Healthcare Improvement Scotland

SIGN
Scottish Intercollegiate Guidelines Network

British guideline on the management of asthma

A national clinical guideline

Consultation Draft 2.0 December 2013

Evidence

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 of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, 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 supporting evidence on which the evidence 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.

Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Asthma is a common condition which produces a significant workload for general practice, hospital outpatient clinics and inpatient admissions. It is clear that much of this morbidity relates to poor management particularly the under use of preventative medicine.

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 (now Primary Care Respiratory Society UK), 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] 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.

1.1.1 UPDATING THE EVIDENCE

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.

The timescale of the literature search for each section is given in Annex 1. It is hoped that this 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.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of asthma. It makes recommendations on management of adults, including pregnant women, adolescents, and children with asthma. In sections 4 and 5 on pharmacological management and inhaler devices respectively, each recommendation has been graded and the supporting evidence assessed for adults and adolescents over 12 years old, children 5-12 years, and children under 5 years. In section 8 recommendations are made on managing asthma in adolescents (10-19 years of ages as defined by the World Health Organisation (WHO).[4]

The guideline considers asthma management in all patients with a diagnosis of asthma irrespective of age or gender (although there is less available evidence for people at either age extreme). The guideline does not cover patients whose primary diagnosis is not asthma, for example those with chronic obstructive pulmonary disease or cystic fibrosis, but patients with these conditions can also have asthma. Under these circumstances many of the principles set out in this guideline will apply to the management of their asthma symptoms.

The key questions on which the guideline is based can be found on the SIGN website, www.sign.ac.uk, as part of the supporting material for this guideline.

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to healthcare professionals involved in the care of people with asthma. The target users are, however, much broader than this, and include people with asthma, their parents/carers and those who interact with people with asthma outside of the NHS, such as teachers. It will also be of interest to those planning the delivery of services in the NHS in England, Wales, Northern Ireland and Scotland.

1.2.3 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

2	Diagnosis	2008, 2011
3	Non-pharmacological management	2008, 2013
4	Pharmacological management	2004, 2005, 2006, 2008, 2009, 2011, 2013
5	Inhaler devices	2005, 2013
6	Management of acute asthma	2004, 2009, 2013
7	Difficult asthma	2008, 2013
8	Asthma in adolescents	2011
9	Asthma in pregnancy	2005, 2008, 2009, 2013
10	Occupational asthma	2005, 2008, 2013
8	Organisation and delivery of care, and audit	2008, 2013
9	Patient education and self management	2004, 2008, 2013

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 2008 guideline 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 2009 revisions include updates to pharmacological management, the management of acute asthma and asthma in pregnancy. Update searches were conducted on inhaler devices but there was insufficient new evidence to change the existing recommendations. The annexes have also been amended to reflect current evidence.

The 2011 revisions include updates to monitoring asthma and pharmacological management, and a new section on asthma in adolescents.

In 2013 the approach to updating the guideline changed and revisions were made to sub-sections throughout the guideline based on new evidence relating to specific key questions. In addition, major revisions were made to the sections on non-pharmacological management, organisation and delivery of care and supported self-management. The structure of the guideline also changed, with section 7 on special situations split into 4 separate sections on difficult asthma, asthma in adolescents, asthma in pregnancy and occupational asthma.

1.3 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.

1.3.1 PATIENT VERSION

Patient versions of this guideline are available from the SIGN website, www.sign.ac.uk

1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[5]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."[5]

The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists).
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources.
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice.
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the

summary of product characteristics (SPC) (electronic Medicines Compendium (eMC) www.medicines.org.uk)

The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[6]

1.3.3 ADDITIONAL ADVICE ON THE USE OF NEW AND EXISTING MEDICINES AND TREATMENTS

The National Institute for Health and Care Excellence (NICE) develops multiple (MTA) and single (STA) technology appraisals that make recommendations on the use of new and existing medicines and treatments within the NHS in England and Wales. Healthcare Improvement Scotland processes MTAs for NHSScotland.

STAs are not applicable to NHSScotland. The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

Practitioners should be aware of this additional advice on medicines and treatments recommended in this guideline and that recommendations made by these organisations and restrictions on their use may differ between England and Wales and Scotland.

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.[7]

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.[8-12] 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

More than one of the following symptoms: wheeze, cough, difficulty breathing, chest tightness, particularly if these symptoms:

- are frequent and recurrent[13-16]
- are worse at night and in the early morning[14, 15, 17]
- 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 colds[13]

- Personal history of atopic disorder[13, 16, 18]
- Family history of atopic disorder and/or asthma[13, 19]
- 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

- Symptoms with colds only, with no interval symptoms[13]
- Isolated cough in the absence of wheeze or difficulty breathing[20]
- History of moist cough[21]
- 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 therapy[22]
- 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.[18, 23] 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.[9, 11, 12, 24] Coexistent 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.[25, 26] Boys with asthma are more likely to “grow out” of their asthma during adolescence than girls.[13, 24, 25, 27-40]

Severity and frequency of previous wheezing episodes

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.[8, 11, 16, 19, 24, 29, 41, 42] 2++

Co-existence 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 2++

and cat dander, predicts later childhood asthma.[43, 44]

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.[9, 37, 40, 45, 46] 2++

Abnormal lung function

Persistent reductions in baseline airway function and increased airway responsiveness during childhood are associated with having asthma in adult life.[26] 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[21]	Cystic fibrosis; bronchiectasis; protracted bronchitis; recurrent aspiration; host defence disorder; ciliary dyskinesia
Excessive vomiting	Gastro-oesophageal reflux (± aspiration)
Dysphagia	Swallowing problems (± 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-aged 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.[14, 15, 17, 47] The addition of spirometry[14, 47] or bronchial hyper-responsiveness testing[48] to these questionnaires adds little to making a diagnosis of 2+

asthma in children.

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 PROBABLITY 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.[22]

✓ 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.[15, 47] However, normal results on testing, especially if performed when the child is asymptomatic, do not exclude a diagnosis of asthma.[49] 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 (FEV_1) and other spirometric indices: FEV_1 is often normal in children with persistent asthma.[49, 50] Serial measures of peak flow variability and FEV_1 show poor concordance with disease activity and do not reliably rule the diagnosis of asthma in or out.[50] 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.[49, 51] 2+

A significant increase in FEV_1 (>12% from baseline)[52] 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.[53] However, an absent response to bronchodilators does not exclude asthma.[54] 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.[55] Of the tests available, specific airways resistance (sRaw), impulse oscillometry (IOS), and measurements of residual volume (RV) appear the most promising.[56] While some of these tests have been useful in research, their role in clinical practice is uncertain.[51, 56, 57] 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,[50] lung volumes and airway responsiveness,[48] 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 spiromentry and have evidence of airways obstruction, assess the change in FEV_1 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.[48, 58] 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.[48] However, a negative methacholine test in children, which has a high negative predictive value, makes a diagnosis of asthma improbable.[58] Similarly, a negative response to an 3

exercise challenge test is helpful in excluding asthma in children with exercise related breathlessness.[59]

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 (FE_{NO}).

Sputum induction is feasible in school-aged children.[60, 61] Higher sputum eosinophil counts are associated with more marked airways obstruction and reversibility, greater asthma severity and atopy.[62] In children with newly diagnosed mild asthma, sputum eosinophilia is present and declines with inhaled steroid treatment.[61] 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 FE_{NO} in unsedated children from the age of 3-4 years.[63] A raised FE_{NO} is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma.[64] FE_{NO} is closely linked with atopic status, age and height.[65, 66] In some studies, FE_{NO} correlated better with atopic dermatitis and allergic rhinitis than with asthma. It is not closely linked with underlying lung function. FE_{NO} could not differentiate between groups once atopy was taken into account.[67] Home measurements of FE_{NO} have a highly variable relationship with other measures of disease activity and vary widely from day to day.[68] 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,[69] blood eosinophilia ≥4%,[13] or a raised specific IgE to cat, dog or mite,[70, 71] increase the probability of asthma in a child with wheeze, particularly in children over five years of age.[69] It is important to recognise that non-atopic wheezing is as frequent as atopic wheezing in school-aged children.[72] 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.[73]

✓ 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.

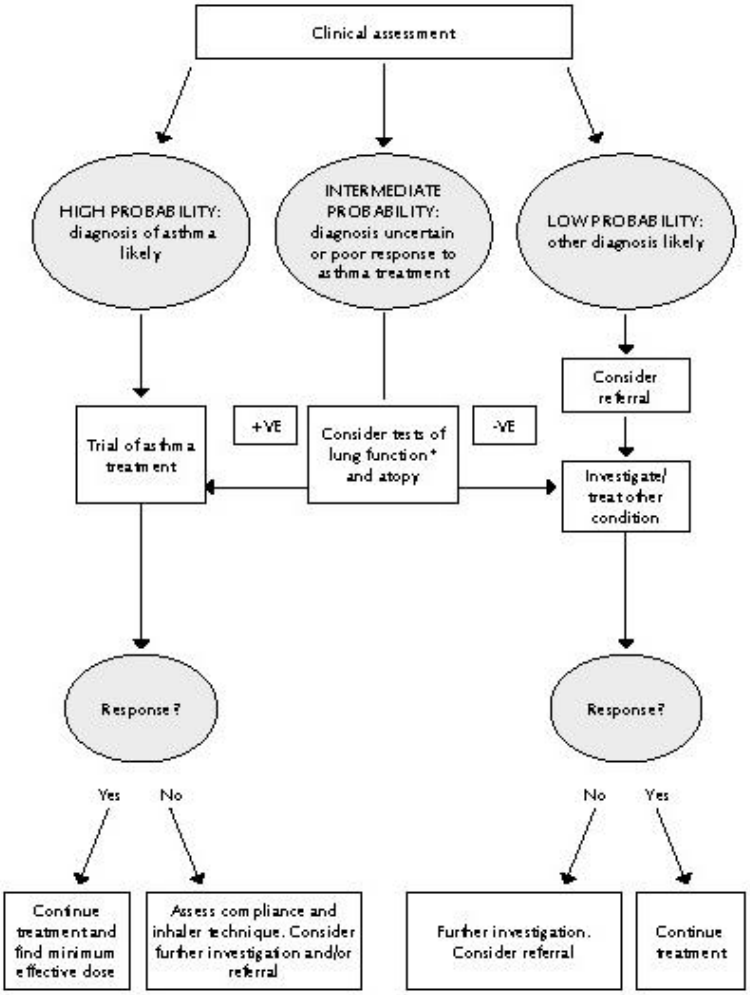
1. **In children with a high probability of asthma:**
   - move straight to a trial of treatment
   - reserve further testing for those with a poor response.
2. **In children with a low probability of asthma:**
   - consider more detailed investigation and specialist referral.

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, offer 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 posseting
▪ 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 400mcg/day or frequent use of steroid tablets)
▪ Parental anxiety or need for reassurance

Figure 1: Presentation with suspected asthma in children



** Lung function to be considered would 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;[74, 75] 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
▪ More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, particularly if: – 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 FEV_1 or PEF (historical or serial readings) ▪ Otherwise unexplained peripheral blood eosinophilia
Features that lower the probability of asthma
▪ 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* *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.

✓ 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.[76-79] 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 co-exist.

✓ 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.*

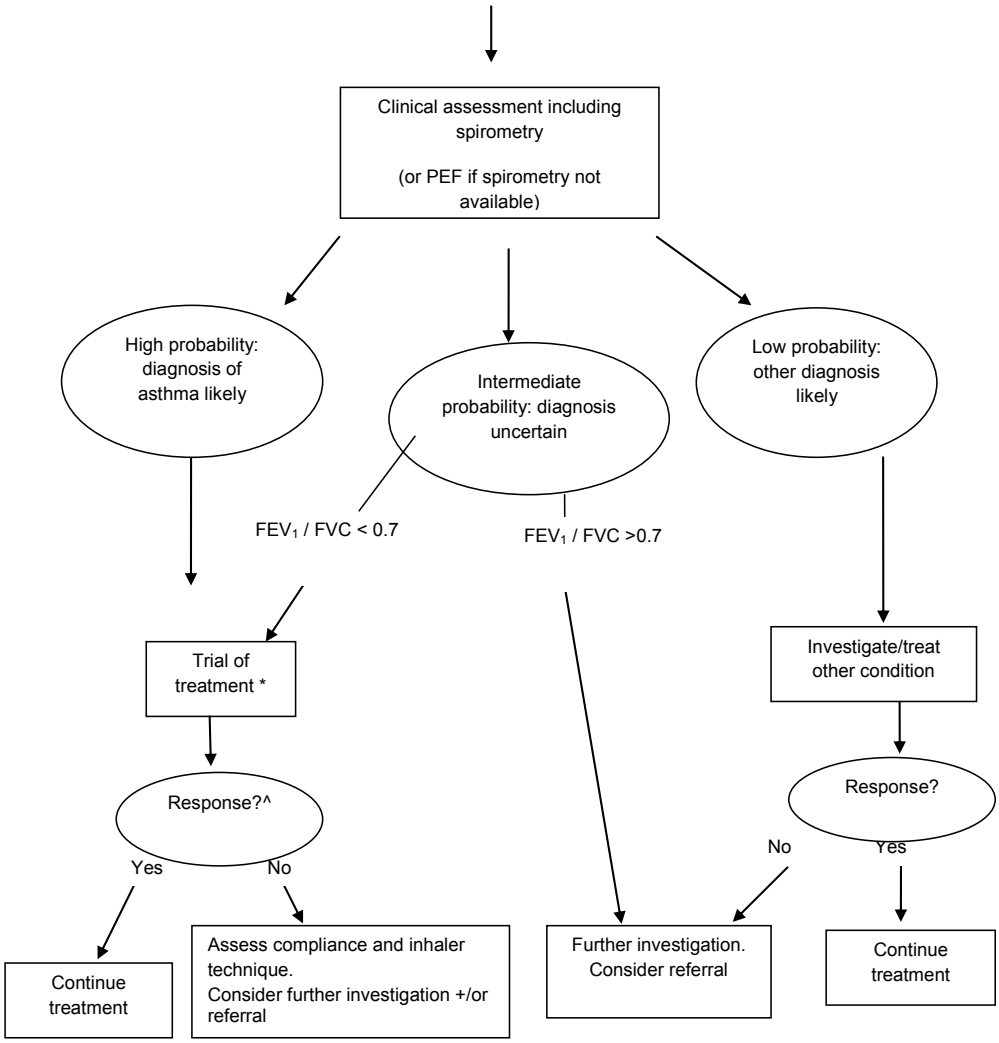
Patients without airways obstruction

In patients with a normal or near-normal spirogram it is more useful to look for evidence of airway hyperresponsiveness and/or airway inflammation.[74, 80-82] 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
▪ Chronic cough syndromes ▪ Hyperventilation syndrome ▪ Vocal cord dysfunction ▪ Rhinitis ▪ Gastro-oesophageal reflux ▪ Cardiac failure ▪ Pulmonary fibrosis
With airflow obstruction
▪ COPD ▪ Bronchiectasis* ▪ Inhaled foreign body* ▪ Obliterative bronchiolitis ▪ Large airway stenosis ▪ Lung cancer* ▪ Sarcoidosis* **may also be associated with non-obstructive spirometry*

✓ 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 are outlined in Box 1.

Box 1: Criteria for specialist referral in adults

- 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 x 109/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.[74, 80, 82] 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.[81, 83] 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.[81, 84-86] There is also evidence that markers of eosinophilic airway inflammation are of value in monitoring the response to corticosteroid treatment.[87-89] 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.[74, 80, 82]

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

PC_{20} = the provocative concentration of methacholine required to cause a 20% fall in FEV_1. FE_{NO} = exhaled nitric oxide concentration. PEF A%H = peak expiratory flow amplitude per cent 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%.[82] A variety of tools to assess asthma control are available to assess the response to a trial of treatment (*see Table 8*). 2+

Using FEV_1 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 beclomethasone (or equivalent) twice daily. In patients with significant airflow obstruction there may be a degree of inhaled corticosteroid resistance[90] and a treatment trial with oral prednisolone 30 mg daily for two weeks is preferred. 2+

A > 400ml improvement in FEV_1 to either β_2-agonists or corticosteroid treatment trials strongly suggests underlying asthma. Smaller improvements in FEV_1 are less discriminatory[74] 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 FEV_1 (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 beclomethasone 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.[91] The patient can be standing or sitting. Further blows should be done if the largest two PEF are not within 40 l/min.[91]

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 estimate[92] but the improved precision is likely to be achieved at the expense of reduced patient compliance.[93]

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.[94-96]

The upper limit of the normal range for the amplitude % highest is around 20% using four or more PEF readings per day[94, 96, 97] but may be lower using twice daily readings.[98] Epidemiological studies have shown sensitivities of between 19 and 33% for identifying physician-diagnosed asthma.[95, 99]

PEF variability can be increased in patients with conditions commonly confused with asthma[74, 76] 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 10.3.1).* A computer generated analysis of occupational records which provides an index of the work effect is available.[100]

✓ 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 FEV_1 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.[101] The response is usually quantified as the concentration (or dose) required to cause a 20% fall in FEV_1 (PC_{20} or PD_{20}) 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 PC_{20} of >8 mg/ml (equivalent to a PD_{20} of >4 micromoles).[95, 102, 103] This value has a sensitivity of between 60-100% in detecting physician-diagnosed asthma.[95, 99, 102, 103]

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*).[74, 80] In contrast, tests of airway responsiveness are of little value in patients with established airflow obstruction as the specificity is low.[76, 79]

Other potentially helpful constrictor challenges include indirect challenges such as inhaled mannitol and exercise.[104] A positive response to these indirect stimuli (ie a > 15% fall in FEV_1) 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.[104, 105]

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 (FE_{NO}).[106, 107] A raised sputum eosinophil count (>2%) or FE_{NO} (>25 ppb at 50 ml/sec) is seen in 70-80% of patients with untreated asthma.[77, 106] Neither finding is specific to asthma: 30-40% of patients with chronic cough[85, 108, 109] and a similar proportion of patients with COPD[84] 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.[84, 86, 108]

Experience with induced sputum and FE_{NO} 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

2.6.1 MONITORING ASTHMA IN CHILDREN

Biomarkers

Studies in children have shown that routine serial measurements of peak expiratory flow,[110-112] airway hyper-responsiveness[113] or exhaled nitric oxide (FE_{NO})[114-117] do not provide additional benefit when added to a symptom-based management strategy as normal lung function does not always indicate well controlled asthma. One clinical trial, however, reported that a 90-day average seasonal 5% reduction in peak flow was associated with a 22% increase in risk of exacerbation (p=0.01).[118] In a further study of children with asthma who were not taking inhaled corticosteroids, compared with children with an FEV_1 ≥100%, children with FEV_1 80% to 99%, 60% to 79%, and <60% were 1.3, 1.8, and 4.8, respectively, more likely to have a serious asthma exacerbation in the following four months.[119]

A small prospective observational study in 40 children suggested that serial measurements of FE_{NO} and/or sputum eosinophilia may guide step down of inhaled corticosteroids (ICS).[120] Another small study of 40 children showed that a rising FE_{NO} predicted relapse after cessation of ICS.[116] The number of children involved in these step-down and cessation studies is small and the results should be interpreted with some caution until replicated in larger datasets.

A better understanding of the natural variability of biomarkers independent of asthma is required and studies are needed to establish whether subgroups of patients can be

identified in which biomarker guided management is effective. Table 8 summarises the methodology, measurement characteristics and interpretation of some of the validated tools used to assess symptoms and other aspects of asthma.

Clinical issues

When assessing asthma control a general question, such as "how is your asthma today?", is likely to yield a non-specific answer; "I am ok". Using closed questions, such as "do you use your blue inhaler every day?", is likely to yield more useful information. As in any chronic disease of childhood, it is good practice to monitor growth at least annually in children diagnosed with asthma.

✓ When assessing asthma control use closed questions.

✓ Growth (height and weight centile) should be monitored at least annually in children with asthma.

✓ Practitioners should be aware that the best predictor of future exacerbations is current control.

2.6.2 MONITORING ASTHMA IN ADULTS

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.[121] Patients with poor lung function and with a history of exacerbations in the previous year may be at greater risk of future exacerbations for a given level of symptoms.

✓ Closer monitoring of individuals with poor lung function and with a history of exacerbations in the previous year should be considered.

A management strategy that controls eosinophilic airway inflammation[87-89] or airway hyperresponsiveness[122] can result in better control of exacerbations than one which controls immediate clinical manifestations; the benefits of inflammation guided management 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.

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 and potential corticosteroid responsiveness (ie sputum eosinophil count, airway responsiveness and FE_{NO}) rather than immediate clinical control. Risk reduction, eg minimising future adverse outcomes such as exacerbations is an important goal of asthma management. Some patients have an accelerated decline in lung function in terms of FEV_1; risk factors and treatment strategies for these patients are poorly defined. Further research in this area is an important priority.

✓ When assessing asthma control in adults use specific questions, such as "how many days a week do you use your blue inhaler?".

