Healthcare Improvement Scotland

SIGN

SIGN 153 • British guideline on the management of asthma

A national clinical guideline

September 2016

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, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
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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
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GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^{+}

GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

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British Thoracic Society

Scottish Intercollegiate Guidelines Network

British guideline on the management of asthma

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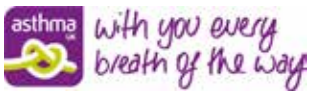

Revised 2016

ISBN 978 1 909103 47 4

First published 2003
Revised edition published 2016

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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 around the 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 evidence-based methodology explicitly. 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 1997, and SIGN augmented this with a search from 1997 onwards.

1.1.1 UPDATING THE EVIDENCE

Between 2004 and 2012 sections within the guideline were updated annually. Subsequently, updating moved to a biennial basis, beginning with the 2014 update. This edition of the guideline was issued in 2016. All updates were made available on both the BTS (www.brit-thoracic.org.uk) and SIGN (www.sign.ac.uk) websites. Any updates to the guideline in the period between scheduled updates will be noted on the SIGN and BTS websites.

A summary of the search histories 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.

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 7 and 8 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. Further information on managing asthma in adolescents (10–19 years of age as defined by the World Health Organisation)[4] is given in section 11.

The guideline considers asthma management in all patients with a diagnosis of asthma, although there is less evidence available 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 particular interest to healthcare professionals involved in the care of people with asthma including general practitioners, consultants and specialists in respiratory medicine, nurses and pharmacists. The guideline will also be of interest to people with asthma, their parents and carers; those who interact with people with asthma outside of the NHS, such as teachers; voluntary organisations with an interest in asthma; and 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	Key recommendations	2014, 2016
3	Diagnosis	2008, 2011, 2016
4	Monitoring asthma	2008, 2011
5	Supported self management	2004, 2008, 2014, 2016
6	Non-pharmacological management	2008, 2014, 2016
7	Pharmacological management	2004, 2005, 2006, 2008, 2009, 2011, 2014, 2016
8	Inhaler devices	2005, 2014
9	Management of acute asthma	2004, 2009, 2014, 2016
10	Difficult asthma	2008, 2014, 2016
11	Asthma in adolescents	2011
12	Asthma in pregnancy	2005, 2008, 2009, 2014
13	Occupational asthma	2005, 2008, 2014, 2016
14	Organisation and delivery of care	2008, 2014, 2016

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, between 2006-2011, the guideline had input from colleagues from Australia and New Zealand.

The 2008 guideline considered literature published up to March 2007. It contained a completely rewritten section on diagnosis for both adults and children, a section on special situations which included 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 included 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 were also amended to reflect current evidence.

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

In 2014 the approach to updating the guideline changed and revisions were made to subsections throughout the guideline based on new evidence relating to specific key questions. In addition, major revisions were made to the section on non-pharmacological management, and the organisation and delivery of care and supported self management sections were revised. The structure of the guideline also changed, with a new section highlighting key recommendations for implementation from across the guideline *(see section 2)*; the original section 7 on special situations split into four separate sections covering difficult asthma, asthma in adolescents, asthma in pregnancy and occupational asthma, and the revised section 4 on supported self management moved to the beginning of the guideline.

Also new for 2014 was the replacement of the term 'asthma exacerbation' with the new term 'asthma attack'. The guideline development group believes that it is more understandable and gives a clearer indication of the need for action.

The 2016 version includes a complete revision of the section on diagnosis, a major update to the section on pharmacological management of asthma, and updates to the sections on supported self management, non-pharmacological management of asthma, acute asthma, difficult asthma, occupational asthma, and organisation and delivery of care.

1.2.4 SUMMARY OF UPDATES TO THE 2016 EDITION OF THE GUIDELINE, BY SECTION

2	Key recommendations	New: 2.1.1 Diagnosis Updated: 2.5 Inhaler devices Minor updates: 2.3 Non-pharmacological management, 2.4 Pharmacological management, 2.6.1 Acute asthma in adults
3	Diagnosis	New: 3.1 Definition and overarching principles, 3.2 Predictive value of individual symptoms, signs and diagnostic tests, 3.3 Practical approach to diagnosis
4	Monitoring asthma	Not updated
5	Supported self management	New: 5.4.2 Assessing medication adherence Updated: 5.4.1 Adherence to monitoring and treatment, 5.4.3 Interventions to improve medication adherence
6	Non-pharmacological management	Updated: 6.1.8 Weight reduction in overweight and obese patients, 6.2.8 Weight reduction in overweight and obese patients with asthma
7	Pharmacological management	New: 7.2 Table 9 Adult doses of inhaled corticosteroids & Table 10 Paediatric doses of inhaled corticosteroids, 7.3.5 Maintenance and reliever therapy, 7.4 Additional add-on therapies, 7.4.2 Leukotriene receptor antagonists, 7.4.3 Tiotropium bromide, Figure 2 Summary of management in adults, Figure 3 Summary of management in children, 7.7.2 Anti-IL-5 monoclonal antibody Updated: 7.1 Intermittent reliever therapy, 7.3.2 Inhaled long-acting β_2 agonist, 7.5 High-dose therapies, 7.7.1 Anti-IgE monoclonal antibody, 7.7.3 Other agents Minor updates: 7.2.3 Frequency of dosing of inhaled corticosteroids, 7.2.4 Comparison of inhaled corticosteroids,
8	Inhaler devices	Updated: 8.4 Prescribing devices Minor updates: 8.5 Use and care of spacers

9	Management of acute asthma	New: 9.9.5 Critical care (in children) Updated: 9.3.8 Antibiotics, 9.3.12 Critical care settings, 9.3.13 Non-invasive ventilation, 9.7 Acute asthma in children, 9.9.3 Intravenous magnesium sulphate (in children), 9.9.4 Other therapies (in children), 9.9.7 Discharge planning (children) Minor updates: 9.1.2 Medical management, 9.3.1 Oxygen, 9.3.2 β_2 agonist bronchodilators, 9.3.3 Steroid therapy, 9.8.2 Inhaled short-acting β_2 agonists (in children), 9.8.4 Steroid therapy (in children), 9.9 Second-line treatment of acute asthma in children, 9.9.1 Intravenous salbutamol (in children)
10	Difficult asthma	Updated: 10.2.1 Poor adherence
11	Asthma in adolescents	Not updated
12	Asthma in pregnancy	Not updated
13	Occupational asthma	New: 13.3.7 Exhaled breath condensate Minor updates: 13.3.4 Bronchial provocation testing
14	Organisation and delivery of care	New: 14.4 Telehealthcare
16	The evidence base	Updated: 16.2 Recommendations for research
	Annexes	Minor updates: Annexes 2 and 4 Management of acute severe asthma in adults in general practice/ hospital, Annexes 5–7 Management of acute asthma in children in general practice/emergency department/ hospital, Annex 8 Management of acute asthma in infants aged <2

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 through a process of shared decision making 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 medical records at the time the relevant decision is taken.

1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

1.3.2 PATIENT VERSION

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

1.3.3 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 'off label' prescribing 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 (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]

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

The National Institute for Health and Care Excellence (NICE) develops multiple and single 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 reviews multiple technology appraisals and provides advice about their applicability for NHSScotland.

Single technology appraisals 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 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 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

In 2013, the National Institute for Health and Care Excellence published a quality standard for asthma comprising 11 quality statements.[7] The quality statements draw on existing guidance including the SIGN/BTS British guideline on the management of asthma. Quality standards describe high priority areas for quality improvement with each quality standard consisting of a prioritised set of specific, concise and measurable statements. The quality statements are shown below under the key recommendations from the guideline that most closely relate to them.

2.1 DIAGNOSIS AND MONITORING

2.1.1 DIAGNOSIS

D **Undertake a structured clinical assessment to assess the initial probability of asthma. This should be based on:**

- **a history of recurrent episodes** (attacks) **of symptoms, ideally corroborated by variable peak flow when symptomatic and asymptomatic**
- **symptoms of wheeze, cough, breathlessness and chest tightness that vary over time**
- **recorded observation of wheeze heard by a healthcare professional**
- **personal/family history of other atopic conditions** (in particular, atopic eczema/dermatitis, allergic rhinitis)
- **no symptoms/signs to suggest alternative diagnoses.**

C **Compare the results of diagnostic tests undertaken whilst a patient is asymptomatic with those undertaken when a patient is symptomatic to detect variation over time.**

D **Carry out quality-assured spirometry using the lower limit of normal to demonstrate airway obstruction, provide a baseline for assessing response to initiation of treatment and exclude alternative diagnoses.**

- **Obstructive spirometry with positive bronchodilator reversibility increases the probability of asthma.**
- **Normal spirometry in an asymptomatic patient does not rule out the diagnosis of asthma.**

✓ In patients with a high probability of asthma:

- record the patient as likely to have asthma and commence a carefully monitored initiation of treatment (typically six weeks of inhaled corticosteroids)
- assess the patient's status with a validated symptom questionnaire, ideally corroborated by lung function tests (FEV_1 at clinic visits or by domiciliary serial peak flows)
- with a good symptomatic and objective response to treatment, confirm the diagnosis of asthma and record the basis on which the diagnosis was made
- if the response is poor or equivocal, check inhaler technique and adherence, arrange further tests and consider alternative diagnoses.

2.1.2 MONITORING ADULTS IN PRIMARY CARE

✓ In adults, the following factors should be monitored and recorded in primary care:

- symptomatic asthma control
- lung function assessed by spirometry or by PEF
- asthma attacks, oral corticosteroid use and time off work since last assessment
- inhaler technique
- adherence
- bronchodilator reliance
- possession of and use of a self-management plan/personal action plan.

NICE quality statement 1: People with newly diagnosed asthma are diagnosed in accordance with BTS/SIGN guidance.

NICE quality statement 6: People with asthma who present with respiratory symptoms receive an assessment of their asthma control.

2.2 SUPPORTED SELF MANAGEMENT

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 **Prior to discharge, inpatients should receive written personalised asthma action plans, given by healthcare professionals with expertise in providing asthma education.**

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

NICE quality statement 3: People with asthma receive a written personalised action plan.

NICE quality statement 5: People with asthma receive a structured review at least annually.

NICE quality statement 9: People admitted to hospital with an acute exacerbation of asthma have a structured review by a member of a specialist respiratory team before discharge.

2.3 NON-PHARMACOLOGICAL MANAGEMENT

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

B **Weight-loss interventions** (including dietary and exercise-based programmes) **can be considered for overweight and obese adults and children with asthma to improve asthma control.**

A **Breathing exercise programmes** (including physiotherapist-taught methods) **can be offered to people with asthma as an adjuvant to pharmacological treatment to improve quality of life and reduce symptoms.**

2.4 PHARMACOLOGICAL MANAGEMENT

✓ Before initiating a new drug therapy practitioners should check adherence with existing therapies, check inhaler technique, and eliminate trigger factors.

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

A **The first choice as add-on therapy to inhaled corticosteroids in adults is an inhaled long-acting β_2 agonist, which should be considered before increasing the dose of inhaled corticosteroids.**

D D **If asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled corticosteroids should be increased from low dose to medium dose in adults or from very low dose to low dose in children** (5–12 years)**, if not already on these doses.**

2.5 INHALER DEVICES

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

✓ Generic prescribing of inhalers should be avoided as this might lead to people with asthma being given an unfamiliar inhaler device which they are not able to use properly.

✓ In children, pMDI and spacer are the preferred method of delivery of β_2 agonists and inhaled corticosteroids. A face mask is required until the child can breathe reproducibly using the spacer mouthpiece. Where this is ineffective a nebuliser may be required.

NICE quality statement 4: People with asthma are given specific training and assessment in inhaler technique before starting any new inhaler treatment.

2.6 ACUTE ASTHMA

2.6.1 ADULTS

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

C **Give controlled supplementary oxygen to all hypoxaemic patients with acute severe asthma titrated to maintain an SpO_2 level of 94–98%. Do not delay oxygen administration in the absence of pulse oximetry but commence monitoring of SaO_2 as soon as it becomes available.**

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

A **Give steroids in adequate doses to all patients with an acute asthma attack.**

2.6.2 CHILDREN

✓ 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 of 94–98%.

A **Inhaled β_2 agonists are the first-line treatment for acute asthma in children.**

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

2.6.3 ALL PATIENTS

✓ 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 attack. Ideally this communication should be directly with a named individual responsible for asthma care within the practice, by means of fax or email.

NICE quality statement 7: People with asthma who present with an exacerbation of their symptoms receive an objective measurement of severity at the time of presentation.

NICE quality statement 8: People aged 5 years or older presenting to a healthcare professional with a severe or life-threatening acute exacerbation of asthma receive oral or intravenous steroids within one hour of presentation.

NICE quality statement 10: People who received treatment in hospital or through out-of-hours services for an acute exacerbation of asthma are followed up by their own GP practice within two working days of treatment.

2.7 DIFFICULT ASTHMA

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 to therapy.**

NICE quality statement 11: People with difficult asthma are offered an assessment by a multidisciplinary difficult asthma service.

2.8 ASTHMA IN PREGNANCY

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.**

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

2.9 OCCUPATIONAL ASTHMA

B **In patients with adult onset, or reappearance of childhood asthma, healthcare professionals should consider that there may be an occupational cause.**

✓ 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.

NICE quality statement 2: Adults with new onset asthma are assessed for occupational causes.

3 Diagnosis

The diagnosis of asthma is a clinical one. The absence of consistent gold-standard diagnostic criteria means that it is not possible to make unequivocal evidence-based recommendations on how to make a diagnosis of asthma.

Section 3.1 defines asthma and highlights overarching principles, section 3.2 describes the diagnostic accuracy of individual symptoms, signs and diagnostic tests, and section 3.3 describes a pragmatic approach to establishing a diagnosis of asthma based on current evidence and the collective experience of the guideline development group.

3.1 DEFINITION AND OVERARCHING PRINCIPLES

3.1.1 DEFINITION

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 both children and adults, have included airway hyper-responsiveness and airway inflammation as components of the disease reflecting a developing understanding of the diverse subtypes (phenotypes and endotypes) of asthma and their underpinning mechanisms.[8]

3.1.2 TESTS INFLUENCE THE PROBABILTY OF ASTHMA BUT DO NOT PROVE A DIAGNOSIS

There is no single diagnostic test for asthma. Building on the definitions in section 3.1.1, diagnosis is based on clinical assessment *(see section 3.3)* supported by objective tests that seek to demonstrate variable airflow obstruction or the presence of airway inflammation *(see section 3.2)*. Both clinical assessment of symptoms and signs and objective tests have significant false positive and false negative rates *(see Table 1)*.

Objective tests influence the probability of a diagnosis of asthma, but the magnitude of that influence depends on the probability prior to testing as well as the predictive value of the test. Therefore, in a patient with a very high probability of asthma prior to testing, the results of a diagnostic test with a substantial false negative rate will have minimal influence. In contrast, in a patient with an intermediate or low probability of asthma, a positive diagnostic test may significantly shift the probability towards an asthma diagnosis *(see section 3.3)*.

3.1.3 ASTHMA STATUS AND THE OUTCOME OF DIAGNOSTIC TESTS FOR ASTHMA VARY OVER TIME

Diagnostic tests are typically performed at a single point in time whereas asthma status varies over time. Patients on primary care asthma registers who have not received prescriptions for a year are considered to be 'inactive',[9] and there is evidence that some patients shift from 'inactive' to 'active' status (and vice versa) over time.[10-12]

Objective tests performed when patients are asymptomatic or during an 'inactive' period may result in false negatives. For example, in primary-care patients with intermittent asthma symptoms, spirometry confirmed obstruction in 16–39% of patients,[13-15] and bronchodilator reversibility was demonstrated in only 15–17% of patients.[15-17] In contrast, in a population admitted to hospital with a physician diagnosed asthma attack, 83% had obstructive lung function.[18] In a prospective longitudinal study in primary care, fractional exhaled nitric oxide (FeNO) was only positive in 40% of people with diagnosed asthma at 12 months, and one in five were falsely negative.[12]

2+
3

Time may, however, be used to advantage if objective signs and tests when a patient is symptomatic are compared to measurements when they are asymptomatic. In the event of diagnostic uncertainty it may be helpful to repeat investigations.

C **Compare the results of diagnostic tests undertaken whilst a patient is asymptomatic with those undertaken when a patient is symptomatic to detect variation over time.**

3.2 PREDICTIVE VALUE OF INDIVIDUAL SYMPTOMS, SIGNS AND DIAGNOSTIC TESTS

The individual symptoms and signs and the diagnostic tests and thresholds typically used in clinical practice and their performance in diagnostic studies are shown in Table 1.

These data, however, need to be interpreted with caution. The performance of the diagnostic tests, as assessed by reported sensitivities/specificities and positive and negative predictive values (PPV/NPV), vary widely. This reflects methodological considerations such as the use of different reference (gold) standards and variation in defined thresholds for tests, as well as the diverse clinical contexts for these studies *(see Table 1)*. The majority of studies assessing diagnostic test accuracy recruited patients from secondary care clinics; the predictive value of tests in people presenting to primary care with undifferentiated respiratory symptoms is less well reported.

The, often poor, predictive value of objective tests reinforces the need for test results to be used in conjunction with a structured clinical assessment to assess the probability of asthma in an individual presenting with respiratory symptoms suggestive of asthma *(see section 3.3.1)*.

3.2.1 SYMPTOMS AND SIGNS

The predictive value of isolated symptoms or signs is poor *(see Table 1)*. In adults, isolated symptoms of cough, wheeze and shortness of breath are neither sensitive nor specific for asthma.[19] Almost all children with asthma have intermittent cough, wheeze and/or exercise induced symptoms, but only about a quarter of children with these symptoms have asthma.[20-22] Enquiring about the episodic nature of symptoms (for example, acute attacks) as opposed to current symptoms may improve the predictive value.[21-24] 2^{++} 2^{+}

Wheezing is one of a number of respiratory noises that occur in children. Parents often use the term 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.[25]

Wheeze heard by a healthcare professional on auscultation is an important sign that increases the probability of asthma.[23] 2^{++}

Combinations of symptoms and signs are clinically more helpful than isolated symptoms, especially in children. For example, two thirds of children with a cluster of cough, wheeze, chest tightness, dyspnoea, and exercise symptoms have asthma. Asthma is very unlikely if a child does not have at least some of these symptoms and signs.[20-22] 2^{+}

3.2.2 SPIROMETRY AND BRONCHODILATOR REVERSIBILITY

Spirometry is the investigation of choice for identification of airflow obstruction and is widely available, including in primary care, although training is required to obtain reliable recordings and to interpret the results, particularly in children. The probability of asthma, differential diagnosis *(see Tables 4 and 5)* and approach to investigation is different in patients with and without airflow obstruction at the time baseline spirometry is undertaken.

Confirmation of an asthma diagnosis hinges on demonstration of airflow variability over short periods of time. A normal spirogram obtained when the patient is asymptomatic does not, therefore, exclude the diagnosis of asthma.[13-15] Alternative reasons for obstructive spirometry, for example chronic obstructive pulmonary disease (COPD) in adults, must also be considered. In a population of adults presenting to primary care with new respiratory symptoms, only a third of those with obstructive spirometry had asthma and almost two thirds had COPD. Only a quarter of those subsequently thought to have asthma had obstructive spirometry at the time of assessment.[26] 2^{++} 2^{+} 3

Measuring lung function in children under 5 years of age is difficult and requires techniques which are not widely available outwith specialist centres. For developmentally mature children over five years of age conventional lung function testing is possible in most settings with an operator trained and experienced in undertaking paediatric spirometry. As in adults, normal results on testing, especially if performed when the child is asymptomatic, do not exclude a diagnosis of asthma.[27] 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, and abnormal results may be seen in children with other respiratory diseases.[27,28] 2^{+}

In children, the relationship between asthma symptoms and lung function tests, including bronchodilator reversibility, is complex. Measures of gas trapping (residual volume and the ratio of residual volume to total lung capacity) may be superior to measurement of expiratory flow at detecting airways obstruction especially in asymptomatic children.[27,29]

✓ Operators should be trained to undertake quality-assured spirometry and be experienced in providing tests in the relevant age groups.

The FEV_1/forced vital capacity (FVC) ratio changes with age. In young children it can be as high as 90% so use of the commonly used fixed ratio of 70% will substantially underestimate airflow limitation. Conversely, in adults over 40 years, levels below 70% may be normal and use of a 70% threshold will overestimate obstruction. Accordingly, use of lower limits of normal is now recommended and is becoming easily available through software built into spirometers.[8,30-32] Detailed data about normal values for different age groups is available from the report of the European Respiratory Society Global Lung function Initiative.[33] From a practical perspective, the spirometers widely used in clinical practice provide the lower and upper limits of the normal range of spirometry parameters (although they usually use the fixed ratio to generate the automated interpretation reports). 2^{+}

In adults with obstructive spirometry, an improvement in FEV_1 of 12% or more in response to either β_2 agonists or corticosteroid treatment trials, together with an increase in volume of 200 ml or more, is regarded as a positive test,[34] although some people with COPD can have significant reversibility.[35] An improvement of greater than 400 ml in FEV_1 strongly suggests underlying asthma. In children, an improvement in FEV_1 of 12% or more is regarded as a positive test.[34] 4

D **Carry out quality-assured spirometry using the lower limit of normal to demonstrate airway obstruction, provide a baseline for assessing response to initiation of treatment and exclude alternative diagnoses.**

- **Obstructive spirometry with positive bronchodilator reversibility increases the probability of asthma.**
- **Normal spirometry in an asymptomatic patient does not rule out the diagnosis of asthma.**

3.2.3 TESTS OF VARIABILITY IN LUNG FUNCTION

Direct challenge tests

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.[36] 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. A PC_{20} of 8 mg/ml or less is regarded as positive.[37-39]

Two thirds, or more, of adults with a positive methacholine challenge have asthma and the false negative rate is less than 10%.[19] Tests of airway responsiveness are of little value in patients with established airflow obstruction as the specificity is low.[40,41]

Methacholine challenge tests in schoolchildren only marginally increase the diagnostic accuracy after the symptom history is taken into account.[42] However, a negative methacholine test in a child, which has a high negative predictive value, makes a diagnosis of asthma improbable.[30] 3

Indirect challenge tests

Other potentially helpful tests of variability in lung function include indirect challenges such as exercise and inhaled mannitol.[43] A positive response to these indirect stimuli, such as a fall in FEV_1 of greater than 15%, is a specific marker of asthma but the tests are less sensitive than challenges using methacholine and histamine, particularly in patients tested while on treatment.[43,44]

In children, a positive exercise challenge test (as opposed to a history of exercise-induced symptoms) is highly predictive of asthma with a false positive rate of less than 10%.[19] A negative response to an exercise challenge test is helpful in excluding asthma in children with exercise related breathlessness.[45]

Peak expiratory flow monitoring

Peak expiratory flow (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.[46] The patient can be standing or sitting. Further blows should be done if the largest two PEF are not within 40 l/min.[46]

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[47] but the improved precision is likely to be achieved at the expense of reduced patient compliance.[48] Use of electronic meters and diaries with time and date stamps can overcome problems of compliance and accuracy when recording peak flows in paper diaries.[49]

PEF variability is usually calculated as the difference between the highest and lowest PEF expressed as a percentage of the average PEF,[39,50,51] although one study showed that three or more days a week with significant variability was more sensitive and specific than calculating mean differences.[52]

The upper limit of the normal range for variability is around 20% using four or more PEF readings per day[50,51,53] but may be lower using twice-daily readings.[54] Studies have shown sensitivities of between 3% and 46% for identifying physician-diagnosed asthma.[19,39,55] One limitation of these epidemiological studies is that it is not always clear whether the participants were symptomatic at the time of the monitoring. PEF charting when asthma is 'inactive' is unlikely to confirm variability; one study showed that significant PEF variability was associated with respiratory symptoms in the previous week.[39]

PEF records from frequent readings taken at work and away from work are useful when considering a diagnosis of occupational asthma *(see section 13.3.1)*. A computer generated analysis of occupational records which provides an index of the work effect is available.[56]

In children, 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.[28]

C **In adults with no evidence of airflow obstruction on initial assessment, and in whom other objective tests are inconclusive but asthma remains a possibility, consider referral for challenge tests.**

✓ A peak flow recorded when symptomatic (eg during the assessment of an asthma attack) may be compared to a peak flow when asymptomatic (eg after recovery from an asthma attack) in order to confirm variability.

✓ In adults, serial peak flow records may demonstrate variability in symptomatic patients, but should be interpreted with caution and with regard to the clinical context. There is no evidence to support the routine use of peak flow monitoring in the diagnosis of asthma in children.

✓ Serial peak flows (at least four readings a day) are the initial investigation of choice in suspected occupational asthma.

3.2.4 TESTS TO DETECT EOSINOPHILIC AIRWAY INFLAMMATION OR ATOPY

Fractional exhaled nitric oxide (FeNO)

A positive FeNO test suggests eosinophilic inflammation and provides supportive, but not conclusive, evidence for an asthma diagnosis. There is overlap between the levels seen in normal non-asthmatic populations and in people with atopic asthma.[32] There are some important confounders. 2+ 4

FeNO levels are:[57-59]

- increased in patients with allergic rhinitis exposed to allergen, even without any respiratory symptoms
- increased by rhinovirus infection in healthy individuals, but this effect is inconsistent in people with asthma
- increased in men; tall people; and by consumption of dietary nitrates
- lower in children
- reduced in cigarette smokers
- reduced by inhaled or oral steroids.

2+ 4

In steroid-naive adults, a FeNO level of 40 parts per billion (ppb) or more is regarded as positive; in schoolchildren a FeNO level of 35 ppb or more is regarded as a positive test.[34]

In eight studies in adults recruited from secondary care with symptoms suggestive of asthma, sensitivities for FeNO ranged from 43–88% and specificities from 60–92%. The PPV and NPV ranged from 54–95% and 65–93%, respectively *(see Table 1)*.[19] On this basis, approximately 1 in 5 people with a positive FeNO test will not have asthma (false positives), and conversely 1 in 5 people with a negative FeNO test will have asthma (false negatives). There are no data from primary care populations.

2++

It is feasible to measure FeNO in children from the age of 3–4 years.[60] In children, FeNO is closely linked with atopic status, age and height.[61,62]

D **Use measurement of FeNO** (if available) **to find evidence of eosinophilic inflammation. A positive test increases the probability of asthma but a negative test does not exclude asthma.**

Tests of atopic status

Positive skin-prick tests,[63] blood eosinophilia ≥4%,[64] or a raised allergen-specific immunoglobulin E (IgE) to a range of common aeroallergens[65,66] increase the probability of asthma in schoolchildren and adults.[34,63] The positive predictive values for individual tests are, however, poor *(see Table 1)*. Non-atopic wheezing is as frequent as atopic wheezing in school-aged children.

2++ 4

D **Use a previous record of skin-prick tests, blood eosinophilia of 4% or more, or a raised allergen-specific IgE to corroborate a history of atopic status, but do not offer these tests routinely as a diagnostic test for asthma.**

Sputum eosinophils

Eosinophilic airway inflammation in adults can be assessed non-invasively using the induced sputum differential eosinophil count.[57,67] Sputum induction is feasible in school-aged children but is technically demanding and time consuming and remains a research tool.[68,69] Experience with induced sputum is limited to a few centres and more research needs to be done before any recommendations can be made on its use as a diagnostic test in clinical practice.

