

101**British Guideline
on the Management of Asthma***A national clinical guideline**May 2008*

NHS Quality Improvement Scotland (NHS QIS) is committed to equality and diversity. This guideline has been assessed for its likely impact on the six equality groups defined by age, disability, gender, race, religion/belief, and sexual orientation.

For the full equality and diversity impact assessment report please see the “published guidelines” section of the SIGN website at www.sign.ac.uk/guidelines/published/numlist.html. The full report in paper form and/or alternative format is available on request from the NHS QIS Equality and Diversity Officer.

British Thoracic Society
Scottish Intercollegiate Guidelines Network

British Guideline on the Management of Asthma

A national clinical guideline



The College of
Emergency Medicine



Royal College
of Physicians
Setting higher medical standards

May 2008

ISBN 978 1 905813 28 5

**First published 2003
Revised edition published 2008**

SIGN and the BTS consent to the photocopying of this guideline for the purpose of implementation in the NHS in England, Wales, Northern Ireland and Scotland.

**Scottish Intercollegiate Guidelines Network
Elliott House, 8 -10 Hillside Crescent
Edinburgh EH7 5EA**

www.sign.ac.uk

**British Thoracic Society
17 Doughty Street,
London, WC1N 2PL**

www.brit-thoracic.org.uk

Contents

1	Introduction	1	6.4	Further investigation and monitoring	59
1.1	Statement of intent	1	6.5	Asthma management protocols and proformas	60
2	Diagnosis	2	6.6	Hospital discharge and follow up	60
2.1	Diagnosis in children	2	6.7	Acute asthma in children aged over 2 years	61
2.2	Other investigations	8	6.8	Treatment of acute asthma in children aged over 2 years	62
2.3	Summary	9	6.9	Assessment of acute asthma in children aged less than 2 years	65
2.4	Diagnosis in adults	11	6.10	Treatment of acute asthma in children aged less than 2 years	65
2.5	Further investigations that may be useful in patients with an intermediate probability of asthma	16			
2.6	Monitoring asthma	18			
3	Non-pharmacological management	24	7	Special situations	67
3.1	Primary prophylaxis	24	7.1	Difficult asthma	67
3.2	Secondary non-pharmacological prophylaxis	27	7.2	Factors contributing to difficult asthma	67
3.3	Other environmental factors	28	7.3	Asthma in pregnancy	70
3.4	Dietary manipulation	29	7.4	Management of acute asthma in pregnancy	71
3.5	Complementary and alternative medicine	31	7.5	Drug therapy in pregnancy	71
3.6	Other complementary or alternative approaches	32	7.6	Management during labour	73
4	Pharmacological management	33	7.7	Drug therapy in breast feeding mothers	73
4.1	Step 1: mild intermittent asthma	34	7.8	Occupational asthma	74
4.2	Step 2: introduction of regular preventer therapy	34	7.9	Management of occupational asthma	76
4.3	Step 3: initial add-on therapy	37	8	Organisation and delivery of care, and audit	77
4.4	Step 4: poor control on moderate dose of inhaled steroid + add-on therapy: addition of fourth drug	39	8.1	Routine primary care	77
4.5	Step 5: continuous or frequent use of oral steroids	40	8.2	Acute exacerbations	79
4.6	Stepping down	45	8.3	Audit	80
4.7	Specific management issues	45	9	Patient education and self management	82
5	Inhaler devices	48	9.1	Self management education and personalised asthma action plans	82
5.1	Technique and training	48	9.2	Compliance and concordance	83
5.2	β_2 agonist delivery	48	9.3	Implementation in practice	85
5.3	Inhaled steroids for stable asthma	49	9.4	Practical advice	85
5.4	CFC propellant pMDI vs HFA propellant pMDI	49	10	Development of the guideline	87
5.5	Prescribing devices	50	10.1	Introduction	87
5.6	Use and care of spacers	50	10.2	Executive and steering groups	87
6	Management of acute asthma	51	10.3	Evidence review groups	88
6.1	Lessons from studies of asthma deaths and near fatal asthma	51	10.4	Dissemination group	91
6.2	Acute asthma in adults	53	10.5	Systematic literature review	91
6.3	Treatment of acute asthma in adults	56	10.6	Consultation and peer review	91
				Abbreviations	93
				Annexes	95
				References	107

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2 Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- Recommended best practice based on the clinical experience of the guideline development group.
- Audit point

1 Introduction

In 1999 the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) agreed to jointly produce a comprehensive new asthma guideline, both having previously published guidance on asthma. The original BTS guideline dated back to 1990 and the SIGN guidelines to 1996. Both organisations recognised the need to develop the new guideline using explicitly evidence based methodology. The joint process was further strengthened by collaboration with Asthma UK, the Royal College of Physicians of London, the Royal College of Paediatrics and Child Health, the General Practice Airways Group, and the British Association of Accident and Emergency Medicine (now the College of Emergency Medicine). The outcome of these efforts was the British Guideline on the Management of Asthma published in 2003.¹

The 2003 guideline was developed using SIGN methodology,² adapted for UK-wide use. Electronic literature searches extended to 1995, although some sections required searches back as far as 1966. The pharmacological management section utilised the North of England Asthma guideline to address some of the key questions on adult management.³ The North of England guideline literature search covered a period from 1984 to December 1997, and SIGN augmented this with a search from 1997 onwards.

Since 2003 sections within the guideline have been updated annually and posted on both the BTS (www.brit-thoracic.org.uk) and SIGN (www.sign.ac.uk) websites. In 2004 the sections on pharmacological management, acute asthma and patient self management and compliance were revised. In 2005 sections on pharmacological management, inhaler devices, outcomes and audit and asthma in pregnancy were updated, and occupational asthma was rewritten with help from the British Occupational Health Research Foundation.

In 2006 the pharmacological management section was again updated. While the web-based alterations appeared successful, it was felt an appropriate time to consider producing a new paper-based version in which to consolidate the various yearly updates. In addition, since 2006, the guideline has had input from colleagues from Australia and New Zealand.

The new 2008 guideline has considered literature published up to March 2007. It contains a completely rewritten section on diagnosis for both adults and children; a section on special situations which includes occupational asthma, asthma in pregnancy and the new topic of difficult asthma; updated sections on pharmacological and non-pharmacological management; and amalgamated sections on patient education and compliance, and on organisation of care and audit. The timescale of the literature search for each section is given in Annex 1.

It is hoped that this 2008 asthma guideline continues to serve as a basis for high quality management of both acute and chronic asthma and a stimulus for research into areas of management for which there is little evidence. Sections of the guideline will continue to be updated on the BTS and SIGN websites on an annual basis.

1.1 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

2 Diagnosis

The diagnosis of asthma is a clinical one; there is no standardised definition of the type, severity or frequency of symptoms, nor of the findings on investigation. The absence of a gold standard definition means that it is not possible to make clear evidence based recommendations on how to make a diagnosis of asthma.

Central to all definitions is the presence of symptoms (more than one of wheeze, breathlessness, chest tightness, cough) and of variable airflow obstruction. More recent descriptions of asthma in children and in adults have included airway hyper-responsiveness and airway inflammation as components of the disease. How these features relate to each other, how they are best measured and how they contribute to the clinical manifestations of asthma, remains unclear.

Although there are many shared features in the diagnosis of asthma in children and in adults there are also important differences. The differential diagnosis, the natural history of wheezing illnesses, the ability to perform certain investigations and their diagnostic value, are all influenced by age.

2.1 DIAGNOSIS IN CHILDREN

Asthma in children causes recurrent respiratory symptoms of:

- wheezing
- cough
- difficulty breathing
- chest tightness.

Wheezing is one of a number of respiratory noises that occur in children. Parents often use “wheezing” as a non-specific label to describe any abnormal respiratory noise. It is important to distinguish wheezing – a continuous, high-pitched musical sound coming from the chest – from other respiratory noises, such as stridor or rattly breathing.⁴

There are many different causes of wheeze in childhood and different clinical patterns of wheezing can be recognised in children. In general, these patterns (“phenotypes”) have been assigned retrospectively. They cannot reliably be distinguished when an individual child first presents with wheezing. In an individual child the pattern of symptoms may change as they grow older.

The commonest clinical pattern, especially in pre-school children and infants, is episodes of wheezing, cough and difficulty breathing associated with viral upper respiratory infections (colds), with no persisting symptoms. Most of these children will stop having recurrent chest symptoms by school age.

A minority of those who wheeze with viral infections in early life will go on to develop wheezing with other triggers so that they develop symptoms between acute episodes (interval symptoms) similar to older children with classical atopic asthma.⁵⁻⁹ | 2⁺⁺

Children who have persisting or interval symptoms are most likely to benefit from therapeutic interventions.

2.1.1 MAKING A DIAGNOSIS IN CHILDREN

Initial clinical assessment

The diagnosis of asthma in children is based on recognising a characteristic pattern of episodic respiratory symptoms and signs (see *Table 1*) in the absence of an alternative explanation for them (see *Tables 2 and 3*).

Table 1: Clinical features that increase the probability of asthma

<p>More than one of the following symptoms: wheeze, cough, difficulty breathing, chest tightness, particularly if these symptoms:</p> <ul style="list-style-type: none"> ◇ are frequent and recurrent¹⁰⁻¹³ ◇ are worse at night and in the early morning^{11,12,14} ◇ occur in response to, or are worse after, exercise or other triggers, such as exposure to pets, cold or damp air, or with emotions or laughter ◇ occur apart from colds¹⁰ ▪ Personal history of atopic disorder^{10,13,15} ▪ Family history of atopic disorder and/or asthma^{10,16} ▪ Widespread wheeze heard on auscultation ▪ History of improvement in symptoms or lung function in response to adequate therapy
--

Table 2: Clinical features that lower the probability of asthma

<ul style="list-style-type: none"> ▪ Symptoms with colds only, with no interval symptoms¹⁰ ▪ Isolated cough in the absence of wheeze or difficulty breathing¹⁷ ▪ History of moist cough¹⁸ ▪ Prominent dizziness, light-headedness, peripheral tingling ▪ Repeatedly normal physical examination of chest when symptomatic ▪ Normal peak expiratory flow (PEF) or spirometry when symptomatic ▪ No response to a trial of asthma therapy¹⁹ ▪ Clinical features pointing to alternative diagnosis (see Table 3)

Several factors are associated with a high (or low) risk of developing persisting wheezing or asthma through childhood.^{15,20} The presence of these factors increases the probability that a child with respiratory symptoms will have asthma.

These factors include:

Age at presentation

The natural history of wheeze is dependent on age at first presentation. In general, the earlier the onset of wheeze, the better the prognosis. Cohort studies show a “break point” at around two years; most children who present before this age become asymptomatic by mid-childhood.^{6,8,9,21} Co-existent atopy is a risk factor for persistence of wheeze independent of age of presentation.

2⁺⁺

Sex

Male sex is a risk factor for asthma in pre-pubertal children. Female sex is a risk factor for the persistence of asthma in the transition from childhood to adulthood.^{22,23} Boys with asthma are more likely to “grow out” of their asthma during adolescence than girls.^{10,21,22,24-37}

Severity and frequency of previous wheezing episodes

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.^{5,8,13,16,21,26,38,39}

2⁺⁺

Coexistence of atopic disease

A history of other atopic conditions such as eczema and rhinitis increases the probability of asthma. Positive tests for atopy in a wheezing child also increase the likelihood of asthma. A raised specific IgE to wheat, egg white, or inhalant allergens such as house dust mite and cat dander, predicts later childhood asthma.^{40,41}

2⁺⁺

Other markers of allergic disease at presentation, such as positive skin prick tests and a raised blood eosinophil count, are related to the severity of current asthma and persistence through childhood.

Family history of atopy

A family history of atopy is the most clearly defined risk factor for atopy and asthma in children. The strongest association is with maternal atopy, which is an important risk factor for the childhood onset of asthma and for recurrent wheezing that persists throughout childhood.^{6,34,37,42,43}

2⁺⁺

Abnormal lung function

Persistent reductions in baseline airway function and increased airway responsiveness during childhood are associated with having asthma in adult life.²³

3

Table 3: Clinical clues to alternative diagnoses in wheezy children (features not commonly found in children with asthma)

Perinatal and family history	Possible diagnosis
Symptoms present from birth or perinatal lung problem	Cystic fibrosis; chronic lung disease of prematurity; ciliary dyskinesia; developmental anomaly
Family history of unusual chest disease	Cystic fibrosis; neuromuscular disorder
Severe upper respiratory tract disease	Defect of host defence; ciliary dyskinesia
Symptoms and signs	
Persistent moist cough ¹⁸	Cystic fibrosis; bronchiectasis; protracted bronchitis; recurrent aspiration; host defence disorder; ciliary dyskinesia
Excessive vomiting	Gastro-oesophageal reflux (\pm aspiration)
Dysphagia	Swallowing problems (\pm aspiration)
Breathlessness with light-headedness and peripheral tingling	Hyperventilation/panic attacks
Inspiratory stridor	Tracheal or laryngeal disorder
Abnormal voice or cry	Laryngeal problem
Focal signs in chest	Developmental anomaly; post-infective syndrome; bronchiectasis; tuberculosis
Finger clubbing	Cystic fibrosis; bronchiectasis
Failure to thrive	Cystic fibrosis; host defence disorder; gastro-oesophageal reflux
Investigations	
Focal or persistent radiological changes	Developmental anomaly; cystic fibrosis; post-infective disorder; recurrent aspiration; inhaled foreign body; bronchiectasis; tuberculosis

Case detection studies have used symptom questionnaires to screen for asthma in school-age children. A small number of questions - about current symptoms, their relation to exercise and their occurrence at night has been sufficient to detect asthma relatively efficiently.^{11,12,14,44} The addition of spirometry^{11,44} or bronchial hyper-responsiveness testing⁴⁵ to these questionnaires adds little to making a diagnosis of asthma in children. 2+

B Focus the initial assessment in children suspected of having asthma on:

- **presence of key features in the history and examination**
- **careful consideration of alternative diagnoses.**

Record the basis on which a diagnosis of asthma is suspected.

2.1.2 ASSESSING THE PROBABILITY OF A DIAGNOSIS OF ASTHMA

Based on the initial clinical assessment it should be possible to determine the probability of a diagnosis of asthma.

With a thorough history and examination, an individual child can usually be classed into one of three groups (see *Figure 1*):

- **high probability** – diagnosis of asthma likely
- **low probability** – diagnosis other than asthma likely
- **intermediate probability** – diagnosis uncertain.

2.1.3 HIGH PROBABILITY OF ASTHMA

In children with a high probability of asthma based on the initial assessment, move straight to a diagnostic trial of treatment. The initial choice of treatment will be based on an assessment of the degree of asthma severity (see *section 4*).

The clinical response to treatment should be reassessed within 2-3 months. In this group, reserve more detailed investigations for those whose response to treatment is poor or those with severe disease.¹⁹

- In children with a high probability of asthma:
- start a trial of treatment
 - review and assess response
 - reserve further testing for those with a poor response.

2.1.4 LOW PROBABILITY OF ASTHMA

Where symptoms, signs or initial investigations suggest that a diagnosis of asthma is unlikely, (see *Table 2*), or they point to an alternative diagnosis (see *Table 3*), consider further investigations. This may require referral for specialist assessment (see *Table 4*).

Reconsider a diagnosis of asthma in those who do not respond to specific treatments.

- In children with a low probability of asthma, consider more detailed investigation and specialist referral.

2.1.5 INTERMEDIATE PROBABILITY OF ASTHMA

In some children, and particularly those below the age of four to five, there is insufficient evidence at the first consultation to make a firm diagnosis of asthma, but no features to suggest an alternative diagnosis. There are several possible approaches to reaching a diagnosis in this group. Which approach is taken will be influenced by the frequency and severity of the symptoms.

These approaches include:

Watchful waiting with review

In children with mild, intermittent wheeze and other respiratory symptoms which occur only with viral upper respiratory infections (colds), it is often reasonable to give no specific treatment and to plan a review of the child after an interval agreed with the parents/carers.

Trial of treatment with review

The choice of treatment (for example, inhaled bronchodilators or corticosteroids) depends on the severity and frequency of symptoms. Although a trial of therapy with inhaled or oral corticosteroids is widely used to help make a diagnosis of asthma, there is little objective evidence to support this approach in children with recurrent wheeze.

It can be difficult to assess the response to treatment as an improvement in symptoms or lung function may be due to spontaneous remission. If it is unclear whether a child has improved, careful observation during a trial of withdrawing the treatment may clarify whether a response to asthma therapy has occurred.

Spirometry and reversibility testing

In children, as in adults, tests of airflow obstruction, airway responsiveness and airway inflammation may provide support for a diagnosis of asthma.^{12,44} However, normal results on testing, especially if performed when the child is asymptomatic, do not exclude a diagnosis of asthma.⁴⁶ Abnormal results may be seen in children with other respiratory diseases. Measuring lung function in young children is difficult and requires techniques which are not widely available.

2+

Above five years of age, conventional lung function testing is possible in most children in most settings. This includes measures of airway obstruction (spirometry and peak flow), reversibility with bronchodilators, and airway hyper-responsiveness.

The relationship between asthma symptoms and lung function tests including bronchodilator reversibility is complex. Asthma severity classified by symptoms and use of medicines correlates poorly with single measurements of forced expiratory volume in one second (FEV₁) and other spirometric indices: FEV₁ is often normal in children with persistent asthma.^{46,47} Serial measures of peak flow variability and FEV₁ show poor concordance with disease activity and do not reliably rule the diagnosis of asthma in or out.⁴⁷ Measures of gas trapping (residual volume and the ratio of residual volume to total lung capacity, RV/TLC) may be superior to measurements of expiratory flow at detecting airways obstruction especially in asymptomatic children.^{46,48}

2+

A significant increase in FEV₁ (>12% from baseline)⁴⁹ or PEF after bronchodilator indicates reversible airflow obstruction and supports the diagnosis of asthma. It is also predictive of a good response to inhaled corticosteroids.⁵⁰ However, an absent response to bronchodilators does not exclude asthma.⁵¹

2+
3

Between 2-5 years of age, many children can perform several newer lung function tests that do not rely on their cooperation or the ability to perform a forced expiratory manoeuvre. In general, these tests have not been evaluated as diagnostic tests for asthma. There is often substantial overlap between the values in children with and without asthma.⁵² Of the tests available, specific airways resistance (sRaw), impulse oscillometry (IOS), and measurements of residual volume (RV) appear the most promising.⁵³ While some of these tests have been useful in research, their role in clinical practice is uncertain.^{48,53,54} Most have only been used in specialist centres and are not widely available elsewhere. It is often not practical to measure variable airway obstruction in children below the age of five.

2+

2.1.6 CHILDREN WITH AN INTERMEDIATE PROBABILITY OF ASTHMA AND EVIDENCE OF AIRWAY OBSTRUCTION

Asthma is the by far the commonest cause of airways obstruction on spirometry in children. Obstruction due to other disorders, or due to multiple causes, is much less common in children than in adults. Spirometry and other lung function tests, including tests of PEF variability,⁴⁷ lung volumes and airway responsiveness,⁴⁵ are poor at discriminating between children with asthma and those with obstruction due to other conditions.

- In children with an intermediate probability of asthma who can perform spirometry and have evidence of airways obstruction, assess the change in FEV₁ or PEF in response to an inhaled bronchodilator (reversibility) and/or the response to a trial of treatment for a specified period:
 - if there is significant reversibility, or if a treatment trial is beneficial, a diagnosis of asthma is probable. Continue to treat as asthma, but aim to find the minimum effective dose of therapy. At a later point, consider a trial of reduction or withdrawal of treatment.
 - if there is no significant reversibility, and a treatment trial is not beneficial, consider tests for alternative conditions (see *Table 3*).

2.1.7 CHILDREN WITH AN INTERMEDIATE PROBABILITY OF ASTHMA WITHOUT EVIDENCE OF AIRWAY OBSTRUCTION

In this group, further investigations, including assessment of atopic status and bronchodilator responsiveness and if possible tests of airway responsiveness, should be considered (see *section 2.2.1*). This is particularly so if there has been a poor response to a trial of treatment or if symptoms are severe. In these circumstances, referral for specialist assessment is indicated.

- C** In children with an intermediate probability of asthma who can perform spirometry and have no evidence of airways obstruction:
 - consider testing for atopic status, bronchodilator reversibility and, if possible, bronchial hyper-responsiveness using methacholine, exercise or mannitol.
 - consider specialist referral.

2.1.8 CHILDREN WITH AN INTERMEDIATE PROBABILITY OF ASTHMA WHO CANNOT PERFORM SPIROMETRY

Most children under five years and some older children cannot perform spirometry. In these children, offer a trial of treatment for a specific period. If there is clear evidence of clinical improvement, the treatment should be continued and they should be regarded as having asthma (it may be appropriate to consider a trial of withdrawal of treatment at a later stage). If the treatment trial is not beneficial, then consider tests for alternative conditions and referral for specialist assessment.

- In children with an intermediate probability of asthma who cannot perform spirometry, offer a trial of treatment for a specified period:
 - if treatment is beneficial, treat as asthma and arrange a review
 - if treatment is not beneficial, stop asthma treatment and consider tests for alternative conditions and specialist referral.

2.2 OTHER INVESTIGATIONS

2.2.1 TESTS OF AIRWAY HYPER-RESPONSIVENESS

The role of tests of airway responsiveness (airway hyper-reactivity) in the diagnosis of childhood asthma is unclear.^{45,55} For example, a methacholine challenge test has a much lower sensitivity than symptoms in diagnosing asthma in children and only marginally increases the diagnostic accuracy after the symptom history is taken into account.⁴⁵ However, a negative methacholine test in children, which has a high negative predictive value, makes a diagnosis of asthma improbable.⁵⁵ Similarly, a negative response to an exercise challenge test is helpful in excluding asthma in children with exercise related breathlessness.⁵⁶

3

2.2.2 TEST OF EOSINOPHILIC AIRWAY INFLAMMATION

Eosinophilic inflammation in children can be assessed non-invasively using induced sputum differential eosinophil count or exhaled nitric oxide concentrations (F_{ENO}).

Sputum induction is feasible in school age children.^{57,58} Higher sputum eosinophil counts are associated with more marked airways obstruction and reversibility, greater asthma severity and atopy.⁵⁹ In children with newly diagnosed mild asthma, sputum eosinophilia is present and declines with inhaled steroid treatment.⁵⁸ Sputum induction is possible in approximately 75% of children tested, but it is technically demanding and time consuming and at present remains a research tool.

2⁺⁺

It is feasible to measure F_{ENO} in unsedated children from the age of 3-4 years.⁶⁰ A raised F_{ENO} is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma.⁶¹ F_{ENO} is closely linked with atopic status, age and height.^{62,63} In some studies, F_{ENO} correlated better with atopic dermatitis and allergic rhinitis than with asthma. It is not closely linked with underlying lung function. F_{ENO} could not differentiate between groups once atopy was taken into account.⁶⁴ Home measurements of F_{ENO} have a highly variable relationship with other measures of disease activity and vary widely from day to day.⁶⁵

2⁺

At present, there is insufficient evidence to support a role for markers of eosinophilic inflammation in the diagnosis of asthma in children. They may have a role in assessing severity of disease or response to treatment.

2.2.3 TESTS OF ATOPY

Positive skin tests,⁶⁶ blood eosinophilia $\geq 4\%$ ¹⁰, or a raised specific IgE to cat, dog or mite,^{67,68} increase the probability of asthma in a child with wheeze, particularly in children over five years of age.⁶⁶ It is important to recognise that non-atopic wheezing is as frequent as atopic wheezing in school-age children.⁶⁹

2⁺⁺

2.2.4 CHEST X-RAY

A study in primary care in children age 0-6 years concluded that a chest X-ray (CXR), in the absence of a clinical indication, need not be part of the initial diagnostic work up.⁷⁰



Reserve chest X-rays for children with severe disease or clinical clues suggesting other conditions.

2.3 SUMMARY

Focus the initial assessment of children suspected of having asthma on:

- presence of key features in the history and clinical examination
- careful consideration of alternative diagnoses.

Record the basis on which the diagnosis of asthma is suspected.

Using a structured questionnaire may produce a more standardised approach to the recording of presenting clinical features and the basis for a diagnosis of asthma.

1. In children with a high probability of asthma:

- move straight to a trial of treatment
- reserve further testing for those with a poor response.

2. In children with a low probability of asthma:

- consider more detailed investigation and specialist referral.

3. In children with an intermediate probability of asthma who can perform spirometry and have evidence of airways obstruction, offer a reversibility test and/or a trial of treatment for a specified period:

- if there is reversibility, or if treatment is beneficial, treat as asthma
- if there is insignificant reversibility, and/or treatment trial is not beneficial, consider tests for alternative conditions.

4. In children with an intermediate probability of asthma who can perform spirometry, and have no evidence of airways obstruction, consider testing for atopic status, bronchodilator reversibility and, if possible, bronchial hyper-responsiveness using methacholine or exercise.

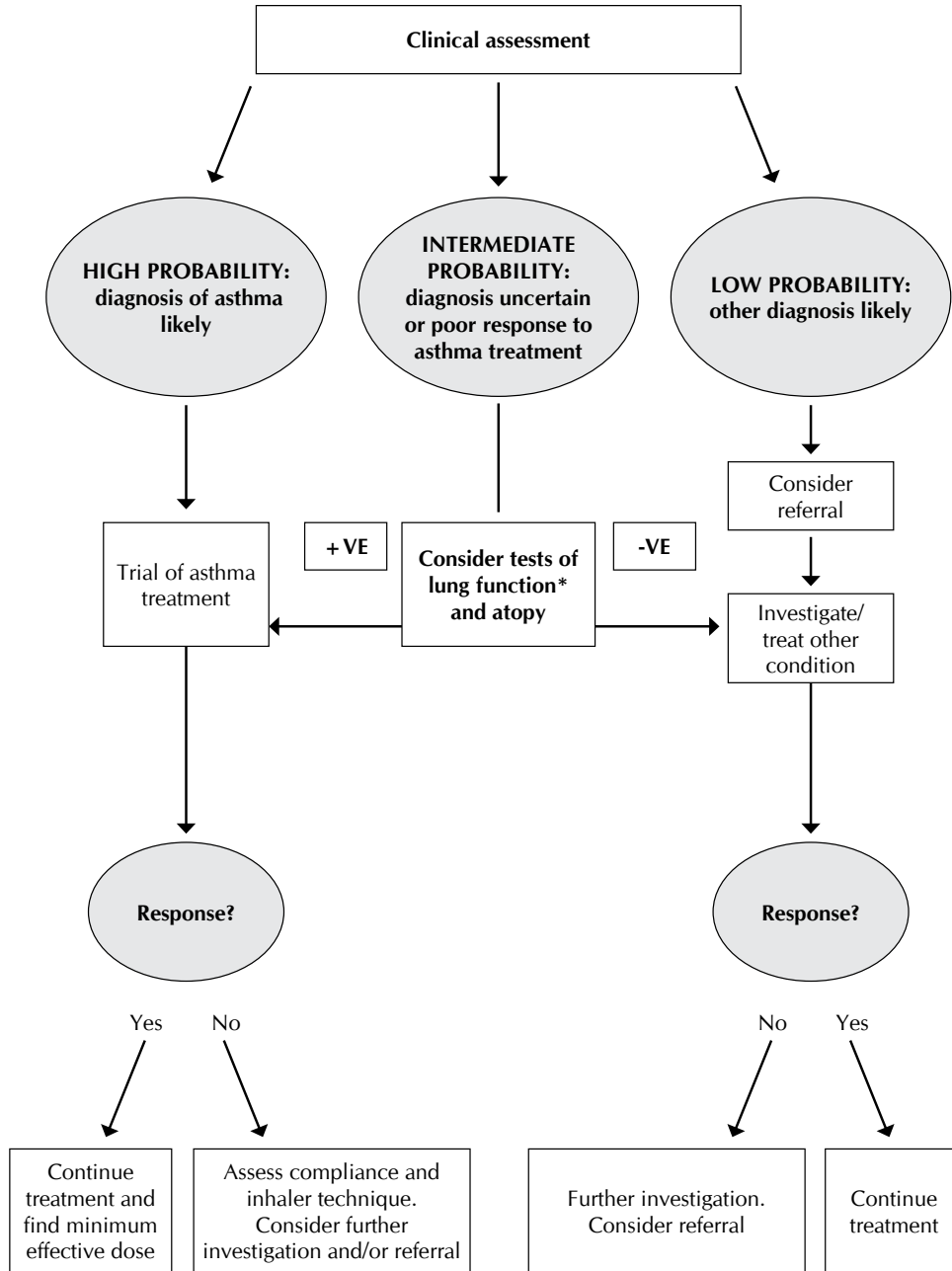
5. In children with an intermediate probability of asthma, who cannot perform spirometry, consider testing for atopic status and offering a trial of treatment for a specified period:

- if treatment is beneficial, treat as asthma
- if treatment is not beneficial, stop asthma treatment, and consider tests for alternative conditions and specialist referral.

Table 4: Indications for specialist referral in children

- Diagnosis unclear or in doubt
- Symptoms present from birth or perinatal lung problem
- Excessive vomiting or possetting
- Severe upper respiratory tract infection
- Persistent wet or productive cough
- Family history of unusual chest disease
- Failure to thrive
- Nasal polyps
- Unexpected clinical findings eg focal signs, abnormal voice or cry, dysphagia, inspiratory stridor
- Failure to respond to conventional treatment (particularly inhaled corticosteroids above 400 mcg/day or frequent use of steroid tablets)
- Parental anxiety or need for reassurance

Figure 1: Presentation with suspected asthma in children



* Lung function tests include spirometry before and after bronchodilator (test of airway reversibility) and possible exercise or methacholine challenge (tests of airway responsiveness). Most children over the age of 5 years can perform lung function tests.

2.4 DIAGNOSIS IN ADULTS

The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them (see *Table 5*). The key is to take a careful clinical history. In many cases this will allow a reasonably certain diagnosis of asthma, or an alternative diagnosis, to be made. If asthma does appear likely, the history should also explore possible causes, particularly occupational.

In view of the potential requirement for treatment over many years, it is important even in relatively clear cut cases, to try to obtain objective support for the diagnosis. Whether or not this should happen before starting treatment depends on the certainty of the initial diagnosis and the severity of presenting symptoms. Repeated assessment and measurement may be necessary before confirmatory evidence is acquired.

Confirmation hinges on demonstration of airflow obstruction varying over short periods of time. Spirometry, which is now becoming more widely available, is preferable to measurement of peak expiratory flow because it allows clearer identification of airflow obstruction, and the results are less dependent on effort. It should be the preferred test where available (although some training is required to obtain reliable recordings and to interpret the results). Of note, a normal spirogram (or PEF) obtained when the patient is not symptomatic does not exclude the diagnosis of asthma.

Results from spirometry are also useful where the initial history and examination leave genuine uncertainty about the diagnosis. In such cases, the differential diagnosis and approach to investigation is different in patients with and without airflow obstruction (see *Figure 2 and Table 6*). In patients with a normal or near-normal spirogram when symptomatic, potential differential diagnoses are mainly non-pulmonary;^{71,72} these conditions do not respond to inhaled corticosteroids and bronchodilators. In contrast, in patients with an obstructive spirogram the question is less whether they will need inhaled treatment but rather exactly what form and how intensive this should be.

Other tests of airflow obstruction, airway responsiveness and airway inflammation can also provide support for the diagnosis of asthma, but to what extent the results of the tests alter the probability of a diagnosis of asthma has not been clearly established, nor is it clear when these tests are best performed.

Table 5: Clinical features in adults that influence the probability that episodic respiratory symptoms are due to asthma

Features that increase the probability of asthma
<ul style="list-style-type: none"> ▪ More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, particularly if: <ul style="list-style-type: none"> ◇ symptoms worse at night and in the early morning ◇ symptoms in response to exercise, allergen exposure and cold air ◇ symptoms after taking aspirin or beta blockers ▪ History of atopic disorder ▪ Family history of asthma and/or atopic disorder ▪ Widespread wheeze heard on auscultation of the chest ▪ Otherwise unexplained low FEV₁ or PEF (historical or serial readings) ▪ Otherwise unexplained peripheral blood eosinophilia
Features that lower the probability of asthma
<ul style="list-style-type: none"> ▪ Prominent dizziness, light-headedness, peripheral tingling ▪ Chronic productive cough in the absence of wheeze or breathlessness ▪ Repeatedly normal physical examination of chest when symptomatic ▪ Voice disturbance ▪ Symptoms with colds only ▪ Significant smoking history (ie > 20 pack-years) ▪ Cardiac disease ▪ Normal PEF or spirometry when symptomatic* <p>* A normal spirogram/spirometry when not symptomatic does not exclude the diagnosis of asthma. Repeated measurements of lung function are often more informative than a single assessment.</p>

- Base initial diagnosis on a careful assessment of symptoms and a measure of airflow obstruction:
 - in patients with a high probability of asthma move straight to a trial of treatment. Reserve further testing for those whose response to a trial of treatment is poor.
 - in patients with a low probability of asthma, whose symptoms are thought to be due to an alternative diagnosis, investigate and manage accordingly. Reconsider the diagnosis of asthma in those who do not respond.
 - the preferred approach in patients with an intermediate probability of having asthma is to carry out further investigations, including an explicit trial of treatments for a specified period, before confirming a diagnosis and establishing maintenance treatment.

D Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction.

2.4.1 FURTHER INVESTIGATION OF PATIENTS WITH AN INTERMEDIATE PROBABILITY OF ASTHMA

Patients with airways obstruction

Tests of peak expiratory flow variability, lung volumes, gas transfer, airway hyper-responsiveness and airway inflammation are of limited value in discriminating patients with established airflow obstruction due to asthma from those whose airflow obstruction is due to other conditions.⁷³⁻⁷⁶ Patients may have more than one cause of airflow obstruction, which complicates the interpretation of any test. In particular, asthma and chronic obstructive pulmonary disease (COPD) commonly coexist.

- Offer patients with airways obstruction and intermediate probability of asthma a reversibility test and/or a trial of treatment for a specified period:
 - if there is significant reversibility, or if a treatment trial is clearly beneficial treat as asthma
 - if there is insignificant reversibility and a treatment trial is not beneficial, consider tests for alternative conditions.*

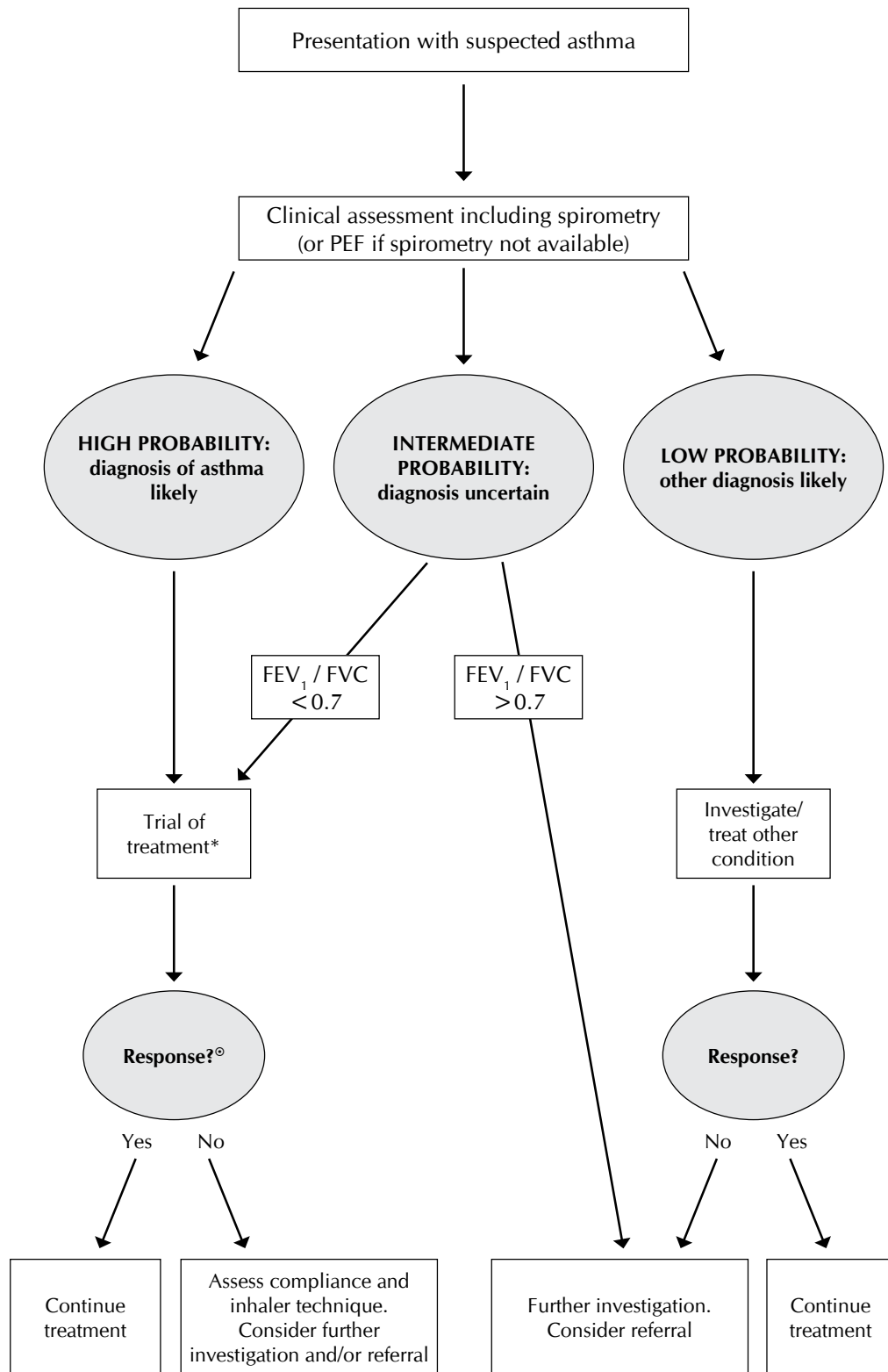
Patients without airways obstruction

In patients with a normal or near-normal spirogram it is more useful to look for evidence of airway hyper-responsiveness and/or airway inflammation^{71,77-79} These tests are sensitive so normal results provide the strongest evidence against a diagnosis of asthma.

- In patients without evidence of airways obstruction and with an intermediate probability of asthma, arrange further investigations* before commencing treatment.

* see section 2.5 for more detailed information on further tests

Figure 2: Presentation with suspected asthma in adults



* See section 2.5.1

Ⓞ See Table 6

Table 6: Differential diagnosis of asthma in adults, according to the presence or absence of airflow obstruction ($FEV_1/FVC < 0.7$).

Without airflow obstruction
<ul style="list-style-type: none"> ▪ Chronic cough syndromes ▪ Hyperventilation syndrome ▪ Vocal cord dysfunction ▪ Rhinitis ▪ Gastro-oesophageal reflux ▪ Heart failure ▪ Pulmonary fibrosis
With airflow obstruction
<ul style="list-style-type: none"> ▪ COPD ▪ Bronchiectasis* ▪ Inhaled foreign body* ▪ Obliterative bronchiolitis ▪ Large airway stenosis ▪ Lung cancer* ▪ Sarcoidosis* <p>*may also be associated with non-obstructive spirometry</p>

- Consider performing chest X-ray in any patient presenting atypically or with additional symptoms or signs. Additional investigations such as full lung function tests, blood eosinophil count, serum IgE and allergen skin prick tests may be of value in selected patients.

Criteria for referral to a specialist are outlined in box 1.

Box 1: Criteria for specialist referral in adults

<ul style="list-style-type: none"> ▪ Diagnosis unclear ▪ Unexpected clinical findings (ie crackles, clubbing, cyanosis, cardiac disease) ▪ Unexplained restrictive spirometry ▪ Suspected occupational asthma ▪ Persistent non-variable breathlessness ▪ Monophonic wheeze or stridor ▪ Prominent systemic features (myalgia, fever, weight loss) ▪ Chronic sputum production ▪ CXR shadowing ▪ Marked blood eosinophilia ($> 1 \times 10^9/l$) ▪ Poor response to asthma treatment ▪ Severe asthma exacerbation
--

2.5 FURTHER INVESTIGATIONS THAT MAY BE USEFUL IN PATIENTS WITH AN INTERMEDIATE PROBABILITY OF ASTHMA

Three studies have looked at tests to discriminate patients with asthma from those with conditions that are commonly confused with asthma.^{71,77,79} These studies provide a basis for evaluating the diagnostic value of different tests. Table 7 summarises the sensitivity and specificity of different findings on investigation. As not all studies included patients with untreated asthma, these values may underestimate the value of the investigations in clinical practice, where many patients will be investigated before treatment is started. The diagnostic value of testing may also be greater when more than one test is done or if there are previous lung function results available in the patient's notes. The choice of test will depend on a number of factors including severity of symptoms and local availability of tests.

An alternative and promising approach to the classification of airways disease is to use tests which best identify patients who are going to respond to corticosteroid therapy.^{78,80} A raised sputum eosinophil count and an increased exhaled nitric oxide concentration (FE_{NO}) are more closely related to corticosteroid response than other tests in a variety of clinical settings.^{78,81-83} There is also evidence that markers of eosinophilic airway inflammation are of value in monitoring the response to corticosteroid treatment.⁸⁴⁻⁸⁶ More experience with these techniques and more information on the long term response to corticosteroid in patients who do not have a raised sputum eosinophil count or FE_{NO} is needed before this approach can be recommended.

Table 7: Estimates of sensitivity and specificity of test results in adults with suspected asthma and normal or near-normal spirometric values.^{71,77,79}

Test	Normal range	Validity	
		sensitivity	specificity
Methacholine PC ₂₀	> 8 mg/ml	High	Medium
Indirect challenges*	varies	Medium [#]	High
FE _{NO}	< 25ppb	High [#]	Medium
Sputum eosinophil count	< 2%	High [#]	Medium
PEF A%H	< 8** < 20%***	Low	Medium

PC₂₀ = the provocative concentration of methacholine required to cause a 20% fall in FEV₁. FE_{NO} = exhaled nitric oxide concentration. PEF A%H = peak expiratory flow amplitude percent highest.

*ie exercise challenge, inhaled mannitol [#] in untreated patients, **with twice daily readings
***with four or more readings

2.5.1 TREATMENT TRIALS AND REVERSIBILITY TESTING

Treatment trials with bronchodilators or inhaled corticosteroids in patients with diagnostic uncertainty should use one or more objective methods of assessment. Using spirometric values or PEF as the prime outcome of interest is of limited value in patients with normal or near-normal pre-treatment lung function since there is little room for measurable improvement. One study has shown that the sensitivity of a positive response to inhaled corticosteroid, defined as a > 15% improvement in PEF, is 24%.⁷⁹ A variety of tools to assess asthma control is available to assess the response to a trial of treatment (see Table 8).

2+

Using FEV₁ or PEF as the primary method to assess reversibility or the response to treatment trials may be more helpful in patients with established airflow obstruction.

In adults, most clinicians would try a 6-8 week treatment trial of 200 mcg inhaled beclometasone (or equivalent) twice daily. In patients with significant airflow obstruction there may be a degree of inhaled corticosteroid resistance⁸⁷ and a treatment trial with oral prednisolone 30 mg daily for two weeks is preferred.

2+

A > 400 ml improvement in FEV₁ to either β₂ agonists or corticosteroid treatment trials strongly suggests underlying asthma. Smaller improvements in FEV₁ are less discriminatory⁷¹ and a decision on continuation of treatment should be based on objective assessment of symptoms using validated tools (see Table 8). Trials of treatment withdrawal may be helpful where there is doubt. 2+

C Assess FEV₁ (or PEF) and/or symptoms:

- **before and after 400 mcg inhaled salbutamol in patients with diagnostic uncertainty and airflow obstruction present at the time of assessment**
- **in other patients, or if there is an incomplete response to inhaled salbutamol, after either inhaled corticosteroids (200 mcg twice daily beclometasone equivalent for 6-8 weeks) or oral prednisolone (30 mg once daily for 14 days).**

2.5.2 PEAK EXPIRATORY FLOW MONITORING

PEF should be recorded as the best of three forced expiratory blows from total lung capacity with a maximum pause of two seconds before blowing.⁸⁸ The patient can be standing or sitting. Further blows should be done if the largest two PEF are not within 40 l/min.⁸⁸

PEF is best used to provide an estimate of variability of airflow from multiple measurements made over at least two weeks. Increased variability may be evident from twice daily readings. More frequent readings will result in a better estimate⁸⁹ but the improved precision is likely to be achieved at the expense of reduced patient compliance.⁹⁰

PEF variability is best calculated as the difference between the highest and lowest PEF expressed as a percentage of either the mean or highest PEF.⁹¹⁻⁹³

The upper limit of the normal range for the amplitude % highest is around 20% using four or more PEF readings per day^{91,93,94} but may be lower using twice daily readings.⁹⁵ Epidemiological studies have shown sensitivities of between 19 and 33% for identifying physician-diagnosed asthma.^{92,96}

PEF variability can be increased in patients with conditions commonly confused with asthma^{71,73} so the specificity of abnormal PEF variability is likely to be less in clinical practice than it is in population studies.

PEF records from frequent readings taken at work and away from work are useful when considering a diagnosis of occupational asthma (see section 7.8). A computer generated analysis of occupational records which provides an index of the work effect is available.⁹⁷

- Peak flow records should be interpreted with caution and with regard to the clinical context. They are more useful in the monitoring of patients with established asthma than in making the initial diagnosis.

2.5.3 ASSESSMENT OF AIRWAY RESPONSIVENESS

Tests of airway responsiveness have been useful in research but are not yet widely available in everyday clinical practice. The most widely used method of measuring airway responsiveness relies on measuring response in terms of change in FEV₁ a set time after inhalation of increasing concentrations of histamine or methacholine. The agent can be delivered by breath-activated dosimeter, via a nebuliser using tidal breathing, or via a hand held atomiser.⁹⁸ The response is usually quantified as the concentration (or dose) required to cause a 20% fall in FEV₁ (PC₂₀ or PD₂₀) calculated by linear interpolation of the log concentration or dose-response curve.

Community studies in adults have consistently shown that airway responsiveness has a unimodal distribution with between 90 and 95% of the normal population having a histamine or methacholine PC₂₀ of > 8 mg/ml (equivalent to a PD₂₀ of > 4 micromoles).^{92,99,100} This value has a sensitivity of between 60-100% in detecting physician-diagnosed asthma.^{92,96,99,100}

In patients with normal or near-normal spirometric values, assessment of airway responsiveness is significantly better than other tests in discriminating patients with asthma from patients with conditions commonly confused with asthma (see *Table 6*).^{71,77} In contrast, tests of airway responsiveness are of little value in patients with established airflow obstruction as the specificity is low.^{73,76}

Other potentially helpful constrictor challenges include indirect challenges such as inhaled mannitol and exercise.¹⁰¹ A positive response to these indirect stimuli (ie a > 15% fall in FEV₁) is a specific indicator of asthma but the tests are less sensitive than tests using methacholine and histamine, particularly in patients tested while on treatment.^{101,102}

2.5.4 TESTS OF EOSINOPHILIC AIRWAY INFLAMMATION

Eosinophilic airway inflammation can be assessed non-invasively using the induced sputum differential eosinophil count or the exhaled nitric oxide concentration (FENO).^{103,104} A raised sputum eosinophil count (> 2%) or FENO (> 25 ppb at 50 ml/sec) is seen in 70-80% of patients with untreated asthma.^{74,103} Neither finding is specific to asthma: 30-40% of patients with chronic cough^{82,105,106} and a similar proportion of patients with COPD⁸¹ have abnormal results. There is growing evidence that measures of eosinophilic airway inflammation are more closely linked to a positive response to corticosteroids than other measures even in patients with diagnoses other than asthma.^{81,83,105}

Experience with induced sputum and FENO is limited to a few centres and more research needs to be done before any recommendations can be made.

C In patients in whom there is diagnostic uncertainty and no evidence of airflow obstruction on initial assessment, test airway responsiveness wherever possible.