2.6.3 MONITORING CHILDREN IN PRIMARY CARE

Asthma is best monitored in primary care by routine clinical review on at least an annual basis *(see section 11.3).*

✓ The factors that should be monitored and recorded include:

- symptom score, eg Children's Asthma Control Test, Asthma Control Questionnaire

- exacerbations, oral corticosteroid use and time off school/nursery due to asthma since last assessment
- inhaler technique (*see section 5*)
- adherence (*see section 12.5*), which can be assessed by reviewing prescription refill frequency
- possession of and use of self management plan/personalised asthma action plan (*see section 12.3.2*)
- exposure to tobacco smoke
- growth (height and weight centile)

2.6.4 MONITORING ADULTS IN PRIMARY CARE

Asthma is best monitored in primary care by routine clinical review on at least an annual basis *(see section 11.3).*

✓ The factors that should be monitored and recorded include:

- symptomatic asthma control: best assessed using directive questions such as the RCP '3 questions',[123] 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. Patients with irreversible airflow obstruction may have an increased risk of exacerbations.
- exacerbations, oral corticosteroid use and time off work or school since last assessment
- inhaler technique (*see section 5*)
- adherence *(see section 12.5)*, 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 12.3.2)*.

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

Measurement	Methodology	Measurement characteristics	Comments
Spirometry [124, 125]	Widely available. Enables clear demonstration of airflow obstruction. FEV_1 largely independent of effort and highly repeatable. Less applicable in acute severe asthma. Only assesses one aspect of the disease state. Can be achieved in children as young as five years.	Normal ranges widely available and robust. In the short term (20 minutes) 95% range for repeat measures of FEV_1 <160 ml; FVC <330 ml, independent of baseline value.	Good for short and longer term reversibility testing in adults with pre-existing airflow obstruction. >400 ml increase in FEV_1 post-bronchodilator highly suggestive of asthma in adults. Values usually within normal range in adults and children with asthma.
Peak expiratory flow (PEF)[91, 94, 95, 110-112, 126]	Widely available and simple. Applicable in a wide variety of circumstances including acute severe asthma. PEF variability can be determined from home readings in most patients. PEF effort dependent and not as repeatable as FEV_1.	Normal ranges of PEF are wide, and currently available normative tables are outdated and do not encompass ethnic diversity. Change in PEF more meaningful than absolute value. >60 l/min increase in PEF suggested as best criteria for defining reversibility. Normal range of PEF variability defined as amplitude % highest varies between <8% or <20%. It is likely to depend on number of readings and degree of patient coaching.	Useful for short and longer term reversibility testing in adults with pre-existing airflow obstruction. PEF monitoring not proven to improve asthma control in addition to symptom score in adults and children. There may be some benefit in adult patients with more severe disease and in those with poor perception of bronchoconstriction.

Measurement	Methodology	Measurement characteristics	Comments
Royal College of Physicians (RCP) 3 Questions[127]	Yes/no or graded response to the following three questions: In the last week (or month) 1. Have you had difficulty sleeping because of your asthma symptoms (including cough)? 2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)? 3. Has your asthma interfered with your usual activities (eg housework, work/ school etc)?	No to all questions consistent with controlled asthma.	Not well validated in adults. Not validated in children. Simplicity is attractive for use in day to day clinical practice. Not validated in children.
Asthma Control Questionnaire (ACQ)[128-131]	Response to 7 questions, 5 relating to symptoms, 1 rescue treatment use and 1 FEV_1. Response usually assessed over the preceding week. Shortened, five question symptom only questionnaire is just as valid.	Well controlled ≤0.75, inadequately controlled ≥1.5. 95% range for repeat measure ± 0.36. Minimal important difference 0.5.	Well validated in adults and childrenolder than 5 years. A composite scoring system with a strong bias to symptoms. Could be used to assess response to longer term treatment trials. Shortened five-point questionnaire is probably best for those with normal or near normal FEV_1.

Measurement	Methodology	Measurement characteristics	Comments
Asthma Control Test (ACT)[132, 133]	Response to 5 questions, 3 related to symptoms, 1 medication use and 1 overall control. 5 point response score.	Reasonably well controlled 20-24; under control 25. Within subject intraclass correlation coefficient 0.77. 95% range for repeat measure and minimally clinically important difference not defined.	Validated in adults and children aged over 3 years Children Asthma Control Test for 4-11 year olds). Could be used to assess response to longer term treatment trials, particularly in those with normal or near normal spirometric values. 95% range for repeat measure and minimally clinically important difference need to be defined.
Mini Asthma Quality of Life Questionnaire (AQLQ)[129, 134, 135]	Response to 15 questions in 4 domains (symptoms, activity limitations, emotional function and environmental stimuli). Response usually assessed over the preceding 2 weeks. Closely related to larger 32-item asthma quality of life questionnaire. The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) has 23 questions each with seven possible responses.	95% range for repeat measure ± 0.36. Minimal important difference 0.5. Scores usually reported as the mean of responses across the four domains with values lying between 1 and 7; higher scores indicate better quality of life.	Well validated quality of life questionnaire. Could be used to assess response to longer term treatment trials. The AQLQ is validated in adults and the PAQLQ has been validated for the age range 7-17 years.

Measurement	Methodology	Measurement characteristics	Comments
Airway responsiveness[122]	Only available in selected secondary care facilities. Responsive to change (particularly indirect challenges such as inhaled mannitol). Less of a ceiling effect than FEV_1 and PEF. Not applicable in patients with impaired lung function (ie FEV_1/FVC <0.7 and FEV_1<70% predicted).	Normal methacholine PC_{20} >8 mg/ml. 95% range for repeat measure ±1.5-2 doubling doses.	Has not been widely used to monitor disease and assess treatment responses. Regular monitoring not proven to improve asthma control in children.
Exhaled nitric oxide (FE_{NO})[81, 88, 106, 116, 120, 136, 137]	Increasingly available in secondary care. Monitors still relatively expensive although expect the technology to become cheaper and more widespread. Measurements can be obtained in almost all adults and most children over 5 years. Results are available immediately. Reasonably close relationship between FE_{NO} and eosinophilic airway inflammation, which is independent of gender, age, atopy and inhaled corticosteroid use. Relationship is lost in smokers. Not closely related to other measures of asthma morbidity.	Normal range <25 ppb at exhaled flow of 50 ml/sec. 95% range for repeat measure 4 ppb. >50 ppb highly predictive of eosinophilic airway inflammation and a positive response to corticosteroid therapy. <25 ppb highly predictive of its absence of and a poor response to corticosteroids or successful step down in corticosteroid therapy.	Raised FE_{NO} (>50 ppb in adults and >25 ppb in children) predictive of a positive response to corticosteroids. The evidence that FE_{NO} can be used to guide corticosteroid treatment is mixed. Protocols for diagnosis and monitoring have not been well defined and more work is needed. Low FE_{NO} (<25 ppb in adults; <20 ppb inthe under 12 year old range) may have a role in identifying patients who can step down corticosteroid treatment safely.

Measurement	Methodology	Measurement characteristics	Comments
Eosinophil differential count in induced sputum[86, 87, 138, 139 120]	Only available in specialist centres although technology is widely available and inexpensive. Information available in 80-90% of patients although immediate results are not available. Sputum eosinophil count not closely related to other measures of asthma morbidity	Normal range <2%; 95% range for repeat measure ± 2-3 fold.	Close relationship between raised sputum eosinophil count and corticosteroid responsiveness in adults. Use of sputum eosinophil count to guide corticosteroid therapy has been shown to reduce exacerbations in adult patients with severe disease. In children, one study found benefit in using sputum eosinophils to guide reductions of inhaled steroid treatment in conjunction with FE_{NO}.

Research is needed to develop exacerbation risk stratification tables on the basis of these data. These might facilitate communication between patients and healthcare professionals resulting in better outcomes, as has been shown in coronary artery disease.

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 prevention- interventions introduced before the onset of disease and designed to reduce its incidence.
2. secondary prevention – interventions introduced after the onset of disease to reduce its impact.

3.1 PRIMARY PREVENTION

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 MONO AND MULTIFACETED ALLERGEN AVOIDANCE

Early life exposure to allergens (including aeroallergens and ingested food allergens) may lead to allergic sensitisation and so increase the risk of subsequent asthma, particularly in high-risk children (ie, children with a family history of asthma or atopy, particularly a parental history). There has been uncertainty as to whether the risk of developing asthma in children is reduced by interventions to reduce exposure to single allergens (mono-faceted), or whether multi-faceted interventions targeting the reduction of more than one type of allergen exposure simultaneously will lead to a better outcome or be more effective.

A Cochrane review assessing the research evidence from trials comparing single (six studies) or multiple interventions (three studies) with a no intervention control, reported that in children who are at risk of developing childhood asthma 'multifaceted' interventions, which involve both dietary allergen reduction and environmental change to reduce exposure to inhaled allergens, reduced the odds of a doctor diagnosing asthma later in childhood by half (>5 years of age, OR 0.52, 95% CI 0.32 to 0.85).[140] However, the effect of these multifaceted interventions on wheeze reported by parents was inconsistent and there was no beneficial effect on night-time coughing or breathlessness. These interventions can be costly, demanding and inconvenient to families, and the cost effectiveness is not established. Health professionals can discuss and support this intervention in families who are motivated to follow the demanding programme. However, more complicated multi-faceted interventions targeting multiple allergens can potentially reduce asthma at the age of 5 years by up to half; 1++

In children at risk of developing asthma, there is no evidence that reducing in-utero or early life exposure to single allergens (either to aeroallergens such as house dust mites or pets, or food allergens) is effective in reducing asthma and single ('monofaceted') interventions were not significantly more effective than controls in the reduction of any outcomes.,

A **Measures to reduce in-utero or early life exposure to single aeroallergens, such as house dust mites or pets, or single food allergens, are not recommended.**

A **Complex, multi-faceted interventions targeting multiple allergens may be considered in families able to meet the costs, demands and inconvenience of such a demanding programme.**

3.1.2 AEROALLERGEN AVOIDANCE

House dust mites

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.[141] Sensitisation to house dust mite is an important risk factor for the development of asthma[142, 143] and a few studies have suggested that high early house dust mite exposure increases the risks of subsequent asthma.[144, 145] 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.[146]

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;[147] others have shown no effect on either allergic sensitisation or symptoms of allergic diseases.[148] 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.[149] Subsequent results showed a paradoxical effect with increased allergy but better lung function in the intervention group.[150] 1+

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

A **Healthcare professional advice on house dust mite aeroallergen avoidance for the primary prevention of asthma is not justified.**

Pets in the home

A large number of birth cohort studies, longitudinal cohort studies and cross-sectional studies have addressed the issue of whether exposure to pets in the home in early life increases or reduces the subsequent risk of asthma and allergy, with contradictory results and messages. Four recent systematic reviews, accessing overlapping data sources, have attempted to synthesize the evidence, again with contradictory messages. Although one review [151] concluded that exposure to cats in early life has a slight preventative effect on subsequent asthma, while exposure to dogs increases risk, and another [152] concluded in contrast that perinatal dog exposure protects against asthma, with no affect from cats, methodological factors such as avoidance behaviour in at-risk families and other potential confounders may have affected the analyses. Two further reviews concluded that exposure to cats and/or dogs in early childhood did not impact on asthma or wheeze in school aged children.[153, 154] The most methodologically sound study used pooled individual participant data from 11 European birth cohort studies so was able to harmonise exposure, outcome and age group definitions and so use individual data rather than pooled risk estimates in heterogeneous groups, and to minimise potential confounding.[154] Several of the studies and reviews reported reduced allergic sensitisation in those with early exposure to pets, but the clinical significance of this is uncertain. 1++ 1+ 1-

A **Healthcare professional advice on whether to avoid or specifically acquire pets for primary prevention of asthma is not justified.**

3.1.3 FOOD ALLERGEN AVOIDANCE

Sensitisation to foods, particularly eggs, frequently precedes the development of aeroallergy and subsequent asthma.[155] Food allergen avoidance in pregnancy and postnatally has not been shown to prevent the later development of asthma.[156] Allergen avoidance during pregnancy may adversely affect maternal, and perhaps fetal, nutrition.[157] High dose food allergen exposure during pregnancy may reduce subsequent sensitisation rates by inducing tolerance. [158] 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.**

3.1.4 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 breastfed for at least four months.[159] 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.[160] 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.**

3.1.5 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.[161] A review of the use of soy formulae found no significant effect on asthma or any other allergic disease.[162] 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. 1+

3.1.6 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.[163] In one study late introduction of egg was associated with a non-significant increase in pre-school wheezing.[164]

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

3.1.7 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.[163] 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.[165] 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.[166] 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.

3.1.8 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),[167] or vitamin E based on maternal pregnancy intake.[168] 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.[163] Observational studies suggest that intervention trials are warranted.

3.1.9 WEIGHT REDUCTION IN OVERWEIGHT AND OBESE PATIENTS

There is consistent evidence that being overweight or obese increases the risk of a subsequent physician diagnosis of asthma by up to 50% in children [169] and adults [170] of both sexes. A high birth weight is also associated with a higher risk of asthma (RR 1.2, 95% CI 1.1 to 1.3). The quality of the evidence is low as confounders were not adjusted for. In addition, since obesity can have direct effects on respiratory symptoms and on lung mechanics, the mechanism of this relationship is unclear. 1- 2-

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

3.1.10 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.[171, 172]

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.[173] 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.[174]

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.

3.1.11 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.[175-178] Evidence suggests that early life ETS exposure is associated with later persistent asthma[179, 180] with a strong interaction with genetic polymorphisms which affect antioxidant activity.[181] 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 3

exposure and antioxidant gene variations.[182-184] 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.[185] Further research is required before recommendations for practice can be made. 4

3.1.12 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.[186] 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.[187]

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 PREVENTION

3.2.1 HOUSE DUST MITE AVOIDANCE

Allergic sensitisation to house dust mite-associated aeroallergens is common in people with asthma and exposure to house dust can act as a trigger in sensitised asthmatic individuals. Physical (for example mattress covers, vacuum-cleaning, heating, ventilation, freezing, washing, air-filtration and ionisers) and chemical (acaricides) measures to reduce house dust mite aeroallergen levels and so reduce exposure have been advocated but there has been uncertainly as to whether the currently available physical and chemical measures, alone or in conjunction, can reduce the exposure levels sufficiently to allow a clinically relevant effect to be apparent.

A Cochrane review including 55 trials and 3,121 patients assessed the evidence relating to different methods of reducing exposure to HDM including:

- chemical measures (acaricides) – 10 trials
- physical measures, for example: mattress covers (26 trials); vacuum-cleaning, heating, ventilation, freezing, washing, air-filtration and ionisers (37 trials)
- combinations of chemical and physical measures (8 trials).[188]

The review showed no evidence of a beneficial effect from any individual or combination of treatments on any outcome measure, physiological or patient reported, including peak flow in the morning, number of patients improved, asthma symptom scores or medication usage. The review concludes that further studies using similar interventions are unnecessary. 1++

A **Physical and chemical methods of reducing house dust mite levels in the home (including acaricides, mattress covers, vacuum-cleaning, heating, ventilation, freezing, washing, air-filtration and ionisers) are ineffective and should not be recommended by health care professionals.**

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[189, 190] or a potential for continued high exposure to induce a degree of tolerance.[191] 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.[192, 193]

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.[194]

Studies of individual aero allergen 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.[195] 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.[196] A systematic review of this topic concluded that more research is required.[197]

3.2.3 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.[198-201]

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.[202, 203] One study in adults with asthma suggested that smoking cessation improved asthma specific quality of life, symptoms and drug requirements.[204] Intervention to reduce smoking has had disappointing outcomes.[205, 206] It is likely that more intensive intervention will be required to achieve meaningful outcomes.[207] 2^+

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 smoke[208] (*see section 4.2.4 for effect of smoking on treatment*). 3

B **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.**

3.2.4 AIR POLLUTION

Challenge studies demonstrate that various pollutants can enhance the response of patients with asthma to allergen inhalation.[209, 210] 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.[211, 212] 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.[213] Much less attention has been focused on indoor pollutants in relation to asthma and more work is required.[214, 215]

3.2.5 ELECTROLYTES

Increasing dietary sodium has been implicated in the geographical variations in asthma mortality[216] and high sodium intake is associated with increased bronchial hyperresponsiveness.[217, 218] 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.[219] Low magnesium intakes have been associated with a higher prevalence of asthma with increasing intake resulting in reduced bronchial hyperresponsiveness and higher lung function.[220] 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.[221] Studies of oral supplementation are limited and more trials are required.[222-224]

3.2.6 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.[225, 226] 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.[227]

3.2.7 ANTIOXIDANTS

Observational studies have reported that low vitamin C, vitamin E and selenium intakes are associated with a higher prevalence of asthma.[163] Intervention studies suggest that neither supplementation with vitamin C, vitamin E or selenium is associated with clinical benefits in people with asthma.[228-230] 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.[231-237] No intervention studies evaluating the intake of fruit or vegetables and their effects on asthma have been reported.

3.2.8 WEIGHT REDUCTION IN OVERWEIGHT AND OBESE PATIENTS WITH ASTHMA

The current evidence base for weight reduction interventions to improve asthma control is inadequate in quantity and quality. A Cochrane review concluded that as the benefit of weight loss as an intervention for asthma control is uncertain, "...clinicians should be prepared to help patients to make a decision that is consistent with their own values...". [238] 1+

C **Weight loss in overweight patients has many health benefits, and should be supported in people with asthma; if successful, it may lead to improvements in asthma control.**

3.2.9 PROBIOTICS

Studies have suggested that an imbalance in gut flora is associated with a higher risk of development of allergy.[239] Trials have investigated the use of probiotics in the treatment of established allergic disease with variable results.[240, 241] Only one study focused on asthma, finding a decrease in eosinophilia but no effect on clinical parameters.[242] 1+ 2+

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

3.2.10 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.[243-246]

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,[247] but results of trials have been disappointing.[248, 249] 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.[250] Studies in children have suggested that immunisation with the vaccine does not exacerbate asthma[251] but has a small beneficial effect on quality of life in children with asthma.[252] The immune response to the immunisation may be adversely affected by high-dose inhaled corticosteroid therapy and this requires further investigation.[253] A Cochrane review of pneumococcal vaccine found very limited evidence to support its use specifically in individuals with asthma.[254] 1++

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

3.2.11 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.[255] 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.[256] Two other trials of acupuncture in relation to induced asthma were also negative.[257, 258] 1+

3.2.12 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.[259] 1++
One study demonstrated an increase in night-time cough to a level which approached statistical significance.[260] 1+

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

3.2.13 BREATHING EXERCISES INCLUDING YOGA AND THE BUTEYKO BREATHING TECHNIQUE

Behavioural programmes centred on breathing exercises and hyperventilation reduction techniques (including physiotherapist-delivered breathing programmes such as the 'Papworth method' and Butekyo method) can improve asthma symptoms, quality of life and reduce bronchodilator requirement in adults with asthma, although have little effect on lung function.[261] These techniques involve instruction by a trained therapist in exercises to reduce respiratory rate, minute volume and to promote nasal, diaphragmatic breathing. Trials that include more than five hours of intervention appeared more likely to be effective. They can help patient's experience of their condition and quality of life although do not affect lung function or airways inflammation. They should ideally be provided as part of integrated medical care. 1++

There is currently insufficient evidence relating to other breathing exercise methods, such as yoga breathing techniques and inspiratory muscle training, on which to base a recommendation.

A **Breathing exercise programmes (including the physiotherapist-taught 'Papworth method') can be offered to people with asthma as an adjuvant to pharmacological treatment.**

3.2.14 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.[262] A more recent double blind placebo controlled trial of a Chinese herb decoction (Ding Chuan Tang) showed improvement in airway hyperresponsiveness in children with stable asthma.[263] It is difficult 1+

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.[264]

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.

3.2.15 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.[265] 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.[266] 1++ 1+

3.2.16 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.[267] 1++

3.2.17 MANUAL THERAPY INCLUDING MASSAGE AND SPINAL MANIPULATION

A Cochrane review identified four relevant RCTs.[268] 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.

3.2.18 PHYSICAL EXERCISE TRAINING

A Cochrane review has shown no effect of physical training on PEF, FEV_1, FVC or VEmax.[269] 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).*

3.2.19 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.[270] 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. Complete 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)
- minimal side effects from medication.

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

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.

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 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 adherence with existing therapies (*see section 12.5*), inhaler technique (*see section 5*) and eliminate trigger factors (*see section 3*).

Until May 2009 all doses of inhaled steroids in this section were referenced against beclometasone (BDP) given via CFC-MDIs (metered dose inhaler). As BDP CFC is now unavailable, the reference inhaled steroid will be the BDP-HFA product, which is available at the same dosage as BDP-CFC. Note that some BDP-HFA (hydrofluroalkane) products are more potent and all should be prescribed by brand (*see Table 8b*). Adjustments to doses will have to be made for other inhaler devices and other corticosteroid molecules (*see section 4.2*).

In this and the following section, each recommendation has been graded and the supporting evidence assessed for adults and adolescents >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 and adolescents aged over 12

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:

	>12 years	5-12 years	<5 years
▪ inhaled short-acting β2 agonists[3]	1++	1+	4
▪ inhaled ipratropium bromide[271]	1+	1++	
▪ β2 agonist tablets or syrup[3]	1++		
▪ theophyllines.[3]	1++		

Short-acting inhaled β_2 agonists work more quickly and/or with fewer side effects than the alternatives.[3]

A B D **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.[272, 273]

>12 years	5-12 years	<5 years
1++	1++	11++

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 patients at risk of fatal or near-fatal asthma.

✓ 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 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. 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.[274] 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 appears to provide equal clinical activity to BDP and budesonide at half the dosage.[275] The relative safety of mometasone is not fully established.

Table 8b: Equivalent doses of inhaled steroids relative to BDP and current licensed age indications

These dosage equivalents are approximate and will depend on other factors such as inhaler technique.