Table 1: Summary of individual diagnostic tests

Strategy	Description*	Parameter*	Range of predictive values* (Note that a single value indicates data from a single study)				Comments**
			Sens[i]	Spec[ii]	PPV[iii]	NPV[iv]	
Clinical assessment							
Symptoms and signs	The commonest symptoms assessed were cough and wheeze and, in adults, shortness of breath.	Cough in adults	16–66%	26–64%	8–44%	18–92%	As isolated symptoms cough, wheeze and shortness of breath are neither sensitive, nor specific for asthma. Most children with asthma have intermittent cough, wheeze and exercise-induced symptoms, but ony about a quarter of children with these symptoms have asthma. Note that the single study in pre-school children compared current symptoms with a diagnosis of asthma two years later.
		Wheeze in adults	9–76%	34–87%	10–81%	28–94%	
		Dyspnoea in adults	11–73%	38–71%	41–59%	26–70%	
		Cough in schoolchildren[20]	63%	75%	14%	97%	
		Wheeze in children[20]	59%	93%	34%	97%	
		Cough in pre-school children	88%	7%	76%	15%	
		Wheeze in pre-school children	54%	57%	80%	27%	
		Shortness of breath in pre-school children	76%	52%	84%	40%	
	Symptom variability	Episodic symptoms in adults	9–40%	36–91%	14–86%	18–93%	Asking about episodic symptoms improves the positive predictive values in children compared to current symptoms.
		Diurnal symptoms in adults	30–56%	36–83%	48–76%	18–67%	
		Symptoms after exercise in adults	5–40%	32–93%	5–81%	58–84%	
		Episodic symptoms in children[21,22]	36–93%	35–93%	40–94%	62–90%	
		Symptoms after exercise in children[21,22]	82–94%	59–73%	54–86%	79–91%	
		Nocturnal symptoms in children[21,22]	57–84%	58–78%	64–85%	57–82%	
	Combinations of symptoms (typically cough, wheeze, chest tightness, dyspnoea, exercise symptoms)	Symptom scores in adults	60%	66%			Combinations of symptoms are clinically more helpful than isolated symptoms, especially in children. For example, two thirds of children with a cluster of cough, wheeze, chest tightness, dyspnoea and exercise symptoms have asthma. Asthma is unlikely if a child does not have at least some of these symptoms.
		Symptom scores in children[20-22]	45–83%	85–97%	44–94%	66–97%	
		Symptoms of cough and wheeze in pre-school children	49%	59%	80%	51%	
History of atopy	Personal/family history of atopic/ allergic diseases	Personal history of atopy in adults	54–55%	68–74%	46–76%	45–79%	Past history (personal or family) of atopic disease has poor sensitivity and specificity for asthma.
		Personal history of rhinitis/eczema in pre-school children	47–62%	20–75%	72–86%	14–30%	
		Family history of atopy in adults	26–60%	56–83%	44–74%	38–70%	
		Family history of atopy in children	43–44%	57–70%	51–77%	24–62%	

Strategy	Description*	Parameter*	Range of predictive values* (Note that a single value indicates data from a single study)				Comments**
Strategies for demonstrating airway obstruction							
Spirometry	Regard a FEV_1/FVC ratio of less than 70% as a positive test for obstructive airway disease.	Obstructive spirometry in adults Obstructive spirometry in children (5-18 yrs)	23–47% 52%	31–100% 73%	45–100% 75%	18–73% 49%	In the four larger studies (adults and children), the NPV was between 18% and 54% which means that more than half of patients being investigated who have normal spirometry will have asthma (ie false negatives).
Strategies for demonstrating variability in airway obstruction							
Broncho-dilator reversibility	In adults, regard an improvement in FEV_1 of ≥12% and ≥200 ml as a positive test. In children regard an improvement in FEV_1 of ≥12% as a positive test.	Bronchodilator reversibility in adults Bronchodilator reversibility in schoolchildren (using a threshold of 9% change in FEV_1)[70]	17–69% 50%	55–81% 86%	53–82%	22–68%	In these secondary care populations, about 1 in 3 people with a positive reversibility test will not have asthma (the cohorts all included people with COPD); and at least 1 in 3 people with a negative bronchodilator reversibility test will have asthma.
Challenge tests	Regard a PC_{20} value of 8 mg/ml or less as a positive test.	Methacholine challenge in adults. Methacholine challenge in children[30,42,71]	51–100% 47–86%	39–100% 36–97%	60–100% 20%	46–100% 94%	Challenge tests are a good indicator for those with a definitive diagnosis of asthma already (based upon clinical judgment, signs and symptoms and response to anti-asthma therapy)
	Fall in FEV_1≥15% at cumulative dose of ≤635 mg is positive	Mannitol in adults Mannitol in children	56% 63%	75% 81%	80%	49%	These data are from a single study in adults and children with symptoms of asthma on questionnaire.
	Exercise challenge	Exercise challenge in adults Exercise challenge in children	26–80% 69–72%	100% 69–72%	100% 90–99%	0% 5–73%	The studies in adults had very small sample sizes. The larger study in children had a false positive rate of 1% (PPV 99%).
Peak flow charting	Monitor peak flows for 2-4 weeks, calculate mean variability. Regard ≥20% variability as a positive test.	PEF charting in adults in a population study - using mean variability of >20% - using mean variability of >15% - using diurnal variation >15% on >3 days/week PEF charting in children - using variation >12.3% (95th centile)	 46% 3–5% 20% 50%	 80% 98–99% 97% 72%	 97% 60–67% 82% 48%	 10% 60% 64% 74%	It is not clear whether the patients in these studies were symptomatic at the time of the charting, and results may not reflect clinical use in symptomatic populations. One study concluded that the number of days with diurnal variation was more accurate than calculating the mean variation.

Strategy	Description*	Parameter*	Range of predictive values* (Note that a single value indicates data from a single study)				Comments**
Strategies for detecting eosinophilic inflammation or atopy							
FeNO	Adults: Regard a FeNO level of 40 ppb or more as a positive test Children 5–16yrs: regard a FeNO level of 35 ppb or more as a positive test.	FeNO in adults FeNO in schoolchildren	43–88% 57%	60–92% 87%	54–95% 90%	65–93% 49%	These studies are all in secondary care populations. Approximately 1 in 5 adults with a positive FeNO test will not have asthma (ie false positives) and 1 in 5 adults with a negative FeNO test will have asthma (ie false negatives).
Blood eosinophils	Suggested thresholds for blood eosinophils: Adults >4.15% Children ≥4%[64]	Blood eosinophils in adults Blood eosinophils in children	15–36% 55–62%	39–100% 67–84%	39–100% 56–69%	27–65% 73%	Elevated blood eosinophil level is poorly predictive. The threshold varies in these studies from 4.0 to 6.3%.
IgE		Any allergen-specific IgE >0.35 kU/l in adults Total IgE in adults >100 kU/l	54–93% 57%	67–73% 78%	5–14% 5%	95–99% 99%	A normal IgE substantially reduces the probability of asthma in adults with a false negative rate of less than 1 in 10, although a positive result is poorly predictive.
Skin prick testing		Any positive test (wheal ≥3 mm) in adults Any positive test (wheal ≥3 mm) in children	61–62% 44–79%	63–69% 56–92%	14–81% 65–92%	39–96% 36–79%	

Notes:
* Data derived from NICE evidence tables unless otherwise specified.[19] Only studies reporting sensitivity, specificity, PPV and NPV are included here
** Comments have been added by the guideline development group as an aid to interpretation of the data presented.
i Sensitivity (Sens) is the probability of a test being positive when asthma is present
ii Specificity (Spec) is the probability of a test being negative when asthma is absent
iii Positive predictive value (PPV) is the proportion of patients with a positive test who actually have asthma (100 minus the PPV is the proportion of patients with a false positive test)
iv Negative predictive value (NPV) is the proportion of patients with a negative test who do not have asthma (100 minus the NPV is the proportion of patients with asthma but in whom test was negative)

Reference tests
In most of the studies, the reference test was spirometry plus either bronchodilator reversibility or a challenge test, although some studies also included a 'typical history of attacks' or diurnal variation, or used physician diagnosis. Studies evaluating methalcholine challenge tests used physician diagnosis or bronchodilator reversibility and/or diurnal peak flow variability. In children, the reference tests used were physician diagnosed asthma plus spirometry, or documented history of wheeze on at least two occasions, and variability in FEV_1 over time or on exercise testing.

3.3 PRACTICAL APPROACH TO DIAGNOSIS

The diagnosis of asthma in children and adults is based on the recognition of a characteristic pattern of respiratory symptoms, signs and test results *(see Table 2)* and the absence of any alternative explanation for these.

At present, there is no definitive evidence to inform the most appropriate choice of algorithm for making a diagnosis of asthma in clinical settings. There are pragmatic observational studies which can inform the clinical process of making a diagnosis,[12,13,15,16,72] or which compare outcomes of diagnostic tests in different settings,[18,24,73] and some potentially useful algorithms,[14,20,23,24,73] or symptom questionnaires in children have been derived.[21,22] This section and the associated diagnostic algorithm (*see Figure 1)*, therefore, represent consensus opinion, building on the overarching principles defined in section 3.1, informed by the evidence available from these pragmatic studies combined with data from the diagnostic studies described in section 3.2. There is an urgent need for diagnostic accuracy studies and implementation research to confirm, prospectively, the diagnostic accuracy of retrospectively derived algorithms and to define the optimal approach to making a diagnosis in different clinical practice settings.

All studies evaluating diagnostic approaches have used a clinical assessment, sometimes using diagnostic,[73] or standard morbidity questions,[16,72] as the basis for the diagnostic process.[13-17,23,72,73] A number of studies have highlighted the diagnostic significance of episodic symptoms and confirmed wheezing as important predictors of asthma.[13,18,20-24,26] Studies also illustrate the importance of observing events over time and documenting the basis on which a diagnosis is made.[12,73]

In adults, absence of smoking and young age of onset are typically included in algorithms designed to distinguish asthma from COPD.[15-17,72,73]

3.3.1 INITIAL STRUCTURED CLINICAL ASSESSMENT

The predictive value of individual symptoms or signs is poor *(see Table 1),* and a structured clinical assessment including all information available from the history, examination and historical records should be undertaken. The clinical features that influence the probability that episodic respiratory symptoms are due to asthma are summarised in Table 2.

Alternative explanations for the symptoms or signs and/or the possibility of comorbid conditions such as COPD in adults with a smoking history, obesity, and dysfunctional breathing, which can produce features that mimic asthma, must be considered *(see Tables 4 and 5)*. For working adults with airflow obstruction, occupational asthma should be considered and suitable screening questions asked *(see section 13.3).*

Table 2: Factors to consider in an initial structured clinical assessment

Episodic symptoms *(see sections 3.2.1 and 3.2.2)*[13,21-24,64,74,75] More than one of the symptoms of wheeze, breathlessness, chest tightness and cough occurring in episodes with periods of no (or minimal) symptoms between episodes. Note that this excludes cough as an isolated symptom in children.[76] For example: • a documented history of acute attacks of wheeze, triggered by viral infection or allergen exposure with symptomatic and objective improvement with time and/or treatment • recurrent intermittent episodes of symptoms triggered by allergen exposure as well as viral infections and exacerbated by exercise and cold air, and emotion or laughter in children • in adults, symptoms triggered by taking non-steroidal anti-inflammatory medication or beta blockers. An historical record of significantly lower FEV_1 or PEF during symptomatic episodes compared to asymptomatic periods provides objective confirmation of the obstructive nature of the episodic symptoms.
Wheeze confirmed by a healthcare professional on auscultation *(see section 3.2.1)*[23,25] It is important to distinguish wheezing from other respiratory noises, such as stridor or rattly breathing. Repeatedly normal examination of chest when symptomatic reduces the probability of asthma.
Evidence of diurnal variability[21-23,34,74] Symptoms which are worse at night or in the early morning. **Atopic history** *(see section 3.2.4)*[19,23,64,75,77,78] Personal history of an atopic disorder (ie eczema or allergic rhinitis) or a family history of asthma and/or atopic disorders, potentially corroborated by a previous record of raised allergen-specific IgE levels, positive skin prick tests to aeroallergens or blood eosinophilia.
Absence of symptoms, signs or clinical history to suggest alternative diagnoses (including but not limited to COPD, dysfunctional breathing, obesity) *(see section 3.3.3).*

D **Undertake a structured clinical assessment to assess the initial probability of asthma. This should be based on:**

- **a history of recurrent episodes** (attacks) **of symptoms, ideally corroborated by variable peak flows when symptomatic and asymptomatic**
- **symptoms of wheeze, cough, breathlessness and chest tightness that vary over time**
- **recorded observation of wheeze heard by a healthcare professional**
- **personal/family history of other atopic conditions** (in particular, atopic eczema/dermatitis, allergic rhinitis)
- **no symptoms/signs to suggest alternative diagnoses.**

3.3.2 HIGH PROBABILITY OF ASTHMA BASED ON INITIAL STRUCTURED CLINICAL ASSESSMENT

Adults and children with a typical clinical assessment including recurrent episodes of symptoms ('attacks'), wheeze heard by a healthcare professional, historical record of variable airflow obstruction and a positive history of atopy *(see Table 2)* and without any features to suggest an alternative diagnosis *(see Tables 4 and 5)* have a high probability of asthma.[23] If there is doubt, the diagnosis should be considered as being of intermediate probability and further investigations will be needed *(see section 3.3.4)*. 2^{+}

Obstructive spirometry and a positive bronchodilator test provide objective evidence of variable airflow obstruction,[19] and further increase the probability of asthma.[20,23,26] However, as spirometry has a false negative rate of at least 50%,[19] normal spirometry does not rule out asthma.[26] If the patient is symptomatic, peak flow charting if performed correctly may provide objective evidence of variability. 2^{++} 2^{+}

✓ In patients with a high probability of asthma:

- record the patient as likely to have asthma and commence a carefully monitored initiation of treatment (typically six weeks of inhaled corticosteroids) *(see Table 3)*
- assess the patient's status with a validated symptom questionnaire, ideally corroborated by lung function tests (FEV_1 at clinic visits or by domiciliary serial peak flows)
- with a good symptomatic and objective response to treatment, confirm the diagnosis of asthma and record the basis on which the diagnosis was made
- if the response is poor or equivocal, check inhaler technique and adherence, arrange further tests and consider alternative diagnoses.

3.3.3 LOW PROBABILITY OF ASTHMA BASED ON INITIAL STRUCTURED CLINICAL ASSESSMENT

Adults and children who do not have any of the typical features on initial structured clinical assessment *(see Table 2)* or who have symptoms suggestive of an alternative diagnosis *(see Tables 4 and 5)* have a low probability of asthma.

✓ If there is a low probability of asthma and/or an alternative diagnosis is more likely, investigate for the alternative diagnosis and/or undertake or refer for further tests of asthma.

Table 3: A monitored initiation of treatment in patients with suspected asthma

In patients with suspected asthma
1. Record the patient as having 'suspected asthma'.
2. Proceed to a carefully monitored initiation of treatment. The initial choice of treatment will be based on an assessment of the degree of asthma severity. Typically this will be six weeks of inhaled steroids through a device the patient can use *(see sections 7.2, 8.1, 8.4)* but in more acute clinical circumstances a course of oral steroids may be appropriate *(see section 9.3.3)*.
3. Assess the baseline status using a validated questionnaire (eg Asthma Control Questionnaire or Asthma Control Test) *(see Table 7)* and/or lung function tests (spirometry or peak expiratory flow) *(see section 3.2.2)*.
4. Arrange a follow-up appointment in 6–8 weeks in order to assess response to treatment.
5. At the follow-up appointment, symptomatic response may be assessed with a validated questionnaire *(see Table 7)*. Lung function may be monitored with FEV_1 at clinic visits or domiciliary serial peak flows.
If the objective response is good (ie a clinically important improvement in symptoms and/or substantial increase in lung function)
6. Confirm the diagnosis of asthma and record the basis on which the diagnosis was made.
7. Adjust the treatment according to the response (for example, titrating down the dose of inhaled steroid) to the lowest dose that maintains the patient free of symptoms. Careful observation during a trial of withdrawing treatment will also identify patients whose improvement was due to spontaneous remission (this is particularly important in children).
8. Provide self-management education and a personalised asthma action plan *(see section 5.2.2*) before arranging repeat prescribing so that the patient is aware of the action to take if their control deteriorates.
If the objective response is poor or equivocal
9. Discuss adherence and recheck inhaler technique as possible causes of treatment failure.
10. Arrange further tests or consider alternative diagnoses (*see section 3.3.3*). It will usually be appropriate to withdraw the treatment.

Table 4: Clinical clues to alternative diagnoses in wheezy children

Clinical clue	Possible diagnosis
Perinatal and family history	
Symptoms present from birth or perinatal lung problem	Cystic fibrosis; chronic lung disease of prematurity; ciliary dyskinesia; developmental lung 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[79]	Cystic fibrosis; bronchiectasis; protracted bacterial bronchitis; recurrent aspiration; host defence disorder; ciliary dyskinesia
Excessive vomiting	Gastro-oesophageal reflux (with or without aspiration)
Paroxysmal coughing bouts leading to vomiting	Pertussis
Dysphagia	Swallowing problems (with or without aspiration)
Breathlessness with light headedness and peripheral tingling	Dysfunctional breathing, 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 lung anomaly; cystic fibrosis; post-infective disorder; recurrent aspiration; inhaled foreign body; bronchiectasis; tuberculosis

Table 5: Clinical clues to alternative diagnoses in adults

Clinical clue	Possible diagnosis
Without airflow obstruction	
Predominant cough without lung function abnormalities	Chronic cough syndromes; pertussis
Prominent dizziness, light-headedness, peripheral tingling	Dysfunctional breathing
Recurrent severe 'asthma attacks' without objective confirmatory evidence	Vocal cord dysfunction
Predominant nasal symptoms without lung function abnormalities	Rhinitis
Postural and food-related symptoms, predominant cough	Gastro-oesophageal reflux
Orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema, pre-existing cardiac disease	Cardiac failure
Crackles on auscultation	Pulmonary fibrosis
With airflow obstruction	
Significant smoking history (ie, >30 pack-years), age of onset >35 years	COPD
Chronic productive cough in the absence of wheeze or breathlessness	Bronchiectasis*; inhaled foreign body*; obliterative bronchioitis; large airway stenosis
New onset in smoker, systemic symptoms, weight loss, haemoptysis	Lung cancer*; sarcoidosis*

* may also be associated with non-obstructive spirometry

3.3.4 INTERMEDIATE PROBABILITY OF ASTHMA BASED ON INITIAL STRUCTURED CLINICAL ASSESSMENT

Adults and children who have some, but not all, of the typical features of asthma on an initial structured clinical assessment *(see Table 2)* or who do not respond well to a monitored initiation of treatment *(see Table 3)* have an intermediate probability of asthma.[20,23,70] They require clinical assessment and investigation before a diagnosis can be made and, unless the clinical condition is acute, before treatment is commenced or continued. Particular care may be needed in conditions known to overlap with or mimic asthma, for example COPD (which may need to be distinguished from fixed airflow obstruction as a result of airway remodelling in chronic asthma), obesity, anxiety/panic, or dysfunctional breathing. 2+ 3

Spirometry enables differentiation of obstructive and non-obstructive lung function, which determines the differential diagnosis *(see Tables 4 and 5)* and approach to investigation. Spirometry is useful for confirming the diagnosis of asthma but is not sufficiently specific to rule it out.[19,80]

D **Spirometry, with bronchodilator reversibility as appropriate, is the preferred initial test for investigating intermediate probability of asthma in adults, and in children old enough to undertake a reliable test.**

Adults and children with airways obstruction

Asthma is the by far the commonest cause of airways obstruction identified through spirometry in children. Obstruction due to other disorders is much more common in adults than in children. Patients may have more than one cause of airflow obstruction, which complicates the interpretation of any test. In particular, asthma and COPD commonly coexist in adults.

A bronchodilator reversibility test and/or a monitored initiation of treatment (typically six weeks of inhaled corticosteroids (ICS) can establish whether or not the airflow obstruction reverses to normal with treatment. Evidence of a symptomatic response, ideally using objective measures of asthma control and lung function, should be sought at a follow-up visit. If there is significant reversibility or improvement in symptom scores, confirm the diagnosis of asthma and record the basis on which the diagnosis was made. Continue to treat as asthma, but aim to find the minimum effective dose of therapy.

If the patient remains asymptomatic consider a trial of reduction or withdrawal of treatment. This is particularly important in children in whom natural resolution of symptoms is more common than in adults.

✓ In adults and children with an intermediate probability of asthma and airways obstruction identified through spirometry, undertake reversibility tests and/or a monitored initiation of treatment assessing the response to treatment by repeating lung function tests and objective measures of asthma control.

Adults and children without airways obstruction

In patients with normal spirometry results consider arranging challenge tests with methacholine, exercise or mannitol in order to test for airway hyper-responsiveness.[19,30,42] Alternatively, a positive FeNO test indicates the presence of eosinophilic inflammation and increases the probability of asthma.[19,34,80-83]

Investigation of atopic status, serum specific-IgE and allergen skin-prick tests may be of value in selected patients; a normal result reduces the probability of asthma.[19] Consider performing additional investigations such as full lung function tests and a chest X-ray in any patient presenting with atypical or additional symptoms or signs. A study in primary care in children age 0–6 years concluded that a chest X-ray, in the absence of a clinical indication, need not be part of the initial diagnostic work up but may be reserved for children with severe disease or clinical clues suggesting other conditions.[84]

✓ In adults and children with an intermediate probability of asthma and normal spirometry results, undertake challenge tests and/or measurement of FeNO to identify eosinophilic inflammation.

Children unable to undertake spirometry

In some children, and particularly pre-school children, 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 that occur only with viral upper respiratory infections, it is often reasonable to give no maintenance treatment and to plan a review of the child after an interval agreed with the parents/carers.

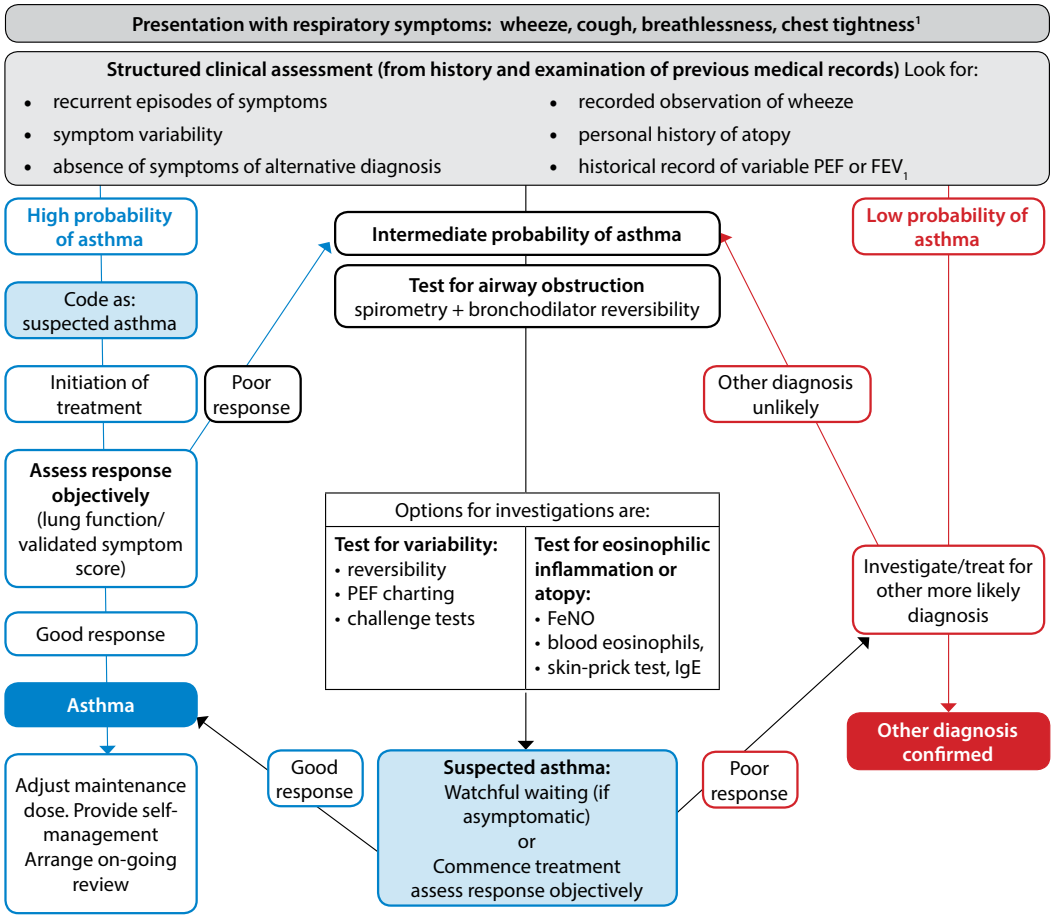
Monitored initiation of treatment (see Table 3). Most children under five years of age and some older children cannot perform spirometry. In these children, offer a monitored initiation of treatment for a specific period. The choice of treatment (for example inhaled corticosteroids) depends on the severity and frequency of symptoms.

Monitor treatment for 6–8 weeks and 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:

- consider watchful waiting if the child is asymptomatic
- offer a carefully monitored initiation of treatment if the child is symptomatic.

Figure 1: Diagnostic algorithm



[1] In children under 5 years and others unable to undertake spirometry in whom there is a high or intermediate probability of asthma, the options are monitored initiation of treatment or watchful waiting according to the assessed probabilityof asthma.

3.3.5 DIAGNOSTIC INDICATIONS FOR REFERRAL

At any point in the diagnostic algorithm, there may be a need for referral for additional

investigations and/or specialist advice. Some key indications for referral to specialist care are listed in Table 6.

Table 6: Diagnostic indications for specialist referral

Adults	Children
Referral for tests not available in primary care	
Diagnosis unclear	Diagnosis unclear
Suspected occupational asthma (symptoms that improve when patient is not at work, adult-onset asthma and workers in high-risk occupations)	
Poor response to asthma treatment	Poor response to monitored initiation of asthma treatment
Severe/life-threatening asthma attack	Severe/life-threatening asthma attack
'Red flags' and indicators of other diagnoses	
Prominent systemic features (myalgia, fever, weight loss)	Failure to thrive
Unexpected clinical findings (eg crackles, clubbing, cyanosis, cardiac disease, monophonic wheeze or stridor)	Unexplained clinical findings (eg focal signs, abnormal voice or cry, dysphagia, inspiratory stridor)
Persistent non-variable breathlessness	Symptoms present from birth or perinatal lung problem
Chronic sputum production	Excessive vomiting or posseting
Unexplained restrictive spirometry	Severe upper respiratory tract infection
Chest X-ray shadowing	Persistent wet or productive cough
Marked blood eosinophilia	Family history of unusual chest disease
	Nasal polyps
Patient or parental anxiety or need for reassurance	

3.4 ORGANISATION OF DIAGNOSTIC SERVICES

A structured clinical assessment and some diagnostic tests (for example spirometry with bronchodilator reversibility) are readily available in primary care, although specialist expertise may be needed in young children. Other tests, such as FeNO and skin-prick testing, are only available in some secondary care settings and a few primary care practices. Some tests (for example challenge tests) will require referral to a diagnostic centre.