2.6 MONITORING ASTHMA

In the majority of patients with asthma symptom-based monitoring is adequate. Patients achieving control of symptoms with treatment have a low risk for exacerbations.¹⁰⁷

Table 8 summarises the methodology, measurement characteristics and interpretation of some of the validated tools used to assess symptoms and other aspects of asthma. Some measures provide information about future risk (ie sputum eosinophil count, airway responsiveness and FENO) rather than immediate clinical control. Risk reduction, eg minimising future adverse outcomes such as exacerbations and accelerated decline in lung function, is also a goal of asthma management.

A management strategy that controls eosinophilic airway inflammation⁸⁴⁻⁸⁶ or airway hyper-responsiveness¹⁰⁸ results in better control of exacerbations than one which controls immediate clinical manifestations. The benefits of this more intensive approach are greater in patients with severe asthma, when exacerbations can occur frequently and unpredictably. More research is needed to assess the relative roles of the different measures and to address the feasibility and cost of incorporating them into monitoring protocols before they can be recommended more widely.

2.6.1 MONITORING IN PRIMARY CARE

Asthma is best monitored in primary care by routine clinical review on at least an annual basis (see *section 8.1.2*).

The factors that should be monitored and recorded include:

- symptomatic asthma control: best assessed using directive questions such as the RCP '3 questions',¹⁰⁹ or the Asthma Control Questionnaire or Asthma Control Test (see *Table 8*), since broad non-specific questions may underestimate symptoms
- lung function, assessed by spirometry or by PEF. Reduced lung function compared to previously recorded values may indicate current bronchoconstriction or a long term decline in lung function and should prompt detailed assessment
- exacerbations, oral corticosteroid use and time off work or school since last assessment
- inhaler technique (see *section 5*)
- compliance (see *section 9.2*) which can be assessed by reviewing prescription refill frequency
- bronchodilator reliance which can be assessed by reviewing prescription refill frequency
- possession of and use of self management plan/personal action plan (see *section 9.1*).

Table 8: Summary of tools that can be used to assess asthma.

Measurement	Methodology	Measurement characteristics	Comments
Spirometry ^{110, 111}	<p>Widely available.</p> <p>Enables clear demonstration of airflow obstruction.</p> <p>FEV₁ largely independent of effort and highly repeatable.</p> <p>Less applicable in acute severe asthma. Only assesses one aspect of the disease state.</p>	<p>Normal ranges widely available and robust.</p> <p>Short term (20 minute) 95% range for repeat measure of FEV₁ < 160 ml; FVC < 330 ml, independent of baseline value.</p>	<p>Good for short and longer term reversibility testing in subjects with pre-existing airflow obstruction.</p> <p>> 400 ml increase in FEV₁ highly suggestive of asthma.</p> <p>Less helpful in subjects with normal pre-treatment values because of ceiling effect.</p>
Peak expiratory flow (PEF) ^{88, 91, 92, 112}	<p>Widely available and simple.</p> <p>Applicable in a wide variety of circumstances including acute severe asthma.</p> <p>PEF variability can be determined from home readings in most subjects.</p> <p>PEF effort dependent and not as repeatable as FEV₁.</p> <p>Only assesses one aspect of the disease state.</p>	<p>Normal ranges of PEF are wide, and currently available normative tables are outdated and do not encompass ethnic diversity.</p> <p>Change in PEF more meaningful than absolute value.</p> <p>> 60 l/min increase in PEF suggested as best criteria for defining reversibility.</p> <p>Normal range of PEF variability defined as amplitude % highest < 8% or < 20% depending on number of readings and degree of patient coaching.</p>	<p>Useful for short and longer term reversibility testing in subjects with pre-existing airflow obstruction.</p> <p>Less helpful in subjects with normal pre-treatment values because of ceiling effect.</p> <p>Little information on the use of PEF variability as an index of treatment response.</p>

Measurement	Methodology	Measurement characteristics	Comments
Royal College of Physicians (RCP) 3 Questions ¹⁰⁹	<p>Yes/no or graded response to the following three questions:</p> <p>In the last week (or month)</p> <p>1. Have you had difficulty sleeping because of your asthma symptoms (including cough)?</p> <p>2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?</p> <p>3. Has your asthma interfered with your usual activities (eg housework, work/school etc)?</p>	No to all questions consistent with controlled asthma.	<p>Not well validated.</p> <p>Simplicity is attractive for use in day to day clinical practice.</p>
Asthma Control Questionnaire ¹¹³⁻¹¹⁵	<p>Response to 7 questions, 5 relating to symptoms, 1 rescue treatment use and 1 FEV₁.</p> <p>Response usually assessed over the preceding week.</p> <p>Shortened, five question symptom only questionnaire is just as valid.</p>	<p>Well controlled ≤ 0.75, inadequately controlled ≥ 1.5.</p> <p>95% range for repeat measure +/- 0.36.</p> <p>Minimal important difference 0.5.</p>	<p>Well validated composite scoring system with a strong bias to symptoms.</p> <p>Could be used to assess response to longer term treatment trials.</p> <p>Shortened five-point questionnaire is probably best for those with normal or near normal FEV₁.</p>
Asthma Control Test (ACT) ^{116, 117}	<p>Response to 5 questions, 3 related to symptoms, 1 medication use and 1 overall control. 5 point response score</p>	<p>Well controlled > 19.</p> <p>Within subject intraclass correlation coefficient 0.77.</p> <p>95% range for repeat measure and minimally clinically important difference not defined.</p>	<p>Could be used to assess response to longer term treatment trials, particularly in those with normal or near-normal spirometric values.</p> <p>95% range for repeat measure and minimally clinically important difference need to be defined.</p>

Measurement	Methodology	Measurement characteristics	Comments
Mini Asthma Quality of Life Questionnaire (AQLQ) ^{114, 118}	<p>Response to 15 questions in 4 domains (symptoms, activity limitations, emotional function and environmental stimuli).</p> <p>Response usually assessed over the preceding week. Closely related to larger 32-item asthma quality of life questionnaire.</p>	<p>95% range for repeat measure +/- 0.36.</p> <p>Minimal important difference 0.5.</p>	<p>Well validated quality of life questionnaire.</p> <p>Could be used to assess response to longer term treatment trials.</p>
Airway responsiveness ^{98, 108}	<p>Only available in selected secondary care facilities.</p> <p>Responsive to change (particularly indirect challenges such as inhaled mannitol).</p> <p>Less of a ceiling effect.</p> <p>Not applicable in severe asthma or in acute severe asthma</p>	<p>Normal methacholine PC₂₀ > 8 mg/ml.</p> <p>95% range for repeat measure +/- 1.5-2 doubling doses.</p>	<p>Has not been widely used to monitor disease and assess treatment responses.</p> <p>Some evidence that using airway responsiveness as an additional measure for monitoring asthma results in a reduction in asthma exacerbations and improved airway pathology.</p>

Measurement	Methodology	Measurement characteristics	Comments
Exhaled nitric oxide (FENO) ^{78, 85, 103, 119, 120}	<p>Not widely available.</p> <p>Monitors still expensive, although expect the technology to become cheaper and more widespread.</p> <p>Measurements can be obtained in almost all adults and children over 5 years.</p> <p>Immediate results are available.</p> <p>Reasonably close relationship between FENO and eosinophilic airway inflammation, which is independent of gender, age, atopy and inhaled corticosteroid use.</p> <p>Relationship is lost in smokers.</p> <p>Not closely related to other measures of asthma morbidity.</p>	<p>Normal range < 25 ppb at exhaled flow of 50 ml/sec. 95% range for repeat measure 4 ppb.</p> <p>> 50 ppb highly predictive of eosinophilic airway inflammation.</p> <p>< 25 ppb highly predictive of its absence.</p>	<p>Raised FENO (> 50 ppb) very predictive of a positive response to corticosteroids.</p> <p>Use of FENO to guide corticosteroid treatment has been shown to result in a non-significant 25% reduction in exacerbations with 40% less corticosteroid.</p> <p>Low FENO (< 25 ppb) may be of particular value in identifying patients who can step down corticosteroid treatment safely.</p> <p>Protocols for diagnosis and monitoring have not been well defined and experience with the technique is limited.</p>
Sputum eosinophil differential count ^{83, 84, 121, 122}	<p>Only available in specialist centres although technology is widely available and inexpensive.</p> <p>Information available in 80-90% of patients although immediate results are not available.</p> <p>Sputum eosinophil count not closely related to other measures of asthma morbidity</p>	<p>Normal range < 2%; 95% range for repeat measure +/- 2-3 fold.</p>	<p>Close relationship between raised sputum eosinophil count and corticosteroid responsiveness.</p> <p>Use of sputum eosinophil count to guide corticosteroid therapy has been consistently shown to result in better outcome for the same exposure to corticosteroids.</p> <p>Benefits are greater in patients with more severe disease.</p>

3 Non-pharmacological management

There is a common perception amongst patients and carers that there are numerous environmental, dietary and other triggers of asthma and that avoiding these triggers will improve asthma and reduce the requirement for pharmacotherapy. Failure to address a patient, parent or carer's concern about environmental triggers may compromise concordance with recommended pharmacotherapy. Evidence that non-pharmacological management is effective can be difficult to obtain and more well controlled intervention studies are required.

This section distinguishes:

1. primary prophylaxis - interventions introduced before the onset of disease and designed to reduce its incidence.
2. secondary prophylaxis - interventions introduced after the onset of disease to reduce its impact.

3.1 PRIMARY PROPHYLAXIS

The evidence for primary interventional strategies is based predominantly on observational studies, though some have been tested using experimental methods. Many are multifaceted and it can be difficult to disentangle the effects of one exposure or intervention from another.

3.1.1 AEROALLERGEN AVOIDANCE

Exposure to high levels of house dust mite allergen in early life is associated with an increased likelihood of sensitisation to house dust mite by three to seven years of age.¹²³ Sensitisation to house dust mite is an important risk factor for the development of asthma^{124,125} and a few studies have suggested that high early house dust mite exposure increases the risks of subsequent asthma.^{126,127} A UK study showed that low levels of house dust mite and cat allergen exposures in early life increased the risk of IgE sensitisation and asthma at five years, with some attenuation at high levels of exposure, but there were significant interactions with heredity and birth order.¹²⁸

Outcomes from intervention studies attempting to reduce exposure to house dust mites are inconsistent. A multifaceted Canadian intervention study showed a reduced prevalence of doctor-diagnosed asthma but no impact on other allergic diseases, positive skin prick tests or bronchial hyper-responsiveness;¹²⁹ others have shown no effect on either allergic sensitisation or symptoms of allergic diseases.¹³⁰ In one UK study, early results from environmental manipulation commenced in early pregnancy and focused mainly on house dust mite avoidance, showed reductions in some respiratory symptoms in the first year of life.¹³¹ Subsequent results showed a paradoxical effect with increased allergy but better lung function in the intervention group.¹³²

1+

The considerable variation in the methodology used in these studies precludes the merging of data or generation of meta-analyses.

Intensive house dust mite avoidance may reduce exposure to a range of other factors including endotoxin. Epidemiological studies suggest that close contact with a cat or a dog in early life may reduce the subsequent prevalence of allergy and asthma.^{133,134} This has raised the question of whether high pet allergen exposure causes high-dose immune tolerance or increases exposure to endotoxin and other microbial products as a component of the "hygiene hypothesis".

In the absence of consistent evidence of benefit from domestic aeroallergen avoidance it is not possible to recommend it as a strategy for preventing childhood asthma.

3.1.2 FOOD ALLERGEN AVOIDANCE

Sensitisation to foods, particularly eggs, frequently precedes the development of aeroallergy and subsequent asthma.¹³⁵ Food allergen avoidance in pregnancy and postnatally has not been shown to prevent the later development of asthma.¹³⁶ Allergen avoidance during pregnancy may adversely affect maternal, and perhaps fetal, nutrition.¹³⁷ High-dose food allergen exposure during pregnancy may reduce subsequent sensitisation rates by inducing tolerance.¹³⁸ 1+

B In the absence of any evidence of benefit and given the potential for adverse effects, maternal food allergen avoidance during pregnancy and lactation is not recommended as a strategy for preventing childhood asthma.

3.1.3 BREAST FEEDING

A systematic review of observational studies on the allergy preventive effects of breast feeding indicates that it is effective for all infants irrespective of allergic heredity. The preventive effect is more pronounced in high-risk infants provided they are breast fed for at least four months.¹³⁹ However, not all studies have demonstrated benefit and in a large birth cohort there was no protective effect against atopy and asthma and maybe even an increase in risk.¹⁴⁰ 2+

Observational studies have the potential to be confounded by, for example, higher rates of breast feeding in atopic families, and taking this into account, the weight of evidence is in favour of breast feeding as a preventive strategy.

C Breast feeding should be encouraged for its many benefits, and as it may also have a potential protective effect in relation to early asthma.

3.1.4 MODIFIED INFANT MILK FORMULAE

Trials of modified milk formulae have not included sufficiently long follow up to establish whether there is any impact on asthma. A Cochrane review identified inconsistencies in findings and methodological concerns amongst studies, which mean that hydrolysed formulae cannot currently be recommended as part of an asthma prevention strategy.¹⁴¹ A review of the use of soy formulae found no significant effect on asthma or any other allergic disease.¹⁴² 1+

In the absence of any evidence of benefit from the use of modified infant milk formulae it is not possible to recommend it as a strategy for preventing childhood asthma.

3.1.5 WEANING

There are conflicting data on the association between early introduction of allergenic foods into the infant diet and the subsequent development of allergy and atopic eczema. No evidence was identified in relation to asthma.¹⁴³ In one study late introduction of egg was associated with a non-significant increase in pre-school wheezing.¹⁴⁴

In the absence of evidence on outcomes in relation to asthma no recommendations on modified weaning can be made.

3.1.6 NUTRITIONAL SUPPLEMENTATION - FISH OILS

Fish oils have a high level of omega-3 polyunsaturated fatty acids (n-3PUFAs). Western diets have a low intake of n-3 PUFAs with a corresponding increase in intake of n-6 PUFAs. This change has been associated with increasing rates of allergic disease and asthma.¹⁴³ Two randomised controlled studies have investigated early life fish oil dietary supplementation in relation to asthma outcomes in children at high risk of atopic disease (at least one parent or sibling had atopy with or without asthma). In a study, powered only to detect differences in cord blood, maternal dietary fish oil supplementation during pregnancy was associated with reduced cytokine release from allergen stimulated cord blood mononuclear cells. However, effects on clinical outcomes at one year, in relation to atopic eczema, wheeze and cough, were marginal.¹⁴⁵ In a second study, fish oil supplementation commencing in early infancy with or without additional house dust mite avoidance, was associated with a significant reduction in wheeze at 18 months of age. By five years of age fish oil supplementation was not associated with effects on asthma or other atopic diseases.¹⁴⁶

1+

In the absence of any evidence of benefit from the use of fish oil supplementation in pregnancy it is not possible to recommend it as a strategy for preventing childhood asthma.

3.1.7 OTHER NUTRIENTS

A number of observational studies have suggested an increased risk of subsequent asthma following reduced (maternal) intakes of selenium (based on umbilical cord levels),¹⁴⁷ or vitamin E based on maternal pregnancy intake.¹⁴⁸ No intervention studies in relation to selenium or vitamin E have yet been conducted and overall there is insufficient evidence to make any recommendations on maternal dietary supplementation as an asthma prevention strategy.¹⁴³ Observational studies suggest that intervention trials are warranted.

3.1.8 MICROBIAL EXPOSURE

The “hygiene hypothesis” suggested that early exposure to microbial products would switch off allergic responses thereby preventing allergic diseases such as asthma. The hypothesis is supported by some epidemiological studies comparing large populations who have or have not had such exposure.^{149,150}

The concept is sometimes described as “the microbial exposure hypothesis”. A double blind placebo controlled trial of the probiotic lactobacillus GG given to mothers resulted in a reduced incidence of atopic eczema in their children but had no effect on IgE antibody or allergic skin test responses. The small sample size and short follow up in this study limit its interpretation.¹⁵¹ Other trials of a range of probiotics and prebiotics are now in progress. There remains insufficient understanding of the ecology of gut flora in infancy in relation to outcomes. Bifido-bacteria may be more important than lactobacilli in reducing susceptibility to allergic disease.¹⁵²

There is insufficient evidence to indicate that the use of dietary probiotics in pregnancy reduces the incidence of childhood asthma.

This is a key area for further work with longer follow up to establish outcomes in relation to asthma.

3.1.9 AVOIDANCE OF TOBACCO SMOKE AND OTHER AIR POLLUTANTS

No evidence has been found to support a link between exposure to environmental tobacco smoke (ETS) or other air pollutants and the induction of allergy.

There is an increased risk of infant wheezing associated with maternal smoking during pregnancy which adversely affects infant lung function.¹⁵³⁻¹⁵⁶ Evidence suggests that early life ETS exposure is associated with later persistent asthma^{157,158} with a strong interaction with genetic polymorphisms which affect antioxidant activity.¹⁵⁹

2+

B

Parents and parents-to-be should be advised of the many adverse effects which smoking has on their children including increased wheezing in infancy and increased risk of persistent asthma.

The limited data on antenatal or early life exposure to other pollutants suggest similar effects to those for ETS, namely increased infant wheezing, enhanced by additional ETS exposure and antioxidant gene variations.¹⁶⁰⁻¹⁶² There is one small study suggesting that vitamin C supplementation will modify the combined effects of genetic polymorphisms and pollution on lung function in children with asthma.¹⁶³ Further research is required before recommendations for practice can be made.

3
4

3.1.10 IMMUNOTHERAPY

Three observational studies with contemporaneous untreated controls in over 8,000 patients have shown that allergen immunotherapy in individuals with a single allergy reduces the numbers subsequently developing new allergic sensitisation over a three to four year follow up.¹⁶⁴⁻¹⁶⁶ One trial compared pollen allergen immunotherapy in children with allergic rhinitis with contemporaneous untreated controls and showed a lower rate of onset of asthma during three years of treatment.¹⁶⁷ This effect was sustained for two years after stopping the therapy.¹⁶⁸ More studies are required to establish whether immunotherapy might have a role in primary prophylaxis.

3.1.11 IMMUNISATION

In keeping with the “microbial exposure hypothesis” some studies have suggested an association between tuberculin responsiveness and subsequent reduced prevalence of allergy, implying a protective effect of BCG. At present, it is not possible to disentangle whether poor tuberculin responsiveness represents an underlying defect which increases the risk of allergy and asthma or whether the immunisation itself has a protective effect.¹⁶⁹

2+

Investigation of the effects of any other childhood immunisation suggests that at worst there is no influence on subsequent allergic disease and maybe some protective effect against the development of asthma.¹⁷⁰

C

All childhood immunisations should proceed normally as there is no evidence of an adverse effect on the incidence of asthma.

3.2 SECONDARY NON-PHARMACOLOGICAL PROPHYLAXIS

3.2.1 HOUSE DUST MITE AVOIDANCE

Increased allergen exposure in sensitised individuals is associated with an increase in asthma symptoms, bronchial hyper-responsiveness and deterioration in lung function.^{127,171,172} However, evidence that reducing allergen exposure can reduce morbidity and/or mortality in asthma is tenuous. In uncontrolled studies, children and adults have derived benefit from removal to a low allergen environment such as occurs at high altitude, although the benefits seen are not necessarily attributable to allergen avoidance alone.¹⁷³

Cochrane reviews on house dust mite control measures in a normal domestic environment have concluded that chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be recommended.¹⁷⁴ Subsequent studies involving large numbers of patients tend to support this conclusion.^{175,176} Heterogeneity between studies with regard to the intervention and monitoring of outcomes makes interpretation of the systematic review difficult.

1++

Studies of mattress barrier systems have suggested that benefits in relation to treatment requirements for asthma and lung function can occur.^{177,178} Larger and more carefully conducted controlled studies employing combinations of house dust mite reduction strategies are required. At present house dust mite control measures do not appear to be a cost-effective method of achieving benefit, although it is recognised that many families are very committed to attempts to reduce exposure to triggers.

2+

Measures to decrease house dust mites have been shown to reduce numbers of house dust mites, but have not been shown to have an effect on asthma severity.

- Families with evidence of house dust mite allergy and who wish to try mite avoidance might consider the following:
 - complete barrier bed-covering systems
 - removal of carpets
 - removal of soft toys from bed
 - high temperature washing of bed linen
 - acaricides to soft furnishings
 - good ventilation with or without dehumidification.

3.2.2 OTHER ALLERGENS

Animal allergens, particularly from cat and dog, are potent provokers of asthma symptoms. The reported effects of removal of pets from homes are paradoxical, with either no benefit for asthma^{179,180} or a potential for continued high exposure to induce a degree of tolerance.¹⁸¹ In homes where there is no cat but still detectable cat allergen, there may be a benefit from introducing additional avoidance measures such as air filters and high efficiency vacuum cleaners for cat allergic patients.^{182,183}

Although fungal exposure has been strongly associated with hospitalisation and increased mortality in asthma, no controlled trials have addressed the efficacy of reduction of fungal exposure in relation to control of asthma. Cockroach allergy is not a common problem in the UK and studies of attempts to avoid this allergen elsewhere have produced conflicting results.¹⁸⁴

Studies of individual aeroallergen avoidance strategies show that single interventions have limited or no benefit. A multi faceted approach is more likely to be effective if it addresses all the indoor asthma triggers. Such approaches may even be cost effective.¹⁸⁵ A strategy with a potential impact on mites, mould allergens and indoor pollutants is the use of a mechanical ventilation system to reduce humidity and increase indoor air exchange. The only trial that has assessed this in a controlled fashion failed to demonstrate any significant effects, but the numbers involved were small.¹²⁰ A systematic review of this topic concluded that more research is required.¹⁸⁶

3.3 OTHER ENVIRONMENTAL FACTORS

3.3.1 SMOKING

Direct or passive exposure to cigarette smoke adversely affects quality of life, lung function, need for rescue medications for acute episodes of asthma and long term control with inhaled steroids.¹⁸⁷⁻¹⁹⁰

There are very few trials which have assessed smoking cessation in relation to asthma control. Two studies have demonstrated decreases in childhood asthma severity when parents were able to stop smoking.^{191,192} One study in adults with asthma suggested that smoking cessation improved asthma-specific quality of life, symptoms and drug requirements.¹⁹³ Intervention to reduce smoking has had disappointing outcomes.^{194,195} It is likely that more intensive intervention will be required to achieve meaningful outcomes.¹⁹⁶

Uptake of smoking in teenagers increases the risks of persisting asthma. One study showed a doubling of risk for the development of asthma over six years in 14 year old children who started to smoke¹⁹⁷ (see section 4.2.4 for effect of smoking on treatment).

- C** Parents with asthma should be advised about the dangers of smoking to themselves and their children with asthma and offered appropriate support to stop smoking.

3.3.2 AIR POLLUTION

Challenge studies demonstrate that various pollutants can enhance the response of patients with asthma to allergen inhalation.^{198,199} Time-series studies suggest that air pollution may provoke acute asthma attacks or aggravate existing chronic asthma although the effects are very much less than those with infection or allergen exposure.^{200,201} While it might seem likely that moving from a highly polluted environment might help, in the UK, asthma is more prevalent in 12-14 year olds in non-metropolitan rather than metropolitan areas.²⁰² Much less attention has been focused on indoor pollutants in relation to asthma and more work is required.^{203,204}

3.3.3 IMMUNOTHERAPY

Subcutaneous immunotherapy

Trials of allergen specific immunotherapy by subcutaneous injection of increasing doses of allergen extracts have consistently demonstrated beneficial effects compared with placebo in the management of allergic asthma. Allergens included house dust mite, grass pollen, tree pollen, cat and dog allergen and moulds. Cochrane reviews have concluded that immunotherapy reduces asthma symptoms, the use of asthma medications and improves bronchial hyper-reactivity. The most recent review included 36 trials with house dust mite, 20 with pollen, 10 with animal allergens, two with cladosporium mould, one with latex and six with multiple allergens.²⁰⁵ 1++

Evidence comparing the roles of immunotherapy and pharmacotherapy in the management of asthma is lacking. One study directly compared allergen immunotherapy with inhaled steroids and found that symptoms and lung function improved more rapidly in the group on inhaled steroids.²⁰⁶ Further comparative studies are required. 2+

Immunotherapy for allergic rhinitis has been shown to have a carry over effect after therapy has stopped.²⁰⁷ 3

B Immunotherapy can be considered in patients with asthma where a clinically significant allergen cannot be avoided. The potential for severe allergic reactions to the therapy must be fully discussed with patients.

Sublingual immunotherapy

There has been increasing interest in the use of sublingual immunotherapy, which is associated with far fewer adverse reactions than subcutaneous immunotherapy. A systematic review suggested there were some benefits for asthma control but the magnitude of the effect was small.²⁰⁸ Further randomised controlled trials are required. 1++

B Sublingual immunotherapy cannot currently be recommended for the treatment of asthma in routine practice.

3.4 DIETARY MANIPULATION

3.4.1 ELECTROLYTES

Increasing dietary sodium has been implicated in the geographical variations in asthma mortality²⁰⁹ and high sodium intake is associated with increased bronchial hyper-responsiveness.^{210,211} A systematic review of intervention studies reducing salt intake identified only minimal effects and concluded that dietary salt reduction could not be recommended in the management of asthma.²¹² Low magnesium intakes have been associated with a higher prevalence of asthma with increasing intake resulting in reduced bronchial hyper-responsiveness and higher lung function.²¹³ Magnesium plays a beneficial role in the treatment of asthma through bronchial smooth muscle relaxation, leading to the use of intravenous or inhaled preparations of magnesium sulphate for acute exacerbations of asthma.²¹⁴ Studies of oral supplementation are limited and more trials are required.²¹⁵⁻²¹⁷

3.4.2 FISH OILS/LIPIDS

In vitro studies suggest that supplementing the diet with omega n-3 fatty acids, which are most commonly found in fish oils, might reduce the inflammation associated with asthma.^{218,219} Results from observational studies are inconsistent and a Cochrane review of nine randomised controlled trials concluded that there was insufficient evidence to recommend fish oil supplementation for the treatment of asthma.²²⁰

3.4.3 ANTIOXIDANTS

Observational studies have reported that low vitamin C, vitamin E and selenium intakes are associated with a higher prevalence of asthma.¹⁴³ Intervention studies suggest that neither supplementation with vitamin C, vitamin E or selenium is associated with clinical benefits in people with asthma.²²¹⁻²²³ Observational studies in both adults and children have also consistently shown that a high intake of fresh fruit and vegetable is associated with less asthma and better pulmonary function.²²⁴⁻²³⁰ No intervention studies evaluating the intake of fruit or vegetables and their effects on asthma have been reported.

3.4.4 WEIGHT REDUCTION IN OBESE PATIENTS WITH ASTHMA

Several studies have reported an association between increasing body mass index and symptoms of asthma.²³¹⁻²³⁴ One randomised parallel group study has shown improved asthma control following weight reduction in obese patients with asthma.²³⁵

3
1+

C **Weight reduction is recommended in obese patients with asthma to promote general health and to improve asthma control.**

3.4.5 PROBIOTICS

Studies have suggested that an imbalance in gut flora is associated with a higher risk of development of allergy.²³⁶ Trials have investigated the use of probiotics in the treatment of established allergic disease with variable results.^{237,238} Only one study focused on asthma, finding a decrease in eosinophilia but no effect on clinical parameters.²³⁹

1+
2+

In the absence of evidence of benefit, it is not possible to recommend the use of probiotics in the management of asthma.

3.4.6 IMMUNISATIONS

A number of large studies have concluded that high vaccination coverage has no significant impact on any allergic outcome or asthma. There is a suggestion that the higher the vaccine coverage the greater the possibility that there is a degree of protection against the development of allergy in the first years of life.²⁴⁰⁻²⁴³

There is some discussion about whether BCG immunisation may confer protection against allergy and asthma. Research has focused on primary prophylaxis, though there are some studies investigating the use of BCG, with or without allergen, as a means to switch off allergic immune responses. There are some observations suggesting that benefit might occur,²⁴⁴ but results of trials have been disappointing.^{245,246} This is an area that requires further investigation.

There has been concern that influenza vaccination might aggravate respiratory symptoms, though any such effect would be outweighed by the benefits of the vaccination.²⁴⁷ Studies in children have suggested that immunisation with the vaccine does not exacerbate asthma²⁴⁸ but has a small beneficial effect on quality of life in children with asthma.²⁴⁹ The immune response to the immunisation may be adversely affected by high-dose inhaled corticosteroid therapy and this requires further investigation.²⁵⁰ A Cochrane review of pneumococcal vaccine found very limited evidence to support its use specifically in individuals with asthma.²⁵¹

1++

B **Immunisations should be administered independent of any considerations related to asthma. Responses to vaccines may be attenuated by high-dose inhaled steroids.**

3.5 COMPLEMENTARY AND ALTERNATIVE MEDICINE

Successive reviews have concluded that the evidence to support any recommendations on complementary or alternative medicine is lacking.²⁵² It is recognised that a lack of evidence does not necessarily mean that treatment is ineffective and high quality research, conducted in the same rigorous and objective fashion as that for conventional therapy, is required.

3.5.1 ACUPUNCTURE

A Cochrane review of 21 trials highlighted many methodological problems with the studies reviewed. Only seven of the trials in 174 patients employed randomisation to active (recognised in traditional Chinese medicine to be of benefit in asthma) or sham acupuncture points (with no recognised activity) for the treatment of persistent or chronic asthma. Blinding was a major problem in the assessment of the results and there were considerable inconsistencies in methodology. The review concluded that there was no evidence for a clinically valuable benefit for acupuncture and no significant benefits in relation to lung function.²⁵³ A later systematic review and meta-analysis of 11 randomised controlled trials found no evidence of an effect in reducing asthma severity but a suggestion that where broncho-constriction was induced to establish efficacy of acupuncture there was a beneficial effect. Concern was expressed about potential preferential publication in favour of positive outcome studies.²⁵⁴ Two other trials of acupuncture in relation to induced asthma were also negative.^{255,256}

1+

3.5.2 AIR IONISERS

Ionisers have been widely promoted as being of benefit for patients with asthma. A Cochrane review of five studies using negative ion generators and one with a positive ion generator found no evidence of benefit in reducing symptoms in patients with asthma.²⁵⁷ One study demonstrated an increase in night-time cough to a level which approached statistical significance.²⁵⁸

1++

1+

A Air ionisers are not recommended for the treatment of asthma.

3.5.3 BREATHING EXERCISES INCLUDING YOGA AND THE BUTEYKO BREATHING TECHNIQUE

The principle of yoga and Buteyko breathing technique is to control hyperventilation by lowering respiratory frequency. A Cochrane review of breathing exercises found no change in routine measures of lung function.²⁵⁹ One study showed a small reduction in airway responsiveness to histamine utilising pranayama, a form of yoga breathing exercise.²⁶⁰

1++

1+

The Buteyko breathing technique specifically focuses on control of hyperventilation and any ensuing hypocapnia. Four clinical trials suggest benefits in terms of reduced symptoms and bronchodilator usage but no effect on lung function.²⁶¹⁻²⁶⁴

1+

B Buteyko breathing technique may be considered to help patients to control the symptoms of asthma.

3.5.4 HERBAL AND TRADITIONAL CHINESE MEDICINE

A Cochrane review identified 17 trials, nine of which reported some improvement in lung function but it was not clear that the results would be generalisable.²⁶⁵ A more recent double blind placebo controlled trial of a Chinese herb decoction (Ding Chuan Tang) showed improvement in airway hyper-responsiveness in children with stable asthma.²⁶⁶ It is difficult to disentangle the effects of multiple ingredients; Ding Chuan Tang for example contains nine components. In a second study, 100 children with asthma found that a five-herb mixture gave some benefits in relation to lung function and symptoms compared with placebo.²⁶⁷

1+

The conclusions of these trials of Chinese herbal therapy are not generalisable due to variations in the herbal mixtures and study designs. There are likely to be pharmacologically active ingredients in the mixtures and further investigations are warranted. There is a need for large appropriately powered placebo controlled studies.

3.5.5 HOMEOPATHY

A Cochrane review identified only three methodologically sound randomised controlled trials, two of which reported some positive effects. A criticism of the studies was that they did not employ individualised homeopathy, which is the essence of this approach to treatment.²⁶⁸ A more recent trial of individualised homeopathy in childhood asthma, which was placebo controlled and appropriately powered, failed to show any evidence of benefit over conventional treatment in primary care.²⁶⁹

1++
1+

3.5.6 HYPNOSIS AND RELAXATION THERAPIES

A systematic review of relaxation therapies, including hypnotherapy, identified five controlled trials, two of which showed some benefits. Overall the methodology of the studies was poor and the review concluded that there was a lack of evidence of efficacy but that muscle relaxation could conceivably benefit lung function in patients with asthma.²⁷⁰

1++

3.6 OTHER COMPLEMENTARY OR ALTERNATIVE APPROACHES

3.6.1 MANUAL THERAPY INCLUDING MASSAGE AND SPINAL MANIPULATION

A Cochrane review identified four relevant RCTs.²⁷¹ The two trials of chiropractic suggest that there is no place for this modality of treatment in the management of asthma. No conclusions can be drawn on massage therapy.

3.6.2 PHYSICAL EXERCISE TRAINING

A Cochrane review²⁵⁹ has shown no effect of physical training on PEF, FEV₁, FVC or VEmax. However, oxygen consumption, maximum heart rate, and work capacity all increased significantly. Most studies discussed the potential problems of exercise induced asthma, but none made any observations on this phenomenon. As physical training improves indices of cardiopulmonary efficiency, it should be seen as part of a general approach to improving lifestyle and rehabilitation in asthma, with appropriate precautions advised about exercise induced asthma (see section 4.7.2).

3.6.3 FAMILY THERAPY

A Cochrane review identified two trials, in 55 children, showing that family therapy may be a useful adjunct to medication in children with asthma.²⁷² Small study size limits the recommendations.

- In difficult childhood asthma, there may be a role for family therapy as an adjunct to pharmacotherapy.

4 Pharmacological management

The aim of asthma management is control of the disease. Control of asthma is defined as:

- no daytime symptoms
- no night time awakening due to asthma
- no need for rescue medication
- no exacerbations
- no limitations on activity including exercise
- normal lung function (in practical terms FEV₁ and/or PEF > 80% predicted or best)

with minimal side effects.

In clinical practice patients may have different goals and may wish to balance the aims of asthma management against the potential side effects or inconvenience of taking medication necessary to achieve perfect control.

- Lung function measurements cannot be reliably used to guide asthma management in children under five years of age.

A stepwise approach aims to abolish symptoms as soon as possible and to optimise peak flow by starting treatment at the level most likely to achieve this. Patients should start treatment at the step most appropriate to the initial severity of their asthma. The aim is to achieve early control and to maintain control by stepping up treatment as necessary and stepping down when control is good (see figures 4, 5 and 6 for summaries of stepwise management in adults and children).

- Before initiating a new drug therapy practitioners should check compliance with existing therapies (see section 9.2), inhaler technique (see section 5) and eliminate trigger factors (see section 3).

All doses of inhaled steroids in this section refer to beclometasone (BDP) given via CFC-MDIs (metered dose inhaler). Although now almost phased out, this is the device used in most of the evidence base that supports current asthma management. Adjustment to dose will have to be made for other devices and other corticosteroid molecules.

In this and the following section, each recommendation has been graded and the supporting evidence assessed for adults (> 12 years old), children 5-12 years, and children under 5 years. The evidence is less clear in children under two and the threshold for seeking an expert opinion should be lowest in these children.

- | | | | |
|---|---|---|-----------------------------------|
| 1 | 2 | 3 | 1 Adults |
| | | | 2 Children aged 5-12 years |
| | | | 3 Children under 5 years |

- Recommendation does not apply to this age group.

4.1 STEP 1: MILD INTERMITTENT ASTHMA

The following medicines act as short-acting bronchodilators:

- inhaled short-acting β_2 agonists²⁷³
- inhaled ipratropium bromide²⁷⁴
- β_2 agonist tablets or syrup²⁷³
- theophyllines.²⁷³

>12 years	5-12 years	<5 years
1 ⁺⁺	1 ⁺	4
1 ⁺	1 ⁺⁺	
1 ⁺⁺		
1 ⁺⁺		

Short-acting inhaled β_2 agonists work more quickly and/or with fewer side effects than the alternatives.²⁷³

A B C Prescribe an inhaled short-acting β_2 agonist as short term reliever therapy for all patients with symptomatic asthma.

4.1.1 FREQUENCY OF DOSING OF INHALED SHORT-ACTING β_2 AGONISTS

Using short acting β_2 agonists as required is at least as good as regular (four times daily) administration.^{275, 276} Unless individual patients are shown to benefit from regular use of inhaled short-acting β_2 agonists then as required use is recommended.

Good asthma control is associated with little or no need for short-acting β_2 agonist. Using two or more canisters of β_2 agonists per month or >10-12 puffs per day is a marker of poorly controlled asthma that puts individuals at risk of fatal or near-fatal asthma.²⁷⁷

>12 years	5-12 years	<5 years
1 ⁺⁺	1 ⁺⁺	1 ⁺⁺
2 ⁺⁺	4	4

B D D Patients with a high usage of inhaled short-acting β_2 agonists should have their asthma management reviewed.

4.2 STEP 2: INTRODUCTION OF REGULAR PREVENTER THERAPY

For steps 2, 3, and 4, treatments have been judged on their ability to improve symptoms, improve lung function, and prevent exacerbations, with an acceptable safety profile. Improvement of quality of life, while important, is the subject of too few studies to be used to make recommendations at present.

4.2.1 INHALED STEROIDS

Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals.²⁷⁸⁻²⁸² There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in infants and younger children with asthma.²⁸³⁻²⁸⁶

Many children with recurrent episodes of viral-induced wheezing in infancy do not go on to have chronic atopic asthma. The majority do not require treatment with regular inhaled steroids (see section 2.1).

A A A Inhaled steroids are the recommended preventer drug for adults and children for achieving overall treatment goals.

Inhaled steroids should be considered for adults, children aged 5-12 and children under the age of five with any of the following features: using inhaled β_2 agonists three times a week or more; symptomatic three times a week or more; or waking one night a week. In addition, inhaled steroids should be considered in adults and children aged 5-12 who have had an exacerbation of asthma requiring oral corticosteroids in the last two years.^{287,288}

>12 years	5-12 years	<5 years
1 ⁺⁺	1 ⁺⁺	1 ⁺⁺
1 ⁺	1 ⁺	

Inhaled steroids should be considered for patients with any of the following asthma-related features:

- | | | | |
|---|---|---|---|
| B | C | | ▪ exacerbations of asthma in the last two years |
| B | C | ☑ | ▪ using inhaled β_2 agonists three times a week or more |
| B | C | ☑ | ▪ symptomatic three times a week or more |
| B | C | ☑ | ▪ waking one night a week. |

Starting dose of inhaled steroids

In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit.²⁸⁹

>12 years	5-12 years	<5 years
1+	1+	

- Start patients at a dose of inhaled steroids appropriate to the severity of disease.
- In adults, a reasonable starting dose will usually be 400 mcg per day and in children 200 mcg per day. In children under five years, higher doses may be required if there are problems in obtaining consistent drug delivery.
- Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

Frequency of dosing of inhaled steroids

Most current inhaled steroids are slightly more effective when taken twice rather than once daily, but may be used once daily in some patients with milder disease.^{273, 279,290}

>12 years	5-12 years	<5 years
1+	4	4

There is little evidence of benefit for dosage frequency more than twice daily.²⁷⁹

- | | | | |
|---|---|---|---|
| A | D | D | Give inhaled steroids initially twice daily, except ciclesonide which is given once daily. |
| A | D | D | Once a day inhaled steroids at the same total daily dose can be considered if good control is established. |

4.2.2 SAFETY OF INHALED STEROIDS

The safety of inhaled steroids is of crucial importance and a balance between benefits and risks for each individual needs to be assessed. Account should be taken of other topical steroid therapy when assessing systemic risk. It has been suggested that steroid warning cards should be issued to patients on higher dose inhaled steroids, but the benefits and possible disadvantages, particularly with regard to compliance, of such a policy remain to be defined.

Adults

There is little evidence that doses below 800 mcg per day cause any short term detrimental effects apart from the local side effects of dysphonia and oral candidiasis. However, the possibility of long term effects on bone has been raised. One systematic review reported no effect on bone density at doses up to 1,000 mcg per day.²⁹¹ The significance of small biochemical changes in adrenocortical function is unknown.

- Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

Children

Administration of inhaled steroids at or above 400 mcg a day of BDP or equivalent may be associated with systemic side effects.²⁹² These may include growth failure and adrenal suppression. Isolated growth failure is not a reliable indicator of adrenal suppression and monitoring growth cannot be used as a screening test of adrenal function.^{290,293}

Clinical adrenal insufficiency has been identified in a small number of children who have become acutely unwell at the time of intercurrent illness. Most of these children had been treated with high doses of inhaled corticosteroids. The dose or duration of inhaled steroid treatment required to place a child at risk of clinical adrenal insufficiency is unknown but is likely to occur at ≥ 800 mcg per day of BDP or equivalent. The low dose ACTH test is considered to provide a physiological stimulation of adrenal responsiveness but it is not known how useful such a sensitive test is at predicting clinically relevant adrenal insufficiency.^{59,294} In addition, it is unknown how frequently tests of adrenal function would need to be repeated if a child remained on high-dose inhaled corticosteroid. At higher doses, add-on agents, for example, long-acting β_2 agonists, should be actively considered.

- Monitor height of children on high doses of inhaled steroids on a regular basis.
- The lowest dose of inhaled steroids compatible with maintaining disease control should be used.

For children treated with ≥ 800 mcg per day of BDP or equivalent:

- Specific written advice about steroid replacement in the event of a severe intercurrent illness should be part of the management plan.
- The child should be under the care of a specialist paediatrician for the duration of the treatment.

Consider the possibility of adrenal insufficiency in any child maintained on inhaled steroids presenting with shock or a decreased level of consciousness; serum biochemistry and blood glucose levels should be checked urgently. Consider whether intramuscular (IM) hydrocortisone is required.

4.2.3 COMPARISON OF INHALED STEROIDS

Many studies comparing different inhaled steroids are of inadequate design and have been omitted from further assessment. In view of the clear differences between normal volunteers and asthma patients in the absorption of inhaled steroids, data from normal volunteers have not been taken into account. Only studies in which more than one dose of at least one of the inhaled steroids or both safety and efficacy had been studied together in the same trial were evaluated. Non-blinded studies also had to be considered because of the problems of obtaining competitors' delivery devices. Most comparisons used BDP-CFC (chlorofluorocarbons) as the reference. A series of Cochrane reviews comparing different inhaled steroids using a different methodology have come to the same conclusion.

BDP and budesonide are approximately equivalent in clinical practice, although there may be variations with different delivery devices. There is limited evidence from two open studies of less than ideal design that budesonide via the turbohaler is more clinically effective.²⁹⁵ However, at present a 1:1 ratio should be assumed when changing between BDP and budesonide.

Fluticasone provides equal clinical activity to BDP and budesonide at half the dosage. The evidence that it causes fewer side effects at doses with equal clinical effect is limited.

Mometasone is a new inhaled steroid that appears to provide equal clinical activity to BDP and budesonide at half the dosage.²⁹⁶ The relative safety of mometasone is not fully established.

Ciclesonide is a new inhaled steroid. Evidence from clinical trials suggests that it has less systemic activity and fewer local oropharyngeal side effects than conventional inhaled steroids.²⁹⁷⁻³⁰¹ The clinical benefit of this is not clear as the exact efficacy to safety ratio compared to other inhaled steroids has not been fully established.

Non-CFC beclometasone is available in more than one preparation, and the potency relative to CFC beclometasone is not consistent between these (see *section 5.4*).

4.2.4 SMOKING

Current and previous smoking reduces the effect of inhaled steroids; which may be overcome with increased doses.^{187,302} 1+

Patients should be advised that smoking reduces the effectiveness of therapy.

B **Clinicians should be aware that higher doses of inhaled steroids may be needed in patients who are smokers or ex-smokers.**

4.2.5 OTHER PREVENTER THERAPIES

Inhaled steroids are the first choice preventer drug. Long-acting inhaled β_2 agonists should not be used without inhaled corticosteroids.³⁰³ Alternative, less effective preventer therapies in patients taking short-acting β_2 agonists alone are:

- | | >12 years | 5-12 years | <5 years |
|--|-----------|------------|----------|
| ▪ Chromones | | | |
| - Sodium cromoglicate is of some benefit in adults ^{273, 304} and is effective in children aged 5-12 ³⁰⁵ | 1+ | 1+ | |
| - Nedocromil sodium is also of benefit in adults and children > 5 ^{306,307} | 1++ | 1+ | |
| - There is no clear evidence of benefit with sodium cromoglicate in children aged < 5 ³⁰⁸ | | | |
| ▪ Leukotriene receptor antagonists have some beneficial clinical effect ^{279,309,310} | 1++ | 1++ | 1++ |
| ▪ Theophyllines have some beneficial effect ^{273,278} | 1+ | 1+ | 1+ |
| ▪ Antihistamines and ketotifen are ineffective. ³¹¹ | 1++ | 1++ | 1++ |

4.3 STEP 3: INITIAL ADD-ON THERAPY

A proportion of patients with asthma may not be adequately controlled at step 2. Before initiating a new drug therapy practitioners should recheck compliance, inhaler technique and eliminate trigger factors. The duration of a trial of add-on therapy will depend on the desired outcome. For instance, preventing nocturnal awakening may require a relatively short trial of treatment (days or weeks), whereas preventing exacerbations of asthma or decreasing steroid tablet use may require a longer trial of therapy (weeks or months). If there is no response to treatment the drug should be discontinued.

4.3.1 CRITERIA FOR INTRODUCTION OF ADD-ON THERAPY

	>12 years	5-12 years	<5 years
No exact dose of inhaled steroid can be deemed the correct dose at which to add another therapy. The addition of other treatment options to inhaled steroids has been investigated at doses from 200-1000 mcg in adults and up to 400 mcg in children. ³¹²⁻³¹⁵ Many patients will benefit more from add-on therapy than from increasing inhaled steroids above doses as low as 200 mcg/day. At doses of inhaled steroid above 800 mcg/day side effects become more frequent. An absolute threshold for introduction of add-on therapy in all patients cannot be defined.	1++	1+	

4.3.2 ADD-ON THERAPY

Options for add-on therapy are summarised in Figure 3.

In adult patients taking inhaled steroids at doses of 200-800 mcg/day and in children taking inhaled steroids at a dose of 400 mcg/day the following interventions are of value:

- | | >12 years | 5-12 years | <5 years |
|---|-----------|------------|----------|
| ▪ first choice would be the addition of an inhaled long-acting β_2 agonist (LABA), which improves lung function and symptoms, and decreases exacerbations. ^{312,316,317} | 1++ | 1+ | |

A **B** **The first choice as add-on therapy to inhaled steroids in adults and children (5-12 years) is an inhaled long-acting β_2 agonist, which should be considered before going above a dose of 400 mcg BDP or equivalent per day and certainly before going above 800 mcg BDP.**

See Figure 6 for options in children under five years old.

If, as occasionally happens, there is no response to inhaled long-acting β_2 agonist, stop the LABA and increase the dose of inhaled steroid to 800 mcg/day (*adults*) or 400 mcg/day (*children*) if not already on this dose. If there is a response to LABA, but control remains suboptimal, continue with the LABA and increase the dose of inhaled steroid to 800 mcg/day (*adults*) or 400 mcg/day (*children 5-12 years*).³¹⁸

>12 years	5-12 years	<5 years
4	4	

D D If asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled steroids should be increased to 800 mcg/day in adults or 400 mcg/day in children (5-12 years), if not already on these doses.

- | | | |
|-----------------|-----------------|----------------|
| >12 years | 5-12 years | <5 years |
| 1 ⁺⁺ | 1 ⁺⁺ | 1 ⁺ |
- **Leukotriene receptor antagonists** may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms.^{310,319,320}
 - **Theophyllines** may improve lung function and symptoms, but side effects occur more commonly.³¹³
 - **Slow-release β_2 agonist tablets** may also improve lung function and symptoms, but side effects occur more commonly.³¹²
- | | | |
|-----------------|----------------|----------|
| >12 years | 5-12 years | <5 years |
| 1 ⁺ | 1 ⁻ | |
| 1 ⁺⁺ | | |

If control remains inadequate after stopping a LABA and increasing the dose of inhaled steroid, consider sequential trials of add-on therapy, ie leukotriene receptor antagonists, theophyllines, slow-release β_2 agonist tablets (this in adults only).