		UK licence covers		
Steroid	**Equivalent dose**	**>12 years**	**5 – 12 years**	**<5 years**
Beclometasone dipropionate CFC	400 micrograms	**No longer available**		
Beclometasone				
Clenil modulite	400 micrograms	✓	✓	✓
Clickhaler		✓	Over age 6	✗
Aerobec Autohaler		✓	✗	✗
Asmabec Clickhaler		✓	Over age 6	✗
Dry powder (Becodisks)		✓	✓	✓
Easyhaler		✓	✗	✗
Pulvinal		✓	Over age 6	✗
Filair		✓	✓	✓
Qvar*	200 to 300 micrograms	✓	✗	✗
Fostair	200 micrograms	Over age 18	✗	✗
Budesonide				
Turbohaler	400 micrograms	✓	✓	✗
Metered dose inhaler		✓	✓	Over age 2
Easyhaler		✓	Over age 6	✗
Novolizer		✓	Over age 6	✗
Symbicort		✓	Over age 6	✗
Symbicort (regular and as required dosing)		Over age 18	✗	✗
Fluticasone				
Metered dose inhaler (HFA)	200 micrograms	✓	✓	Over age 4
Accuhaler		✓	✓	Over age 4
Seretide HFA		✓	✓	Over age 4
Seretide (Accuhaler)		✓	✓	Over age 4
Mometasone	200 micrograms	✓	✗	✗
Ciclesonide	200 to 300 micrograms	✓	✗	✗

* When changing over to Qvar from BDP-CFC, if (a) control is good on BDP-CFC change to half the dose of Qvar; (b) control is not good on BDP-CFC change to Qvar at the same daily dose.

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.[276-280] 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).*

4.2.2 INHALED STEROIDS

>12 years	5-12 years	<5 years
1^{++}	1^{++}	1^{++}

Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals.[281-285] There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma. [286-296]

Many non-atopic children with recurrent episodes of viral-induced wheezing in children under five 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.**

>12 years	5-12 years	<5 Years
1^{+}	1^{+}	1^{+}

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.[297-301]

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 B B **using inhaled β2 agonists three times a week or more**

B B B **symptomatic three times a week or more**

B C ✓ **waking one night a week.**

>12 years	5-12 years	<5 years
1^{+}	1^{+}	

Starting dose of inhaled steroids

In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit.[302]

✓ Start patients at a dose of inhaled steroids appropriate to the severity of disease.

✓ In adults, a reasonable starting dose will usually be 400 micrograms BDP per day and in children 200 micrograms BDP 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.

>12 years	5-12 years	<5 years
1^{+}	1^{+}	1^{+}

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 and good or complete control of their asthma.[3, 282, 299, 303, 304]

There is little evidence of benefit for dosage frequency more than twice daily.[282]

A A A **Give inhaled steroids initially twice daily, except ciclesonide**

which is given once daily.

A A A **Once a day inhaled steroids at the same total daily dose can be considered if good control is established.**

4.2.3 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 adherence, to such a policy remain to be established.

Adults

There is little evidence that doses below 800 micrograms BDP 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 micrograms BDP per day.[305] 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 micrograms BDP a day or equivalent may be associated with systemic side effects.[306] 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.[303, 307]

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 micrograms BDP per day 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.[62, 308] 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.

While the use of inhaled corticosteroids may be associated with adverse effects (including the potential to reduced bone mineral density) with careful inhaled steroid dose adjustment this risk is likely to be outweighed by their ability to reduce the need for multiple bursts of oral corticosteroids.[309]

✓ Monitor growth (height and weight centile) of children with asthma on an annual basis.

✓ The lowest dose of inhaled steroids compatible with maintaining disease control should be used.

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

✓ Specific written advice about steroid replacement (eg Steroid Alert Card) in the event of a severe intercurrent illness or surgery should be part of the management plan.

✓ The child should be under the care of a specialist paediatrician for the duration of the treatment.

Adrenal insufficiency is a possibility 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. Intramuscular (IM) hydrocortisone may also be required.

4.2.4 SMOKING

	>12 years	5-12 years	<5 years
Current and previous smoking reduces the effect of inhaled steroids; which may be overcome with increased doses.[198, 310]	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

	>12 years	5-12 years	<5 years
Inhaled steroids are the first choice preventer drug. Long-acting inhaled β_2 agonists should not be used without inhaled corticosteroids.[311] Alternative, less effective preventer therapies in patients taking short-acting β_2 agonists alone are:			
▪ Leukotriene receptor antagonists have some beneficial clinical effect[282, 312, 313]	1^{++}	1^{++}	1^{++}
- In children under five years who are unable to take inhaled corticosteroids, leukotriene receptor antagonists may be used as an alternative preventer.			
▪ Chromones			
- Sodium cromoglicate is of some benefit in adults[3, 314] and is effective in children aged 5-12[315]	1^{+}	1^{+}	
- Nedocromil sodium is also of benefit in adults and children >5[3, 316]	1^{++}	1^{+}	
- There is no clear evidence of benefit with sodium cromoglicate in children aged <5[317]			
▪ Theophyllines have some beneficial effect[3, 281]	1^{++}	1^{++}	1^{++}
▪ Antihistamines and ketotifen are ineffective.[318]	1^{++}	1^{++}	1^{++}

✓ In children under five years who are unable to take inhaled corticosteroids, leukotriene receptor antagonists are an effective first line preventer.

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 recheckadherence, 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

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 200-1,000 micrograms BDP in adults and up to 400 micrograms BDP in children.[319-322] Many patients will benefit more from add-on therapy than from increasing inhaled steroids above doses as low as 200 micrograms BDP/day. At doses of inhaled steroid above 800 micrograms BDP/day side effects become more frequent. An absolute threshold for introduction of add-on therapy in all patients cannot be defined.

>12 years	5-12 years	<5 years
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 micrograms BDP/day and in children taking inhaled steroids at a dose of 400 micrograms/day the following interventions are of value:

- **Inhaled long-acting β_2 agonist (LABA)** is the first choice for add-on therapy;) it improves lung function and symptoms, and decreases exacerbations.[319, 323-328]

>12 years	5-12 years	<5 years
1^{++}	1^{++}	

- **Leukotriene receptor antagonists** may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms.[313, 329-331]

>12 years	5-12 years	<5 Years
1^{++}	1^{++}	1^{+}

- **Theophyllines** may improve lung function and symptoms, but side effects occur more commonly.[320]

>12 years	5-12 years	<5 Years
1^{+}	1^{-}	

- **Slow-release β_2 agonist tablets** may also improve lung function and symptoms, but side effects occur more commonly.[319]

>12 years	5-12 years	<5 Years
1^{++}		

- **Long-acting muscarinic antagonists** appear to be as effective as salmeterol in the short term and may be superior to doubling the dose of ICS. Longer term studies are required to confirm this evidence. There would also appear to be benefit in adding tiotropium to ICS and salmeterol in patients who remain symptomatic despite these medications.

Comment [b1]: REFS?

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 micrograms BDP or equivalent per day and certainly before going above 800 micrograms BDP.**

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 micrograms BDP/day (adults) or 400 micrograms BDP/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 micrograms/day (adults) or 400 micrograms/day (children 5-12 years).[332]

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

B **The first choice as add-on therapy to inhaled steroids in children under five years old is leukotriene receptor antagonists.**

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 micrograms/day in adults or 400 micrograms/day in children** (5-12 years)**, if not already on these doses.**

✓ 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.[321, 333] Addition of nedocromil is of marginal benefit.[314, 322]

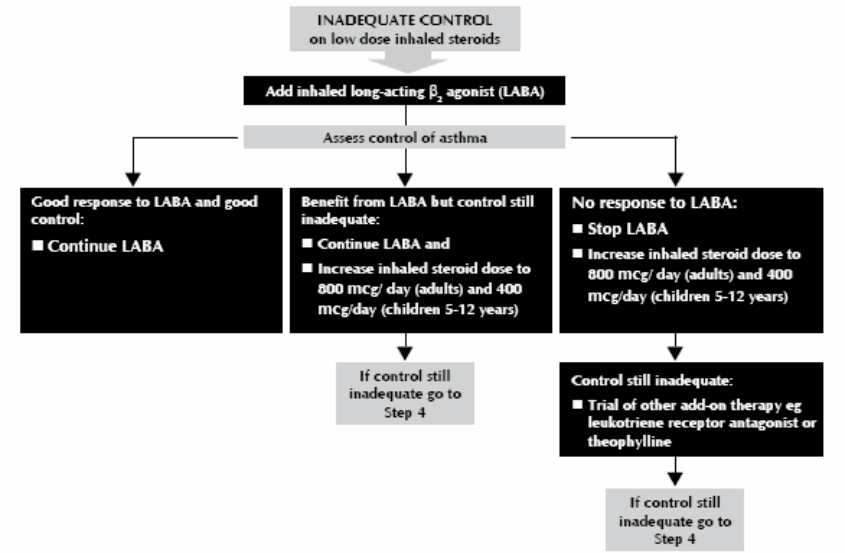
>12 years	5-12 years	<5 years
1^{+}		

4.3.3 SAFETY OF LONG-ACTING β_2 AGONISTS

Following a review in 2007 of long-acting β_2-agonists (LABA) in the treatment of adults, adolescents, and children with asthma, the Medicines and Healthcare products Regulatory Agency (MHRA) further reviewed the use of LABA, specifically in children younger than age 12 years and concluded that the benefits of these medicines used in conjunction with inhaled corticosteroids (ICS) in the control of asthma symptoms outweigh any apparent risks.[6]

✓ Long-acting inhaled β_2 agonists should only be started in patients who are already on inhaled corticosteroids, and the inhaled corticosteroid should be continued.

Figure 3: Summary of step 3 in adults and children>5 years: Add-on therapy



4.3.4 COMBINATION INHALERS

	>12 years	5-12 years	<5 years
In efficacy studies, where there is generally good compliance, there is no difference in efficacy in giving inhaled steroid and a long-acting β_2 agonist in combination or in separate inhalers.[332]	1++	1++	

In clinical practice, however it is generally considered that combination inhalers aid compliance and also have the advantage of guaranteeing that the long-acting β_2 agonist is not taken without the inhaled steroids.

✓ Combination inhalers are recommended to:

- guarantee that the long-acting β2 agonist is not taken without inhaled steroid
- improve inhaler adherence.

Use of a single combination inhaler (SMART)

In selected adult patients at step 3 who are poorly controlled or in selected adult patients at step 2 (above BDP 400 micrograms/day and 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 controller therapy has been shown to be an effective treatment regime.[334-338] When this management option is introduced the total

regular dose of daily inhaled corticosteroids should not be decreased. The regular maintenance dose of inhaled steroids may be budesonide 200 micrograms twice daily or budesonide 400 micrograms twice daily. Patients taking rescue budesonide/formoterol once a day or more on a regular basis should have their treatment reviewed. Careful education of patients about the specific issues around this management strategy 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 micrograms BDP 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 *(see section 4.3.2)*.

D D

If control remains inadequate on 800 micrograms BDP daily (adults) **and 400 micrograms daily** (children) **of an inhaled steroid plus a long-acting β_2 agonist, consider the following interventions:**

- **increasing inhaled steroids to 2000 micrograms BDP/day** (adults) **or 800 micrograms BDP/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, refer patients with inadequately controlled asthma, especially children, to specialist care.

✓ Although there are no controlled trials, children (all ages) who are under specialist care may benefit from a trial of higher doses ICS (greater than 800 micrograms/day) before moving to step 5.

4.5 STEP 5: CONTINUOUS OR FREQUENT USE OF ORAL STEROIDS

The aim of treatment is to control asthma using the lowest possible doses of medication.

Some patients with very severe asthma not controlled at step 4 with high dose inhaled corticosteroids, and who have also been tried on or are still taking Long-acting β-agonists, leukotriene antagonists or theophyllines, require regular long term steroid tablets.

✓ 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.[62]

- blood pressure should be monitored
- urine or blood sugar and cholesterol should be checked. Diabetes mellitus and hyperlipidaemia may occur
- bone mineral density should be monitored in adults. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered (see British Osteoporosis Society guidelines, www.nos.org.uk)[339]
- bone mineral density should be monitored in children >5 (see Statement from the American Academy of Pediatrics)[340]
- growth (height and weight centile)should be monitored in children
- cataracts may be screened for in children through community optometric services.

4.5.2 STEROID FORMULATIONS

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

4.5.3 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. No evidence was identified to guide timing of dose or dose splitting.

4.5.4 OTHER MEDICATIONS AND POTENTIAL STEROID TABLET-SPARING TREATMENTS

Anti IgE monoclonal antibody

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE, markedly reducing levels of free serum IgE.[341, 342] In adults and children over 6 years of age, 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 <1300 IU/ml for children over 6 years of age.[343] In adults and children >12 years, the licensed indication is a IgE up to 1500 IU/ml but there is no published data to support its efficacy and safety above 700 IU/ml.

	>12 years	5-12 years	<5 years
In a study in adults and children >12 years, 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 significant 2.8% increase in FEV_1 (p=0.043), a non-significant 0.5 puffs/day decrease in β_2 agonist use and 13% more patients having clinically meaningful improvement in health related quality of life compared with those taking placebo (60.8% vs 47.8%, p=0.008).. At IgE levels below 76 IU/ml the beneficial effect is reduced.[344]	1^-	1^-	1^-
Omalizumab as add-on therapy to inhaled corticosteroids has been studied in children 6-12 years of age with moderate to severe asthma and has been shown to significantly reduce clinically significant exacerbations over a period of 52 weeks. The majority of children were taking long acting β_2 agonists and many a leukotriene antagonist.[343]	>12 years	5-12 years 1^{++}	<5 years

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 in accordance with national recommendations.

Other agents

	>12 years	5-12 years	<5 years
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.[345]	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.

	>12 years	5-12 years	<5 years
Colchicine and intravenous immunoglobulin have not been shown to have any beneficial effect in adults.[345]	1+		
Continuous subcutaneous terbutaline infusion has been reported to be beneficial in severe asthma but efficacy and safety have not been assessed in RCTs.[346-348]	4	3	3
Anti-TNF alpha therapy has been investigated in severe asthma 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.[349, 350]			

Patients on oral steroids not previously tried on inhaled therapy

For patients who are on long term steroid tablets and have not been tried on adequate doses of inhaled medication an aim is to control the asthma using the lowest possible dose of oral steroid or, if possible, to stop long term steroid tablets completely.

	>12 years	5-12 years	<5 years
Inhaled steroids are the most effective drug for decreasing requirement for long term steroid tablets.[283, 284]	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.[351]			

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 micrograms/day, if required.

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

4.5.5 IMMUNOTHERAPY FOR ASTHMA

Studies using both subcutaneous and sublingual allergen immunotherapy (SCIT and SLIT) have overall shown some benefit in reducing asthma symptoms and BHR in children and adults currently on a range of other preventative strategies including ICS. There are few comparative studies comparing IT with ICS or of adding IT to ICS so there is difficulty precisely defining where IM should sit in a step-wise asthma guideline.

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.[352]	>12 years 1++	5-12 years	<5 years
The effect of immunotherapy is difficult to quantify due to the use of different symptom scores and variation in the way outcomes are reported. Reductions in asthma medication use and a small symptomatic benefit have been reported but there are significant side effects including 1 in 16 patients reporting a local adverse reaction and 11% reporting a systemic adverse reaction defined as anaphylaxis, asthma, rhinitis, urticaria or a combination of these.[353] Immunotherapy is not licensed for the treatment of asthma; the current license is for grass pollen induced allergic rhinitis.	>12 years 1++	5-12 years	<5 years
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.[354] Further comparative studies are required.	>12 years 2+	5-12 years	<5 years
Immunotherapy for allergic rhinitis has been shown to have a carry over effect after therapy has stopped.[355]	>12 years 3	5-12 years	<5 years

B B **The use of subcutaneous immunotherapy is not recommended in adults or children.**

Sublingual immunotherapy

There has been increasing interest in the use of sublingual immunotherapy, which is associated with far fewer adverse reactions than subcutaneous immunotherapy. The results of a systematic review are inconclusive as although the study suggested there were some benefits for asthma control but that the magnitude of the effect was small, this is based on mixed results for allergic symptoms overall (including asthma, rhinitis and conjunctivitis).[356] The review showed no significant effect on asthma symptoms or asthma medication use but did show a significant increase in side effects.	>12 years 1++	5-12 years	<5 years
In patients with rhinitis and asthma, sublingual immunotherapy seems well tolerated. The current evidence indicates that immunotherapy should not be used in patients with poorly controlled or severe asthma.			
A systematic review of 5 earlier meta-analyses, including 43 studies, 17 of which were included than more than one meta-analysis, highlighted a number of problems relating to earlier meta-analyses, including possible misinterpretation of study findings and publication bias.[357]			
A meta-analysis of SLIT for house dust mites, reported a significant reduction in symptoms and medication required in children, although differences in reporting of symptoms scores mean it is not possible to determine the magnitude of the effect.[358] The analysis included only one study on adults which showed no effect on symptoms or medication use.	>12 years 1++	5-12 years	<5 years
NB Sublingual immunotherapy is not licensed for use in the treatment of asthma.			

? ? ? **Sublingual immunotherapy cannot currently be recommended for the treatment of asthma in routine practice in children or adults.**

4.5.6 BRONCHIAL THERMOPLASTY

In selected adult patients with moderate to severe asthma (aged 18-65 years), steps 4 and 5, who have poorly controlled asthma despite maximal therapy, bronchial thermoplasty treatment has been shown to reduce the frequency of severe exacerbations, emergency	>12 years 1++	5-12 years	<5 years

department visits and days lost from school or work in the year after treatment.[359] Emergency department visits, but not severe exacerbations, are reduced in the period from first treatment to one year post-treatment.[359] The reduction in the frequency of exacerbations and emergency department visits may persist for up to 5 years after treatment.[360]	2-		
Bronchial thermoplasty results in a modest improvement in asthma quality of life in the year after treatment.[361]	1++		
Bronchial thermoplasty produces no consistent improvement in asthma symptoms or FEV1, [359, 362, 363] and at best a very small increase in PEF.	1++ 1+		
Bronchial thermoplasty results in increases in asthma-related symptoms and hospital admissions during the treatment period.[361] Despite this, there is no overall increase in hospital admissions with bronchial thermoplasty at one year.[361]]	1++		
There is some evidence for the long-term safety of the procedure from one up to 5 years post treatment in relation to adverse events reporting, stable lung function and lack of increase in hospital admissions and emergency room visits.[360, 364]	1+ 2-		

A [redacted] **Bronchial thermoplasty is a modestly effective treatment option for selected patients with moderate to severe asthma who have poorly controlled asthma despite maximal therapy.**

✓ Assessment and treatment for bronchial thermoplasty should be undertaken in centres that have expertise in the assessment of difficult to control asthma and in fibreoptic bronchoscopic procedures.

✓ The balance of risks and benefits of bronchial thermoplasty treatment should be discussed with patients being considered for the procedure.

✓ Longer term follow-up of treated patients is recommended. In the UK all patients undergoing bronchial thermoplasty should have demographic and procedure details recorded in the British Thoracic Society Difficult Asthma Registry.

✓ Further research is recommended into factors that identify patients who will nor will not benefit from bronchial thermoplasty treatment.