In the future, this may require additional provision of specialist-led diagnostic services to support general practitioner (GP) assessment. For example a regional asthma-COPD diagnostic service in the Netherlands available to support GPs' assessment reported that the service agreed with the GPs' working diagnosis of asthma in 62% of cases, and was able to provide a diagnosis for 95% of the patients in whom GPs were uncertain.[16,72]

C **Streamlined referral pathways should be developed for tests not available or appropriate in primary care.**

3.5 WHEEZING IN PRE-SCHOOL CHILDREN AND THE FUTURE RISK OF DEVELOPING PERSISTENT ASTHMA

Several factors are associated with a high (or low) risk of developing persisting wheezing or asthma through childhood.[77,85] 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.[86-89] 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.[90,91] Boys with asthma are more likely to grow out of their asthma during adolescence than girls.[64,86,90,92-105]

Severity and frequency of previous wheezing episodes

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.[75,78,86,88,94,106-108]

Coexistence of atopic disease

A history of other atopic conditions such as eczema and rhinitis increases the probability of asthma. Positive tests for atopy in a wheezing child also increase the likelihood of asthma. A raised specific IgE to wheat, egg white, or inhalant allergens such as house dust mite and cat dander, predicts later childhood asthma.[109,110] 2++

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

Family history of atopy

A family history of atopy is the most clearly defined risk factor for atopy and asthma in children. The strongest association is with maternal atopy, which is an important risk factor for the childhood onset of asthma and for recurrent wheezing that persists throughout childhood.[87,102,105,111,112] 2++

Abnormal lung function

Persistent reductions in baseline airway function and increased airway responsiveness during childhood are associated with having asthma in adult life.[91] 3

4 Monitoring asthma

4.1 MONITORING ASTHMA IN CHILDREN

4.1.1 BIOMARKERS

Studies in children have shown that routine serial measurements of peak expiratory flow,[113-115] airway hyper-responsiveness[116] or FeNO[117-120] 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 asthma attack (p=0.01).[121] In a further study of children with asthma who were not taking ICS, 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 attack in the following four months.[122]

A small prospective observational study in 40 children suggested that serial measurements of FeNO and/or sputum eosinophilia may guide step down of ICS.[123] Another small study of 40 children showed that a rising FeNO predicted relapse after cessation of ICS.[119] 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 7 summarises the methodology, measurement characteristics and interpretation of some of the validated tools used to assess symptoms and other aspects of asthma.

4.1.2 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 reliever (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.

✓ Healthcare professionals should be aware that the best predictor of future asthma attacks is current control.

4.2 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 of asthma attacks.[124] Patients with poor lung function and with a history of asthma attacks in the previous year may be at greater risk of future asthma attacks for a given level of symptoms.

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

A management strategy that controls eosinophilic airway inflammation[125-127] or airway hyper-responsiveness[128] can result in better control of asthma attacks than one which controls immediate clinical manifestations; the benefits of inflammation-guided management are greater in patients with severe asthma, when asthma attacks 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 7 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, such as sputum eosinophil count, airway responsiveness and FeNO, rather than immediate clinical control. Risk reduction, for example minimising future adverse outcomes such as asthma attacks, 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 reliever (blue) inhaler?".

4.3 MONITORING CHILDREN IN PRIMARY CARE

Asthma is best monitored in primary care by routine clinical review on at least an annual basis *(see section 14.3)*.

✓ The factors that should be monitored and recorded include:

- symptom score, eg Children's Asthma Control Test, Asthma Control Questionnaire
- asthma attacks, oral corticosteroid use and time off school/nursery due to asthma since last assessment
- inhaler technique
- adherence, which can be assessed by reviewing prescription refill frequency
- possession of and use of a self-management plan/written personalised asthma action plan
- exposure to tobacco smoke
- growth (height and weight centile).

4.4 MONITORING ADULTS IN PRIMARY CARE

Asthma is best monitored in primary care by routine clinical review on at least an annual basis *(see section 14.3)*. The factors that should be monitored and recorded include: symptomatic asthma control; lung function; asthma attacks, oral corticosteroid use and time off work or school since last assessment; inhaler technique *(see section 8);* adherence *(see section 5.4)*; bronchodilator overuse, especially more than 12 short-acting β_2 agonist (SABA) inhalers per year *(see sections 7.1.1 and 9.1.2)*; and possession of and use of a self-management plan/written personalised asthma action plan *(see section 5.3.2)*.

Symptomatic asthma control is best assessed using directive questions such as the Royal College of Physicians' '3 questions',[129] or the Asthma Control Questionnaire or Asthma Control Test (*see Table 7*), since broad non-specific questions may underestimate symptoms. 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 asthma attacks. Adherence to treatment and bronchodilator reliance can both be assessed by reviewing prescription refill frequency.

✓ In adults the following factors should be monitored and recorded in primary care:

- symptomatic asthma control
- lung function assessed by spirometry or by PEF
- asthma attacks, oral corticosteroid use and time off work since last assessment
- inhaler technique
- adherence
- bronchodilator reliance
- possession of and use of a self-management plan/personal action plan.

Table 7: Summary of tools that can be used to assess asthma

Measurement	Methodology	Measurement characteristics	Comments
Spirometry[130,131]	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)[39,46,50,113-115,132]	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 is 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 3 Questions[129]	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.
Asthma Control Questionnaire (ACQ)[133-136]	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 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 children older 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 [137,138]	Response to 5 questions, 3 related to symptoms, 1 medication use and 1 overall control. Five-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 need to be defined.	Validated in adults and children aged 4 years and older (the childhood asthma control test is valid 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 not defined.
Mini Asthma Quality of Life Questionnaire [134,139,140]	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 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 Asthma Quality of Life Questionnaire is validated in adults and the Paediatric Asthma Quality of Life Questionnaire has been validated for the age range 7–17 years.

Measurement	Methodology	Measurement characteristics	Comments
Airway responsiveness[128]	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 (FeNO)[57,83,119,123,126,141,142]	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 FeNO and eosinophilic airway inflammation, which is independent of gender, age, atopy and ICS 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 FeNO (>50 ppb in adults and >35 ppb in children) is predictive of a positive response to corticosteroids. The evidence that FeNO 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 FeNO (<25 ppb in adults; <20 ppb in the 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[125,143-145 123]	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 asthma attacks in adult patients with severe disease. In children, one study found benefit in using sputum eosinophils to guide reductions of ICS treatment in conjunction with FeNO.

Research is needed to develop asthma attack 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.

5 Supported self management

Self management has been defined as the tasks that individuals must undertake to live with chronic conditions including, "having the confidence to deal with medical management, role management and emotional management of their conditions".[146] In the context of asthma, self management has focused 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.[147]

5.1 EFFECTIVENESS OF SUPPORTED SELF MANAGEMENT

There is a substantial body of evidence to show that self-management education incorporating written PAAPs improves health outcomes for people with asthma. Twenty-two systematic reviews of 261 randomised controlled trials (RCTs) encompass evidence from a broad range of demographic, clinical and healthcare contexts.[148-169] In addition, 35 RCTs provide further evidence about self management in pre-school children,[170-178] ethnic minorities,[179-190] and primary care-based populations.[188,191-199] 1+

Self-management education delivered to adults or children with asthma (and/or their parents/carers): 1++

- reduces emergency use of healthcare resources, including emergency department (ED) visits, hospital admissions and unscheduled consultations[148,150,154-157,159,169]
- improves markers of asthma control, including reduced symptoms and days off work, and improves quality of life.[148,150,151,157,159-161]

Patients with all severities of asthma were included in these systematic reviews, although some focused specifically on people who had attended EDs,[169] or with severe or difficult asthma.[154] Most self-management education was delivered in healthcare settings, but some specifically evaluated school,[163] home,[165] or community-based interventions.[166] Typically, education was delivered by healthcare professionals either in individual consultations or group settings, but some systematic reviews included technology-based interventions,[152,153] or were part of community-health interventions for deprived and/or ethnic minority groups.[167,168]

5.2 COMPONENTS OF A SELF-MANAGEMENT PROGRAMME

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

5.2.1 PATIENT EDUCATION

Education is a core component of effective self-management programmes in adults.[148,154,169] and children.[155-159] There is evidence that educational interventions that were supported by a written PAAP and regular professional review were more effective than less intensive regimes.[148,151,156,158,159] 1++

Information technology (IT)-based education has been shown to have potential, but as yet there is no consistent evidence on which to base recommendations on format, target audiences or the context in which it should be delivered.[152]

5.2.2 PERSONALISED ASTHMA ACTION PLANS

Written PAAPs (for example, those for adults and children from Asthma UK, available at www.asthma.org.uk/resources/#action plans*)* are crucial components of effective self-management education.[91,148,150,160-162,169] One systematic review identified the features of PAAPs associated with beneficial outcomes *(see Table 8)*.[150] These include:

- specific advice about recognising loss of asthma control, assessed by symptoms or peak flows or both.[91,150,151] In children, symptom-based written plans are effective in reducing emergency consultations for asthma, although (in older children) peak flow-based plans may be as effective for other outcomes.[160,161] 1++ 1+
- actions, summarised as two or three action points, to take if asthma deteriorates, including seeking emergency help, starting oral steroids (which may include provision of an emergency course of steroid tablets), restarting or temporarily increasing (as opposed to just doubling) ICS, as appropriate to clinical severity[150] *(see Table 8 for further advice)*.

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

Every asthma consultation is an opportunity to review, reinforce and extend both the patient's knowledge and skills. This is true whether the patient is seen in primary care, the ED 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 asthma attack. 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.
- Education should include personalised discussion of issues such as trigger avoidance and achieving a smoke-free environment to support people and their families living with asthma.
- Brief simple education linked to patient goals is most likely to be acceptable to patients.

The role of telehealthcare interventions in supporting self management is covered in section 14.4.

Table 8. Summary of the key components of a written personalised asthma action plan (adapted from Gibson et al)[150]

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

5.3 SELF MANAGEMENT IN SPECIFIC PATIENT GROUPS

A range of different patient populations are included in the trials of self management. It cannot be assumed that a successful intervention in one setting will be feasible or appropriate in another.

5.3.1 PRIMARY CARE

Studies of self-management interventions based in primary care have shown that they can: 1^{++} 1^{+}

- reduce emergency use of healthcare resources, including ED attendances, hospital admissions and unscheduled consultations[188,194]
- improve markers of asthma control.[188,191,192,194-197,201]

Implementation of self-management interventions is challenging. The improved asthma control demonstrated in trials of interventions delivered by members of the research team[188,194] or in a centrally administered initiative[195,196] are reflected in some,[191,192,197,201] but not all,[198,199] 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.[193] Studies based in the USA suggest that in deprived and/or ethnic communities the involvement of community health workers reduces ED attendance.[166] 2

A **Self-management education, supported by a written personalised 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 of self-management interventions 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 ongoing support and advice
- IT-based education and monitoring
- involvement of community workers to support clinical teams in deprived and/or ethnic minority communities.

5.3.2 SECONDARY CARE

There is good evidence that self-management education targeted at people who have a history of ED attendances[169] or hospital admissions[189,202] can reduce subsequent use of healthcare resources. Self-management education delivered prior to discharge can reduce readmissions[203-205] and should be a core component of discharge planning *(see section 9.9.7)*. 1++

One wide-reaching review of the evidence for self management in severe or difficult asthma concluded that provision of psychoeducational interventions (especially those incorporating formal self management) may reduce hospital admissions and, in children, improve symptoms.[154] 1+

A **Prior to discharge, inpatients should receive written personalised asthma action plans, given by healthcare professionals with expertise in providing asthma education.**

5.3.3 SCHOOLCHILDREN

School-based asthma education has been shown to:

- improve process outcomes (knowledge, self efficacy, self-management behaviours)[163]
- improve markers of asthma control (number of days and nights with asthma symptoms, school absences, asthma-related quality of life).[163,164] 1++

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.[163]

A **School health services should consider providing in-school asthma self-management education programmes provided by appropriately trained personnel.**

5.3.4 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 ED visits, hospital admissions and unscheduled consultations,[172,177] and no[172] or limited[177] reduction in symptoms, despite increased ownership of PAAPs.[177] 1-

Other trials including pre-school children and children up to the age of eight years showed only small and often transient effects of no apparent clinical significance.[170,171,174-176]

5.3.5 ETHNIC MINORITY GROUPS

Interventions specifically designed for ethnic minority groups, predominantly deprived African-American, Hispanic or Puerto Rican populations from inner cities in the USA,[168,179-187] can: 1++ 1+ 1- 2+

- reduce emergency use of healthcare resources, including ED attendances, hospital admissions and unscheduled consultations[167,168,182,183,185]
- improve markers of asthma control[167,168,179,180,183,185]
- improve process outcomes (knowledge).[167,168,184,186]

In two UK-based RCTs, however, interventions which provided appropriate language materials and were delivered by bilingual professionals were reported as showing no or less benefit on healthcare outcomes in the South Asian population compared to the benefits seen in the white European population.[188,189] 1++ 1+

There is insufficient evidence to identify all the aspects of cultural tailoring which may potentially contribute to effectiveness of self-management interventions, but addressing language barriers (for example, 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.[188,189] 1++ 1+

The strategies employed in ethnic minority groups are varied and include community-based neighbourhood projects,[181,185,186] family-based education,[182] nurse-led home visits,[180] IT-based programmes,[179,183,184] and school-based educational interventions.[183,187] No one strategy stands out as being always effective, or always ineffective. Lack of engagement with programmes and high drop-out rates are major barriers to effectiveness of self-management interventions.[180,181,185,186] Reconfiguration of the supporting healthcare system appears to increase the impact.[168] 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 community languages with ethnically appropriate pictures
- asthma educators fluent in community languages
- identifying culturally appropriate support agencies within the local community
- inclusion of culturally specific beliefs and practices
- reference to culturally appropriate role models
- involvement of a local community health worker to support clinical teams.

5.4 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 healthcare professional's instructions.[206] Sharing decision making and achieving concordance improves (though does not guarantee) adherence.[207]

5.4.1 ADHERENCE TO MONITORING AND TREATMENT

Adherence to regular monitoring with peak flow meters, even in clinical drug trials is poor, with recorded daily use as low as 6%.[208,209] The lack of evidence supporting long-term peak flow monitoring,[49,210-212] 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, and as part of a PAAP during asthma attacks.[212] Comparison should be with the patient's best peak flow (not predicted).[150]

It is estimated that between a third and a half of all medicines prescribed for long-term conditions are not taken as recommended,[213] and evidence in asthma confirms widespread non-adherence to regular preventer medication,[214-219] that increases over time.[214,216] Poor adherence should always be considered when there is a failure to control asthma symptoms. 1+ 3

Non-adherence to medication use may be intentional and/or unintentional and may be understood as the result of the interaction of perceptual factors (for example, beliefs about illness and treatment) and practical factors (forgetfulness, capacity, resources and opportunity).[213] 4

A widely recognised model for understanding patients' decisions about medication use is the Necessity-Concerns framework which describes the balance between the potential benefits and 'necessity' of taking prescribed treatment and the perceived disadvantages or 'concerns' about taking medication.[220] The relative weight of these opposing arguments influences the decision to take medication (or not).[221,222]

5.4.2 ASSESSING MEDICATION ADHERENCE

In most clinical contexts, the key strategies for assessing adherence are self reporting and the prescribing record, although biochemical assays may have a role in asthma clinics for patients with severe asthma *(see section 10.2.1)*. In a research context electronic dose monitoring is the gold standard; counting doses used is another approach that is frequently used.

Patient self reporting is simple, inexpensive and feasible in most clinical settings. Self reporting typically overestimates adherence by a third compared to electronic monitoring[213,216,219] or dose counting.[214,215] This applies both in trial populations[214,216,219] and clinical settings.[215] Underuse is over-reported,[214-216,219] and overuse is under-reported,[219] reflecting socially acceptable answers.[213] Patients/caregivers who report missing doses or not taking medication are likely to be non-adherent,[213,215,216] though their estimate of dosages taken may still be inaccurate.[213] Being non-judgemental, and asking specific questions about use of a treatment over a short time period (for example, in the last week/month) can help elicit an accurate response.[213] Questionnaires have been validated for use in research,[220] but have not been validated as a tool in clinical use.[213] 1+ 3 4

Computerised prescribing records

Computerised prescribing records, normally readily available in primary care consultations and/or pharmacy dispensing records, provide a useful indication of adherence to prescribed asthma regimens. At an individual level, prescribing data does not correlate with self-reported adherence and may be a useful strategy for opening a discussion about suspected poor adherence.[221] At a population level, formulae (such as 'proportion of days covered' by the prescription recorded over a defined period) have been devised to assess adherence from routine prescribing/dispensing databases.[217,218,221,223]

Biomarker testing

Biomarker testing with FeNO or biochemical urinary assays (for example a metabolite of fluticasone propionate) may have a role in establishing (non-)adherence in people with severe/difficult asthma.[224,225] Suppression of FeNO after five days of directly observed inhaled steroid dosage has been shown to be an objective test to distinguish adherent from non-adherent patients with difficult asthma *(see section 10.2.1)*.[224] 2+

Electronic monitoring

Electronic monitoring is the gold standard for assessing adherence in the research context, although not normally available in routine clinical practice.[216,219] Dose counting is also used as a comparator, although unlikely to be feasible in a clinical context.[214,215]

1+
3

D **To assess adherence, ask specific questions about medication use and assess prescribing and any other data available. Explore attitudes to medication as well as practical barriers to adherence in a non-judgemental way.**

✓ Questions about adherence should be open ended, acknowledge that poor adherence is the norm, and avoid use of potentially judgmental terminology. The questions are designed to stimulate an open discussion.

- Explore perceived benefits ("How do you think that the inhaler is helping you control your asthma?" "Are there times when you find that you don't need your inhaler?")
- Ask about adverse reactions ("How much bother do you have from side effects?")
- Acknowledge general concerns about regular medication ("Some people worry about taking regular medication… what do you think?")
- Acknowledge practical difficulties with regular medication ("People sometimes find it difficult to remember to take regular treatment…")
- Ask about adherence over a specific time period ("How often did you use your preventer inhaler last week?")

5.4.3 INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

Six systematic reviews were identified that evaluated interventions to improve adherence, one specifically in asthma,[226] and five including a number of long-term conditions including asthma.[227-231] The body of evidence represents 26 unique asthma trials.

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.

Multifaceted interventions to improve adherence have:

1++
1+
1-
2+

- modest effects on adherence[226,227,229,230,232-237]
- less, or sometimes no, effect on clinical outcomes.[227,229,230,232,234-237]

The effect is greater if the intervention:

1++
1+
1-
2+
3

- includes behavioural components[229,230,232]
- includes practical facilitators (such as simplified dosage regimes),[237] strategies to aid integration into daily routines,[238] automated reminders,[234-236] monitoring and follow up[226]
- is monitored, delivered and sustained as part of a comprehensive programme of accessible proactive asthma care.[226,227-

Innovative, IT-based ways to support adherence show some promise (for example, providing daily medication reminders,[234] feedback on adherence,[236] refill reminders[235]) especially if they are interactive,[235,236] but as components of, as opposed to replacement for, on-going supportive care *(see section 14.4.1)*.[226,227] 1++ 1+ 1-

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

✓ Initiatives to promote adherence to regular treatment should consider:

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

5.5 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.[239,240] 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.

A systematic review (including 14 RCTs, 2,438 patients, 107 doctors and 43 primary care teams) investigated the promotion of PAAP ownership and usage.[241] In addition, 19 implementation studies from the USA,[195,198,242-248] UK,[11,199,249,250] Scandinavia,[251-253] Italy,[254] and Brazil were identified.[255,256]

5.5.1 TYPES OF INTERVENTION

The interventions in the implementation studies adopted four main strategies:

- primarily professional training[198,199]
- primarily organisational change[11,249,251]
- primarily patient education[195,243-246,254]
- a whole systems approach with components operating explicitly at patient, professional and organisational levels.[242,247,248,250,252,253,255,256]

Study designs varied, with five cluster randomised trials,[198,199,244,245,249] a preference trial with randomised groups,[195] or controlled implementation.[11] Seven were based on longitudinal, often large, databases,[242,243,246-248,252,253,256] one with a control cohort,[255] and two uncontrolled before-and-after[250,254] or cross-sectional studies.[251]

5.5.2 IMPLEMENTATION OF INTERVENTIONS

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++ 1-

- improved knowledge[248] and action plan ownership[241,246,250]
- reduced unscheduled care,[247,248,252,255,256] and improved markers of control.[246-248,252,253]

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.[198,199] Organisational change to support self management improves process outcomes such as the proportion of patients with PAAPs or achieving a review,[11,249,251] but improved asthma control in only one of the studies.[251] Targeting the patient with educational material,[246] support from pharmacists,[243] school,[244,254] or telephone calls[195,244,245] improved medication use,[195,245] knowledge,[244] and ownership of PAAPs,[243] 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 an organisation which prioritises and actively supports self management. This should include strategies to proactively engage and empower patients and train and motivate professionals as well as providing an environment that promotes self management and monitors implementation.**

6 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.

6.1 PRIMARY PREVENTION

The evidence for primary interventional strategies is based predominantly on observational studies, although some interventions 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.

6.1.1 MONO- AND MULTIFACETED ALLERGEN AVOIDANCE

Early life exposure to allergens (including aeroallergens and ingested food allergens) may lead to allergic sensitisation and so potentially increase the risk of subsequent asthma, particularly in children at high risk (that is, children with a family history of asthma or atopy, particularly a parental history). It is unclear whether the risk of developing asthma in children is reduced by interventions to reduce exposure to single allergens (monofaceted), or whether multifaceted 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 of trials comparing single (six studies) or multiple (three studies) interventions 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, odds ratio (OR) 0.52, 95% confidence interval (CI) 0.32 to 0.85).[257] 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. Healthcare professionals can discuss and support this intervention in families who are motivated to follow the demanding programme. 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.[257] 1++

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 for the primary prevention of asthma.**

A **For children at risk of developing asthma, complex, multifaceted interventions targeting multiple allergens may be considered in families able to meet the costs, demands and inconvenience of such a demanding programme.**

6.1.2 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.[258] Sensitisation to house dust mite is an important risk factor for the development of asthma,[259,260] and a few studies have suggested that high early house dust mite exposure increases the risks of subsequent asthma.[261,262] 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 associations with family history and birth order.[263]

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;[264] others have shown no effect on either allergic sensitisation or symptoms of allergic diseases.[265] In one UK study, early results from environmental manipulation started in early pregnancy and focused mainly on house dust mite avoidance, showed reductions in some respiratory symptoms in the first year of life.[266] Subsequent results showed a paradoxical effect with increased allergy but better lung function in the intervention group.[267] 1+

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

A **Healthcare professionals should not recommend house dust mite aeroallergen avoidance for the primary prevention of asthma.**

Pets in the home

A large number of birth cohort studies, longitudinal cohort studies and cross-sectional studies have addressed whether exposure to pets in the home in early life increases or reduces the subsequent risk of asthma and allergy, with contradictory results. Four recent systematic reviews, synthesising evidence from overlapping data sources, have provided conflicting results. One review concluded that exposure to cats in early life has a slight preventative effect on subsequent asthma, while exposure to dogs increases risk.[268] Another concluded, in contrast, that perinatal dog exposure protects against asthma, with no affect from cats.[269] Methodological factors, however, 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.[270,271] The most methodologically sound study pooled individual participant data from 11 European birth cohort studies 2++ 2+ 2-

and so was able to harmonise exposure, outcome and age group definitions and use individual data rather than pooled risk estimates in heterogeneous groups, to minimise potential confounding.[271] This review concluded that exposure to cats and/or dogs in infancy does not impact on a diagnosis of asthma or on wheezing symptoms in later life, although may influence allergic sensitisation, and that parents should not make choices on pet ownership based on the desire to prevent or reduce asthma symptoms. 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. 2++ 2+ 2-

B **Healthcare professionals should not offer advice on pet ownership as a strategy for preventing childhood asthma.**

6.1.3 FOOD ALLERGEN AVOIDANCE

Sensitisation to foods, particularly eggs, frequently precedes the development of aeroallergy and subsequent asthma.[272] Food allergen avoidance in pregnancy and postnatally has not been shown to prevent the later development of asthma.[273] Allergen avoidance during pregnancy may adversely affect maternal, and perhaps fetal, nutrition.[274] High-dose food allergen exposure during pregnancy may reduce subsequent sensitisation rates by inducing tolerance.[275] 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.**

6.1.4 BREASTFEEDING

A systematic review of observational studies on the allergy preventive effects of breastfeeding indicates that it is effective for all infants irrespective of family history of allergy. The preventive effect is more pronounced in infants at high risk provided they are breastfed for at least four months.[276] However, not all studies have demonstrated benefit and a large birth cohort reported no protective effect against atopy and asthma.[277] 2+

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

C **Breastfeeding should be encouraged for its many benefits, including a potential protective effect in relation to early asthma.**

6.1.5 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.[278] A review of the use of soy formulae found no significant effect on asthma or any other allergic disease.[279] 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.

6.1.6 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.[280] In one study late introduction of egg was associated with a non-significant increase in wheezing in pre-school children.[281]

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

6.1.7 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-3PUFAs with a corresponding increase in intake of n-6PUFAs. This change has been associated with increasing rates of allergic disease and asthma.[280] 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.[282] In a second study, fish oil supplementation started 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.[283] 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.

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),[284] or vitamin E based on maternal pregnancy intake.[285] 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.[280] Observational studies suggest that intervention trials are warranted.

6.1.8 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 and adults of both sexes.[286,287] A high birth weight is also associated with a higher risk of asthma (risk ratio (RR) 1.2, 95% CI 1.1 to 1.3).[286] 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. 2-

Two systematic reviews looking at the association between being overweight or obese in childhood and the development of asthma concluded that high BMI increases the risk of incident asthma, with a dose dependent relationship that was stronger in boys.[288,289] These reviews are, however, based on epidemiological studies and cannot confirm a causal link. 2+

A systematic review of the association between maternal obesity and gestational weight gain in pregnancy, and childhood asthma, concluded that maternal obesity was associated with an increased risk of diagnosed asthma and of ever-wheeze in children from these pregnancies, with each 1 kg/m^2 increase in maternal BMI associated with a 2–3% increase in odds of childhood asthma. High gestational weight gain was associated with higher odds of asthma or ever-wheeze in children (OR 1.16).[290] Prospective studies of weight-loss programmes during pregnancy for obese women and those with high gestational weight gain are needed to clarify the role of this intervention in the prevention of asthma in children resulting from these pregnancies. 2+

C **Weight reduction is recommended in obese patients to promote general health and to reduce subsequent respiratory symptoms consistent with asthma.**

C **Obese and overweight children should be offered weight-loss programmes to reduce the likelihood of respiratory symptoms suggestive of asthma.**

6.1.9 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.[291,292]

The concept is sometimes described as the 'microbial exposure hypothesis'. A double blind placebo controlled trial of the probiotic *Lactobacillus rhamnosus* 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.[293] 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.[294]

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.

6.1.10 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.[295-298] Evidence suggests that early life ETS exposure is associated with later persistent asthma,[299,300] with a strong interaction with genetic polymorphisms which affect antioxidant activity.[30] 2+

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

The limited data on antenatal or early life exposure to other pollutants suggest similar effects to those for ETS, namely increased infant wheezing, enhanced by additional ETS exposure and antioxidant gene variations.[302-304] 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.[305] Further research is required before recommendations for practice can be made. 3 4

6.1.11 IMMUNISATION

In keeping with the microbial exposure hypothesis some studies have suggested an association between tuberculin responsiveness and subsequent reduced prevalence of allergy, implying a protective effect of Bacillus Calmette-Guérin (BCG). At present, it is not possible to determine 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.[306] 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.[307]

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

6.2 SECONDARY NON-PHARMACOLOGICAL PREVENTION

6.2.1 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 (HDM) 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 of 55 trials including 3,121 patients assessed the evidence relating to different methods of reducing exposure to HDM including:

- chemical measures, for example 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).[308] 1++

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.