Addition of short-acting anticholinergics is generally of no value.^{314,321} Addition of nedocromil is of marginal benefit.^{304,315}

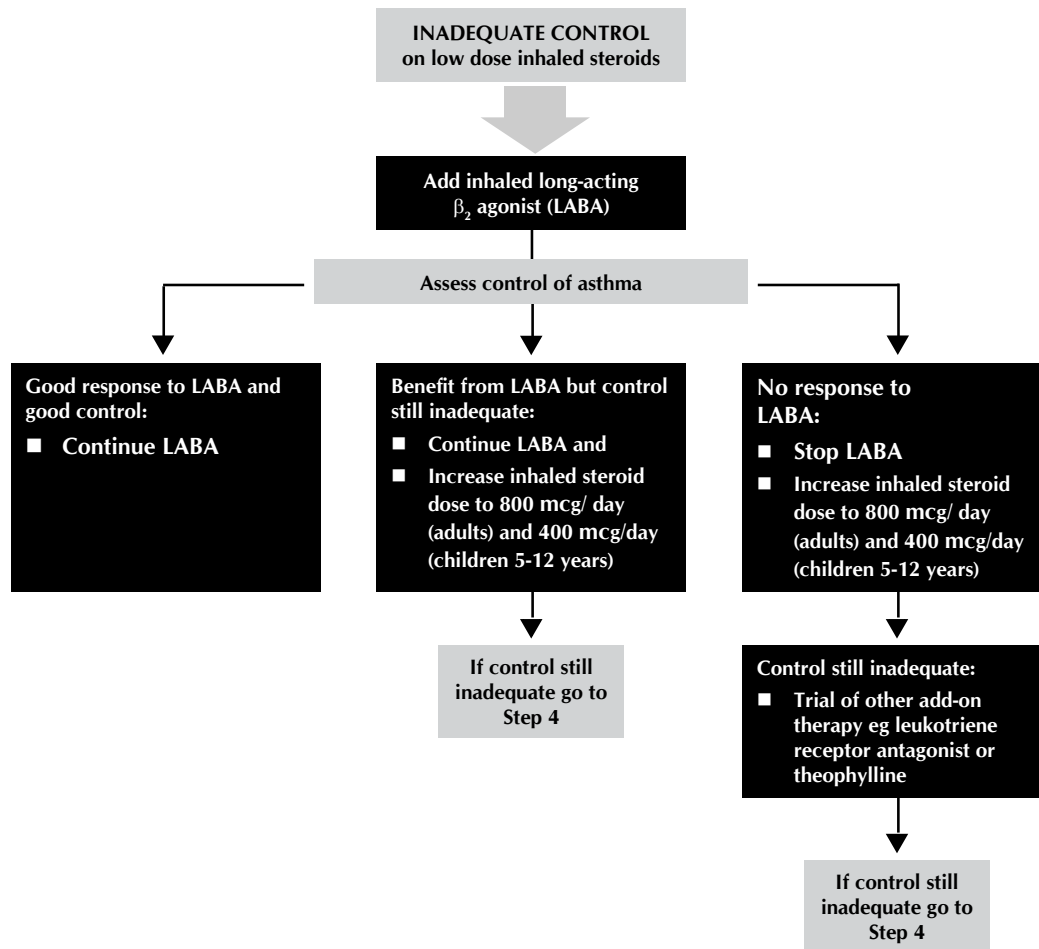
>12 years	5-12 years	<5 years
1 ⁺		

In patients on inhaled steroids whose asthma is stable, no intervention has been consistently shown to decrease inhaled steroid requirement in a clinically significant manner compared to placebo.

The Medicines and Healthcare products Regulatory Agency (MHRA) has completed a full review of the balance of risks and benefits associated with long-acting β_2 agonists in the management of asthma and chronic obstructive pulmonary disease.³²² They have concluded that long-acting β_2 agonists can continue to be used in the management of asthma provided they are used with inhaled corticosteroids. This issue has been reviewed by the guideline development group, which came to the same conclusion.

Long-acting inhaled β_2 agonists should only be started in patients who are already on inhaled corticosteroids.

Figure 3: Summary of step 3: Add-on therapy



4.3.3 COMBINATION INHALERS

There is no difference in efficacy in giving inhaled steroid and long-acting β_2 agonist in combination or in separate inhalers.³¹⁸

>12 years	5-12 years	<5 years
1++	1++	

Once a patient is on stable therapy, combination inhalers have the advantage of guaranteeing that the long-acting β_2 agonist is not taken without inhaled steroid.

In adult patients at step 3 who are poorly controlled, the use of budesonide/formoterol in a single inhaler as rescue medication instead of a short-acting β_2 agonist, in addition to its regular use as a controller treatment, has been shown to be an effective treatment option.³²³⁻³²⁷ This management technique has not been investigated with other combination inhalers. Before instituting this management careful patient education is required.

4.4 STEP 4: POOR CONTROL ON MODERATE DOSE OF INHALED STEROID + ADD-ON THERAPY: ADDITION OF FOURTH DRUG

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting β_2 agonist as required, inhaled steroid (800 mcg daily), and an additional drug, usually a long-acting β_2 agonist. There are very few clinical trials in this specific patient group to guide management. The following recommendations are largely based on extrapolation from trials of add-on therapy to inhaled steroids alone.

D	D		<p>If control remains inadequate on 800 mcg daily (adults) and 400 mcg daily (children) of an inhaled steroid plus a long-acting β_2 agonist, consider the following interventions:</p> <ul style="list-style-type: none"> ▪ increasing inhaled steroids to 2000 mcg/day (adults) or 800 mcg/day (children 5-12 years) * ▪ leukotriene receptor antagonists ▪ theophyllines ▪ slow release β_2 agonist tablets, though caution needs to be used in patients already on long-acting β_2 agonists.
---	---	--	--

* at high doses of inhaled steroid via MDI, a spacer should be used.

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and β_2 agonist tablets.

- If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled steroid, reduce to the original dose).
- Before proceeding to step 5, consider referring patients with inadequately controlled asthma, especially children, to specialist care.

4.5 STEP 5: CONTINUOUS OR FREQUENT USE OF ORAL STEROIDS

- For the small number of patients not controlled at step 4, use daily steroid tablets in the lowest dose providing adequate control.

4.5.1 PREVENTION AND TREATMENT OF STEROID TABLET-INDUCED SIDE EFFECTS

Patients on long term steroid tablets (eg longer than three months) or requiring frequent courses of steroid tablets (eg three to four per year) will be at risk of systemic side effects.⁵⁹

- blood pressure should be monitored
- diabetes mellitus and hyperlipidaemia may occur
- bone mineral density should be monitored. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered (see British Osteoporosis Society guidelines, www.nos.org.uk)³²⁸
- growth should be monitored in children
- cataracts may be screened for in children through community optometric services.

4.5.2 STEROID TABLET-SPARING MEDICATION

The aim of treatment is to control the asthma using the lowest possible dose or, if possible, to stop long term steroid tablets completely.

Inhaled steroids are the most effective drug for decreasing requirement for long term steroid tablets.^{280,281}

>12 years	5-12 years	<5 years
1 ⁺⁺	4	

There is limited evidence for the ability of long-acting β_2 agonists, theophyllines, or leukotriene receptor antagonists to decrease requirement for steroid tablets, but they may improve symptoms and pulmonary function.³²⁹

A **D** **█** **In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2,000 mcg/day, if required.**

D **D** **D** **In children aged 5-12, consider very carefully before going above an inhaled steroid dose of 800 mcg/day.**

D **D** **D** **There is a role for a trial of treatment with long-acting β_2 agonists, leukotriene receptor antagonists, and theophyllines for about six weeks. They should be stopped if no improvement in steroid dose, symptoms or lung function is detected.**

Immunosuppressants (methotrexate, ciclosporin and oral gold) decrease long term steroid tablet requirements, but all have significant side effects. There is no evidence of persisting beneficial effect after stopping them; and there is marked variability in response.³³⁰

>12 years	5-12 years	<5 years
1 ⁺⁺	3	

Immunosuppressants (*methotrexate, ciclosporin and oral gold*) may be given as a three month trial, once other drug treatments have proved unsuccessful. Their risks and benefits should be discussed with the patient and their treatment effects carefully monitored. Treatment should be in a centre with experience of using these medicines.

Colchicine and intravenous immunoglobulin have not been shown to have any beneficial effect in adults.³³⁰

>12 years	5-12 years	<5 years
1 ⁺⁺		

Continuous subcutaneous terbutaline infusion has been reported to be beneficial in severe asthma but efficacy and safety have not been assessed in RCTs.^{331,332}

4

Anti-TNF alpha therapy has been investigated in severe asthma^{333,334} but these studies are too small and too short term to allow recommendation of anti-TNF therapy outside the context of a controlled clinical trial.

4.5.3 STEROID FORMULATIONS

Prednisolone is the most widely used steroid tablet for maintenance therapy in chronic asthma. There is no evidence that other formulations offer any advantage.

4.5.4 FREQUENCY OF DOSING OF STEROID TABLETS

Although popular in paediatric practice, there are no studies to show whether alternate day steroids produce fewer side effects than daily steroids.

Figure 4: Summary of stepwise management in adults

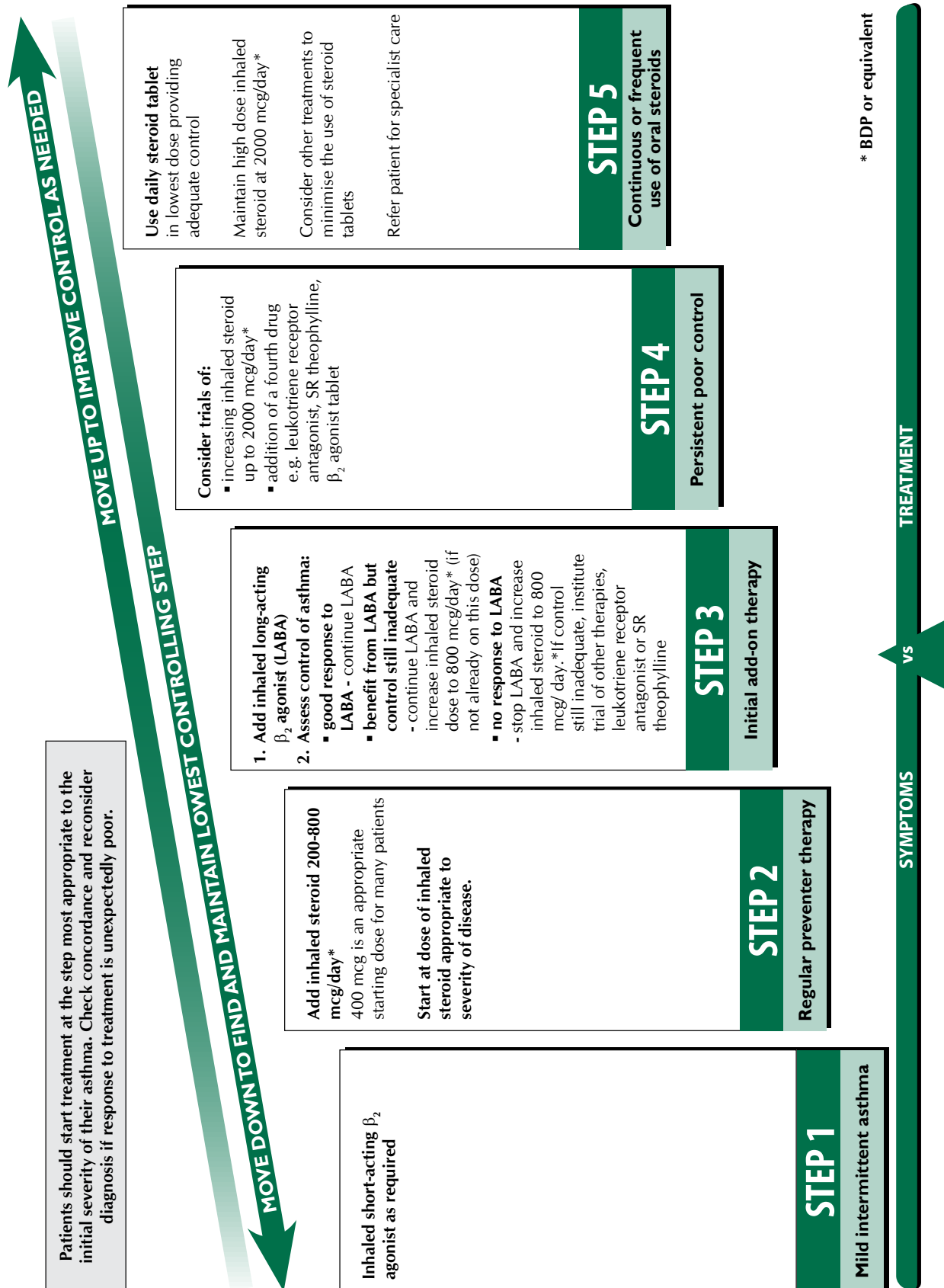


Figure 5: Summary of stepwise management in children aged 5-12 years

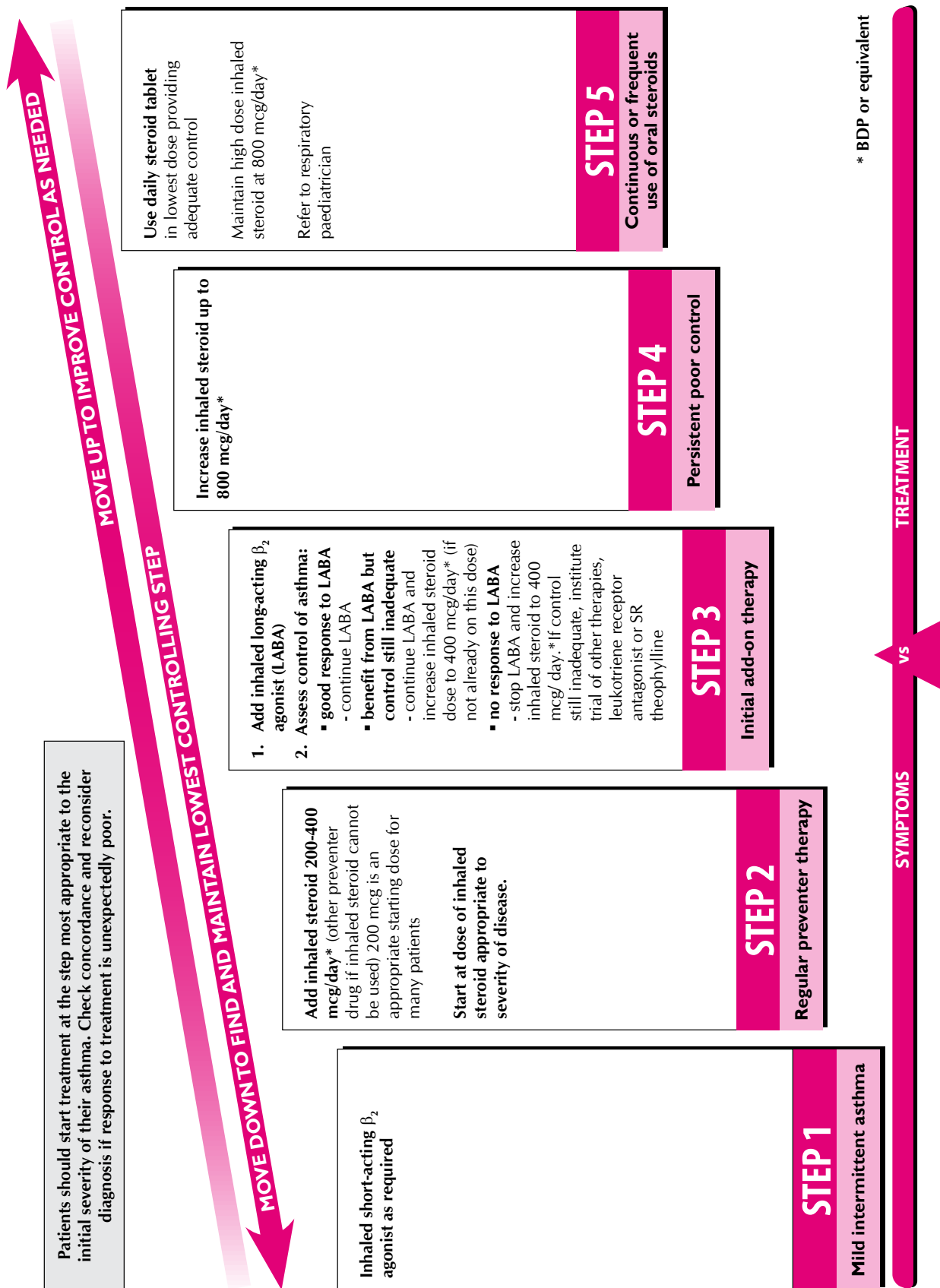
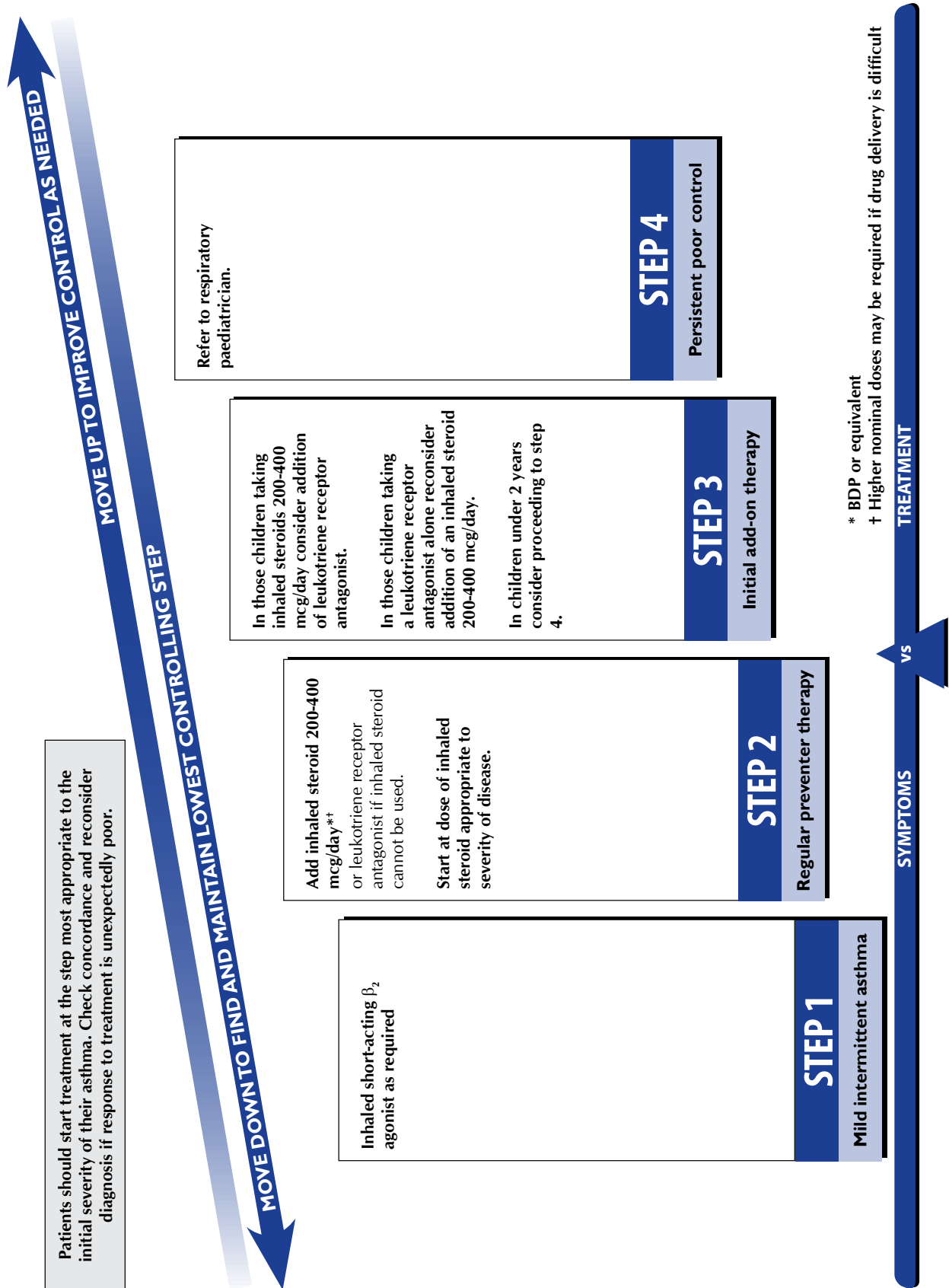


Figure 6: Summary of stepwise management in children less than 5 years



4.6 STEPPING DOWN

Stepping down therapy once asthma is controlled is recommended, but often not implemented leaving some patients over-treated. There are few studies that have investigated the most appropriate way to step down treatment. A study in adults on at least 900 mcg per day of inhaled steroids has shown that for patients who are stable it is reasonable to attempt to halve the dose of inhaled steroids every three months.³³⁴

- ☑ Regular review of patients as treatment is stepped down is important. When deciding which drug to step down first and at what rate, the severity of asthma, the side effects of the treatment, time on current dose, the beneficial effect achieved, and the patient's preference should all be taken into account.
- ☑ Patients should be maintained at the lowest possible dose of inhaled steroid. Reduction in inhaled steroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25-50% each time.

4.7 SPECIFIC MANAGEMENT ISSUES

4.7.1 EXACERBATIONS OF ASTHMA

Although recommended for both adults and children in previous guidelines and as part of asthma action plans, doubling the dose at the time of an exacerbation is of unproven value.³³⁵ In adult patients on a low dose (200 mcg) of inhaled steroids, a fivefold increase in dose at the time of exacerbation leads to a decrease in the severity of exacerbations.^{335,336} This study should not be extrapolated to patients already taking higher doses of inhaled steroids and further evidence in this area is required.

4.7.2 EXERCISE INDUCED ASTHMA

When given chronically the following medicines give protection against exercise induced asthma:

- inhaled steroids^{280, 281,337}
- short-acting β_2 agonists²⁷³
- long-acting β_2 agonists³³⁸
- theophyllines^{329,339}
- leukotriene receptor antagonists³⁴⁰
- chromones³⁴¹
- β_2 agonist tablets.³⁴²

The following medicines do not give protection against exercise induced asthma at normal doses:

- anticholinergics³⁴³
- ketotifen³⁴⁴
- antihistamine.³⁴⁵

Long-acting β_2 agonists and leukotriene antagonists provide more prolonged protection than short-acting β_2 agonists, but a degree of tolerance develops with LABA particularly with respect to duration of action. No tolerance has been demonstrated with leukotriene receptor antagonists.^{338,340}

>12 years	5-12 years	<5 years
1++	1++	
1++	1++	
1++	1++	
1+	2+	
1++	2+	
1++	1+	
1+	1+	
1+	1+	
1++	1++	
>12 years	5-12 years	<5 years
1++		

- ☑ For most patients, exercise induced asthma is an expression of poorly controlled asthma and regular treatment including inhaled steroids should be reviewed.

If exercise is a specific problem in patients taking inhaled steroids who are otherwise well controlled, consider the following therapies:

A	C	■	▪ leukotriene receptor antagonists
A	A	■	▪ long-acting β_2 agonists
C	C	■	▪ chromones
A	A	■	▪ oral β_2 agonists
C	C	■	▪ theophyllines

Immediately prior to exercise, inhaled short-acting β_2 agonists are the drug of choice.²⁷³

>12 years 1 ⁺⁺	5-12 years	<5 years
---------------------------------	---------------	-------------

A A ■ Immediately prior to exercise, inhaled short-acting β_2 agonists are the drug of choice.

4.7.3 RHINITIS

Patients with asthma often have rhinitis. The most effective therapy is intranasal steroids.³⁴⁶ Treatment of allergic rhinitis with intranasal steroids has not been shown in double blind placebo-controlled trials to improve asthma control.

>12 years 1 ⁺	5-12 years	<5 years
--------------------------------	---------------	-------------

4.7.4 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

In adult patients with allergic bronchopulmonary aspergillosis (ABPA), itraconazole may decrease steroid tablet dose and improve asthma control.^{347,348}

1 ⁺		
2 ⁺		

C ■ ■ In adult patients with ABPA, a four month trial of itraconazole should be considered.

Careful monitoring for side effects, particularly hepatic, is recommended.

4.7.5 ASPIRIN-INTOLERANT ASTHMA

There are theoretical reasons to suggest that leukotriene receptor antagonists might be of particular value in the treatment of aspirin-intolerant asthma. However, there is little evidence to justify managing patients with aspirin-intolerant asthma in a different manner to other patients with asthma, apart from the rigorous avoidance of non-steroidal anti-inflammatory medications.³⁴⁹

4.7.6 GASTRO-OESOPHOGEAL REFLUX

A Cochrane review of twelve double blind controlled trials found that treatment of gastro-oesophageal reflux had no benefit on asthma symptoms or lung function when both conditions were present. Reduction in dry cough was observed although this was probably not due to improved asthma control.^{350,351}

4.7.7 β -BLOCKERS

β -blockers, including eye drops, are contraindicated in patients with asthma.

4.7.8 ANTI IgE MONOCLONAL ANTIBODY

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE, markedly reducing levels of free serum IgE.^{350,351} In adults and children over 12, it is licensed in the UK with the following indication; patients on high-dose inhaled steroids and long-acting β_2 agonists who have impaired lung function are symptomatic with frequent exacerbations, and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every two to four weeks depending on dose. The total IgE must be less than 700 iu/litre for it to be effective.

In the single study in the licensed group, there was a 19% reduction in exacerbations of asthma requiring oral steroids which was non-significant. When corrected for imbalance in the exacerbation history at baseline, there was a 26% reduction in severe exacerbations (0.91 on placebo vs 0.68 on omalizumab over a 28 week period, $p=0.042$). This was associated with a 2.8% increase in FEV₁, a non-significant 0.5 puffs/day decrease in β_2 agonist use and 13% more patients having a significant improvement in health related quality of life. At IgE levels below 76 iu/l the beneficial effect is reduced.

Local skin reactions may occur. Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as the first dose, but has also occurred after one year. Due to risk of anaphylaxis, omalizumab should only be administered to patients in a healthcare setting under direct medical supervision.

- Omalizumab treatment should only be initiated in specialist centres with experience of evaluation and management of patients with severe and difficult asthma.

5 Inhaler devices

Although studies of inhaler devices are more suitable for an evidence based approach than many other aspects of asthma management, a number of methodological issues complicate evidence review in this area. In young (0-5 years) children, little or no evidence is available on which to base recommendations.

5.1 TECHNIQUE AND TRAINING

Studies of technique and the effects of training have used arbitrary non-standardised scores making comparison difficult. Although technique will have some bearing, it does not necessarily relate to clinical effectiveness.

The proportion of patients making no mistakes with an inhaler in one well conducted study was 23-43% for pMDI, 53-59% for dry powder inhaler (DPI) and 55-57% for pMDI + spacer. When technique was assessed as number of steps correct out of the total number of steps, pMDI + spacer was slightly better than DPI.³⁵²

Teaching technique improved the correct usage score from a mean of 60% to 79%. Figures for no mistakes post-teaching were 63% for pMDI, 65% for DPI, and 75% for breath-actuated MDI (the latter figure based on one study of 2,467 patients).³⁵²

>12 years 1 ⁺⁺	5-12 years	<5 years
---------------------------------	---------------	-------------

B **Prescribe inhalers only after patients have received training in the use of the device and have demonstrated satisfactory technique.**

5.2 β_2 AGONIST DELIVERY

5.2.1 ACUTE ASTHMA

pMDI + spacer is at least as good as a nebuliser at treating mild and moderate exacerbations of asthma in children and adults.³⁵³⁻³⁵⁶

>12 years 1 ⁺⁺	5-12 years 1 ⁺⁺	<5 years
---------------------------------	----------------------------------	-------------

A **A** **B** **Children and adults with mild and moderate exacerbations of asthma should be treated by pMDI + spacer with doses titrated according to clinical response.**

There are no data to make recommendations in severe (life threatening) asthma.

5.2.2 STABLE ASTHMA

For children aged 0-5, there is no evidence comparing nebuliser and other inhalers and the data are insufficiently extensive or robust to draw conclusions for pMDI vs. DPI.

In children aged 5-12 there is no significant difference between pMDI and DPI. In adults there is no significant difference between pMDI + spacer and DPI. The lower pulse rate with pMDI v Turbohaler is the only difference with regard to side effects. Patients have been shown to prefer Turbohaler to pMDI.^{352,357,358}

>12 years 1 ⁺⁺	5-12 years 1 ⁺⁺	<5 years
---------------------------------	----------------------------------	-------------

A **In children aged 5-12, pMDI + spacer is as effective as any other hand held inhaler.**

A **In adults, pMDI ± spacer is as effective as any other hand held inhaler, but patients may prefer some types of DPI.**

There are no data to make recommendations in children under five.

Choice of reliever inhaler for stable asthma should be based on patient preference and assessment of correct use. Many patients will not be prepared to carry a spacer.

5.3 INHALED STEROIDS FOR STABLE ASTHMA

There are no comparative data on inhaled steroids for stable asthma in children under five years. A single study included 4-5 year olds, but the data were not extractable.

For the delivery of inhaled steroids in stable asthma in children aged 5-12 years, pMDI is as effective as Clickhaler,^{359,360} and Pulvinal is as effective as Diskhaler.³⁶¹ No significant clinical difference was found between pMDI and Turbohaler at half the dose for the same drug (budesonide).^{352,362} This comparison cannot necessarily be made against other inhaled steroid /device combinations.

In adults, there is no clinical difference in effectiveness of pMDI ± spacer v DPI. Breath-actuated MDI is as effective as pMDI. More recent DPIs are as effective as older DPIs.³⁰⁵ Nebulisers have not been shown to be superior to pMDI + spacer for delivery of inhaled steroids in chronic asthma. A specialised specific nebuliser may provide improved lung function and reduced rescue therapy use, but at high prescribed doses. Higher doses (> 2 mg) are generally only licensed for use from a nebuliser.^{352,362}

>12 years	5-12 years	<5 years
1 ⁺⁺	1 ⁺⁺	



In children aged 5-12 years, pMDI + spacer is as effective as any DPI.



In adults, a pMDI ± spacer is as effective as any DPI.

No recommendation can be given for nebulised therapy in children aged 5-12 years and there is no evidence relating to children aged < 5 years.

5.4 CFC PROPELLANT PMDI VS HFA PROPELLANT PMDI

HFA pMDI salbutamol is as effective as CFC pMDI salbutamol at standard therapeutic doses.^{359,363-368}

>12 years	5-12 years	<5 years
1 ⁺⁺		

It is important to differentiate Qvar from other HFA beclametasone products. Many studies now show Qvar equivalence at half the dose of CFC BDP pMDI, whereas non-Qvar HFA BDP pMDI studies show equivalence at 1:1 dosing.^{360,369-375}

HFA fluticasone is as effective as CFC fluticasone across the standard clinical dose range.³⁷⁶⁻³⁸⁰

>12 years	5-12 years	<5 years
1 ⁺⁺		



Salbutamol HFA can be substituted for salbutamol CFC at 1:1 dosing.



HFA BDP pMDI (Qvar) may be substituted for CFC BDP pMDI at 1:2 dosing. This ratio does not apply to reformulated HFA BDP pMDIs.



Fluticasone HFA can be substituted for fluticasone CFC at 1:1 dosing.

5.5 PRESCRIBING DEVICES

There is no evidence to dictate an order in which devices should be tested for those patients who cannot use pMDI. In the absence of evidence, the most important points to consider are patient preference and local cost.

- The choice of device may be determined by the choice of drug.
 - If the patient is unable to use a device satisfactorily an alternative should be found.
 - The patient should have their ability to use an inhaler device assessed by a competent healthcare professional (see *section 5.1*).
 - The medication needs to be titrated against clinical response to ensure optimum efficacy.
 - Reassess inhaler technique as part of structured clinical review (see *section 8.1.2*).
- In children aged 0-5 years, pMDI and spacer are the preferred method of delivery of β_2 agonists or inhaled steroids. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. Where this is ineffective a nebuliser may be required.

5.6 USE AND CARE OF SPACERS

- The spacer should be compatible with the pMDI being used.
 - The drug should be administered by repeated single actuations of the metered dose inhaler into the spacer, each followed by inhalation.
 - There should be minimal delay between pMDI actuation and inhalation.
 - Tidal breathing is as effective as single breaths.
 - Spacers should be cleaned monthly rather than weekly as per manufacturer's recommendations or performance is adversely affected. They should be washed in detergent and allowed to dry in air. The mouthpiece should be wiped clean of detergent before use.
 - Drug delivery may vary significantly due to static charge. Metal and other antistatic spacers are not affected in this way.
 - Plastic spacers should be replaced at least every 12 months but some may need changing at six months.

6 Management of acute asthma

6.1 LESSONS FROM STUDIES OF ASTHMA DEATHS AND NEAR-FATAL ASTHMA

Confidential enquires into over 200 asthma deaths in the UK conclude there are factors associated with the disease, the medical management and the patient's behaviour or psychosocial status which contribute to death. Most deaths occurred before admission to hospital.³⁸¹⁻³⁸⁵

6.1.1 DISEASE FACTORS

Most patients who died of asthma had chronically severe asthma. In a minority the fatal attack occurred suddenly in a patient with mild or moderately severe background disease.³⁸¹⁻³⁸⁶ | 2++

6.1.2 MEDICAL MANAGEMENT

Many of the deaths occurred in patients who had received inadequate treatment with inhaled steroid or steroid tablets and/or inadequate objective monitoring of their asthma. Follow up was inadequate in some and others should have been referred earlier for specialist advice. There was widespread under-use of written management plans. Heavy or increasing use of β_2 agonist therapy was associated with asthma death.^{381-385,387,388} | 2++

Deaths have continued to be reported following inappropriate prescription of β -blocker therapy or heavy sedation (see section 4.7.7).

A small proportion of patients with asthma were sensitive to non-steroidal anti-inflammatory agents; all asthma patients should be asked about past reactions to these agents.

6.1.3 ADVERSE PSYCHOSOCIAL AND BEHAVIOURAL FACTORS

Behavioural and adverse psychosocial factors were recorded in the majority of patients who died of asthma.³⁸¹⁻³⁸⁵ The most important are shown in Table 9.

Table 9: Patients at risk of developing near-fatal or fatal asthma

A COMBINATION OF SEVERE ASTHMA recognised by one or more of:
<ul style="list-style-type: none"> ▪ previous near-fatal asthma, eg previous ventilation or respiratory acidosis ▪ previous admission for asthma especially if in the last year ▪ requiring three or more classes of asthma medication ▪ heavy use of β_2 agonist ▪ repeated attendances at ED for asthma care especially if in the last year ▪ “brittle” asthma.
AND ADVERSE BEHAVIOURAL OR PSYCHOSOCIAL FEATURES recognised by one or more of:
<ul style="list-style-type: none"> ▪ non-compliance with treatment or monitoring ▪ failure to attend appointments ▪ self discharge from hospital ▪ psychosis, depression, other psychiatric illness or deliberate self harm ▪ current or recent major tranquilliser use ▪ denial ▪ alcohol or drug abuse ▪ obesity ▪ learning difficulties ▪ employment problems ▪ income problems ▪ social isolation ▪ childhood abuse ▪ severe domestic, marital or legal stress.

Case control studies support most of these observations.^{389,390} Compared with control patients admitted to hospital with asthma, those who died were significantly more likely to have learning difficulties; psychosis or prescribed antipsychotic drugs; financial or employment problems; repeatedly failed to attend appointments or discharged themselves from hospital; drug or alcohol abuse; obesity; or a previous near-fatal attack.

2⁺⁺

Compared with control patients with asthma in the community, patients who died had more severe disease; more likelihood of a hospital admission or visit to the ED for their asthma in the previous year; more likelihood of a previous near-fatal attack; poor medical management; failure to measure pulmonary function; and non-compliance.

B Healthcare professionals must be aware that patients with severe asthma and one or more adverse psychosocial factors are at risk of death.

Studies comparing near-fatal asthma with deaths from asthma have concluded that patients with near-fatal asthma have identical adverse factors to those described in table 9, and that these contribute to the near-fatal asthma attack.³⁹¹⁻³⁹³ Compared with patients who die, those with near-fatal asthma are significantly younger, are significantly more likely to have had a previous near-fatal asthma attack, are less likely to have concurrent medical conditions, are less likely to experience delay in receiving medical care, and more likely to have ready access to acute medical care.

2⁺

With near-fatal asthma it is advisable to involve a close relative when discussing future management.

Patients with brittle or difficult asthma should also be identified (see sections 6.2.3 and 7.1.1 and Table 10).

- Keep patients who have had near-fatal asthma or brittle asthma under specialist supervision indefinitely.

6.1.4 SEASONAL FACTORS

In the UK there is a peak of asthma deaths in young people (aged up to 44 years) in July and August and in December and January in older people.^{391,394} | 2⁺⁺

6.1.5 PREDICTION AND PREVENTION OF A SEVERE ASTHMA ATTACK

Most attacks of asthma severe enough to require hospital admission develop relatively slowly over a period of six hours or more. In one study, over 80% developed over more than 48 hours.³⁹⁵⁻⁴⁰⁰ There is therefore time for effective action to reduce the number of attacks requiring hospitalisation. There are many similarities between patients who die from asthma, patients with near-fatal asthma and control patients with asthma who are admitted to hospital. | 2⁺⁺

- A respiratory specialist should follow up patients admitted with severe asthma for at least one year after the admission.

6.2 ACUTE ASTHMA IN ADULTS

Annexes 2-4 contain algorithms summarising the recommended treatment for patients presenting with acute or uncontrolled asthma in primary care (*Annex 2*), ED (*Annex 3*), and hospital (*Annex 4*).

6.2.1 RECOGNITION OF ACUTE ASTHMA

Definitions of increasing levels of severity of acute asthma exacerbations are provided in table 10.^{322,401-405} Predicted PEF values⁴⁰⁶ should be used only if the recent best PEF (within two years) is unknown. | 2⁺
4

6.2.2 SELF TREATMENT BY PATIENTS DEVELOPING ACUTE OR UNCONTROLLED ASTHMA

Many patients with asthma, and all patients with severe asthma, should have an agreed written action plan and their own peak flow meter, with regular checks of inhaler technique and compliance. They should know when and how to increase their medication and when to seek medical assistance. Asthma action plans can decrease hospitalisation for⁴⁰⁷ and deaths from⁴⁰⁸ asthma (see section 9.1).

6.2.3 INITIAL ASSESSMENT

All possible initial contact personnel, eg practice receptionists, ambulance call takers, NHS Direct (England and Wales), NHS 24 (Scotland), should be aware that asthma patients complaining of respiratory symptoms may be at risk and should have immediate access to a doctor or trained asthma nurse. The assessments required to determine whether the patient is suffering from an acute attack of asthma, the severity of the attack and the nature of treatment required are detailed in tables 10 and 11. It may be helpful to use a systematic recording process. Proformas have proved useful in the ED setting.⁴⁰⁹

Table 10: Levels of severity of acute asthma exacerbations

Near-fatal asthma	Raised PaCO ₂ and/or requiring mechanical ventilation with raised inflation pressures ³⁹¹⁻³⁹³	
Life threatening asthma	Any one of the following in a patient with severe asthma:	
	- PEF < 33% best or predicted	- bradycardia
	- SpO ₂ < 92%	- arrhythmia
	- PaO ₂ < 8kPa	- hypotension
	- normal PaCO ₂ (4.6 – 6.0 kPa)	- exhaustion
	- silent chest	- confusion
	- cyanosis	- coma
	- feeble respiratory effort	
Acute severe asthma	Any one of: - PEF 33-50% best or predicted - respiratory rate ≥ 25/min - heart rate ≥ 110/min - inability to complete sentences in one breath	
Moderate asthma exacerbation	- Increasing symptoms - PEF > 50-75% best or predicted - no features of acute severe asthma	
Brittle asthma	- Type 1: wide PEF variability (> 40% diurnal variation for > 50% of the time over a period > 150 days) despite intense therapy - Type 2: sudden severe attacks on a background of apparently well controlled asthma	

6.2.4 PREVENTION OF ACUTE DETERIORATION

A register of patients at risk may help primary care health professionals to identify patients who are more likely to die from their asthma. A system should be in place to ensure that these patients are contacted if they fail to attend for follow up.

6.2.5 CRITERIA FOR REFERRAL

D Refer to hospital any patients with features of acute severe or life threatening asthma.

Other factors, such as failure to respond to treatment, social circumstances or concomitant disease, may warrant hospital referral.

Table 11: Initial assessment - the role of symptoms, signs and measurements

Clinical features	<p>Clinical features, symptoms and respiratory and cardiovascular signs can identify some patients with severe asthma, eg severe breathlessness (including too breathless to complete sentences in one breath), tachypnea, tachycardia, silent chest, cyanosis or collapse.^{322, 401-405}</p> <p><i>None of these singly or together is specific and their absence does not exclude a severe attack.</i></p>	2+
PEF or FEV₁	<p>Measurements of airway calibre improve recognition of the degree of severity, the appropriateness or intensity of therapy, and decisions about management in hospital or at home.^{410, 411}</p> <p>PEF or FEV₁ are both useful and valid measures of airway calibre. PEF is more convenient and cheaper.</p> <p>PEF expressed as a percentage of the patient's previous best value is most useful clinically. PEF as a percentage of predicted gives a rough guide in the absence of a known previous best value. Different peak flow meters give different readings. Where possible the same or similar type of peak flow meter should be used. The Nunn and Gregg nomogram is recommended for use with peak flow meter, or the European Coal and Steel published normal values for use with FEV₁.⁴¹²</p>	2+
Pulse oximetry	<p>Measure oxygen saturation (SpO₂) with a pulse oximeter to determine the adequacy of oxygen therapy and the need for arterial blood gas (ABG) measurement. The aim of oxygen therapy is to maintain SpO₂ ≥92%.</p>	2+
Blood gases (ABG)	<p>Patients with SpO₂ <92% or other features of life threatening asthma require ABG measurement.^{322, 401-403, 405 413}</p>	2+
Chest X-ray	<p>Chest X-ray is not routinely recommended in patients in the absence of:</p> <ul style="list-style-type: none"> – suspected pneumomediastinum or pneumothorax – suspected consolidation – life threatening asthma – failure to respond to treatment satisfactorily – requirement for ventilation. 	4
Systolic paradox	<p>Systolic paradox (<i>pulsus paradoxus</i>) is an inadequate indicator of the severity of an attack and should not be used.^{322, 401-405, 414}</p>	2+

6.2.6 CRITERIA FOR ADMISSION

- B** Admit patients with any feature of a life threatening or near-fatal attack.^{381-385, 391, 393}
- B** Admit patients with any feature of a severe attack persisting after initial treatment.^{381-385, 391, 393}
- C** Patients whose peak flow is greater than 75% best or predicted one hour after initial treatment may be discharged from ED unless they meet any of the following criteria, when admission may be appropriate:
- still have significant symptoms
 - concerns about compliance
 - living alone/socially isolated
 - psychological problems
 - physical disability or learning difficulties
 - previous near-fatal or brittle asthma
 - exacerbation despite adequate dose steroid tablets pre-presentation
 - presentation at night
 - pregnancy.

Criteria for admission in adults are summarised in annexes 2 and 3.

6.3 TREATMENT OF ACUTE ASTHMA IN ADULTS

6.3.1 OXYGEN

Patients with acute severe asthma are hypoxaemic.⁴¹⁵⁻⁴¹⁸ This should be corrected urgently using high concentrations of inspired oxygen (usually 40-60%) and a high flow mask such as a Hudson mask. Unlike patients with COPD there is little danger of precipitating hypercapnea with high flow oxygen. Hypercapnea indicates the development of near-fatal asthma and the need for emergency specialist/anaesthetic intervention. Oxygen saturations of at least 92% should be aimed for.

2+

- C** Give high flow oxygen to all patients with acute severe asthma.

Oxygen-driven nebulisers are preferred to nebulise β_2 agonist bronchodilators in hospitals, ambulances and primary care because of the theoretical risk of oxygen desaturation while using air driven compressors.^{322,353,419} (NB: To generate the flow rate of 6 l/min required to drive most nebulisers, a high flow regulator must be fitted to the oxygen cylinder). The absence of supplemental oxygen should not prevent nebulised therapy from being administered when appropriate.⁴²⁰

1++
4

- A**
- In hospital, ambulance and primary care, nebulised β_2 agonist bronchodilators should be driven by oxygen.
 - Outside hospital, high dose β_2 agonist bronchodilators may be delivered via large volume spacers or nebulisers.
- C** The absence of supplemental oxygen should not prevent nebulised therapy being given if indicated.

6.3.2 β_2 AGONIST BRONCHODILATORS

In most cases inhaled β_2 agonists given in high doses act quickly to relieve bronchospasm with few side effects.⁴²¹⁻⁴²³ There is no evidence for any difference in efficacy between salbutamol and terbutaline. | 1+

In acute asthma without life threatening features, β_2 agonists can be administered by repeated activations of a pMDI via an appropriate large volume spacer or by wet nebulisation driven by oxygen, if available.³⁵³ Inhaled β_2 agonists are as efficacious and preferable to intravenous β_2 agonists (meta-analysis has excluded subcutaneous trials) in adult acute asthma in the majority of cases.⁴²⁴ | 1++

A Use high-dose inhaled β_2 agonists as first line agents in acute asthma and administer as early as possible. Reserve intravenous β_2 agonists for those patients in whom inhaled therapy cannot be used reliably.

In acute asthma with life threatening features the nebulised route (oxygen-driven) is recommended.

Parenteral β_2 agonists, in addition to inhaled β_2 agonists, may have a role in ventilated patients or those in extremis; however there is limited evidence to support this.

Continuous nebulisation of β_2 agonists is as efficacious as bolus nebulisation in relieving acute asthma.⁴²⁵⁻⁴²⁷ Most cases of acute asthma will respond adequately to bolus nebulisation of β_2 agonists. | 1+

A In severe asthma (*PEF or FEV₁ < 50% best or predicted*) and asthma that is poorly responsive to an initial bolus dose of β_2 agonist, consider continuous nebulisation.

Repeat doses of β_2 agonists at 15-30 minute intervals or give continuous nebulisation of salbutamol at 5-10 mg/hour (requires appropriate nebuliser) if there is an inadequate response to initial treatment. Higher bolus doses, eg 10 mg of salbutamol, are unlikely to be more effective. | 4

6.3.3 STEROID THERAPY

Steroids reduce mortality, relapses, subsequent hospital admission and requirement for β_2 agonist therapy. The earlier they are given in the acute attack the better the outcome.^{428,429} | 1++

A Give steroids in adequate doses in all cases of acute asthma.

Steroid tablets are as effective as injected steroids, provided they can be swallowed and retained.⁴²⁸ Prednisolone 40-50 mg daily or parenteral hydrocortisone 400 mg daily (100 mg six-hourly) are as effective as higher doses.⁴³⁰ For convenience, steroid tablets may be given as 2 x 25 mg tablets daily rather than 8-12 x 5 mg tablets. | 1++

Continue prednisolone 40-50 mg daily for at least five days or until recovery.

Following recovery from the acute exacerbation steroids can be stopped abruptly. Doses do not need tapering provided the patient receives inhaled steroids^{431,432} (apart from patients on maintenance steroid treatment or rare instances where steroids are required for three or more weeks). | 1+

There is no evidence that inhaled steroids should be substituted for steroid tablets in treating patients with acute severe, or life threatening asthma. Further randomised controlled trials to determine the role of inhaled steroids in these patients are required.

Inhaled steroids do not provide benefit in addition to the initial treatment,⁴³³ but should be continued (or started as soon as possible) to start the chronic asthma management plan. | 1++

6.3.4 IPRATROPIUM BROMIDE

Combining nebulised ipratropium bromide with a nebulised β_2 agonist produces significantly greater bronchodilation than a β_2 agonist alone, leading to a faster recovery and shorter duration of admission. Anticholinergic treatment is not necessary and may not be beneficial in milder exacerbations of asthma or after stabilisation.⁴³⁴⁻⁴³⁶

1++

B Add nebulised ipratropium bromide (0.5 mg 4-6 hourly) to β_2 agonist treatment for patients with acute severe or life threatening asthma or those with a poor initial response to β_2 agonist therapy.