Figure 4: Summary of stepwise management in adults

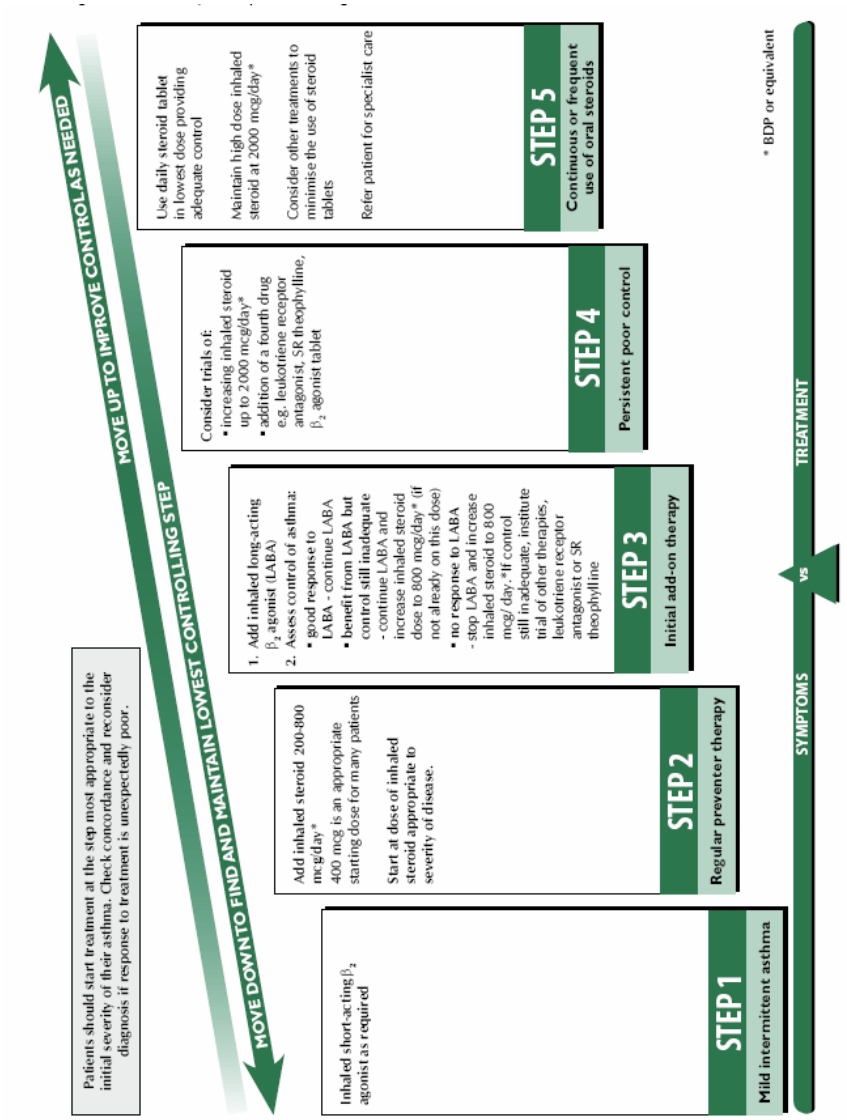


Figure 5: Summary of stepwise management in children aged 5-12 years

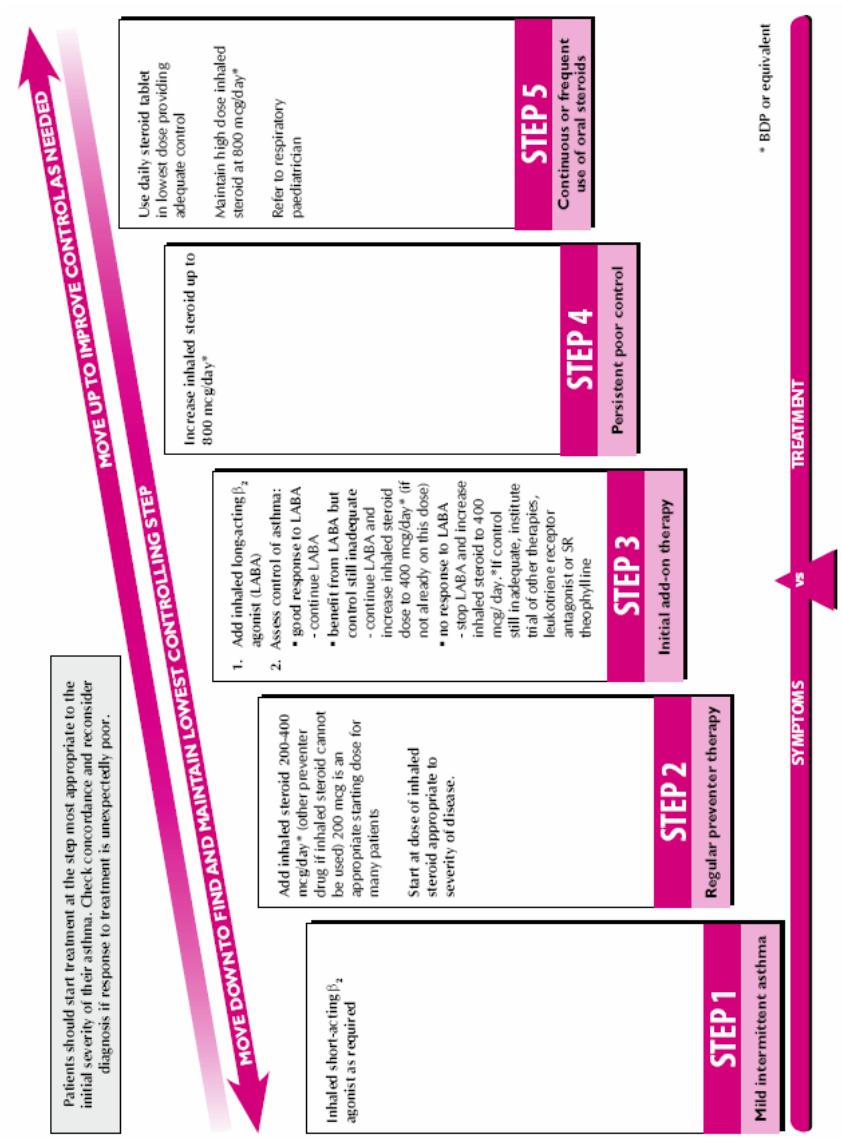
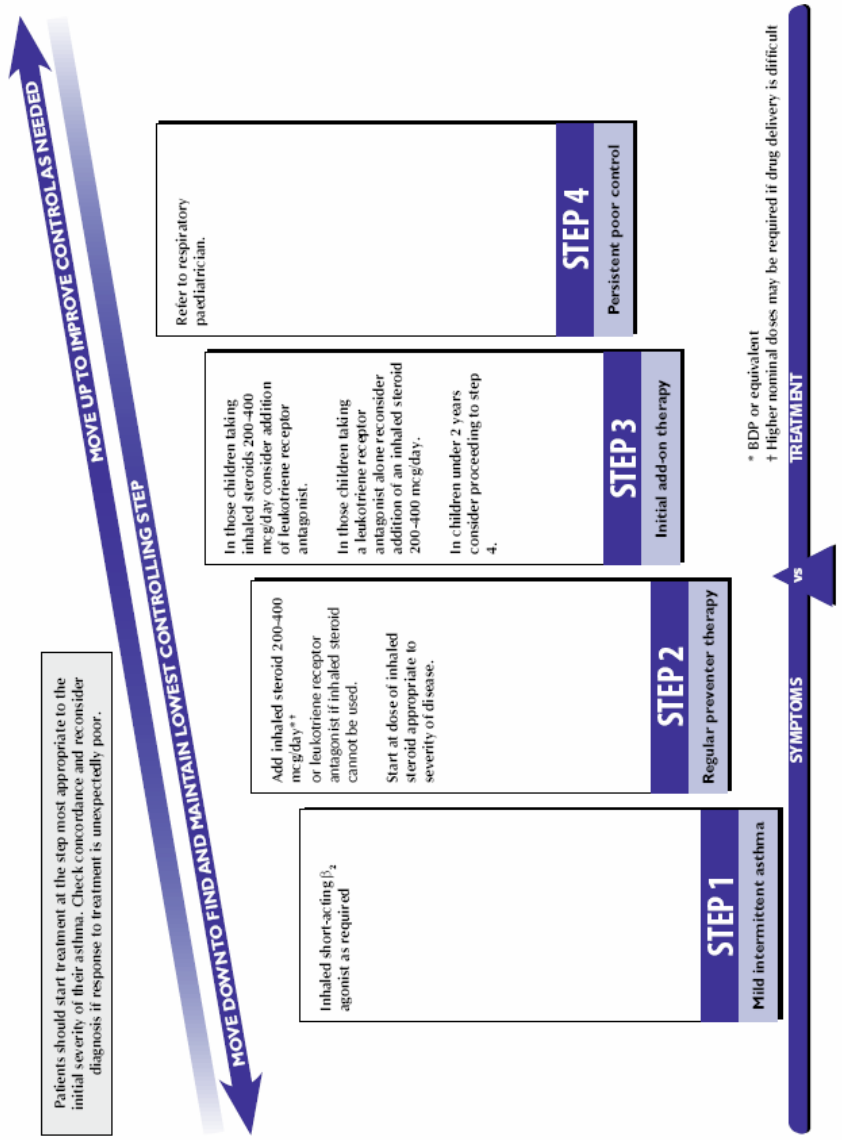


Figure 6: Summary of stepwise management in children less than 5years



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 micrograms 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.[350]

Some children with milder asthma and a clear seasonal pattern to their symptoms may have a more rapid dose reduction during their 'good' season.

✓ 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 of inhaled steroid at the time of an exacerbation is of unproven value.[365] In adult patients on a low dose (200 micrograms BDP) of inhaled steroids, a fivefold increase in dose at the time of exacerbation leads to a decrease in the severity of exacerbations.[365] This study cannot be extrapolated to patients already taking higher doses of inhaled steroids and further evidence in this area is required.

	>12 Years	5-12 years	<5 years
A Cochrane review including five trials (3 in adults >15 years; one including adolescents >13 years; and one including children 6-14 years) and 1,222 adults and 28 children, showed that doubling the dose of ICS, from 1000 to 2000 mcg/day, at the onset of an exacerbation did not reduce the risk of exacerbations requiring rescue oral corticosteroids.[366]	1++		I
There is some limited evidence that leukotriene antagonists may be used intermittently in children with episodic asthma. Treatment is started at the onset of either asthma symptoms or of coryzal symptoms and continued for seven days.[367]	>12 years	5-12 years 1^{++}	<5 years 1^{++}

4.7.2 EXERCISE INDUCED ASTHMA

The following medicines have been shown to give protection against exercise induced asthma:	>12 years	5-12 years	<5 years
▪ inhaled steroids[283, 284, 368]	1^{++}	1^{++}	
▪ short-acting β2 agonists [3, 369]	1^{++}	1^{++}	
▪ long-acting β_2 agonists[370]	1^{++}	1^{++}	
▪ theophyllines[351, 371]	1^{-}	2^{+}	
▪ leukotriene receptor antagonists[372]	1^{++}	2^{+}	
▪ chromones[373]	1^{++}	2^{+}	
▪ β_2 agonist tablets.[374]	1^{++}	1^{+}	

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

normal doses:

	>12 years	5-12 years	<5 years
▪ anticholinergics[375]	1^{+}	1^{+}	
▪ ketotifen[376]	1^{+}	1^{+}	
▪ antihistamine.[377]	1^{++}	1^{++}	

	>12 years	5-12 years	<5 years
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.[370, 372, 378]	1^{++}	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 adding one of 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.**

	>12 years	5-12 years	<5 years
Immediately prior to exercise, inhaled short-acting β_2 agonists are the drug of choice.[3, 369]	1^{++}	1^{++}	

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

4.7.3 CO-MORBID RHINITIS

	>12 years	5-12 years	<5 years
Patients with asthma often have rhinitis. The most effective therapy for rhinitis is intranasal steroids.[379, 380] Treatment of allergic rhinitis with intranasal steroids has not been shown in double blind placebo-controlled trials to improve asthma control.	1^{+}	1^{+}	

4.7.4 ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

	>12 years	5-12 years	<5 years
In adult patients with allergic bronchopulmonary aspergillosis (ABPA), itraconazole may decrease steroid tablet dose and improve asthma control.[381, 382]	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.[383]

4.7.6 CO-MORBID GASTRO-OESOPHOGEAL REFLUX

A Cochrane review of twelve double blind controlled trials found that treatment of gastro-oesophageal reflux (GORD) 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.[384, 385]

A systematic review identified a single RCT which found that proton pump inhibitors did not improve asthma symptoms in children with GORD.[386]

A further systematic review, including 11 trials and 2,524 patients who had received at least four weeks of daily therapy with proton pump inhibitors (PPIs) found a small but statistically significant improvement in morning PEFR (8.86L/min, 95% CI 2.35 to 15.02) differences between study participants and controls, but no differences in asthma symptom score, Asthma Quality of Life Questionnaire score, evening PEF, FEV_1 and adverse events. The review concluded that there was insufficient evidence to support the routine use of PPIs in the treatment of asthma.[387] 1++

4.7.7 β-BLOCKERS

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

	>12 years	5-12 years	<5 years
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.[388]	1^{++}		
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).[388]			

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

5.2 B_2 AGONIST DELIVERY

5.2.1 ACUTE ASTHMA

	>12 years	5-12 years	<5 years
pMDI + spacer is at least as good as a nebuliser at treating mild and moderate exacerbations of asthma in children and adults.[389-392]	1^{++}	1^{++}	

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.

	>12 years	5-12 years	<5 years
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.[388, 393, 394]	1^{++}	1^{++}	

	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.

	>12 years	5-12 years	<5 years
For the delivery of inhaled steroids in stable asthma in children aged 5-12 years, pMDI is as effective as Clickhaler,[395, 396] and Pulvinal is as effective as Diskhaler.[397] No significant clinical difference was found between pMDI and Turbohaler at half the dose for the same drug (budesonide).[388, 398] 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.[315] 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.[388, 398]	1^{++}	1^{++}	

[redacted] A [redacted] **In children aged 5-12 years, pMDI + spacer is as effective as any DPI.**

A [redacted] [redacted] **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 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 health care 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 11.3)*.

✓ 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.

No prospective controlled trials were found that compared mixed types of inhaler to a single type for preventer and controller inhalers in adults and children with asthma. Two cross-sectional studies found an association between increased errors in the use of inhalers when different types of inhaler were used.[399, 400] 4

✓ Prescribing mixed inhaler types may cause confusion and lead to increased errors in use. Using the same type of device to deliver preventer and controller medications may thus improve outcomes.

5.5 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.[401-405] There is an ongoing UK-wide National Review of Asthma Deaths (NRAD) which is due to report in 2014.

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.[401-406] 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.[401-405, 407, 408] 2^{++}

Deaths continue to be reported following inappropriate prescription of β-blockers and NSAIDs; all asthma patients should be asked about past reactions to these agents *(see section 4.7.7).*

Patients with acute asthma should not be sedated unless this is to allow anaesthetic or intensive care procedures (*see section 6.3.11*).[406]

6.1.3 ADVERSE PSYCHOSOCIAL AND BEHAVIOURAL FACTORS

Behavioural and adverse psychosocial factors were recorded in the majority of patients who died of asthma.[401-405] The most important are shown in table 8.

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

A COMBINATION OF SEVERE ASTHMA recognised by one or more of:
▪ 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"
AND ADVERSE BEHAVIOURAL OR PSYCHOSOCIAL FEATURES recognised by one or more of:
▪ non-compliance with treatment or monitoring ▪ failure to attend appointments ▪ fewer GP contacts ▪ frequent home visits ▪ 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.[409, 410] 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.

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. 2^{++}

B **Health care 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 8, and that these contribute to the near fatal asthma attack.[411-413] 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 2^{+}

have ready access to acute medical care.

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 & 8.1 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.[411, 414] 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.[415-420] 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 *(Annex2)*, ED *(Annex3)*, and hospital *(Annex4)*.

6.2.1 RECOGNITION OF ACUTE ASTHMA

Definitions of increasing levels of severity of acute asthma exacerbations are provided in table 10.[421-426] Predicted PEF values[427] 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

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 for[428] and deaths from[429] asthma *(see section 12.3.2)*.

6.2.3 INITIAL ASSESSMENT

All possible initial contact personnel, eg practice receptionists, ambulance call takers, NHS 111 (England & Wales), NHS 24 (Scotland), and out-of-hours providers, 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.[430]

Table 10: Levels of severity of acute asthma exacerbations

Near-fatal asthma	Raised PaCO2 and/or requiring mechanical ventilation with raised inflation pressures[410-413]	
Life threatening asthma	Any one of the following in a patient with severe asthma:	
	Clinical signs	Measurements
	Altered conscious level	PEF <33% best or predicted
	Exhaustion	SpO_2 < 92%
	Arrhythmia	PaO2 < 8 kPa
	Hypotension	"normal" $PaCO_2$ (4.6–6.0 kPa)
	Cyanosis	
	Silent chest	
	Poor 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	Clinical features can identify some patients with severe asthma, eg severe breathlessness (including too breathless to complete sentences in one breath), tachypnea, tachycardia, silent chest, cyanosis, accessory muscle use, altered consciousness or collapse.[421-426, 431] None of these singly or together is specific. Their absence does not exclude a severe attack.	2^+
PEF or FEV_1	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.[432, 433] PEF or FEV_1 are useful and valid measures of airway calibre. PEF is more convenient in the acute situation. 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.	2^+
Pulse oximetry	Measure oxygen saturation (SpO_2) 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 SpO_2 94-98%.[434]	2^+
Blood gases (ABG)	Patients with SpO_2 <92% (irrespective of whether the patient is on air or oxygen) or other features of life threatening asthma require ABG measurement.[421-424, 426, 435] SpO_2 <92% is associated with a risk of hypercapnea. Hypercapnea is not detected by pulse oximetry.[435] In contrast the risk of hypercapnea with SpO_2 >92% is much less.[434]	2^+ 4
Chest X-ray	Chest X-ray is not routinely recommended in patients in the absence of: – suspected pneumomediastinum or pneumothorax – suspected consolidation – life threatening asthma – failure to respond to treatment satisfactorily – requirement for ventilation.	4
Systolic paradox	Systolic paradox (*pulsus paradoxus*) is an inadequate indicator of the severity of an attack and should not be used.[421-426, 436]	2^+

6.2.6 CRITERIA FOR ADMISSION

B **Admit patients with any feature of a life threatening or near-fatal attack.**[401-405, 411, 413]

B **Admit patients with any feature of a severe attack persisting after initial treatment.**[401-405, 411 413]

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 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

Many patients with acute severe asthma are hypoxaemic.[437-440] Supplementary oxygen should be given urgently to hypoxaemic patients, using a face mask, Venturi mask or nasal cannulae with flow rates adjusted as necessary to maintain SpO_2 of 94-98%.[434] — 2^+, 4

Hypercapnea indicates the development of near-fatal asthma and the need for emergency specialist/anaesthetic intervention.

C **Give supplementary oxygen to all hypoxaemic patients with acute severe asthma to maintain an SpO_2 level of 94-98%. Lack of pulse oximetry should not prevent the use of oxygen.**

Oxygen-driven nebulisers are preferred for nebulising β_2 agonist bronchodilators because of the risk of oxygen desaturation while using air-driven compressors.[389, 421, 441] — 1^{++}

Emergency oxygen should be available in hospitals, ambulances and primary care. A flow rate of 6 l/min is required to drive most nebulisers. Where oxygen cylinders are used, a high flow regulator must be fitted.[434] — 4

The absence of supplemental oxygen should not prevent nebulised therapy from being administered when appropriate.[442] — 4

A **In hospital, ambulance and primary care, nebulised β_2 agonist bronchodilators should preferably be driven by oxygen.**

6.3.2 B_2 AGONIST BRONCHODILATORS

In most cases inhaledβ_2 agonists given in high doses act quickly to relieve bronchospasm with few side effects.[443-445] There is no evidence for any difference in efficacy between salbutamol and terbutaline. Nebulised adrenaline (epinephrine), a non-selective β_2 agonist, does not have significant benefit over salbutamol or terbutaline.[446] — 1+, 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.[447] 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.[448] — 1^{++}

Metered dose inhalers with spacers can be used for patients with exacerbations of asthma other than life threatening.[447] — 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.

Most cases of acute asthma will respond adequately to bolus nebulisation of β_2 agonists. Continuous nebulisation of β_2 agonists with an appropriate nebuliser may be more effective than bolus nebulisation in relieving acute asthma for patients with a poor response to initial therapy.[449-452] 1++ 1^+

A **In severe asthma that is poorly responsive to an initial bolus dose of β_2 agonist, consider continuous nebulisation with an appropriate nebuliser.**

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.

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.[453, 454] 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.[453] Prednisolone 40-50 mg daily or parenteral hydrocortisone 400 mg daily (100 mg six-hourly) are as effective as higher doses.[455] For convenience, steroid tablets may be given as 2 x 25 mg tablets daily rather than 8-10 x 5 mg tablets. Where necessary soluble prednisolone (sodium phosphate) 5 mg tablets are available. In cases where oral treatment may be a problem consider intramuscular methylprednisolone 160 mg as an alternative to a course of oral prednisolone.[456] 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[457, 458] (apart from patients on maintenance steroid treatment or rare instances where steroids are required for three or more weeks). 1^+

It is not known if inhaled steroids provide further benefit in addition to systemic steroids. Inhaled steroids should however be started, or continued as soon as possible to commence the chronic asthma management plan.[459, 460] 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.[461-463] 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 MAGNESIUM SULPHATE

There is some evidence that magnesium sulphate has bronchodilator effects.[464] 1++

A review of 16 trials involving 838 patients showed that nebulised magnesium sulphate when used in addition to nebulised β_2 agonist (with or without nebulised ipratropium) provided no benefit in terms of lung function or need for hospital admission.[465] 1++

A double-blink, placebo controlled study of 1,109 patients aged over 16 years presenting with acute asthma to 34 emergency departments across the UK randomised patients to IV or nebulised magnesium or to placebo.[466] Many of these patients had PEF >50% at presentation and the study failed to show improvement in either rate of hospital admission or breathlessness as judged by visual analogue score. A single dose of IV magnesium sulphate is safe and may improve lung function and reduce intubation rates in patients with acute severe asthma.[221, 467, 468] The safety and efficacy of repeated IV doses have not been assessed. Repeated doses could cause hypermagnesaemia with muscle weakness and respiratory fatigue. 1++ 1+

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

A **Nebulised magnesium is not recommended for treatment in adults with acute asthma.**

B **Consider giving a single dose of IV magnesium sulphate to patients with acute severe asthma (PEF <50% best or predicted) who have not had a good initial response to inhaled bronchodilator therapy.**

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

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.[469] 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.[469] 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

Current evidence on oral leukotriene receptor antagonists does not support their use in acute asthma.[470] further studies are required to assess whether IV treatment is effective and safe. 1++

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.[471] 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), either as a driving gas for nebulisers, as a breathing gas, or for artificial ventilation in adults with acute asthma is not supported on the basis of present evidence.[472, 473] A systematic review of ten trials, including 544 patients with acute asthma, found no improvement in pulmonary function or other outcomes in adults treated with heliox, although the possibility of benefit in patients with more severe obstruction exists.[474, 475] Heliox requires the use of specifically designed or modified breathing circuits and ventilators. 1^{+} 1^{++}

B **Heliox is not recommended for use in acute asthma outside a clinical trial setting.**

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 NEBULISED FUROSEMIDE

Although theoretically furosemide may produce bronchodilation, a review of three small trials failed to show any significant benefit of treatment with nebulised furosemide compared to β_2 agonists.[476] 1^{+}

6.3.12 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, altered conscious state
- respiratory arrest.[421, 422]

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.[421, 422]

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

6.3.13 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 4

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.[477]

A Cochrane review found only one trial, with 30 patients, on NIV which showed improvement in hospitalisation rates, discharge from emergency departments and lung function. Larger RCTs are needed to determine the role of NIV in treating patients with acute asthma.[478] 1++

✓ NIV should only be considered in an ICU or equivalent clinical setting.