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 healthcare professionals.**

6.2.2 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[309,310] or a potential for continued high exposure to induce a degree of tolerance.[311] 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.[312,313]

Although fungal exposure has been strongly associated with hospitalisation and increased mortality in asthma, no controlled trials have addressed the efficacy of reducing 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.[314]

Studies of individual aeroallergen avoidance strategies show that single interventions have limited or no benefit. A multifaceted approach is more likely to be effective if it addresses all the indoor asthma triggers. Such approaches may even be cost effective.[315] 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.[316] A systematic review of this topic concluded that more research is required.[317]

6.2.3 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 ICS.[318-321]

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.[322,323] One study in adults with asthma suggested that smoking cessation improved asthma specific quality of life, symptoms and drug requirements.[324] Intervention to reduce smoking has had disappointing outcomes.[325,326] It is likely that more intensive intervention will be required to achieve meaningful outcomes.[327] 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 *(see section 7.2.6 for the effect of smoking on treatment)*.[328] 3

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

6.2.4 AIR POLLUTION

Challenge studies demonstrate that various pollutants can enhance the response to allergen inhalation in patients with asthma.[329,330] 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 in those with infection or allergen exposure.[331,332] Much less attention has been focused on indoor pollutants in relation to asthma and more work is required.[333,334]

Information on current levels of air pollution, recommended actions and health advice is available from The Daily Air Quality Indicator (www.uk-air.defra.gov.uk/air-pollution/daqi).

6.2.5 ELECTROLYTES

Increasing dietary sodium has been implicated in the geographical variations in asthma mortality and high sodium intake is associated with increased bronchial hyper-responsiveness.[335-337] 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.[338] Low magnesium intake has been associated with a higher prevalence of asthma with increasing intake resulting in reduced bronchial hyper-responsiveness and higher lung function.[339] 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 asthma attacks.[340] Studies of oral supplementation are limited and more trials are required.[341-343]

6.2.6 FISH OILS/LIPIDS

In vitro studies suggest that supplementing the diet with n-3PUFAs, which are most commonly found in fish oils, might reduce the inflammation associated with asthma.[344,345] Results from observational studies are inconsistent and a Cochrane review of nine RCTs concluded that there was insufficient evidence to recommend fish oil supplementation for the treatment of asthma.[346]

6.2.7 ANTIOXIDANTS

Observational studies have reported that low vitamin C, vitamin E and selenium intakes are associated with a higher prevalence of asthma.[280] Intervention studies suggest that neither supplementation with vitamin C, vitamin E nor selenium is associated with clinical benefits in people with asthma.[347-349] 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.[350-356] No intervention studies evaluating the intake of fruit or vegetables and their effects on asthma have been reported.

6.2.8 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...".[357] The management of obesity is covered in SIGN 115.[358]

Two more recent RCTs (one small, one large) in adults and one pilot RCT in children investigating the effects of interventions to reduce weight on asthma control and biomarkers of asthma severity, reported reductions in BMI but varying effects on asthma control and biomarkers.[359-361] The pilot study in children (n=32) reported that a 10-week dietary intervention improved asthma control and lung function but had no effect on inflammation. This study was not, however, powered to determine clinical changes; baseline differences between control and intervention groups and in interactions with healthcare staff may have influenced the results.[359] In adults, the smaller trial (n=46) combining dietary (including two free meal replacements a day) and exercise (free gym membership and personal training sessions) components reported improved lung function, asthma symptoms and biomarkers of neutrophilic inflammation with a 5–10% weight loss.[361] The larger trial (n=330), however, reported no significant differences in asthma outcomes between obese adults with asthma receiving a weight loss intervention (combining dietary and exercise components) and those in the control group. Weight loss of more than 10% in either group was, however, associated with improvements in asthma symptom control compared with those with unchanged weight.[360] 1++

Although evidence is limited, these studies show that dietary and weight-loss interventions are feasible in overweight or obese adults and children with asthma and that they may improve asthma control, lung function and inflammation, although weight loss of greater than 10% may be necessary to achieve benefit. 1+

B **Weight-loss interventions** (including dietary and exercise-based programmes) **can be considered for overweight and obese adults and children with asthma to improve asthma control.**

6.2.9 PROBIOTICS

Studies have suggested that an imbalance in gut flora is associated with a higher risk of development of allergy.[362] Trials have investigated the use of probiotics in the treatment of established allergic disease with variable results.[363,364] Only one study focused on asthma, finding a decrease in eosinophilia but no effect on clinical parameters.[365] 1+ 2+

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

6.2.10 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.[366-369]

There is some discussion about whether BCG immunisation may confer protection against allergy and asthma. Research has focused on primary prophylaxis, although 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,[370] but results of trials have been disappointing.[371,372] This is an area that requires further investigation.

There has been concern that influenza vaccination might aggravate respiratory symptoms, although any such effect would be outweighed by the benefits of the vaccination.[373] Studies in children have suggested that immunisation with the vaccine does not exacerbate asthma,[374] but has a small beneficial effect on quality of life in children with asthma.[375] The immune response to the immunisation may be adversely affected by high-dose ICS therapy and this requires further investigation.[376] A Cochrane review of pneumococcal vaccine found very limited evidence to support its use specifically in individuals with asthma.[377] 1++

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

6.2.11 ACUPUNCTURE

A Cochrane review of 21 trials highlighted many methodological problems with the studies reviewed. Only seven of the trials, involving 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 from acupuncture and no significant benefits in relation to lung function.[378] 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 bronchoconstriction 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.[379] Two other trials of acupuncture in relation to induced asthma were also negative.[380,381] 1+

6.2.12 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.[382] One study demonstrated an increase in night-time cough to a level which approached statistical significance.[383] 1++ 1+

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

6.2.13 BREATHING EXERCISES

Behavioural programmes centred on breathing exercises and dysfunctional breathing reduction techniques (including physiotherapist-delivered breathing programmes such as the Papworth method, and the Buteyko method) can improve asthma symptoms, quality of life and reduce bronchodilator requirement in adults with asthma, although have little effect on lung function.[384] 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 physiotherapist-taught methods) **can be offered to people with asthma as an adjuvant to pharmacological treatment to improve quality of life and reduce symptoms.**

6.2.14 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.[385] A more recent double blind placebo-controlled trial of a Chinese herb decoction (Ding Chuan Tang) showed improvement in airway hyper-responsiveness in children with stable asthma.[386] It is difficult to disentangle the effects of multiple ingredients; Ding Chuan Tang for example contains nine components. In a second study, 100 children with asthma found that a five-herb mixture gave some benefits in relation to lung function and symptoms compared with placebo.[387] 1+

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

6.2.15 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.[388] 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.[389] 1++ 1+

6.2.16 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.[390] 1++

6.2.17 MANUAL THERAPY INCLUDING MASSAGE AND SPINAL MANIPULATION

A Cochrane review identified four relevant RCTs.[391] The two trials of chiropractic suggest that there is no role for this modality of treatment in the management of asthma. No conclusions can be drawn on massage therapy.

6.2.18 PHYSICAL EXERCISE TRAINING

A Cochrane review has shown no effect of physical training on PEF, FEV_1, FVC or ventilation at maximal exercise capacity (V_{Emax}).[392] 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 people with asthma, with appropriate precautions advised about exercise-induced asthma (*see section 7.11.2).*

6.2.19 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.[393] Small study size limits the recommendations.

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

7 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 asthma attacks
- no limitations on activity including exercise
- normal lung function (in practical terms FEV_1 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 phased 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 level most appropriate to the initial severity of their asthma. The aim is to achieve early control and to maintain it by increasing treatment as necessary and decreasing treatment when control is good *(see Figures 2 and 3 for summaries of management in adults and children)*.

✓ Before initiating a new drug therapy practitioners should check adherence with existing therapies (*see section 5.4*), check inhaler technique (*see section 8*), and eliminate trigger factors (*see section 6*).

Until May 2009 all doses of ICS in this section were referenced against beclometasone dipropionate (BDP) given via chlorofluorocarbon metered dose inhalers (CFC-MDIs). BDP-CFC is now unavailable. There are differences in how the doses of ICS are expressed (ex-valve - labelled or ex-actuator - delivered) so it is increasingly difficult to cover all the possible doses in the text. The doses of ICS are therefore expressed as very low (generally paediatric doses), low (generally starting dose for adults), medium and high (*see Tables 9 and 10*). Adjustments to doses will have to be made for other inhaler devices and other corticosteroid molecules (*see section 8.2*).

Recommendations in sections 7 and 8 have been graded and the supporting evidence assessed for adults and adolescents over 12 years old, children aged 5–12 years, and children aged 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.**

7.1 INTERMITTENT RELIEVER THERAPY

Adults and children with a diagnosis of asthma should be prescribed a short-acting bronchodilator to relieve symptoms. For those with infrequent short-lived wheeze occasional use of reliever therapy may be the only treatment required. For exercise-induced asthma see section 7.11.2.

The following medicines act as short-acting bronchodilators:	>12 years	5-12 years	<5 years
• inhaled short-acting β_2 agonists[3]	1^{++}	1^{+}	4
• inhaled ipratropium bromide[394]	1^{+}	1^{++}	
• β_2 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.**

7.1.1 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.[395,396]	>12 years	5-12 years	<5 years
	1^{++}	1^{++}	1^{++}

Good asthma control is associated with little or no need for short-acting β_2 agonist.

✓	Anyone prescribed more than one short acting bronchodilator inhaler device a month should be identified and have their asthma assessed urgently and measures taken to improve asthma control if this is poor.

7.2 REGULAR PREVENTER THERAPY

Treatments have been judged on their ability to improve symptoms, improve lung function, and prevent asthma attacks, 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.

7.2.1 INHALED CORTICOSTEROIDS

Inhaled corticosteroids are the most effective preventer drug for adults and older children for achieving overall treatment goals.[397-401] There is an increasing body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma.[402-412]	>12 years	5-12 years	<5 years
	1^{++}	1^{++}	1^{++}

Many non-atopic children under five with recurrent episodes of viral-induced wheezing do not go on to have chronic atopic asthma. The majority do not require treatment with regular ICS *(see section 3.3)*.

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

Inhaled corticosteroids 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, ICS should be considered in adults and children aged 5–12 who have had an asthma attack requiring oral corticosteroids in the last two years.[413-417]

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

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

- B C ■ • **asthma attack in the last two years**
- B B B • **using inhaled β_2 agonists three times a week or more**
- B B B • **symptomatic three times a week or more**
- B C ✓ • **waking one night a week.**

Alternative initial preventer therapies are available but are less effective than ICS *(see section 7.2.7)*.

7.2.2 STARTING DOSE OF INHALED CORTICOSTEROIDS

In mild to moderate asthma, starting at high doses of ICSs and stepping down confers no benefit.[418]

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

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

✓ A reasonable starting dose of inhaled corticosteroids will usually be low dose for adults *(see Table 9)* and very low dose for children *(see Table 10)*.

✓ Titrate the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained.

7.2.3 FREQUENCY OF DOSING OF INHALED CORTICOSTEROIDS

Most current ICS 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.[3,398,415,419,420]

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

There is little evidence of benefit for dosage frequency more than twice daily.[398]

An RCT comparing daily ICS with intermittent (rescue) ICS in children aged 6–18 years with mild persistent asthma suggests that daily ICS are more effective at preventing asthma attacks.[421]

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

A A A **Give inhaled corticosteroids initially twice daily** (except ciclesonide which is given once daily).

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

7.2.4 COMPARISON OF INHALED CORTICOSTEROIDS

Many studies comparing different ICS 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 ICS, data from normal volunteers have not been taken into account. Only studies in which more than one dose of at least one of the ICS 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 ICS 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 suboptimal design that budesonide via the Turbohaler® is more clinically effective.[422] However, at present a 1:1 ratio should be assumed when changing between BDP and budesonide.

Fluticasone propionate 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.[423] It is difficult to establish the exact equipotent dose of fluticasone furoate.[424,425]

7.2.5 SAFETY OF INHALED CORTICOSTEROIDS

The safety of ICS 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 (for example the *High Dose Inhaled Corticosteroid Safety Card* developed by the London Respiratory Network for NHS England[426]) should be issued to patients on higher dose ICS, 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 low doses 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.[427] The significance of small biochemical changes in adrenocortical function is unknown.

✓ Titrate the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained.

Children

Administration of medium or high dose ICS *(See Table 10)* may be associated with systemic side effects.[428] 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.[419,429]

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 ICS. The dose or duration of ICS 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 (medium dose ICS and above). The low-dose adrenocorticotrophic hormone 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.[430,431] 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 ICS may be associated with adverse effects (including the potential to reduced bone mineral density) with careful ICS dose adjustment this risk is likely to be outweighed by their ability to reduce the need for multiple bursts of oral corticosteroids.[432]

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

✓ The lowest dose of inhaled corticosteroids compatible with maintaining asthma control should be used.

For children treated with medium or high dose ICS:

✓ Specific written advice about steroid replacement 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 ICS 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.

7.2.6 SMOKING AND INHALED CORTICOSTEROIDS

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

Current and previous smoking reduces the effect of ICS, which may be overcome with increased doses.[318,433]

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

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

7.2.7 OTHER PREVENTER THERAPIES

	>12 years	5-12 years	<5 years
Inhaled corticosteroids are the first choice preventer drug. There are alternative, less effective preventer therapies for patients taking short-acting β_2 agonists alone.			
• Leukotriene receptor antagonists (LTRA) have some beneficial clinical effect[398,434,435]	1^{++}	1^{++}	1^{+}
- In children under five years who are unable to take ICS, leukotriene receptor antagonists may be used as an alternative preventer[436,437]			1^{+}
• Sodium cromoglicate and nedocromil sodium			
- Sodium cromoglicate is of some benefit in adults[3,438] and is effective in children aged 5–12[439]	1^{+}	1^{+}	
- Nedocromil sodium is of benefit in adults and children >5[3,440]	1^{++}	1^{+}	
- There is no clear evidence of benefit with sodium cromoglicate in children aged <5[441]			
• Theophyllines have some beneficial effect[3,397]	1^{++}	1^{++}	1^{++}
• Antihistamines and ketotifen are ineffective.[442]	1^{++}	1^{++}	1^{++}

Table 9: Adult doses of inhaled corticosteroids (see Figure 2)

ICS	Dose		
	Low dose	**Medium dose**	**High dose***
Pressurised metered dose inhalers (pMDI)			
Beclometasone dipropionate			
Non-proprietary	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day	200 micrograms four puffs twice a day
Clenil Modulite	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day 250 micrograms two puffs twice a day	
Qvar (extrafine) Qvar autohaler Qvar Easi-breathe	50 micrograms two puffs twice a day	100 micrograms two puffs twice a day	100 micrograms four puffs twice a day
Ciclesonide			
Alvesco Aerosol inhaler	80 micrograms two puffs once a day	160 micrograms two puffs once a day	
Fluticasone propionate			
Flixotide Evohaler	50 micrograms two puffs twice a day	125 micrograms two puffs twice a day	250 micrograms two puffs twice a day
Dry powder inhalers			
Beclometasone			
Non-proprietary Easyhaler	200 micrograms one puff twice a day	200 micrograms two puffs twice a day	
Asmabec	100 micrograms one puff twice a day	100 micrograms two puffs twice a day	
Pulvinal	100 micrograms one puff twice a day	200 micrograms one puff twice a day	400 micrograms one puff twice a day
Budesonide			
Non-proprietary Easyhaler	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day	400 micrograms two puffs twice a day
Budelin Novolizer		200 micrograms two puffs twice a day	200 micrograms four puffs twice a day
Pulmicort Turbohaler	100 micrograms two puffs twice a day 200 micrograms one puff twice a day	200 micrograms two puffs twice a day 400 micrograms one puff twice a day	400 micrograms two puffs twice a day
Fluticasone propionate			
Flixotide Accuhaler	100 micrograms one puff twice a day	250 micrograms one puff twice a day	500 micrograms one puff twice a day
Mometasone			
Asmanex Twisthaler	200 micrograms one puff twice a day	400 micrograms one puff twice a day	

* High doses (shaded boxes) should only be used after referring the patient to secondary care

ICS	Dose		
	Low dose	Medium dose	High dose*
Combination inhalers			
Beclometasone dipropionate (extrafine) with formoterol			
Fostair (pMDI)	100/6 one puff twice a day	100/6 two puffs twice a day	200/6 two puffs twice a day
Fostair (NEXThaler)	100/6 one puff twice a day	100/6 two puffs twice a day	
Budesonide with formoterol			
DuoResp Spiromax	200/6 one puff twice a day	200/6 two puffs twice a day 400/12 one puff twice a day	400/12 two puffs twice a day
Symbicort Turbohaler	100/6 two puffs twice a day 200/6 one puff twice a day	200/6 two puffs twice a day 400/12 one puff twice a day	400/12 two puffs twice a day
Fluticasone propionate with formoterol			
Flutiform	50/5 two puffs twice a day	125/5 two puffs twice a day	250/10 two puffs twice a day
Fluticasone propionate with salmeterol			
Seretide Accuhaler	100/50 one puff twice a day	250/50 one puff twice a day	500/50 one puff twice a day
Seretide Evohaler	50/25 two puffs twice a day	125/25 two puffs twice a day	250/25 two puffs twice a day
Fluticasone furoate with vilanterol			
Relvar		92/22 one puff once a day	184/22 one puff once a day

*High doses (shaded boxes) should only be used after referring the patient to secondary care.

Table 10: Paediatric doses of inhaled corticosteroids (see Figure 3)

ICS	Dose		
	Very low dose	**Low dose**	**Medium dose#**
Pressurised metered dose inhalers (pMDI) with spacer			
Beclometasone dipropionate			
Non-proprietary	50 micrograms two puffs twice a day	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day
Clenil Modulite	50 micrograms two puffs twice a day	100 micrograms two puffs twice a day	200 micrograms two puffs twice a day
Qvar (extrafine)* Qvar autohaler Qvar Easi-breathe		50 micrograms two puffs twice a day	100 micrograms two puffs twice a day
Ciclesonide			
Alvesco Aerosol inhaler		80 micrograms two puffs once a day	160 micrograms two puffs once a day
Fluticasone propionate			
Flixotide Evohaler	50 micrograms one puff twice a day	50 micrograms two puffs twice a day	125 micrograms two puffs twice a day
Dry powder inhalers			
Beclometasone			
Asmabec**		100 micrograms one puff twice a day	100 micrograms two puffs twice a day
Budesonide			
Non-proprietary Easyhaler		100 micrograms two puffs twice a day	200 micrograms two puffs twice a day
Pulmicort Turbohaler	100 micrograms one puff twice a day	100 micrograms two puffs twice a day 200 micrograms one puff twice a day	200 micrograms two puffs twice a day 400 micrograms one puff twice a day
Fluticasone propionate			
Flixotide Accuhaler	50 micrograms one puff twice a day	100 micrograms one puff twice a day	250 micrograms one puff twice a day
Mometasone			
Asmanex Twisthaler		200 micrograms one puff twice a day	
Combination inhalers			
Budesonide with formoterol			
Symbicort Turbohaler	100/6 one puff twice a day**	100/6 two puffs twice a day** 200/6 one puff twice a day*	
Fluticasone propionate with salmeterol			
Seretide Accuhaler		100/50 one puff twice a day	
Seretide Evohaler		50/25 two puffs twice a day	

* Not licensed for children under 12 years ** Not licensed for children under 6 years
# Medium doses (shaded boxes) should only be used after referring the patient to secondary care

7.3 INITIAL ADD-ON THERAPY

A proportion of patients with asthma may not be adequately controlled with low-dose ICS alone. Before initiating a new drug therapy practitioners should recheck adherence *(see section 5.4)*, 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 asthma attacks 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.

7.3.1 CRITERIA FOR INTRODUCTION OF ADD-ON THERAPY

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

No exact dose of ICS can be deemed the correct dose at which to add another therapy. The addition of other treatment options to ICS has been investigated at doses from 200–1,000 micrograms BDP in adults and up to 400 micrograms BDP in children.[443-446] Many patients will benefit more from add-on therapy than from increasing ICS above doses as low as 200 micrograms BDP/day. At doses of ICS 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.

7.3.2 INHALED LONG-ACTING β_2 AGONIST

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

The addition of an inhaled long-acting β_2 agonist (LABA) to ICS alone improves lung function and symptoms, and decreases asthma attacks in adults and children.[443,447-453] Long-acting inhaled β_2 agonists should not be used without IC

Evidence to guide the choice of initial add-on therapy is stronger in adults than in children. On the basis of current evidence, LABA are the first choice initial add-on therapy in adults *(see sections 7.3.1 and 7.4)*.

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

In children, options for initial add-on therapy are limited to LABA and LTRA, with evidence to support both individually, but insufficient evidence to support use of one over the other *(see section 7.4.2)*.[453] LABA are not licensed for use in children under four years of age and evidence for use of LTRA in this age group is limited to studies comparing LTRA with ICS or placebo *(see section 7.2.7)*.

A **The first choice as add-on therapy to inhaled corticosteroids in adults is an inhaled long-acting β_2 agonist, which should be considered before increasing the dose of inhaled corticosteroid.**

B **In children aged five and over, an inhaled long-acting β_2 agonist or a leukotriene receptor antagonist can be considered as initial add-on therapy.**

7.3.3 SAFETY OF LONG-ACTING β_2 AGONISTS

Following a review in 2007 of 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 12 years of age and concluded that the benefits of these medicines used in conjunction with ICS in the control of asthma symptoms outweigh any apparent risks.[455]

✓ 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.

7.3.4 COMBINATION INHALED CORTICOSTEROID/LONG-ACTING β_2 AGONIST INHALERS

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

In efficacy studies, where there is generally good adherence, there is no difference in efficacy in giving ICS and a LABA in combination or in separate inhalers.[456]

In clinical practice it is generally considered that combination inhalers aid adherence and also have the advantage of guaranteeing that the LABA is not taken without the ICS.

✓ Combination inhalers are recommended to:

- guarantee that the long-acting β_2 agonist is not taken without inhaled corticosteroid
- improve inhaler adherence.

7.3.5 MAINTENANCE AND RELIEVER THERAPY

In selected adult patients who are poorly controlled with ICS and LABA or in selected adult patients on medium dose ICS alone, maintenance and reliever therapy combining ICS and LABA in a single inhaler has been shown to be an effective treatment regime.[457-461]

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

Two systematic reviews comparing a combined ICS/LABA inhaler as maintenance and reliever therapy with ICS/LABA as maintenance and SABA as reliever, [462] or with ICS alone or with current best practice (ICS with or without LABA)[463] have shown that maintenance and reliever therapy can reduce the risk of asthma attacks requiring oral steroids in patients who are not well controlled on ICS alone and who have a history of asthma attacks. The latter review reported more withdrawals due to adverse events in the maintenance and reliever therapy group (possibly because patients did not adjust well to the change in inhaler) compared with the current best practice group, but no significant difference between the groups in serious adverse events.

When this management option is introduced the total regular dose of daily ICS should not be decreased. Patients taking rescue doses of their combination inhaler 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.

At present maintenance and reliever therapy is only licenced for use with budesonide/formoterol or beclomethasone/formoterol in adults over the age of 18. Not all combination products are licenced for maintenance and reliever therapy. The appropriate combination inhaler should be prescribed by brand name.

A **In adults over the age of 18, combined maintenance and reliever therapy can be considered for patients who have a history of asthma attacks on medium dose ICS or ICS/LABA**

7.4 ADDITIONAL ADD-ON THERAPIES

If control remains poor on low-dose ICS plus a LABA, recheck the diagnosis, assess adherence to existing medication and check inhaler technique before increasing therapy. If more intense treatment is appropriate, then the following alternatives can be considered.

If there is an improvement when a LABA is added but control remains inadequate:

- continue the LABA and increase the dose of ICS *(see section 7.4.1)*
- continue the LABA and the ICS and add an LTRA or a long acting muscarinic agent (LAMA) or a theophylline *(see sections 7.4.2, 7.4.3 and 7.4.4, respectively)*.

If there is no improvement when a LABA is added, stop the LABA and try:

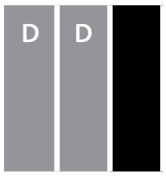
- an increased dose of ICS *(see section 7.4.1)*
- an LTRA *(see section 7.4.2)*
- a LAMA *(see section 7.4.3)*. LAMA are not licensed for this indication.

7.4.1 INCREASED DOSE OF INHALED CORTICOSTEROIDS

If there is a response to LABA, but control remains suboptimal, continue with the LABA and increase the dose of ICS to medium (adults) or low dose (children 5–12 years).[456]

If, as occasionally happens, there is no response to inhaled long-acting β_2 agonist, stop the LABA and increase the dose of ICS to medium (adults) or low dose (children) if not already on this dose.[456]

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



If asthma control remains suboptimal after the addition of an inhaled long-acting β_2 agonist then the dose of inhaled corticosteroids should be increased from low dose to medium dose in adults or from very low dose to low dose in children (5–12 years)**, if not already on these doses.**

7.4.2 LEUKOTRIENE RECEPTOR ANTAGONISTS

Evidence to support the use of leukotriene receptor antagonists (LTRA) as an add-on therapy to ICS plus LABA is lacking and evidence for their use is largely based on extrapolation from trials of LTRA as add-on therapy to ICS alone. The addition of LTRA to ICS may provide improvement in lung function, a decrease in asthma attacks, and an improvement in symptoms in adults and children over five years of age, although reported benefits differ between studies and evidence is limited in children.[435,464,465]

A systematic review of studies comparing the addition of LTRA to ICS with the addition of LABA to ICS showed that the addition of LABA to ICS was more effective at reducing asthma attacks (the primary outcome) and improving secondary outcomes including SABA use, symptoms and quality of life in adults, although differences were generally small. There was insufficient evidence on which to base conclusions regarding which add-on therapy is more effective in children.[453]

In adults, the addition of LTRA to ICS is superior to ICS alone and has a similar effect on asthma control to high-dose ICS. High-dose ICS, however, appears superior to ICS-LTRA for some pulmonary function indices, although further studies to investigate this are required.[466]

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

7.4.3 TIOTROPIUM BROMIDE

A review of RCTs in adults taking tiotropium bromide, a long-acting muscarinic antagonist (LAMA), in addition to ICS plus LABA compared with ICS plus LABA, reported fewer asthma exacerbations (although results were inconclusive), improved lung function and some benefits relating to asthma control in those taking tiotropium, but no improvement in quality of life. Evidence relating to serious adverse effects was inconclusive but fewer non-serious adverse events were reported in those taking tiotropium. In two of the three trials included in the review patients were taking high-dose ICS, although it was not possible to draw conclusions about the effect of tiotropium in those taking different doses of ICS plus LABA.[467]

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

There is insufficient evidence to suggest that addition of tiotropium to ICS in patients inadequately controlled on ICS alone has any benefit over addition of LABA to ICS.[468] The addition of LABA to ICS remains the first choice for add-on treatment in adults. In adults with asthma who do not respond to ICS plus LABA, the addition of tiotropium to ICS is a possible, although 'off-label' alternative.[469 470]

A review comparing the addition of tiotropium to ICS with increased dose of ICS in adults found only one study suitable for inclusion and insufficient evidence to say whether adding tiotropium to ICS ('off-label' use) is safer or more effective than increasing the dose of ICS.[471]

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

7.4.4 OTHER APPROACHES

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

Theophyllines may improve lung function and symptoms, but side effects occur more commonly.[444]

Slow-release β_2 agonist tablets may also improve lung function and symptoms, but side effects occur more commonly.[443]

Addition of short-acting anticholinergics is generally of no value.[445,472] Addition of nedocromil is of marginal benefit.[438,446]

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

7.5 HIGH-DOSE THERAPIES

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting β_2 agonist as required, medium-dose ICS, and an additional drug, usually a LABA. There are very few clinical trials in this specific patient group to guide management.