6.3.5 INTRAVENOUS MAGNESIUM SULPHATE

A single dose of IV magnesium sulphate is safe and effective in patients with acute severe asthma.⁴³⁷

1++

The safety and efficacy of repeated doses have not been assessed. Repeated doses could cause hypermagnesaemia with muscle weakness and respiratory failure.

B Consider giving a single dose of IV magnesium sulphate for patients with:

- acute severe asthma who have not had a good initial response to inhaled bronchodilator therapy.
- life threatening or near fatal asthma.

IV magnesium sulphate (1.2-2 g IV infusion over 20 minutes) should only be used following consultation with senior medical staff.

More studies are needed to determine the optimal frequency and dose of IV magnesium sulphate therapy.

6.3.6 INTRAVENOUS AMINOPHYLLINE

In acute asthma, IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroids. Side effects such as arrhythmias and vomiting are increased if IV aminophylline is used.⁴³⁸

1++

Use IV aminophylline only after consultation with senior medical staff.

Some patients with near-fatal asthma or life threatening asthma with a poor response to initial therapy may gain additional benefit from IV aminophylline (5 mg/kg loading dose over 20 minutes unless on maintenance oral therapy, then infusion of 0.5-0.7 mg/kg/hr). Such patients are probably rare and could not be identified in a meta-analysis of trials.⁴³⁸ If IV aminophylline is given to patients on oral aminophylline or theophylline, blood levels should be checked on admission. Levels should be checked daily for all patients on aminophylline infusions.

6.3.7 LEUKOTRIENE RECEPTOR ANTAGONISTS

There is insufficient evidence at present to make a recommendation about the use of leukotriene receptor antagonists in the management of acute asthma.

6.3.8 ANTIBIOTICS

When an infection precipitates an exacerbation of asthma it is likely to be viral. The role of bacterial infection has been overestimated.⁴³⁹

1++

B Routine prescription of antibiotics is not indicated for acute asthma.

6.3.9 HELIOX

The use of heliox (helium/oxygen mixture in a ratio of 80:20 or 70:30) in acute adult asthma cannot be recommended on the basis of present evidence.^{440,441}

1+

6.3.10 INTRAVENOUS FLUIDS

There are no controlled trials, observational or cohort studies of differing fluid regimes in acute asthma. Some patients with acute asthma require rehydration and correction of electrolyte imbalance. Hypokalaemia can be caused or exacerbated by β_2 agonist and/or steroid treatment and must be corrected.

6.3.11 REFERRAL TO INTENSIVE CARE

Indications for admission to intensive care or high-dependency units include patients requiring ventilatory support and those with severe acute or life threatening asthma who are failing to respond to therapy, as evidenced by:

- deteriorating PEF
- persisting or worsening hypoxia
- hypercapnea
- arterial blood gas analysis showing fall in pH or rising H^+ concentration
- exhaustion, feeble respiration
- drowsiness, confusion
- coma or respiratory arrest.^{322,401}

2+

Not all patients admitted to the Intensive Care Unit (ICU) need ventilation, but those with worsening hypoxia or hypercapnea, drowsiness or unconsciousness and those who have had a respiratory arrest require intermittent positive pressure ventilation. Intubation in such patients is very difficult and should ideally be performed by an anaesthetist or ICU consultant.

^{322,401}

C All patients transferred to intensive care units should be accompanied by a doctor suitably equipped and skilled to intubate if necessary.

6.3.12 NON-INVASIVE VENTILATION

Non-invasive ventilation (NIV) is well established in the management of ventilatory failure caused by extrapulmonary restrictive conditions and exacerbations of COPD. Hypercapneic respiratory failure developing during an acute asthmatic episode is an indication for urgent ICU admission. It is unlikely that NIV would replace intubation in these very unstable patients but it has been suggested that this treatment can be used safely and effectively.⁴⁴²

4

Future studies might usefully examine its role in the gradually tiring patient, but at present this treatment cannot be recommended outside randomised controlled trials.

6.4 FURTHER INVESTIGATION AND MONITORING

- ☑ ▪ Measure and record PEF 15-30 minutes after starting treatment, and thereafter according to the response. Measure and record PEF before and after nebulised or inhaled β_2 agonist bronchodilator (*at least four times daily*) throughout the hospital stay and until controlled after discharge.
- Record oxygen saturation by oximetry and maintain arterial $SaO_2 > 92\%$.
- Repeat measurements of blood gas tensions within two hours of starting treatment if:
 - the initial PaO_2 is < 8 kPa unless SaO_2 is $> 92\%$; or
 - the initial $PaCO_2$ is normal or raised; or
 - the patient's condition deteriorates.

- ☑ ▪ Measure them again if the patient's condition has not improved by 4-6 hours.
- Measure and record the heart rate.
- Measure serum potassium and blood glucose concentrations.
- Measure the serum theophylline concentration if aminophylline is continued for more than 24 hours (*aim at a concentration of 55-110 mcgmol/l*).

6.5 ASTHMA MANAGEMENT PROTOCOLS AND PROFORMAS

The use of structured proformas facilitates improvements in the process of care in emergency departments and hospital wards and improves patient outcomes. The use of this type of documentation can assist data collection aimed at determining quality of care and outcomes.^{409,443,445} | 2++

6.6 HOSPITAL DISCHARGE AND FOLLOW UP (see annex 4)

6.6.1 TIMING OF DISCHARGE

No single physiological parameter defines absolutely the timing of discharge from an admission with acute asthma. Patients should have clinical signs compatible with home management, be on reducing amounts of β_2 agonist (preferably no more than four hourly) and be on medical therapy they can continue safely at home.

Although diurnal variability of PEF is not always present during an exacerbation, evidence suggests that patients discharged with PEF < 75% best or predicted and with diurnal variability > 25% are at greater risk of early relapse and readmission.^{446,447} | 2+

6.6.2 PATIENT EDUCATION

Following discharge from hospital or emergency departments, a proportion of patients re-attend with more than 15% re-attending within two weeks. Some repeat attenders need emergency care, but many delay seeking help, and are under-treated and/or under-monitored.⁴⁴⁸ | 2+

Prior to discharge, trained staff should give asthma education. This should include education on inhaler technique and PEF record keeping, with a written PEF and symptom-based action plan being provided allowing the patient to adjust their therapy within recommendations. These measures have been shown to reduce morbidity after the exacerbation and reduce relapse rates.⁴⁴⁹ | 1++

There is some experience of a discrete population of patients who use emergency departments rather than primary care services for their asthma care.⁹⁰

For the above groups there is a role for a trained asthma liaison nurse based in, or associated with, the emergency department.

6.6.3 FOLLOW UP

A careful history should elicit the reasons for the exacerbation and explore possible actions the patient should take to prevent future emergency presentations.

Medication should be altered depending upon the assessment and the patient provided with an asthma action plan aimed at preventing relapse, optimising treatment and preventing delay in seeking assistance in the future.

Follow up should be arranged prior to discharge with the patient's general practitioner or asthma nurse within two working days; and with a hospital specialist asthma nurse or respiratory physician at about one month after admission.

- It is essential that the patient's primary care practice is informed within 24 hours of discharge from the emergency department or hospital following an asthma exacerbation. Ideally this communication should be directly with a named individual responsible for asthma care within the practice, by means of fax or email.

6.7 ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

6.7.1 INITIAL ASSESSMENT

Table 12 details criteria for assessment of severity of acute asthma attacks in children. See also annexes 5-7.

Table 12: Clinical features for assessment of severity

Acute severe	Life threatening
Can't complete sentences in one breath or too breathless to talk or feed	<ul style="list-style-type: none"> ▪ Silent chest ▪ Cyanosis ▪ Poor respiratory effort ▪ Hypotension ▪ Exhaustion ▪ Confusion ▪ Coma
Pulse > 120 in children aged > 5 years > 130 in children aged 2-5 years	
Respiration > 30 breaths/min aged > 5 years > 50 breaths/min aged 2-5 years	

Before children can receive appropriate treatment for acute asthma in any setting, it is essential to assess accurately the severity of their symptoms. The following clinical signs should be recorded:

- Pulse rate
(increasing tachycardia generally denotes worsening asthma; a fall in heart rate in life threatening asthma is a pre-terminal event)
- Respiratory rate and degree of breathlessness
(ie too breathless to complete sentences in one breath or to feed)
- Use of accessory muscles of respiration
(best noted by palpation of neck muscles)
- Amount of wheezing
(which might become biphasic or less apparent with increasing airways obstruction)
- Degree of agitation and conscious level
(always give calm reassurance).

Clinical signs correlate poorly with the severity of airways obstruction.⁴⁵⁰⁻⁴⁵³ Some children with acute severe asthma do not appear distressed. | 2⁺⁺

Objective measurements of PEF and SpO₂ are essential. Suitable equipment should be available for use by all health professionals assessing acute asthma in both primary and secondary care settings.

Low oxygen saturations after initial bronchodilator treatment selects a more severe group of patients.^{450,453} | 2⁺⁺

B Consider intensive inpatient treatment for children with SpO₂ < 92% on air after initial bronchodilator treatment.

- Decisions about admission should be made by trained physicians after repeated assessment of the response to further bronchodilator treatment.

A measurement of < 50% predicted PEF or FEV₁ with poor improvement after initial bronchodilator treatment is predictive of a more prolonged asthma attack.

- Attempt to measure PEF or FEV₁ in all children aged > 5 years, taking the best of three measurements, ideally expressed as percentage of personal best for PEF (as detailed in a written action plan) or alternatively as percentage of predicted for PEF or FEV₁.

Chest X-rays and ABG measurements rarely provide additional useful information and are not routinely indicated.^{454,455}

6.8 TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

Emergency units attending to children with acute asthma should have a registered sick children's nurse available on duty at all times and staff familiar with the specific needs of children. The use of proformas can increase the accuracy of severity assessment.

An assessment-driven algorithm has been shown to reduce treatment costs and hospital stay.⁴⁵⁶ | 2+

D The use of structured care protocols detailing bronchodilator usage, clinical assessment, and specific criteria for safe discharge is recommended.

6.8.1 OXYGEN

Children with life threatening asthma or SpO₂ < 92% should receive high flow oxygen via a tight fitting face mask or nasal cannula at sufficient flow rates to achieve normal saturations.

6.8.2 β₂ AGONIST BRONCHODILATORS

A Inhaled β₂ agonists are the first line treatment for acute asthma.⁴⁵⁷⁻⁴⁶⁰

pMDI + spacer is an effective alternative to nebulisers for bronchodilator inhalation to treat mild to moderate asthma.^{353,461} Children receiving β₂ agonists via pMDI + spacer are less likely to have tachycardia and hypoxia than when the same drug is given via a nebuliser.³⁵³ | 1+

A pMDI + spacer is the preferred option in mild to moderate asthma.

Information about implementing evidence based guidelines using such devices has been published.⁴⁶² Children aged < 3 years are likely to require a face mask connected to the mouthpiece of a spacer for successful drug delivery. Inhalers should be actuated into the spacer in individual puffs and inhaled immediately by tidal breathing.

Frequent doses of β₂ agonists are safe for the treatment of acute asthma,⁴⁵⁷⁻⁴⁵⁹ although children with mild symptoms benefit from lower doses.⁴⁶⁰ | 1+

B Individualise drug dosing according to severity and adjust according to the patient's response.

Two to four puffs repeated every 20-30 minutes according to clinical response might be sufficient for mild attacks although up to 10 puffs might be needed for more severe asthma.

Children with acute asthma in primary care who have not improved after receiving up to 10 puffs of β₂ agonist should be referred to hospital. Further doses of bronchodilator should be given as necessary whilst awaiting transfer.

Treat children transported to hospital by ambulance with oxygen and nebulised β₂ agonists during the journey.

Transfer children with severe or life threatening asthma urgently to hospital to receive frequent doses of nebulised β₂ agonists (2.5-5 mg salbutamol or 5-10 mg terbutaline).

Doses can be repeated every 20-30 minutes. Continuous nebulised β₂ agonists are of no greater benefit than the use of frequent intermittent doses in the same total hourly dosage.^{463,464}

6.8.3 IV SALBUTAMOL

The role of intravenous β_2 agonists in addition to nebulised treatment remains unclear.⁴²⁴ One study has shown that an IV bolus of salbutamol given in addition to near-maximal doses of nebulised salbutamol results in clinically significant benefits.⁴²⁴ | 1+

B The early addition of a bolus dose of intravenous salbutamol (15 mcg/kg) can be an effective adjunct to treatment in severe cases.

Continuous intravenous infusion should be considered when there is uncertainty about reliable inhalation or for severe refractory asthma. Doses above 1-2 mcg/kg/min (200 mcg/ml solution) should be given in a paediatric intensive care unit (PICU) setting (up to 5 mcg/kg/min) with regular monitoring of electrolytes.

6.8.4 STEROID THERAPY

Steroid tablets

The early use of steroids for acute asthma can reduce the need for hospital admission and prevent a relapse in symptoms after initial presentation.^{428,429} Benefits can be apparent within three to four hours. | 2+
1+

A Give prednisolone early in the treatment of acute asthma attacks.

A soluble preparation dissolved in a spoonful of water is preferable in those unable to swallow tablets. Use a dose of 20 mg for children 2-5 years old and 30-40 mg for children > 5 years.

Oral and intravenous steroids are of similar efficacy.^{430,465,466} Intravenous hydrocortisone (4 mg/kg repeated four hourly) should be reserved for severely affected children who are unable to retain oral medication. | 1+

Larger doses do not appear to offer a therapeutic advantage for the majority of children.⁴⁶⁷ There is no need to taper the dose of steroid tablets at the end of treatment. | 2+

- Use a dose of 20 mg prednisolone for children aged 2-5 years and a dose of 30-40 mg for children > 5 years. Those already receiving maintenance steroid tablets should receive 2 mg/kg prednisolone up to a maximum dose of 60 mg.
- Repeat the dose of prednisolone in children who vomit and consider intravenous steroids in those who are unable to retain orally ingested medication.
- Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery.

Inhaled steroids

There is insufficient evidence to support the use of inhaled steroids as alternative or additional treatment to steroid tablets for acute asthma.^{433,468-470}

- Do not initiate inhaled steroids in preference to steroid tablets to treat acute childhood asthma.

Children with chronic asthma not receiving regular preventative treatment will benefit from initiating inhaled steroids as part of their long term management. There is no evidence that increasing the dose of inhaled steroids is effective in treating acute symptoms, but it is good practice for children already receiving inhaled steroids to continue with their usual maintenance doses.

6.8.5 IPRATROPIUM BROMIDE

There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide used in addition to β_2 agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients.⁴⁷¹ | 1+

A If symptoms are refractory to initial β_2 agonist treatment, add ipratropium bromide (250 mcg/dose mixed with the nebulised β_2 agonist solution).

Frequent doses up to every 20-30 minutes (250 mcg/dose mixed with the β_2 agonist solution in the same nebuliser) should be used early. The dose frequency should be reduced as clinical improvement occurs.

Repeated doses of ipratropium bromide should be given early to treat children poorly responsive to β_2 agonists.

Children with continuing severe asthma despite frequent nebulised β_2 agonists and ipratropium bromide and those with life threatening features need urgent review by a specialist with a view to transfer to a high dependency unit (HDU) or PICU.

6.8.6 IV AMINOPHYLLINE

There is no evidence that aminophylline is of benefit for mild to moderate asthma and side effects are common and troublesome.^{438, 472} However, one well conducted study has shown evidence for benefit in severe acute asthma unresponsive to multiple doses of β_2 agonists and steroids.⁴⁷³ | 1+
2+

A Aminophylline is not recommended in children with mild to moderate acute asthma.

C Consider aminophylline in a HDU or PICU setting for children with severe or life threatening bronchospasm unresponsive to maximal doses of bronchodilators and steroid tablets.

A 5 mg/kg loading dose should be given over 20 minutes with ECG monitoring (omit in those receiving maintenance oral theophyllines) followed by a continuous infusion at 1 mg/kg/hour. Estimate serum theophylline levels in patients already receiving oral treatment and in those receiving prolonged treatment.

6.8.7 OTHER THERAPIES

There is no evidence to support the use of heliox or leukotriene receptor antagonists for the treatment of acute asthma in childhood.

There is insufficient evidence to support or refute the role of antibiotics in acute asthma,⁴⁷⁴ but the majority of acute asthma attacks are triggered by viral infection.

Do not give antibiotics routinely in the management of acute childhood asthma.

6.8.8 INTRAVENOUS FLUIDS

Children with prolonged severe asthma not tolerating oral fluids will require intravenous hydration. Two thirds of the child's maintenance requirement should be given because of the possibility of inappropriate antidiuretic hormone secretion. Serum electrolytes should be measured and hypokalaemia corrected if detected.

ECG monitoring is mandatory for all intravenous treatments.

6.8.9 IV MAGNESIUM SULPHATE

Intravenous magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet established.^{437,475} Doses of up to 40 mg/kg/day (maximum 2 g) by slow infusion have been used. Studies of efficacy for severe childhood asthma unresponsive to more conventional therapies have been inconsistent in providing evidence of benefit. | 1+

6.8.10 FURTHER INVESTIGATION AND MONITORING

Children can be discharged when stable on 3-4 hourly inhaled bronchodilators that can be continued at home.⁴⁷⁶ PEF and/or FEV₁ should be >75% of best or predicted and SpO₂ >94%.

Adult studies show that “optimal care” comprising self monitoring, regular review and a written asthma action plan can improve outcomes.⁴⁰⁷ Acute asthma attacks should be considered a failure of preventive therapy and thought should be given about how to help families avoid further severe episodes. Discharge plans should address the following:

- Check inhaler technique
- Consider the need for regular inhaled steroids
- Provide a written asthma action plan for subsequent asthma with clear instructions about the use of bronchodilators, seeking urgent medical attention in the event of worsening symptoms and, if appropriate, starting a course of oral steroids
- Arrange follow up by a GP within one week
- Arrange follow up in a paediatric asthma clinic within one to two months.

6.9 ASSESSMENT OF ACUTE ASTHMA IN CHILDREN AGED LESS THAN 2 YEARS

The assessment of acute asthma in early childhood can be difficult (*see annex 8*). Intermittent wheezing attacks are usually due to viral infection and the response to asthma medication is inconsistent. Prematurity and low birth weight are risk factors for recurrent wheezing. The differential diagnosis of symptoms includes aspiration pneumonitis, pneumonia, bronchiolitis, tracheomalacia, and complications of underlying conditions such as congenital anomalies and cystic fibrosis. These guidelines are intended for those who are thought to have asthma causing acute wheeze. They should not be used as a guide for treating acute bronchiolitis.

6.10 TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED LESS THAN 2 YEARS

6.10.1 β_2 AGONIST BRONCHODILATORS

A trial of bronchodilator therapy should be considered when symptoms are of concern. If inhalers have been successfully administered but there is no response, review the diagnosis and consider the use of other treatment options.

Oral β_2 agonists have not been shown to affect symptom score or length of hospital stay for acute asthma in infancy when compared to placebo.⁴⁷⁷ | 1+

B Oral β_2 agonists are not recommended for acute asthma in infants.

Inhaled β_2 agonists are the initial treatment of choice for acute asthma. Close fitting face masks are essential for optimal drug delivery. The dose received is increased if the child is breathing appropriately and not taking large gasps because of distress and screaming.

There is good evidence that pMDI + spacer is as effective as, if not better than, nebulisers for treating mild to moderate asthma in children aged ≤ 2 years.^{355,478,479} | 1+

A For mild to moderate acute asthma, a pMDI + spacer is the optimal drug delivery device.

Whilst β_2 agonists offer marginal benefits to children aged <2 years with acute wheeze, there is little evidence for an impact on the need for hospital admission or length of hospital stay.⁴⁸⁰⁻⁴⁸² | 1+

6.10.2 STEROID THERAPY

Steroid tablets in conjunction with β_2 agonists have been shown to reduce hospital admission rates when used in the emergency department.⁴⁸³ Steroid tablets have also been shown to reduce the length of hospital stay.^{477,480,483} 1+

B Consider steroid tablets in infants early in the management of moderate to severe episodes of acute asthma in the hospital setting.

One study has shown similar benefits when comparing oral and nebulised steroids for acute asthma.⁴⁸⁰

Steroid tablet therapy (10 mg of soluble prednisolone for up to three days) is the preferred steroid preparation for use in this age group.

6.10.3 IPRATROPIUM BROMIDE

The addition of ipratropium bromide to β_2 agonists for acute severe asthma may lead to some improvement in clinical symptoms and reduce the need for more intensive treatment. It does not reduce the length of hospital stay either in combination with β_2 agonists or in comparison with placebo.⁴⁸⁴ 1+

B Consider inhaled ipratropium bromide in combination with an inhaled β_2 agonist for more severe symptoms.

6.10.4 FURTHER INVESTIGATION AND MONITORING

Many children with recurrent episodes of viral-induced wheezing in infancy do not go on to have chronic atopic asthma. The majority do not require treatment with regular inhaled steroids. Parents should be advised about the relationship between cigarette smoke exposure and wheezy illnesses (see sections 3.1.9 and 3.3.1). Referral to suitable agencies should be offered to those who wish to give up smoking.

Parents of wheezy infants should receive appropriate discharge plans along similar lines to those given for older children (see section 6.8.10).

7 Special situations

7.1 DIFFICULT ASTHMA

7.1.1 DEFINING AND ASSESSING DIFFICULT ASTHMA

The term difficult asthma generally refers to a clinical situation where a prior diagnosis of asthma exists, and asthma-like symptoms and exacerbations persist, despite prescription of high-dose asthma therapy. There is no universally agreed definition of difficult asthma in children or adults, and specifically at what level of treatment prescription or exacerbation frequency, the term difficult asthma should apply. Consequently there are no precise data on the prevalence of this clinical problem. Previous consensus studies have suggested failure to achieve symptom control despite prescribed high-dose inhaled steroid as a minimum requirement, whilst more recent consensus work has stipulated a treatment level equivalent to at least step 4 (see section 4.4 and Figures 4, 5 and 6), before labelling as “difficult”.^{485,486}

In this guideline difficult asthma is defined as persistent symptoms and/or frequent exacerbations despite treatment at step 4 or step 5.

Observational uncontrolled studies in subjects with difficult asthma, using multidisciplinary assessment models have identified high rates of alternative or coexistent diagnoses and psychological comorbidity.^{29,487-489} These uncontrolled studies, using systematic multidisciplinary assessment and management, have suggested improved outcomes in adults and children, but controlled clinical trials are required. Within this broadly defined group of subjects with difficult asthma, a proportion will have refractory disease, which is relatively resistant to currently available therapies. This group can only be identified after detailed evaluation, including exclusion of alternative causes of persistent symptoms, management of other comorbidities and confirmation of adherence with therapy.

D Patients with difficult asthma should be systematically evaluated, including:

- confirmation of the diagnosis of asthma and
- identification of the mechanism of persisting symptoms and assessment of adherence with therapy.

D This assessment should be facilitated through a dedicated multidisciplinary difficult asthma service, by a team experienced in the assessment and management of difficult asthma.

7.2 FACTORS CONTRIBUTING TO DIFFICULT ASTHMA

7.2.1 POOR ADHERENCE

Poor adherence with asthma medication is associated with poor asthma outcome in adults and children (see section 9.2). Few studies have addressed this issue in subjects defined as having difficult asthma. In a case control series, poor adherence based on prescription records was identified in 22% of children with difficult to control asthma, though adherence was not reported in the stable controls.⁴⁹⁰ In a descriptive study of 100 adult subjects, with a physician diagnosis of ‘severe asthma’ 28 patients were on > 15 mg prednisolone and of these nine (32%) were found to be non-adherent with prednisolone.⁴⁸⁸ There is no published evidence that poor adherence, if identified, can be successfully addressed in this population.

C Poor adherence with maintenance therapy should be considered as a possible mechanism in difficult asthma.

3

2+
3

7.2.2 PSYCHOSOCIAL FACTORS

Fatal and near-fatal asthma have been associated with psychosocial dysfunction (see section 6.1.3). Most observational studies^{29, 488, 491-494} and a case control study⁴⁹⁵ in subjects with difficult asthma have also suggested a high level of psychological morbidity, though this observation has not been universal.^{496, 497}

3
2+

A meta-analysis of behavioural adjustment in children suggested increasing 'asthma severity', defined on the basis of treatment requirements was associated with greater behavioural difficulties.⁴⁹⁸ The core issue of 'cause and effect' remains unclear; specifically the extent to which persistent asthma symptoms despite aggressive treatment results in psychological morbidity or whether pre-existing psychological morbidity makes asthma difficult to control.

2++

There is a lack of evidence that interventions specifically targeting psychological morbidity in difficult asthma are of benefit. A small proof of concept study targeting depression demonstrated a reduction in oral steroid use⁴⁹⁹ and an observational study in 'high-risk' children with asthma suggested potential benefit from joint consultation with a child psychiatrist with an improvement in symptom scores and adherence with therapy.⁵⁰⁰ However, a non-blinded randomised intervention study in adults with difficult asthma showed no benefit from a six month nurse-delivered psychoeducational programme.⁵⁰¹ A meta-analysis of psychoeducational interventions in difficult asthma concluded that many of the studies were of poor quality, though there was some evidence of positive effect of psychosocial educational interventions on hospital admissions in adults and children and on symptoms in children. There was not enough evidence to warrant significant changes in clinical practice and little information available on cost effectiveness.⁵⁰²

1+
3

C Healthcare professionals should be aware that difficult asthma is commonly associated with coexistent psychological morbidity.

D Assessment of coexistent psychological morbidity should be performed as part of a difficult asthma assessment. In children this may include a psychosocial assessment of the family.

7.2.3 DYSFUNCTIONAL BREATHING

Observational uncontrolled studies in subjects with difficult asthma have identified high rates of dysfunctional breathing as an alternative or concomitant diagnosis to asthma causing symptoms.^{29, 488} It remains unclear what is the best mechanism of identifying and managing this problem.

3

D Dysfunctional breathing should be considered as part of a difficult asthma assessment.

7.2.4 ALLERGY

Acute asthma has been associated with IgE dependent sensitisation to indoor allergens.⁵⁰³ In case control studies, mould sensitisation has been associated with recurrent admission to hospital and oral steroid use^{504, 505} and with intensive care unit admissions and respiratory arrest.^{506, 507} There is no published evidence of any intervention study in this group. Research in this area is required.

2++
3

C In patients with difficult asthma and recurrent hospital admission, allergen testing to moulds should be performed.

7.2.5 MONITORING AIRWAY RESPONSE

Two randomised blinded controlled trials and one open randomised study have supported the use of titrating steroid treatment against sputum eosinophilia in adults with moderate to severe asthma, with greatest benefit seen in patients receiving higher doses of inhaled steroid therapy.^{84,86,508} In the study with the largest numbers of patients receiving high dose inhaled steroid treatment, patients who were considered to be poorly adherent with treatment, or had inadequately controlled aggravating factors, such as rhinitis or gastro-oesophageal reflux were specifically excluded.⁸⁴ Case series have suggested that sputum induction is safe in patients with difficult to control asthma.^{57,509-512}

1+
1-
3

Controlled studies using FENO to target treatment have not specifically targeted adults or children with difficult asthma.^{85,513,514}

1+

B In patients with difficult asthma, consider monitoring induced sputum eosinophil counts to guide steroid treatment.

7.3 ASTHMA IN PREGNANCY

7.3.1 NATURAL HISTORY

Several physiological changes occur during pregnancy that could worsen or improve asthma, but it is not clear which, if any, are important in determining the course of asthma during pregnancy. Pregnancy can affect the course of asthma and asthma can affect pregnancy outcomes.

The natural history of asthma during pregnancy is extremely variable. In a prospective cohort study of 366 pregnancies in 330 asthmatic women, asthma worsened during pregnancy in 35%.⁵¹⁵ Studies suggest that 11-18% of pregnant women with asthma will have at least one emergency department visit for acute asthma and of these 62% will require hospitalisation.^{516,517} There is also some evidence that the course of asthma is similar in successive pregnancies.⁵¹⁵ Severe asthma is more likely to worsen during pregnancy than mild asthma,⁵¹⁵ but some patients with very severe asthma may experience improvement, while symptoms may deteriorate in some patients with mild asthma.

2-
2+

D Offer pre-pregnancy counselling to women with asthma regarding the importance and safety of continuing their asthma medications during pregnancy to ensure good asthma control.

The conclusions of a meta-analysis of 14 studies is in agreement with the commonly quoted generalisation that during pregnancy about one third of asthma patients experience an improvement in their asthma, one third experience a worsening of symptoms, and one third remain the same.⁵¹⁸

2++

In a large cohort study, the most severe symptoms were experienced by patients between the 24th and 36th week of pregnancy. Thereafter symptoms decreased significantly in the last four weeks and 90% had no asthma symptoms during labour or delivery. Of those who did, only two patients required anything more than inhaled bronchodilators.⁵¹⁵ A further study has confirmed the observation that the last month of pregnancy is the one in which patients are least likely to have an asthma exacerbation.⁵¹⁹

2-
2+

A cohort study comparing 198 pregnant women with asthma to 198 women without asthma reported that non-atopic patients with asthma tend to have more severe asthma. Pre-eclampsia was also more common in this group. However with adequate surveillance and treatment, pregnancy and delivery complications can be avoided.⁵²⁰ A systematic review has shown that baseline asthma severity does determine what happens to the course of asthma in pregnancy and asthma may affect the risk of adverse outcomes.⁵²¹

2+
2++

C Monitor pregnant women with asthma closely so that any change in course can be matched with an appropriate change in treatment.

Uncontrolled asthma is associated with many maternal and fetal complications, including hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, complicated labour, intrauterine growth restriction, preterm birth, increased perinatal mortality, and neonatal hypoxia.⁵²²⁻⁵²⁵ A large Swedish population-based study using record linkage data demonstrated increased risks for pre-term birth, low birth weight, perinatal mortality and pre-eclampsia in women with asthma. The risks for prematurity and low birth weight were higher in women with more severe asthma necessitating admission.⁵²⁶

2+

In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.^{515,516} Pregnancy should therefore be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute exacerbation.

Advise women who smoke about the dangers for themselves and their babies and give appropriate support to stop smoking.

7.4 MANAGEMENT OF ACUTE ASTHMA IN PREGNANCY

The management of acute asthma in pregnancy may be affected by concerns about harmful effects of medication on the fetus. In a prospective controlled study of 51 pregnant women and 500 non-pregnant women presenting with acute asthma to an emergency department in Boston, USA, pregnant patients with asthma were less likely to receive appropriate treatment with steroids and, as a result, were more likely to experience ongoing exacerbation at two weeks.⁵²⁷ Available studies give little cause for concern regarding treatment side effects (see section 7.3) and the maternal and fetal risks of uncontrolled asthma are much greater than the risks from using conventional asthma medications for management of acute asthma. In the last two confidential enquiries into maternal deaths in the UK (covering 1994-1999) there were eight deaths from asthma.^{528,529}

2+

Oxygen should be delivered to maintain saturation above 95% in order to prevent maternal and fetal hypoxia. Drug therapy should be given as for a non-pregnant patient with acute asthma, including repeated doses of inhaled β_2 agonists and early administration of steroid tablets.^{515,517,519,522,523} In severe cases, intravenous aminophylline or intravenous β_2 agonists can be used as indicated. Continuous fetal monitoring should be performed when asthma is uncontrolled or severe, or when fetal assessment on admission is not reassuring.

- C** Give drug therapy for acute asthma as for the non-pregnant patient.
- D** Deliver oxygen immediately to maintain saturation above 95%.
- D** Acute severe asthma in pregnancy is an emergency and should be treated vigorously in hospital.
- Continuous fetal monitoring is recommended for severe acute asthma.
- For women with poorly controlled asthma during pregnancy there should be close liaison between the respiratory physician and obstetrician.

7.5 DRUG THERAPY IN PREGNANCY

In general, the medicines used to treat asthma are safe in pregnancy.⁵³⁰ The risk of harm to the fetus from severe or chronically under-treated asthma outweighs any small risk from the medications used to control asthma.

2+

7.5.1 β_2 AGONISTS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to β_2 agonists.^{530,531} A prospective study of 259 pregnant patients with asthma who were using bronchodilators compared with 101 pregnant patients with asthma who were not, and 295 control patients, found no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, apgar scores or labour/delivery complications.⁵³² Evidence from prescription event monitoring suggests that salmeterol is also safe in pregnancy.⁵³³

2+
3

- C** Use β_2 agonists as normal during pregnancy.

7.5.2 INHALED STEROIDS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to inhaled steroids.^{530,534-537} Inhaled anti-inflammatory treatment has been shown to decrease the risk of an acute attack of asthma in pregnancy⁵¹⁹ and the risk of readmission following asthma exacerbation.⁵¹⁷

2-
2+
2++

- C** Use inhaled steroids as normal during pregnancy.

7.5.3 THEOPHYLLINES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.^{530,538}

For women requiring therapeutic levels of theophylline to maintain asthma control, measurement of theophylline levels is recommended. Since protein binding decreases in pregnancy, resulting in increased free drug levels, a lower therapeutic range is probably appropriate.⁵³⁹

2+
4

C Use oral and intravenous theophyllines as normal during pregnancy.

D Check blood levels of theophylline in acute severe asthma and in those critically dependent on therapeutic theophylline levels.

7.5.4 STEROID TABLETS

The balance of evidence suggests that steroid tablets are not teratogenic.^{522, 530, 540} Data from many studies have failed to demonstrate an association between first trimester exposure to steroid tablets and oral clefts.⁵⁴⁰ Although one meta-analysis found an increased risk,⁵⁴¹ a prospective study by the same group found no difference in the rate of major birth defects in prednisolone-exposed and control babies.⁵⁴¹ One case control study that may have influenced the findings of the meta-analysis found a significant association between exposure to steroids in the first trimester and an increased risk of cleft lip,⁵⁴² although this increase is not significant if only paired controls are considered.

2+
2-

Even if the association is real, the benefit to the mother and the fetus of steroids for treating a life threatening disease justify their use in pregnancy.⁵²⁴ Pregnant women with acute asthma exacerbation are less likely to be treated with steroid tablets than non-pregnant women.⁵²⁷ This failure to administer steroid tablets when indicated increases the risk of ongoing exacerbation and therefore the risks to the mother and her fetus.

2+

Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia and pre-term labour,⁵²⁰ but severe asthma may be a confounding variable.

C Use steroid tablets as normal when indicated during pregnancy for severe asthma. Steroid tablets should never be withheld because of pregnancy.

7.5.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

Data regarding the safety of leukotriene antagonists in pregnancy are extremely limited. Animal studies and post-marketing surveillance for zafirlukast and montelukast are reassuring. There are animal data of concern for zileuton.⁵⁴³

4

D Do not commence leukotriene antagonists during pregnancy. They may be continued in women who have demonstrated significant improvement in asthma control with these agents prior to pregnancy not achievable with other medications.

7.5.6 CHROMONES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to chromones.^{529,530}

C Use chromones as normal during pregnancy.

7.6 MANAGEMENT DURING LABOUR

Acute attacks of asthma are very rare in labour due to endogenous steroid production. In women receiving steroid tablets there is a theoretical risk of maternal hypothalamic-pituitary-adrenal axis suppression. Women with asthma may safely use all forms of pain relief in labour.

In some studies there is an association between asthma and an increased caesarean section rate,^{520,544,545} but this may be due to planned caesarean sections⁵¹⁹ or inductions of labour rather than due to any direct effect of asthma on intrapartum indications. 2+

Data suggest that the risk of postpartum exacerbation of asthma is increased in women having caesarean sections.⁵⁴⁴ This may relate to the severity of their asthma rather than to the caesarean section, or to factors such as postoperative pain with diaphragmatic splinting, hypoventilation and atelectasis. Prostaglandin E₂ may safely be used for labour inductions.⁵³⁹ Prostaglandin F_{2α} (carboprost/hemobate®) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.⁵³⁹ Although ergometrine may cause bronchospasm particularly in association with general anaesthesia,⁵³⁹ this is not a problem encountered when syntometrine (syntocinon/ergometrine) is used for postpartum haemorrhage prophylaxis. 2-
3

Although suppression of the fetal hypothalamic-pituitary-adrenal axis is a theoretical possibility with maternal systemic steroid therapy, there is no evidence from clinical practice or the literature to support this.⁵⁴⁶

- Advise women that acute asthma is rare in labour.
- Advise women to continue their usual asthma medications in labour.
- In the absence of acute severe asthma, reserve caesarean section for the usual obstetric indications.
- C** **If anaesthesia is required, regional blockade is preferable to general anaesthesia in women with asthma.**
- Women receiving steroid tablets at a dose exceeding prednisolone 7.5 mg per day for more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6-8 hourly during labour.
- D** **Use prostaglandin F_{2α} with extreme caution in women with asthma because of the risk of inducing bronchoconstriction.**

7.7 DRUG THERAPY IN BREASTFEEDING MOTHERS

The medicines used to treat asthma, including steroid tablets, have been shown in early studies to be safe to use in nursing mothers.⁵⁴⁷ There is less experience with newer agents. Less than 1% of the maternal dose of theophylline is excreted into breast milk.⁵⁴⁷ 2+

Prednisolone is secreted in breast milk, but milk concentrations of prednisolone are only 5-25% of those in serum.³⁵¹ The proportion of an oral or intravenous dose of prednisolone recovered in breast milk is less than 0.1%.⁵⁴⁸⁻⁵⁵⁰ For maternal doses of at least 20 mg once or twice daily the nursing infant is exposed to minimal amounts of steroid with no clinically significant risk.⁵⁴⁸⁻⁵⁵⁰ 2+
3

- C** **Encourage women with asthma to breast feed.**
- C** **Use asthma medications as normal during lactation, in line with manufacturers' recommendations.**

7.8 OCCUPATIONAL ASTHMA

7.8.1 INCIDENCE

The true frequency of occupational asthma is not known, but under-reporting is likely. Published reports, which come from surveillance schemes, compensation registries or epidemiological studies, estimate that occupational asthma may account for about 9-15% of adult onset asthma.⁵⁵¹⁻⁵⁵³ It is now the commonest industrial lung disease in the developed world with over 400 reported causes.⁵⁵⁴⁻⁵⁵⁶

2⁺⁺

The diagnosis should be suspected in all adults with symptoms of airflow limitation, and positively searched for in those with high-risk occupations or exposures. Patients with pre-existing asthma aggravated non-specifically by dust and fumes at work (work-aggravated asthma) should be distinguished from those with pre-existing asthma who become additionally sensitised to an occupational agent.

B

In patients with adult onset, or reappearance of childhood asthma, clinicians should be suspicious that there may be an occupational cause.

7.8.2 AT-RISK POPULATIONS

Several hundred agents have been reported to cause occupational asthma and new causes are reported regularly in the medical literature.

The most frequently reported causative agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.⁵⁵⁷⁻⁵⁶⁵

The workers most commonly reported to occupational asthma surveillance schemes include paint sprayers, bakers and pastry makers, nurses, chemical workers, animal handlers, welders, food processing workers and timber workers.^{557,558,560,562-568}

2⁺⁺

Workers reported to be at increased risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastics and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, waiters, cleaners, painters, dental workers and laboratory technicians.⁵⁶⁹⁻⁵⁷²

2⁺

7.8.3 DIAGNOSIS

Occupational asthma should be considered in all workers with symptoms of airflow limitation. The best screening question to ask is whether symptoms improve on days away from work. This is more sensitive than asking whether symptoms are worse at work, as many symptoms deteriorate in the hours after work or during sleep.

Adults with airflow obstruction should be asked:

- Are you better on days away from work?
- Are you better on holiday?

Those with positive answers should be investigated for occupational asthma.

These questions are not specific for occupational asthma and also identify those with asthma due to agents at home (who may improve on holidays), and those who do much less physical exertion away from work.⁵⁷³

Occupational asthma can be present when tests of lung function are normal, limiting their use as a screening tool. Asthmatic symptoms improving away from work can produce false negative diagnoses, so further validation is needed.

Serial measurement of peak respiratory flow is the most readily available initial investigation, and the sensitivity and specificity of serial peak flow measurement in the diagnosis of occupational asthma are high.⁵⁷⁴⁻⁵⁸⁰

3

Although skin prick tests or blood tests for specific IgE are available, there are few standardized allergens commercially available which limits their use. A positive test denotes sensitisation, which can occur with or without disease. The diagnosis of occupational asthma can usually be made without specific bronchial provocation testing, considered to be the gold standard diagnostic test. The availability of centres with expertise and facilities for specific provocation testing is very limited in the UK and the test itself is time consuming.

As a general observation, the history is more useful in excluding occupational asthma than in confirming it. A significant proportion of workers with symptoms that improve on days away from work or on holiday have been shown by objective tests not to have occupational asthma.⁵⁸¹ Expert histories have poor specificity compared with specific challenge testing. Free histories taken by experts have high sensitivity but their specificity is lower.⁵⁸²⁻⁵⁸⁷

D In suspected work-related asthma, the diagnosis of asthma should be confirmed using standard objective criteria.

7.8.4 SENSITIVITY AND SPECIFICITY OF SERIAL PEAK FLOW MEASUREMENTS

Direct and blinded comparisons of serial peak flow measurement with either specific bronchial provocation testing, or an expert diagnosis based on a combination of other types of evidence, reported consistently high sensitivities and specificities, averaging 80% and 90% respectively.^{575-578,580,588,589}

Just one computed method of analysis has been reported, with a sensitivity of 75% and a specificity of 94%.^{97,590}

Computed analysis of peak flow records has good diagnostic performance, but statistical analysis of serial peak flow measurements appears to be of limited diagnostic value compared to expert interpretation.^{578,588,589}

Serial measurements of peak expiratory flow

Measurements should be made every two hours from waking to sleeping for four weeks, keeping treatment constant and documenting times at work.

Minimum standards for diagnostic sensitivity > 70% and specificity > 85% are:

- At least three days in each consecutive work period
- At least three series of consecutive days at work with three periods away from work (usually about three weeks)
- At least four evenly spaced readings per day.⁵⁸⁰

The analysis is best done with the aid of a criterion-based expert system. Suitable record forms and support are available from www.occupationalasthma.com

D Objective diagnosis of occupational asthma should be made using serial peak flow measurements, with at least four readings per day.

7.8.5 NON-SPECIFIC REACTIVITY

Studies of non-specific reactivity are confounded by different methods used, different cut-offs for normality and the interval between last occupational exposure and the performance of the test (increasing time may allow recovery of initial hyper-reactors). Such studies show that non-specific bronchial hyper-reactivity may be normal in 5-40% of specific challenge positive workers. Testing with higher concentrations of methacholine or histamine, at which some people without asthma would react, reduces the number of non-reacting people with occupational asthma, but still leaves some non-reactors. One study showed no additional benefit of non-specific bronchial reactivity measurement over and above a history and specific IgE to inhaled antigens. A normal test of non-specific reactivity is not sufficiently specific to exclude occupational asthma in clinical practice.^{576,581,583,586,587,589,591-602}

Changes in non-specific reactivity at and away from work alone have been found to have only moderate sensitivity and specificity for diagnosis. Three studies were identified where at and away from work exposure measurements were attempted. One did not investigate workers further when at work reactivity was normal, limiting its interpretation. Using a 3.2 fold change in reactivity, one study found a sensitivity of 48% and a specificity of 64%. Reducing the required change to twofold increased the sensitivity to 67%, reducing specificity to 54%. A smaller study with 14 workers with occupational asthma showed a sensitivity of 62% and specificity of 78%.^{577,589,601}

2-

7.8.6 SPECIFIC BRONCHIAL PROVOCATION TESTING

Specific provocation challenges are usually used as the gold standard for occupational asthma diagnosis making assessments of their diagnostic validity difficult. In addition, there are no standardised methods for many occupational agents. There is also evidence that the threshold exposure increases with time since last exposure, making the tests less sensitive after prolonged absence from work. There are reports of people having non-specific reactions to specific challenges at concentrations likely to be found in the workplace or of negative reactions to specific challenges in workers with otherwise good evidence of occupational asthma when challenge concentrations are confined to levels below occupational exposure standards.^{594,597,600,603,604}

4

D A negative specific bronchial challenge in a worker with otherwise good evidence of occupational asthma is not sufficient to exclude the diagnosis.

7.9 MANAGEMENT OF OCCUPATIONAL ASTHMA

The aim of management is to identify the cause, remove the worker from exposure, and for the worker to have worthwhile employment.

Complete avoidance of exposure may or may not improve symptoms and bronchial hyper-responsiveness. Both the duration of continued exposure following the onset of symptoms and the severity of asthma at diagnosis may be important determinants of outcome. Early diagnosis and early avoidance of further exposure, either by relocation of the worker or substitution of the hazard offer the best chance of complete recovery. Workers who remain in the same job and continue to be exposed to the same causative agent after diagnosis are unlikely to improve and symptoms may worsen. The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent.^{576,605-613}

2++

Several studies have shown that the prognosis for workers with occupational asthma is worse for those who remain exposed for more than one year after symptoms develop, compared with those removed earlier.⁶¹⁴⁻⁶¹⁶

D Relocation away from exposure should occur as soon as diagnosis is confirmed, and ideally within 12 months of the first work-related symptoms of asthma.

There is consistent evidence from clinical and workforce case series that about one third of workers with occupational asthma are unemployed after diagnosis. It is unclear whether this risk is higher than that for other adults with asthma.^{582,617,618} The risk of unemployment may fall with increasing time after diagnosis.⁶¹⁹ There is consistent evidence that loss of employment following a diagnosis of occupational asthma is associated with loss of income. Adults with occupational asthma may find employment more difficult than adults with non-occupational asthma.^{617,618} Approximately one third of workers with occupational asthma have been shown to be unemployed up to six years after diagnosis.^{582,617-624}

2-

8 Organisation and delivery of care, and audit

8.1 ROUTINE PRIMARY CARE

8.1.1 ACCESS TO ROUTINE PRIMARY CARE

Primary care services delivered by doctors and nurses trained in asthma management improves diagnosis, prescribing, education, monitoring, and continuity of care.^{625,626} Successful training programmes typically include outreach educational visits to practices or practitioners using interactive educational methods focused around clinical guidelines, occasionally including audit and feedback of care.^{625,627,628}

1+

A All people with asthma should have access to primary care services delivered by doctors and nurses with appropriate training in asthma management.

❖ *Audit the percentage of clinicians who have taken part in a suitable asthma educational update within last two years.*

8.1.2 STRUCTURED REVIEW

Proactive clinical review of people with asthma improves clinical outcomes. Evidence for benefit is strongest when reviews include discussion and use of a written action plan.⁴⁰⁷ Benefits include reduced school or work absence, reduced exacerbation rate, improved symptom control and reduced attendance at the emergency department.^{629,630} Proactive structured review, as opposed to opportunistic or unscheduled review, is associated with reduced exacerbation rate and days lost from normal activity.^{626,631,632} It is difficult to be prescriptive about the frequency of review as need will vary with the severity of the disease. Outcome is probably similar whether a practice nurse (PN), or a general practitioner (GP) conducts the review. Clinicians trained in asthma management achieve better outcomes for their patients.^{626,633,634}

2+

3

4

1+

A In primary care, people with asthma should be reviewed regularly by a nurse or doctor with appropriate training in asthma management. Review should incorporate a written action plan.

❖ *Audit the percentage of patients reviewed annually. Consider focusing on particular groups such as those overusing bronchodilators, patients on higher treatment steps, those with exacerbations or from groups with more complex needs.*

❖ *Audit the percentage of patients receiving action plans. Consider focusing on subgroups listed above.*

READ coding of patients who are newly diagnosed or register at a practice will ensure a meaningful database for audit and review purposes. Specifically identifying patients with high risk asthma (eg those with frequent admissions) in an effort to target more detailed input is logical but supported by limited evidence.⁶³⁵ Not all patients want regular review, or are willing to attend a pre-arranged appointment. Reviews carried out by telephone may be as effective as those using face-to-face consultations,⁶³⁶ but face-to-face review will be appropriate for some patients, such as those with poor asthma control or inhaler-related problems.