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
- Record oxygen saturation by oximetry and maintain arterial SpO2 at 94-98%.
- Repeat measurements of blood gas tensions within one hour of starting treatment if:
  - the initial PaO2 is <8 kPa unless SpO2 is >92%; or
  - the initial PaCO2 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 10-20mg/l or 55-110 mol/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.[430, 479, 480] 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.[481, 482] 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- 2+

monitored.[483]

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.[484] 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] Education has been shown to reduce subsequent hospital admission and improve scheduled appointments and self management techniques but does not improve re-attendance at emergency departments.[485] 1++

For the above groups there is a role for a trained asthma liaison nurse based in, or associated with, the emergency department.[485]

See also section 12

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.

In a small RCT follow-up care by a nurse specialist was effective and safe as that given by a respiratory doctor.[486] 1-

Assisting patients in making appointments while being treated for acute asthma in emergency departments may improve subsequent attendance at primary care centres.[487] 1+

✓ 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 CLINICAL 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[488]

Life threatening asthma	Any one of the following in a child with severe asthma:	
	Clinical signs	Measurements
	Silent chest	SpO_2 < 92%
	Cyanosis	PEF <33% best or predicted
	Poor respiratory effort	
	Hypotension	
	Exhaustion	
	Confusion	
Acute severe asthma	Can't complete sentences in one breath or too breathless to talk or feed SpO_2 < 92% PEF 33-50% best or predicted Pulse >140 in children aged 2-5 years >125 in children aged >5 years Respiration >40 breaths/min aged 2-5 years >30 breaths/min aged >5 years	
Moderate asthma exacerbation	Able to talk in sentences SpO_2 ≥92% PEF ≥ 50% best or predicted Heart rate ≤140/min in children aged 2-5 years ≤ 125/min in children > 5 years Respiratory rate ≤ 40/min in children aged 2-5 years ≤ 30/min in children > 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.[489-492] Some children with acute severe asthma do not appear distressed. 2^{++}

✓ Decisions about admission should be made by trained clinicians after repeated assessment of the response to bronchodilator treatment.

6.7.2 PULSE OXIMETRY

Accurate measurements of oxygen saturation are essential in the assessment of all children with acute wheezing. Oxygen saturation monitors 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.[489, 492] 2++

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

6.7.3 PEF

PEF measurements can be of benefit in assessing children who are familiar with the use of such devices. The best of three PEF measurements, ideally expressed as a percentage of personal best, can be useful in assessing the response to treatment.

A measurement of <50% predicted PEF or FEV_1 with poor improvement after initial bronchodilator treatment is predictive of a more prolonged asthma attack.

6.7.4 CHEST X-RAY

Chest X-rays rarely provide additional useful information and are not routinely indicated.[493, 494]

✓ A chest X-ray should be performed if there is subcutaneous emphysema, persisting unilateral signs suggesting pneumothorax, lobar collapse or consolidation and/or life threatening asthma not responding to treatment.

6.7.5 BLOOD GASES

Blood gas measurements should be considered if there are life threatening features not responding to treatment. Arteriolised ear lobe blood gases can be used to obtain an accurate measure of pH and pCO_2.[434] If ear lobe sampling is not practicable a finger prick sample can be an alternative. Normal or raised pCO_2 levels are indicative of worsening asthma. A more easily obtained free flowing venous blood pCO_2 measurement of < 6kPA (45mm Hg) excludes hypercapnia.[434] 4

6.8 INITIAL TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

There is good evidence supporting recommendations for the initial treatment of acute asthma presenting to primary and secondary healthcare resources. There is less evidence to guide the use of second line therapies to treat the small number of severe cases poorly responsive to first line measures. Despite this, the risks of death and other adverse outcomes after admission to hospital are extremely small irrespective of the treatment options chosen.

✓ ß2 agonists should be given as first line treatment. Increase ß2 agonist dose by two puffs every two minutes according to response up to ten puffs.

✓ Children with acute asthma at home and symptoms not controlled by up to 10 puffs of salbutamol via pMDI and spacer, or 2.5-5 mg of nebulised salbutamol, should seek urgent medical attention. Additional doses of bronchodilator should be given as

needed whilst awaiting medical attention if symptoms are severe.

✓ Paramedics attending to children with acute asthma should administer nebulised salbutamol driven by oxygen if symptoms are severe whilst transferring the child to the emergency department.

✓ Children with severe or life threatening asthma should be transferred to hospital urgently.

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. Using a proforma can increase the accuracy of severity assessment.

The use of an assessment-driven algorithm and an integrated care pathway has been shown to reduce hospital stay without substantial increases in treatment costs.[495] 4

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 SpO_2 <94% 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 INHALED β_2 AGONISTS (SALBUTAMOL/TERBUTALINE)

A **Inhaled β_2 agonists are the first line treatment for acute asthma.[496-499]**

Assessment of response should be based on accurately recorded clinical observations and repeat measurements of oxygenation (SpO_2). Children receiving β_2 agonists via pMDI + spacer are less likely to have tachycardia and hypoxia than when the same drug is given via a nebuliser.[389] 1^+

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

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 (for five breaths).

Frequent doses of β_2 agonists are safe for the treatment of acute asthma,[496-498] although children with mild symptoms benefit from lower doses.[499] 1^+

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

Two to four puffs of a salbutamol 100 mcg repeated every 10-20 minutes according to clinical response might be sufficient for mild attacks although up to 10 puffs might be needed for more severe asthma. Single puffs should be given one at a time and inhaled separately with five tidal breaths. If hourly doses of bronchodilators are needed for more than 4-6 hours, the patient should be switched to nebulised bronchodilators.

Children with severe or life threatening asthma (SpO_2 < 92%) should receive frequent doses of nebulised bronchodilators driven by oxygen (2.5-5 mg salbutamol or 5-10 mg terbutaline).

Doses can be repeated every 20-30 minutes. Continuous nebulised β_2 agonists are of no greater benefit than the use of frequent intermittent doses in the same total hourly

dosage.[500, 501] If there is poor response to the initial dose of $ß_2$ agonists, subsequent doses should be given in combination with nebulised ipratropium bromide.

✓ Discontinue long-acting β_2 agonists when short-acting β_2 agonists are required more often than four-hourly.

6.8.3 IPRATROPIUM BROMIDE

There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide (every 20-30 minutes) 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.[502] 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 5 mg of salbutamol solution in the same nebuliser) should be used for the first few hours of admission. Salbutamol dose should be weaned to one-to two-hourly thereafter according to clinical response. The ipratropium dose should be weaned to four-to-six-hourly or discontinued. Once improving on two- to four-hourly salbutamol, patients should be switched to pMDI and spacer treatment as tolerated.

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

6.8.4 STEROID THERAPY

Steroid tablets

The early use of steroids in emergency departments and assessment units can reduce the need for hospital admission and prevent a relapse in symptoms after initial presentation.[453, 454] Benefits can be apparent within three to four hours. In head to head comparisons there is insufficient evidence to suggest that dexamethasone offers an advantage over prednisolone for the management of mild to moderate acute asthma in children. Further, correctly powered studies may indicate whether a single dose of dexamethasone may offer clinical benefit over multiple doses of prednisolone.[503-505] 2+ 1+ 1-

A **Give oral steroids early in the treatment of acute asthma attacks.**

B **Oral prednisolone is the steroid of choice for mild to severe asthma in children unless the patient is unable to tolerate the dose.**

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

Oral and intravenous steroids are of similar efficacy.[455, 506, 507] 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.[508] 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. Weaning is unnecessary unless the course of steroids exceeds 14 days.[457, 458]

A large study of UK pre-school children with mild to moderate wheeze associated with viral infection showed no reduction in hospital stay (of other outcomes) following treatment with oral steroids. In the actue situation, it is often difficult to determine whether a pre-school child has asthma or episodic viral wheeze. Children with severe symptoms requiring hospital admission should still receive oral steroids. In children who present with moderate to severe wheeze without a previous diagnosis of asthma it is still advisable to give oral steroids. For children with frequent episodes of wheeze associated with viruses caution should be taken in prescribing multiple courses of oral steroids.[509] 1+

Inhaled steroids

There is insufficient evidence to support the use of inhaled steroids as alternative or additional treatment to steroid tablets for acute asthma.[510-518] 1+

A **Do not use inhaled steroids in place of oral steroids to treat children with acute asthma exacerbation.**

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.

✓ It is good practice for children already receiving inhaled steroids to continue with their usual maintenance dose during an exacerbation whilst receiving additional treatment.

6.8.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

Initiating oral montelukast in primary care settings, early after the onset of acute asthma symptoms, can result in decreased asthma symptoms and the need for subsequent healthcare attendances in those with mild exacerbations.[367, 519] 1++ Current evidence shows no benefit for the addition of leukotriene receptor antagonists to standard asthma treatment for moderate to severe asthma exacerbations.[470] 1+

6.8.6 NEBULISED MAGNESIUM SULPHATE

There is no evidence to support the use of nebulised magnesium sulphate, either in place of or in conjunction with inhaled β_2 agonists in mild to moderate asthma.[465] A sub-group analysis from a large RCT suggests a possible role in children with more severe asthma (oxygen saturation less than 92%)or with short duration of deterioration. Further studies are required to evaluate which clinical groups would benefit the most from this intervention.[520] 1++

A **Nebulised magnesium sulphate is not recommended for children with mild to moderate exacerbations of asthma.**

A **Consider adding 2.5ml magnesium sulphate to each nebulised salbutamol and ipratropium in the first hour in children with a short duration of acute severe asthma symptoms presenting with an oxygen saturation less than 92%.**

6.9 SECOND LINE TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

Children with continuing severe asthma despite frequent nebulised $ß_2$ agonists and 1++

ipratropium bromide plus oral steroids, and those with life threatening features, need urgent review by a specialist with a view to transfer to a high dependency unit or paediatric intensive care unit (PICU) to receive second line intravenous therapies. There are three options to consider; salbutamol, aminophylline and magnesium sulphate. There is no clear evidence that one IV therapy is preferential to another. A systematic review of four paediatric trials comparing IV salbutamol with IV aminophylline demonstrated equivalence. One study resulted in a shorter length of stay in the aminophylline group although these patients received a bolus followed by an infusion, compared to a single bolus of IV salbutamol. Both IV salbutamol and IV aminophylline can cause side effects and should be administered with appropriate monitoring. There are no head to head studies with magnesium sulphate and one or other IV therapy.[521]

6.9.1 IV SALBUTAMOL

The role of intravenous $ß_2$ agonists in addition to nebulised treatment remains unclear.[448] 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 for those with moderate to severe asthma.[448] 1+

B **Consider early addition of a single bolus dose of intravenous salbutamol (15 mcg/kg over 10 minutes) in severe cases where the patient has not responded to initial inhaled therapy.**

A continuous intravenous infusion of salbutamol should be considered when there is uncertainty about reliable inhalation or for severe refractory asthma. This should be given in a high dependency unit with continuous ECG monitoring and twice daily electrolyte monitoring. Doses above 1-2 mcg/kg/min (200 mcg/ml solution) should be given in a PICU setting (up to 5 mcg/kg/min). Nebulised bronchodilators should be continued while the patient is receiving intravenous bronchodilators. Once the patient is improving the intravenous infusion should be reduced before reducing the frequency of nebulised bronchodilators.

✓ When inserting an IV cannula take a blood sample to measure serum electrolytes. Serum potassium levels are often low after multiple doses of B_2 agonists and should be replaced.

6.9.2 IV AMINOPHYLLINE

There is no evidence that aminophylline is of benefit for mild to moderate asthma and side effects are common and troublesome.[469, 522] One well conducted study has shown evidence of benefit in severe acute asthma unresponsive to multiple doses of β_2 agonists and steroids, although the loading dose used was double that currently recommended in the UK and a third of patients were withdrawn from active medication because of vomiting.[523] 1+ 2+ 2+

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

B **Consider aminophylline for children with severe or life threatening asthma unresponsive to maximal doses of bronchodilators and steroids.**

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. Measure serum theophylline levels in patients already receiving oral treatment and in those receiving prolonged treatment.

6.9.3 IV MAGNESIUM SULPHATE

Intravenous magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet established.[468, 524] Doses of up to 40 mg/kg/day (maximum 2 g) by 1+

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.

6.9.4 OTHER THERAPIES

There is no evidence to support the use of heliox, DNase or mucolytics for the treatment of acute asthma in childhood. Nebulised magnesium sulphate is being evaluated as a treatment for acute asthma but is not yet recommended.

There is insufficient evidence to support or refute the role of antibiotics in acute asthma,[315] but the majority of acute asthma attacks are triggered by viral infection.

✓ Do not give antibiotics routinely in the management of children with acute asthma.

6.9.5 DISCHARGE PLANNING

Children can be discharged when stable on 3-4 hourly inhaled bronchodilators that can be continued at home.[525] PEF and/or FEV_1 should be >75% of best or predicted and SpO_2 >94%.

Adult studies show that "optimal care" comprising self monitoring, regular review and a written asthma action plan can improve outcomes.[428] 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 preventer treatment
- provide a written asthma action plan for subsequent asthma exacerbations with clear instructions about the use of bronchodilators and the need to seek urgent medical attention in the event of worsening symptoms not controlled by up to 10 puffs of salbutamol 4 hourly
- arrange follow up by primary care services within 48 hours
- arrange follow up in a paediatric asthma clinic within one to two months
- arrange referral to a paediatric respiratory specialist if there have been life threatening features.

6.10 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 (see SIGN 91: Bronchiolitis in children).[526]

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

6.11.1 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.

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.[391, 527, 528] 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.[529-531] 1+

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.[532] 1+

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

6.11.2 STEROID THERAPY

Steroid tablets in conjunction with β_2 agonists have been shown to reduce hospital admission rates when used in the emergency department.[533] Steroid tablets have also been shown to reduce the length of hospital stay.[529, 532, 533] 1+

A large study of UK pre-school children with mild to moderate wheeze associated with viral infection showed no reduction in hospital stay (of other outcomes) following treatment with oral steroids. In the acute situation, it is often difficult to determine whether a pre-school child has asthma or episodic viral wheeze. Children with severe symptoms requiring hospital admission should still receive oral steroids. In children who present with moderate to severe wheeze without a previous diagnosis of asthma it is still advisable to give oral steroids. For children with frequent episodes of wheeze associated with viruses caution should be taken in prescribing multiple courses of oral steroids.[509] 1+

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

One study has shown similar benefits when comparing oral and nebulised steroids for acute asthma.[529]

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

6.11.3 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.[534] 1+

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

6.11.4 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 6.9.5).*

7 Difficult asthma

7.1 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 and figures 4, 5 & 6)*, before labelling as "difficult".[535, 536]

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.[32, 537-539] 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 co-morbidities and confirmation of adherence with therapy. 3

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 12.5*). Two UK studies in adults attending specialist difficult asthma services documented high levels of poor adherence identified by low prescription filling. A study of 182 patients in the Northern Ireland Regional Difficult Asthma Service found that 63 patients (35%) filled 50% or fewer inhaled LABA/inhaled steroid prescriptions and 88% admitted poor adherence with inhaled therapy after initial denial; 23 of the 51 patients (45%) prescribed oral steroids were found to be non-adherent using serum prednisolone/cortisol testing.[540] In another study, 75 of 115 (65.2%) patients filled prescriptions for <80% of inhaled steroid medication and had significantly worse lung function, higher sputum eosinophil counts and prior ventilation compared to adherent patients.[541] A study of 71 school aged children with persistent symptoms, despite treatment at Step 4/5 of the BTS/SIGN guidelines, attending one hospital in London, found that 56 (79%) had potentially modifiable risk factors, the two most common of which were psychosocial factors (59%) and medication issues including adherence (48%). In 39 2+ 3

children (55%) the factors identified and the interventions recommended meant that further escalation of treatment was avoided.[542] In a paediatric 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.[543] 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.[538]

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

7.2.2 PSYCHOSOCIAL FACTORS

Fatal and near-fatal asthma have been associated with psychosocial dysfunction *(see section 6.1.3)*. Most observational studies[32, 538, 544-547] and a case control study[548] in subjects with difficult asthma have also suggested a high level of psychological morbidity, though this observation has not been universal.[549, 550] 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.[551] 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 use[552] 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.[553] However, a non-blinded randomised intervention study in adults with difficult asthma showed no benefit from a six month nurse-delivered psychoeducational programme.[554] A meta-analysis of psycho-educational 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.[555] 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.[32, 538] It remains unclear what is the best mechanism of identifying and managing this problem. 2+ 2- 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.[556] In case control studies, mould sensitisation has been associated with recurrent admission to hospital and oral steroid use[557, 558] and with intensive care unit admissions and 2++ 3

respiratory arrest.[559, 560] There is no published evidence of any intervention study in this group. Research in this area is required.

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.[87, 89, 561] 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.[87] Case series have suggested that sputum induction is safe in patients with difficult to control asthma.[60, 562-565] 1+ 1- 3

Controlled studies using FE_{NO} to target treatment have not specifically targeted adults or children with difficult asthma.[88, 116] 1+

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

8 Asthma in adolescents

8.1 DEFINITIONS

Adolescence is the transitional period of growth and development between puberty and adulthood, defined by the World Health Organisation (WHO) as between 10 and 19 years of age.[4]

There is international agreement on best practice for working with adolescents with health problems outlined in consensus publications.[566-568] Key elements of working effectively with adolescents in the transition to adulthood include: [Royal Australasian College of Physicians Joint Adolescent Health Committee. Confidential Health Care for Adolescents and Young People 2010]

- seeing them on their own, separate from their parents, for part of the consultation, and
- discussing confidentiality and its limitations.

For diagnosing and managing asthma in adolescents, the evidence base is limited. Much recent research has focused on the prevalence of asthma and ecological risk associations rather than on diagnosis and management of asthma in adolescents.

8.2 PREVALENCE OF ASTHMA IN ADOLESCENCE

Asthma is common in adolescence with a prevalence of wheeze in Western Europe in the past 12 months (current wheeze) in 13-14 year olds of 14.3%.[569] For more severe asthma (defined as ≥4 attacks of wheeze or ≥1 night per week sleep disturbance from wheeze or wheeze affecting speech in the past 12 months) the prevalence was 6.2%.

There is evidence of under-diagnosis of asthma in adolescents, with estimates of 20-30% of all asthma present in this age group being undiagnosed.[569-572] This has been attributed to under-reporting of symptoms. A number of risk factors have independently been associated with under-diagnosis including: female gender, smoking (both current smoking and passive exposure), low socioeconomic status, family problems, low physical activity and high body mass and race/ethnicity.[572] Children with undiagnosed frequent wheezing do not receive adequate healthcare for their illness[572] and the health consequences of not being diagnosed with asthma are substantial.[573, 574]

Although feasible, there is insufficient evidence to support screening for asthma in adolescents.[575, 576]

✓ Clinicians seeing adolescents with any cardio-respiratory symptoms should ask about symptoms of asthma.

8.3 DIAGNOSIS AND ASSESSMENT

No evidence was identified to suggest that the symptoms and signs of asthma in adolescents are different from those of other age groups.

8.3.1 EXERCISE-RELATED SYMPTOMS

Exercise-related wheezing and breathlessness are common asthma symptoms in adolescents. However, these symptoms are poor predictors of exercise-induced asthma. Only a minority of adolescents referred for assessment of exercise-induced respiratory symptoms show objective evidence of exercise-induced bronchospasm.[577] Other diagnoses producing reproducible symptoms on exercise include normal physiological exercise limitation, with and without poor physical fitness, vocal cord dysfunction, hyperventilation, habit cough, and supraventricular tachycardia.[59]

Most exercise-related wheezing in adolescents can be diagnosed and managed by careful clinical assessment.[578] The absence of other features of asthma and an absent response to pre-treatment with β_2-agonist make exercise-induced asthma unlikely. Exercise testing with cardiac and respiratory monitoring that reproduces the symptoms may be helpful in identifying the specific cause.[59]

8.3.2 USE OF QUESTIONNAIRES

When using questionnaires, the prevalence of current symptoms is higher when the adolescent completes the questions rather than the parents, while questions about the last 12 months give similar results between the parents and the adolescent.[579]

In one study in adolescents, internet and written questionnaires about asthma provided equivalent results.[580] The asthma control questionnaire (ACQ) and the asthma control test (ACT) have been validated in adolescents with asthma (*see Table 8*).[131]

8.3.3 QUALITY OF LIFE MEASURES

Quality of life (QoL) scales (such as AQLQ12+) can be used in adolescents.[581, 582]

8.3.4 LUNG FUNCTION

In adolescents with asthma, tests of airflow obstruction and airway responsiveness may provide support for a diagnosis of asthma. However, most adolescents with asthma have normal lung function despite having symptoms.