In adults, the addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive *(see section 7.4.3)*. Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.[467] The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone *(see section 7.4)*.

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

D D

If control remains inadequate on medium dose (adults) **or low dose** (children) **of an inhaled corticosteroid plus a long-acting β_2 agonist, the following interventions can be considered:**

- **increase the inhaled corticosteroids to high dose** (adults) **or medium dose** (children 5-12 years)***** ***or***
- **add a leukotriene receptor antagonist** ***or***
- **add a theophylline** ***or***
- **add slow-release β_2 agonist tablets, although caution needs to be used in patients already on long-acting β_2 agonists,** ***or***
- **add tiotropium** (adults)**.**

* at high doses of inhaled corticosteroid via a pressurised metered dose inhaler (pMDI), 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 corticosteroid, reduce to the original dose).

✓ Before proceeding to continuous or frequent use of oral steroid therapy, 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 use of oral steroids.

7.6 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 with high-dose ICS, 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 on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control.

7.6.1 PREVENTION AND TREATMENT OF STEROID TABLET-INDUCED SIDE EFFECTS

Patients on long-term steroid tablets (for example, longer than three months) or requiring frequent courses of steroid tablets (for example three to four per year) will be at risk of systemic side effects.[430]

- 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 (further guidance is available from the British Osteoporosis Society, www.nos.org.uk)[473]
- bone mineral density should be monitored in children >5 (further advice is available from the American Academy of Pediatrics)[474]
- growth (height and weight centile) should be monitored in children
- cataracts and glaucoma may be screened for through community optometric services.

7.6.2 STEROID FORMULATIONS

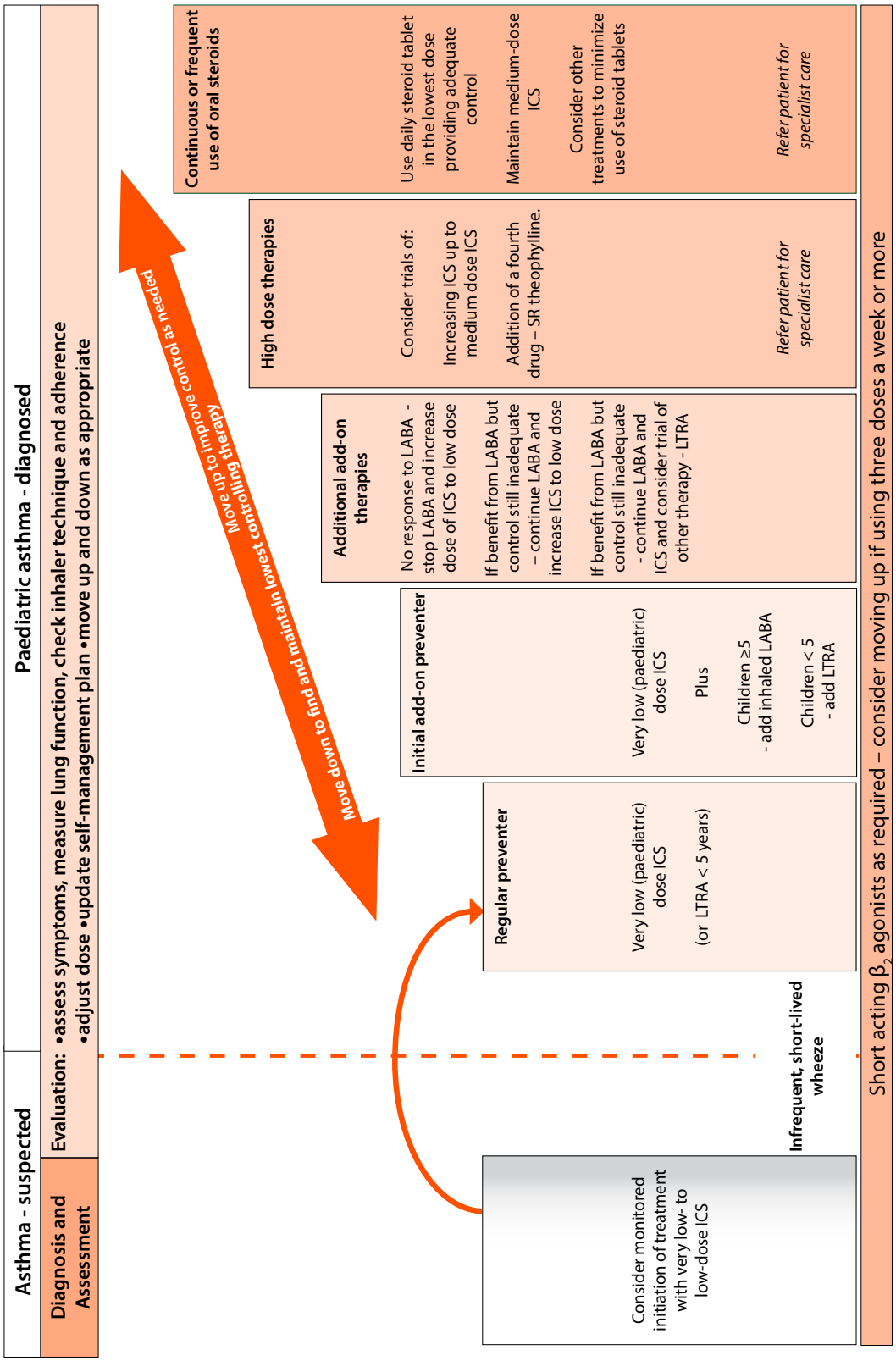
Prednisolone is the most widely used steroid for maintenance therapy in patients with chronic asthma. There is no evidence that other steroids offer an advantage.

7.6.3 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.

Figure 2: Summary of management in adults

Figure 3: Summary of management in children



7.7 OTHER MEDICATIONS AND POTENTIAL STEROID TABLET-SPARING TREATMENTS

7.7.1 ANTI-IgE MONOCLONAL ANTIBODY

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE, reducing levels of free serum IgE.[475,476] In adults and children over 6 years of age, it is licensed in the UK with the following indication: patients on high-dose ICS and long-acting β_2 agonists who have impaired lung function, are symptomatic with frequent asthma attacks, and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every two or four weeks depending on the patient's IgE level and weight. The total IgE must be <1,300 international units (IU)/ml for children over 6 years of age.[477] In adults and children >12 years, the licensed indication is a IgE up to 1,500 IU/ml but there is no published data to support its efficacy and safety above 700 IU/ml.

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

>12 years	5-12 years	<5 years
1^{++} 2^{++}	1^{++} 2^{++}	

Omalizumab given by subcutaneous injection can reduce the steroid burden for the patient without increasing the risk of adverse events.[478-480] Three systematic reviews reported reductions in asthma exacerbations in patients with moderate or severe allergic asthma receiving omalizumab compared with placebo in addition to oral corticosteroids (OCS) or ICS.[478-480] These studies all reported that more patients on omalizumab compared with placebo withdrew steroids (OCS,[478] ICS but not OCS,[479] unclear if OCS or ICS or both[480]).

B **Omalizumab given by subcutaneous injection may be considered in patients with a high steroid burden.**

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

7.7.2 ANTI-INTERLEUKIN-5 MONOCLONAL ANTIBODY

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

A systematic review of mepolizumab compared with placebo reported some improvement in health-related quality of life and reductions in exacerbations in adults and adolescents (≥12 years) with severe eosinophilic asthma, but concluded that further studies were needed to establish dosage, dosing regimens and duration of treatment.[481] Seven of the eight studies included in the review used an unlicensed intravenous route of administration, thus limiting the usefulness of the findings.

An RCT including 135 patients with severe eosinophilic asthma receiving 100 mg of mepolizumab subcutaneously every four weeks reported a significant glucocorticoid-sparing effect with mepolizumab compared with placebo (28% *v* 11%, respectively), improved secondary outcomes including fewer exacerbations and improved ACQ-5 scores, and a similar safety profile.[482]

7.7.3 OTHER AGENTS

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.[483]

>12 years	5-12 years	<5 years
1++	3	

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

Colchicine and intravenous immunoglobulin have not been shown to have any beneficial effect in adults.[483]

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

Continuous subcutaneous terbutaline infusion has been reported to be beneficial in patients with severe asthma but efficacy and safety have not been assessed in RCTs.[484-486]

>12 years	5-12 years	<5 years
4	3	3

Anti-tumour necrosis factor alpha (anti-TNF alpha) therapy has been investigated in patients with severe asthma but these studies are too small and too short term to allow recommendation of anti-TNF alpha therapy outside the context of a controlled clinical trial.[487,488]

A systematic review of the use of macrolides in patients with chronic asthma concluded that they confer no benefit over placebo in terms of clinical outcomes. There was some evidence of possible benefit in improved lung function but concern about the risk of increased antimicrobial resistance. Subgroup analyses in two of the included studies suggested improved outcomes in patients with non-eosinophilic asthma, but patient numbers were small and no conclusions can be drawn from the data available.[489] There is insufficient evidence to support the addition of macrolides to existing treatment for patients with severe asthma.

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

7.7.4 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.

Inhaled corticosteroids are the most effective drug for decreasing requirement for long-term steroid tablets.[399,400]

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

There is limited evidence for the ability of long-acting β_2 agonists, theophyllines, or leukotriene receptor antagonists to decrease requirement for steroid tablets, but they may improve symptoms and pulmonary function.[490]

A D **In adults, the recommended method of eliminating or reducing the dose of steroid tablets is high-dose inhaled corticosteroids.**

In children aged 5–12, consider very carefully before going above a medium dose inhaled corticosteroid.

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.**

7.8 IMMUNOTHERAPY FOR ASTHMA

Studies using both subcutaneous and sublingual allergen immunotherapy (SCIT and SLIT) have shown some benefit in reducing asthma symptoms and bronchial hyper-reactivity (BHR) in children and adults currently on a range of other preventative strategies including ICS. There are, however, few studies comparing immunotherapy with ICS or of adding immunotherapy to ICS so there is difficulty precisely defining where in asthma management this approach should sit.

7.8.1 SUBCUTANEOUS IMMUNOTHERAPY

	>12 years	5-12 years	<5 years
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 42 trials with house dust mite, 27 with pollen, 10 with animal allergens, two with *Cladosporium* mould, two with latex and six with multiple allergens.[491]	1^{++}		
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.[491] Immunotherapy is not licensed for the treatment of asthma; the current license is for grass pollen induced allergic rhinitis.	1^{++}	1^{++}	
One study directly compared allergen immunotherapy with ICS and found that symptoms and lung function improved more rapidly in the group on ICS.[492]	2^{+}		
Immunotherapy for allergic rhinitis has been shown to have a carry over effect after therapy has stopped.[493]	3		

B B **The use of subcutaneous immunotherapy is not recommended for the treatment of asthma in adults or children.**

7.8.2 SUBLINGUAL IMMUNOTHERAPY

	>12 years	5-12 years	<5 years
There has been increasing interest in the use of sublingual immunotherapy, which is associated with far fewer adverse reactions than subcutaneous immunotherapy. A systematic review reported that although there appeared to be some benefits in terms of asthma control, the magnitude of the effect was small and was based on mixed results for allergic symptoms overall (including asthma, rhinitis and conjunctivitis).[494] The review showed no significant effect on asthma symptoms or asthma medication use but did show a significant increase in side effects.	1^{++}	1^{++}	
A systematic review of five earlier meta-analyses, including 43 studies, 17 of which were included in more than one meta-analysis, highlighted a number of problems relating to earlier meta-analyses, including possible misinterpretation of study findings and publication bias.[495]	1^{+}		
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.[496]	1^{+}	1^{+}	

The analysis included only one study in adults which showed no effect on symptoms or medication use.

Sublingual immunotherapy is not licensed for use in the treatment of asthma.

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

7.9 BRONCHIAL THERMOPLASTY

	>12 years	5-12 years	<5 years
In selected adult patients with moderate to severe asthma (aged 18–65 years) who have poorly controlled asthma despite maximal therapy, bronchial thermoplasty treatment has been shown to reduce the frequency of severe asthma attacks, emergency department visits and days lost from school or work in the year after treatment.[497] Emergency department visits, but not severe asthma attacks, are reduced in the period from first treatment to one year post-treatment.[497] The reduction in the frequency of asthma attacks and emergency department visits may persist for up to five years after treatment.[498]	1^{++} 3		
Bronchial thermoplasty results in a modest improvement in asthma quality of life in the year after treatment.[499]	1^{++}		
Bronchial thermoplasty produces no consistent improvement in asthma symptoms or FEV_1,[497,500,501] 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.[499] Despite this, there is no overall increase in hospital admissions with bronchial thermoplasty at one year.[499]	1^{++}		
There is some evidence for the long-term safety of the procedure from one up to five years post-treatment in relation to adverse events reporting, stable lung function and lack of increase in hospital admissions and emergency room visits.[498,502]	1^{+} 3		

A **Bronchial thermoplasty may be considered for the treatment of adult patients who have poorly controlled asthma despite optimal 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.

✓ Further research is recommended into factors that identify patients who will or will not benefit from bronchial thermoplasty treatment.

7.10 DECREASING TREATMENT

Decreasing therapy once asthma is controlled is recommended, but often not implemented leaving some patients overtreated. There are few studies that have investigated the most appropriate way to decrease treatment. A study in adults on high dose ICS has shown that for patients who are stable it is reasonable to attempt to halve the dose of ICS every three months.[488]

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 decreased is important. When deciding which drug to decrease 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 corticosteroid. Reduction in inhaled corticosteroid 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.

7.11 SPECIFIC MANAGEMENT ISSUES

7.11.1 ASTHMA ATTACKS

Although recommended for both adults and children in previous guidelines and as part of asthma action plans, doubling the dose of ICS at the time of an exacerbation is of unproven value.[503] In adult patients on a very low dose of ICS, a fivefold increase in dose at the time of an asthma attack leads to a decrease in the severity of asthma attacks.[503] This study cannot be extrapolated to patients already taking higher doses of ICS and further evidence in this area is required *(see Tables 9 and 10)*.

	>12 years	5-12 years	<5 years
A Cochrane review including five trials in 1,222 adults and 28 children (three in adults >15 years; one including adolescents >13 years; and one including children 6–14 years), showed that doubling the dose of ICS in patients on high dose ICS, was of unproven benefit in reducing rescue oral corticosteroids.[504]	1^{++}		
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.[505]		1^{++}	1^{++}

7.11.2 EXERCISE INDUCED ASTHMA

The following medicines have been shown to give protection against exercise induced asthma:	>12 years	5-12 years	<5 years
• inhaled corticosteroids[399,400,506]	1^{++}	1^{++}	
• short-acting β_2 agonists[3,507]	1^{++}	1^{++}	
• long-acting β_2 agonists[508]	1^{++}	1^{++}	
• theophyllines[490,509]	1^{-}	2^{+}	
• leukotriene receptor antagonists[510]	1^{++}	2^{+}	
• sodium cromoglicate or nedocromil sodium[511]	1^{++}	2^{+}	
• β_2 agonist tablets.[512]	1^{++}	1^{+}	

The following medicines do not give protection against exercise induced asthma at normal doses	>12 years	5-12 years	<5 years
• anticholinergics[513]	1^{+}	1^{+}	
• ketotifen[514]	1^{+}	1^{+}	
• antihistamine.[515]	1^{++}	1^{++}	

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.[508,510,516]

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

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

If exercise is a specific problem in patients taking inhaled corticosteroids 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 — **sodium cromoglicate or nedocromil sodium**
- A A — **oral β_2 agonists**
- C C — **theophyllines.**

Immediately prior to exercise, inhaled short-acting β_2 agonists are the drug of choice.[3,507]

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

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

7.11.3 COMORBID RHINITIS

Patients with asthma often have rhinitis. The most effective therapy for rhinitis is intranasal steroids.[517,518] Treatment of allergic rhinitis with intranasal steroids has not been shown, in double blind placebo-controlled trials, to improve asthma control.

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

7.11.4 ALLERGIC BRONCOPULMONARY ASPERGILLOSIS

In adult patients with allergic bronchopulmonary aspergillosis, itraconazole may decrease steroid tablet dose and improve asthma control.[519,520]

>12 years	5-12 years	<5 years
1^{++} 2^{+}	1^{+}	

C **In adult patients with allergic bronchopulmonary aspergillosis, a four month trial of itraconazole should be considered.**

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

7.11.5 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.[521]

7.11.6 COMORBID 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.[522,523]

A systematic review identified a single RCT which found that proton pump inhibitors did not improve asthma symptoms in children with GORD.[524]

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 found a small but statistically significant improvement in morning peak expiratory flow (8.86 l/min, 95% CI 2.35 to 15.02) in study participants compared to 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 proton pump inhibitors in the treatment of asthma.[525]	>12 years 1^{++}	5-12 years	<5 years

7.11.7 β-BLOCKERS

β-blockers, including eye drops, are contraindicated in patients with asthma *(see BNF for current guidance)*.[5]

8 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.

8.1 TECHNIQUE AND TRAINING

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

The proportion of patients making no mistakes with an inhaler in one well-conducted study was 23–43% for pressurised metered dose inhaler (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.[526]

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

Teaching technique improved the correct usage score from a mean of 60% to 79%. Figures for no mistakes after 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).[526]

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

8.2 β_2 AGONIST DELIVERY

8.2.1 ACUTE ASTHMA

A pMDI + spacer is at least as good as a nebuliser at treating mild and moderate asthma attacks in children and adults.[527-530]

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

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

There are no data on which to make recommendations in acute severe or life-threatening asthma.

8.2.2 STABLE ASTHMA

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

In children aged 5–12 there is no significant difference between a pMDI + spacer and a DPI. In adults there is no significant difference between a pMDI ± spacer and a DPI. The lower pulse rate with a pMDI compared to a Turbohaler is the only difference with regard to side effects. Patients have been shown to prefer a Turbohaler to a pMDI.[526,531,532]

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

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

In adults, a 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 for children under five years old.

✓ 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.

8.3 INHALED CORTICOSTEROIDS FOR STABLE ASTHMA

No comparative data on ICS for stable asthma in children under five years old were identified.

>12 years	5-12 years	<5 years

For the delivery of ICS in children aged 5–12 years with stable asthma, a pMDI is as effective as a Clickhaler.[533,534534] No significant clinical difference was found between a pMDI and a Turbohaler at half the dose for the same drug (budesonide).[526,535] This comparison cannot necessarily be made against other ICS/device combinations.

1^{++}	1^{++}	

In adults, there is no clinical difference in effectiveness of a pMDI ± spacer compared to a DPI. A breath-actuated MDI is as effective as a pMDI. More recent DPIs are as effective as older DPIs.[439] Nebulisers have not been shown to be superior to pMDIs + spacer for delivery of ICS in patients with 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.[526,535]

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

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 under 5 years old.

8.4 PRESCRIBING DEVICES

There is no evidence to dictate an order in which devices should be tested for those patients who cannot use a 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 the prescribed inhaler device (particularly for any change in device) assessed by a competent healthcare professional *(see section 8.1)*.
- The medication needs to be titrated against clinical response to ensure optimum efficacy.
- Reassess inhaler technique as part of structured clinical review *(see section 14.3)*.

✓ Generic prescribing of inhalers should be avoided as this might lead to people with asthma being given an unfamiliar inhaler device which they are not able to use properly.

✓ In children, a pMDI and spacer are the preferred method of delivery of β_2 agonists and inhaled corticosteroids. 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 using different devices for preventer and reliever treatments with using the same device for both treatments. Two cross-sectional studies found an association between increased errors in the use of inhalers when different types of inhaler were used *(see section 7.3.4)*.[536,537]

>12 years	5-12 years	<5 years
3		

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

8.5 USE AND CARE OF SPACERS

✓
- The spacer should be compatible with the pMDI being used. A change in spacer may alter effective dose delivered.
- 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 via a spacer 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.

9 Management of acute asthma

9.1 LESSONS FROM 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.[538-542] The report of the UK-wide National Review of Asthma Deaths (NRAD) in 2014 reiterates many of the findings from earlier studies.[543]

9.1.1 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.[538-542,544] 2++

9.1.2 MEDICAL MANAGEMENT

Many of the deaths occurred in patients who had received inadequate treatment with ICS 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 underuse of written management plans. Heavy or increasing use of β_2 agonist therapy was associated with asthma death.[538-542,545,546] The NRAD report recommended that prescription of more than 12 SABA inhalers a year should prompt review of a patient's management.[543] 2++

Deaths continue to be reported following inappropriate prescription of β-blockers and non-steroidal anti-inflammatory drugs; all asthma patients should be asked about past reactions to these agents *(see sections 7.11.5 and 7.11.7)*.

Patients with an acute asthma attack should not be sedated unless this is to allow anaesthetic or intensive care procedures (*see section 9.3.12*).[544]

The NRAD report highlighted that there is an increased risk of death within one month of discharge from hospital following an acute attack and that follow up in primary care is therefore essential *(see section 9.6)*.[543]

9.1.3 ADVERSE PSYCHOSOCIAL AND BEHAVIOURAL FACTORS

Behavioural and adverse psychosocial factors were recorded in the majority of patients who died of asthma.[538-542] The most important of these are shown in Table 11.

Case-control studies support most of these observations.[547,548] Compared with control patients admitted to hospital with asthma, those who died were significantly more likely to have learning difficulties, psychosis or prescribed antipsychotic drugs, financial or employment problems, repeatedly failed to attend appointments or discharged themselves from hospital, drug or alcohol abuse, obesity or a previous near-fatal attack. 2++

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

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

Table 11: Patients at risk of developing near-fatal or fatal asthma[538-542,545,546]

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-adherence 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

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 11, and that these contribute to the near-fatal asthma attack.[549-551] Compared with patients who die, those with near-fatal asthma are significantly younger, are significantly more likely to have had a previous near-fatal asthma attack, are less likely to have concurrent medical conditions, are less likely to experience delay in receiving medical care, and more likely to have ready access to acute medical care. 2+

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

Patients with difficult asthma should also be identified *(see section 10.1)*.

✓ Keep patients who have had a near-fatal asthma attack under specialist supervision indefinitely.

9.1.4 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.[549,552] 2++

9.1.5 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.[553-558] 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 a severe asthma attack for at least one year after the admission.

9.2 ACUTE ASTHMA IN ADULTS

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

9.2.1 RECOGNITION OF ACUTE ASTHMA

Definitions of increasing levels of severity of acute asthma attacks are provided in Table 12.[559-564] Predicted PEF values should be used only if the recent best PEF (within two years) is unknown.[565] 2+ 4

9.2.2 SELF TREATMENT BY PATIENTS DEVELOPING ACUTE OR UNCONTROLLED ASTHMA

Patients with asthma, and all patients with severe asthma, should have an agreed written PAAP and their own peak flow meter, with regular checks of inhaler technique and adherence. They should know when and how to increase their medication and when to seek medical assistance. Written PAAPs can decrease hospitalisation for,[148] and deaths from asthma *(see section 5.3.2)*.[566]

9.2.3 INITIAL ASSESSMENT

All possible initial contact personnel, for example practice receptionists, ambulance call takers, NHS 111 (England and 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 12 and 13. It may be helpful to use a systematic recording process. Proformas have proved useful in the ED setting.[567]

Table 12: Levels of severity of acute asthma attacks in adults[559-564]

<table>
<tr><td>Moderate acute asthma</td><td colspan="2">Increasing symptoms
PEF >50–75% best or predicted
No features of acute severe asthma</td></tr>
<tr><td>Acute severe asthma</td><td colspan="2">Any one of:
- PEF 33–50% best or predicted
- respiratory rate ≥25/min
- heart rate ≥110/min
- inability to complete sentences in one breath</td></tr>
<tr><td rowspan="9">Life-threatening asthma</td><td colspan="2">Any one of the following in a patient with severe asthma:</td></tr>
<tr><td>Clinical signs</td><td>Measurements</td></tr>
<tr><td>Altered conscious level</td><td>PEF <33% best or predicted</td></tr>
<tr><td>Exhaustion</td><td>SpO_2 <92%</td></tr>
<tr><td>Arrhythmia</td><td>PaO_2 <8 kPa</td></tr>
<tr><td>Hypotension</td><td>'normal' $PaCO_2$ (4.6–6.0 kPa)</td></tr>
<tr><td>Cyanosis</td><td></td></tr>
<tr><td>Silent chest</td><td></td></tr>
<tr><td>Poor respiratory effort</td><td></td></tr>
<tr><td>Near-fatal asthma</td><td colspan="2">Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures[548-551]</td></tr>
</table>

SpO_2: oxygen saturation measured by a pulse oximeter

PaO_2: partial arterial pressure of oxygen

kPa: kilopascals

$PaCO_2$: partial arterial pressure of carbon dioxide

9.2.4 PREVENTION OF ACUTE DETERIORATION

A register of patients at risk may help healthcare professionals in primary care 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.

9.2.5 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 13: Initial assessment 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), tachypnoea, tachycardia, silent chest, cyanosis, accessory muscle use, altered consciousness or collapse.[559-564,568] 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.[569,570] 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%.[571]	
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.[559-562,564,572] SpO_2 <92% is associated with a risk of hypercapnia. Hypercapnia is not detected by pulse oximetry.[572] In contrast, the risk of hypercapnia with SpO_2 >92% is much less.[571]	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.[559-564,573]	2^+

9.2.6 CRITERIA FOR ADMISSION

Adult patients with any feature of a life-threatening or near-fatal asthma attack or a severe asthma attack that does not resolve after initial treatment should be admitted to hospital. Admission may also be appropriate when peak flow has improved to greater than 75% best or predicted one hour after initial treatment but concerns remain about symptoms, previous history or psychosocial issues *(see sections 9.1 and 9.2)*.[549,551,559-564] 2^{++} 2^{+}

B **Admit patients with any feature of a life-threatening or near-fatal asthma attack.**

B **Admit patients with any feature of a severe asthma attack persisting after initial treatment.**

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 adherence**
- **living alone/socially isolated**
- **psychological problems**
- **physical disability or learning difficulties**
- **previous near-fatal asthma attack**
- **asthma attack despite adequate dose steroid tablets prior to presentation**
- **presentation at night**
- **pregnancy.**

9.3 TREATMENT OF ACUTE ASTHMA IN ADULTS

9.3.1 OXYGEN

Many patients with acute severe asthma are hypoxaemic.[574-577] 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%,[571] taking care to avoid overoxygenation which may be detrimental.[578] 1^{+} 2^{+} 4

Emergency oxygen should be available in hospitals, ambulances and primary care.