2++

B Consider carrying out routine reviews by telephone for people with asthma.

Asthma clinics in primary care may be a convenient way of delivering care, but there is limited evidence that they themselves improve outcome.²⁹¹ Most practices will provide asthma reviews as part of routine appointment sessions. It is what happens during the review consultation that matters.⁶³⁷⁻⁶⁴⁰ Audit that feeds back guidelines recommendations on the management of individual patients may improve outcomes.^{641,642}

C General practices should maintain a register of people with asthma.

C Clinical review should be structured and utilise a standard recording system.

B Feedback of audit data to clinicians should link guidelines recommendations to management of individual patients.

The ideal content of an asthma review consultation is uncertain. Discussion and provision of a written action plan leads to improved outcomes.⁶⁴³ Other activities likely to be important are reviewing understanding of medication role and use, checking inhaler technique, recording lung function. Structured review systems such as the Royal College of Physicians 'Three Key Questions',¹⁰⁹ the Tayside Asthma Stamp,⁶⁴⁴ and the modified Jones Morbidity Index⁶⁴⁵ improve the recording of relevant data and may prompt a search for causes of suboptimal asthma control, such as under-treatment, poor adherence or poor inhaler technique. However, such tools can lead to a more physician-centred or template-directed consultation. Reviewing patients using a patient-centred style of consultation can lead to improved outcomes.⁶²⁵

8.1.3 SHARED CARE

Shared care schemes have been shown to be effective in some healthcare environments. There are no UK studies directly comparing primary and secondary care management, but international work suggests there may be little difference: what is done would appear to be more important than who by or where.⁶⁴⁶

Integrated care schemes such as Grampian Asthma Study in Integrated Care (GRASSIC) suggest that place of care is not directly linked to clinical outcome.⁶⁴⁷⁻⁶⁵⁰ Shared care had a similar outcome to outpatient care. Outreach support for primary care by asthma specialist nurses may reduce unscheduled asthma care but only if targeted around follow-up of patients recently attending secondary care with exacerbations.

Community pharmacists trained in asthma care and teaching self management skills may improve asthma control,^{651,652} although evidence is sparse and inconsistent.⁶⁵³

8.1.4 PATIENT SUBGROUPS

Ethnic subgroups have adverse clinical outcomes, including higher hospital admission and exacerbation rates.^{654,655} In some countries ethnic minority groups have higher death rates due to asthma than do their contemporaries.^{656,657} Minority groups describe poorer access to primary care and acute medical care,⁶⁵⁸ and compared with majority groups, have a higher use of emergency facilities for routine care.⁶⁵⁹ Educating primary care clinicians improves diagnosis, prescribing, education, and continuity of care for minority group children.⁶⁵⁹ There is an established link between poor socioeconomic status and adverse asthma outcome.⁶⁶⁰⁻⁶⁶⁴

Adolescents and the elderly are particularly vulnerable to the adverse effects of asthma. Adolescents and young adults make more frequent use of emergency asthma healthcare services, make less use of structured clinical review services than other age groups, and have high reliance on bronchodilators.^{665,666} Asthma in the elderly is a neglected area of research, despite high mortality and morbidity.^{391,667,668}

D Healthcare professionals who provide asthma care should have heightened awareness of the complex needs of ethnic minorities, socially disadvantaged groups, adolescents, the elderly and those with communication difficulties.

❖ *Audit asthma outcomes in relevant subgroups of the population.*

8.2 ACUTE EXACERBATIONS

People with asthma who experience deterioration in symptom control leading to an acute exacerbation can access a wide variety of sources of care. Few studies have looked at the relative merits of one type of service compared to another. Exceptions include a UK study showing a better outcome for patients managed by a specialist respiratory ward compared to a general medical ward, and a US study showing more favourable outcome in patients managed by specialist allergists compared to generalists.^{669,670}

2+
3

C Manage hospital inpatients with asthma in specialist rather than general units.

☑ All services involved in the care of acute asthma should be staffed by appropriately trained personnel and have access to all the equipment needed to manage acute asthma.

❖ *Audit the percentage of inpatients receiving care from specialist asthma nurse or chest physician.*

Models of care addressing access such as NHS Direct/NHS 24 produce similar outcomes to routine general practice, but have high referral rates and are unlikely to promote the continuity of care required for longer term management.⁶⁷¹

3

A structured clinical assessment and a standardised recording system are associated with favourable outcome in acute exacerbations.⁶⁷² Audit of the management of patients with acute asthma attacks is associated with improved concordance with recommended guidelines and in turn improved clinical outcome and reduced exacerbation rate.⁶⁷³⁻⁶⁷⁵

2+
2-
3

There is no evidence that the publication of guidelines per se improves care: clinicians need to link best practice to the management of individual patients. This effect is apparent in hospital and general practice care.⁴⁴⁷ Certain actions, for example early prescription of oral corticosteroids for acute exacerbations of asthma, reduce hospitalisation and relapse rates. Clinicians should refer to relevant chapters in this guideline for advice.

B Clinicians in primary and secondary care should treat asthma according to recommended guidelines.

❖ *Audit the percentage of patients treated according to key guideline recommendations.*

Using acute asthma management protocols and clinical pathways can be beneficial and cost effective. Sub-optimal control of asthma leading to exacerbation is more expensive to manage than well controlled asthma.⁶³⁰ Early discharge schemes from hospital and emergency departments may be cost effective.^{445,676}

2+
3

The safety of telephone help lines has not been established. 'Direct dial' emergency admission schemes may be of benefit to a small group of patients with severe or 'brittle' asthma but there is insufficient evidence to justify their widespread introduction.⁶⁷⁷ Admission criteria are discussed elsewhere (see section 6.2.6).

4

Criteria for and timing of discharge from hospital and emergency departments has been studied. The key event in recovery appears to be improved symptoms and peak flow rather than a complete return to normality. Discharge when improvement is apparent may be as safe as discharge when full stability is achieved. Asthma specialist nurse education of adults and school-age (but not pre-school) children at or shortly after hospital attendance improves symptom control, self management and re-attendance rates.⁶⁷⁸⁻⁶⁸³

1+
2+
2+
2-

Making an appointment for review in primary care prior to discharge improves follow-up rates (but not outcomes).⁶⁸⁴ Review within 30 days after hospital attendance with acute asthma is associated with reduced risk of further acute episodes.⁶⁸⁵ There is most evidence of benefit when follow up is provided by specialist nurses. Various types of follow up after an acute exacerbation have been evaluated including GP care, hospital outpatient, and telephone follow up.^{680,686} There would appear to be little difference in outcome depending on place or personnel involved in follow up (see section 6.6).⁶⁷⁶

3
1+

A Discharge from hospital or the emergency department should be a planned, supervised event which includes self management planning. It may safely take place as soon as clinical improvement is apparent.

A All people attending hospital with acute exacerbations of asthma should be reviewed by a clinician with particular expertise in asthma management, preferably within 30 days.

❖ Audit the percentage of people receiving specialist nurse advice including self management planning before discharge.

❖ Audit the percentage of people reviewed within 30 days after hospital attendance with acute exacerbation of asthma.

8.3 AUDIT

Audit is a moderately effective way to improve the process and probably outcome of care.⁶⁸⁷ Its impact is increased if combined with other strategies to change clinician behaviour, for example outreach education programmes. Whilst trials of audit in asthma care are few, those showing benefits have tended to incorporate feedback data to clinicians on the process of care such as frequency of review, checking of inhaler technique or lung function measurement. Passive feedback of aggregated data, for instance on prescribing patterns, does not change practice.⁶⁸⁸

8.3.1 TYPES OF AUDIT IN ASTHMA CARE

National or regional audits of asthma deaths have focused attention on delivery of care for severe asthma. Some primary care trusts have PCT-wide programmes of audit which extract practice data electronically and feedback comparative data on process of care, promoting a benchmarking approach to quality improvement.⁶⁸⁹ The GMS Quality and Outcomes Framework (QOF) links audit of asthma care to financial incentives. Critical event audit focuses on an adverse event such as an asthma death, or failure of delivery care. How effective these activities are in improving outcomes of asthma care is uncertain.

Common sense suggests that auditing activities shown to improve patient outcomes is worthwhile. This chapter links suggestions for audit to guideline recommendations. Audit datasets are available at www.brit-thoracic.org.uk.

8.3.2 SUMMARY OF RECOMMENDED AUDITS

Diagnosis

Audit the percentage of adults with an Asthma Control Questionnaire score recorded and an Asthma Control Questionnaire of >0.75.

Non-pharmacological management

Audit the percentage of patients and parents-to be with smoking status recorded and the percentage who have received smoking cessation advice.

Pharmacological management

Audit:

- *the percentage of patients with potential adverse effects of treatment, for example, the percentage of children prescribed or using >800 micrograms/day of inhaled beclometasone who are not under the care of a specialist respiratory physician*
- *the percentage of patients in whom there has been documented consideration of downward dose titration for inhaled corticosteroid*
- *the percentage of patients using >800 micrograms/day of inhaled beclometasone without documented consideration of add-on therapy*
- *the percentage of patients in whom there has been documented consideration of downward dose titration for inhaled corticosteroid.*

Inhaler devices

Audit the percentage of patients in whom there is a record of satisfactory inhaler technique.

Audit the percentage of patients using a spacer device for mild to moderately severe exacerbations.

Management of acute asthma

Audit the percentage of patients in whom key steps in the management of acute asthma have been followed, for example, the percentage with a PEF measurement, the percentage with a justified X-ray on admission to hospital, or the percentage receiving corticosteroid tablets in adequate dosage and duration.

Asthma in pregnancy

Audit:

- *the percentage of pregnant women with documented discussion of the need to continue β_2 agonists and inhaled corticosteroid medication in pregnancy*
- *the percentage of pregnant women and partners who smoke with documented advice on smoking cessation.*

Occupational asthma

Audit the number of adults with adult-onset asthma for whom an occupational cause has been considered.

Organisation and delivery of care

Audit:

- *the percentage of clinicians who have taken part in suitable asthma educational update within last two years*
- *the percentage of patients reviewed annually. Consider focusing on particular groups such as those overusing bronchodilators, patients on higher treatment steps, those with exacerbations or from groups with more complex needs*
- *asthma outcomes in relevant subgroups of the population*
- *the percentage of inpatients receiving care from specialist asthma nurse or chest physician*
- *the percentage of patients treated according to key guideline recommendations*
- *the percentage of people receiving specialist nurse advice including self management planning before discharge*
- *the percentage of people reviewed within 30 days after hospital attendance with acute exacerbation of asthma.*

Patient education and self management

Audit the percentage of patients receiving written action plans.

Concordance and compliance

Audit prescription requests to determine compliance.

9 Patient education and self management

9.1 SELF-MANAGEMENT EDUCATION AND PERSONALISED ASTHMA ACTION PLANS

Written personalised action plans as part of self management education have been shown to improve health outcomes for people with asthma.^{407,678,679,682,690-710} The evidence is particularly good for those in secondary care with moderate to severe disease, and those who have had recent exacerbations where successful interventions have reduced hospitalisations and emergency department attendances in people with severe asthma.^{682,705,711,712} A consistent finding in many studies has been improvement in patient outcomes such as self-efficacy, knowledge and confidence.^{690,701-703,709,713-727}

1+

A Patients with asthma should be offered self-management education that focuses on individual needs, and be reinforced by a written personalised action plan.

A Prior to discharge, in-patients should receive written personalised action plans, given by clinicians with expertise in asthma management.

9.1.1 COMPONENTS OF A SELF MANAGEMENT PROGRAMME

Self management education is a multi-faceted intervention with wide variation in the construction of programmes.^{728,729} One systematic review has identified key components associated with beneficial outcome (see *Table 13*).⁷³⁰ While self management programmes are effective, individual components are not effective in isolation reinforcing the need to support the provision of personalised action plans with patient education.^{728,731}

1+

Successful programmes vary considerably, but encompass:

- Structured education, reinforced with written personal action plans, though the duration, intensity and format for delivery may vary.^{690,729}
- Specific advice about recognising loss of asthma control, though this may be assessed by symptoms or peak flows or both.^{678,679,690,692,696-698,728,730,732-735}
- Actions, summarised as two or three action points, to take if asthma deteriorates, including seeking emergency help, commencing oral steroids (which may include provision of an emergency course of steroid tablets) recommencing or temporarily increasing inhaled steroids, as appropriate to clinical severity.⁷³⁰

Some published studies report long, intensive programmes.^{709,736-738} However, there is evidence that short programmes are as effective,^{679,739} and that usual care can be raised to a standard that incorporates many of the core elements of the successful extensive programmes.^{740,741}

1+

A Introduce personalised action plans as part of a structured educational discussion.

Checklist 1. Suggested content for an educational programme/discussion

This checklist is intended as an example, which health professionals should adapt to meet the needs of individual patients and/or carers. The purpose of education is to empower patients and/or carers to undertake self management more appropriately and effectively. Information given should be tailored to individual patient's social, emotional and disease status, and age. Different approaches are needed for different ages.

- Nature of the disease
- Nature of the treatment
- Identify areas where patient most wants treatment to have effect
- How to use the treatment
- Development of self monitoring/self assessment skills
- Negotiation of the personalised action plan in light of identified patient goals
- Recognition and management of acute exacerbations
- Appropriate allergen or trigger avoidance.

9.1.2 SELF MANAGEMENT PROGRAMMES IN SPECIFIC PATIENT GROUPS

A range of different patient populations are included in the trials. It cannot be assumed that a successful intervention in one setting will be feasible or appropriate in another. The greatest benefits are shown in those managed in secondary care.^{682,711,712} Primary care studies have also shown benefit,^{698,700,702,741} though effects are weaker, perhaps because clinical benefit is harder to demonstrate in people with mild asthma. Innovative approaches to self management education in teenagers (web-based, peer delivered within schools) appear to have more success than more traditional programmes.^{699-701,706,709,742-744} A different approach may be needed for pre-school children, many of whom have viral induced wheeze.^{683,745,746} There are no studies which specifically address the provision of self-management education to the elderly. Sub group analyses from UK trials have suggested that existing self-management programmes may be of less benefit in ethnic minority groups, but there is a lack of studies evaluating more appropriate interventions.^{698,705}

Self management programmes will only achieve better health outcomes if the prescribed asthma treatment is appropriate and within guideline recommendations.^{713,717} There is some evidence that ownership of a self management plan may attract better treatment (ie increased steroid provision from attending physicians).^{682,698,701}

9.2 COMPLIANCE AND CONCORDANCE

The term compliance embodies a traditional model of prescriptive care which refers to the objectively measured usage of prescribed medication, or frequency of monitoring. Non-compliance may be intentional or unintentional. The term 'concordance' signifies a negotiated agreement between the professional and the patient. Non-concordance describes an inability of both parties to come to an understanding, not merely a failure of the patient to follow the health professional's instructions.⁷⁴⁷ Studies which assess whether or not the patient believes that their behaviour is appropriate find correlations between beliefs about illness and medicine and concordance.^{748,749} Achieving concordance is likely to improve (though not guarantee) compliance.

9.2.1 COMPLIANCE WITH MONITORING AND TREATMENT

Compliance with regular monitoring with peak flow meters, even in clinical drug trials is poor, with recorded daily use as low as 6%.^{750,751} The lack of evidence supporting long term peak flow monitoring,^{647,735,752,753} however, does not negate the use of home charting at critical times: for example, at diagnosis and initial assessment, when assessing response to changes in treatment, as part of a personalised action plan during exacerbations.⁷³⁵ Comparison should be with the patients' best peak flow (not predicted).⁷³⁰

Patients are more likely to under-use than over-use treatment⁷⁵⁴⁻⁷⁵⁶ and under-use should be considered when there is a failure to control asthma symptoms. Patient self reporting and health care professional assessment both overestimate regular use of prophylactic medication.^{754,755,757} Computer repeat-prescribing systems, widely available in general practice, provide a good indication of adherence with prescribed asthma regimens. Electronic monitoring, whilst the most accurate method, is only practical in clinical drug trials.⁷⁵⁴

- Computer repeat-prescribing systems provide a useful index of compliance.
- Where the patient agrees with the health professional that the action is appropriate compliance is more likely.

9.2.2 INTERVENTIONS TO IMPROVE COMPLIANCE AND CONCORDANCE

Compliance can be improved by simple written instructions and reminders of when to use medication.⁷⁵⁸ There is a suggestion in the literature that interventions designed to improve communication between patients and health professionals achieve better programme adherence.^{625,737,759} Presenting important information first and repeating it can improve patient recall.⁷⁶⁰ Computer,⁷⁶¹ and innovative web-based self management programmes may increase use of regular medication.⁷⁶² Within managed care programmes, nurse-led telephone-based self management education supported by written information can increase the use of inhaled steroids.^{763,764}

- Provide simple, verbal and written instructions and information on drug treatment for patients and carers.

There is insufficient evidence to make clear recommendations on how the broader issues of concordance may be improved. Some practical tips for improving compliance are given in checklist 2.

Checklist 2: Practical tips for improving concordance

Open-ended questions like "If we could make one thing better for your asthma what would it be?" may help to elicit a more patient-centred agenda.
 Make it clear you are listening and responding to the patient's concerns and goals.
 Reinforce practical information and negotiated treatment plans with written instruction.
 Consider reminder strategies.
 Recall patients who miss appointments.

9.3 IMPLEMENTATION IN PRACTICE

Successful interventions have been delivered by trained asthma healthcare professionals, in the UK usually doctors and nurses, though a quality improvement programme which trained professionals in asthma self management showed no impact on clinical outcomes.^{678,679,690,692,694,765}

Three primary care studies explicitly link the provision of self management education with the facilitation of regular, structured review, consistent with the concept of 'guided self management'. All three increased ownership of personalised action plans and one showed a reduction in episodes of 'speech limiting wheeze'.^{631,741,766}

1+

B Initiatives which encourage regular, structured review explicitly incorporating self management education should be used to increase ownership of personalised action plans.

9.4 PRACTICAL ADVICE

9.4.1 AVAILABLE RESOURCES

A number of resources are available to support health professionals, including the 'Be in Control' materials produced by Asthma UK. Annex 11 reproduces the Asthma UK personalised action plan available from their website www.asthma.org.uk/control. Additional support and information for patients and carers is also available from the Asthma UK website (www.asthma.org.uk) and their Adviceline run by asthma specialist nurses: 08457 01 02 03 which includes an interpreting service covering 22 languages and Typetalk.

9.4.2 GOOD PRACTICE POINTS

Every asthma consultation is an opportunity to review, reinforce and extend both knowledge and skills. This is true whether the patient is seen in primary care, the accident and emergency department or the outpatient clinic. It is important to recognise that education is a process and not a single event.

- A hospital admission represents a window of opportunity to review self management skills. No patient should leave hospital without a written personalised action plan and the benefit may be greatest at first admission.
 - An acute consultation offers the opportunity to determine what action the patient has already taken to deal with the exacerbation. Their self management strategy may be reinforced or refined and the need for consolidation at a routine follow up considered.
 - A consultation for an upper respiratory tract infection or other known trigger is an opportunity to rehearse with the patient their self management in the event of their asthma deteriorating.
 - Brief simple education linked to patient goals is most likely to be acceptable to patients.

Table 13. Summary of the key components of a personalised action plan (adapted from Gibson et al)⁷³⁰

Component of an action plan	Result	Practical considerations
<p><i>Format of action points:</i></p> <p>Symptom vs peak flow triggered</p> <p>Standard written instructions</p> <p>Traffic light configuration</p>	<p>Similar effect</p> <p>Consistently beneficial</p> <p>Not clearly better than standard instructions</p>	<p>Asthma UK action plans include both symptom triggers and peak flow levels at which action should be taken.</p>
<p><i>Number of action points</i></p> <p>2-3 action points</p> <p>4 action points</p>	<p>Consistently beneficial</p> <p>Not clearly better than 2-3 points</p>	<p>Usual action points are:</p> <p>PEF < 80% best: increase inhaled steroids</p> <p>PEF < 60% best: commence oral steroids</p> <p>PEF < 40% best: seek urgent medical advice</p>
<p><i>Peak expiratory flow (PEF) levels</i></p> <p>Based on percentage personal best PEF</p> <p>Based on percentage predicted PEF</p>	<p>Consistently beneficial</p> <p>Not consistently better than usual care</p>	<p>Personal best should be assessed once treatment has been optimised and peak flows are stable.</p> <p>Best peak flow should be updated every few years in adults, and more frequently in growing children.</p>
<p><i>Treatment instructions</i></p> <p>Individualised using inhaled and oral steroids</p> <p>Individualised using oral steroids only</p> <p>Individualised using inhaled steroids</p>	<p>Consistently beneficial</p> <p>Insufficient data to evaluate</p> <p>Insufficient data to evaluate</p>	<p>Patients may safely hold an emergency supply of prednisolone tablets for use if their symptoms continue to deteriorate and/or if their peak flow falls to 60% of their best.</p> <p>Increasing inhaled steroids is ineffective if patients are already taking moderate or high doses (≥ 400 mcg daily) and these patients should be advised to move straight to the oral steroid step.</p> <p>Those on low doses (eg 200 mcg) of inhaled steroids may be advised to increase the dose substantially (eg to 1,200 mcg daily) at the onset of a deterioration.⁶³¹</p> <p>Any patients who have stopped medication should be reminded to recommence their inhaled steroids.</p>

10 Development of the guideline

10.1 INTRODUCTION

The guideline has been developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

Development involved the work of ten different multidisciplinary evidence review groups, a steering group and an executive group, chaired jointly by Dr Bernard Higgins on behalf of the BTS and Dr Graham Douglas on behalf of SIGN.

All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

10.2 EXECUTIVE AND STEERING GROUPS

Dr Graham Douglas* (Co-chair)	<i>Consultant Respiratory Physician, Aberdeen Royal Infirmary</i>
Dr Bernard Higgins* (Co-chair)	<i>Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne</i>
Professor Neil Barnes	<i>Consultant Respiratory Physician, Barts and The London NHS Trust</i>
Dr Anne Boyter	<i>Senior Lecturer, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow</i>
Professor Sherwood Burge	<i>Consultant Respiratory Physician, Birmingham Heartlands Hospital</i>
Dr Chris Cates*	<i>Senior Research Fellow, St George’s, University of London</i>
Dr Gary Connett	<i>Consultant Paediatrician, Southampton General Hospital</i>
Dr Jon Couriel*	<i>Consultant in Paediatric Respiratory Medicine, Alder Hey Children’s Hospital, Liverpool</i>
Dr Paul Cullinan	<i>Consultant Physician/Reader, Imperial College, London</i>
Mrs Sheila Edwards*	<i>Chief Executive, British Thoracic Society, London</i>
Ms Erica Evans	<i>Asthma Care Development Manager, Asthma UK, London</i>
Ms Monica Fletcher	<i>Chief Executive, Education for Health, Warwick</i>
Professor Chris Griffiths	<i>Professor of Primary Care, Institute of Health Science Education, London</i>
Dr Liam Heaney	<i>Senior Lecturer in Respiratory Medicine, Queen’s University, Belfast</i>
Ms Michele Hilton Boon*	<i>Information Officer, SIGN Executive</i>
Dr Steve Holmes	<i>General Practitioner and Chair, General Practice Airways Group, Somerset</i>
Mrs Ruth McArthur	<i>Practice Nurse/National Training Co-ordinator, Education for Health, East Kilbride</i>
Dr Cathy Nelson-Piercy	<i>Consultant Obstetric Physician, St Thomas’ Hospital, London</i>
Professor Martyn Partridge*	<i>Professor of Respiratory Medicine, Imperial College, London and Chief Medical Adviser, Asthma UK</i>
Dr James Paton*	<i>Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow</i>

Professor Ian Pavord*	<i>Consultant Physician/Honorary Professor of Medicine, Glenfield Hospital, Leicester</i>
Ms Elaine Carnegie	<i>Asthma Policy Officer, Asthma UK, Scotland</i>
Dr Hilary Pinnock	<i>General Practitioner, Whitstable Medical Practice, Kent</i>
Dr Safia Qureshi*	<i>Programme Director, SIGN</i>
Professor Colin Robertson	<i>Consultant in Emergency Medicine, Edinburgh Royal Infirmary</i>
Professor Mike Shields	<i>Professor of Child Health, Queen's University, Belfast</i>
Professor John Warner	<i>Professor of Paediatrics and Head of Department, Imperial College, London</i>
Dr John White	<i>Consultant Respiratory Physician, York District Hospital</i>

* Executive group

10.3 EVIDENCE REVIEW GROUPS

DIAGNOSIS

Dr Jon Couriel (Co-chair)	<i>Consultant in Paediatric Respiratory Medicine, Royal Liverpool Children's Hospital</i>
Dr James Paton (Co-chair)	<i>Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow</i>
Professor Ian Pavord (Co-chair)	<i>Consultant Physician/Honorary Professor of Medicine, Glenfield Hospital, Leicester</i>
Professor Justin Beilby	<i>Head of the Department of General Practice, University of Adelaide, Australia</i>
Professor Anne Chang	<i>Head of Child Health Division, Menzies School of Health Research, Darwin and Royal Children's Hospital, Brisbane, Australia</i>
Dr Peter Gibson	<i>Adult Respiratory Physician, John Hunter Chest Institute, New South Wales, Australia</i>
Professor Peter Helms	<i>Professor of Child Health, University of Aberdeen</i>
Dr Bernard Higgins	<i>Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne</i>
Mrs Ruth McArthur	<i>Practice Nurse/National Training Co-ordinator, Education for Health, East Kilbride</i>
Dr Sarah Mayell	<i>Specialist Registrar, Alder Hey Hospital, Liverpool</i>
Dr Dominick Shaw	<i>Specialist Registrar, City Hospital Campus, Nottingham</i>
Dr Mike Thomas	<i>Asthma UK Senior Research Fellow, University of Aberdeen/ General Practitioner, Gloucestershire</i>

NON-PHARMACOLOGICAL MANAGEMENT

Dr Paul Cullinan (Co-chair)	<i>Reader in Occupational and Environmental Lung Disease, Royal Brompton Hospital, London</i>
Professor John Warner (Co-chair)	<i>Professor of Paediatrics and Head of Department, Imperial College, London</i>
Dr David Bellamy	<i>General Practitioner, Bournemouth and Pool Primary Care Trust</i>
Dr Graham Devereux	<i>Consultant in Thoracic Medicine, Aberdeen Royal Infirmary</i>
Dr David Reilly	<i>Lead Consultant Physician, Glasgow Homoeopathic Hospital</i>

Dr Janet Rimmer	<i>Respiratory Physician, Darlinghurst, New South Wales, Australia</i>
Dr Lyn Smurthwaite	<i>Research Development Manager, Asthma UK, London</i>
Mrs Deryn Thompson	<i>Nursing Tutor, Division of Health Sciences, University of South Australia</i>

PHARMACOLOGICAL MANAGEMENT

Professor Neil Barnes (Co-chair)	<i>Consultant Respiratory Physician, Barts and The London NHS Trust</i>
Professor Mike Shields (Co-chair)	<i>Professor of Child Health, Queen's University, Belfast</i>
Dr Anne Boyter	<i>Senior Lecturer, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow</i>
Dr Steve Cunningham	<i>Consultant Paediatrician, Royal Hospital for Sick Children, Edinburgh</i>
Dr Graeme Currie	<i>Consultant Physician, Aberdeen Royal Infirmary</i>
Ms Grainne d'Ancona	<i>Lead Pharmacist for Medicine, Guys and St Thomas' Hospital, London</i>
Dr Mike McKean	<i>Consultant in Respiratory Paediatrics, Royal Victoria Infirmary, Newcastle upon Tyne</i>
Ms Linda Pearce	<i>Respiratory Nurse Consultant, West Suffolk Hospital</i>
Dr Savitha Pushparajah	<i>General Practitioner, London</i>
Dr Mike Smith	<i>Consultant Paediatrician, Craigavon Area Group Hospital, Northern Ireland</i>
Dr David Spencer	<i>Consultant Respiratory Paediatrician, Freeman Hospital, Newcastle upon Tyne</i>
Dr Alison Whittaker	<i>Consultant Physician, Newport Chest Clinic, Gwent</i>

INHALER DEVICES

Dr John White (Chair)	<i>Consultant Respiratory Physician, York District Hospital</i>
Dr Chris Cates	<i>Senior Research Fellow, St George's, University of London</i>
Sr Karen Heslop	<i>Respiratory Nurse Specialist, Royal Victoria Infirmary, Newcastle upon Tyne</i>
Dr Alex Horsley	<i>Specialist Registrar, Western General Hospital, Edinburgh</i>

MANAGEMENT OF ACUTE ASTHMA

Dr Gary Connett (Co-chair)	<i>Consultant Paediatrician, Southampton General Hospital</i>
Professor Colin Robertson (Co-chair)	<i>Consultant in Emergency Medicine, Edinburgh Royal Infirmary</i>
Dr Richard Chavasse	<i>Consultant in Respiratory Paediatrics, St Helier Hospital, Surrey</i>
Dr Mike Greenstone	<i>Consultant Physician, Castle Hill Hospital, East Yorkshire</i>
Dr Nick Innes	<i>Consultant in Respiratory and General Medicine, The Ipswich Hospital</i>
Dr Mark Levy	<i>General Practitioner, The Kenton Bridge Medical Centre, Middlesex</i>
Dr Rob Niven	<i>Senior Lecturer in Respiratory Medicine, Whythenshawe Hospital, Manchester</i>

Dr Ronan O'Driscoll	<i>Respiratory Physician, Hope Hospital, Salford</i>
Dr Peter Weller	<i>Consultant Paediatrician (Respiratory Medicine), Birmingham Children's Hospital</i>

DELIVERY/ ORGANISATION OF CARE

Professor Chris Griffiths (Chair)	<i>Professor of Primary Care, Institute of Health Science Education, London</i>
Ms Monica Fletcher	<i>Chief Executive, Education for Health, Warwick</i>
Professor David Price	<i>GPIAG Professor of Primary Care Respiratory Medicine, Foresterhill Health Centre, Aberdeen</i>
Dr Richard Russell	<i>Consultant Physician, Heatherwood and Wexham Park Hospitals, Berkshire</i>

PATIENT EDUCATION, SELF MANAGEMENT AND COMPLIANCE

Dr Hilary Pinnock (Chair)	<i>General Practitioner, Whitstable Medical Practice, Kent</i>
Dr Graham Douglas	<i>Consultant Respiratory Physician, Aberdeen Royal Infirmary</i>
Mrs Erica Evans	<i>Care Development Manager, Asthma UK, London</i>
Dr Liesl Osman	<i>Senior Research Fellow, Aberdeen Royal Infirmary</i>

SPECIAL SITUATIONS

Difficult asthma

Dr Liam Heaney (Chair)	<i>Senior Lecturer in Respiratory Medicine, Queens University, Belfast</i>
Dr Chris Brightling	<i>Senior Clinical Research Fellow, Glenfield Hospital, Leicester</i>
Dr Andrew Menzies-Gow	<i>Consultant Respiratory Physician, Royal Brompton Hospital, London</i>
Dr Brian Smith	<i>South Australian State President of the Thoracic Society of Australia</i>
Dr Nicola Wilson	<i>Honorary Consultant Paediatrician, Royal Brompton Hospital, London</i>

Asthma in pregnancy

Dr Cathy Nelson-Piercy (Chair)	<i>Consultant Obstetric Physician, St Thomas' Hospital, London</i>
Dr Graham Douglas	<i>Consultant Respiratory Physician, Aberdeen Royal Infirmary</i>
Dr Bernard Higgins	<i>Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne</i>
Mrs Ruth McArthur	<i>Practice Nurse/National Training Co-ordinator Education for Health, East Kilbride</i>

Occupational asthma

Dr Sherwood Burge (Chair)	<i>Consultant Respiratory Physician, Birmingham Heartlands Hospital</i>
Professor Anthony Frew	<i>Professor of Allergy and Respiratory Medicine, Brighton General Hospital</i>

10.4 DISSEMINATION GROUP

Professor Martyn Partridge (Chair)	<i>Professor of Respiratory Medicine, Imperial College, London and Chief Medical Adviser, Asthma UK</i>
Mrs Sheila Edwards	<i>Chief Executive, British Thoracic Society, London</i>
Ms Monica Fletcher	<i>Chief Executive, Education for Health, Warwick</i>
Dr Bernard Higgins	<i>Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne</i>
Dr Steve Holmes	<i>General Practitioner and Chair, General Practice Airways Group, Somerset</i>
Dr James Paton	<i>Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow</i>
Dr Hilary Pinnock	<i>General Practitioner, Whitstable Medical Practice, Kent</i>
Dr Safia Qureshi	<i>Programme Director, SIGN</i>
Mrs Sally Welham	<i>Deputy Chief Executive, British Thoracic Society, London</i>

10.5 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline built on the reviews carried out for the original (2003) version of the guideline and subsequent updates. The specific areas updated in this version of the guideline were:

- Non-pharmacological management
- Paediatric diagnosis
- Pharmacological management
- Difficult asthma.

All searches covered the Cochrane Library, Embase, and Medline. The time period covered depended on the topic, but all were brought up to date for the beginning of 2007. A copy of the search narrative, including listings of strategies, is available on the SIGN website as part of the supporting material for this guideline.

10.6 CONSULTATION AND PEER REVIEW

10.6.1 CONSULTATION

The most recent changes to this guideline were presented for discussion in draft form at the Winter Meeting of the British Thoracic Society in December 2007. The draft guideline was also available on the SIGN and BTS websites for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

10.6.2 SPECIALIST REVIEWERS

The guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN and the BTS are very grateful to all of these experts for their contribution to the guideline.

Dr Sandra Anderson	<i>Principal Hospital Scientist, Royal Prince Alfred Hospital, Sydney, Australia</i>
Professor Richard Beasley	<i>Professor of Medicine, Medical Research Institute of New Zealand, Wellington</i>
Mr Michael Dennis	<i>Deputy Head of Prescribing, Great Yarmouth and Waveney (Teaching) PCT, Suffolk</i>
Dr Kevin Gruffydd-Jones	<i>Education Member, General Practice Airways Group and General Practitioner, Box Surgery, Wiltshire</i>
Dr John Haughney	<i>General Practitioner, Alison Lea Medical Centre, East Kilbride</i>
Miss Tracy Horner	<i>Medicines Management Technician, Bexhill Hospital, East Sussex</i>
Dr Norman Johnson	<i>Chairman of the BTS Standards of Care Committee, British Thoracic Society, London</i>
Dr Duncan Keeley	<i>General Practitioner, Thame Health Centre, Oxon</i>
Professor Helen Redell	<i>Clinical Associate Professor, University of Sydney, Australia</i>
Dr Robert Scott-Jupp	<i>Consultant Paediatrician, Salisbury District Hospital, Salisbury</i>
Professor Anne Tattersfield	<i>Head of Respiratory Medicine, University of Nottingham</i>
Professor Neil C Thomson	<i>Professor of Respiratory Medicine, Gartnavel General Hospital, Glasgow</i>
Dr Mark Woodhead	<i>Consultant in General and Respiratory Medicine, Central Manchester and Manchester Children's University Hospitals</i>

Abbreviations

ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ACT	Asthma Control Test
ACTH	adrenocorticotrophic hormone
AQLQ	Asthma Quality of Life Questionnaire
BDP	beclometasone
BTS	British Thoracic Society
COPD	chronic obstructive pulmonary disease
CXR	chest X-ray
DPI	dry powder inhaler
ED	emergency department
ETS	environmental tobacco smoke
FE _{NO}	exhaled nitric oxide concentration
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
GMS	General Medical Services
GP	general practitioner
GRASSIC	Grampian Asthma Study in Integrated Care
HDU	high dependency unit
ICU	intensive care unit
IM	intramuscular
IOS	impulse oscillometry
LABA	long-acting β_2 agonist
MDI	metered dose inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
n-3PUFA	omega-3 polyunsaturated fatty acid
NIV	non-invasive ventilation
PaCO ₂	partial pressure of carbon dioxide in arterial blood
PaO ₂	partial pressure of oxygen in arterial blood
PC ₂₀	the provocative concentration of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV ₁
PD ₂₀	the provocative dose of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV ₁
PEF	peak expiratory flow
PEF A%H	peak expiratory flow amplitude percent highest
PICU	paediatric intensive care unit
PN	practice nurse

ppb	parts per billion
QOF	Quality and Outcomes Framework
RCP	Royal College of Physicians
RCT	randomised controlled trial
RV	residual volume
SIGN	Scottish Intercollegiate Guidelines Network
SpO ₂	saturation of peripheral oxygen
sRaw	specific airways resistance
VE _{max}	ventilation at maximal exercise capacity

Annex 1

Summary of search histories by section

Literature searches to support the various sections of this guideline are conducted on a rolling basis. This summary indicates the currency of the searches supporting each section. Searches in all databases began with the earliest year available at that time, which varied from database to database; for example, searches in Embase extended back to 1980 and in CINAHL to 1982. Specific date coverage is provided for Medline. Detailed search strategies are available on the SIGN website in the supplementary material section. Sections that have not been updated since 2006 will be the subject of renewed searches in 2008-09, after which the guideline will be updated on line.

Section 2 Diagnosis

Diagnosis in children

The search was last updated in April 2007. Coverage in Medline extends from 2003-2006. This search supplemented the broader search on diagnosis conducted for the original 2003 diagnosis section.

Diagnosis in adults; monitoring

The search was last updated in February 2006. Coverage in Medline extends from 1966-2005.

Section 3 Non-pharmacological management

The search was last updated in February 2006. Coverage in Medline extends from 1966-2005.

Section 4 Pharmacological management

The search was last updated in June 2007. Coverage in Medline extends from 1966-May 2007.

Section 5 Inhaler devices

The search was last updated in January 2004. Coverage in Medline extends from 1998-January 2004.

Section 6 Management of acute asthma

The search was last updated in January 2004. Coverage in Medline extends from 1966-2003.

Section 7 Special situations

Difficult asthma

The search was conducted in July 2007 and covered 1996-June 2007.

Asthma in pregnancy

The search was last updated in February 2004. Coverage in Medline extends from 1966-January 2004.

Occupational asthma

The search was last updated by SIGN in March 2003. In 2005, a systematic review by the British Occupational Health Research Foundation was used as the basis for updating this section.

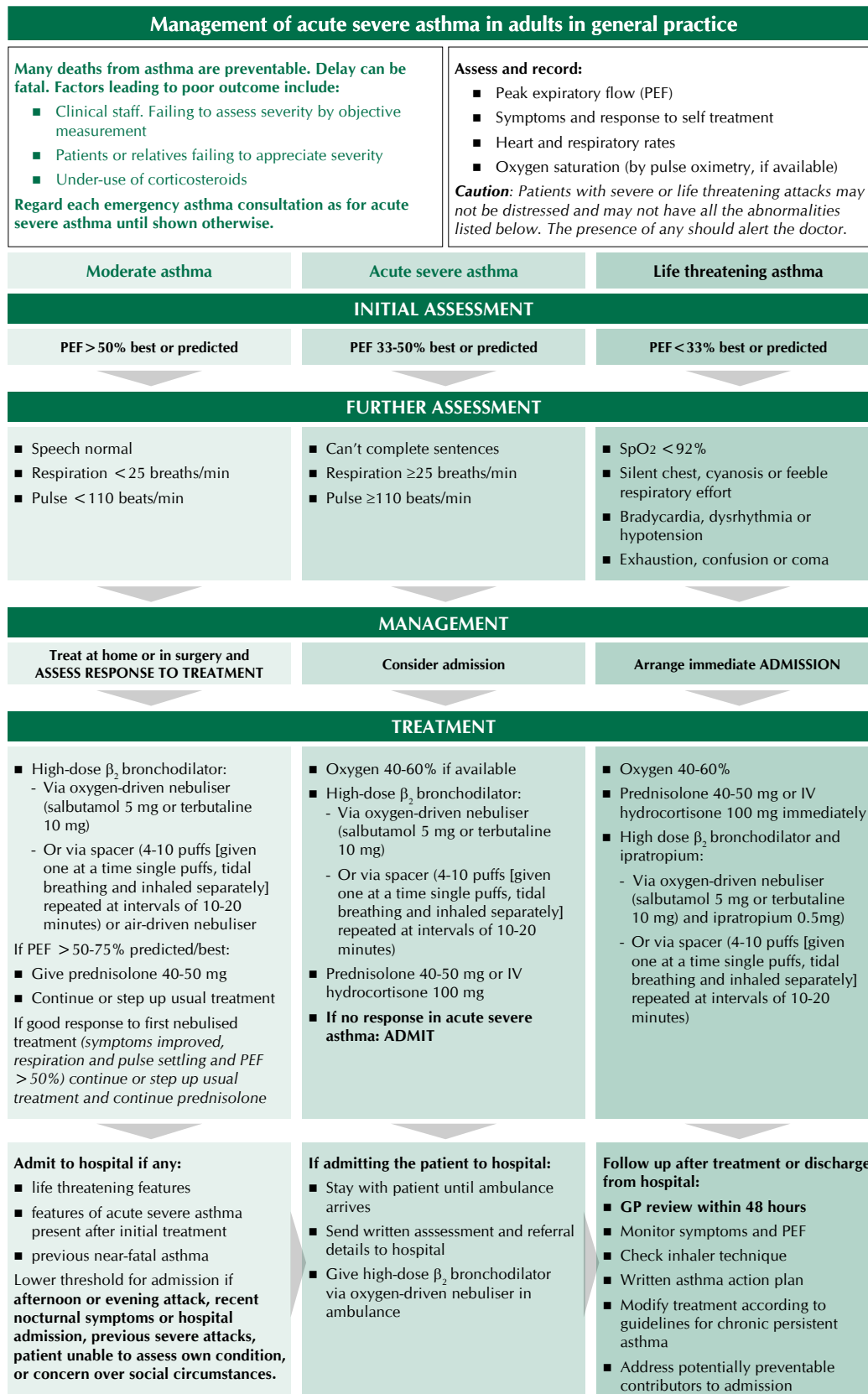
Section 8 Organisation and delivery of care, and audit

The search was last updated in March 2003. Coverage in Medline extends from 1966-2003.

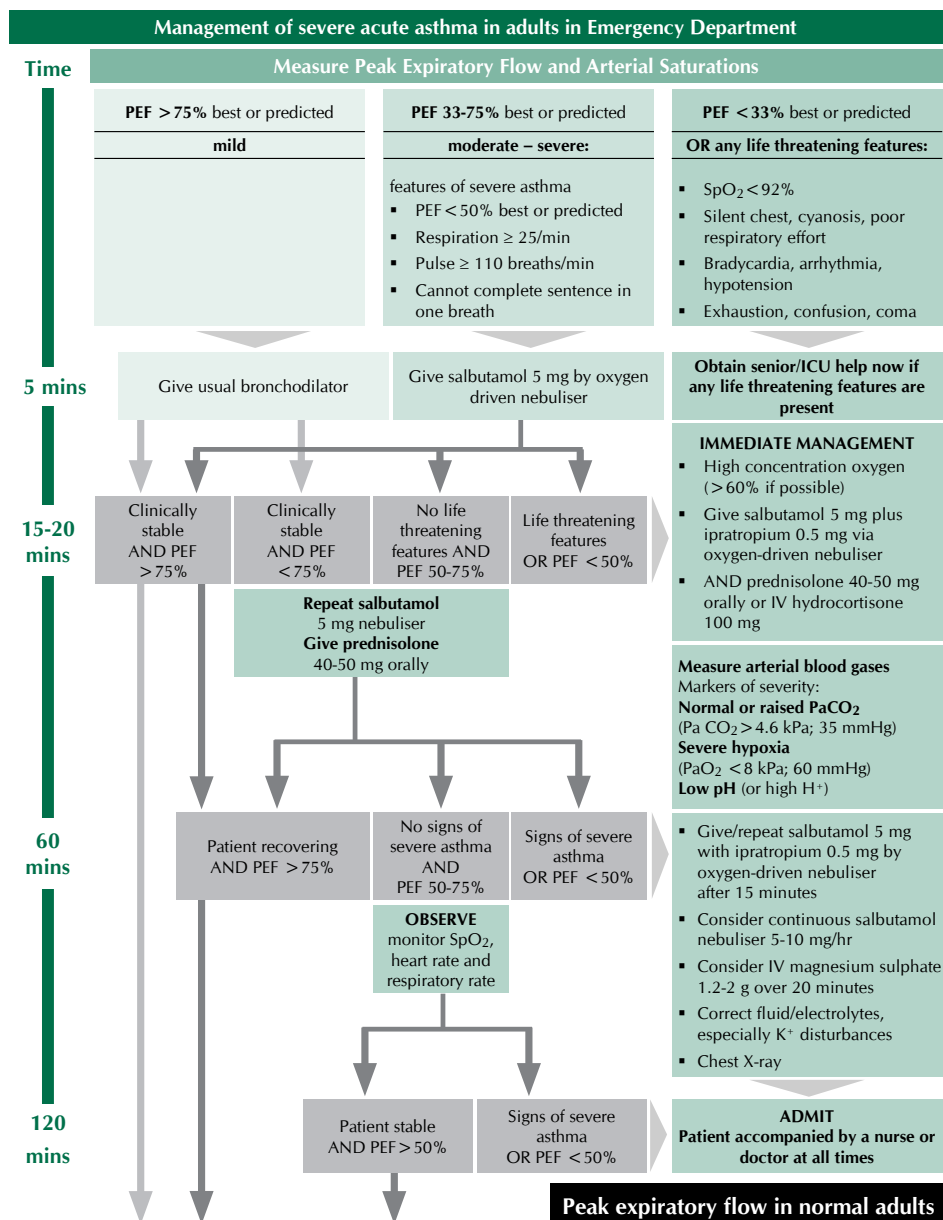
Section 9 Patient education and self management

The search was last updated in February 2006. Coverage in Medline extends from 1966-2005.

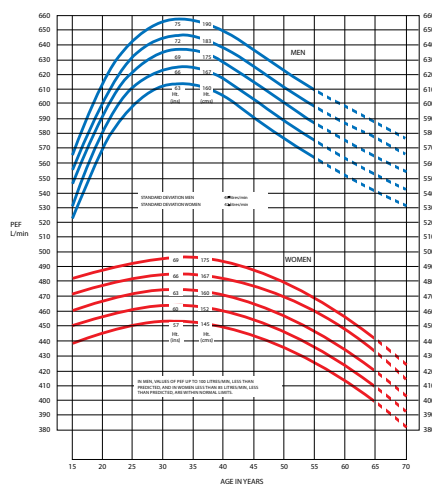
Annex 2



Annex 3

**POTENTIAL DISCHARGE**

- In all patients who received nebulised β_2 agonists prior to presentation, consider an extended observation period prior to discharge
- If PEF < 50% on presentation, give prednisolone 40-50 mg/day for 5 days
- In all patients ensure treatment supply of inhaled steroid and β_2 agonist and check inhaler technique
- Arrange GP follow up 2 days post-discharge
- Fax discharge letter to GP
- Refer to asthma liaison nurse/chest clinic

Peak expiratory flow in normal adults

Annex 4

Management of acute severe asthma in adults in hospital

Features of acute severe asthma

- Peak expiratory flow (PEF) 33-50% of best (use % predicted if recent best unknown)
- Can't complete sentences in one breath
- Respirations ≥ 25 breaths/min
- Pulse ≥ 110 beats/min

Life threatening features

- PEF $< 33\%$ of best or predicted
- SpO₂ $< 92\%$
- Silent chest, cyanosis, or feeble respiratory effort
- Bradycardia, dysrhythmia, or hypotension
- Exhaustion, confusion, or coma

If a patient has any life threatening feature, measure arterial blood gases. No other investigations are needed for immediate management.

Blood gas markers of a life threatening attack:

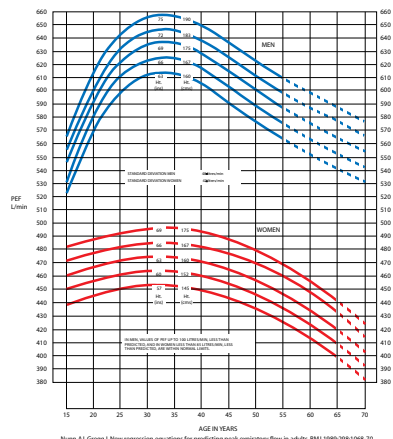
- Normal (4.6-6 kPa, 35-45 mmHg) PaCO₂
- Severe hypoxia: PaO₂ < 8 kPa (60mmHg) irrespective of treatment with oxygen
- A low pH (or high H⁺)

Caution: Patients with severe or life threatening attacks may not be distressed and may not have all these abnormalities. The presence of any should alert the doctor.