8.3.5 BRONCHIAL HYPER-REACTIVITY

Although many children with asthma go into long lasting clinical remission at adolescence, bronchial hyper-reactivity (BHR) may persist. Whether persisting BHR reflects ongoing airway inflammation is debated.[583]

A negative response to an exercise test is helpful in excluding asthma in children with exercise-related breathlessness.[59]

8.4 RISK FACTORS

There is a body of evidence from cohort studies highlighting risk factors for asthma in adolescents.

8.4.1 ATOPY

Studies confirm that atopic dermatitis and atopic rhinitis are amongst the factors most strongly associated with asthma persisting into teenage years.[584-587]

8.4.2 PREMATURITY AND EARLY LIFE WHEEZING

Adolescents who were very low birth weight due to prematurity (as opposed to intrauterine growth retardation) were more prone to chronic cough, wheezing and asthma and showed medium and small airway obstruction compared with matched controls.[588]

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.[8, 11, 16, 19, 24, 29, 41, 42, 587]

8.4.3 GENDER

During adolescence there is a reversal of the gender association of asthma with the disease being more prevalent in females than males from 13-14 years onwards.[589] The same change is seen with asthma exacerbations with risk of an asthma admission in females becoming double that observed in males from around 13-14 years.[590] This phenomenon has been attributed to a greater incidence of asthma among teenage girls.[591]

8.4.4 CHLORINATED SWIMMING POOLS

Exposure to chlorinated swimming pools has been associated with an increased risk of asthma, airway inflammation and some respiratory allergies.[592] Such associations were not found among adolescents without atopy or in those who attended copper-silver sanitised pools.[593]

8.5 CO-MORBIDITIES AND MODIFIABLE BEHAVIOURS

8.5.1 ANXIETY AND DEPRESSIVE DISORDERS

Asthma in adolescence is associated with an increased likelihood of major depression, panic attacks and anxiety disorder. This may reflect effects of common factors associated with anxiety and depressive disorders rather than a direct causal link with asthma.[594] In young people with asthma, the presence of an anxiety or depressive disorder is highly associated with increased asthma symptom burden.[595] Depressive symptoms were one risk factor identified in children and adolescents who died of asthma. Assessment of anxiety may help identify individuals who are at risk for poorer asthma specific quality of life.[596]

Clinical conditions associated with anxiety may be mistaken for, or overlap with asthma. These include dysfunctional breathing (hyperventilation syndrome and sighing dyspnoea), vocal cord dysfunction, and psychogenic cough. These conditions can present acutely and may often be frightening to the young person. This may lead to a cycle of bronchodilator overuse, which then further exacerbates the symptoms. Detailed medical assessment with careful attention to the adolescent's personal perceptions and experiences of their symptoms is required to make an accurate diagnosis.[597]

Brief screening questionnaires for anxiety and depression suitable for use in adolescents are available and may help identify those with significant anxiety and depression.[598]

8.5.2 OBESITY

The evidence on whether asthma is more common in overweight and obese adolescents with asthma is conflicting.[584, 599-601] While weight reduction in obese adults with asthma improves lung function, symptoms, morbidity and health status, this has not yet been established in adolescents with asthma.

8.5.3 GASTRO-OESOPHAGEAL REFLUX AND GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux and gastro-oesophageal disease (GORD) is common in asthma patients, including adolescents.[602] A systematic review confirmed an association between GORD and asthma in children and adolescents in secondary and tertiary referral settings. The nature of the association, however, is unclear.[603] There is no evidence that treatment for GORD improves asthma symptoms in children and adolescents with GORD and asthma.[385, 386]

8.6 ASTHMA EXACERBATIONS AND THE RISK OF HOSPITAL ADMISSION

Clinical characteristics and markers of severity, including frequent respiratory symptoms, airway hyper-responsiveness, atopy, and low lung function, identify those at high risk of hospitalisation for asthma, particularly with respect to multiple admissions.[604]

8.7 LONG TERM OUTLOOK AND ENTRY INTO THE WORK PLACE

A long term follow-up study of vocational and working careers found that adolescents and young adults (10-22 years) with relatively mild asthma had slightly more limitations in vocational and professional careers than those without asthma. They had a small increased risk of limitations in daily activity attributable to respiratory health and of absence

from work. In the majority, however, the differences amounted to only a few days per year.[605] Young adults with asthma had a low awareness of occupations that might worsen asthma (for example, exposure to dusts, fumes, spray, exertion and temperature changes) and did not generally discuss career plans with their general practitioner. Further details about occupational asthma can be found in section10.

✓ Clinicians should discuss future career choices with adolescents with asthma and highlight occupations that might increase susceptibility to work related asthma symptoms.

8.8 NON-PHARMACOLOGICAL MANAGEMENT

8.8.1 TOBACCO SMOKING AND ENVIRONMENTAL EXPOSURE TO TOBACCO SMOKE

Exposure to passive smoking remains a significant health risk.

One study of asthma morbidity among urban young adolescents (mean approximately 11 years of age) found at baseline that 28% of caregivers reported exposure to environmental tobacco smoke (ETS) in the home and 19% reported exposure outside the primary household. Children who received a 20 minute educational intervention about ETS exposure and whose ETS exposure had decreased at follow-up had fewer hospitalisations (p=0.034) and emergency department visits (p≤0.001) reported in the next 12 months) as well as fewer episodes of poor asthma control (p=0.042).[606]

In a national survey in Denmark, 37.7% of adolescents with asthma smoked currently, 16.5% daily. Smoking was more common in girls. More of those with asthma smoked daily, smoked more cigarettes and had tried to quit smoking.[607] 2+

Among adolescents, smoking is a risk factor for asthma.[585, 608-610] A longitudinal study of asthma and allergic disease in school children in Sweden found that both passive and active smoking were significantly related to asthma and wheeze in adolescents. Maternal ETS exposure was associated with lifetime symptoms, but daily smoking among the adolescents was more strongly related to current symptoms.[611] 3 4

NICE has recommended that all smokers should be offered a brief intervention about stopping smoking. Young people aged 12-17 years who have a strong commitment to quit smoking should be offered advice on how to stop and encouraged to use local NHSsmoking cessation services by providing details of when, where and how to access them.

✓ Adolescents with asthma (and their parents and carers) should be encouraged to avoid exposure to environmental tobacco smoke and should be informed about the risks and urged not to start smoking.

✓ Adolescents with asthma should be asked if they smoke personally. If they do and wish to stop, they should be offered advice on how to stop and encouraged to use local NHS smoking cessation services.

8.8.2 COMPLEMENTARY AND ALTERNATIVE MEDICINE

In a small study, sixteen percent of Italian teenagers had used complementary and alternative medicine (homeopathy, acupuncture, herbal medicines).[612] In a US study, 80% of urban adolescents (aged 13-18 years) with asthma reported that they had used CAM, most commonly rubs, herbal teas, prayer and massage.[613] While most adolescents used CAM with conventional asthma therapy, 27% reported they used it instead of prescribed therapy,[613] suggesting that CAM use may be a marker of non-adherence with prescribed asthma treatment. 2-

✓ Health care professionals should be aware that CAM use is common in adolescents and should ask about its use.

8.9 PHARMACOLOGICAL MANAGEMENT

Specific evidence about the pharmacological management of adolescents with asthma is limited and is usually extrapolated from paediatric and adult studies. Recommendations for pharmacological management of asthma in children and adults can be found in section 4.

8.10 INHALER DEVICES

Specific evidence about inhaler device use and choice in adolescents is limited. Inhaler devices are covered in section 5.

Two small studies comparing two different types of inhalers in adolescents found that both dry powder inhalers (DPI) and pressurised metered dose inhalers (pMDIs) plus spacer are of value in adolescent asthma.[614, 615] There were no differences between the two inhaler devices in terms of symptoms or lung function but patients preferred the DPI. 2+

Though adolescents with asthma may be competent at using their inhaler devices, their actual adherence to treatment may be affected by other factors such as preference. In particular, many adolescents prescribed a pMDI with spacer do not use the spacers as they are felt to be too inconvenient.[616, 617] 3

✓ Adolescent preference for inhaler device should be taken into consideration as a factor in improving adherence to treatment.

✓ As well as checking inhaler technique it is important to enquire about factors that may affect inhaler device use in real life settings such as school.

✓ Consider prescribing a more portable device (as an alternative to a pMDI with spacer) for delivering bronchodilators when away from home.

8.11 ORGANISATION AND DELIVERY OF CARE

8.11.1 HEALTHCARE SETTING

Very little evidence was identified to determine the best healthcare setting to encourage attendance amongst adolescents with asthma.

A two-year follow-up study found that a multi-disciplinary day programme improved asthma control in a group of adolescents with very severe asthma. This study involved a highly selected group of patients and a wide range of interventions and is not generalisable to most adolescents with asthma.[537] 3

8.11.2 SCHOOLS AS A SETTING FOR HEALTHCARE DELIVERY AND ASTHMA EDUCATION

Some innovative approaches have used schools as setting for asthma education and review. One focus has been on healthcare delivery such as school-based clinics. Evidence from a single cluster randomised, controlled trial suggests that school-based, nurse-led asthma clinics increase the uptake of asthma reviews in adolescents from 51% in practice care to 91%.[618] Knowledge of asthma, inhaler techniques and positive attitudes increased and a majority of the adolescents preferred the setting, but there was no improvement in clinical outcomes. This may be because the nurses were not able to change or prescribe treatment (which relied on a separate visit to a doctor). 1+

Other approaches have used schools as a setting for asthma education including peer-led education. In a single, well-conducted RCT peer-led education in schools improved quality of life, asthma control and days off school for adolescents with asthma.[619] In a US study, a randomised trial of a web-based tailored asthma management programme delivered using

school computers found that, after 12 months students reported fewer symptoms, school days missed, restricted-activity days, and hospitalisations for asthma than control students. The programme was inexpensive to deliver.[620]

A number of countries, particularly Australia and New Zealand, have developed national programmes to ensure that schools can deliver appropriate first aid and emergency response to students with asthma as well as encouraging participation in sporting activities.[621]

B **School based clinics may be considered for adolescents with asthma to improve attendance.**

B **Peer-led interventions for adolescents in the school setting should be considered.**

✓ Integration of school based clinics with primary care services is essential.

8.11.3 TRANSITION TO ADULT BASED HEALTHCARE

Transition to adult services is important for all adolescents with asthma, irrespective of the asthma severity. No studies on transition of adolescents with asthma to adult services were identified although there are many studies looking at transition of adolescents with chronic illness. Few studies compare different approaches and many recommendations come from consensus statements rather than randomised, controlled trials.[566-568] In the UK, information on transition is available from the Royal College of Paediatrics and Child Health and Department of Health websites

It is important that the process of transition is coordinated and it is recommended that a healthcare professional be identified to oversee transition and either link with a counterpart in adult services or remain involved until the young person is settled within adult services.[622, 623]

✓ In the initial period After transition to adult services in secondary care, adolescents are best seen by one consultant to build their confidence and encourage attendance.

8.11.4 PREPARATION FOR TRANSITION

Transition should be seen as a process and not just the event of transfer to adult services.[622] It should begin early, be planned and involve the young person and be both age and developmentally appropriate (*see Table 1)*[622]

Table 13: Recommendations for organising transition services[622]

Young people should be given the opportunity to be seen without their parents/carers
Transition services must address the needs of parents/carers whose role in their child's life is evolving at this time
Transition services must be multi-disciplinary and multi-agency. Optimal care requires a cooperative working relationship between adult and paediatric services, particularly where the young person has complex needs with multiple specialty involvement
Co-ordination of transitional care is critical. There should be an identified coordinator who supports the young person until he or she is settled within the adult system
Young people should be encouraged to take part in transition/support programmes and/or put in contact with other appropriate youth support groups
The involvement of adult physicians prior to transfer supports attendance and adherence to treatment
Transition services must undergo continued evaluation

8.12 PATIENT EDUCATION AND SELF-MANAGEMENT

8.12.1 EDUCATION IN SELF-MANAGEMENT

Section 12 covers self-management education and the components of a self-management programme.

Effective transition care involves preparing adolescents with asthma to take independent responsibility for their own asthma management and enabling them to be able to negotiate the health system effectively (*see Table 14*). Clinicians need to educate and empower adolescents to manage as much of their asthma care as they are capable of doing while supporting parents gradually to hand over responsibility for management to their child.[624]

Table 14: Specific knowledge, attitudes and skills that underpin independent self-management practices in adolescents with asthma[624]

Can name and explain their condition
Can list their medications, treatments or other management practices (eg special diet)
Can explain why each medication or management practice is necessary
Can remember to take their medications most of the time
Can answer questions asked of them by doctors or health professionals
Can ask questions of their doctor or other health professional
Can arrange (and cancel) appointments
Can consult with a doctor or other health professional without a parent/carer
Remembers to order more medication before it runs out
Can have prescriptions filled at pharmacy
Develops the desire for their healthcare to be independent of their parents/carers
Can prioritise their health over (some) other desires

For adolescents with asthma, the available evidence about self-management is mainly qualitative and provides insight about the concerns adolescents have about their asthma and its management. Adolescents with asthma report embarrassment over using inhalers in front of others, sadness over not being able to take part in normal activities, frustration and anger at the way they are treated by their families (eg being limited in what they are allowed to do, being fussed over by parents). They also report specific anxieties around fear of dying and feeling guilty over the effect their illness has on the rest of the family. They are concerned about needing to rely on someone else when they have a bad asthma attack and that teachers do not know what to do. They stress the importance of support from friends at school, especially those with asthma.[625, 626] 3

Studies of adolescents with chronic illness (including adolescents with asthma) have highlighted factors that adolescents feel are important in delivering education about self-management to them.[627] These included:

- education must be adapted to meet individual needs and repeated and developed as understanding and experience increases and should include emotional support for coping with feelings
- education should be delivered by educators that respect, engage, encourage and motivate the adolescents
- accompanying information, both written and oral, should be personalised rather than general and use non-medical language that adolescents can understand
- education should be delivered in an appropriate and uninterrupted setting and make appropriate use information technology.

3

D **Design of individual or group education sessions delivered by healthcare professionals should address the needs of adolescents with asthma.**

8.12.2 ADHERENCE

Adherence with asthma treatment, and with asthma trigger avoidance, is often poor in adolescents. The evidence for poor adherence comes mainly from questionnaire-based and qualitative studies rather than objective electronic monitoring.[628]

When directly asked, most adolescents admit they do not always follow their treatment plans. Reasons for not adhering include both unintentional reasons (confusion about medications and forgetfulness) and intentional reasons (inhalers being ineffective/hard to use; treatment plan too complicated; more important things to do; concern about side-effects; denial; can't be bothered and embarrassment).[617, 629] Background factors, such as younger age, family size, exercise and not smoking or drinking alcohol as well as disease-related factors such as sense of normality, energy and will-power, support from the parents, physicians and nurses, and a positive attitude towards the disease and treatment were related to good reported adherence.[630]

Non-adherence to medication regimens in adolescents has been linked to other health risk behaviours including tobacco, alcohol and drug use and also to depression.[631] Not only are specific behaviours such as smoking, poor adherence to medication regimens or medical review appointments detrimental to asthma control, they also have been highlighted as potential beacons of distress in adolescents.[632] Clinical tools such as the HEADSS (Home, Education/Employment, Activities, Drugs, Sexuality, Suicide/depression) adolescent health screen provide practitioners with an easily usable psychosocial screen.[633] 3

Strategies to improve adherence in adolescents emphasise the importance of focusing on the individual and their lifestyle and using individualised asthma planning and personal goal setting.[634] One study found that once-daily supervised asthma preventer therapy at school improved asthma control and quality of life.[635]

9 Asthma in pregnancy

9.1 NATURAL HISTORY AND MANAGEMENT OF STABLE ASTHMA

The majority of women with asthma have normal pregnancies and the risk of complications is small in those with well controlled asthma. 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 and its treatment can affect pregnancy outcomes.

9.1.1 COURSE OF ASTHMA IN PREGNANCY

The natural history of asthma during pregnancy is extremely variable. In a prospective cohort study of 366 pregnancies in 330 women with asthma, the asthma worsened during pregnancy in 35%.[636] A prospective cohort study of 1,739 pregnant women showed an overall improvement in 23% and deterioration in 30.3%.[637] 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.[638] There is also some evidence that the course of asthma is similar in successive pregnancies.[636, 639] A systematic review showed no effect of pregnancy or stage of pregnancy on FEV_1.[640] 1+ 2+

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.[641, 642] Severe asthma is more likely to worsen during pregnancy than mild asthma,[636] but some patients with very severe asthma may experience improvement, whilst symptoms may deteriorate in some patients with mild asthma. In a large US study, the rates of asthma exacerbation were 13%, 26% and 52% in those with mild, moderate and severe asthma respectively.[637] The corresponding rates of hospitalisation were 2%, 7% and 27%. 2- 2+

A systematic review concluded that, if symptoms do worsen, this is most likely in the second and third trimesters, with the peak in the sixth month.[639] 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.[636] 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.[643] 2+

9.1.2 EFFECT OF ASTHMA IN PREGNANCY

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.[644] 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.[645] 2^{++} 2^{+}

Uncontrolled asthma is associated with many maternal and fetal complications, including hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, complicated labour, fetal growth restriction, pre-term birth, increased perinatal mortality, and neonatal hypoxia.[637, 646-649] 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 pre-term delivery and low birth weight were higher in women with more severe asthma necessitating admission.[650] 2^{+}

A large prospective cohort study comparing women with moderate and severe asthma with women without asthma found the only significant difference was an increased Caesarean section rate (OR 1.4, 95% CI, 1.1 to 1.8).[637] Logistic regression analysis of 2+ 2^{++}

the severe group showed an increased risk of gestational diabetes (AOR 3, 95% CI, 1.2 to 7.8) and pre-term delivery <37 weeks (AOR 2.2 (95% CI, 1.2 to 4.2)) but this could have been an effect of corticosteroids. In the Yale asthma study no effect of asthma symptoms or severity was seen on pre-term delivery but oral steroids increased the rate of pre-term delivery and reduced gestation by 2.2 weeks AOR 1.05 (95% CI, 1.01 to1.09).[651] Daily asthma symptoms were associated with an increased risk of fetal growth restriction (AOR 2.25, 95% CI, 1.25 to 4.06) and there was a 24% increase with each increased symptom step. This is supported by a systematic review of four studies that concluded asthma exacerbation in pregnancy increases the risk of low birth weight.[652] The RR was 2.54 (95% CI, 1.52 to 4.25) compared to women without asthma. In a large cohort study of 2123 women with asthma, there was an association of both mean FEV_1 and mean FEV_1 <80% predicted with gestational hypertension, pre-term delivery <37 weeks, <32 weeks and low birth weight.[653]

In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[636, 641] Pregnancy should therefore be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute exacerbation. 2+

C **Monitor pregnant women with moderate/severe asthma closely to keep their asthma well controlled.**

B **Women should be advised of the importance of maintaining good control of their asthma during pregnancy to avoid problems for both mother and baby.**

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

9.2 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.[654] Available studies give little cause for concern regarding treatment side effects (*see section 7.2*) 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 five confidential enquiries into maternal deaths in the UK (covering 1994-2008) there were 22 deaths from asthma.[655-658] [REF Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118(Suppl. 1):1–203] 2^+

Oxygen should be delivered to maintain saturation 94-98% in order to prevent maternal and fetal hypoxia.[434] When interpreting arterial blood gases in pregnancy it should be remembered that the progesterone-driven increase in minute ventilation may lead to relative hypocapnia and a respiratory alkalosis, and higher PaO_2 [659, 660] but oxygen saturations are unaltered.[661] Acidosis is poorly tolerated by the fetus. 4

Drug therapy should be given as for a non-pregnant patient with acute asthma, including nebulised β_2 agonists and early administration of steroid tablets.[636, 642, 643, 646, 647] In severe cases, intravenous β_2 agonists, aminophylline, or intravenous bolus magnesium sulphate can be used as indicated.[662] 2+

Continuous fetal monitoring should be performed when asthma is uncontrolled or severe, or when fetal assessment on admission is not reassuring. Consideration should be given to early referral to critical care services as impaired ventilatory mechanics in late pregnancy can lower functional residual capacity and may result in earlier oxygen desaturation.[663]

Pregnant women may be more difficult to intubate due to anatomical changes especially if they have pre-eclampsia.[664]

C **Give drug therapy for acute asthma as for the non-pregnant patient including systemic steroids and magnesium sulphate.**

D **Deliver high flow oxygen immediately to maintain saturation 94-98%.**

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, with early referral to critical care physicians for women with acute severe asthma.