Hypercapnia indicates the development of near-fatal asthma and the need for emergency specialist/anaesthetic intervention. In this situation care should be taken to avoid hypoxia as well as overoxygenation.

C **Give controlled supplementary oxygen to all hypoxaemic patients with acute severe asthma titrated to maintain an SpO_2 level of 94–98%. Do not delay oxygen administration in the absence of pulse oximetry but commence monitoring of SaO_2 as soon as it becomes available.**

9.3.2 β_2 AGONIST BRONCHODILATORS

In most cases inhaled β_2 agonists given in high doses act quickly to relieve bronchospasm with few side effects.[579-581] 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.[582] 1++ 1+

In patients with 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.[583] 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.[584] If intravenous β_2 agonists are used, consider monitoring serum lactate.[585] 1++ 3

Metered dose inhalers with spacers can be used for patients with asthma attacks other than life threatening.[583] 1++

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

✓ If intravenous β_2 agonists are used, consider monitoring serum lactate to monitor for toxicity.

Oxygen-driven nebulisers are preferred for nebulising β_2 agonist bronchodilators because of the risk of oxygen desaturation while using air-driven compressors.[527,559,586] 1++

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.[571] 4

The absence of supplemental oxygen should not prevent nebulised therapy from being administered when appropriate.[587] 4

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

✓ In patients with 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 acute asthma attacks 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.[588-591] 1+

A **In patients with 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 the appropriate nebuliser) if there is an inadequate response to initial treatment. Higher bolus doses, for example 10 mg of salbutamol, are unlikely to be more effective.

9.3.3 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.[592,593] 1++

A **Give steroids in adequate doses to all patients with an acute asthma attack.**

Steroid tablets are as effective as injected steroids, provided they can be swallowed and retained.[592] Prednisolone 40–50 mg daily or parenteral hydrocortisone 400 mg daily (100 mg six-hourly) are as effective as higher doses.[594] 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.[595] 1++

✓ Continue prednisolone (40–50 mg daily) for at least five days or until recovery.

Following recovery from the acute asthma attack steroids can be stopped abruptly. Doses do not need tapering provided the patient receives ICS (apart from patients on maintenance steroid treatment or rare instances where steroids are required for three or more weeks).[596,597] 1+

It is not known if ICS provide further benefit in addition to systemic steroids.[598,599] 1+

✓ Do not stop inhaled corticosteroids during prescription of oral corticosteroids.

9.3.4 IPRATROPIUM BROMIDE

Combining nebulised ipratropium bromide with a nebulised β_2 agonist produces significantly greater bronchodilation than β_2 agonist alone, leading to faster recovery and shorter duration of admission. Anticholinergic treatment is not necessary and may not be beneficial in milder asthma attacks or after stabilisation.[600-602] 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.**

9.3.5 MAGNESIUM SULPHATE

There is some evidence that magnesium sulphate has bronchodilator effects.[603] 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.[604] 1++

A double-blind, placebo-controlled study of 1,109 patients aged over 16 years presenting with an acute asthma attack to 34 emergency departments across the UK randomised patients to intravenous (IV) or nebulised magnesium or to placebo.[605] 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 a 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.[340,606-608] Intravenous magnesium sulphate may also reduce hospital admissions in adults with acute asthma who have had little or no response to standard treatment. However, the heterogeneous nature of the studies included in this review and lack of information on the severity of the asthma attack or when IV magnesium was given in relation to standard treatment limit the conclusions that can be drawn.[608] 1++ 1+

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

A **Nebulised magnesium sulphate 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.**

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

9.3.6 INTRAVENOUS AMINOPHYLLINE

In an acute asthma attack, 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.[609] 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.[609] If IV aminophylline is given to patients already taking oral aminophylline or theophylline, blood levels should be checked on admission. Levels should be checked daily for all patients on aminophylline infusions.

9.3.7 LEUKOTRIENE RECEPTOR ANTAGONISTS

Current evidence on oral leukotriene receptor antagonists does not support their use in patients with acute asthma.[610] Further studies are required to assess whether IV treatment is effective and safe. 1++

9.3.8 ANTIBIOTICS

When an infection precipitates an asthma attack it is likely to be viral. The role of bacterial infection has been overestimated.[611] Decision making regarding the use of antibiotics in patients with acute asthma should be guided by objective measures including procalcitonin where available.[612,613] 1++ 1+

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

9.3.9 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 current evidence.[614,615] 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.[616,617] Heliox requires the use of specifically designed or modified breathing circuits and ventilators. 1++ 1+

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

9.3.10 INTRAVENOUS FLUIDS

There are no controlled trials, observational or cohort studies of differing fluid regimes in patients with acute asthma. Some patients 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.

9.3.11 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.[618] 1+

9.3.12 CRITICAL CARE SETTINGS

In adults with acute asthma and a poor response to standard therapy (inhaled bronchodilators, steroids, oxygen and intravenous bronchodilators) other therapies may be considered in the appropriate critical care setting with the appropriate available expertise. There is little high-quality evidence to guide treatment at this stage of an acute asthma attack and it is important to involve a clinician with the appropriate skills in airway management and critical care support as early as possible.

Indications for admission to intensive care or high-dependency units include patients requiring ventilatory support and those with acute severe or life-threatening asthma who are failing to respond to therapy, as evidenced by:[559,560]

- deteriorating PEF
- persisting or worsening hypoxia
- hypercapnia
- arterial blood gas analysis showing fall in pH or rising hydrogen concentration
- exhaustion, feeble respiration
- drowsiness, confusion, altered conscious state
- respiratory arrest.

Ketamine

A review (including 12 case reports, three RCTs and five other observational studies) of ketamine use in adults and children in status asthmaticus reported that ketamine is a potential bronchodilator but that prospective trials are needed before conclusions about effectiveness can be drawn.[619] 2

Recombinant human deoxyribonuclease

A pilot RCT of the use of recombinant human deoxyribonuclease (rhDNAse) in severely ill, non-intubated adults with asthma refractory to bronchodilators reported no benefit of rhDNAse.[620] 1^+

✓ Adults with asthma not responding to standard treatment should be evaluated by a specialist with the appropriate experience and skills to use and assess medication encountered in critical care settings.

✓ In patients with acute severe or life-threatening asthma, anaesthetists and intensivists should be notified as soon as possible if there is no improvement in or deterioration of asthma.

Not all patients admitted to the intensive care unit (ICU) need ventilation, but those with worsening hypoxia or hypercapnia, 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 be performed by an anaesthetist or ICU consultant.[559,560] 2^+

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

9.3.13 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. Hypercapnic respiratory failure developing during an acute asthmatic attack is an indication for urgent ICU admission. It is unlikely that NIV would replace intubation in these very unstable patients but it has been suggested that this treatment can be used safely and effectively.[621] 1^{++} 1^+ 2^-

Evidence to support the use of NIV in adults is limited and inconclusive. A Cochrane review found only one trial on NIV, with 30 patients, which showed improvement in hospitalisation rates, discharge from emergency departments and lung function.[622] Two further small studies suggest that NIV may be safe and feasible in treating patients with severe asthma exacerbations but provide little evidence of benefit compared with standard care.[623,624] 4

Larger RCTs are needed to determine the role of NIV in treating patients with acute asthma.[622] Future trials should include measurable clinical outcomes such as respiratory parameters, physiological variables and blood gases.

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

9.4 FURTHER INVESTIGATION AND MONITORING

✓
- Measure and record PEF 15–30 minutes after starting treatment, and thereafter according to the response. Measure and record PEF before and after nebulised or inhaled β_2 agonist.
- Record oxygen saturation by oximetry and maintain arterial SpO_2 at 94–98%.
- Repeat measurements of blood gas tensions within one hour of starting treatment if:
  - the initial PaO_2 is <8 kPa unless SpO_2 is >92%; or
  - the initial $PaCO_2$ is normal or raised; or
  - the patient's condition deteriorates.

✓
- Measure them again if the patient's condition has not improved by 4–6 hours.
- Measure and record the heart rate.
- Measure serum potassium and blood glucose concentrations.
- Measure the serum theophylline concentration if aminophylline is continued for more than 24 hours (aim for a concentration of 10–20 mg/l or 55–110 mol/l).

9.5 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 the quality of care and outcomes.[567,625,626] 2^{++}

9.6 HOSPITAL DISCHARGE AND FOLLOW UP

Annex 4 summarises management of acute severe asthma in hospital.

An asthma care bundle developed by the BTS is also available from the BTS website (www.brit-thoracic.org.uk).

9.6.1 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 asthma attack, 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.[627,628] 2^{+}

9.6.2 PATIENT EDUCATION

Following discharge from hospital or emergency departments, a proportion of patients reattend with more than 15% reattending within two weeks. Some repeat attenders need emergency care, but many delay seeking help, and are undertreated and/or undermonitored.[629] 2+

Prior to discharge, trained staff should give asthma education. This should include education on inhaler technique and PEF record keeping, with a written PEF and symptom-based PAAP being provided allowing the patient to adjust their therapy within recommendations. These measures have been shown to reduce morbidity after the asthma attack and reduce relapse rates.[630] 1++

Some patients may use emergency departments rather than primary care services for their asthma care. Education has been shown to reduce subsequent hospital admission and improve scheduled appointments and self-management techniques but does not improve reattendance at emergency departments.[169] 1++

For the above groups there is a role for a trained asthma liaison nurse based in, or associated with, the emergency department.[169]

Patient education is covered in section 5.2.1

9.6.3 FOLLOW UP

A careful history should elicit the reasons for the asthma attack 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.

Prior to discharge, follow up should be arranged 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 as effective and safe as that given by a respiratory doctor.[631] 1+

Assisting patients in making appointments while being treated for an acute asthma attack in emergency departments may improve subsequent attendance at primary care centres.[632] 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 attack. Ideally this communication should be directly with a named individual responsible for asthma care within the practice, by means of fax or email.

9.7 ACUTE ASTHMA IN CHILDREN

The assessment of acute asthma in children under five can be difficult. Intermittent wheezing attacks are usually triggered by viral infection and the response to asthma medication may be 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. This guideline is intended for children who are thought to have acute wheeze related to underlying asthma and should be used with caution in younger children who do yet have a considered diagnosis

of asthma, particularly those under two years of age. The guideline is not intended for children under one year of age unless directed by a respiratory paediatrician. The guideline should not be used to treat acute bronchiolitis

9.7.1 CLINICAL ASSESSMENT

Table 14 details criteria for assessment of severity of acute asthma attacks in children. Annexes 5–8 contain algorithms summarising the recommended treatments for children presenting with acute or uncontrolled asthma in primary care *(see Annex 5)*, the ED *(see Annex 6)*, and hospital *(see Annexes 7 and 8)*.

Table 14: Levels of severity of acute asthma attacks in children[633]

Moderate asthma	Able to talk in sentences SpO_2 ≥92% PEF ≥50% best or predicted Heart rate ≤140/min in children aged 1–5 years ≤125/min in children >5 years Respiratory rate ≤40/min in children aged 1–5 years ≤30/min in children >5 years	
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 Heart rate >140/min in children aged 1–5 years >125/min in children >5 years Respiratory rate >40/min in children aged 1–5 years >30/min in children >5 years	
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	

Before children can receive appropriate treatment for an acute asthma attack 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.[634-637] 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.

9.7.2 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 healthcare professionals assessing acute asthma in both primary and secondary care settings.

Low oxygen saturations after initial bronchodilator treatment selects a group of patients with more severe asthma.[634,637] | 2^{++}

B **Consider intensive inpatient treatment of children with SpO_2 <92% in air after initial bronchodilator treatment.**

9.7.3 PEAK EXPIRATORY FLOW

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.

9.7.4 CHEST X-RAY

Chest X-rays rarely provide additional useful information and are not routinely indicated.[638,639]

✓ 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.

9.7.5 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 $PaCO_2$.[571] If ear lobe sampling is not practicable a finger prick sample can be an alternative. Normal or raised $PaCO_2$ levels are indicative of worsening asthma. A more easily obtained free flowing venous blood $PaCO_2$ measurement of <6 kPa (45 millimetres of mercury) excludes hypercapnia.[571] 4

9.8 INITIAL TREATMENT OF ACUTE ASTHMA IN CHILDREN

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

Emergency departments attending to children with acute asthma should have a nurse trained in paediatrics 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. 4

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.[640]

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

9.8.1 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 of 94–98%.

9.8.2 INHALED SHORT-ACTING β_2 AGONISTS

Inhaled β_2 agonists are the first line treatment for acute asthma in children aged 2 years and over.[641-644] Assessment of response should be based on accurately recorded clinical observations and repeat measurements of oxygenation (SpO_2) (*see Table 14)*. Children receiving $\beta_2$agonists via a pMDI + spacer are less likely to have tachycardia and hypoxia than when the same drug is given via a nebuliser.[527] In children under two who have a poor initial response to β_2 agonists administered with adequate technique, consider an alternative diagnosis and other treatment options. 1^+

A **Inhaled β_2 agonists are the first-line treatment for acute asthma in children.**

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

A **A pMDI + spacer is the preferred option for children with mild to moderate asthma.**

Children less than three years of age 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,[641-643] although children with mild symptoms benefit from lower doses.[644] 1+

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

Two to four puffs of salbutamol (100 micrograms via a pMDI + spacer) might be sufficient for mild asthma attacks, although up to 10 puffs might be needed for more severe attacks. Single puffs should be given one at a time and inhaled separately with five tidal breaths. Relief from symptoms should last 3–4 hours. If symptoms return within this time a further or larger dose (maximum 10 puffs) should be given and the parents/carer should seek urgent medical advice.

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). If there is poor response to the initial dose of β_2 agonists, subsequent doses should be given in combination with nebulised ipratropium bromide (*see section 9.8.3*). Doses of nebulised bronchodilator 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.[645,646] Once improving on two- to four-hourly salbutamol, patients should be switched to a pMDI and spacer treatment as tolerated.

Schools can hold a generic reliever inhaler enabling them to treat an acutely wheezy child whilst awaiting medical advice. This is safe and potentially life saving.

✓ Increase β_2 agonist dose by giving one puff every 30–60 seconds, according to response, up to a maximum of ten puffs.

✓ Parents/carers of children with an acute asthma attack at home, and symptoms not controlled by up to 10 puffs of salbutamol via a pMDI and spacer, should seek urgent medical attention.

✓ If symptoms are severe additional doses of bronchodilator should be given as needed whilst awaiting medical attention.

✓ Paramedics attending to children with an acute asthma attack should administer nebulised salbutamol, using a nebuliser 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.

9.8.3 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.[647] 1+

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

Frequent doses up to every 20–30 minutes (250 micrograms/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 tapered to one- to two-hourly thereafter according to clinical response. The ipratropium dose should be tapered to four- to six-hourly or discontinued.

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

9.8.4 STEROID THERAPY

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.[592,593] 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 studies may indicate whether a single dose of dexamethasone may offer clinical benefit over multiple doses of prednisolone.[648-650] 1+ 1-

A large UK study of pre-school children with mild to moderate wheeze associated with viral infection showed no reduction in hospital stay (or 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.[651] 1++

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

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

Use a dose of 10 mg of prednisolone for children under 2 years of age, a dose of 20 mg for children aged 2–5 years and a dose of 30–40 mg for children older than 5 years.

Oral and intravenous steroids are of similar efficacy.[594,652,653] 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.[654] There is no need to taper the dose of steroid tablets at the end of treatment.[596,597] 2+

✓
- Use a dose of 10 mg prednisolone for children under 2 years of age, 20 mg for children aged 2–5 years and 30–40 mg for children older than 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 predisolone 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. Tapering is unnecessary unless the course of steroids exceeds 14 days.

Inhaled corticosteroids

There is insufficient evidence to support the use of ICS as alternative or additional treatment to steroid tablets for children with acute asthma.[598,655-662] 1++ 1+ 1-

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

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

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

9.8.5 ANTIBIOTICS

There is insufficient evidence to support or refute the role of antibiotics in acute asthma,[439] 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.

9.8.6 LEUKOTRIENE RECEPTOR ANTAGONISTS

Initiating oral montelukast in primary care settings, early after the onset of an acute asthma attack, can result in decreased asthma symptoms and the need for subsequent healthcare attendances in those with mild asthma attacks.[505,663] Current evidence shows no benefit for the addition of leukotriene receptor antagonists to standard asthma treatment for moderate to severe asthma attacks.[610] 1++ 1+

9.8.7 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 children with mild to moderate asthma.[604] A subgroup analysis from a large RCT suggests a possible role in children with more severe asthma attacks (SpO_2 <92%) or with short duration of deterioration. Further studies are required to evaluate which clinical groups would benefit the most from this intervention.[664] 1++

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

C **Consider adding 150 mg 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 SpO_2 <92%.**

9.9 SECOND-LINE TREATMENT OF ACUTE ASTHMA IN CHILDREN

Children with continuing severe asthma despite optimal first-line treatments, frequent nebulised β_2 agonists and ipratropium bromide plus oral steroids, and those with life-threatening features, need urgent review by a specialist with a view to management in an appropriate high-dependency area or transfer to a paediatric intensive care unit to receive second-line intravenous therapies.

Three options, IV magnesium sulphate, IV β_2 agonist or IV aminophylline can be considered. In one RCT comparing all three agents in 100 children, a bolus of magnesium sulphate was shown to reduce clinical symptoms faster than the other treatments. There were no significant side effects documented in the magnesium sulphate group.[665] A systematic review of four paediatric trials comparing IV salbutamol with IV aminophylline demonstrated equivalence. One study found 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.[666] 1++ 1+

9.9.1 INTRAVENOUS SALBUTAMOL

The role of intravenous β_2 agonists in addition to nebulised treatment remains unclear.[584] 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.[584] 1+

B **Consider early addition of a single bolus dose of intravenous salbutamol** (15 micrograms/kg over 10 minutes) **in a severe asthma attack where the child 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 electrocardiogram (ECG) monitoring and twice daily electrolyte monitoring. Doses above 1–2 micrograms/kg/min (200 micrograms/ml solution) should be given in a paediatric intensive care unit setting (up to 5 micrograms/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 β_2 agonists and should be replaced.

✓ If intravenous β_2 agonist infusions are used, consider monitoring serum lactate to monitor for toxicity.

9.9.2 INTRAVENOUS AMINOPHYLLINE

There is no evidence that aminophylline is of benefit for mild to moderate asthma and side effects are common and troublesome.[609,667] One well-conducted study has shown evidence of benefit in children with acute severe 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.[668] 1⁻ 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 (omit in those receiving maintenance oral theophyllines) with ECG monitoring 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.

9.9.3 INTRAVENOUS MAGNESIUM SULPHATE

Intravenous magnesium sulphate is a safe treatment for acute asthma in children not responding to first-line treatment.[607,665,669] Doses of up to 50 mg/kg/day (maximum 2 g) have been used. The potential side effect of hypotension is rare. [665] 1⁺

B **In children who respond poorly to first-line treatments, consider the addition of intravenous magnesium sulphate as first-line intravenous treatment** (40 mg/kg/day).

9.9.4 OTHER THERAPIES

Heliox

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

Recombinant human deoxyribonuclease

There is no evidence to support the use of recombinant human deoxyribonuclease (rhDNAase) in acute asthma in children.

9.9.5 CRITICAL CARE

In children with acute asthma and a poor response to standard therapy (inhaled bronchodilators, steroids, oxygen and intravenous bronchodilators) other therapies may be considered in the appropriate critical care setting with the appropriate available expertise. There is little high-quality evidence to guide treatment at this stage of an acute asthma attack and it is important to involve a clinician with the appropriate skills in airway management and critical care support as early as possible.

Ketamine

A systematic review of the use of ketamine for the management of acute asthma attacks in children found only one small study (n=68), among non-intubated children, suitable for inclusion. No benefit from ketamine compared with placebo in terms of respiratory rate, oxygen saturation, hospital admission rate, need for mechanical ventilation, or need for other adjuvant therapy was found.[670] 1++ 2-

Sevoflurane

A small (n=7) non-comparative study of sevoflurane in children with life-threatening asthma reported that sevoflurane inhalation corrects high levels of $PaCO_2$ and provides clinical improvement in mechanically ventilated children.[671] Use of this agent is, however, limited to areas with appropriate scavenging facilities to extract gas in order to protect healthcare staff. 3

There is little high-quality evidence to guide treatment of acute asthma in children with a poor response to standard therapy (inhaled bronchodilators, steroids, oxygen and intravenous bronchodilators). It is, therefore, important to involve a clinician with the appropriate skills in airway management and critical care support as soon as possible.

✓ Children with asthma not responding to standard treatment should be evaluated by a specialist with the appropriate experience and skills to use and assess medication familiar to those in critical care settings.

9.9.6 NON-INVASIVE VENTILATION

Non-invasive ventilation as a treatment approach for children admitted to hospital with status asthmaticus has been reported in two small studies, one a pilot study for an RCT.[672,673] Although there is some evidence that NIV is safe and feasible for use in this population, there is little evidence of its effectiveness and insufficient evidence on which to base a recommendation. 1+ 3

Future trials, including measurable clinical outcomes such as respiratory parameters, physiological variables and blood gases, are needed to assess the role of NIV in treating children with status asthmaticus.

9.9.7 DISCHARGE PLANNING

Children can be discharged when stable on 3–4 hourly inhaled bronchodilators that can be continued at home.[674] PEF and/or FEV_1 should be >75% of best or predicted and SpO2 >94%. An asthma care bundle developed by BTS is also available from the BTS website (www.brit-thoracic.org.uk). Adult studies show that optimal care comprising self monitoring, regular review and a written PAAP can improve outcomes.[148] 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:

- the diagnosis – clearly document the criteria used to diagnose asthma
- check inhaler technique
- consider the need for preventer treatment or optimising/adjusting previously prescribed preventer treatments
- provide a written PAAP for subsequent asthma attacks 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
- assess exposure to environmental tobacco smoke or actual smoking in older children and refer to suitable agencies where appropriate
- identify the trigger of the acute attack and discuss future management plans for exposure
- arrange follow up by primary care services within two working days
- 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.

Many children with recurrent episodes of wheeze triggered by viruses do not go on to develop atopic asthma. The need for regular preventer treatment may depend on the severity and frequency of episodes. Many may not require inhaled corticosteroids.

10 Difficult asthma

10.1 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 asthma attacks 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 asthma attack 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 ICS as a minimum requirement, whilst more recent consensus work has stipulated a treatment level equivalent to at least high-dose therapies *(see section 7.5 and Figures 2 and 3)*, before labelling as 'difficult'.[675,676]

In this guideline difficult asthma is defined as persistent symptoms and/or frequent asthma attacks despite treatment with high-dose therapies *(see section 7.5)* or continuous or frequent use of oral steroids *(see section 7.6)*

Observational uncontrolled studies in participants with difficult asthma, using multidisciplinary assessment models have identified high rates of alternative or coexistent diagnoses and psychological comorbidity.[97,677-679] 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 participants with difficult asthma, a proportion will have refractory disease, which is relatively resistant to currently available therapies. This group can only be identified after detailed evaluation, including exclusion of alternative causes of persistent symptoms, management of other comorbidities and confirmation of adherence with therapy. 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 to 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.**

10.2 FACTORS CONTRIBUTING TO DIFFICULT ASTHMA

10.2.1 POOR ADHERENCE

Poor adherence with asthma medication is associated with poor asthma outcome in adults and children (*see section 5.4*). 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/ICS 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.[680] In another study, 75 of 115 (65.2%) patients filled prescriptions for <80% of ICS medication and had significantly worse lung function, higher sputum eosinophil counts and prior ventilation compared to adherent patients.[681] A study of 71 school-aged children with persistent symptoms, 2+ 3

despite high-dose treatment or continuous or frequent use of oral steroids, 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 children (55%) the factors identified and the interventions recommended meant that further escalation of treatment was avoided.[682] In a paediatric case-control series, poor adherence based on prescription records was identified in 22% of children with difficult to control asthma, although adherence was not reported in the stable controls.[683] In a descriptive study of 100 adult participants 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.[678] 2+ 3

There is a need to identify patients who have poor control solely as a result of poor adherence to simple, currently available therapies. In theory, improving adherence through monitoring and intervention could potentially reduce asthma attacks, target resources for genuine therapy-resistant cases and reduce overall health costs by minimising asthma attacks, hospitalisation and health resource use.

Monitoring adherence is likely to be beneficial to asthma control and there is some evidence that it can improve lung function and quality of life.[684] Adherence monitoring based on self assessment is unlikely to be accurate and objective measures are therefore needed. An ancillary study to an RCT showed that there was very poor agreement between objective (doses remaining in Turbohaler device) and subjective (self-reported) measurements of adherence in children aged 5–12 years with mild or moderate asthma and airway hyper-responsiveness to methacholine, and that self reporting failed to detect poor adherence.[214] Objective measurement of non-adherence based on FeNO suppression in adults with difficult asthma was demonstrated in one study although further validation of this test is required.[224] Some other objective measures such as prescription filling are problematical because patients may fill prescriptions but not take the medication. 1+

C **Healthcare professionals should always consider poor adherence to maintenance therapy before escalating treatment in patients with difficult asthma.**

10.2.2 PSYCHOSOCIAL FACTORS

Fatal and near-fatal asthma have been associated with adverse psychosocial factors *(see section 9.1.3)*. Most observational studies[97,678,685-688] and a case-control study[689] in patients with difficult asthma have also suggested a high level of psychological morbidity, though this observation has not been universal.[690,691] 2+ 3

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.[692] 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 treatment of depression demonstrated a reduction in oral steroid use,[693] 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 to therapy.[694] However, a non-blinded randomised intervention study in adults with difficult asthma showed no benefit from a six month nurse-delivered psychoeducational programme.[695] A meta-analysis of psychoeducational interventions in patients with difficult asthma concluded that many of the studies were of poor quality, although there was some evidence of a positive effect from 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.[696] 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.**

10.2.3 DYSFUNCTIONAL BREATHING

Observational uncontrolled studies in patients with difficult asthma have identified high rates of dysfunctional breathing as an alternative or concomitant diagnosis to asthma causing symptoms.[97,678] It remains unclear what is the best mechanism of identifying and managing this problem. 3

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

10.2.4 ALLERGY

Acute asthma has been associated with IgE dependent sensitisation to indoor allergens.[697] In case-control studies, mould sensitisation has been associated with recurrent admission to hospital and oral steroid use [698,699] and with intensive care unit admissions and respiratory arrest.[700,701] There is no published evidence of any intervention study in this patient group. Research in this area is required. 2++ 3

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

10.2.5 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 ICS therapy.[125,127,702] In the study with the largest number of patients receiving high dose ICS 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.[125] Case series have suggested that sputum induction is safe in patients with difficult to control asthma.[68,703-706]

1+
1-
3

Controlled studies using FeNO to target treatment have not specifically targeted adults or children with difficult asthma.[119,126]

1+

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

11 Asthma in adolescents

11.1 DEFINITIONS

Adolescence is the transitional period of growth and development between puberty and adulthood, defined by the 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.[707-709] Key elements of working effectively with adolescents in the transition to adulthood include:[710]

- 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.

11.2 PREVALENCE OF ASTHMA IN ADOLESCENCE

Asthma is common in adolescence with a prevalence of wheeze in 13–14 year olds in Western Europe in the past 12 months (current wheeze) of 14.3%.[711] 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 underdiagnosis of asthma in adolescents, with estimates of 20–30% of all asthma present in this age group being undiagnosed.[711-714] This has been attributed to under-reporting of symptoms. A number of risk factors have independently been associated with underdiagnosis 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.[714] Children with undiagnosed frequent wheezing do not receive adequate healthcare for their illness[714] and the health consequences of not being diagnosed with asthma are substantial.[715,716]

Although feasible, there is insufficient evidence to support screening for asthma in adolescents.[717,718]

✓ Clinicians seeing adolescents with any cardiorespiratory symptoms should ask about symptoms of asthma.