Near fatal asthma

- Raised PaCO₂
- Requiring mechanical ventilation with raised inflation pressures

Peak expiratory flow in normal adults



IMMEDIATE TREATMENT

- Oxygen 40-60% (CO₂ retention is not usually aggravated by oxygen therapy in asthma)
- Salbutamol 5 mg or terbutaline 10 mg via an oxygen-driven nebuliser
- Ipratropium bromide 0.5 mg via an oxygen-driven nebuliser
- Prednisolone tablets 40-50 mg or IV hydrocortisone 100 mg or both if very ill
- No sedatives of any kind
- Chest X ray if pneumothorax or consolidation are suspected or patient requires mechanical ventilation

IF LIFE THREATENING FEATURES ARE PRESENT:

- Discuss with senior clinician and ICU team
- Add IV magnesium sulphate 1.2-2 g infusion over 20 minutes (unless already given)
- Give nebulised β_2 agonist more frequently e.g. salbutamol 5 mg up to every 15-30 minutes or 10 mg continuously hourly

SUBSEQUENT MANAGEMENT

IF PATIENT IS IMPROVING continue:

- 40-60% oxygen
- Prednisolone 40-50mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulised β_2 agonist and ipratropium 4-6 hourly

IF PATIENT NOT IMPROVING AFTER 15-30 MINUTES:

- Continue oxygen and steroids
- Give nebulised β_2 agonist more frequently e.g. salbutamol 5 mg up to every 15-30 minutes or 10 mg continuously hourly
- Continue ipratropium 0.5 mg 4-6 hourly until patient is improving

IF PATIENT IS STILL NOT IMPROVING:

- Discuss patient with senior clinician and ICU team
- IV magnesium sulphate 1.2-2 g over 20 minutes (unless already given)
- Senior clinician may consider use of IV β_2 agonist or IV aminophylline or progression to mechanical ventilation

MONITORING

- Repeat measurement of PEF 15-30 minutes after starting treatment
- Oximetry: maintain SpO₂ $> 92\%$
- Repeat blood gas measurements within 2 hours of starting treatment if:
 - initial PaO₂ < 8 kPa (60 mmHg) unless subsequent SpO₂ $> 92\%$
 - PaCO₂ normal or raised
 - patient deteriorates
- Chart PEF before and after giving β_2 agonists and at least 4 times daily throughout hospital stay

Transfer to ICU accompanied by a doctor prepared to intubate if:

- Deteriorating PEF, worsening or persisting hypoxia, or hypercapnea
- Exhaustion, feeble respirations, confusion or drowsiness
- Coma or respiratory arrest

DISCHARGE

When discharged from hospital, patients should have:

- Been on discharge medication for 24 hours and have had inhaler technique checked and recorded
- PEF $> 75\%$ of best or predicted and PEF diurnal variability $< 25\%$ unless discharge is agreed with respiratory physician
- Treatment with **oral and inhaled steroids** in addition to bronchodilators
- Own PEF meter and **written asthma action plan**
- GP follow up arranged within 2 working days
- Follow up appointment in respiratory clinic within 4 weeks

Patients with severe asthma (indicated by need for admission) and adverse behavioural or psychosocial features are at risk of further severe or fatal attacks

- Determine reason(s) for exacerbation and admission
- Send details of admission, discharge and potential best PEF to GP

Management of acute asthma in children in general practice

Age 2-5 years

ASSESS ASTHMA SEVERITY

<p>Moderate exacerbation</p> <ul style="list-style-type: none"> ■ SpO₂ ≥92% ■ Able to talk ■ Heart rate ≤130/min ■ Respiratory rate ≤50/min 	<p>Severe exacerbation</p> <ul style="list-style-type: none"> ■ SpO₂ <92% ■ Too breathless to talk ■ Heart rate >130/min ■ Respiratory rate >50/min ■ Use of accessory neck muscles 	<p>Life threatening asthma</p> <p>SpO₂ < 92% plus any of:</p> <ul style="list-style-type: none"> ■ Silent chest ■ Poor respiratory effort ■ Agitation ■ Altered consciousness ■ Cyanosis
<p>■ β₂ agonist 4-6 puffs via spacer ± facemask</p> <p>■ Consider soluble prednisolone 20 mg</p>	<p>■ Oxygen via face mask</p> <p>■ 4-6 puffs of β₂ agonist [given one at a time single puffs, tidal breathing and inhaled separately] at intervals of 10-20 minutes or nebulised salbutamol 2.5 mg or terbutaline 5 mg</p> <p>■ Soluble prednisolone 20 mg</p>	<p>■ Oxygen via face mask</p> <p>■ Nebulise:</p> <ul style="list-style-type: none"> - salbutamol 2.5 mg or terbutaline 5 mg + - ipratropium 0.25 mg <p>■ Soluble prednisolone 20 mg or</p> <p>■ IV hydrocortisone 50 mg</p>
<p>Increase β₂ agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response</p>	<p>Assess response to treatment 15 mins after β₂ agonist</p>	
<p>IF POOR RESPONSE ARRANGE ADMISSION</p>	<p>IF POOR RESPONSE REPEAT β₂ AGONIST AND ARRANGE ADMISSION</p>	<p>REPEAT β₂ AGONIST VIA OXYGEN-DRIVEN NEBULISER WHILEST ARRANGING IMMEDIATE HOSPITAL ADMISSION</p>
<p>GOOD RESPONSE</p> <ul style="list-style-type: none"> ■ Continue β₂ agonist via spacer or nebuliser, as needed but not exceeding 4-hourly ■ If symptoms are not controlled repeat β₂ agonist and refer to hospital ■ Continue prednisolone for up to 3 days ■ Arrange follow-up clinic visit 	<p>POOR RESPONSE</p> <ul style="list-style-type: none"> ■ Stay with patient until ambulance arrives ■ Send written assessment and referral details ■ Repeat β₂ agonist via oxygen-driven nebuliser in ambulance 	

LOWER THRESHOLD FOR ADMISSION IF:

- Attack in late afternoon or at night
- Recent hospital admission or previous severe attack
- Concern over social circumstances or ability to cope at home

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

Age > 5 years

ASSESS ASTHMA SEVERITY

<p>Moderate exacerbation</p> <ul style="list-style-type: none"> ■ SpO₂ ≥92% ■ PEF ≥50% best or predicted ■ Able to talk ■ Heart rate ≤120/min ■ Respiratory rate ≤30/min 	<p>Severe exacerbation</p> <ul style="list-style-type: none"> ■ SpO₂ <92% ■ PEF ≥50% best or predicted ■ Too breathless to talk ■ Heart rate >120/min ■ Respiratory rate >30/min ■ Use of accessory neck muscles 	<p>Life threatening asthma</p> <p>SpO₂ <92% plus any of:</p> <ul style="list-style-type: none"> ■ PEF <33% best or predicted ■ Silent chest ■ Poor respiratory effort ■ Agitation ■ Altered consciousness ■ Cyanosis
<p>■ β₂ agonist 4-6 puffs via spacer</p> <p>■ Consider soluble prednisolone 30-40 mg</p>	<p>■ Oxygen via face mask</p> <p>■ 4-6 puffs of β₂ agonist [given one at a time single puffs, tidal breathing and inhaled separately] at intervals of 10-20 minutes or nebulised salbutamol 2.5-5 mg or terbutaline 5-10 mg</p> <p>■ Soluble prednisolone 30-40 mg</p>	<p>■ Oxygen via face mask</p> <p>■ Nebulise:</p> <ul style="list-style-type: none"> - salbutamol 5 mg or terbutaline 10 mg + - ipratropium 0.25 mg <p>■ Soluble prednisolone 30-40 mg or</p> <p>■ IV hydrocortisone 100 mg</p>
<p>Increase β₂ agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response</p>	<p>Assess response to treatment 15 mins after β₂ agonist</p>	
<p>IF POOR RESPONSE ARRANGE ADMISSION</p>	<p>IF POOR RESPONSE REPEAT β₂ AGONIST AND ARRANGE ADMISSION</p>	<p>REPEAT β₂ AGONIST VIA OXYGEN-DRIVEN NEBULISER WHILEST ARRANGING IMMEDIATE HOSPITAL ADMISSION</p>
<p>GOOD RESPONSE</p> <ul style="list-style-type: none"> ■ Continue β₂ agonist via spacer or nebuliser, as needed but not exceeding 4-hourly ■ If symptoms are not controlled repeat β₂ agonist and refer to hospital ■ Continue prednisolone for up to 3 days ■ Arrange follow-up clinic visit 	<p>POOR RESPONSE</p> <ul style="list-style-type: none"> ■ Stay with patient until ambulance arrives ■ Send written assessment and referral details ■ Repeat β₂ agonist via oxygen-driven nebuliser in ambulance 	

LOWER THRESHOLD FOR ADMISSION IF:

- Attack in late afternoon or at night
- Recent hospital admission or previous severe attack
- Concern over social circumstances or ability to cope at home

NB: If a patient has signs and symptoms across categories, always treat according to their most severe features

Annex 5

Annex 6

Management of acute asthma in children in Emergency Department

Age 2-5 years

ASSESS ASTHMA SEVERITY



Age > 5 years

ASSESS ASTHMA SEVERITY



Management of acute asthma in children in hospital

Age 2-5 years

ASSESS ASTHMA SEVERITY

Moderate exacerbation	Severe exacerbation	Life threatening asthma
<ul style="list-style-type: none"> SPO₂ ≥ 92% No clinical features of severe asthma 	<ul style="list-style-type: none"> SPO₂ < 92% Too breathless to talk or eat Heart rate > 130/min Respiratory rate > 50/min Use of accessory neck muscles 	<ul style="list-style-type: none"> SPO₂ < 92% plus any of: <ul style="list-style-type: none"> Silent chest Poor respiratory effort Agitation Altered consciousness Cyanosis
Oxygen via face mask/nasal prongs to achieve normal saturations		
<ul style="list-style-type: none"> β₂ agonist 4-6 puffs via spacer ± facemask (given one at a time single puffs, tidal breathing and inhaled separately) Increase β₂ agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response Consider soluble oral prednisolone 20 mg 	<ul style="list-style-type: none"> β₂ agonist 4-10 puffs via spacer ± facemask or nebulised salbutamol 2.5 mg or terbutaline 5 mg Soluble prednisolone 20 mg or IV hydrocortisone 4 mg/kg Repeat β₂ agonist up to every 20-30 minutes according to response If poor response add 0.25 mg nebulised ipratropium bromide 	<ul style="list-style-type: none"> Nebulised β₂ agonist: salbutamol 2.5 mg or terbutaline 5 mg plus ipratropium bromide 0.25 mg nebulised IV hydrocortisone 4 mg/kg
Reassess within 1 hour		Discuss with senior clinician, PICU team or paediatrician
		Repeat bronchodilators every 20-30 minutes

ASSESS RESPONSE TO TREATMENT
Record respiratory rate, heart rate and oxygen saturation every 1-4 hours

RESPONDING	NOT RESPONDING
<ul style="list-style-type: none"> Continue bronchodilators 1-4 hours pm Discharge when stable on 4 hourly treatment Continue oral prednisolone for up to 3 days 	<ul style="list-style-type: none"> Arrange HDU/PICU transfer Consider: <ul style="list-style-type: none"> Chest X-ray and blood gases IV salbutamol 1.5 mcg/kg bolus over 10 minutes followed by continuous infusion 1-5 mcg/kg/min (dilute to 200 mcg/ml) IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1 mg/kg/hour
At discharge	
<ul style="list-style-type: none"> Ensure stable on 4 hourly inhaled treatment Review the need for regular treatment and the use of inhaled steroids Review inhaler technique Provide a written asthma action plan for treating future attacks Arrange follow up according to local policy 	

Age > 5 years

ASSESS ASTHMA SEVERITY

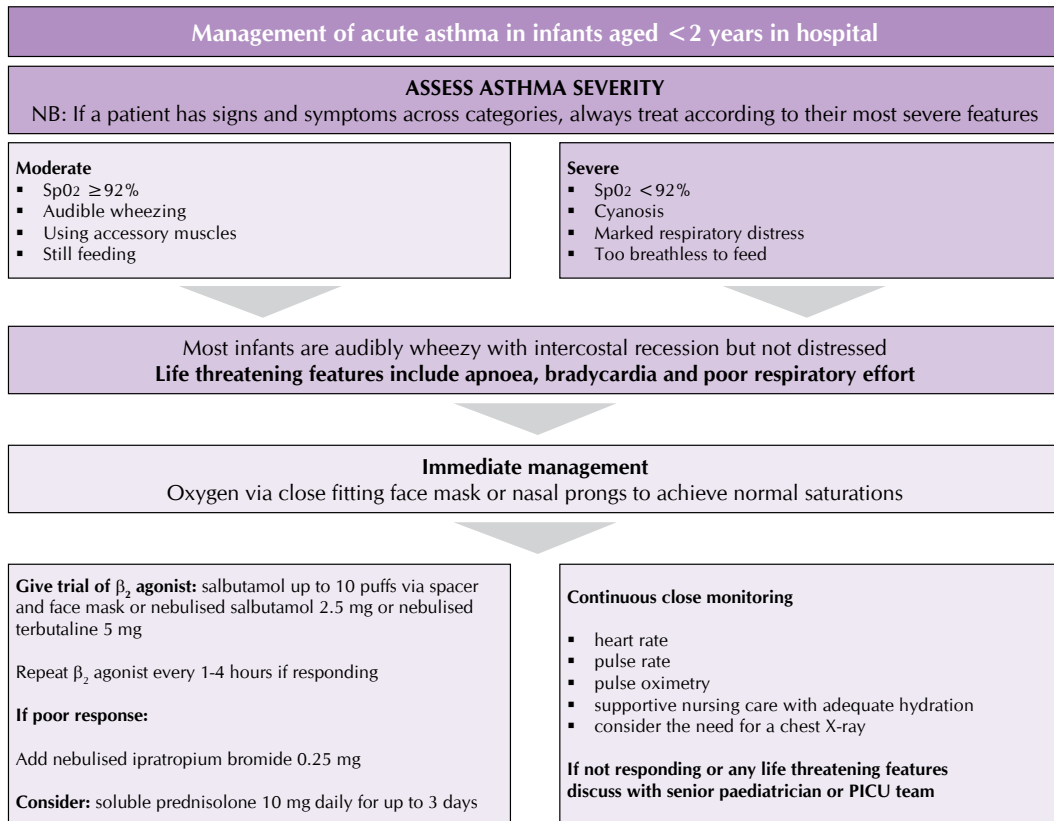
Moderate exacerbation	Severe exacerbation	Life threatening asthma
<ul style="list-style-type: none"> SPO₂ ≥ 92% PEF < 50% best or predicted No clinical features of severe asthma 	<ul style="list-style-type: none"> SPO₂ < 92% PEF < 50% best or predicted Heart rate > 120/min Respiratory rate > 30/min Use of accessory neck muscles 	<ul style="list-style-type: none"> SPO₂ < 92% plus any of: <ul style="list-style-type: none"> PEF < 33% best or predicted Silent chest Poor respiratory effort Altered consciousness Cyanosis
Oxygen via face mask/nasal prongs to achieve normal saturations		
<ul style="list-style-type: none"> β₂ agonist 4-6 puffs via spacer Increase β₂ agonist dose by 2 puffs every 2 minutes up to 10 puffs according to response Oral prednisolone 30-40 mg 	<ul style="list-style-type: none"> β₂ agonist 4-10 puffs via spacer or nebulised salbutamol 2.5-5 mg or terbutaline 5-10 mg Oral prednisolone 30-40 mg or IV hydrocortisone 4 mg/kg if vomiting If poor response nebulised ipratropium bromide 0.25 mg Repeat β₂ agonist and ipratropium up to every 20-30 minutes according to response 	<ul style="list-style-type: none"> Nebulised β₂ agonist: salbutamol 5 mg or terbutaline 10 mg plus ipratropium bromide 0.25 mg nebulised IV hydrocortisone 4 mg/kg
Reassess within 1 hour		Discuss with senior clinician, PICU team or paediatrician
		Repeat bronchodilators every 20-30 minutes

ASSESS RESPONSE TO TREATMENT
Record respiratory rate, heart rate, oxygen saturation and PEF/FEV every 1-4 hours

RESPONDING	NOT RESPONDING
<ul style="list-style-type: none"> Continue bronchodilators 1-4 hours pm Discharge when stable on 4 hourly treatment Continue oral prednisolone 30-40 mg for up to 3 days 	<ul style="list-style-type: none"> Continue 20-30 minute nebulisers and arrange HDU/PICU transfer Consider: Chest X-ray and blood gases Consider risks and benefits of: <ul style="list-style-type: none"> Bolus IV salbutamol 1.5 mcg/kg if not already given Continuous IV salbutamol infusion 1-5 mcg/kg/min (200 mcg/ml solution) IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1mg/kg/hour Bolus IV infusion of magnesium sulphate 40 mg/kg (max 2 g) over 20 minutes
At discharge	
<ul style="list-style-type: none"> Ensure stable on 4 hourly inhaled treatment Review the need for regular treatment and the use of inhaled steroids Review inhaler technique Provide a written asthma action plan for treating future attacks Arrange follow up according to local policy 	

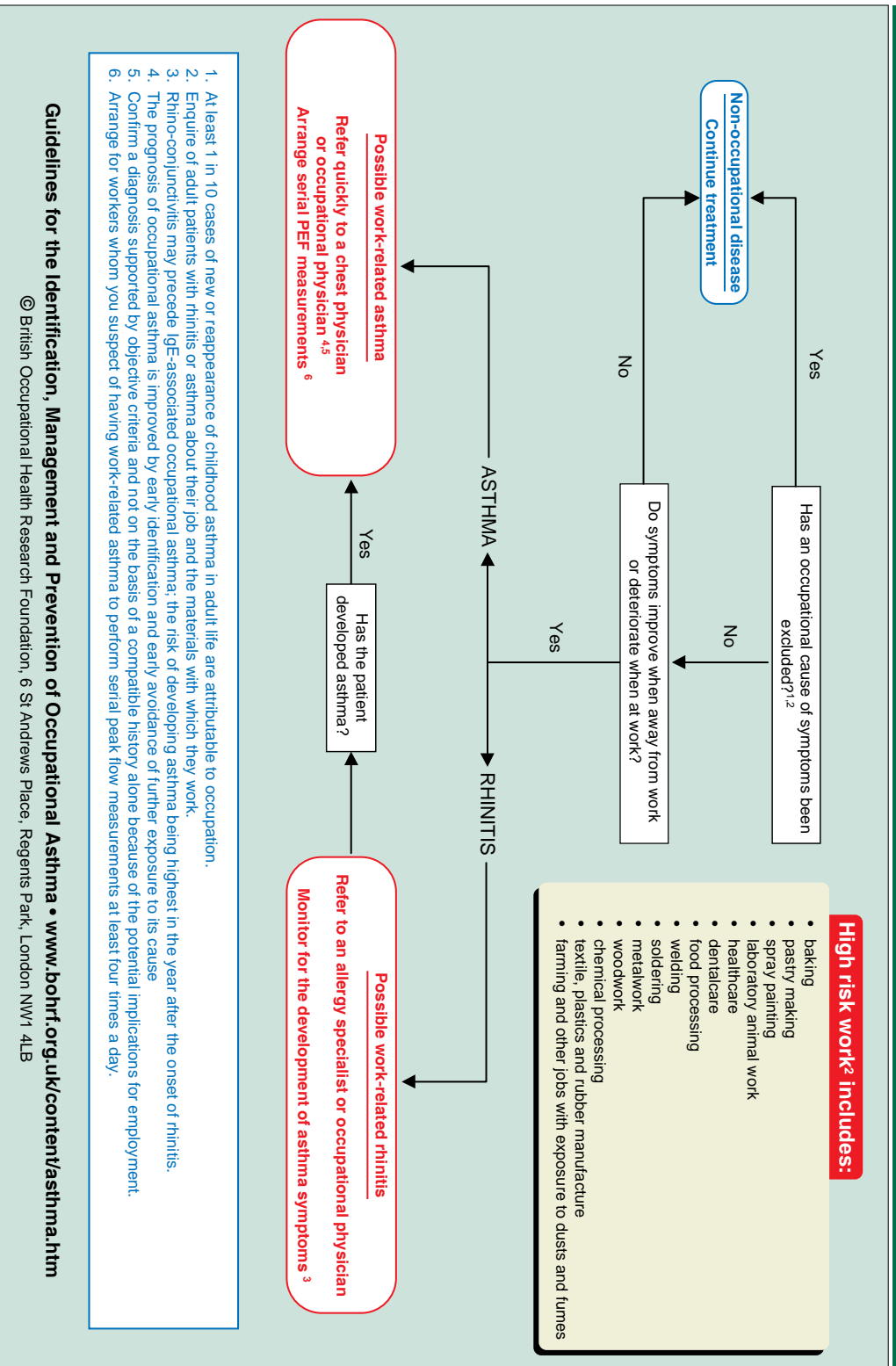
Annex 7

Annex 8



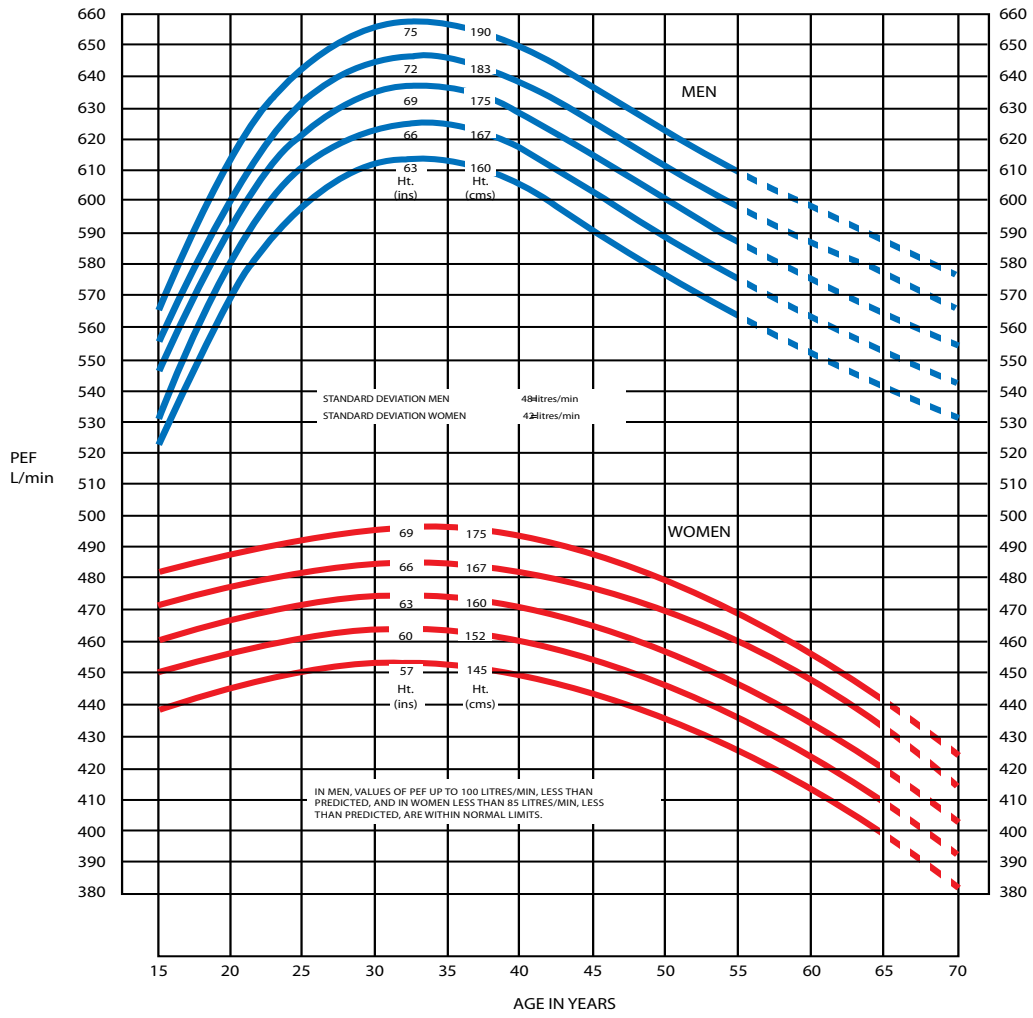
Annex 9

WORK-RELATED ASTHMA AND RHINITIS: CASE FINDING AND MANAGEMENT IN PRIMARY CARE



Annex 10

Peak expiratory flow in normal adults



Nunn AJ, Gregg I. New regression equations for predicting peak expiratory flow in adults. BMJ 1989;298:1068-70.

Annex 11

About your personal asthma action plan

This plan is intended to be used by people with asthma aged 12 and above.

Your doctor or nurse will fill in this plan with you and explain the different medicines that you should take to control your asthma. It shows you how to recognise when your asthma is getting worse and what you can do about it. It is reassuring to know that by taking steps early, severe asthma attacks can usually be prevented.

Updating your personal asthma action plan

Because your asthma symptoms can change from day to day, your doctor or nurse may need to change your plan. You should have your asthma reviewed at least once a year.

If your medicine has been changed or increased, visit your doctor or nurse after one month to review your asthma. Do not stop taking your asthma medicines without talking to your doctor or nurse first.





Asthma UK advice line
Ask an asthma nurse specialist
08457 01 02 03
asthma.org.uk/advice

Asthma UK membership
Receive a number of Asthma UK newsletters a year
020 7704 5888
members@asthma.org.uk

Asthma UK website
Read the latest independent advice and news on asthma
asthma.org.uk

Asthma UK publications
Request booklets, brochures and our e-newsletters with information on every aspect of asthma.
020 7704 5888
info@asthma.org.uk

Asthma UK, Providence House, Providence Place, London W1 0PT
T: 020 7704 2266 F: 020 7704 0740
© 2004 Asthma UK. Registered charity number 262314

Asthma UK advice line
Ask an asthma nurse specialist
08457 01 02 03
asthma.org.uk/advice

Asthma UK publications
Request a personal asthma action plan and our specialist advice independent, specialist advice and more expert advice
020 7704 5888
info@asthma.org.uk

Asthma UK website
Read the latest independent advice and news on asthma
asthma.org.uk

Asthma UK membership
Receive a number of Asthma UK newsletters a year
020 7704 5888
members@asthma.org.uk

Personal asthma action plan

Be in control

Asthma UK, Providence House, Providence Place, London W1 0PT
T: 020 7704 2266 F: 020 7704 0740
© 2004 Asthma UK. Registered charity number 262314

Asthma medicine card

Name: _____

Relationship to you: _____

Next of kin contact number: _____

Doctor or nurse contact number: _____

Best peak flow and date taken: _____

Drug allergies: _____

Date plan updated: _____

Notes: _____

What you can do

Make sure you are taking your medicines as discussed with your doctor or nurse – this information should be written in this card.

Ask your doctor or nurse for a personal asthma action plan. This will help you to know what to do if your symptoms get worse or do not improve.

Annex 11 (contd)

Date you started this diary		2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	
Have you had difficulty sleeping because of your asthma symptoms (excluding cough)?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Has your asthma interfered with your usual activities (eg recreation, work or school)?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Your medicine (ie, how much?)																						
When?																						
700																						
600																						
500																						
400																						
300																						
200																						
180																						
160																						
140																						
120																						
M																						
T																						
W																						
T																						
F																						
S																						
M																						
T																						
W																						
T																						
F																						
S																						
M																						
T																						
W																						
T																						
F																						
S																						
M																						
T																						
W																						
T																						
F																						
S																						

References

- British Guideline on the Management of Asthma. *Thorax* 2003;58(Suppl 1):i1-94.
- Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developer's Handbook. Edinburgh: SIGN; 2008.
- North of England Evidence Based Guideline Development Project. The primary care management of asthma in adults. Newcastle upon Tyne: University of Newcastle upon Tyne, Centre for Health Services Research; 1999. Report No. 97.
- Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;82(4):327-32.
- Dodge R, Martinez FD, Cline MG, Lebowitz MD, Burrows B. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. *J Allergy Clin Immunol* 1996;98(1):48-54.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.
- Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986;61(7):642-6.
- Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood - a birth cohort study. *Arch Dis Child* 1991;66(9):1050-3.
- Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312(7040):1195-9.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1):1403-6.
- Galant SP, Crawford LJ, Morpew T, Jones CA, Bassin S. Predictive value of a cross-cultural asthma case-detection tool in an elementary school population. *Pediatrics* 2004;114(3):e307-16.
- Gerald LB, Grad R, Turner-Henson A, Hains C, Tang S, Feinstein R, et al. Validation of a multistage asthma case-detection procedure for elementary school children. *Pediatrics*. 2004;114(4):e459-68.
- Ly NP, Gold DR, Weiss ST, Celedon JC. Recurrent wheeze in early childhood and asthma among children at risk for atopy. *Pediatrics* 2006;117(6):e1132-8.
- Jones CA, Morpew T, Clement LT, Kimia T, Dyer M, Li M, et al. A school-based case identification process for identifying inner city children with asthma: the Breathmobile program. *Chest* 2004;125(3):924-34.
- Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *Eur Respir J*. 2003;22(5):767-71.
- Schonberger H, van Schayck O, Muris J, Bor H, van den Hoogen H, Knottnerus A, et al. Towards improving the accuracy of diagnosing asthma in early childhood. *Eur J Gen Pract*. 2004;10(4):138-45,51.
- Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. *Chest* 2006;129(5):1132-41.
- Marchant JM, Masters IB, Taylor SM, Chang AB. Utility of signs and symptoms of chronic cough in predicting specific cause in children. *Thorax*. 2006;61(8):694-8.
- Saglani S, Nicholson AG, Scallan M, Balfour-Lynn J, Rosenthal M, Payne DN, et al. Investigation of young children with severe recurrent wheeze: any clinical benefit? *Eur Respir J*. 2006;27(1):29-35.
- Kurukulaaratchy RJ, Matthews S, Arshad SH. Relationship between childhood atopy and wheeze: what mediates wheezing in atopic phenotypes? *Ann Allergy Asthma Immunol*. 2006;97(1):84-91.
- Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. *BMJ* 1994;309(6947):90-3.
- Aberg N, Engstrom I. Natural history of allergic diseases in children. *Acta Paediatr Scand*. 1990;79(2):206-11.
- Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. *Eur Respir J*. 2004;23(1):66-70.
- Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. *Thorax* 1992;47(7):537-42.
- Barbee RA, Murphy S. The natural history of asthma. *J Allergy Clin Immunol* 1998;102(4 Pt 2):S65-72.
- Blair H. Natural history of childhood asthma. 20-year follow-up. *Arch Dis Child* 1977;52(8):613-9.
- Johnstone DE. A study of the natural history of bronchial asthma in children. *Am J Dis Child* 1968;115(2):213-6.
- Laor A, Cohen L, Danon YL. Effects of time, sex, ethnic origin, and area of residence on prevalence of asthma in Israeli adolescents. *BMJ* 1993;307(6908):841-4.
- Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003;58(7):561-6.
- Luyt DK, Burton PR, Simpson H. Epidemiological study of wheeze, doctor diagnosed asthma, and cough in preschool children in Leicestershire. *BMJ* 1993;306(6889):1386-90.
- Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. *BMJ* 1980;280(6229):1397-400.
- Robertson CF, Heycock E, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. *BMJ* 1991;302(6785):1116-8.
- Roorda RJ. Prognostic factors for the outcome of childhood asthma in adolescence. *Thorax* 1996;51(Suppl 1):S7-12.
- Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 1996;75(5):392-8.
- Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. *Am J Epidemiol* 1990;132(1):83-95.
- Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics* 1995;95(4):500-5.
- Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;101(5):587-93.
- Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1473-80.
- Reijonen TM, Kotaniemi-Syrjanen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics* 2000;106(6):1406-12.
- Kotaniemi-Syrjanen A, Reijonen TM, Romppanen J, Korhonen K, Savolainen K, Korppi M. Allergen-specific immunoglobulin E antibodies in wheezing infants: the risk for asthma in later childhood. *Pediatrics* 2003;111(3):e255-61.
- Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. *Clin Exp Allergy* 1989;19(4):419-24.
- Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997;99(4):454-60.
- Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1617-22.
- Yu IT, Wong TW, Li W. Using child reported respiratory symptoms to diagnose asthma in the community. *Arch Dis Child*. 2004;89(6):544-8.
- Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. *Thorax* 2002;57(2):120-6.
- Bacharier LB, Strunk RC, Mauger D, White D, Lemanske Jr RF, Sorkness CA. Classifying asthma severity in children: Mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med*. 2004;170(4):426-32.
- Brouwer AF, Roorda RJ, Brand PLP. Home spirometry and asthma severity in children. *Eur Respir J*. 2006;28(6):1131-7.
- Verini M, Peroni DG, Rossi N, Nicodemo A, De Stradis R, Spagnolo C, et al. Functional assessment of allergic asthmatic children while asymptomatic. *Allergy Asthma Proc* 2006;27(4):359-64.
- Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948-68.
- Tantisira KG, Fuhlbrigge AL, Tonascia J, Van Natta M, Zeiger RS, Strunk RC, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. *J Allergy Clin Immunol*. 2006;117(6):1264-71.
- Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. *Thorax* 2005;60(1):13-6.
- Arets HGM, Brackel HJL, van der Ent CK. Applicability of interrupter resistance measurements using the MicroRint in daily practice. *Respir Med*. 2003;97(4):366-74.
- Olaguibel JM, Alvarez-Puebla MJ, Anda M, Gomez B, Garcia BE, Tabar AI, et al. Comparative analysis of the bronchodilator response measured by impulse oscillometry (IOS), spirometry and body plethysmography in asthmatic children. *J Investig Allergol Clin Immunol*. 2005;15(2):102-6.
- Marotta A, Klinnert MD, Price MR, Larsen GL, Liu AH. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. *J Allergy Clin Immunol*. 2003;112(2):317-22.
- Joseph-Bowen J, de Klerk NH, Firth MJ, Kendall GE, Holt PG, Sly PD. Lung function, bronchial responsiveness, and asthma in a community cohort of 6-year-old children. *Am J Respir Crit Care Med*. 2004;169(7):850-4.

56. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol.* 2005;94(3):366-71.
57. Lex C, Payne DN, Zacharasiewicz A, Li AM, Wilson NM, Hansel TT, et al. Sputum induction in children with difficult asthma: safety, feasibility, and inflammatory cell pattern. *Pediatr Pulmonol.* 2005;39(4):318-24.
58. Ryttila P, Pelkonen AS, Metso T, Nikander K, Haahtela T, Turpeinen M. Induced sputum in children with newly diagnosed mild asthma: The effect of 6 months of treatment with budesonide or disodium cromoglycate. *Allergy* 2004;59(8):839-44.
59. Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J, et al. Safety and application of induced sputum analysis in childhood asthma. *J Allergy Clin Immunol.* 2004;114(3):575-82.
60. Malmberg LP, Turpeinen H, Ryttila P, Sarna S, Haahtela T. Determinants of increased exhaled nitric oxide in patients with suspected asthma. *Allergy* 2005;60(4):464-8.
61. Brussee JE, Smit HA, Kerckhof M, Koopman LP, Wijga AH, Postma DS, et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. *Eur Respir J.* 2005;25(3):455-61.
62. Barreto M, Villa MP, Monti F, Bohmerova Z, Martella S, Montesano M, et al. Additive effect of eosinophilia and atopy on exhaled nitric oxide levels in children with or without a history of respiratory symptoms. *Pediatr Allergy Immunol.* 2005;16(1):52-8.
63. Malmberg LP, Petays T, Haahtela T, Laatikainen T, Jousilahti P, Vartiainen E, et al. Exhaled nitric oxide in healthy nonatopic school-age children: Determinants and height-adjusted reference values. *Pediatr Pulmonol.* 2006;41(7):635-42.
64. Prasad A, Langford B, Stradling JR, Ho LP. Exhaled nitric oxide as a screening tool for asthma in school children. *Respir Med.* 2006;100(1):167-73.
65. Pijnenburg MW, Floor SE, Hop WC, De Jongste JC. Daily ambulatory exhaled nitric oxide measurements in asthma. *Pediatr Allergy Immunol.* 2006;17(3):189-93.
66. Chan EY, Dundas I, Bridge PD, Healy MJ, McKenzie SA. Skin-prick testing as a diagnostic aid for childhood asthma. *Pediatr Pulmonol.* 2005;39(6):558-62.
67. Eysink PE, ter Riet G, Aalberse RC, van Aalderen WM, Roos CM, van der Zee JS, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. *Br J Gen Pract.* 2005;55(511):125-31.
68. Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol.* 2005;116(4):744-9.
69. Kurukulaaratchy RJ, Fenn M, Matthews S, Arshad SH. Characterisation of atopic and non-atopic wheeze in 10 year old children. *Thorax* 2004;59(7):563-8.
70. Hederos CA, Janson S, Andersson H, Hedlin G. Chest X-ray investigation in newly discovered asthma. *Pediatr Allergy Immunol* 2004;15(2):163-5.
71. Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest* 2002;121(4):1051-7.
72. Joyce DP, Chapman KR, Kesten S. Prior diagnosis and treatment of patients with normal results of methacholine challenge and unexplained respiratory symptoms. *Chest* 1996;109(3):697-701.
73. Brand PL, Postma DS, Kerstjens HA, Koeter GH. Relationship of airway hyperresponsiveness to respiratory symptoms and diurnal peak flow variation in patients with obstructive lung disease. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1991;143(5 Pt 1):916-21.
74. Gibson PG, Fujimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. *Thorax* 2002;57(2):178-82.
75. James AL, Finucane KE, Ryan G, Musk AW. Bronchial responsiveness, lung mechanics, gas transfer, and corticosteroid response in patients with chronic airflow obstruction. *Thorax* 1988;43(11):916-22.
76. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. *Thorax* 1984;39(12):912-8.
77. Goldstein MF, Veza BA, Dunsky EH, Dvorin DJ, Belecanech GA, Haralabatos IC. Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV(1) responses, and methacholine inhalation challenges in the evaluation of suspected asthma. *Chest* 2001;119(4):1001-10.
78. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med.* 2005;172(4):453-9.
79. Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med.* 2004;169(4):473-8. (34 ref).
80. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. *Thorax* 2006;61(9):817-27.
81. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000;356(9240):1480-5.
82. Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N, et al. Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med* 1999;159(6):1810-3.
83. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet* 1999;353(9171):2213-4.
84. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360(9347):1715-21.
85. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352(21):2163-73.
86. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: Effect on exacerbations. *Eur Respir J.* 2006;27(3):483-94.
87. Berry M, Hargadon B, Morgan A, Shelley M, Richter J, Shaw D, et al. Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. *Eur Respir J* 2005;25(6):986-91.
88. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusion and recommendations of a working party of the European Respiratory Society. *Eur Respir J Suppl.* 1997;24:2S-8S.
89. D'Alonzo GE, Steinijans VW, Keller A. Measurements of morning and evening airflow grossly underestimate the circadian variability of FEV1 and peak expiratory flow rate in asthma. *Am J Respir Crit Care Med* 1995;152(3):1097-9.
90. Chowiecnyk PJ, Parkin DH, Lawson CP, Cochrane GM. Do asthmatic patients correctly record home spirometry measurements? *BMJ* 1994;309(6969):1618.
91. Higgins BG, Britton JR, Chinn S, Jones TD, Jenkinson D, Burney PG, et al. The distribution of peak flow variability in a population sample. *Am Rev Respir Dis* 1989;140(5):1368-72.
92. Higgins BG, Britton JR, Chinn S, Cooper S, Burney PG, Tattersfield AE. Comparison of bronchial reactivity and peak expiratory flow variability measurements for epidemiologic studies. *Am Rev Respir Dis* 1992;145(3):588-93.
93. Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. Relationship to symptoms and respiratory disease. *Am Rev Respir Dis* 1991;143(2):323-30.
94. Lebowitz MD, Krzyzanowski M, Quackenboss JJ, O'Rourke MK. Diurnal variation of PEF and its use in epidemiological studies. *Eur Respir J Suppl.* 1997(24):49S-56S.
95. Boezen HM, Schouten JP, Postma DS, Rijcken B. Distribution of peak expiratory flow variability by age, gender and smoking habits in a random population sample aged 20-70 yrs. *Eur Respir J* 1994;7(10):1814-20.
96. Siersted HC, Hansen HS, Hansen NC, Hyldebrandt N, Mostgaard G, Oxhøj H. Evaluation of peak expiratory flow variability in an adolescent population sample. The Odense Schoolchild Study. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):598-603.
97. Gannon PF, Newton DT, Belcher J, Pantin CF, Burge PS. Development of OASYS-2: a system for the analysis of serial measurement of peak expiratory flow in workers with suspected occupational asthma. *Thorax* 1996;51(5):484-9.
98. Crapo R. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000;161(1):309-29.
99. Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7(3):235-43.
100. Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. *J Allergy Clin Immunol* 1992;89(1 Pt 1):23-30.
101. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlen B, et al. Indirect airway challenges. *Eur Respir J* 2003;21(6):1050-68.
102. Anderton RC, Cuff MT, Frith PA, Cockcroft DW, Morse JL, Jones NL, et al. Bronchial responsiveness to inhaled histamine and exercise. *J Allergy Clin Immunol* 1979;63(5):315-20.
103. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005;171(8):912-30.
104. Pavord ID, Pizzichini MM, Pizzichini E, Hargreave FE. The use of induced sputum to investigate airway inflammation. *Thorax* 1997;52(6):498-501.
105. Brightling CE, Pavord ID. Eosinophilic bronchitis: an important cause of prolonged cough. *Ann Med* 2000;32(7):446-51.
106. Carney IK, Gibson PG, Murree-Allen K, Saltos N, Olson LG, Hensley MJ. A systematic evaluation of mechanisms in chronic cough. *Am J Respir Crit Care Med* 1997;156(1):211-6.
107. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170(8):836-44.

108. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1043-51.
109. Pearson MG, CE B, editors. *Measuring clinical outcome in asthma: a patient-focused approach* London: Royal College of Physicians; 1999.
110. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.
111. Tweeddale PM, Alexander F, McHardy GJ. Short term variability in FEV1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. *Thorax* 1987;42:487-90.
112. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. *Thorax* 1992;47(3):162-6.
113. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100(4):616-21.
114. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902-7.
115. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553-8.
116. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65.
117. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;117(3):549-56.
118. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993;147(4):832-8.
119. Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *Eur Respir J*. 2003;21(3):433-8.
120. Berry M, Shaw D, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;35:1175-1179.
121. Belda J, Leigh R, Parameswaran K, O'Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. *Am J Respir Crit Care Med* 2000;161(2 Pt 1):475-8.
122. Djukanovic R, Sterk PJ, Fahy JV, Hargreave FE. Standardised methodology of sputum induction and processing. *Eur Respir J Suppl* 2002;37:1s-2s.
123. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;99(6 Pt 1):763-9.
124. Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, et al. House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. *Pediatr Allergy Immunol* 2006;17(5):329-36.
125. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000;356(9239):1392-7.
126. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: A randomised controlled study. *Thorax* 2003;58(6):489-93.
127. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p 1) and the development of asthma in childhood. *N Engl J Med* 1990;323:502-7.
128. Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax* 2004;59(10):855-61.
129. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: Outcomes at 7 years of age. *J Allergy Clin Immunol*. 2005;116(1):49-55.
130. Horak F, Jr., Matthews S, Ithorst G, Arshad SH, Frischer T, Kuehr J, et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study – 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy*. 2004;34(8):1220-5.
131. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during the first year of life: a randomised trial. *Lancet* 2001;358(9277):188-93.
132. Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004;170(4):433-9.
133. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999;29:611-7.
134. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;108:509-15.
135. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. *Pediatr Allergy Immunol* 2004;15(2):103-11.
136. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;15(4):291-307.
137. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2006. London: John Wiley & Sons Ltd 138. Vance GH, Grimshaw KE, Briggs R, Lewis SA, Mullee MA, Thornton CA, et al. Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy. *Clin Exp Allergy* 2004;34(12):1855-61.
139. van Odijk J, Kl, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, Host A, Kuitunen M, Ol, sen SF, Skerfving S, Sundell J, Willie S. Breast feeding and allergic disease: a multi-disciplinary review of the literature (1996-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy* 2003;58(9):833-43.
140. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet*. 2002;360(9337):901-7.
141. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2006. Chichester: John Wiley
142. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2006. London: John Wiley & Sons Ltd.
143. Tricon S, Willers S, Smit HA, Burney PG, Devereux G, Frew AJ, et al. Nutrition and allergic disease. *Clin Exp Allergy Reviews* 2006;6(5):117-88.
144. Zutavern A, von Mutius E, Harris J, Mills P, Moffatt S, White C, et al. The introduction of solids in relation to asthma and eczema. *Arch Dis Child*. 2004;89(4):303-8.
145. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol*. 2003;112(6):1178-84.
146. Miharshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM, et al. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. *Pediatr Allergy Immunol*. 2004;15(6):517-22.
147. Shaheen SO, Newson RB, Henderson AJ, Emmett PM, Sherriff A, Cooke M. Umbilical cord trace elements and minerals and risk of early childhood wheezing and eczema. *Eur Respir J* 2004;24(2):292-7.
148. Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med* 2006;174(5):499-507.
149. Holt PG, Sly PD, Bjorksten B. Atopic versus infectious diseases in childhood: a question of balance? *Pediatr Allergy Immunol* 1997;8(2):53-8.
150. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;55(Suppl 1):S2-10.
151. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357(9262):1076-9.
152. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch Dis Child* 2006;91(10):814-9.
153. Cook DG, Strachan DP. Health effects of passive smoking-10: Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;54(4):357-66.
154. Dezauteau C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999;159(2):403-10.
155. Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 2000;55(4):271-6.

