsatisfactory and for instance correlates very poorly with objective recording of night cough.[41] Measurement of bronchial hyperresponsiveness has been extensively employed but it has yet to be established whether this provides any indication of the severity of the underlying disease process. It is not yet considered ethical to do fibreoptic bronchoscopy, bronchoalveolar lavage, and bronchial biopsy in clinical trials in childhood. In longer term trials it is imperative to utilise measures of general health, growth, and development.

Statistical analysis comparing large groups of patients on active or placebo treatment has become the essential prerequisite for publication of a clinical trial. A statistician must be involved at the outset, during the design of a study. However, it is also important to appreciate that sometimes individual differences might be missed in the analysis. It may sometimes be appropriate to subdivide the patient groups for further analysis, as some drugs may only work on very restricted categories of patients. High placebo responses make control essential in most studies.

Clinical trials are often conducted jointly between clinicians and the pharmaceutical industry. Such studies should be analysed independently and submitted for publication irrespective of the results. The data must be available to all parties at an agreed time. Sponsorship should be acknowledged in the publications and the use of trial results for marketing and advertising should be based on published data and by agreement between the participants. Unpublished trials should not be used in advertising material. Where a multicentre trial is conducted, one clinician should be selected to act on behalf of all the medical participants, to ensure a totally ethical approach.

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