11.3 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.

11.3.1 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.[719] Other diagnoses producing reproducible symptoms on exercise include normal physiological exercise limitation, with and without poor physical fitness, vocal cord dysfunction, dysfunctional breathing, habit cough, and supraventricular tachycardia.[45]

Most exercise-related wheezing in adolescents can be diagnosed and managed by careful clinical assessment.[720] 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.[45]

11.3.2 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.[721]

In one study in adolescents, internet-based and written questionnaires about asthma provided equivalent results.[722] The ACQ and the Asthma Control Test have been validated in adolescents with asthma (*see Table 7*).[136]

11.3.3 QUALITY OF LIFE MEASURES

Quality of life (QoL) scales (such as AQLQ12+) can be used in adolescents.[723,724]

11.3.4 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.

11.3.5 BRONCHIAL HYPER-REACTIVITY

Although many children with asthma go into long-lasting clinical remission at adolescence, BHR may persist. Whether persisting BHR reflects ongoing airway inflammation is debated.[725]

A negative response to an exercise test is helpful in excluding asthma in children with exercise-related breathlessness.[45]

11.4 RISK FACTORS

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

11.4.1 ATOPY

Studies confirm that atopic dermatitis and atopic rhinitis are amongst the factors most strongly associated with asthma persisting into teenage years.[726-729]

11.4.2 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.[730]

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.[75,78,86,88,94,106-108,729]

11.4.3 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.[731] The same change is seen with asthma attacks, with risk of an asthma admission in females becoming double that observed in males from around 13–14 years.[732] This phenomenon has been attributed to a greater incidence of asthma among teenage girls.[733]

11.4.4 CHLORINATED SWIMMING POOLS

Exposure to chlorinated swimming pools has been associated with an increased risk of asthma, airway inflammation and some respiratory allergies.[734] Such associations were not found among adolescents without atopy or in those who attended copper-silver sanitised pools.[735]

11.5 COMORBIDITIES AND MODIFIABLE BEHAVIOURS

11.5.1 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.[736] In young people with asthma, the presence of an anxiety or depressive disorder is highly associated with increased asthma symptom burden.[737] 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.[738]

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.[739]

Brief screening questionnaires for anxiety and depression suitable for use in adolescents are available and may help identify those with significant anxiety and depression.[740]

11.5.2 OBESITY

The evidence on whether asthma is more common in overweight and obese adolescents with asthma is conflicting.[726,741-743] 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.

11.5.3 GASTRO-OESOPHAGEAL REFLUX AND GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux and GORD is common in patients with asthma, including adolescents.[744] 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.[745] There is no evidence that treatment for GORD improves asthma symptoms in children and adolescents with GORD and asthma.[523,524]

11.6 ASTHMA ATTACKS 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.[746]

11.7 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.[747] Young adults with asthma had a low awareness of occupations that might worsen asthma (for example exposure to dusts, fumes, sprays, exertion and temperature changes) and did not generally discuss career plans with their general practitioner. Further details about occupational asthma can be found in section 13.

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

11.8 NON-PHARMACOLOGICAL MANAGEMENT

11.8.1 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 ($p\leq0.001$) reported in the next 12 months, as well as fewer episodes of poor asthma control ($p=0.042$).[748]

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.[749] 2+ 3 4

Among adolescents, smoking is a risk factor for asthma.[727,750-752] 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.[753]

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 NHS smoking 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.

11.8.2 COMPLEMENTARY AND ALTERNATIVE MEDICINE

In a small study, 16% of Italian teenagers had used complementary and alternative medicine (CAM; homeopathy, acupuncture, herbal medicines).[754] In a study in the USA, 80% of urban adolescents (aged 13–18 years) with asthma reported that they had used CAM, most commonly rubs, herbal teas, prayer and massage.[755] While most adolescents used CAM with conventional asthma therapy, 27% reported they used it instead of prescribed therapy,[755] suggesting that CAM use may be a marker of non-adherence to prescribed asthma treatment. 2-

✓ Healthcare professionals should be aware that complementary alternative medicine use is common in adolescents and should ask about its use.

11.9 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 7.

11.10 INHALER DEVICES

Specific evidence about inhaler device use and choice in adolescents is limited. Inhaler devices are covered in section 8.

Two small studies comparing two different types of inhalers in adolescents found that both DPIs and pMDIs plus spacer are of value in adolescent asthma.[756,757] There were no differences between the two inhaler devices in terms of symptoms or lung function but patients preferred the DPI. 2+ 3

Although 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.[758,759]

✓ 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.

11.11 ORGANISATION AND DELIVERY OF CARE

11.11.1 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 multidisciplinary 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.[677] 3

11.11.2 SCHOOLS AS A SETTING FOR HEALTHCARE DELIVERY AND ASTHMA EDUCATION

Some innovative approaches have used schools as a 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%.[760] 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).

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.[761] In a study in the USA, 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.[183] 1^+

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.[762]

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.

11.11.3 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.[707-709]

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.[763,764]

✓ 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.

11.11.4 PREPARATION FOR TRANSITION

Transition should be seen as a process and not just the event of transfer to adult services.[763] It should begin early, be planned, involve the young person, and be both age and developmentally appropriate (*see Table 15)*.[763]

Table 15: Recommendations for organising transition services[763]

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 multidisciplinary and multiagency. Optimal care requires a co-operative 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 co-ordinator 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.

11.12 PATIENT EDUCATION AND SELF MANAGEMENT

11.12.1 EDUCATION IN SELF MANAGEMENT

Section 5 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 16)*. Clinicians need to educate and empower adolescents to manage as much of their asthma care as they are capable of doing while supporting parents to gradually hand over responsibility for management to their child.[765]

Table 16: Specific knowledge, attitudes and skills that underpin independent self-management practices in adolescents with asthma[765]

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 other healthcare professionals
Can ask questions of their doctor or other healthcare professional
Can arrange (and cancel) appointments
Can consult with a doctor or other healthcare professional without a parent/carer
Remembers to order more medication before it runs out
Can have prescriptions filled at the 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 (for example 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.[766,767] 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.[768] 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 of information technology.

3

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

11.12.2 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.[769]

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 adverse effects, denial, can't be bothered and embarrassment).[759,770] 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.[771]

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.[772] 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.[773] Clinical tools such as the Home, Education/Employment, Activities, Drugs, Sexuality, Suicide/depression adolescent health screen provide practitioners with an easily usable psychosocial screen.[774]

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.[775] One study found that once-daily supervised asthma preventer therapy at school improved asthma control and quality of life.[776]

12 Asthma in pregnancy

12.1 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.

12.1.1 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%.[777] A prospective cohort study of 1,739 pregnant women showed an overall improvement in 23% and deterioration in 30.3%.[778] 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.[779] There is also some evidence that the course of asthma is similar in successive pregnancies.[777,780] A systematic review showed no effect of pregnancy or stage of pregnancy on $FEV_{1.}$[781] 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.[782,783] Severe asthma is more likely to worsen during pregnancy than mild asthma,[777] but some patients with very severe asthma may experience improvement, whilst symptoms may deteriorate in some patients with mild asthma. In a large study in the USA, the rates of asthma attack were 13%, 26% and 52% in those with mild, moderate and severe asthma respectively.[778] 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.[780] 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.[777] 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 attack.[784] 2+

12.1.2 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.[785] 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.[786] 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.[778,787-790] 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.[791] 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).[778] Logistic regression analysis of the severe group showed an increased risk of gestational diabetes (adjusted odds ratio (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 to 1.09).[792] 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.[793] The RR was 2.54 (95% CI 1.52 to 4.25) compared to women without asthma. In a large cohort study of 2,123 women with asthma, there was an association of both mean FEV_1 and mean FEV_1 <80% predicted with gestational hypertension, preterm delivery <37 weeks and <32 weeks, and low birth weight.[794] 2+ 2++

In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.[777,782] Pregnancy should therefore be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute asthma attacks. 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.

12.2 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 asthma attacks at two weeks.[795] Available studies give little cause for concern regarding treatment side effects 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.[796-799 800] The recent report from the Intensive Care National Audit and Research Centre on female admissions to adult critical care units in England, Wales and Northern Ireland between 2009 and 2012 found that of 1,188 currently pregnant women, 94 (8%) were admitted with acute asthma and of 5,605 postpartum women, 32 (0.6%) were admitted with acute asthma.[801] 2+

Oxygen should be delivered to maintain saturation 94–98% in order to prevent maternal and fetal hypoxia.[571] 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 [802,803] but oxygen saturations are unaltered.[804] 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 *(see section 9)*.[777,783,784,787,788] In severe cases, intravenous β_2 agonists, aminophylline, or intravenous bolus magnesium sulphate can be used as indicated.[805] 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.[806] Pregnant women may be more difficult to intubate due to anatomical changes especially if they have pre-eclampsia.[807]

C **Give drug therapy for acute asthma as for non-pregnant patients 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 pregnant women with acute severe 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.

12.3 DRUG THERAPY IN PREGNANCY

In general, the medicines used to treat asthma are safe in pregnancy.[808,809] 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.[810] The risk of harm to the fetus from severe or chronically undertreated 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.**

12.3.1 β_2 AGONISTS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to short-acting β_2 agonists.[808-812] 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 participants, found no differences in perinatal mortality, congenital abnormalities, prematurity, mean birth weight, Apgar scores or labour/delivery complications.[813] 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.[778] 2++ 2+ 3

With regard to LABAs, evidence from prescription event monitoring suggests that salmeterol is safe in pregnancy and although there are some data on formoterol, numbers are small.[814,815] A systematic review of studies including 190 exposures to LABA demonstrated no increased risk of congenital malformations, pre-term delivery or pre-eclampsia.[816] A case control study including 156 infants exposed to LABA found no increased risk of major congenital malformations.[810] As in other settings, LABAs should be used with an ICS, ideally as a combination product.[817] 2+

Data on the use of combination products in pregnancy are limited although there are no theoretical reasons why these would be more harmful than the same agents given separately. There are some safety data for seretide (salmeterol/fluticasone propionate) but with small numbers.[818]

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

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

12.3.2 INHALED CORTICOSTEROIDS

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to ICS.[808,810,816,819-827] A meta-analysis of four studies of ICS use in pregnancy showed no increase in the rate of major malformations, preterm delivery, low birth weight or pregnancy-induced hypertension.[828] The UK case-control study included 1,429 infants exposed to ICSs and found no increased risk of major congenital malformations.[810] 2++ 2+ 2-

Inhaled anti-inflammatory treatment has been shown to decrease the risk of an acute attack of asthma in pregnancy and the risk of readmission following an asthma attack.[783,784] 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 attacks resulting in medical intervention, but inhaled beclometasone was better tolerated.[778] 2+

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

12.3.3 THEOPHYLLINES

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to methylxanthines.[808,829] 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.[830] 4

C **Use oral and intravenous theophyllines as normal during pregnancy.**

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

12.3.4 STEROID TABLETS

There is much published literature showing that steroid tablets are not teratogenic,[787,808,831] but there is 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.[831,832] One case control study, however, found a significant association, although this increase is not significant if only paired controls are considered.[833] Although one meta-analysis reported an increased risk,[834] a prospective study by the same group found no difference in the rate of major birth defects in prednisolone-exposed and control babies.[834] 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 to 2.6) for cleft lip.[835] Another case-control study including 262 exposed infants found no such association, although this was not limited to first trimester exposure.[810] 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.[789,802] 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 metabolised 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 attacks are less likely to be treated with steroid tablets than non-pregnant women.[795] Failure to administer steroid tablets when indicated increases the risk of ongoing asthma attacks and therefore the risk to the mother and her fetus. 2+

Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia, pre-term labour[786] and fetal growth but severe asthma may be a confounding variable.[836] 2+

C **Use steroid tablets as normal when indicated during pregnancy for women with 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.**

12.3.5 LEUKOTRIENE RECEPTOR ANTAGONISTS

Data regarding the safety of LTRAs 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 β_2 agonists.[836] A systematic review found no increased risk of malformations or pre-term delivery in nine exposed women.[792,816] Three studies looking at infant outcomes in women exposed to LTRAs (two in women taking montelukast) showed no increased risk of congenital malformations.[837-839] 2++ 2+ 2- 4

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

12.3.6 SODIUM CROMOGLICATE AND NEDOCROMIL SODIUM

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to sodium cromoglicate and nedocromil sodium.[816 808,836] 2+

C **Use sodium cromoglicate and nedocromil sodium as normal during pregnancy.**

12.3.7 IMMUNOMODULATION THERAPY

There are as yet no clinical data on the use of omalizumab for moderate-severe allergic asthma in pregnancy.

12.4 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,[786,840,841] but this may be due to planned Caesarean sections or inductions of labour rather than due to any direct effect of asthma on intrapartum indications.[784] 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).[778] 2+

Data suggest that the risk of postpartum asthma attacks is increased in women having Caesarean sections.[840] 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.[830] Prostaglandin F2α (carboprost/hemobate®) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.[830] Although ergometrine may cause bronchospasm particularly in association with general anaesthesia,[830] 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.[842]

✓ Advise women that an acute asthma attack is rare in labour.

✓ Advise women to continue their usual asthma medications in labour.

✓ In the absence of an acute severe asthma attack, 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.**

12.5 DRUG THERAPY FOR BREASTFEEDING MOTHERS

The medicines used to treat asthma, including steroid tablets, have been shown in early studies to be safe to use in breastfeeding mothers.[843] There is less experience with newer agents. Less than 1% of the maternal dose of theophylline is excreted into breast milk.[843] 2^+

Prednisolone is secreted in breast milk, but milk concentrations of prednisolone are only 5–25% of those in serum.[523] The proportion of an oral or intravenous dose of prednisolone recovered in breast milk is less than 0.1%.[844-846] 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.[844 845,846] 2^+ 3

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

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

13 Occupational asthma

13.1 INCIDENCE

The true frequency of occupational asthma is not known, but underreporting 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.[847-849] It is now the commonest industrial lung disease in the developed world with over 400 reported causes.[850-852] 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, healthcare professionals should consider that there may be an occupational cause.**

13.2 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.[853-861]

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.[853,854,856,858-864] 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.[865-868] 2+

13.3 DIAGNOSIS

Occupational asthma should be considered in all workers with symptoms of airflow limitation *(see Annex 9)*. 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.[869] 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.[869] 4

One study notes a relatively low positive predictive value of work related symptoms.[870] 3

✓ 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.[871-878] 3

Although skin-prick tests or blood tests for specific IgE are available, there are few standardised 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.[879] 3

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

13.3.1 SENSITIVITY AND SPECIFICITY OF SERIAL PEAK FLOW MEASUREMENTS

In a meta-analysis of 31 studies 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% *v* 71%) but less specific (69% *v* 91%) than computer-based methods.[878] 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).[880]

Shorter records without the requirement for three consecutive days at work can be analysed using the area between curves score. This requires at least eight readings a day on eight work days and three rest days.[881] A statistical method using the addition of timepoint analysis requires the waking time to be similar on rest and work days.[882] 2+ 3

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

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

13.3.2 DIAGNOSIS OF VALIDATED CASES OF OCCUPATIONAL ASTHMA USING IgE TESTING

A review by the British Occupational Health Research Foundation 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".[869] 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 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.[869] The review concluded that skin-prick testing or tests for specific IgE should be used in the investigation of occupational asthma caused by 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.[869] 4

D **Skin-prick testing or tests for specific IgE should be used in the investigation of occupational asthma caused by high molecular weight agents.**

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

13.3.3 NON-SPECIFIC REACTIVITY

Studies of non-specific reactivity are confounded by the different methods used, different cut-offs for normality and the interval between last occupational exposure and the performance of the test (an increase in time interval 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.[869,883] 3 4

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

13.3.4 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: a control challenge on a separate day; a gradual increase of exposure to the suspected occupational agent; close monitoring of airway calibre during the challenge and for at least six hours after the end of the exposure.[884] When carrying out specific challenge testing, an increased duration of allergen exposure may increase the overall diagnostic sensitivity of the tests[885] 3 4

A positive 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.[886] Equivocal reactions can sometimes be clarified by finding changes in non-specific bronchial responsiveness, sputum eosinophils or exhaled nitric oxide. SIC 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. SIC remains the gold standard for making a diagnosis of occupational asthma.

13.3.5 SPUTUM EOSINOPHILIA

Eosinophilic bronchial inflammation can be assessed by cell counts in fresh sputum, induced by inhaling hypertonic saline.[869] 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.[869,883,887] In the clinical setting the absence of sputum eosinophilia does not exclude a diagnosis of occupational asthma.[869]

2+
3
4

13.3.6 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".[869] The review concluded that the role of exhaled nitric oxide measurements in the diagnosis of occupational asthma in this setting is not established.[869]

4

13.3.7 EXHALED BREATH CONDENSATE

Exhaled breath condensate may offer assistance in those undergoing diagnostic testing for occupational asthma. Its definitive utility is not yet understood.[888,889]

3

13.4 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.[873,890-898]

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.[899-901]

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.[902-904] The risk of unemployment may fall with increasing time after diagnosis.[905] 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.[903,904] Approximately one third of workers with occupational asthma have been shown to be unemployed up to six years after diagnosis.[901-909]

2-

14 Organisation and delivery of care

14.1 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."[910]

There is little high-quality evidence from randomised trials addressing the impact of care pathways for asthma. Pathways have usually been implemented through 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 ED attendance and hospitalisation.[911,912] Pathways for inpatient care can improve processes of care, such as prescription of oral prednisolone and use of written asthma action plans in children,[913] and can reduce length of stay for children, [640,914] but have not improved follow up in general practice after discharge.[915]

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.

14.2 EDUCATING CLINICIANS

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) found that:

- educational outreach visits (for example training visits to general practices) lead to small to moderate improvements in outcomes[916]
- mixed interactive and didactic education is more effective than either alone.[917]

1++

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. 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,[171,918] or adaptations of it for Australian and UK practice,[199,919] and have shown reductions in ED visits,[918] improved symptom control,[199] and increased use of written asthma action plans.[919] The PACE intervention has not been tested for adult populations 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 attacks in children.[920] 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 asthma attacks.

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 healthcare use.[921-924] 1+ 1=

Remote IT educational interventions, such as remote spirometry training,[925] may be effective 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**

14.3 ASTHMA CLINICS

14.3.1 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 PAAP.[148] Benefits include reduced school or work absence, reduced asthma attack rate, improved symptom control and reduced attendance at the emergency department.[926,927] Proactive structured review, as opposed to opportunistic or unscheduled review, is associated with reduced rates of asthma attack and days lost from normal activity.[200,928,929] 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, or a general practitioner conducts the review. Clinicians trained in asthma management achieve better outcomes for their patients.[928,930,931] 1+ 2+ 3 4

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 focusing on particular groups such as those overusing bronchodilators, patients on higher dose therapies, those with asthma attacks or from groups with more complex needs.

14.3.2 PRIMARY CARE ASTHMA CLINICS

Primary care asthma clinics can be defined as a "...proactive system of care sited in primary care (eg GP clinic) which occupies a defined and often regular clinical session for the routine review of patients with asthma".[932]

Within primary care, structured reviews may be delivered as appointments in routine surgeries, or within dedicated asthma clinics.

One systematic review which included three small studies of the asthma clinic model, showed no evidence of improvement in important outcomes such as hospitalisation, ED attendances, or quality of life, although there was a reduction in night-time waking, and no evidence that clinics were cost effective.[932] The poor quality of the included studies led the review to conclude that there was a lack of evidence to inform the best way to organise structured asthma care in practice. 1+

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

14.3.3 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.[154] The review focused on psychoeducational 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 ED 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 psychoeducational interventions in clinics for adults and children with difficult asthma.**

14.4 TELEHEALTHCARE

Terminology in this rapidly evolving area is changing and is used inconsistently in the literature and in practice. In this guideline, 'telehealthcare' is used as an overarching term for all technology-enabled healthcare. Within this, telemonitoring implies collection and transfer of patient data; teleconsultation is the use of technology to enable remote consultation between a patient and a clinician; and telemedicine is interprofessional consultation.

14.4.1 SUPPORTING SELF MANAGEMENT

Telehealthcare embraces a range of functionalities which target different aspects of self-management behaviour including automated medication reminders to improve adherence,[234] educational 'games' to improve knowledge[152,163,244,933] or effect behavioural change,[183,934,935] and telemonitoring with various levels of professional oversight to support self management.[194,936-941] These functions may use different IT modalities (text messaging,[153,942] automated telephone calls,[245] 'apps',[939] computer games,[152,163,244] cloud-based electronic health records,[939-941]) and may be delivered in different contexts (primary/community care,[194,245,938,939] hospital outpatients,[933] school based[163,183,244,935]) which may influence their impact. In the fast moving context of telehealthcare, the aim of the intervention and the theoretical underpinning is likely to be more important to interpreting the evidence than details of the mode of delivery. 1++ 1+ 1- 2++ 2+

Automated reminders to improve adherence

In the short term, and in the context of a clinical trial, automated reminders (delivered by text messaging, alarms, or automated telephone calls) can improve adherence to medication, but do not have an impact on clinical outcomes.[234] As part of more complex telehealthcare interventions, reminders may contribute to improved adherence to monitoring or medication use.[153,940-942]

1+
1-
2++

Computer-based educational games to improve knowledge or affect behaviour

Educational 'games' improved asthma knowledge in most, but not all participants in school-based interventions,[152,163,244] and children attending a UK outpatients clinic.[933] The latter study showed reduced school absenteeism and the number of steroid courses,[933] but overall there is an inconsistent effect on clinical outcomes,[152,163,244] and no impact on use of healthcare resources.[163,244,933]

1+
1-
2+

Games based on behavioural change theories have resulted in some improvement in self-management skills, although impact on symptoms and use of healthcare resources is variable.[934] A generic health behaviour game which targeted teenagers with specific behavioural traits (such as rebelliousness, poor emotional support or low self esteem), improved asthma control, reduced absenteeism, and reduced admissions, but did not reduce ED attendances.[183,935]

1+

Telemonitoring to support self management

Telemonitoring, the transmission of monitoring data from a patient to an electronic health record which can be shared with (or monitored by) healthcare professionals, is promoted as having the potential to improve outcomes.

Some studies have demonstrated improvement in at least one clinical outcome, such as measures of asthma control,[938,941] lung function,[194] quality of life, reduced risk of activity limitation,[194] and school absenteeism, exacerbations, and use of unscheduled care.[194] Other trials, however, have shown no impact on asthma control or use of healthcare resources.[937,939]

1++
1+

These interventions are heterogeneous, and the impact of the telemonitoring is likely to be strongly influenced by the demographic context (deprivation status and cultural background[194,938]) and the level of professional support provided (frequency of monitoring,[194,940] personalisation of feedback,[940] access to case management support[938]). People with poorly-controlled asthma have the potential to gain more by engaging with telemonitoring than those whose control is already optimal.[941] Telehealthcare-supported self management offered no clinical benefits over traditionally delivered care that was already guideline standard.[939]

Despite the heterogenous interventions, the overarching findings from the systematic reviews are consistent and show that telehealthcare:

- can improve process outcomes, such as knowledge,[152,163,943] adherence to monitoring,[153] self-efficacy/self-management skills,[163,934,943] and increased use of preventer medication,[234,942,943] at least in the short term[234]
- has an inconsistent effect on clinical outcomes, such as symptoms,[152,153,163,934,936,937,942,943] SABA use,[152] lung function,[152,153,936,942,943] school absenteeism,[163,943] activity limitation,[936,943] quality of life,[163,936,937,943] and oral steroid courses[934] 1+ 1- 2++ 2+ 2-
- generally has no effect on unscheduled use of healthcare resources, such as hospitalisations and ED attendances,[152,937,942,943] out-of-hours consultations,[937] and GP consultations[937,943]
- has cost implications relating to providing and supporting telehealthcare services[153,937]
- has no identified harms and whilst the telehealthcare intervention was often no better than usual care, there were no instances in which it was less effective.+

Telehealthcare is a means of delivering care, not a panacea. Overall, clinical outcomes with telehealthcare are at least as good as, though not consistently superior to, traditionally delivered care. IT-based approaches may, therefore, be considered where organisational/clinical/social circumstances or clinician and patient preferences or convenience suggest they may be appropriate.

C **Telehealthcare may be considered as an option for supporting self management.**

14.4.2 REMOTE CONSULTING

Remote consulting can be either asynchronous, with information exchanged sequentially, for example via email, text or web, or synchronous, with information exchange by, for example, telephone.

Evidence to support either approach in patients with asthma is very limited. Two systematic reviews of asynchronous remote consulting covering 15 RCTs and 52 mostly observational studies included only four studies addressing asthma, two of them RCTs, one of which was of poor quality.[944,945] Although both reviews suggest that asynchronous telehealth led to significant reductions in healthcare use and some improvement in disease status (for example HbA1C in diabetes), the evidence relating to asthma is limited and of low quality and no conclusions can be drawn about its effectiveness in this patient group. 1+

Evidence to support synchronous consulting in patients with asthma is also limited and, in general, did not address major outcomes of importance. Of four RCTs identified,[195,245,946,947] two were considered to be of low methodological quality.[195,245] There is some evidence to suggest that synchronous consulting can lead to improvements in parental QoL,[946] and equivalent health status to people reviewed in 'traditional' face-to-face consultations.[947] 1++ 1-

14.4.3 COMPUTERISED DECISION SUPPORT SYSTEMS

Computerised decision support systems (CDSS) can broadly be divided into systems targeted at healthcare professionals and integrated within the electronic health record, and web-based systems that are used by patients (and their healthcare professionals) to support self management.

A systematic review of eight RCTs considering the impact on asthma control of CDSS used by healthcare practitioners found little effect on patient outcomes because the healthcare practitioners rarely used the CDSS being evaluated and when used, rarely followed the advice given. Future CDSS need to align better with professional workflows so that pertinent and timely advice is easily accessible within the consultation. The authors concluded that integration of CDSS into electronic health records is cumbersome and a major factor in their ineffectiveness.[948] 1+

A second review of 19 RCTs concluded that CDSS can improve chronic disease processes and outcomes. This conclusion, however, reflects the inclusion of four trials of systems used by patients to promote self management, three of which reported improved asthma control or QoL, although one, with a high risk of bias, improved symptoms and QoL but led to increased unscheduled care.[949] 1++

A **Computerised decision support systems for patient use can be considered as an approach to supporting self management.**

14.5 SCHOOL-BASED INTERVENTIONS

Most school-based asthma interventions focus on education delivered by adults (usually healthcare professionals) to school children.[163] Other approaches include peer education, whereby students are trained and then, in turn, train their peers,[761,950] web-based programmes,[183] or directly observed therapy with ICS medication,[776] which may additionally include education of parents.[951] One study tested a multifaceted intervention combining education of schoolchildren with additional training of their doctor, including provision of self-management plans.[952] Most evaluations have been based in the USA, often involving minority ethnic groups not directly applicable to 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.[163] Peer education was effective for adolescents[761] but not pre-teens.[950] In two studies, directly observed therapy improved symptom control.[776,951] Of all the school-based interventions tested, Bruzzese's multifaceted programme had the most impact, improving symptoms, quality of life, emergency department use and hospitalisation.[952] 1+ 1- 2+

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

14.6 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. Further details on the aspects of tailoring can be found in section 5.3.5.