156. Lodrup Carlsen KC, Carlsen KH, Nafstad P, Bakkeiteig L. Perinatal risk factors for recurrent wheeze in early life. *Pediatr Allergy Immunol* 1999;10(2):89-95.
157. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest* 2005;127(2):502-8.
158. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. *Am J Public Health* 2004;94(1):136-40.
159. Kabesch M, Hoefler C, Carr D, Leupold W, Weiland SK, von Mutius E. Glutathione S transferase deficiency and passive smoking increase childhood asthma. *Thorax* 2004;59(7):569-73.
160. Belanger K, Beckett W, Triche E, Bracken MB, Holford T, Ren P, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. *Am J Epidemiol* 2003;158(3):195-202.
161. Lee YL, Lin YC, Lee YC, Wang JY, Hsiue TR, Guo YL. Glutathione S-transferase P1 gene polymorphism and air pollution as interactive risk factors for childhood asthma. *Clin Exp Allergy* 2004;34(11):1707-13.
162. Miller RL, Garfinkel R, Horton M, Camann D, Perera FP, Whyatt RM, et al. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. *Chest* 2004;126(4):1071-8.
163. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Estela del Rio-Navarro B, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. *Thorax* 2004;59(1):8-10.
164. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001;31(8):1295-302.
165. Pajno GB, Barberio G, de Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;31(9):1392-7.
166. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with standardized dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99(4):450-3.
167. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002;109(2):251-6.
168. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. *Allergy* 2006;61(7):808-11.
169. Kemp A, Bjorksten B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. *Pediatr Allergy Immunol* 2003;14(2):74-80.
170. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? *Pediatr Allergy Immunol* 2005;16(3):193-200.
171. Peat JK, Salome CM, Woolcock AJ. Longitudinal changes in atopy during a 4-year period: relation to bronchial hyperresponsiveness and respiratory symptoms in a population sample of Australian schoolchildren. *J Allergy Clin Immunol* 1990;85(1 Pt 1):65-74.
172. Platts-Mills TA, Thomas WR, Aalberse RC, Vervloet D, Chapman MD. Dust mite allergens and asthma: report of a second international workshop. *J Allergy Clin Immunol* 1992;89(5):1046-60.
173. Peroni DG, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1994;149(6):1442-6.
174. Gøtzsche PC, Johansen HK, Schmidt LM, Burr ML. House dust mite control measures for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2004. London: John Wiley & Sons Ltd.
175. Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z, Oosting AJ, de Monchy JG, Brujinzeel-Koomen CA, et al. The effect of encasings on quality of life in adult house dust mite allergic patients with rhinitis, asthma and/or atopic dermatitis. *Allergy* 2005;60(7):888-93.
176. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med*. 2003;349(3):225-36.
177. Halken S, Host A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol*. 2003;111(1):169-76.
178. Van Den Bemt L, Van Knapen L, De Vries MP, Jansen M, Cloosterman S, Van Schayck CP. Clinical effectiveness of a mite allergen-impermeable bed-covering system in asthmatic mite-sensitive patients. *J Allergy Clin Immunol*. 2004;114(4):858-62.
179. Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. *J Allergy Clin Immunol* 1989;83(4):730-4.
180. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med* 1998;158(1):115-20.
181. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001;357(9258):752-6.
182. Francis H, Fletcher G, Anthony C, Pickering C, Oldham L, Hadley E, et al. Clinical effects of air filters in homes of asthmatic adults sensitized and exposed to pet allergens. *Clin Exp Allergy*. 2003;33(1):101-5.
183. Popplewell EJ, Innes VA, Lloyd-Hughes S, Jenkins EL, Khdir K, Bryant TN, et al. The effect of high-efficiency and standard vacuum-cleaners on mite, cat and dog allergen levels and clinical progress. *Pediatr Allergy Immunol* 2000;11(3):142-8.
184. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol* 2001;108(5):732-7.
185. Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: A randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. *Am J Public Health*. 2005;95(4):652-9.
186. Singh M, Bara A, Gibson P. Humidity control for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2002. London: John Wiley & Sons Ltd.
187. Chalmers GW, MacLeod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax*. 2002;57(3):226-30.
188. Ehrlich R, Jordaan E, Du TD, Potter P, Volmink J, Zwarenstein M, et al. Household smoking and bronchial hyperresponsiveness in children with asthma. *J Asthma*. 2001;38(3):239-51.
189. Gallefoss F, Bakke PS. Does smoking affect the outcome of patient education and self-management in asthmatics? *Patient Educ Couns*. 2003;49(1):91-7.
190. Mannino DM, Homa DM, Redd SC. Involuntary smoking and asthma severity in children: Data from the Third National Health and Nutrition Examination Survey. *Chest*. 2002;122(2):409-15.
191. Murray AB, Morrison BJ. The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke. *J Allergy Clin Immunol* 1993;91(1 Pt 1):102-10.
192. Wilson SR, Yamada EG, Sudhakar R, Roberto L, Mannino D, Mejia C, et al. A controlled trial of an environmental tobacco smoke reduction intervention in low-income children with asthma. *Chest*. 2001;120(5):1709-22.
193. Tonnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin A, et al. Effects of smoking cessation and reduction in asthmatics. *Nicotine Tob Res* 2005;7(1):139-48.
194. Wakefield M, Banham D, McCaul K, Martin J, Ruffin R, Badcock N, et al. Effect of feedback regarding urinary cotinine and brief tailored advice on home smoking restrictions among low-income parents of children with asthma: a controlled trial. *Prev Med*. 2002;34(1):58-65.
195. Irvine L, Crombie IK, Clark RA, Slane PW, Feyerabend C, Goodman KE, et al. Advising parents of asthmatic children on passive smoking: randomised controlled trial. *BMJ* 1999;318(7196):1456-9.
196. Hovell MF, Meltzer SB, Wahlgren DR, Matt GE, Hofstetter CR, Jones JA, et al. Asthma management and environmental tobacco smoke exposure reduction in Latino children: a controlled trial. *Pediatrics*. 2002;110(5):946-56.
197. Rasmussen F, Siersted HC, Lambrechtsen J, Hansen HS, Hansen NC. Impact of airway lability, atopy, and tobacco smoking on the development of asthma-like symptoms in asymptomatic teenagers. *Chest* 2000;117(5):1330-5.
198. Devalia JL, Rusznak C, Herdman MJ, Trigg CJ, Tarraf H, Davies RJ. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet* 1994;344(8938):1668-71.
199. Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, et al. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. *Lancet* 1991;338(8761):199-203.
200. Committee on the Medical Effects of Air Pollutants. *Asthma and outdoor air pollution*. London: HMSO; 1995.
201. Lin M, Chen Y, Burnett RT, Villeneuve PJ, Krewski D. Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: A bi-directional case-crossover analysis. *J Epidemiol Community Health*. 2003;57(1):50-5.
202. Kaur B, Anderson HR, Austin J, Burr M, Harkins LS, Strachan DP, et al. Prevalence of asthma symptoms, diagnosis, and treatment in 12-14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). *BMJ* 1998;316(7125):118-24.
203. Norbäck D, Björnsson E, Janson C, Widstrom J, Boman G. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. *Occup Environ Med* 1995;52(6):388-95.
204. Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet* 1994;344(8939-40):1733-6.

205. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. London: John Wiley & Sons Ltd.
206. Shaikh WA. Immunotherapy vs inhaled budesonide in bronchial asthma: an open, parallel, comparative trial. *Clin Exp Allergy* 1997;27(11):1279-84.
207. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341(7):468-75.
208. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006;61(10):1162-72.
209. Burney P. A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. *Chest* 1987;91(6 Suppl):143S-8S.
210. Burney PG. The causes of asthma—does salt potentiate bronchial activity? Discussion paper. *J R Soc Med* 1987;80(6):364-7.
211. Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusion capacity in exercise-induced asthma. *Med Sci Sports Exerc.* 2005;37(6):904-14.
212. Ardem KD, Ram FS. Dietary salt reduction or exclusion for allergic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2001. London: John Wiley & Sons Ltd.
213. Britton J, Pavord I, Richards K, Wisniewski A, Knox A, Lewis S, et al. Dietary magnesium, lung function, wheezing, and airway hyperreactivity in a random adult population sample. *Lancet* 1994;344(8919):357-62.
214. Blitz M, Blitz S, Beasley R, Diner BM, Hughes R, Knopp JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2005. London: John Wiley & Sons Ltd. 2005;
215. Bede O, Suranyi A, Pinter K, Szlavik M, Gyurkovits K. Urinary magnesium excretion in asthmatic children receiving magnesium supplementation: a randomized, placebo-controlled, double-blind study. *Magnes Res* 2003;16(4):262-70.
216. Fogarty A, Lewis SA, Scrivener SL, Antoniuk M, Pacey S, Pringle M, et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. *Clin Exp Allergy.* 2003;33(10):1355-9.
217. Hill J. Magnesium and airway reactivity. *Clin Sci* 1998;95(2):111-2.
218. Prescott SL, Calder PC. N-3 polyunsaturated fatty acids and allergic disease. *Curr Opin Clin Nutr Metab Care* 2004;7(2):123-9.
219. Stephensen CB. Fish oil and inflammatory disease: is asthma the next target for n-3 fatty acid supplements? *Nutr Rev* 2004;62(12):486-9.
220. Woods RK, Thien FC, Abramson MJ. Dietary marine fatty acids (fish oil) for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
221. Allam MF, Lucane RA. Selenium supplementation for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004. London: John Wiley & Sons Ltd.
222. Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. *Thorax* 2004;59(8):652-6.
223. Ram FS, Rowe BH, Kaur B. Vitamin C supplementation for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2004. London: John Wiley & Sons Ltd.
224. Butland BK, Strachan DP, Anderson HR. Fresh fruit intake and asthma symptoms in young British adults: confounding or effect modification by smoking? *Eur Respir J* 1999;13(4):744-50.
225. Carey IM, Strachan DP, Cook DG. Effects of changes in fresh fruit consumption on ventilatory function in healthy British adults. *Am J Respir Crit Care Med* 1998;158(3):728-33.
226. Cook DG, Carey IM, Whincup PH, Papacosta O, Chirico S, Bruckdorfer KR, et al. Effect of fresh fruit consumption on lung function and wheeze in children. *Thorax* 1997;52(7):628-33.
227. Ellwood P, Asher MI, Bjorksten B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. *Eur Respir J* 2001;17(3):436-43.
228. Gilliland FD, Berhane KT, Li YF, Gauderman WJ, McConnell R, Peters J. Children's lung function and antioxidant vitamin, fruit, juice, and vegetable intake. *Am J Epidemiol* 2003;158(6):576-84.
229. Heinrich J, Holscher B, Bolte G, Winkler G. Allergic sensitization and diet: ecological analysis in selected European cities. *Eur Respir J* 2001;17(3):395-402.
230. Strachan DP, Cox BD, Erzincinoglu SW, Walters DE, Whichelow MJ. Ventilatory function and winter fresh fruit consumption in a random sample of British adults. *Thorax* 1991;46(9):624-9.
231. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmatic symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med.* 2001;163(6):1344-9.
232. Chinn S, Jarvis D, Burney P. Relation of bronchial responsiveness to body mass index in the ECRHS. *Thorax.* 2002;57(12):1028-33.
233. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;115(5):897-909.
234. Jarvis D, Chinn S, Potts J, Burney P, Community E. Association of body mass index with respiratory symptoms and atopy: results from the European Community Respiratory Health Survey. *Clinical & Experimental Allergy.* 2002;32(6):831-7.
235. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ* 2000;320(7238):827-32.
236. Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001;108(4):516-20.
237. Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, *Lactobacillus rhamnosus* (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. *Allergy* 2002;57(3):243-6.
238. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. *Clin Exp Allergy* 2000;30(11):1604-10.
239. Wheeler JG, Shema SJ, Bogle ML, Shirrell MA, Burks AW, Pittler A, et al. Immune and clinical impact of *Lactobacillus acidophilus* on asthma. *Annals of Allergy, Asthma, & Immunology* 1997;79(3):229-33.
240. Gruber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics* 2003;111(3):e282-8.
241. Gruber C, Meinschmidt G, Bergmann R, Wahn U, Stark K. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds. *Pediatr Allergy Immunol* 2002;13(3):177-81.
242. Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. *BMJ* 1999;318(7192):1173-6.
243. Nilsson L, Kjellman NI, Bjorksten B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. *Arch Pediatr Adolesc Med* 1998;152(8):734-8.
244. Choi IS, Koh YI. Therapeutic effects of BCG vaccination in adult asthmatic patients: a randomized, controlled trial. *Annals of Allergy, Asthma, & Immunology.* 2002;88(6):584-91.
245. Arikian C, Bahceciler NN, Deniz G, Akdis M, Akkoc T, Akdis CA, et al. *Bacillus Calmette-Guerin*-induced interleukin-12 did not additionally improve clinical and immunologic parameters in asthmatic children treated with sublingual immunotherapy. *Clinical & Experimental Allergy* 2004;34(3):398-405.
246. Tsai JJ, Peng HJ, Shen HD. Therapeutic effect of *Bacillus Calmette-Guerin* with allergen on human allergic asthmatic patients. *Journal of Microbiology, Immunology & Infection.* 2002;35(2):99-102.
247. Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, Wiselka MJ, Leese J, Ayres J, et al. Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. *Lancet* 1998;351(9099):326-31.
248. Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *American Journal of Respiratory & Critical Care Medicine* 2004;169(4):488-93.
249. Bueving HJ, van der Wouden JC, Raat H, Bernsen RMD, de Jongste JC, van Suijlekom-Smith LWA, et al. Influenza vaccination in asthmatic children: Effects on quality of life and symptoms. *European Respiratory Journal* 2004;24(6):925-31.
250. Hanania NA, Sockrider M, Castro M, Holbrook JT, Tonascia J, Wise R, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. *Journal of Allergy & Clinical Immunology* 2004;113(4):717-24.
251. Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2002. London: John Wiley & Sons Ltd.
252. Steurer-Stey C, Russi EW, Steurer J. Complementary and alternative medicine in asthma: do they work? *Swiss Med Wkly* 2002;132(25-26):338-44.
253. Linde K, Jobst K, Panton J. Acupuncture for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
254. Martin J, Donaldson AN, Villarroel R, Parmar MK, Ernst E, Higginson IJ. Efficacy of acupuncture in asthma: systematic review and meta-analysis of published data from 11 randomised controlled trials. *Eur Respir J* 2002;20(4):846-52.
255. Gruber W, Eber E, Malle-Scheid D, Pfleger A, Weinhandl E, Dorfer L, et al. Laser acupuncture in children and adolescents with exercise induced asthma. *Thorax.* 2002;57(3):222-5.

256. Malmstrom M, Ahlner J, Carlsson C, Schmekel B. No effect of chinese acupuncture on isocapnic hyperventilation with cold air in asthmatics, measured with impulse oscillometry. *Acupuncture in Medicine*. 2002;20(2-3):66-73.
257. Blackhall K, Appleton S, Cates CJ. Ionisers for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. London: John Wiley & Sons Ltd.
258. Warner JA, Marchant JL, Warner JO. A double blind trial of ionisers in children with asthma sensitive to the house dust mite. *Thorax* 1993;48(4):330-3.
259. Holloway E, Ram FSF. Breathing exercises for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
260. Singh V, Wisniewski A, Britton J, Tattersfield A. Effect of yoga breathing exercises (pranayama) on airway reactivity in subjects with asthma. *Lancet* 1990;335(8702):1381-3.
261. Cooper S, Osborne J, Newton S, Harrison V, Thompson Coon J, Lewis S, et al. Effect of two breathing exercises (Buteyko and pranayama) in asthma: a randomised controlled trial. *Thorax* 2003;58(8):674-9.
262. McHugh P, Aitchison F, Duncan B, Houghton F. Buteyko breathing technique for asthma: An effective intervention. *N Z Med J* 2003;116(1187):U710.
263. Bowler SD, Green A, Mitchell CA. Buteyko breathing techniques in asthma: a blinded randomised controlled trial. *Med J Aust* 1998;169(11-12):575-8.
264. Opat AJ, Cohen MM, Bailey MJ, Abramson MJ. A clinical trial of the Buteyko Breathing Technique in asthma as taught by a video. *J Asthma* 2000;37(7):557-64.
265. Huntley A, Ernst E. Herbal medicines for asthma: a systematic review. *Thorax* 2000;55(11):925-9.
266. Chan CK, Kuo ML, Shen JJ, See LC, Chang HH, Huang JL, Ding Chuan Tang, a Chinese herb decoction, could improve airway hyper-responsiveness in stabilized asthmatic children: a randomized, double-blind clinical trial. *Pediatr Allergy Immunol* 2006;17(5):316-22.
267. Hsu CH, Lu CM, Chang TT. Efficacy and safety of modified Mai-Men-Dong-Tang for treatment of allergic asthma. *Pediatric Allergy & Immunology* 2005;16(1):76-81.
268. Linde K, Jobst KA. Homeopathy for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
269. White A, Slade P, Hunt C, Hart A, Ernst E. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial. *Thorax* 2003;58(4):317-21.
270. Huntley A, White AR, Ernst E. Relaxation therapies for asthma: a systematic review. *Thorax* 2002;57(2):127-31.
271. Hondras MA, Linde K, Jones AP. Manual therapy for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
272. Pantoni J, Barley EA. Family therapy for asthma in children (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2000. London: John Wiley & Sons Ltd.
273. North of England Evidence Based Guideline Development Project. The primary care management of asthma in adults. Newcastle upon Tyne: University of Newcastle upon Tyne, Centre for Health Services Research; 1999.
274. Pharmacological management of asthma. Evidence table 4.2: ipratropium bromide. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
275. Dennis SM, Sharp SJ, Vickers MR, Frost CD, Crompton GK, Barnes PJ, et al. Regular inhaled salbutamol and asthma control: the TRUST randomised trial. Therapy Working Group of the National Asthma Task Force and the MRC General Practice Research Framework. *Lancet* 2000;355(9216):1675-9.
276. Walters EH, Walters J. Inhaled short acting beta2-agonist use in asthma: regular versus as needed treatment (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
277. Pharmacological management of asthma. Evidence table 4.1: inhaled short acting beta 2 agonists. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
278. Pharmacological management of asthma. Evidence table 4.4a: inhaled corticosteroid vs theophylline. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
279. Pharmacological management of asthma. Evidence table 4.4c: inhaled corticosteroid vs leukotriene receptor antagonists. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
280. Adams N, Bestall J, Jones PW. Inhaled fluticasone propionate for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
281. Adams NP, Bestall JB, Jones PW. Inhaled beclometasone versus placebo for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
282. Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. *J Allergy Clin Immunol* 1997;100(4):452-7.
283. Carlsen KCL SS, Kamin W, et al. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med* 2005;99(11):1393-402.
284. Teper AM CA, Kofman CD, et al. Effects of Inhaled Fluticasone Propionate in Children Less Than 2 Years Old with Recurrent Wheezing. *Pediatr Pulmonol* 2004;37(2):111-5.
285. Teper AM KC, Szulman GA, et al. . Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. *Am J Respir Crit Care Med* 2005;171(6):587-90.
286. Bisgaard H AD, Milanowski J, et al. . Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004;113(2):e87-94.
287. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial.[comment]. *American Journal of Respiratory & Critical Care Medicine*. 2001;164(8 Pt 1):1392-7.
288. Pauwels RA PS, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361(9363):1071-6.
289. Pharmacological management of asthma. Evidence table 4.7: high dose step-down. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
290. Hodges IGC, Netherway TA. Once-daily fluticasone propionate is as effective as twice-daily treatment in stable, mild-to-moderate childhood asthma. *Clin Drug Invest*. 2005;25(1):13-22.
291. Ram FS, Jones A, Fay JK. Primary care based clinics for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. London: John Wiley & Sons Ltd.
292. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. *Pediatrics* 2000;106(1):E8.
293. Dunlop KA, Carson DJ, Steen HJ, McGovern V, McNaboe J, Shields MD. Monitoring growth in asthmatic children treated with high dose inhaled glucocorticoids does not predict adrenal suppression. *Arch Dis Child* 2004;89(8):713-6.
294. Bernstein D AD. Evaluation of tests of hypothalamic-pituitary-adrenal axis function used to measure effects of inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2007;98(2):118-27.
295. Pharmacological management of asthma. Evidence table 4.25: budesonide vs beclometasone. Edinburgh: 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
296. Pharmacological management of asthma. Evidence table 4.15: mometasone furoate dry powder inhalation evidence. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
297. Boulet LP, Drollmann A, Magyar P, Timar M, Knight A, Engelstatter R, et al. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. *Respir Med* 2006;100(5):785-94.
298. Buhl R, Vinkler I, Magyar P, Gyori Z, Rybacki C, Middle MV, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. *Pulm Pharmacol Ther* 2006;19(6):404-12.
299. Niphadkar P, Jagannath K, Joshi JM, Awad N, Boss H, Hellbardt S, et al. Comparison of the efficacy of ciclesonide 160 microg QD and budesonide 200 microg BID in adults with persistent asthma: a phase III, randomized, double-dummy, open-label study. *Clin Ther* 2005;27(11):1752-63.
300. Pearlman DS, Berger WE, Kerwin E, Laforce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2005;116(6):1206-12.
301. Szeffler S, Rohatagi S, Williams J, Lloyd M, Kundu S, Banerji D. Ciclesonide, a novel inhaled steroid, does not affect hypothalamic-pituitary-adrenal axis function in patients with moderate-to-severe persistent asthma. *Chest* 2005;128(3):1104-14.
302. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;60(4):282-7.
303. Salmeterol (Severant) and formoterol (Oxis) in asthma management. *Curr Probl Pharmacovigilanc* 2003;29(5).
304. Edwards A SM. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. *Eur Respir J* 1993;6(1):35-41.
305. Pharmacological management of asthma. Evidence table 4.24a: Other preventor therapies - Chromones in children aged 5-12. Edinburgh: SIGN; 2005. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>

306. Table 16: nedocromil and sodium cromoglycate studies not included in the nedocromil meta-analysis. In: North of England Evidence Based Guideline Development Project, editor. The primary care management of asthma in adults. Newcastle upon Tyne: University of Newcastle upon Tyne, Centre for Health Services Research; 1999. p.46-7.
307. Pharmacological management of asthma. Evidence table 4.4j: Do cromones works as first line preventor in children > 5 years? Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
308. Pharmacological management of asthma. Evidence table 4.24b: Other preventor therapies - Chromones in children aged < 5. Edinburgh: SIGN; 2005. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
309. Pharmacological management of asthma. Evidence table 4.4d: leukotriene receptor antagonists with short-acting beta-agonists. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
310. Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence. *BMJ* 2003;362(7390):621.
311. Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J* 1997;10(10):2216-24.
312. Pharmacological management of asthma. Evidence table 4.11b: Add-on drugs for inhaled steroids: long acting or oral B2 agonists. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
313. Pharmacological management of asthma. Evidence table 4.11d: Add-on drugs for inhaled steroids: theophylline, beclomethasone dipropionate, budesonide. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
314. Pharmacological management of asthma. Evidence table 4.11c: Add-on drugs for inhaled steroids: anticholinergics. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
315. Pharmacological management of asthma. Evidence table 4.11a: Add-on drugs for inhaled steroids: cromones. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
316. Becker AB, Simons FE. Formoterol, a new long-acting selective beta 2-adrenergic receptor agonist: double-blind comparison with salbutamol and placebo in children with asthma. *J Allergy Clin Immunol* 1989;84(6 Pt 1):891-5.
317. Kips JC, Pauwels RA. Long-acting inhaled beta(2)-agonist therapy in asthma. *Am J Respir Crit Care Med* 2001;164(6):923-32.
318. Pharmacological management of asthma. Evidence table 4.22: Combined therapy of inhaled steroids and long acting B2 agonists. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
319. Pharmacological management of asthma. Evidence table 4.8c: Children with poor asthma control on ICS - is addition of leukotriene receptor antagonists helpful? Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
320. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E48.
321. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. London: John Wiley & Sons Ltd.
322. British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London in association with the General Practitioner in Asthma Group, The British Association of Accident and Emergency Medicine, The British Paediatric Respiratory Society, Royal College of Paediatrics and Child Health. The British guidelines on asthma management 1995 review and position statement. *Thorax* 1997;52(Suppl 1):S1-S21.
323. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract* 2007;61(5):725-36.
324. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171(2):129-36.
325. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368(9537):744-53.
326. Scicchitano. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Current Medical Research and opinions* 2004;20(9):1403-18.
327. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005;26(5):819-28.
328. National Osteoporosis Society. Guidance on the prevention and management of corticosteroid induced osteoporosis. Bath: National Osteoporosis Society; 1998.
329. Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. *N Engl J Med* 1981;304(2):71-5.
330. Pharmacological management of asthma. Evidence table 4.13a: Immunosuppressive agents. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
331. O'Driscoll BR, Ruffles SP, Ayres JG, Cochrane GM. Long term treatment of severe asthma with subcutaneous terbutaline. *Br J Dis Chest* 1988;82(4):360-7.
332. Payne D, Balfour-Lynn I, Biggart E, Bush A, Rosenthal M. Subcutaneous terbutaline in children with chronic severe asthma. *Pediatr Pulmonol*. 2002;33(5):356-61.
333. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med*. 2006;354(7):697-708.
334. Hawkins G, McMahon AD, Twaddle S, Wood S, Ford J, NC. T. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;326(7399):1115.
335. Pharmacological management of asthma. Evidence table 4.9: Exacerbation. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
336. Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. On behalf of the Italian Study Group. *Chest* 2000;117(2):440-6.
337. Henriksen JM, Agertoft L, Pedersen S. Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children. *J Allergy Clin Immunol* 1992;89(6):1176-82.
338. Pharmacological management of asthma. Evidence table 4.3a: Long acting B2 agonists in exercise induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
339. Pharmacological management of asthma. Evidence table 4.3c: Theophyllines in exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
340. Pharmacological management of asthma. Evidence table 4.3d: Leukotriene receptor antagonists in exercise induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
341. Kelly K, Spooner CH, Rowe BH. Nedocromil sodium versus sodium cromoglycate for preventing exercise-induced bronchoconstriction in asthmatics (Cochrane Review). In: The Cochrane Library, Issue 3, 2001. London: John Wiley & Sons Ltd.
342. Pharmacological management of asthma. Evidence table 4.3g: Oral B2 agonists for exercise induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
343. Pharmacological management of asthma. Evidence table 4.3f: Anticholinergic therapy for exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
344. Pharmacological management of asthma. Evidence table 4.3b: Ketotifen for exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
345. Pharmacological management of asthma. Evidence table 4.3e: Antihistamines for exercise-induced asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
346. Pharmacological management of asthma. Evidence table 4.10: Rhinitis. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
347. Pharmacological management of asthma. Evidence table 4.19: Allergic bronchopulmonary aspergillosis. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
348. Wark PAB, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. London: John Wiley & Sons Ltd.
349. Pharmacological management of asthma. Evidence table 4.21: Aspirin intolerant asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
350. Coughlan J. Oesophagitis does not consistently improve asthma control: A systematic review. *Thorax* 2001;56(3):198-204.
351. Gibson PG, Henry RL, Coughlan JL. Gastro oesophageal reflux treatment for asthma in adults and children (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. London: John Wiley & Sons Ltd.

352. Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technol Assess* 2001;5(26):1-149.
353. Cates CJ, Rowe BH, Bara A, Crilly JA. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
354. Leversha AM, Campanella SG, Aickin RP, Asher MI. Costs and effectiveness of spacer versus nebuliser in young children with moderate and severe acute asthma. *J Pediatr* 2000;136(4):497-502.
355. Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C. Efficacy of bronchodilators administered by nebulizers versus spacer devices in infants with acute wheezing. *Pediatr Pulmonol* 1998;26(5):344-8.
356. Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulizers vs metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department. *Archives of Pediatrics & Adolescent Medicine*. 2003;157(1):76-80.
357. Ram FS, Wright J, Brocklebank D, White JE. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering beta 2 (agonists) bronchodilators in asthma. *BMJ* 2001;323(7318):901-5.
358. Broeders M, Molema J, Hop WCJ, Vermue NA, Folgering HTM. Does the inhalation device affect the bronchodilatory dose response curve of salbutamol in asthma and chronic obstructive pulmonary disease patients? *European Journal of Clinical Pharmacology* 2003;59(5-6):449-55.
359. Hughes DA, Woodcock A, Walley T. Review of therapeutically equivalent alternatives to short acting beta(2) adrenoceptor agonists delivered via chlorofluorocarbon-containing inhalers. *Thorax* 1999;54(12):1087-92.
360. Farmer IS, Middle M, Savic J, Perri VL, Herdman MJ. Therapeutic equivalence of inhaled beclometasone dipropionate with CFC and non-CFC (HFA 134a) propellants both delivered via the Easibreathe inhaler for the treatment of paediatric asthma. *Respir Med* 2000;94(1):57-63.
361. De Benedictis FM, Boner A, Cavagni G, Caffarelli C, Ferraro L, Cantini L. Treating asthma in children with beclometasone dipropionate: Pulvinal versus Diskhaler. *Journal of Aerosol Medicine* 2000;13(1):35-41.
362. Adams N, Cates CJ, Bestall J. Holding chambers versus nebulisers for inhaled steroids in chronic asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
363. Lumry W, Noveck R, Weinstein S, Barnhart F, Vandermeer A, Murray A, et al. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. *Ann Allergy Asthma Immunol* 2001;86(3):297-303.
364. Gross G, Cohen RM, Guy H. Efficacy response of inhaled HFA-albuterol delivered via the breath-actuated Autohaler inhalation device is comparable to dose in patients with asthma. *Journal of Asthma* 2003;40(5):487-95.
365. Gustafsson P, Kallman S, Whitehead PJ. Clinical equivalence between salbutamol hydrofluoroalkane pMDI and salbutamol Turbuhaler at the same cumulative microgram doses in paediatric patients. *Respiratory Medicine* 2002;96(11):957-9.
366. Hawksworth RJ, Sykes AP, Faris M, Mant T, Lee TH. Albuterol HFA is as effective as albuterol CFC in preventing exercise-induced bronchoconstriction. *Annals of Allergy, Asthma, & Immunology* 2002;88(5):473-7.
367. Shapiro G, Bronsky E, Murray A, Barnhart F, VanderMeer A, Reisner C. Clinical comparability of ventolin formulated with hydrofluoroalkane or conventional chlorofluorocarbon propellants in children with asthma. *Arch Pediatr Adolescent Med* 2000;154(12):1219-25.
368. Shapiro GS, Klinger NM, Ekholm BP, Colice GL. Comparable bronchodilation with hydrofluoroalkane-134a (HFA) albuterol and chlorofluorocarbons-11/12 (CFC) albuterol in children with asthma. *Journal of Asthma* 2000;37(8):667-75.
369. Anderson PB, Langley SJ, Mooney P, Jones J, Addlestone R, Rossetti A, et al. Equivalent efficacy and safety of a new HFA-134a formulation of BDP compared with the conventional CFC in adult asthmatics. *J Investig Allergol Clin Immunol* 2002;12(2):107-13.
370. Lee TL, Adler L, McLaren G, Rossetti A, Cantini L. Assessment of efficacy and systemic safety of a new chlorofluorocarbon-free formulation of inhaled beclometasone dipropionate in asthmatic children. *Pediatr Asthma Allergy Immunol* 2001;15(3):133-43.
371. Vondra V, Sladek K, Kotasova J, Terl M, Rossetti A, Cantini L. A new HFA-134a propellant in the administration of inhaled BDP via the Jet spacer: controlled clinical trial vs the conventional CFC. *Respiratory Medicine* 2002;96(10):784-9.
372. Ederle K, Multicentre Study Group. Improved control of asthma symptoms with a reduced dose of HFA-BDP extrafine aerosol: an open-label, randomised study. *European Review for Medical & Pharmacological Sciences* 2003;7(2):45-55.
373. Fireman P, Prenner BM, Vincken W, Demedts M, Mol SJ, Cohen RM. Long-term safety and efficacy of a chlorofluorocarbon-free beclometasone dipropionate extrafine aerosol. *Annals of Allergy, Asthma, & Immunology* 2001;86(5):557-65.
374. Pedersen S, Warner J, Wahn U, Staab D, Le Bourgeois M, Van Essen-Zandvliet E, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclometasone dipropionate formulations: an open-label, randomized comparison of extrafine and conventional aerosols in children. *Pediatrics*. 2002;109(6):e92.
375. Szeffler SJ, Warner J, Staab D, Wahn U, Le Bourgeois M, van Essen-Zandvliet EE, et al. Switching from conventional to extrafine aerosol beclometasone dipropionate therapy in children: a 6-month, open-label, randomized trial. *Journal of Allergy & Clinical Immunology* 2002;110(1):45-50.
376. Ayres JG, Millar AB, Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg twice daily administered via a HFA 134a pressurized metered dose inhaler to patients with severe asthma. *Respiratory Medicine* 2000;94(Suppl B):S42-S50.
377. Fowler SJ, Orr LC, Sims EJ, Wilson AM, Currie GP, McFarlane L, et al. Therapeutic ratio of hydrofluoroalkane and chlorofluorocarbon formulations of fluticasone propionate. *Chest*. 2002;122(2):618-23.
378. Langley SJ, Holden J, Derham A, Hedgeland P, Sharma RK, Woodcock A. Fluticasone propionate via the Diskhaler or hydrofluoroalkane-134a metered-dose inhaler on methacholine-induced airway hyperresponsiveness. *Chest*. 2002;122(3):806-11.
379. Lyttle B, Gilles J, Panov M, Emeryk A, Wixon C. Fluticasone propionate 100 microg bid using a non-CFC propellant, HFA 134a, in asthmatic children. *Canadian Respiratory Journal* 2003;10(2):103-9.
380. Perruchoud AP, Lundback B, Yigla M, Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg per day administered via a HFA 134a pressurized metered dose inhaler to patients with moderate to severe asthma. *Resp Med* 2000;94(Suppl B):S35-S41.
381. Accuracy of death certificates in bronchial asthma. Accuracy of certification procedures during the confidential inquiry by the British Thoracic Association. A subcommittee of the BTA Research Committee. *Thorax* 1984;39(7):505-9.
382. Bucknall CE, Slack R, Godley CC, Mackay TW, Wright SC. Scottish Confidential Inquiry into Asthma Deaths (SCIAD), 1994-6. *Thorax* 1999;54(11):978-84.
383. Burr ML, Davies BH, Hoare A, Jones A, Williamson IJ, Holgate SK, et al. A confidential inquiry into asthma deaths in Wales. *Thorax* 1999;54(11):985-9.
384. Mohan G, Harrison BD, Badminton RM, Mildenhall S, Wareham NJ. A confidential enquiry into deaths caused by asthma in an English health region: implications for general practice. *Br J Gen Pract* 1996;46(410):529-32.
385. Wareham NJ, Harrison BD, Jenkins PF, Nicholls J, Stableforth DE. A district confidential enquiry into deaths due to asthma. *Thorax* 1993;48(11):1117-20.
386. Harrison BDW, Slack R, Berrill WT, Burr ML, Stableforth DE, Wright SC. Results of a national confidential enquiry into asthma deaths. *Asthma J* 2000;5(4):180-6.
387. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326(8):501-6.
388. Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. *Eur Respir J* 1994;7(9):1602-9.
389. Jalaludin BB, Smith MA, Chey T, Orr NJ, Smith WT, Leeder SR. Risk factors for asthma deaths: A population-based, case-control study. *Aust NZ J Pub Health* 1999;23(6):595-600.
390. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. *Thorax* 1986;41(11):833-9.
391. Campbell MJ, Cogman GR, Holgate ST, Johnston SL. Age specific trends in asthma mortality in England and Wales, 1983-95: results of an observational study. *BMJ* 1997;314(7092):1439-41.
392. Richards GN, Kolbe J, Fenwick J, Rea HH. Demographic characteristics of patients with severe life threatening asthma: comparison with asthma deaths. *Thorax* 1993;48(11):1105-9.
393. Innes NJ, Reid A, Halstead J, Watkin SW, Harrison BD. Psychosocial risk factors in near-fatal asthma and in asthma deaths. *J R Coll Phys Lond* 1998;32(5):430-4.
394. Khot A, Evans N, Lenney W. Seasonal trends in childhood asthma in south east England. *Br Med J (Clin Res Ed)* 1983;287(6401):1257-8.
395. Barr RG, Woodruff PG, Clark S, Camargo CA Jr. Sudden-onset asthma exacerbations: clinical features, response to therapy, and 2-week follow-up. Multicenter Airway Research Collaboration (MARC) investigators. *Eur Respir J* 2000;15(2):266-73.
396. Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. *Thorax* 1998;53(4):241-7.
397. Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: demographics, health care, and management of the acute attack. *Thorax* 2000;55(12):1007-15.
398. Rodrigo GJ, Rodrigo C. Rapid-onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. *Chest* 2000;118(6):1547-52.

399. Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998;157(6 Pt 1):1804-9.
400. Woodruff PG, Emond SD, Singh AK, Camargo CA Jr. Sudden-onset severe acute asthma: clinical features and response to therapy. *Acad Emerg Med* 1998;5(7):695-701.
401. Scottish Intercollegiate Guidelines Network. Emergency management of acute asthma. Edinburgh: SIGN; 1999.
402. International consensus report on the diagnosis and treatment of asthma. National Heart, Lung, and Blood Institute, National Institutes of Health. Bethesda, Maryland 20892. Publication no. 92-3091, March 1992. *Eur Respir J* 1992;5(5):601-41.
403. Neville E, Gribbin H, Harrison BD. Acute severe asthma. *Respir Med* 1991;85(6):463-74.
404. Brenner B, Kohn MS. The acute asthmatic patient in the ED: to admit or discharge. *Am J Emerg Med* 1998;16(1):69-75.
405. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian asthma consensus report, 1999. Canadian asthma consensus group. *Canadian Medical Association Journal* 1999;161(11 Suppl):S1-61.
406. Nunn AJ, Gregg I. New regression equations for predicting peak expiratory flow in adults. *BMJ* 1989;298(6680):1068-70.
407. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. London: John Wiley & Sons Ltd.
408. Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, et al. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med* 2001;163(1):12-8.
409. Robinson SM, Harrison BD, Lambert MA. Effect of a preprinted form on the management of acute asthma in an accident and emergency department. *J Accid Emerg Med* 1996;13(2):93-7.
410. Shim CS, Williams MH Jr. Evaluation of the severity of asthma: patients versus physicians. *Am J Med* 1980;68(1):11-3.
411. Emerman CL, Cydulka RK. Effect of pulmonary function testing on the management of acute asthma. *Arch Intern Med* 1995;155(20):2225-8.
412. Standardized lung function testing. Report working party. *Bull Eur Physiopathol Respir* 1983;19(Suppl 5):1-95.
413. Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? *Thorax* 1995;50(2):186-8.
414. Pearson MG, Spence DP, Ryland I, Harrison BD. Value of pulsus paradoxus in assessing acute severe asthma. *British Thoracic Society Standards of Care Committee*. *BMJ* 1993;307(6905):659.
415. McFadden ER Jr, Lyons HA. Arterial-blood gas tension in asthma. *N Engl J Med* 1968;278(19):1027-32.
416. Rebusk AS, Read J. Assessment and management of severe asthma. *Am J Med* 1971;51(6):788-98.
417. Jenkins PF, Benfield GF, Smith AP. Predicting recovery from acute severe asthma. *Thorax* 1981;36(11):835-41.
418. Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. *N Engl J Med* 1991;324(5):285-8.
419. Gleeson JG, Green S, Price JF. Air or oxygen as driving gas for nebulised salbutamol. *Arch Dis Child* 1988;63(8):900-4.
420. Douglas JG, Rafferty P, Fergusson RJ, Prescott RJ, Crompton GK, Grant IW. Nebulised salbutamol without oxygen in severe acute asthma: how effective and how safe? *Thorax* 1985;40(3):180-3.
421. McFadden ER Jr. Critical appraisal of the therapy of asthma - an idea whose time has come. *Am Rev Respir Dis* 1986;133(5):723-4.
422. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. *Am Rev Respir Dis* 1980;122(3):365-71.
423. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. *Am Rev Respir Dis* 1985;132(2):283-6.
424. Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
425. Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. *Ann Emerg Med* 1993;22(12):1847-53.
426. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. *Ann Emerg Med* 1993;22(12):1842-6.
427. Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous vs intermittent albuterol, at high and low doses, in the treatment of severe acute asthma in adults. *Chest* 1996;110(1):42-7.
428. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
429. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
430. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
431. Hatton MQ, Vathenen AS, Allen MJ, Davies S, Cooke NJ. A comparison of 'abruptly stopping' with 'tailing off' oral corticosteroids in acute asthma. *Respir Med* 1995;89(2):101-4.
432. O'Driscoll BR, Kalra S, Wilson M, Pickering CA, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993;341(8841):324-7.
433. Edmonds ML, Camargo CA, Saunders LD, Brenner BE, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
434. Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. *Chest* 1998;114(2):365-72.
435. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999;107(4):363-70.
436. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. *Ann Emerg Med* 1999;34(1):8-18.
437. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
438. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
439. Graham VA, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. *Lancet* 1982;1(8269):418-20.
440. Kass JE, Terregino CA. The effect of heliox in acute severe asthma: a randomized controlled trial. *Chest* 1999;116(2):296-300.
441. Henderson SO, Acharya P, Kilagbhan T, Perez J, Korn CS, Chan LS. Use of heliox-driven nebulizer therapy in the treatment of acute asthma. *Ann Emerg Med* 1999;33(2):141-6.
442. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. *Chest* 1996;110(3):767-74.
443. Lim KL, Harrison BD. A criterion based audit of inpatient asthma care. Closing the feedback loop. *J R Coll Physicians Lond* 1992;26(1):71-5.
444. McFadden ER Jr, Elsanadi N, Dixon L, Takacs M, Deal EC, Boyd KK, et al. Protocol therapy for acute asthma: therapeutic benefits and cost savings. *Am J Med* 1995;99(6):651-61.
445. Goldberg R, Chan L, Haley P, Harmata-Booth J, Bass G. Critical pathway for the emergency department management of acute asthma: effect on resource utilization. *Ann Emerg Med* 1998;31(5):562-7.
446. Udwardia ZF, Harrison BD. An attempt to determine the optimal duration of hospital stay following a severe attack of asthma. *J R Coll Physicians Lond* 1990;24(2):112-4.
447. Pearson MG, Ryland I, Harrison BD. National audit of acute severe asthma in adults admitted to hospital. *Standards of Care Committee, British Thoracic Society. Qual Health Care* 1995;4(1):24-30.
448. Emerman CL, Woodruff PG, Cydulka RK, Gibbs MA, Pollack CV Jr, Camargo CA Jr. Prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. MARC investigators. *Multicenter Asthma Research Collaboration. Chest* 1999;115(4):919-27.
449. Cowie RJ, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest* 1997;112(6):1534-8.
450. Connett GJ, Lenney W. Use of pulse oximetry in the hospital management of acute asthma in childhood. *Pediatr Pulmonol* 1993;15(6):345-9.
451. Geelhoed GC, Landau LI, Le Seouf PN. Evaluation of SaO2 as a predictor of outcome in 280 children presenting with acute asthma. *Ann Emerg Med* 1994;23(6):1236-41.
452. Schuh S, Johnson D, Stephens D, Callahan S, Canny G. Hospitalization patterns in severe acute asthma in children. *Pediatr Pulmonol* 1997;23(3):184-92.
453. Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre- and posttreatment pulse oximetry in acute childhood asthma. *Acad Emerg Med* 1997;4(2):114-7.
454. Brooks LJ, Cloutier MM, Afshani E. Significance of roentgenographic abnormalities in children hospitalized for asthma. *Chest* 1982;82(3):315-8.
455. Gershel JC, Goldman HS, Stein RE, Shelov SP, Zirprkowski M. The usefulness of chest radiographs in first asthma attacks. *N Engl J Med* 1983;309(6):336-9.

456. McDowell KM, Chatburn RL, Myers TR, O'Riordan MA, Kerckmar CM. A cost-saving algorithm for children hospitalized for status asthmaticus. *Arch Paediatr Adolesc Med* 1998;152(10):977-84.
457. Schuh S, Parkin P, Rajan A, Canny G, Healy R, Rieder M, et al. High-versus low-dose, frequently administered, nebulised albuterol in children with severe, acute asthma. *Pediatrics* 1989;83(4):513-8.
458. Schuh S, Reider MJ, Canny G, Pender E, Forbes T, Tan YK, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. *Pediatrics* 1990;86(4):509-13.
459. Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. *J Pediatr* 1985;106(4):672-4.
460. Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebuliser in children with mild acute asthma. *J Pediatr* 1999;135(1):22-7.
461. Dewar AL, Stewart A, Cogswell JJ, Connett GJ. A randomised controlled trial to assess the relative benefits of large volume spacers and nebulisers to treat acute asthma in hospital. *Arch Dis Child* 1999;80(5):421-3.
462. Powell CV, Maskell GR, Marks MK, South M, Robertson CF. Successful implementation of spacer treatment guideline for acute asthma. *Arch Dis Child* 2001;84(2):142-6.
463. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. *Acad Emerg Med* 1996;3(11):1019-24.
464. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med* 1993;21(10):1479-86.
465. Becker JM, Arora A, Scarfone RJ, Spector ND, Fontana-Penn ME, Gracely E, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. *J Allergy Clin Immunol* 1999;103(4):586-90.
466. Barnett PL, Caputo GL, Baskin M, Kuppermann N. Intravenous versus oral corticosteroids in the management of acute asthma in children. *Ann Emerg Med* 1997;29(2):212-7.
467. Langton Hower S, Hobbs J, Reid F, Lenney W. Prednisolone in acute childhood asthma: clinical responses to three dosages. *Respir Med* 1998;92(3):541-6.
468. Edmonds ML, Camargo CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
469. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
470. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000;343(10):689-94.
471. Plotnick LH, Ducharme FM. Combined inhaled anticholinergic agents and beta-2-agonists for initial treatment of acute asthma in children (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
472. Goodman DC, Littenberg B, O'Connor GT, Brooks JG. Theophylline in acute childhood asthma: a meta-analysis of its efficacy. *Pediatr Pulmonol* 1996;21(4):211-8.
473. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;79(5):405-10.
474. Graham V, Lasserson T, Rowe BH. Antibiotics for acute asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
475. Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Paediatr Adolesc Med* 2000;154(10):979-83.
476. Stormon MO, Mellis CM, Van Asperen PP, Kilham HA. Outcome evaluation of early discharge of asthmatic children from hospital: a randomized control trial. *J Qual Clin Pract* 1999;19(3):149-54.
477. Fox GF, Marsh MJ, Milner AD. Treatment of recurrent acute wheezing episodes in infancy with oral salbutamol and prednisolone. *Eur J Pediatr* 1996;155(6):512-6.
478. LeSouef PN. Aerosol delivery to wheezy infants: a comparison between a nebulizer and two small volume spacers. *Pediatr Pulmonol* 1997;23(3):212-6.
479. Rubilar L, Castro-Rodriguez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. *Pediatr Pulmonol* 2000;29(4):264-9.
480. Daugbjerg P, Brenoe E, Forchhammer H, Frederiksen B, Glazowski MJ, Ibsen KK, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatrica* 1993;82(6-7):547-51.
481. Bentur L, Canny GJ, Shields MD, Kerem E, Schuh S, Reisman JJ, et al. Controlled trial of nebulized albuterol in children younger than 2 years of age with acute asthma. *Pediatrics* 1992;89(1):133-7.
482. Prah P, Petersen NT, Hornsleth A. Beta 2-agonists for the treatment of wheezy bronchitis? *Ann Allergy* 1986;57(6):439-41.
483. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. *Pediatrics* 1990;86(3):350-6.
484. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F. Anticholinergic drugs for wheeze in children under the age of two years (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
485. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: The need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. *European Respiratory Journal* 1999;13(5):1198-208.
486. Prys-Picard CO, Campbell SM, Ayres JG, Miles JF, Niven RM, Consensus on Difficult Asthma Consortium UK. Defining and investigating difficult asthma: developing quality indicators. *Respiratory Medicine* 2006;100(7):1254-61.
487. Bratton DL, Price M, Gavin L, Glenn K, Brenner M, Gelfand EW, et al. Impact of a multidisciplinary day program on disease and healthcare costs in children and adolescents with severe asthma: a two-year follow-up study. *Pediatric Pulmonology* 2001;31(3):177-89.
488. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, et al. Systematic assessment of difficult-to-treat asthma. *European Respiratory Journal* 2003;22(3):478-83.
489. Weinstein AG, McKee L, Stapleford J, Faust D. An economic evaluation of short-term inpatient rehabilitation for children with severe asthma. *Journal of Allergy & Clinical Immunology*. Vol. 1996;98(2):264-73.
490. Ranganathan SC, Payne DN, Jaffe A, McKenzie SA. Difficult asthma: defining the problems. *Pediatr Pulmonol* 2001;31(2):114-20.
491. Vamos M, Kolbe J. Psychological factors in severe chronic asthma. *Aust N Z J Psychiatry*. 1999;33(4):538-44.
492. Vila G, Nollet-Clemencon C, De Blic J, Mouren-Simeoni MC, Scheinmann P. Asthma severity and psychopathology in a tertiary care department for children and adolescent. *Eur Child Adolesc Psychiatry*. 1998;7(3):137-44.
493. Wainwright NWJ, Surtees PG, Wareham NJ, Harrison BDW. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. *Allergy*. 2007;62(5):554-60.
494. Wamboldt MZ, Weintraub P, Krafchick D, Wamboldt FS. Psychiatric family history in adolescents with severe asthma. *Journal of the American Academy of Child & Adolescent Psychiatry* 1996;35(8):1042-9.
495. Miles JF, Garden GM, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. *Clinical & Experimental Allergy* 1997;27(10):1151-9.
496. Ten Brinke A, Ouwerkerk ME, Bel EH, Spinhoven P. Similar psychological characteristics in mild and severe asthma. *J Psychosom Res*. 2001;50(1):7-10.
497. Wamboldt MZ, Fritz G, Mansell A, McQuaid EL, Klein RB. Relationship of asthma severity and psychological problems in children. *J Amer Acad Child Adolescent Psychiatry* 1998;37(9):943-50.
498. McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: A meta-analysis. *J Dev Behav Pediatr*. 2001;22(6):430-9.
499. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biological Psychiatry* 2005;58(11):865-70.
500. Godding V, Kruth M, Jamart J. Joint consultation for high-risk asthmatic children and their families, with pediatrician and child psychiatrist as co-therapists: model and evaluation. *Family Process* 1997;36(3):265-80.
501. Smith JR, Mildenhall S, Noble MJ, Shepstone L, Koutantji M, Mugford M, et al. The Coping with Asthma Study: a randomised controlled trial of a home based, nurse led psychoeducational intervention for adults at risk of adverse asthma outcomes. *Thorax* 2005;60(12):1003-11.
502. Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, et al. A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma. *Health Technology Assessment* 2005;9(23):iii-iv,1-167.
503. Position statement. Environmental allergen avoidance in allergic asthma. Ad Hoc Working Group on Environmental Allergens and Asthma. *J Allergy Clin Immunol* 1999;103(2 Pt 1):203-5.
504. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. *BMC Pulmonary Medicine* 2005;5(4).
505. Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F, et al. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002;325(7361):411-4.
506. Black PN, Udy AA, Brodie SM. Sensitivity to fungal allergens is a risk factor for life-threatening asthma. *Allergy* 2000;55(5):501-4.