9.3 DRUG THERAPY IN PREGNANCY

In general, the medicines used to treat asthma are safe in pregnancy.[665, 666] A large UK population based case control study found no increased risk of major congenital malformations in children of women receiving asthma treatment in the year before or during pregnancy.[667] 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^+

B **Counsel women with asthma regarding the importance and safety of continuing their asthma medications during pregnancy to ensure good asthma control.**

9.3.1 B_2 AGONISTS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to short-acting β_2 agonists.[665-669] 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 subjects, found no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, apgar scores or labour/delivery complications.[670] A case control study including 2,460 infants exposed to short-acting β_2 agonists found no increased risk of congenital malformations in exposed infants.[637] 2^+ 3

With regard to long-acting β_2 agonists (LABAs), evidence from prescription event monitoring suggests that salmeterol is safe in pregnancy[671] and although there are some data on formoterol, numbers are small.[672] Systematic review of studies including 190 exposures to LABA demonstrated no increased risk of congenital malformations, pre-term delivery or pre-eclampsia.[673] A case control study including 156 infants exposed to LABA found no increased risk of major congenital malformations.[667] As in other settings, LABAs should be used with an inhaled corticosteroid, ideally as a combination product.[674] 2^+

Data on the use of combination products in pregnancy are scarce although there are no theoretical reasons why these would be harmful than the same agents given separately. There are some safety data for seretide (salmeterol/fluticasone) but with small numbers.[675]

B **Use short acting β_2 agonists as normal during pregnancy.**

C **Use long acting β_2 agonists (LABA) as normal during pregnancy.**

9.3.2 INHALED STEROIDS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to inhaled steroids.[665, 667, 673, 676-680] [681-684] A meta-analysis of four studies of inhaled corticosteroid use in pregnancy showed no increase in the rate of major malformations, pre-term delivery, low birth weight or pregnancy-induced hypertension.[685] The UK case control study included 1,429 infants exposed to inhaled steroids and found no increased risk of major congenital malformations.[667]

1+
1-
2-
2^{+}
2^{++}

Inhaled anti-inflammatory treatment has been shown to decrease the risk of an acute attack of asthma in pregnancy[643] and the risk of readmission following asthma exacerbation.[642] A randomised placebo controlled trial of inhaled beclometasone versus oral theophylline in moderate asthma in pregnancy showed no difference in the primary outcome of one or more asthma exacerbations resulting in medical intervention, but inhaled beclometasone was better tolerated.[637]

2^{+}

B **Use inhaled steroids as normal during pregnancy.**

9.3.3 THEOPHYLLINES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.[665, 686]

2^{+}

For women requiring 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.[687]

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.**

9.3.4 STEROID TABLETS

There is much published literature showing that steroid tablets are not teratogenic[646 665, 688] but a slight concern that they may be associated with oral clefts. Data from several studies have failed to demonstrate this association with first trimester exposure to steroid tablets[688, 689] but one case control study found a significant association, although this increase is not significant if only paired controls are considered.[690] Although one meta-analysis reported an increased risk,[691] a prospective study by the same group found no difference in the rate of major birth defects in prednisolone-exposed and control babies.[691] A more recent population based case control study revealed a crude odds ratio of corticosteroid exposure from four weeks before through to 12 weeks after conception of 1.7 (95% CI, 1.1-2.6) for cleft lip.[692] Another case control study including 262 exposed infants found no such association, although this was not limited to first trimester exposure.[667]

2^{+}
2^{-}

The association is therefore not definite and even if it is real, the benefit to the mother and the fetus of steroids for treating a life threatening disease justify the use of steroids in pregnancy.[648, 659] Moreover, the various studies of steroid exposure include many patients with conditions other than asthma, and the pattern of steroid use was generally as a regular daily dose rather than as short courses, which is how asthma patients would typically receive oral steroids.

2^{+}

Prednisolone is extensively metabolized by placental enzymes so only 10% reaches the fetus, making this the oral steroid of choice to treat maternal asthma in pregnancy. Pregnant women with acute asthma exacerbation are less likely to be treated with steroid tablets than non-pregnant women.[654] Failure to administer steroid tablets when indicated increases the risk of ongoing exacerbation and therefore the risk to the mother and her

2^{+}

fetus.

Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia, pre-term labour[645] and fetal growth but severe asthma may be a confounding variable.[693] 2+

C **Use steroid tablets as normal when indicated during pregnancy for severe asthma. Steroid tablets should never be withheld because of pregnancy. Women should be advised that the benefits of treatment with oral steroids outweigh the risks.**

9.3.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

Data regarding the safety of leukotriene antagonists (LTRA) in pregnancy are limited. A case control study with 96 cases exposed to LTRAs found no increased risk of major malformations between women with asthma exposed to LTRA and women with asthma taking only beta agonists.[693] A systematic review found no increased risk of malformations or pre-term delivery in nine exposed women.[651, 673] Three studies looking at infant outcomes in women exposed to LTRAs (2 in women taking montelukast) showed no increased risk of congenital malformations.[694-696]] 2- 4 2+ 2++

C **If leukotriene antagonists are required to achieve adequate control of asthma then they should not be withheld in pregnancy.**

9.3.6 CHROMONES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to chromones.[673 665, 693] 2+

C **Use chromones as normal during pregnancy.**

9.3.7 IMMUNOMODULATION THERAPY

There are as yet no clinical data on the use of omalizumab for moderate-severe allergic asthma in pregnancy. There are some reassuring animal studies re teratogenicity (classed as FDA category B). A registry of pregnancy exposures is being undertaken.

9.4 MANAGEMENT DURING LABOUR

Acute attacks of asthma are very rare in labour, perhaps 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 usual labour analgesia.

In some studies there is an association between asthma and an increased Caesarean section rate,[645, 697, 698] but this may be due to planned Caesarean sections[643] or inductions of labour rather than due to any direct effect of asthma on intrapartum indications. A large prospective cohort study comparing women with moderate and severe asthma with women without asthma found the only significant difference was an increased Caesarean section rate (OR 1.4, 95% CI 1.1-1.8).[637] 2+

Data suggest that the risk of postpartum exacerbation of asthma is increased in women having Caesarean sections.[697] 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.[687] Prostaglandin F2α (carboprost/hemobate®) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.[687] Although ergometrine may cause bronchospasm particularly in association with general anaesthesia,[687] 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.[699]

✓ 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 F2α with extreme caution in women with asthma because of the risk of inducing bronchoconstriction.**

9.5 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.[700] There is less experience with newer agents. Less than 1% of the maternal dose of theophylline is excreted into breast milk.[700] 2^+

Prednisolone is secreted in breast milk, but milk concentrations of prednisolone are only 5-25% of those in serum.[385] The proportion of an oral or intravenous dose of prednisolone recovered in breast milk is less than 0.1%.[701-703] 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.[701 702, 703] 2^+ 3

C **Encourage women with asthma to breastfeed.**

C **Use asthma medications as normal during lactation, in line with manufacturers' recommendations.**

10 Occupational asthma

10.1 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.[704-706] It is now the commonest industrial lung disease in the developed world with over 400 reported causes.[707-709] 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.**

10.2 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.[710-718]

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.[710, 711, 713, 715-721] 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.[722-725] 2+

10.3 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. Asthma symptoms reported by the use of a questionnaire to be better on days away from work have been shown to have a sensitivity of 58-100% for subsequently validated occupational asthma and specificities of between 45-100%, with wheeze and shortness of breath the most commonly reported symptoms.[726] There is also some evidence, that free histories taken by experts may have a higher sensitivity than patient questionnaires administered by experts, but their specificity may be lower for a diagnosis of occupational asthma.[726] 4

One study notes a relatively low positive predictive value of work related symptoms.[727]

✓ 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.

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.[728-735] 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.[736] 3?

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

10.3.1 SENSISTIVITY AND SPECIFICITY OF SERIAL PEAK FLOW MEASUREMENTS

In a meta-analysis of 31 papers in which a variety of reference standards were used, the 'pooled' sensitivity and specificity of serial PEF measurements were 75% and 79% respectively. Higher values (82% and 88%) were obtained from pooling studies where more complete series of measurements had been made, achieved by 61% of the analysed population. Visual analysis was more sensitive (78% vs 71%) but less specific (69% vs 91%) than computer-based methods.[735] 2-

There are several validated methods for interpreting serial PEF records for a diagnosis of occupational asthma which differ in their minimal data requirements. The original discriminant analysis method requires:

- At least three days in each consecutive work period
- At least four evenly spaced readings per day.
- At least three series of consecutive days at work with three periods away from work (usually about three weeks.[737]

Shorter records without the requirement for three consecutive days at work can be analysed using the area-between curves (ABC) score. This requires at least eight readings a day on eight work days and 3 rest days.[738] A statistical method using timepoint analysis in addition requires the waking time to be similar on rest and work days.[739] 2+ 3

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

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

10.3.2 IGE TESING IN THE DIAGNOSIS OF VALIDATED CASES OF OCCUPATIONAL ASTHMA

A review by the British Occupational Health Research Foundation[726] states that, "...the respective sensitivities and specificities of the ability of skin prick or serological tests to detect specific IgE vary between allergens and depend on the setting of positive cut-offs. The sensitivities and specificities of serum specific IgE antibodies to low molecular weight agents depends on whether the antibodies have been properly characterised and the 4

availability of appropriate hapten-conjugates. The presence of specific IgE confirms sensitisation but alone does not confirm the presence of occupational asthma, nor necessarily its cause." The review concluded that skin prick testing or tests for specific IgE should be used in the investigation of occupational asthma due to high molecular weight agents but are less sensitive for detecting specific IgE and occupational asthma caused by low molecular weight agents. In neither case are the tests specific for diagnosing asthma.[726]

D **Skin prick testing or tests for specific IgE should be used in the investigation of occupational asthma due to high molecular weight agents**

D **Skin prick testing or tests for specific IgE should not be used in the investigation of occupational asthma due to low molecular weight agents**

10.3.3 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). A single measurement of non-specific reactivity has been shown to have only moderate specificity and sensitivity for the validation of occupational asthma and changes in non-specific reactivity at and away from work alone have only moderate sensitivity and specificity for diagnosis.[726, 740] 3 4

D **A single measurement of non-specific reactivity should not be used for the validation of occupational asthma.**

10.3.4 SPECIFIC BRONCHIAL PROVOCATION TESTING

Specific inhalation challenges (SIC) with occupational agents should only be carried out in hospitals with expertise in using occupational agents, and should always include; (i) a control challenge on a separate day (ii) a gradual increase of exposure to the suspected occupational agent (iii) close monitoring of airway calibre during the challenge and for at least six hours after the end of exposure. 4

A positive Specific Inhalation Challenge (SIC) is one in which the FEV_1 falls by ≥15% from baseline; either within the first hour after exposure (an immediate reaction) or later (a late reaction) or both. Alternatively for late reactions, two measurements below the 95% CI for three days away from exposure have been validated as a positive test. [Stenton 1994]. Equivocal reactions can sometimes be clarified by finding changes in non-specific bronchial responsiveness, sputum eosinophils or exhaled nitric oxide. Specific Inhalation Challenge is generally a safe procedure; excessive reactions are rare with <3% of patients needing repeated doses of a bronchodilator and steroid treatment. ?

The sensitivity and specificity of SIC are high but not easily quantified as the method is usually used as the reference standard for the diagnosis of occupational asthma. False negative tests also occur, and SIC testing may be of less value where complex workplace exposures cannot be replicated in the laboratory. Specific Inhalation Challenge remains the gold standard for making a diagnosis of occupational asthma.

10.3.5 SPUTUM EOSINOPHILIA

Eosinophilic bronchial inflammation can be assessed by cell counts in fresh sputum, induced by inhaling hypertonic saline.[726] Studies have shown that induced sputum eosinophilia is not sufficiently sensitive or specific to help in the diagnosis of occupational asthma although it may help in the interpretation of equivocal SIC reactions.[726, 740, 741] In the clinical setting the absence of sputum eosinophilia does not exclude a diagnosis of occupational asthma.[726] 2+ 3 4

10.3.6 EXHALED NITRIC OXIDE

The 2010 review by the British Occupational Health Research Foundation states that, "...the measurement of exhaled nitric oxide produced by inflammatory and epithelial cells in the respiratory tract is non-invasive and has been studied extensively in non-occupational asthma, although it has not been fully validated as an effective diagnostic test for occupational asthma".[726] The review concluded that the role of exhaled nitric oxide measurements in the diagnosis of occupational asthma in this setting is not established.[726] 4

10.4 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.[730, 742-750] 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.[751-753]

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.[754-756] The risk of unemployment may fall with increasing time after diagnosis.[757] 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.[755, 756] Approximately one third of workers with occupational asthma have been shown to be unemployed up to six years after diagnosis.[753-761] 2-

11 Organisation and delivery of care, and audit

11.1 CARE PATHWAYS

Clinical care pathways are, "...structured multidisciplinary care plans used by health services to detail essential steps in the care of patients with a specific clinical problem. They aim to link evidence to practice and optimise clinical outcomes whilst maximising clinical efficiency."[762]

There is little high quality evidence from randomised trials addressing the impact of care pathways for asthma. Pathways have usually been implemented via a training session or programme. Two interventions, one to establish pathways for the management of people with high risk asthma in UK primary care, the other to establish pathways for children with acute and chronic asthma in New Zealand primary care, led to non-significant reductions in A&E attendance and hospitalisation.[763, 764] Pathways for inpatient care can improve processes of care, such as prescription of oral prednisolone and use of written asthma action plans in children,[765] and can reduce length of stay for children,[766, 767] but have not improved follow up in general practice after discharge.[768] 1+ 1-

Further well conducted studies are needed to define the benefits of care pathways for asthma. These should include large, suitably powered, studies to clarify the impact of pathways promoting systematic management of people with high risk asthma in UK primary care, and pathways integrating asthma care across the primary/secondary care interface.

11.2 EDUCATING PHYSICIANS

There is strong evidence that educating clinicians can improve health outcomes for patients. Two large Cochrane systematic reviews (covering all clinical conditions, not just asthma) show that:[769, 770] 1++

- educational outreach visits (for example training visits to general practices) lead to small to moderate improvements in outcomes[769]
- mixed interactive and didactic education is more effective than either alone.[770]

Several models of clinician education specifically for asthma have been tested in randomised trials and these broadly support the conclusions of the two Cochrane reviews above. The most consistently effective of these for asthma comprises educational outreach visits which deliver multifaceted training, based on theoretical models of behaviour change, including training in consultation styles and delivery of key messages. Several studies have tested the American-developed Physician Asthma Care Education (PACE) paediatric asthma programme,[771, 772] or adaptations of it for Australian[773] and UK[774] practice, and have shown reductions in A&E visits,[771] improved symptom control[774] and increased use of written asthma action plans[773]. The PACE intervention has not been tested for adult populations, however, and there is little experience of its use in the UK. 1++ 1+

In the USA, peer education comprising intensive training of a 'practice asthma champion' who in turn trained and supported colleagues, led to fewer asthma exacerbations in children.[775] Practice asthma champions were trained in pharmacotherapy and physician behaviour change techniques, and received ongoing support for their role as a 'change agent'. They received guideline summaries, key targets for their physician colleagues and feedback on their colleagues' performance along with monthly support from a nurse coordinator. When this peer education programme was combined with intensively trained outreach nurses implementing patient reviews (the Planned Care Model), children experienced fewer asthma symptoms and fewer exacerbations. 1+

These interventions illustrate that, to effect change, interventions need to be of sufficient

intensity to engage with, and change, the way practices are organised

Less intensive educational interventions, such as brief outreach visits comprising simple group education are less effective, showing no impact on symptoms, quality of life, or health care use.[776-779] 1+ 1-

Remote IT educational interventions, such as remote spirometry training,[780] show promise but have not been widely tested.

Further large scale studies, carried out in the UK, are needed to test the impact of intensive educational interventions such as adapted PACE and peer education programmes

B **Training for primary care clinicians should include educational outreach visits using multifaceted programmes that include consultation training including goal setting**

11.3 ASTHMA CLINICS

11.3.1 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.[428] Benefits include reduced school or work absence, reduced exacerbation rate, improved symptom control and reduced attendance at the emergency department.[781, 782] Proactive structured review, as opposed to opportunistic or unscheduled review, is associated with reduced exacerbation rate and days lost from normal activity.[783-785] 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.[783, 786, 787] 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**

✓ It is good practice to audit the percentage of patients reviewed annually. Consider focussing on particular groups such as those overusing bronchodilators, patients on higher treatment steps, those with exacerbations or from groups with more complex needs.

11.3.2 PRIMARY CARE ASTHMA CLINICS

Primary care asthma clinics can be defined as a, "...pro-active system of care sited in primary care (e.g. GP clinic) which occupies a defined and often regular clinical session for the routine review of patients with asthma".[788]

A systematic review identified only three RCTs testing the impact of primary care asthma clinics and these trials were small, of poor quality and more than ten years old.[788] The evidence of benefit from these trials was limited to a small reduction in night time waking, a surrogate marker of asthma control. There was no evidence of improvement in important outcomes such as hospitilisation, A&E attendances, or quality of life and no evidence that such clinics were cost effective. There is thus insufficient evidence to support the provision of primary care-based asthma clinics as a way of improving patient outcomes. 1++

There is, however, no evidence that these clinics do harm. Asthma reviews in primary care may best be carried out during routine surgeries rather than a dedicated asthma clinic.

11.3.3 SPECIALIST ASTHMA CLINICS

The evidence for whether specialist asthma clinics improve outcomes for people with severe or difficult asthma was limited to one systematic review, including 17 studies, many of poor quality and underpowered.[789] The review focussed on psycho-educational interventions mostly for adults and adolescents (16 and above) with difficult or severe asthma, so provided incomplete evidence on the ideal content of such clinics. The review found that these interventions reduced hospitalisations (but not A&E attendances) in adults and children, and improved symptoms in children. The authors concluded that the strength of evidence was insufficient to change practice. 2+

Further trials testing the impact of clinics run by specialists in asthma care are needed.

C **Consider including psycho-educational interventions in clinics for adults and children with difficult asthma.**

11.4 TELEHEALTHCARE INTERVENTIONS

Telehealthcare interventions for asthma comprise a range of types including telephone calls; video-conferencing; internet; mobile phone apps; text messaging, or a combination of these. A systematic review of telehealthcare interventions for asthma showed no improvement in quality of life but a significant reduction in hospital admissions over 12 months (OR 0.21, 95% CI 0.07 to 0.61) with the predominant effect on more severe asthma managed in secondary care.[790] Subsequent studies have shown less consistently beneficial effects, including improvements in symptom control but not healthcare use,[791-795] or no benefits in either.[796] 1++ 1+

Overall, telehealthcare interventions that include advice from a specialist asthma nurse appear to improve outcomes. However, further studies of telehealthcare interventions are needed to disentangle the effects of the technology itself from the addition of specialist nurse advice to patients.

B **Consider telehealthcare interventions for asthma.**

11.5 SCHOOL-BASED INTERVENTIONS

Most school-based asthma interventions focus on education delivered by adults (usually health professionals) to schoolchildren.[797] Other approaches include peer education, whereby students are trained and then, in turn, train their peers,[619, 798] web-based programmes,[799] or directly observed therapy (DOT) of inhaled steroid medication,[635] which may additionally include education of parents.[800] One study tested a multifaceted intervention combining education of schoolchildren with academic detailing of their doctor, including provision of self management plans.[801] Most evaluations have been based in the USA, often involving minority ethnic groups infrequently seen in the UK.

Education for children in schools generally led to improvements in symptom control and quality of life, but had no impact on healthcare use.[797] Peer education was effective for adolescents[619] but not pre-teens.[798] DOT in two studies improved symptom control.[635, 800] Of all the school-based interventions tested, Brezzese's multifaceted programme had the most impact, improving symptoms, quality of life, emergency department use and hospitalisation 1+ 1- 2+

B **Consider school-based asthma education programmes comprising a multifaceted approach targeting children's health professionals as well as children themselves.**

11.6 ETHNICITY/CULTURE-BASED INTERVENTIONS

The majority of studies examining ethnicity and culture-based interventions that tailor asthma education for people from minority ethnic groups have been carried out in the USA. These are reviewed in Section 12 on Self-Management, which gives detail on aspects of tailoring. A review of system-level interventions concluded that the most effective at reducing further health care use were those that targeted people who had attended emergency care or had been hospitalised.[802] Interventions were usually intensive, multi-session clinic-based programmes. They were nurse-led or used experts including pharmacists or allergy specialists.[802] These findings mirror the little work published in the UK, which showed that a primary care based clinic was ineffective,[803] whilst a specialist nurse led intervention targeted at those attending emergency care reduced further unscheduled care, albeit less in people from ethnic minority groups than in those from white populations.[804] ?

Further studies examining the impact of interventions on people from minority ethnic groups in the UK are needed.

C **Establish intensive clinic-based programmes for people from ethnic minority groups who have attended emergency care.**

11.7 LAY-LED INTERVENTIONS

Educational interventions led by lay, rather than health professionals, have become popular in the last decade. The NHS Expert Patient Programme – a six week group education programme - is an example. Programmes are usually generic – ie, people attending may have a range of conditions, not specifically asthma.

A systematic review including 17 randomised trials of lay-led self-management education programmes was reviewed.[805] Only two of the included trials specifically addressed people with asthma, and these found no improvements in breathlessness, health related quality of life, health care use, days/nights spent in hospital, and no change in disease specific knowledge. Overall, lay-led self-management interventions may lead to small, short-term improvements in participants' self-efficacy, self-rated health, cognitive symptom management, and frequency of aerobic exercise. There is, however, currently no evidence to suggest that these interventions alter healthcare use or are cost-effective. 1+

A **Lay-led self-managment programmes for people with asthma are not currently recommended.**

11.8 PHARMACIST-LED INTERVENTIONS

Pharmacists have opportunities to provide education for people with asthma, and furthermore, may be able to identify those with poor asthma control. The body of evidence for pharmacy-based interventions is, however, methodologically weak or of limited relevance. Two systematic reviews were assessed, both of which were of limited relevance and methodologically poor. One review addressed interventions in low and middle income countries, while another addressed pharmacy interventions more generally.[806, 807]

Interventions generally involved educating community pharmacists to, in turn, educate patients.[808-810] Other models or elements included follow-up reviews for newly prescribed medication,[811] or identifying those with poor control by using questionnaires such as the Asthma Control Test,[810] or searching prescribing databases for patients using large numbers of reliever inhalers,[812] and targeting reviews or referral to general practitioners.[812]

Overall, the most consistent improvements in outcomes were seen in inhaler technique,[808-810] with a few studies showing improvements in reduced dispensing of, or need for, 1+ 1-

reliever inhalers.[810, 812] There was no convincing evidence of reductions in healthcare use.