507. O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. *N Engl J Med* 1991;324(6):359-63.
508. Chlumsky J, Striz I, Terl M, Vondracek J. Strategy aimed at reduction of sputum eosinophils decreases exacerbation rate in patients with asthma. *J Int Med Res* 2006;34(2):129-39.
509. Fahy JV, Boushey HA, Lazarus SC, Mauger EA, Cherniack RM, Chinchilli VM, et al. Safety and reproducibility of sputum induction in asthmatic subjects in a multicenter study. *Am J Respir Crit Care Med*. 2001;163(6):1470-5.
510. Grootendorst DC, van den Bos JW, Romeijn JJ, Veselic-Charvat M, Duiverman EJ, Vrijlandt EJ, et al. Induced sputum in adolescents with severe stable asthma. Safety and the relationship of cell counts and eosinophil cationic protein to clinical severity. *Eur Respir J* 1999;13(3):647-53.
511. Loh LC, Kanabar V, D'Amato M, Barnes NC, O'Connor BJ. Sputum induction in corticosteroid-dependant asthmatics: risks and airway cellular profile. *Asian Pacific Journal of Allergy & Immunology* 2005;23(4):189-96.
512. Tarodo de la Fuente P, Romagnoli M, Carlsson L, Godard P, Bousquet J, Chanez P. Eosinophilic inflammation assessed by induced sputum in corticosteroid-dependent asthma. *Respiratory Medicine*. 1999;93(3):183-9.
513. Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005;60(3):215-8.
514. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide to guide asthma management: A randomised controlled trial. *Am J Respir Crit Care Med* 2007;176:231-7
515. Schatz M, Harden K, Forsythe A, Chillingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. *J Allergy Clin Immunol* 1988;81(3):509-17.
516. Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. *Am J Respir Crit Care Med* 1995;151(4):1170-4.
517. Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. *Am J Obstet Gynecol* 1996;175(1):150-4.
518. Juniper EF, Newhouse MT. Effect of pregnancy on asthma - a systematic review and meta-analysis. In: Schatz M, Zeiger RS, Claman HC, editors. *Asthma and immunological diseases in pregnancy and early infancy*. New York: Marcel Dekker; 1993. p.401-27.
519. Stenius-Aarniala BS, Hedman J, Terano KA. Acute asthma during pregnancy. *Thorax* 1996;51(4):411-4.
520. Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. *Thorax* 1988;43(1):12-8.
521. Schatz M. Interrelationships between asthma and pregnancy: a literature review. *J Allergy Clin Immunol* 1999;103(2 Pt 2):S330-6.
522. Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. *J Allergy Clin Immunol* 1986;78(2):349-53.
523. Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. *Am J Obstet Gynecol* 1992;167(4 Pt 4):964-7.
524. Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. *Chest* 1990;98(2):389-92.
525. Demissie K, Breckenbridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998;158(4):1091-5.
526. Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy-a population based study. *Eur J Epidemiol* 2000;16(2):167-71.
527. Cydulka RK, Emerman CL, Schreiber D, Molander KH, Woodruff PG, Carmargo CA Jr. Acute asthma among pregnant women presenting to the emergency department. *Am J Respir Crit Care Med* 1999;160(3):887-92.
528. Department of Health. *Why mothers die. Confidential enquiries into maternal deaths in the United Kingdom 1994-96*. London: The Stationery Office; 1998. [cited 06 Mar 2008]. Available from url: <http://www.archive.official-documents.co.uk/document/doh/wmd/wmd-hm.htm>
529. Lewis G, editor. *Why mothers die 1997-1999. The fifth report of the confidential enquiries into maternal deaths in the United Kingdom 1997-99*. London: RCOG Press; 2001.
530. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997;100(3):301-6.
531. Rayburn WF, Atkinson BD, Gilbert K, Turnbull GL. Short-term effects of inhaled albuterol on maternal and fetal circulations. *Am J Obstet Gynecol* 1994;171(3):770-3.
532. Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chillingar LM, et al. The safety of inhaled beta-agonist bronchodilators during pregnancy. *J Allergy Clin Immunol* 1988;82(4):686-95.
533. Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996;49(2):247-50.
534. Greenberger PA, Patterson R. Beclometasone dipropionate for severe asthma during pregnancy. *Ann Intern Med* 1983;98(4):478-80.
535. Dombrowski M, Thom E, McNellis D. Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy. *J Allergy Clin Immunol* 1999;103(2 Pt 2):S356-9.
536. Dombrowski MP, Brown CL, Berry SM. Preliminary experience with triamcinolone acetonide in pregnancy. *J Matern Fetal Med* 1996;5(6):310-3.
537. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 1999;93(3):392-5.
538. Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. *Chest* 1995;107(3):642-7.
539. Schatz M. Asthma during pregnancy: interrelationships and management. *Ann Allergy* 1992;68(2):123-33.
540. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology* 1997;56(5):335-40.
541. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Junnisset L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62(6):385-92.
542. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology* 1998;58(1):2-5.
543. The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI). *Ann Allergy Asthma Immunol* 2000;84(5):475-80.
544. Mabie WC, Barton JR, Wasserstrum N, Sibai BM. Clinical observations on asthma in pregnancy. *J Matern Fetal Med* 1992;1(1):45-50.
545. Lao TT, Huengsbuerg M. Labour and delivery in mothers with asthma. *Eur J Obstet Gynecol Reprod Biol* 1990;35(2-3):183-90.
546. Arad I, Landau H. Adrenocortical reserve of neonates born of long-term, steroid-treated mothers. *Eur J Pediatr* 1984;142(4):279-80.
547. Turner ES, Greenberger PA, Patterson R. Management of the pregnant asthmatic patient. *Ann Intern Med* 1980;93(6):905-18.
548. Ost L, Wettrell G, Bjorkhem I, Rane A. Prednisolone excretion in human milk. *J Paediatr* 1985;106(6):1008-11.
549. McKenzie SA, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. *Arch Dis Child* 1975;50(11):894-6.
550. Greenberger PA, Odeh YK, Frederiksen MC, Atkinson AJ Jr. Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993;53(3):324-8.
551. Meredith S, Nordman H. Occupational asthma: measures of frequency from four countries. *Thorax* 1996;51(4):435-40.
552. Blanc PD, Toren K. How much adult asthma can be attributed to occupational factors? *Am J Med* 1999;107(6):580-7.
553. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;167(5):787-97.
554. Ross DJ. Ten years of the SWORD project. Surveillance of Work-related and Occupational Respiratory Disease. *Clin Exp Allergy* 1999;29(6):750-3.
555. Hendrick DJ, Burge PS. Asthma. In: Hendrick DJ, Beckett W, Burge PS, Chung A, editors. *Occupational disorders of the lung. Recognition, management and prevention*. London: WB Saunders; 2002. p.33-76.
556. Banks DE, Wang ML. Occupational asthma: „the big picture“. *Occup Med* 2000;15(2):335-58.
557. Ameille J, Pauli G, Calastreng-Crinquand A, Vervloet D, Iwatsubo Y, Popin E, et al. Reported incidence of occupational asthma in France, 1996-99: the ONAP programme. *Occup Environ Med* 2003;60(2):136-41.
558. Brhel P. Occupational respiratory diseases in the Czech Republic. *Ind Health* 2003;41(2):121-3.
559. Cortona G, Pisati G, Dellabianca A, Moscato G. Respiratory occupational allergies: the experience of the Hospital Operative Unit of Occupational Medicine in Lombardy from 1990 to 1998 [Italian]. *G Ital Med Lav Ergon* 2001;23(1):64-70.
560. Gannon PF, Burge PS. The SHIELD scheme in the West Midlands Region, United Kingdom. Midland Thoracic Society Research Group. *Br J Ind Med* 1993;50(9):791-6.
561. Hnizdo E, Esterhuizen TM, Rees D, Laloo UG. Occupational asthma as identified by the Surveillance of Work-related and Occupational Respiratory Diseases programme in South Africa. *Clin Exp Allergy* 2001;31(1):32-9.

562. McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989-97. *Occup Environ Med* 2000;57(12):823-9.
563. Meyer JD, Holt DL, Cherry NM, McDonald JC. SWORD ,98: surveillance of work-related and occupational respiratory disease in the UK. *Occup Med (Oxf)* 1999;49(8):485-9.
564. Sallie BA, Ross DJ, Meredith SK, McDonald JC. SWORD ,93. Surveillance of work-related and occupational respiratory disease in the UK. *Occup Med (Oxf)* 1994;44(4):177-82.
565. Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. *Scand J Work Environ Health* 1999;25(5):430-5.
566. Meredith SK, Taylor VM, McDonald JC. Occupational respiratory disease in the United Kingdom 1989: a report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. *Br J Ind Med* 1991;48(5):292-8.
567. Karjalainen A, Kurppa K, Martikainen R, Karjalainen J, Klaukka T. Exploration of asthma risk by occupation—extended analysis of an incidence study of the Finnish population. *Scand J Work Environ & Health* 2002;28(1):49-57.
568. Reijula K, Haahela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. *Chest* 1996;110(1):58-61.
569. Jaakkola JJ, Piipari R, Jaakkola MS. Occupation and asthma: a population-based incident case-control study. *Am J Epidemiol* 2003;158(10):981-7.
570. Johnson AR, Dimich-Ward HD, Manfreda J, Becklake MR, Ernst P, Sears MR, et al. Occupational asthma in adults in six Canadian communities. *Am J Respir Crit Care Med* 2000;162(6):2058-62.
571. Kogevinas M, Anto JM, Soriano JB, Tobias A, Burney P. The risk of asthma attributable to occupational exposures. A population-based study in Spain. Spanish Group of the European Asthma Study. *Am J Respir Crit Care Med* 1996;154(1):137-43.
572. Kogevinas M, Anto JM, Sunyer J, Tobias A, Kromhout H, Burney P. Occupational asthma in Europe and other industrialised areas: a population-based study. *European Community Respiratory Health Survey Study Group. Lancet* 1999;353(9166):1750-4.
573. Lundh T, Stahlbom B, Akesson B. Dimethylethylamine in mould core manufacturing: exposure, metabolism, and biological monitoring. *Br J Ind Med* 1991;48(3):203-7.
574. Burge PS, Pantin CF, Newton DT, Gannon PF, Bright P, Belcher J, et al. Development of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma. Midlands Thoracic Society Research Group. *Occup Environ Med* 1999;56(11):758-64.
575. Bright P, Newton DT, Gannon PF, Pantin CF, Burge PS. OASYS-3: improved analysis of serial peak expiratory flow in suspected occupational asthma. *Monaldi Arch Chest Dis* 2001;56(3):281-8.
576. Burge PS. Occupational asthma in electronics workers caused by colophony fumes: follow-up of affected workers. *Thorax* 1982;37(5):348-53.
577. Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC20 and peak expiratory flow rate in cedar asthma. *J Allergy Clin Immunol* 1990;85(3):592-8.
578. Leroyer C, Perfetti L, Trudeau C, L'Archeveque J, Chan-Yeung M, Malo JL. Comparison of serial monitoring of peak expiratory flow and FEV1 in the diagnosis of occupational asthma. *Am J Respir Crit Care Med* 1998;158(3):827-32.
579. Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. *Chest* 1991;100(1):63-9.
580. Malo JL, Cote J, Cartier A, Boulet LP, L'Archeveque J, Chan-Yeung M. How many times per day should peak expiratory flow rates be assessed when investigating occupational asthma? *Thorax* 1993;48(12):1211-7.
581. Malo JL, Ghezze H, L'Archeveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991;143(3):528-32.
582. Axon EJ, Beach JR, Burge PS. A comparison of some of the characteristics of patients with occupational and non-occupational asthma. *Occup Med (Oxf)* 1995;45(2):109-11.
583. Koskela H, Taivainen A, Tukiainen H, Chan HK. Inhalation challenge with bovine dander allergens: who needs it? *Chest* 2003;124(1):383-91.
584. Malo JL, Ghezze H, L'Archeveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991;143(3):528-32.
585. Malo JL, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;10(7):1513-5.
586. Ricciardi L, Fedele R, Saitta S, Tigano V, Mazzeo L, Fogliani O, et al. Occupational asthma due to exposure to iroko wood dust. *Ann Allergy Asthma Immunol* 2003;91(4):393-7.
587. Vandenplas O, Binard-Van Cangh F, Brumagne A, Caroyer JM, Thimpont J, Sohy C, et al. Occupational asthma in symptomatic workers exposed to natural rubber latex: evaluation of diagnostic procedures. *J Allergy Clin Immunol* 2001;107(3):542-7.
588. Cote J, Kennedy S, Chan-Yeung M. Quantitative versus qualitative analysis of peak expiratory flow in occupational asthma. *Thorax* 1993;48(1):48-51.
589. Perrin B, Lagier F, L'Archeveque J, Cartier A, Boulet LP, Cote J, et al. Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge. *Eur Respir J* 1992;5(1):40-8.
590. Baldwin DR, Gannon P, Bright P, Newton DT, Robertson A, Venables K, et al. Interpretation of occupational peak flow records: level of agreement between expert clinicians and Oasys-2. *Thorax* 2002;57(10):860-4.
591. Baur X, Huber H, Degens PO, Allmers H, Ammon J. Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. *Am J Ind Med* 1998;33(2):114-22.
592. Anees W, Huggins V, Pavord ID, Robertson AS, Burge PS. Occupational asthma due to low molecular weight agents: eosinophilic and non-eosinophilic variants. *Thorax* 2002;57(3):231-6.
593. Brisman J, Lillienberg L, Belin L, Ahman M, Jarvholm B. Sensitisation to occupational allergens in bakers' asthma and rhinitis: a case-referent study. *Int Arch Occup Environ Health* 2003;76(2):167-70.
594. Cartier A, Grammer L, Malo JL, Lagier F, Ghezze H, Harris K, et al. Specific serum antibodies against isocyanates: association with occupational asthma. *J Allergy Clin Immunol* 1989;84(4 Pt 1):507-14.
595. Hargreave FE, Ramsdale EH, Pugsley SO. Occupational asthma without bronchial hyperresponsiveness. *Am Rev Respir Dis* 1984;130(3):513-5.
596. Lemiere C, Cartier A, Malo JL, Lehrer SB. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med* 2000;162(3 Pt 1):976-80.
597. Lin FJ, Chen H, Chan-Yeung M. New method for an occupational dust challenge test. *Occup Environ Med* 1995;52(1):54-6.
598. Merget R, Schultze-Werninghaus G, Bode F, Bergmann EM, Zachgo W, Meier-Sydow J. Quantitative skin prick and bronchial provocation tests with platinum salt. *Br J Ind Med* 1991;48(12):830-7.
599. Merget R, Dierkes A, Rueckmann A, Bergmann EM, Schultze-Werninghaus G. Absence of relationship between degree of nonspecific and specific bronchial responsiveness in occupational asthma due to platinum salts. *Eur Respir J* 1996;9(2):211-6.
600. Moscato G, Dellabianca A, Vinci G, Candura SM, Bossi MC. Toluene diisocyanate-induced asthma: clinical findings and bronchial responsiveness studies in 113 exposed subjects with work-related respiratory symptoms. *J Occup Med* 1991;33(6):720-5.
601. Tarlo SM, Broder I. Outcome of assessments for occupational asthma. *Chest* 1991;100(2):329-35.
602. Vandenplas O, Delwiche JP, Evrard G, Aimont P, van der Brempt X, Jamart J, et al. Prevalence of occupational asthma due to latex among hospital personnel. *Am J Respir Crit Care Med* 1995;151(1):54-60.
603. Burge PS, O'Brien IM, Harries MG. Peak flow rate records in the diagnosis of occupational asthma due to colophony. *Thorax* 1979;34(3):308-16.
604. Burge PS, O'Brien IM, Harries MG. Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. *Thorax* 1979;34(3):317-23.
605. Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Med* 1982;72(3):411-5.
606. Merget R, Schulte A, Gebler A, Breitstadt R, Kulzer R, Berndt ED, et al. Outcome of occupational asthma due to platinum salts after transferral to low-exposure areas. *Int Arch Occup Environ Health* 1999;72(1):33-9.
607. Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, et al. Occupational asthma: a longitudinal study on the clinical and socioeconomic outcome after diagnosis. *Chest* 1999;115(1):249-56.
608. Pisati G, Baruffini A, Zedda S. Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure. *Br J Ind Med* 1993;50(1):60-4.
609. Rosenberg N, Garnier R, Rousselin X, Mertz R, Gervais P. Clinical and socio-professional fate of isocyanate-induced asthma. *Clin Allergy* 1987;17(1):55-61.
610. Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. *Occup Environ Med* 1997;54(10):756-61.
611. Valentino M, Pizzichini MA, Monaco F, Governa M. Latex-induced asthma in four healthcare workers in a regional hospital. *Occup Med (Oxf)* 1994;44(3):161-4.
612. Valentino M, Rapisarda V. Course of isocyanate-induced asthma in relation to exposure cessation: longitudinal study of 50 subjects [Italian]. *G Ital Med Lav Ergon* 2002;24(1):26-31.

613. Vandenas O, Delwiche JP, Depelchin S, Sibille Y, Vande Weyer R, Delaunois L. Latex gloves with a lower protein content reduce bronchial reactions in subjects with occupational asthma caused by latex. *Am J Respir Crit Care Med* 1995;151(3 Pt 1):887-91.
614. Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (*Thuja plicata*). *J Allergy Clin Immunol* 1987;79(5):792-6.
615. Malo JL, Cartier A, Ghezzi H, Lafrance M, McCants M, Lehrer SB. Patterns of improvement in spirometry, bronchial hyperresponsiveness, and specific IgE antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. *Am Rev Respir Dis* 1988;138(4):807-12.
616. Gannon PF, Weir DC, Robertson AS, Burge PS. Health, employment, and financial outcomes in workers with occupational asthma. *Brit J Ind Med* 1993;50(6):491-6.
617. Cannon J, Cullinan P, Newman Taylor A. Consequences of occupational asthma. *BMJ* 1995;311(7005):602-3.
618. Larbanois A, Jamart J, Delwiche JP, Vandenas O. Socioeconomic outcome of subjects experiencing asthma symptoms at work. *Eur Respir J* 2002;19(6):1107-13.
619. Ross DJ, McDonald JC. Health and employment after a diagnosis of occupational asthma: a descriptive study. *Occup Med (Oxf)* 1998;48(4):219-25.
620. Ameille J, Pairon JC, Bayeux MC, Brochard P, Choudat D, Conso F, et al. Consequences of occupational asthma on employment and financial status: a follow-up study. *Eur Respir J* 1997;10(1):55-8.
621. Gannon PF, Weir DC, Robertson AS, Burge PS. Health, employment, and financial outcomes in workers with occupational asthma. *Br J Ind Med* 1993;50(6):491-6.
622. Marabini A, Dimich-Ward H, Kwan SY, Kennedy SM, Waxler-Morrison N, Chan-Yeung M. Clinical and socioeconomic features of subjects with red cedar asthma. A follow-up study. *Chest* 1993;104(3):821-4.
623. Vandenas O, Jamart J, Delwiche JP, Evrard G, Larbanois A. Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. *J Allergy Clin Immunol* 2002;109(1):125-30.
624. Venables KM, Davison AG, Newman Taylor AJ. Consequences of occupational asthma. *Respir Med* 1989;83(5):437-40.
625. Clark NM, Gong M, Schork MA, Evans D, Roloff D, Hurwitz M, et al. Impact of education for physicians on patient outcomes. *Pediatrics* 1998;101(5):831-6.
626. Feder G, Griffiths C, Highton C, Eldridge S, Spena M, Southgate L. Do clinical guidelines introduced with practice based education improve care of asthmatic and diabetic patients? A randomised controlled trial in general practitioners in east London. *BMJ* 1995;311(7018):1473-8.
627. Battleman DS, Callahan MA, Silber S, Munoz CI, Santiago L, Abularrage J, et al. Dedicated asthma center improves the quality of care and resource utilization for pediatric asthma: a multicenter study. *Academic Emergency Medicine*. 2001;8(7):709-15.
628. Premaratne UN, Sterne JA, Marks GB, Webb JR, Azima H, Burney PG. Clustered randomised trial of an intervention to improve the management of asthma: Greenwich asthma study. *BMJ* 1999;318(7193):1251-5.
629. Charlton I, Charlton G, Broomfield J, Mullee MA. Audit of the effect of a nurse run asthma clinic on workload and patient morbidity in a general practice. *Br J Gen Pract* 1991;41(347):227-31.
630. Hoskins G, Neville RG, Smith B, Clark RA. Focus on asthma. The link between nurse training and asthma outcomes. *Br J Comm Nursing* 1999;4(5):222-8.
631. Heard AR, Richards IJ, Alpers JH, Pilotto LS, Smith BJ, Black JA. Randomised controlled trial of general practice based asthma clinics. *Med J Aust* 1999;171(2):68-71.
632. Bryce FP, Neville RG, Crombie IK, Clark RA, McKenzie P. Controlled trial of an audit facilitator in diagnosis and treatment of childhood asthma in general practice. *BMJ* 1995;310(6983):838-42.
633. Dickinson J, Hutton S, Atkin A, Jones K. Reducing asthma morbidity in the community: the effect of a targeted nurse-run asthma clinic in an English general practice. *Respir Med* 1997;91(10):634-40.
634. Lindberg M, Ahlner J, Moller M, Ekstrom T. Asthma nurse practice - a resource-effective approach in asthma management. *Respir Med* 1999;93(8):584-8.
635. Sondergaard J, Andersen M, Vach K, Kragstrup J, Maclure M, Gram LF. Detailed postal feedback about prescribing to asthma patients combined with a guideline statement showed no impact: a randomised controlled trial. *European Journal of Clinical Pharmacology*. 2002;58(2):127-32.
636. Pinnock H, Bawden R, Proctor S, Wolfe S, Scullion J, Price D, et al. Accessibility, acceptability, and effectiveness in primary care of routine telephone review of asthma: pragmatic, randomised controlled trial. *BMJ* 2003;326(7387):477-9.
637. Smeele IJ, Grol RP, van Schayck CP, van den Bosch WJ, van den Hoogen HJ, Muris JW. Can small group education and peer review improve care for patients with asthma/chronic obstructive pulmonary disease? *Qual Health Care* 1999;8(2):92-8.
638. Paterson C, Britten N. Organising primary health care for people with asthma: the patient's perspective. *Br J Gen Pract*. 2000;50(453):299-303.
639. Barnes G, Partridge MR. Community asthma clinics: 1993 survey of primary care by the National Asthma Task Force. *Qual Health Care* 1994;3(3):133-6.
640. Ng TP. Validity of symptom and clinical measures of asthma severity for primary outpatient assessment of adult asthma. *Br J Gen Pract* 2000;50(450):7-12.
641. Gibson PG, Wilson AJ. The use of continuous quality improvement methods to implement practice guidelines in asthma. *J Qual Clin Pract* 1996;16(2):87-102.
642. Neville RG, Hoskins G, Smith B, Clark RA. Observations on the structure, process and clinical outcomes of asthma care in general practice. *Br J Gen Pract* 1996;46(411):583-7.
643. Eccles M, McColl E, Steen N, Rousseau N, Grimshaw J, Parkin D, et al. Effect of computerised evidence based guidelines on management of asthma and angina in adults in primary care: cluster randomised controlled trial. *BMJ*. 2002;325(7370):941.
644. Neville R. Two approaches to effective asthma audit. *Practitioner* 1995;239(1548):203-5.
645. Jones K, Cleary R, Hyland M. Predictive value of a simple asthma morbidity index in a general practice population. *Br J Gen Pract* 1999;49(438):23-6.
646. Worrall G, Chaulk P, Freaque D. The effects of clinical practice guidelines on patient outcomes in primary care: a systematic review. *Canadian Medical Association Journal* 1997;156(12):1705-12.
647. Effectiveness of routine self monitoring of peak flow in patients with asthma. Grampian Asthma Study of Integrated Care (GRASSIC). *BMJ* 1994;308(6928):564-7.
648. Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Integrated care for asthma: a clinical, social, and economic evaluation. Grampian Asthma Study of Integrated Care (GRASSIC). *BMJ* 1994;308(6928):559-64.
649. Osman LM, Abdalla MI, Russell IT, Fiddes J, Friend JA, Legge JS, et al. Integrated care for asthma: matching care to the patient. *Eur Respir J* 1996;9(3):444-8.
650. Buckingham K, Drummond N, Cameron I, Meldrum P, Douglas G. Costing shared care. *Health Serv Manage* 1994;90(2):22-5.
651. Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care: a multicentre study in seven European countries. *Drugs & Aging* 2001;18(1):63-77.
652. Schulz M, Verheyen F, Muhlig S, Muller JM, Muhlbaier K, Knop-Schneicker E, et al. Pharmaceutical care services for asthma patients: a controlled intervention study. *Journal of Clinical Pharmacology*. 2001;41(6):668-76.
653. Cordina M, McElnay JC, Hughes CM. Assessment of a community pharmacy-based program for patients with asthma. *Pharmacotherapy*. 2001;21(10):1196-203.
654. Burr ML, Verrall C, Kaur B. Social deprivation and asthma. *Respir Med* 1997;91(10):603-8.
655. Rona RJ. Asthma and poverty. *Thorax* 2000;55(3):239-44.
656. Carey OJ, Cookson JB, Britton J, Tattersfield AE. The effect of lifestyle on wheeze, atopy, and bronchial hyperreactivity in Asian and white children. *Am J Respir Crit Care Med* 1996;154(2 Pt 1):537-40.
657. Mielck A, Reitmair P, Wjst M. Severity of childhood asthma by socioeconomic status. *Int J Epidemiol* 1996;25(2):388-93.
658. Griffiths C, Kaur G, Gantley M, Feder G, Hillier S, Goddard J, et al. Influences on hospital admission for asthma in south Asian and white adults: qualitative interview study. *BMJ* 2001;323(7319):962-6.
659. Evans D, Mellins R, Lobach K, Ramos-Bonoan C, Pinkett-Heller M, Wiesemann S, et al. Improving care for minority children with asthma: professional education in public health clinics. *Pediatrics* 1997;99(2):157-64.
660. Higgins BG, Britton JR. Geographical and social class effects on asthma mortality in England and Wales. *Respir Med* 1995;89(5):341-6.
661. Mowat DHR, McCowan C, Neville RG, Crombie IK, Thomas G, Ricketts IW, et al. Socio-economic status and childhood asthma. *Asthma Gen Pract* 1998;6(1):9-11.
662. Partridge MR. In what way may race, ethnicity or culture influence asthma outcomes? *Thorax* 2000;55(3):175-6.
663. Williams MV, Baker DW, Honig EG, Lee TM, Nowlan A. Inadequate literacy is a barrier to asthma knowledge and self-care. *Chest* 1999;114(4):1008-15.
664. Griffiths C, Naish J, Sturdy P, Pereira F. Prescribing and hospital admissions for asthma in east London. *BMJ* 1996;312(7029):481-2.
665. Gibson PG, Henry RL, Vimpani GV, Halliday J. Asthma knowledge, attitudes, and quality of life in adolescents. *Arch Dis Child* 1995;73(4):321-6.
666. Neville RG, McCowan C, Hoskins G, Thomas G. Cross-sectional observations on the natural history of asthma. *Br J Gen Pract* 2001;51(466):361-5.
667. Dyer CA, Hill SL, Stockley RA, Sinclair AJ. Quality of life in elderly subjects with a diagnostic label of asthma from general practice registers. *Eur Respir J* 1999;14(1):39-45.

668. Enright PL, McClelland RL, Newman AB, Gottlieb DJ, Lebowitz MD. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. *Chest* 1999;116(3):603-13.
669. Bucknall CE, Robertson C, Moran F, Stevenson RD. Management of asthma in hospital: a prospective audit. *Br Med J (Clin Res Ed)* 1988;296(6637):1637-9.
670. Vollmer WM, O'Hollaren M, Ettinger KM, Stibolt T, Wilkins J, Buist AS, et al. Specialty differences in the management of asthma. A cross-sectional assessment of allergists' patients and generalists' patients in a large HMO. *Arch Intern Med* 1997;157(11):1201-8.
671. Grant C, Nicholas R, Moore L, Salisbury C. An observational study comparing quality of care in walk-in centres with general practice and NHS Direct using standardised patients. *BMJ* 2002;324(7353):1556.
672. Pearson MG, Ryland I, Harrison BD. Comparison of the process of care of acute severe asthma in adults admitted to hospital before and 1yr after the publication of national guidelines. *Respir Med* 1996;90(9):539-45.
673. Beasley R, Miles J, Fishwick D, Leslie H. Management of asthma in the hospital emergency department. *Br J Hosp Med* 1996;55(5):253-7.
674. Neville RG, Clark RC, Hoskins G, Smith B. National asthma attack audit 1991-2. General Practitioners in Asthma Group. *BMJ* 1993;306(6877):559-62.
675. Neville RG, Hoskins G, Smith B, Clark RA. How general practitioners manage acute asthma attacks. *Thorax* 1997;52(2):153-6.
676. McDermott MF, Murphy DG, Zalenski RJ, Rydman RJ, McCarren M, Marder D, et al. A comparison between emergency diagnostic and treatment unit and inpatient care in the management of acute asthma. *Arch Intern Med* 1997;157(18):2055-62.
677. Crompton GK, Grant IW. Edinburgh emergency asthma admission service. *BMJ* 1975;4(5998):680-2.
678. Madge P, McColl J, Paton J. Impact of a nurse-led home management training programme in children admitted to hospital with acute asthma: a randomised controlled study. *Thorax* 1997;52(3):223-8.
679. Wesseldine LJ, McCarthy P, Silverman M. Structured discharge procedure for children admitted to hospital with acute asthma: a randomised controlled trial of nursing practice. *Arch Dis Child* 1999;80(2):110-4.
680. Levy ML, Robb M, Allen J, Doherty C, Bland JM, Winter RJ. A randomized controlled evaluation of specialist nurse education following accident and emergency department attendance for acute asthma. *Respir Med* 2000;94(9):900-8.
681. Smith E, Alexander V, Booker C, McCowan C, Ogston S, Mukhopadhyay S. Effect of hospital asthma nurse appointment on inpatient asthma care. *Respir Med* 2000;94(1):82-6.
682. Osman LM, Calder C, Godden DJ, Friend JA, McKenzie L, Legge JS, et al. A randomised trial of self-management planning for adult patients admitted to hospital with acute asthma. *Thorax*. 2002;57(10):869-74.
683. Stevens CA, Wesseldine LJ, Couriel JM, Dyer AJ, Osman LM, Silverman M. Parental education and guided self-management of asthma and wheezing in the pre-school child: a randomised controlled trial.[comment]. *Thorax*. 2002;57(1):39-44.
684. Baren JM, Shofer FS, Ivey B, Reinhard S, DeGeus J, Stahmer SA, et al. A randomized, controlled trial of a simple emergency department intervention to improve the rate of primary care follow-up for patients with acute asthma exacerbations. *Annals of Emergency Medicine*. 2001;38(2):115-22.
685. Sin DD, Bell NR, Svenson LW, Man SF. The impact of follow-up physician visits on emergency readmissions for patients with asthma and chronic obstructive pulmonary disease: a population-based study. *Am J Med*. 2002;112(2):120-5.
686. Boudreaux ED, Clark S, Camargo CA Jr. Telephone follow-up after the emergency department visit: experience with acute asthma. *Ann Emerg Med* 2000;35(6):555-63.
687. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, et al. Educational outreach visits: effects on professional practice and health care outcomes (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. London: John Wiley & Sons Ltd.
688. Pharmacological management of asthma. Evidence table: Audit and asthma. Edinburgh: SIGN; 2002. Available from url: <http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html>
689. Bart and the London School for Medicine and Dentistry. Centre for Health Sciences. Clinical Effectiveness Group. Available from <http://www.ihse.qmul.ac.uk/chs/nhs/ceg/index.html>: [Accessed. 6 March. 2008.]
690. Cote J, Bowie DM, Robichaud P, Parent JG, Battisti L, Boulet LP. Evaluation of two different educational interventions for adult patients consulting with an acute asthma exacerbation. *Am J Respir Crit Care Med* 2001;163(6):1415-9.
691. Cote J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M, et al. Influence of asthma education on asthma severity, quality of life and environmental control. *Can Respir J* 2000;7(5):395-400.
692. Gallefoss F, Bakke PS. Impact of patient education and self-management on morbidity in asthmatics and patients with chronic obstructive pulmonary disease. *Respir Med* 2000;94(3):279-87.
693. Gallefoss F, Bakke PS, Rsgaard PK. Quality of life assessment after patient education in a randomized controlled study on asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;159(3):812-7.
694. George MR, O'Dowd LC, Martin I, Lindell KO, Whitney F, Jones M, et al. A comprehensive educational program improves clinical outcome measures in inner-city patients with asthma. *Arch Intern Med* 1999;159(15):1710-6.
695. Ghosh CS, Ravindran P, Josh M, Stearns SC. Reductions in hospital use from self-management training for chronic asthmatics. *Soc Sci Med* 1998;46(8):1087-93.
696. Ignacio-Garcia JM, Gonzalez-Santos P. Asthma self-management education program by home monitoring of peak expiratory flow. *Am J Respir Crit Care Med* 1995;151(2 Pt 1):353-9.
697. Lahdensuo A, Haahtela T, Herrala J, Kava T, Kiviranta K, Kuusisto P, et al. Randomised comparison of guided self management and traditional treatment of asthma over one year. *BMJ* 1996;312(7033):748-52.
698. Moudgil H, Marshall T, Honeybourne D. Asthma education and quality of life in the community: a randomised controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. *Thorax* 2000;55(3):177-83.
699. Cicutto L, Murphy S, Coutts D, O'Rourke J, Lang G, Chapman C, et al. Breaking the access barrier: Evaluating an asthma center's efforts to provide education to children with asthma in schools. *Chest* 2005;128(4):1928-35.
700. Guendelman S, Meade K, Benson M, Chen YQ, Samuels S. Improving asthma outcomes and self-management behaviors of inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary.[comment]. *Archives of Pediatrics & Adolescent Medicine*. 2002;156(2):114-20.
701. Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, et al. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial.[comment]. *BMJ*. 2001;322(7286):583-5.
702. Thoonen BP, Schermer TR, Van den BG, Molema J, Folgering H, Akkermans RP, et al. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. *Thorax*. 2003;58(1):30-6.
703. Wolf FM, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. London: John Wiley & Sons Ltd.
704. Greineder DK, Loane KC, Parks P. A randomized controlled trial of a pediatric asthma outreach program. *J Allergy Clin Immunol* 1999;103(3 Pt 1):436-40.
705. Griffiths C, Foster G, Barnes N, Eldridge S, Tate H, Begum S, et al. Specialist nurse intervention to reduce unscheduled asthma care in a deprived multiethnic area: the east London randomised controlled trial for high risk asthma (ELECTRA). *BMJ* 2004;328(7432):144.
706. Guendelman S, Meade K, Chen YQ, Benson M. Asthma control and hospitalizations among inner-city children: Results of a randomized trial. *Telemedicine Journal & E Health* 2004;10(2):235-44.
707. Liu C, Feekery C. Can asthma education improve clinical outcomes? An evaluation of a pediatric asthma education program. *J Asthma* 2001;38(3):269-78.
708. Magar Y, Vervloet D, Steenhouwer F, Smaga S, Mechin H, Rocca Serra JP, et al. Assessment of a therapeutic education programme for asthma patients: „un souffle nouveau“. *Patient Education & Counseling* 2005;58(1):41-6.
709. Shames RS, Sharek P, Mayer M, Robinson TN, Hoyte EG, Gonzalez-Hensley F, et al. Effectiveness of a multicomponent self-management program in at-risk, school-aged children with asthma. *Annals of Allergy, Asthma, & Immunology*. 2004;92(6):611-8.
710. Urek MC, Tudoric N, Plavec D, Urek R, Koprivic-Milenovic T, Stojic M. Effect of educational programs on asthma control and quality of life in adult asthma patients. *Patient Education & Counseling* 2005;58(1):47-54.
711. Osman LM, Abdalla MI, Beattie JA, Ross SJ, Russell IT, Friend JA, et al. Reducing hospital admission through computer supported education for asthma patients. *BMJ* 1994;308(6928):568-71.
712. Yoon R, McKenzie DK, Bauman A, Miles DA. Controlled trial evaluation of an asthma education programme for adults. *Thorax* 1993;48(11):1110-6.
713. Allen RM, Jones MP, Oldenburg B. Randomised trial of an asthma self-management programme for adults. *Thorax* 1995;50(7):731-8.
714. Bartholomew LK, Gold RS, Parcel GS, Czyzewski DJ, Sockrider MM, Fernandez M, et al. Watch, Discover, Think, and Act: evaluation of computer-assisted instruction to improve asthma self-management in inner-city children. *Patient Educ Couns* 2000;39(2-3):269-80.
715. Charlton I, Antoniou AG, Atkinson J, Campbell MJ, Chapman E, Mackintosh T, et al. Asthma at the interface: bridging the gap between general practice and a district general hospital. *Arch Dis Child* 1994;70(4):313-8.

716. Clark NM, Feldman CH, Evans D, Levison MJ, Wasilewski Y, Mellins RB. The impact of health education on frequency and cost of health care use by low income children with asthma. *J Allergy Clin Immunol* 1986;78(1 Pt 1):108-15.
717. Cote J, Cartier A, Robichaud P, Boutin H, Malo JL, Rouleau M, et al. Influence on asthma morbidity of asthma education programs based on self-management plans following treatment optimization. *Am J Respir Crit Care Med* 1997;155(5):1509-14.
718. Couturaud F, Proust A, Frachon I, Dewitte JD, Oger E, Quiot JJ, et al. Education and self-management: a one-year randomized trial in stable adult asthmatic patients. *J Asthma*. 2002;39(6):493-500.
719. Cowie RL, Underwood MF, Little CB, Mitchell I, Spier S, Ford GT. Asthma in adolescents: a randomized, controlled trial of an asthma program for adolescents and young adults with severe asthma. *Canadian Respiratory Journal*. 2002;9(4):253-9.
720. Dolinar RM, Kumar V, Coutu-Wakulczyk G, Rowe BH. Pilot study of a home-based asthma health education program. *Patient Educ Couns* 2000;40(1):93-102.
721. Kauppinen R, Viikka V, Sintonen H, Klaukka T, Tukiainen H. Long-term economic evaluation of intensive patient education during the first treatment year in newly diagnosed adult asthma. *Respiratory Medicine*. 2001;95(1):56-63.
722. Klein JJ, van der PJ, Uil SM, Zielhuis GA, Seydel ER, van Herwaarden CL. Benefit from the inclusion of self-treatment guidelines to a self-management programme for adults with asthma. *European Respiratory Journal*. 2001;17(3):386-94.
723. Marabini A, Brugnami G, Curradi F, Casciola G, Stopponi R, Pettinari L, et al. Short-term effectiveness of an asthma educational program: results of a randomized controlled trial. *Respiratory Medicine*. 2002;96(12):993-8.
724. Morice AH, Wrench C. The role of the asthma nurse in treatment compliance and self-management following hospital admission. *Respiratory Medicine*. 2001;95(11):851-6.
725. Perneger TV, Sudre P, Muntner P, Uldry C, Courteheuse C, Naef AF, et al. Effect of patient education on self-management skills and health status in patients with asthma: a randomized trial. *American Journal of Medicine*. 2002;113(1):7-14.
726. van der Palen J, Klein JJ, Zielhuis GA, van Herwaarden CL, Seydel ER. Behavioural effect of self-treatment guidelines in a self-management program for adults with asthma. *Patient Educ Couns* 2001;43(2):161-9.
727. Wilson SR, Scamagas P, German DF, Hughes GW, Lulla S, Coss S, et al. A controlled trial of two forms of self-management education for adults with asthma. *Am J Med* 1993;94(6):564-76.
728. Lefevre F, Piper M, Weiss K, Mark D, Clark N, Aronson N. Do written action plans improve patient outcomes in asthma? An evidence-based analysis. *J Fam Pract*. 2002;51(10):842-48.
729. Sudre P, Jacquemet S, Uldry C, Perneger TV. Objectives, methods and content of patient education programmes for adults with asthma: systematic review of studies published between 1979 and 1998. *Thorax* 1999;54(8):681-7.
730. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax* 2004;59(2):94-9.
731. Toelle BG, Ram FS. Written individualised management plans for asthma in children and adults (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004. London: John Wiley & Sons Ltd.
732. Adams RJ, Boath K, Homan S, Campbell DA, Ruffin RE. A randomized trial of peak-flow and symptom-based action plans in adults with moderate-to-severe asthma. *Respirology*. 2001;6(4):297-304.
733. Ayres JG, Campbell LM. A controlled assessment of an asthma self-management plan involving a budesonide dose regimen. *OPTIONS Research Group*. *Eur Respir J* 1996;9(5):886-92.
734. Charlton I, Charlton G, Broomfield J, Mullee MA. Evaluation of peak flow and symptoms only self management plans for control of asthma in general practice. *BMJ* 1990;301(6765):1355-9.
735. Yoos HL, Kitzman H, McMullen A, Henderson C, Sidora K. Symptom monitoring in childhood asthma: a randomized clinical trial comparing peak expiratory flow rate with symptom monitoring. *Annals of Allergy, Asthma, & Immunology*. 2002;88(3):283-91.
736. Brown JV, Bakeman R, Celano MP, Demi AS, Kobrynski L, Wilson SR. Home-based asthma education of young low-income children and their families. *J Pediatr Psychol*. 2002;27(8):677-88.
737. Colland VT. Learning to cope with asthma: a behavioural self-management program for children. *Patient Educ Couns* 1993;22(3):141-52.
738. Wilson SR, Latini D, Starr NJ, Fish L, Loes LM, Page A, et al. Education of parents of infants and very young children with asthma: a developmental evaluation of the Wee Wheezers program. *J Asthma* 1996;33(4):239-54.
739. Ronchetti R, Indinnimeo L, Bonci E, Corrias A, Evans D, Hindi-Alexander M, et al. Asthma self-management programmes in a population of Italian children: a multicentric study. *Italian Study Group on Asthma Self-Management Programmes*. *Eur Respir J* 1997;10(6):1248-53.
740. Bailey WC, Kohler CL, Richards JM Jr, Windsor RA, Brooks CM, Gerald LB, et al. Asthma self-management: do patient education programs always have an impact? *Arch Intern Med* 1999;159(20):2422-8.
741. Glasgow NJ, Ponsobny AL, Yates R, Beilby J, Dugdale P. Proactive asthma care in childhood: general practice based randomised controlled trial. *BMJ* 2003;327(7416):659.
742. Homer C, Susskind O, Alpert HR, Owusu M, Schneider L, Rappaport LA, et al. An evaluation of an innovative multimedia educational software program for asthma management: report of a randomized, controlled trial. *Pediatrics* 2000;106(1 Pt 2):210-5.
743. Rubin DH, Leventhal JM, Sadock RT, Letovsky E, Schottland P, Clemente I, et al. Educational intervention by computer in childhood asthma: a randomized clinical trial testing the use of a new teaching intervention in childhood asthma. *Pediatrics* 1986;77(1):1-10.
744. van Es SM, Nagelkerke AF, Colland VT, Scholten RJ, Bouter LM. An intervention programme using the ASE-model aimed at enhancing adherence in adolescents with asthma. *Patient Educ Couns*. 2001;44(3):193-203.
745. Haby MM, Waters E, Roberston CF, Gibson PG, Ducharme FM. Interventions for educating children who have attended the emergency room for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
746. Klinnert MD, Liu AH, Pearson MR, Ellison MC, Budhiraja N, Robinson JL. Short-term impact of a randomized multifaceted intervention for wheezing infants in low-income families. *Archives of Pediatrics & Adolescent Medicine* 2005;159(1):75-82.
747. Royal Pharmaceutical Society of Great Britain. *From compliance to concordance: achieving shared goals in medicine taking*. London: The Society; 1997.
748. Hand CH, Bradley C. Health beliefs of adults with asthma: toward an understanding of the difference between symptomatic and preventive use of inhaler treatment. *J Asthma* 1996;33(5):331-8.
749. Byer B, Myers, LB. Psychological correlates of adherence to medication in asthma. *Psychol Health Med* 2000;5(4):389-93.
750. Garrett J, Fenwick JM, Taylor G, Mitchell E, Rea H. Peak expiratory flow meters (PEFMs)—who uses them and how and does education affect the pattern of utilisation? *Aust N Z J Med* 1994;24(5):521-9.
751. Redline S, Wright EC, Kattan M, Kerckmar C, Weiss K. Short-term compliance with peak flow monitoring: results from a study of inner city children with asthma. *Pediatr Pulmonol* 1996;21(4):203-10.
752. Burkhart PV, Dunbar-Jacob JM, Fireman P, Rohay J. Children's adherence to recommended asthma self-management. *Pediatr Nurs*. 2002;28(4):409-14.
753. Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. *Thorax*. 2001;56(3):180-2.
754. Berg J, Dunbar-Jacob J, Sereika SM. An evaluation of a self-management program for adults with asthma. *Clin Nurs Res* 1997;6(3):225-38.
755. Cochrane MC, Bala MV, Downs KE, Mausekopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest* 2000;117(2):542-50.
756. Jonasson G, Carlsen KH, Sodal A, Jonasson C, Mowinckel P. Patient compliance in a clinical trial with inhaled budesonide in children with mild asthma. *Eur Respir J* 1999;14(1):150-4.
757. Braunstein GL, Trinquet G, Harper AE. Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination. Compliance Working Group. *Eur Respir J* 1996;9(5):893-8.
758. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. London: John Wiley & Sons Ltd.
759. Gibson PG, Shah S, Mamoon HA. Peer-led asthma education for adolescents: impact evaluation. *J Adolesc Health* 1998;22(1):66-72.
760. Schraa JC, Dirks JF. Improving patient recall and comprehension of the treatment regimen. *J Asthma* 1982;19(3):159-62.
761. Huss K, Salerno M, Huss RW. Computer-assisted reinforcement of instruction: effects on adherence in adult atopic asthmatics. *Res Nurs Health* 1991;14(4):259-67.
762. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. *Journal of Allergy & Clinical Immunology* 2005;115(6):1137-42.
763. Delaronde S, Peruccio DL, Bauer BJ. Improving asthma treatment in a managed care population. *Am J Manag Care*. 2005;11(6):361-8.
764. Feifer RA, Verbrugge RR, Khalid M, Levin R, O'Keefe GB, Aubert RE. Improvements in asthma pharmacotherapy and self-management: An example of a population-based disease management program. *Dis Manag Health Outcomes* 2004;12(2):93-102.
765. Homer CJ, Forbes P, Horvitz L, Peterson LE, Wypij D, Heinrich P. Impact of a quality improvement program on care and outcomes for children with asthma. *Arch Pediatr Adolesc Med* 2005;159(5):464-9.
766. Kemple T, Rogers C. A mailed personalised self-management plan improves attendance and increases patients' understanding of asthma. *Prim Care Respir J* 2003;12(4):110-4.

ISBN 978 1 905813 28 5

British Thoracic Society

17 Doughty Street, London WC1N 2PL
www.brit-thoracic.org.uk

Scottish Intercollegiate Guidelines Network

Elliott House, 8 -10 Hillside Crescent, Edinburgh EH7 5EA
www.sign.ac.uk