Further high quality randomised trials testing pharmacist-led interventions to improve asthma outcomes are needed

C **Consider training pharmacists to provide education for people with asthma, particularly targeting those with poorly controlled asthma.**

12 Supported self-management

Self-management has been defined as, "...task(s) that individuals must undertake to live with chronic conditions...", including, "...dealing with medical, role and emotional management of their conditions."[813] In the context of asthma, self-management has focussed on the medical aspects of living with a variable condition and emphasised the importance of recognising and acting on symptoms and signs of deterioration. Personalised asthma action plans (PAAPs), however, need to be seen in the context of the broader challenges of living with asthma.[814]

12.1 THE EVIDENCE BASE

There is a substantial body of evidence to show that self-management education incorporating written PAAPs improves health outcomes for people with asthma.[428, 485, 789, 797, 802, 815-832] These 23 systematic reviews represent a total of 261 RCTs which encompass evidence from a broad range of demographic, clinical and healthcare contexts. In addition, 35 RCTs provide further evidence about self-management in pre-school children,[772, 833-840] ethnic minorities,[620, 803, 804, 841-849] and primary care-based populations.[774, 803, 850-857] 1+

12.2 EFFECTIVENESS OF SUPPORTED SELF-MANAGEMENT

Self-management education delivered to adults or children with asthma (and/or their parents/carers):

- reduces emergency use of healthcare resources, including A&E visits, hospital admissions and unscheduled consultations[428, 789, 817, 821-823, 825, 858]
- improves markers of asthma control, including reduced symptoms and days off work, and improves quality of life.[428, 817, 818, 823, 825, 827, 859]

1++

Patients with all severities of asthma were included in these reviews, though some focussed specifically on people who had attended A&E departments,[858] or with severe or difficult asthma.[789] Most self-management education was delivered in healthcare settings, but some specifically evaluated school,[797] home,[830] or community-based interventions.[831] Typically, education was delivered by healthcare professionals either in individual consultations or group settings, but some reviews included technologically-based interventions,[819, 820] or were part of community health interventions for deprived and/or ethnic minority groups.[802, 832]

12.3 COMPONENTS OF A SELF-MANAGEMENT PROGRAMME

Successful programmes varied considerably, but core components included structured education, reinforced with written PAAPs, though the duration, intensity and format for delivery may vary.

12.3.1 PATIENT EDUCATION

Education is a core component of effective self-management programmes in adults.[428, 789, 858] and children.[821-825] There is evidence that educational interventions that were supported by a written PAAP and regular professional review were more effective than less intensive regimes.[428, 818, 822, 824, 825] 1++

IT-based education has been shown to have potential, but as yet there is no consistent evidence on which to advise about format, target audiences or the context in which it should be delivered.[819]

12.3.2 PERSONALISED ASTHMA ACTION PLANS

Written PAAPS are crucial components of effective self-management education.[26, 428, 817, 827, 828, 858, 859] One systematic review has identified features of PAAPs associated with 1++ 1+

beneficial outcomes *(see Table 15)*.[817] These include:

- specific advice about recognising loss of asthma control, though this may be assessed by symptoms or peak flows or both.[26, 817, 818] In children, symptom-based written plans are effective in reducing emergency consultations for asthma, though (in older children) peak-flow based plans may be as effective for other outcomes[827, 859]
- 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.[817]

A **All people with asthma (and/or their parents or carers) should be offered self-management education which should include a written personalised asthma action plan and be supported by regular professional review.**

A **In adults, personalised asthma action plans may be based on symptoms and/or peak flows: symptom- based plans are generally preferable for children.**

Table 15. Summary of the key components of a personalised asthma action plan (adapted from Gibson et al)[817]

Component of an action plan	Result	Practical considerations
Format of action points: Symptom vs peak flow triggered Standard written instructions Traffic light configuration	Similar effect Consistently beneficial Not clearly better than standard instructions	Asthma UK personalised asthma action plans include both symptom triggers and peak flow levels at which action should be taken.
Number of action points 2-3 action points 4 action points	Consistently beneficial Not clearly better than 2-3 points	Commonly used action pointshave been: PF <80% best: increase inhaled steroids PF <60% best: commence oral steroids and seek medical advice PF <40% best: seek urgent medical advice
Peak expiratory flow (PEF) levels Based on percentage personal best PEF Based on percentage predicted PEF	Consistently beneficial Not consistently better than usual care	Personal best should be assessed once treatment has been optimised and peak flows are stable. Best peak flow should be updated every few years in adults, and more frequently in growing children.
Treatment instructions Individualised using inhaled and oral steroids Individualised using oral steroids only Individualised using inhaled steroids	Consistently beneficial Insufficient data to evaluate Insufficient data to evaluate	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. Increasing inhaled steroids is ineffective if patients are already taking moderate or high doses (≥400mcg daily) and these patients should be advised to move straight to the oral steroid step. Those on low doses (e.g.200mcg) of inhaled steroids may be advised to increase the dose substantially (eg to 1,200mcg daily) at the onset of a deterioration.[784] Patients who have stopped medication should be reminded to recommence their inhaled steroids.

12.4 SELF-MANAGEMENT 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.

12.4.1 SCHOOLCHILDREN

School-based asthma education has been shown to:

- improve process outcomes (knowledge, self-efficacy, self-management behaviours)[797] 1++
- improve markers of asthma control (number of days and nights with asthma symptoms, school absences, asthma-related quality of life.[797, 829]

There was considerable heterogeneity in the school-based interventions which incorporated combinations of classroom teaching for all pupils, peer support groups, individual education sessions with school nurses, interactive computer programmes, and involvement of parents.[797]

A **School health services should consider providing in-school asthma self-management education programmes.**

12.4.2 PRE-SCHOOL CHILDREN

There is a paucity of evidence about effective self-management strategies delivered to parents of pre-school children. Trials recruiting only pre-school children (5 years of age or under) showed no impact on emergency use of healthcare resources, including A&E visits, hospital admissions and unscheduled consultations,[834, 839] and no[834] or limited[839] reduction in symptoms, despite increased ownership of PAAPs.[839] 1-

Other trials including children up to the age of eight years showed only small and often transient effects of doubtful clinical significance.[772, 833, 836-838]

12.4.3 SELF-MANAGEMENT IN SECONDARY CARE

There is good evidence that self-management education targeted at people who have a history of A&E attendances[858], or hospital admissions[804, 860] can reduce subsequent use of health care resources. Self-management education delivered prior to discharge can reduce readmissions.[861-863] 1++

One wide-reaching review of the evidence for self-management in severe or difficult ashma concluded that provision of psycho-educational interventions (especially those incorporating formal self-management) may reduce hospital admissions and, in children, improve symptoms.[789] 1+

A **Prior to discharge, in-patients should receive personalised asthma action plans, given by health care professionals with relevant expertise in asthma management.**

12.4.4 SELF-MANAGEMENT PROGRAMMES IN PRIMARY CARE

Studies of self-management interventions based in primary care have shown that they can:

- reduce emergency use of healthcare resources, including A&E attendances, hospital admissions and unscheduled consultations[803, 853] 1+
- improve markers of asthma control.[803, 850, 851, 853-856, 864] 1++

Implementation is challenging. The improved asthma control demonstrated in trials of interventions delivered by members of the research team[803, 853] or in a centrally administered initiative[855 854] are reflected in some [850, 851, 856, 864] but not all[774, 857] trials in which members of the practice team are trained to deliver self-management education in routine clinical care. 1+

One study showed no difference in outcomes when self-management education was delivered by lay people compared to practice asthma nurses.[852]. US based studies suggest that in deprived and/or ethnic communities the involvement of community health workers reduces A&E department attendance.[831] 2

A **Self-management education, supported by a written asthma action plan, should be offered to all patients on general practice 'active asthma' registers.**

A **Primary care practices should ensure that they have trained professionals and an environment conducive to providing supported self-management.**

✓ Implementation is challenging in the non-specialist environment of primary care and needs to consider not only specific training in self-management skills, but also the logistics of when and how self-management education is incorporated into routine care. Strategies that have been used in effective interventions include:

- the use of proactive triggers to ensure routine reviews
- structured protocols for asthma reviews
- support of community pharmacists
- routine mailing of educational resources
- telephone calls to provide on-going support and advice
- IT-based education and monitoring
- involvement of community workers (in deprived and/or ethnic minority communities).

12.4.5 SELF-MANAGEMENT PROGRAMMES IN ETHNIC MINORITY GROUPS

Interventions specifically designed for ethnic minority groups, predominantly deprived African-American, Hispanic or Puerto-Rican populations from US inner cities,[620, 802, 841-848] can: 1++

- reduce emergency use of healthcare resources, including A&E attendances, hospital admissions and unscheduled consultations[620, 802, 832, 844, 846] [REFS Bailey 2009, Press 2012, Joseph 2007, Flores 2009, Griffiths 2004, La Roche 2006] 1+ 1- 2+
- improve markers of asthma control[620, 802, 832, 841, 842, 846]
- improve process outcomes (knowledge).[802, 832, 845, 847]

In two UK-based RCTs, however, interventions which provided appropriate language materials and were delivered by bilingual professionals were reported as showing no[803] or less[804] benefit on healthcare outcomes in the South Asian population compared to the benefits seen in the white European population. 1++ 1+

There is insufficient evidence to identify all the aspects of cultural tailoring which may potentially contribute to effectiveness, but addressing language barriers (eg, with appropriate language materials and bilingual support) is not sufficient to enable an intervention to deliver equivalent outcomes in an ethnic minority group compared to a white European group.[803, 804] 1++ 1+

The strategies employed are varied and include community-based neighbourhood

projects,[843, 846, 847] family-based education,[844] nurse-led home visits,[842] IT-based programmes,[620, 841, 845] and school-based educational interventions.[620, 848] No one strategy stands out as being always effective, or always ineffective. Lack of engagement with programmes and high levels of attrition are major barriers.[842, 843, 846, 847] Reconfiguration of the supporting healthcare system appears to increase the impact.[802] 1++ 1+ 1-

B **Culturally appropriate supported self-management education should be provided for people with asthma in ethnic minority groups. Addressing language barriers is insufficient.**

✓ Consideration should be given to:

- translation of materials into local languages with ethnically appropriate pictures
- asthma educators fluent in local languages
- locating contingency plans within cultural resources
- inclusion of culturally specific beliefs and practices
- reference to culturally appropriate role models
- involvement of a local community health worker.

12.5 ADHERENCE AND CONCORDANCE

The term adherence (or compliance) embodies a traditional model of prescriptive care which refers to the objectively measured usage of prescribed medication, or frequency of monitoring. 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.[865] Sharing decision making and achieving concordance improves (though does not guarantee) adherence.[866]

Adherence with monitoring and treatment

Adherence with regular monitoring with peak flow meters, even in clinical drug trials is poor, with recorded daily use as low as 6%.[867, 868] The lack of evidence supporting long-term peak flow monitoring,[869-872] however, does not negate the use of home peak flow monitoring at critical times: for example, at diagnosis and initial assessment, when assessing response to changes in treatment, as part of a PAAP during exacerbations.[872] Comparison should be with the patients' best peak flow (not predicted).[817]

Non-adherence may be intentional and/or unintentional and may be understood as a combination of perceptual factors (eg, beliefs about illness and treatment) and practical factors (capacity, resources and opportunity).[873] It is thought that between a third and a half of all medicines prescribed for long-term conditions are not taken as recommended[873] and poor adherence should be considered when there is a failure to control asthma symptoms.

Patient self-reporting is simple, inexpensive and feasible in most clinical settings, though typically overestimates adherence to regular medication. [Nunes 2009] Being non-judgemental, and asking specific questions about use of a treatment over a short time period (eg, in the last week/month) can help elicit an accurate response. [Nunes 2009] Computer repeat-prescribing systems, widely available in general practice, provide a useful indication of adherence with prescribed asthma regimens. Electronic monitoring, whilst the most accurate method, is only practical in clinical drug trials.

✓ Computer repeat-prescribing systems provide a practical index of adherence and should be used in conjunction with a non-judgemental discussion about adherence.

12.5.1 THE EVIDENCE BASE

Six systematic reviews were identified that evaluated interventions to improve compliance, one specifically in asthma,[874] and five including a number of long-term conditions including asthma.[875-879] The body of evidence represents 26 unique asthma trials.

12.5.2 INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

The interventions were divided into 'informational' interventions (individual and/or group sessions with or without written/electronic materials), or 'behavioural' interventions (including dosage simplification, regular monitoring including assessment of medication use with feedback, psychological therapies) or a combination of these two approaches.

Interventions to improve adherence have modest effects on adherence [874, 875, 877, 878] and less, or sometimes no, effect on clinical outcomes.[875, 877, 878] 1++

The effect is greater if interventions:

- include behavioural components[877, 878]
- include practical facilitators (such as simplified dosage regimes), monitoring and follow-up[874, 875]
- are delivered and sustained as part of a comprehensive programme of accessible proactive asthma care.[874]

1++

Innovative, IT-based ways to provide this supportive care have shown some promise in other disease areas but have not been explored in the context of improving asthma adherence.[879]

A **Adherence to long-term asthma treatment should be routinely and regularly addressed by all health care professionals within the context of a comprehensive programme of accessible proactive asthma care.**

✓ Initiatives to promote adherence to regular treatment should consider:

- information requirements, eg individual and/or group sessions, written/electronic materials, on-going access to information
- practical facilitators, eg simple dosage regimes
- behavioural support, eg regular monitoring including assessment of medication use with feedback, counselling, psychological therapies
- context – accessible proactive asthma care, eg, Chronic Care Model.
- consultation skills required to achieve shared decision-making – adherence is more likely when the patient and the health professional agree that the action is appropriate.

Comment [b2]: Hilary – I have changed 'compliance' to 'adherence'.

12.6 IMPLEMENTATION IN PRACTICE

Despite the robust evidence base for self-management education, implementation in routine practice remains poor with only a third of people with asthma having a PAAP.[880, 881] Compare your Care. 2013] Implementation in routine clinical practice depends as much on the context in which it is delivered as the content of the intervention. Given the diversity of healthcare systems, generalising approaches from one context to another is problematic. Despite these limitations, however, the evidence reviewed identified consistent messages that are suitable for adoption and adaptation in different healthcare settings.

12.6.1 THE EVIDENCE BASE

A systematic review (including 14 RCTs, 2,438 patients, 107 doctors and 43 primary care

teams) investigated the promotion of PAAP ownership and usage.[882] In addition, we reviewed 19 implementation studies from the USA,[854, 857, 883-889] UK,[774, 890-892] Scandinavia,[893-895] Italy,[896] and Brazil.[897, 898][1]

The interventions in the implementation studies adopted four main strategies:

- primarily professional training[774, 857]
- primarily organisational change[890, 891, 893]
- primarily patient education[854, 884-887, 896]
- a whole systems approach with components operating explicitly at patient, professional and organisational levels.[883, 888, 889, 892, 894, 895, 897, 898]

Study designs varied, with five cluster randomised trials,[774, 857, 885, 886, 890] a preference trial with randomised groups,[854] or controlled implementation.[891] Seven were based on longitudinal, often large, databases,[883, 884, 887-889, 894, 895, 898] [one with a control cohort,[897] and two uncontrolled before-and-after[892, 896] or cross-sectional studies.[893]

12.6.2 EVIDENCE FOR IMPLEMENTATION

Complex whole systems interventions in which motivated informed patients and trained professionals operate within an organisation with a culture of supported asthma self-management were associated with: 1++

- improved knowledge[889] and action plan ownership[882, 887, 892] 1-
- reduced unscheduled care,[888, 889, 894, 897, 898] and improved markers of control.[887-889, 894, 895]

Implementing single components of the whole systems approach is insufficient to bring about consistent benefits. Improving professionals' knowledge is a core component of effective self-management programmes, but on its own does not improve clinical outcomes.[774, 857] Organisational change to support self-management improves process outcomes such as the proportion of patients with PAAPs[890, 893] or achieving a review,[891] but improved asthma control in only one of the studies.[893] Targeting the patient with educational material,[887] support from pharmacists,[884] school,[885, 896] or telephone calls[854, 885, 886] improved medication use,[854, 886] knowledge,[885] and ownership of PAAPs,[884] and had variable effects on clinical outcomes. 2++ 2+

B **Commissioners and providers of services for people with asthma should consider how they can develop interventions that proactively engage and empower patients, train and motivate professionals within the context of an organisation which prioritises and actively supports self-management.**

12.7 PRACTICAL ADVICE

12.7.1 AVAILABLE RESOURCES

A number of resources are available to support health professionals, including those produced by Asthma UK. Annex 11 reproduces the Asthma UK personalised asthma action plan available from their website http://www.asthma.org.uk/Shop/your-asthma-action-plan Additional support and information for patients and carers is also available from the Asthma UK website (www.asthma.org.uk) and their telephone Adviceline run by asthma specialist nurses: 0800 121 62 94, which includes an interpreting service covering 100 languages

[1] The searches, quality assessment and data extraction for the implementation studies in asthma self-management were kindly provided by the PRISMS group (Taylor S, Pinnock H, Epiphaniou E, Pearce G, Parke H) who are conducting a systematic review of self-management support interventions for people with long term conditions as part of a project funded by the National Institute for Health Research Health Services and Delivery Research programme (project number 1/1014/04). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the National Institute for Health Research Health Services and Delivery Research programme, NIHR, NHS or the Department of Health.

and Typetalk.

12.7.2 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 asthma action plan.
- 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.

13 Provision of information

This section is not available in this draft

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing asthma with patients and carers and in guiding the production of locally produced information materials.

13.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

13.2 SOURCES OF FURTHER INFORMATION

Title
Address 1, Address 2, City, Postcode
Tel: number • Fax: number
www.website.org.uk • E-mail: emailaddress@emailaddress.co.uk

14 Implementing the guideline

This section is not available in this draft.

14.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN.The implementation strategy for this guideline encompasses the following tools and activities.

14.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

14.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

14.4 ADDITIONAL ADVICE TO NHS SCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

15 The evidence base

This section is not available in this draft.

15.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was XXXX-YYYY. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

The evidence base builds on the reviews carried out for the original (2003) version of the guideline and subsequent updates. See Annex 1 for details of the time period covered for each topic. 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.

15.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*) The following areas for further research have been identified:

- Is there additional benefit of nebulised magnesium sulphate in children with acute severe asthma receiving maximal doses of inhaled bronchodilators and steroids?
- Head to head comparison of intravenous magnesium sulphate bolus with intravenous beta 2 agonist bolus and/or aminophylline. Which intravenous therapy should be used as first line treatment?
- Recommendation
- Recommendation
- Recommendation
- Recommendation
- Recommendation
- Recommendation
- Recommendation
- Recommendation

15.3 REVIEW AND UPDATING

This guideline was issued in 2014 and sections of the guideline will be updated on biennial basis. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

16 Development of the guideline

16.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are 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**

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

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

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16.5 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the

development of SIGN 101: British guideline on the management of asthma, on which this guideline is based. SIGN would also like to acknowledge the contribution of the following individuals who were involved in the early stages of development of this updated version.

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16.6 CONSULTATION AND PEER REVIEW

16.6.1 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 2013. The draft guideline was also available on the SIGN and BTS web sites for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

16.6.2 SPECIALIST REVIEW

This 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. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN and the BTS are very grateful to all of these experts for their contribution to the guideline.

Title and full name	*Job title, Work place, City*
Title and full name	*Job title, Work place, City*
Title and full name	*Job title, Work place, City*
Title and full name	*Job title, Work place, City*
Title and full name	*Job title, Work place, City*
Title and full name	*Job title, Work place, City*

The following organisations also commented

16.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

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Dr Roberta James	*Programme Lead, SIGN; Co-Editor*
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Abbreviations

	ABG	arterial blood gas	
	ABPA	allergic bronchopulmonary aspergillosis	
	ACT	Asthma Control Test	
	ACTH	adrenocorticotropic hormone	
	AQLQ	Asthma Quality of Life Questionnaire	
	BDP	beclometasone	
	BTS	British Thoracic Society	
	COPD	chronic obstructive pulmonary disease	
	CXR	chest X-ray	
	DOT	directly observed therapy	
	DPI	dry powder inhaler	
	ED	emergency department	
	ETS	environmental tobacco smoke	
	FENO	exhaled nitric oxide concentration	
	FEV1	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	
	IM	intramuscular	
	IOS	impulse oscillometry	
	LABA	long-acting β2 agonist	
	MDI	metered dose inhaler	
	MHRA	Medicines and Healthcare products Regulatory Agency	
	n-3PUFAs	omega-3 polyunsaturated fatty acids	
	NIV	non-invasive ventilation	
	NRAD	National Review of Asthma Deaths	
	PACE	Physician Asthma Care Education	
	PaCO2	partial pressure of carbon dioxide in arterial blood	
	PaO2	partial pressure of oxygen in arterial blood	
	PAAPs	Personalised asthma action plans	
	PC20	the provocative concentration of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV1	
	PD20	the provocative dose of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV1	

	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	
	SpO2	saturation of peripheral oxygen	
	sRaw	specific airways resistance	
	VEmax	ventilation at maximal exercise capacity	

Annex 1
Summary of search histories by section

Not available in this draft.

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