A review of system level interventions concluded that the most effective at reducing further healthcare use were those targeted at people who had attended emergency care or had been hospitalised.[168] Interventions were usually intensive, multisession clinic-based programmes. They were nurse-led or used experts including pharmacists or allergy specialists.[168] These findings mirror the little work published in the UK, which showed that a clinic based in primary care was ineffective,[188] while 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.[189] 1+

Further studies examining the impact of interventions on people from minority ethnic groups in the UK are needed. 1+

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

14.7 LAY-LED INTERVENTIONS

Educational interventions led by lay, rather than healthcare 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; 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 identified.[953] Only two of the included trials specifically addressed people with asthma, and these found no improvements in breathlessness, health-related quality of life, healthcare 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-management programmes for people with asthma are not recommended.**

14.8 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. One review addressed interventions in low and middle income countries, while another addressed pharmacy interventions more generally.[954,955]

Interventions generally involved educating community pharmacists to, in turn, educate patients.[956-958] Other models or elements included follow-up reviews for newly prescribed medication,[959] identifying those with poor control by using questionnaires such as the Asthma Control Test,[958] searching prescribing databases for patients using large numbers of reliever inhalers,[960] and targeting reviews or referral to general practitioners.[960]

Overall, the most consistent improvements in outcomes were seen in inhaler technique,[956-958] with a few studies showing improvements in reduced dispensing of, or need for, reliever inhalers.[958,960] There was no convincing evidence of reduction in healthcare use. 1+ 1-

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

✓ Consider training pharmacists to provide education for people with asthma.

15 Provision of information

The provision of accurate information to patients and carers is of great importance in order to achieve good adherence to treatment and improved patient outcomes. Specific recommendations and good practice points relating to provision of information by healthcare professionals to patients and carers are found throughout this guideline. In addition, supported self management is covered in detail in section 5, including sections on personalised asthma action plans *(see section 5.2.2 and Table 8, Annex 10)* and adherence and concordance *(see section 5.4)*.

Patient versions of this guideline, in booklet form, covering the management of asthma in adults (for patients and their families and carers) and the management of asthma in children (for parents and carers) are available on the SIGN website (www.sign.ac.uk) or directly from SIGN and could be a useful addition to the patient's PAAP. Healthcare professionals are encouraged to inform patients and carers that these booklets are available. The patient versions are reviewed and updated in line with the clinical guideline. In addition to information on care and treatment, the booklets include contact details for, and brief information about, a number of organisations that provide information for patients *(see section 15.1)*.

15.1 SOURCES OF FURTHER INFORMATION

15.1.1 NATIONAL ORGANISATIONS FOR PEOPLE WHO HAVE ASTHMA

Asthma UK
18 Mansell Street, London, E11 8AA
Tel: 0300 222 5800
Asthma UK's Helpline nurses: 0300 222 5800 (9am-5pm, Mon-Fri) – nurses provide advice for people with asthma and for healthcare professionals.
www.asthma.org.uk • General enquiries: info@asthma.org.uk

Asthma UK is a charity dedicated to improving the health and wellbeing of people who are affected by asthma. The charity provides a wide range of information and resources on their website, including downloadable asthma action plans. Printed information booklets and other resources are available on request and bulk copies are available for purchase by healthcare professionals.

British Lung Foundation
73–75 Goswell Road, London, EC1V 7ER
Tel: 020 7688 5555 • Helpline: 08458 50 50 20
www.lunguk.org

The British Lung Foundation aims to help people understand and live with lung disease. They run the Breathe Easy support network which offers information, support and friendship to anyone affected by lung disease.

15.1.2 OTHER ORGANISATIONS

Allergy UK
Planwell House, Lefa Business Park, Edgington Way, Sidcup, Kent, DA14 5BH
Helpline: 01322 619898
www.allergyuk.org

Allergy UK is a charity which aims to increase people's understanding and awareness of allergies, and helps people manage their allergies.

ASH (Action on Smoking and Health)
First Floor, 144–145 Shoreditch High Street, London, E1 6JE
Tel: 020 7739 4732
www.ash.org.uk

ASH is the leading voluntary organisation campaigning for effective tobacco-control legislation and providing an expert information service.

NHS 111
Freephone: 111

This is a 24-hour helpline for people in England and Wales. It is led by nurses who provide confidential healthcare advice and information 24 hours, 365 days a year.

NHS 24
Freephone: 111
www.nhs24.com

This is a 24-hour helpline for people in Scotland. It is led by nurses who provide confidential healthcare advice and information 24 hours, 365 days a year.

Department of Work and Pensions (DWP)
www.dwp.gov.uk

The website gives details of state benefits patients may be entitled to.

16 The evidence base

16.1 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 Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. 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. Annex 1 provides 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.

16.2 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 the supporting material for the guideline on the SIGN website)* The following areas for further research have been identified:

- Diagnostic accuracy studies and implementation research to:
  - identify and assess the diagnostic accuracy of novel biomarkers
  - test the accuracy of a structured clinical assessment in assessing pretest probability of a diagnosis of asthma
  - confirm, prospectively, the diagnostic accuracy of retrospectively derived algorithms
  - define the optimal approach to making a diagnosis in different clinical practice settings.
- What are the benefits or harms of weight loss interventions in pregnancy in obese women or women with high gestational weight gain?
- Is there additional benefit from 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 β_2 agonist bolus and/or aminophylline. Which intravenous therapy should be used as first-line treatment?
- Is intermittent ICS therapy more, the same, or less effective than daily ICS therapy?
- How effective are long-acting muscinaric agents compared to other treatments available as high-dose therapies?
- At what dose of ICS should additional treatment strategies be considered?
- Is once-daily ICS of equal efficacy to twice daily treatment for comparable ICS molecules?
- Is combined maintenance and reliever therapy more effective, the same as, or less effective than twice daily dosing of ICS at reducing asthma symptoms and attacks in adults and children?
- Does once-daily dosing of ICS in adults and children improve adherence?
- How effective is procalcitonin in assessing infection in acute asthma attacks?

- In patients with severe asthma, is non-invasive ventilation, safe, feasible and effective compared to standard care or to invasive ventilation in different clinical settings? Are measurable clinical outcomes, including respiratory parameters, physiological variables and blood gasses improved?
- For patients with asthma not responding to conventional treatment, what additional treatments in the critical care setting are effective and how do outcomes for patients differ between one additional treatment approach and another?
- Is intravenous magnesium sulphate more effective, less effective or equivalent to intravenous salbutamol or intravenous aminophylline in treating acute asthma attacks in children?
- Is administration of intravenous magnesium sulphate safe and effective following administration of nebulised magnesium sulphate?
- In patients with difficult asthma, what objective measures of adherence are available and what impact does monitoring of adherence have on long-term asthma outcomes including exacerbations and hospitalisation?
- What practical tools enable clinicians to assess adherence, explore reasons for non-adherence and elicit attitudes to medication use in patients with asthma?
- Assuming that telehealthcare interventions are equivalent to usual care, what outcomes could assess advantages to patients, organisational impact and cost effectiveness?
- How do patient and professional preferences for modes of delivery influence outcomes?
- In which subgroups or specific circumstances does telehealthcare add value to usual care?
- What is the impact of asynchronous and synchronous remote consulting for people with asthma?
- Do e-health games reduce the frequency of asthma attacks and emergency attendances/admissions and improve outcomes and quality of life in young people with asthma?
- What technical improvements to computerised decision support systems improve their integration into healthcare records and improve use of CDSS amongst healthcare practitioners at the point of care?

17 Development of the guideline

17.1 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.** This guideline was developed according to the 2011 edition of SIGN 50.

SIGN and BTS have worked in partnership since 2001 to produce the British Guideline on the Management of Asthma. Governance arrangements including a Memorandum of Understanding between SIGN and BTS approved by Healthcare Improvement Scotland, SIGN Council and the BTS Executive Committee, are in place. These arrangements cover production of each update and appointment of members to each of the groups that comprise the overall guideline development group.

17.2 EXECUTIVE AND STEERING GROUPS

*Dr James Paton *(Co-Chair)*	*Reader and Honorary Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow*
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Dr Chris Cates	*Senior Research Fellow, St George's Hospital, University of London*
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*Mrs Sheila Edwards	*Chief Executive, British Thoracic Society*
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Professor Chris Griffiths	*Professor of Primary Care, Institute of Health Science Education, London*
Ms Jenny Harbour	*Evidence and Information Scientist, Healthcare Improvement Scotland*
*Dr Roberta James	*Programme Lead, SIGN Executive*
Mr Michael McGregor	*Lay Representative*
Ms Sonia Munde	*Head of Asthma UK helpline and Nurse Manager, Asthma UK, Senior Respiratory Physiologist and Physiotherapist*
Dr Rob Niven	*Senior Lecturer in Respiratory Medicine, Whythenshawe Hospital, Manchester*

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Professor Graham Roberts	*Professor and Honorary Consultant Paediatrician, University of Southampton*
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Dr Steve Turner	*Senior Lecturer in Paediatrics, University of Aberdeen*
*Ms Sally Welham	*Deputy Chief Executive, British Thoracic Society*

* Executive group

17.3 EVIDENCE REVIEW GROUPS

17.3.1 DIAGNOSIS

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17.3.2 MONITORING

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17.3.3 SUPPPORTED SELF MANAGEMENT

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17.3.4 NON-PHARMACOLOGICAL MANAGEMENT

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17.3.5 PHARMACOLOGICAL MANAGEMENT

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Dr Steve Cunningham	*Consultant Paediatrician, Royal Hospital for Sick Children, Edinburgh*
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Professor Neil Thomson	*Professor of Respiratory Medicine, Gartnavel Hospital, Glasgow*

17.3.6 INHALER DEVICES

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17.3.7 MANAGEMENT OF ACUTE ASTHMA

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Dr David Jackson	*Senior Clinical Research Fellow, Imperial College, London*
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Dr Zaheer Mangera	*Specialist Respiratory Trainee, London Chest Hospital*
Dr Catherine McDougall	*Consultant in Paediatric Intensive Care and Respiratory Medicine, Royal Hospital for Sick Children, Edinburgh*
Dr Philip Short	*Clinical Lecturer in Respiratory Medicine, Ninewells Hospital, Dundee*
Dr Tim Sutherland	*Respiratory Consultant, St James' Hospital, Leeds*
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17.3.8 DIFFICULT ASTHMA

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17.3.9 ASTHMA IN ADOLESCENTS

Professor Graham Roberts (Chair)	*Professor and Honorary Consultant Paediatrician, University of Southampton*
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Dr Mitesh Patel	*Clinical Lecturer in Respiratory Medicine, University of Nottingham*

17.3.10 ASTHMA IN PREGNANCY

Dr Sarah Winfield	*Consultant Obstetrician, Leeds General Hospital*

17.3.11 OCCUPATIONAL ASTHMA

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17.3.12 ORGANISATION AND DELIVERY OF CARE

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Dr Raj Rajakulasingam	*Consultant Respiratory Physician and Honorary Reader, Homerton Univeristy Hospital, London*
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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. A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

Karen Graham	*Patient Involvement Officer*
Karen King	*Distribution and Officer Co-ordinator*
Stuart Neville	*Publications Designer*
Gaynor Rattray	*Guideline Co-ordinator*

17.4 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, and all guideline development group members who were involved in updating SIGN 101 from 2009 to 2011, and in producing SIGN 141 in 2014. 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.

Professor Mike Shields	*Professor of Child Health, Queen's University, Belfast*
Dr Robin Carr	*General Practitioner, Nuffield Health Centre, Witney, Oxford*

SIGN would like to acknowledge the PRISMS group who kindly provided the searches, quality assessment and data extraction for the implementation studies in asthma self-management *(see section 5.5)* based on their systematic review of self-management support interventions for people with long-term conditions conducted as part of a project funded by the National Institute for Health Research Health Services and Delivery Research programme (project number 11/1014/04).(Taylor SJC, Pinnock H, Epiphaniou E, et al. A rapid synthesis of the evidence on interventions supporting self-management for people with long-term conditions. (PRISMS Practical Systematic Review of Self-Management Support for long-term conditions). *Health Serv Deliv Res* 2014;2:54). The considered judgement and recommendations (in section 5.5) were developed by the self-management Evidence Review Group in accordance with SIGN methodology. The views and opinions expressed therein are those of the SIGN/BTS guideline development group and do not necessarily reflect those of the PRISMS authors, NIHR, NHS or the Department of Health.

17.5 CONSULTATION AND PEER REVIEW

17.5.1 CONSULTATION

Selected changes to this guideline were presented for discussion in draft form at the Winter Meeting of the British Thoracic Society in December 2015. The draft guideline was also available on the SIGN and BTS websites for five weeks to allow all interested parties to comment. A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

17.5.2 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.

Mrs Lisa Chandler	*Public Health Principal, Wakefield Local Authority*
Dr Graham Douglas	*Retired Consultant Physician, Aberdeen*
Mrs Noreen Downes	*Principal Pharmacist, Scottish Medicines Consortium, Glasgow*
Dr Bernard Higgins	*Consultant Respiratory Physician, Freeman Hospital, Newcastle upon Tyne*
Dr Colville Laird	*Medical Director, BASICS Scotland, Aberuthven*
Mrs Jane Scullion	*Respiratory Nurse Consultant, University Hospital of Leicester*

The following organisations also commented

Asthma UK, London

National Paediatric Respiratory and Allergy Nurses Group, Birmingham

Primary Care Respiratory Society UK

Royal College of General Practitioners, London

Royal College of Physicians, London

Royal College of Physicians Edinburgh

17.5.3 EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council and members of the Governance Committee for the SIGN British guideline on the management of asthma 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 SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website **www.sign.ac.uk**

Dr Martin Allen	*Honorary Secretary, British Thoracic Society*
Mr Gary Cook	*Principal Clinicial Pharmacist, NHS Tayside*
Mrs Sheila Edwards	*Chief Executive, British Thoracic Society*
Dr Colin Gelder	*Chair, BTS Standards of Care Committee*
Dr Roberta James	*Programme Lead, SIGN; Co-Editor*
Professor John Kinsella	*Chair of SIGN; Co-Editor*
Dr Karen Ritchie	*Head of Knowledge and Information, Healthcare Improvement Scotland*
Ms Sally Welham	*Deputy Chief Executive, British Thoracic Society*

Abbreviations

ACQ	Asthma Control Questionnaire
AOR	adjusted odds ratio
Apgar score	A number expressing the physical condition of a newborn infant (a score of ten representing the best possible condition).
BCG	Bacillus Calmette-Guérin
BDP	beclometasone dipropionate
BHR	bronchial hyper-reactivity
BNF	British National Formulary
BTS	British Thoracic Society
CAM	complementary and alternative medicine
CDSS	computerised decision support systems
CFC	chloroflurocarbon
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DPI	dry powder inhaler
ECG	electrocardiogram
ED	emergency department
eMC	electronic Medicines Compendium
ETS	environmental tobacco smoke
FeNO	exhaled nitric oxide concentration
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GMC	General Medical Council
GORD	gastro-oesophageal reflux disease
GP	general practitioner
HDM	house dust mite
ICS	inhaled corticosteroids
ICU	intensive care unit
IgE	immunoglobulin E
IM	intramuscular
IT	information technology
IU	international unit
IV	intravenous
kPa	kilopascals
LABA	long-acting β_2 agonist

LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonists
MA	marketing authorisation
MDI	metered dose inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
mmHg	millimetres of mercury
n-3PUFAs	omega-3 polyunsaturated fatty acids
NICE	National Institute for Health and Care Excellence
NIV	non-invasive ventilation
NPV	negative predictive value
NRAD	National Review of Asthma Deaths
OCS	oral corticosteroids
OR	odds ratio
PAAP	personalised asthma action plan
PACE	Physician Asthma Care Education
$PaCO_2$	partial arterial pressure of carbon dioxide
PaO_2	partial arterial pressure of oxygen
PC_{20}	the provocative concentration of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV_1
PD_{20}	the provocative dose of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV_1
PEF	peak expiratory flow
pMDI	pressurised metered dose inhaler
ppb	parts per billion
PPV	positive predictive value
QoL	quality of life
RCT	randomised controlled trial
rhDNAse	recombinant human deoxyribonuclease
RR	risk ratio
SABA	short-acting β_2 agonist
SCIT	subcutaneous immunotherapy
SIC	specific inhalation challenge
SIGN	Scottish Intercollegiate Guidelines Network
SLIT	sublingual immunotherapy
SMC	Scottish Medicines Consortium
SpO_2	oxygen saturation measured by a pulse oximeter
TNF	tumour necrosis factor
V_{Emax}	ventilation at maximal exercise capacity

Annex 1

Summary of search histories by section

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Literature searches to support the various sections of this guideline are conducted on a rolling basis. This summary indicates the currency of the searches supporting each section. Searches in all databases began with the earliest year available at that time, which varied from database to database; for example, searches in Embase extended back to 1980 and in CINAHL to 1982. Specific date coverage is provided for Medline.

The 2016 revision saw updating of multiple sections of the guideline identified as priority areas by the guideline development group. Literature searches were conducted in Medline, Embase, CINAHL and the Cochrane Library for all topics to identify systematic reviews and RCTs published between January 2011 and January 2015. Additional literature search coverage for the specific topics considered in this update is described below.

Detailed search strategies are available on the SIGN website in the supplementary material section.

Section 3 Diagnosis and monitoring

Diagnosis in children

The search was updated in January 2015 with coverage extending from 2011–2015. This was a broad search for studies relating to diagnosis and monitoring of asthma. No study design filter was applied.

Section 4 Supported self management

The search was updated in June 2015 to cover adherence to asthma treatment (2011–2015). The Cochrane Library, Medline, Embase and CINAHL were searched. No study type filters were applied.

Section 5 Non-pharmacological management

An update search was conducted in October 2015 to identify additional studies on bariatric surgery related weight loss. The search covered 2011–2015 in Medline, the Cochrane Library and CINAHL. No study design filters were applied.

Section 6 Pharmacological management

The 2016 revision updated searches for inhaled steroids, long-acting β_2 agonists theophyllines, leukotriene receptor antagonists, tiotropium, anticholinergics, frequency and dose of inhaled steroids, step-up and step-down therapies, IgE monoclonal antibodies, intermittent steroid therapy and macrolides.

The Cochrane Library, Medline and Embase were searched from 2011–2015. SIGN systematic review and RCT filters were applied.

Section 7 Inhaler devices

Although the literature search was updated for 2011–2015, this section was not selected by the group for this update.

Section 8 Management of acute asthma

The 2016 revision updated the searches for nebulised magnesium, nebulised β_2 agonists, management of care in different hospital settings, dealing with poor response to standard therapies, side effects of IV bronchodilators and positive pressure ventilation. The Cochrane Library, Medline and Embase were searched from 2011–2015. No study type filter was applied.

Section 9 Difficult asthma

The 2016 revision updated the searches on management models and non-adherence. Medline and CINAHL were searched from 2011–2015. No study filter was applied.

Section 10 Asthma in adolescents

Although the literature search was updated for 2011–2015, this section was not selected by the group for this update.

Section 11 Asthma in pregnancy

Although the literature search was updated for 2011–2015, this section was not selected by the group for this update.

Section 12 Occupational asthma

In 2005, a systematic review by the British Occupational Health Research Foundation (BOHRF) was used as the basis for updating this section.

In the 2016 update literature searches were conducted for occupational asthma diagnosis and relocation away from occupational exposures. Medline and Health Management Information Consortium were searched from 2011–2015. No study type filter was applied.

Section 13 Organisation and delivery of care

A literature search was conducted to identify systematic reviews on telemedicine. The Cochrane Library, Medline and CINAHL were searched from 2005–2015. The SIGN systematic review filter was applied.

Annex 2

Management of acute severe asthma in adults in general practice

Many deaths from asthma are preventable. Delay can be fatal. Factors leading to poor outcome include:

- Clinical staff failing to assess severity by objective measurement
- Patients or relatives failing to appreciate severity
- Under-use of corticosteroids

Regard each emergency asthma consultation as for acute severe asthma until shown otherwise.

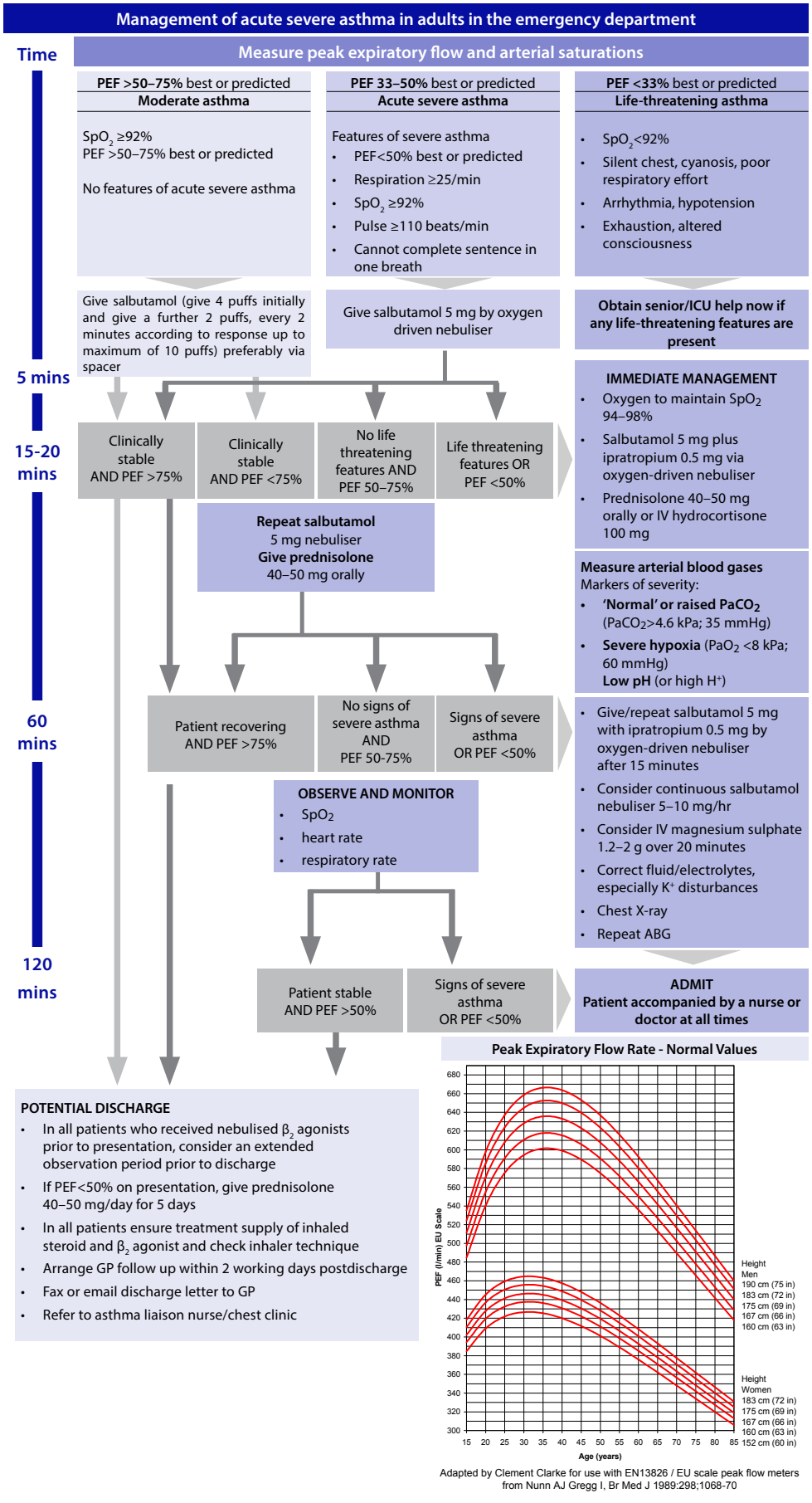
Assess and record:

- Peak expiratory flow (PEF)
- Symptoms and response to self treatment
- Heart and respiratory rates
- Oxygen saturation (by pulse oximetry)

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

Moderate asthma	Acute severe asthma	Life-threatening asthma
INITIAL ASSESSMENT		
PEF>50-75% best or predicted	**PEF 33-50% best or predicted**	**PEF<33% best or predicted**
FURTHER ASSESSMENT		
• SpO_2 ≥92% • Speech normal • Respiration <25 breaths/min • Pulse <110 beats/min	• SpO_2 ≥92% • Can't complete sentences • Respiration ≥25 breaths/min • Pulse ≥110 beats/min	• SpO_2 <92% • Silent chest, cyanosis or poor respiratory effort • Arrhythmia or hypotension • Exhaustion, altered consciousness
MANAGEMENT		
Treat at home or in surgery and ASSESS RESPONSE TO TREATMENT	**Consider admission**	**Arrange immediate ADMISSION**
TREATMENT		
• β_2 bronchodilator: – via spacer (give 4 puffs initially and give a further 2 puffs every 2 minutes according to response up to maximum of 10 puffs) If PEF >50–75% predicted/best: • Nebuliser (preferably oxygen driven) (salbutamol 5 mg) • Give prednisolone 40–50 mg • Continue or increase usual treatment If good response to first treatment (symptoms improved, respiration and pulse settling and PEF >50%) continue or increase usual treatment and continue prednisolone	• Oxygen to maintain SpO_2 94–98% if available • β_2 bronchodilator: – nebuliser (preferably oxygen driven) (salbutamol 5 mg) – or via spacer (give 4 puffs initially and give a further 2 puffs every 2 minutes according to response up to maximum of 10 puffs) • Prednisolone 40–50 mg or IV hydrocortisone 100 mg • **If no response in acute severe asthma: ADMIT**	• Oxygen to maintain SpO2 94–98% • β_2 bronchodilator and ipratropium: – nebuliser (preferably oxygen driven) (salbutamol 5 mg and ipratro pium 0.5mg) – or via spacer (give 4 puffs initially and give a further 2 puffs every 2 minutes according to response up to maximum of 10 puffs) • Prednisolone 40–50 mg or IV hydrocortisone 100 mg immediately
Admit to hospital if any: • Life-threatening features • Features of acute severe asthma present after initial treatment • Previous near-fatal asthma Lower threshold for admission if afternoon or evening attack, recent nocturnal symptoms or hospital admission, previous severe attacks, patient unable to assess own condition, or concern over social circumstances	**If admitting the patient to hospital:** • Stay with patient until ambulance arrives • Send written asssessment and referral details to hospital • β_2 bronchodilator via oxygen-driven **nebuliser in ambulance**	**Follow up after treatment or discharge from hospital:** • **GP review within 2 working days** • Monitor symptoms and PEF • Check inhaler technique • **Written asthma action plan** • Modify treatment according to guidelines for chronic persistent asthma • Address potentially preventable contributors to admission

Annex 3



Adapted by Clement Clarke for use with EN13826 / EU scale peak flow meters from Nunn AJ Gregg I, Br Med J 1989:298;1068-70

Annex 4

Management of acute severe asthma in adults in hospital

Features of acute severe asthma

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

Life-threatening features

- PEF <33% of best or predicted
- SpO_2 <92%
- Silent chest, cyanosis, or feeble respiratory effort
- Arrhythmia or hypotension
- Exhaustion, altered consciousness

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

Blood gas markers of a life-threatening attack:

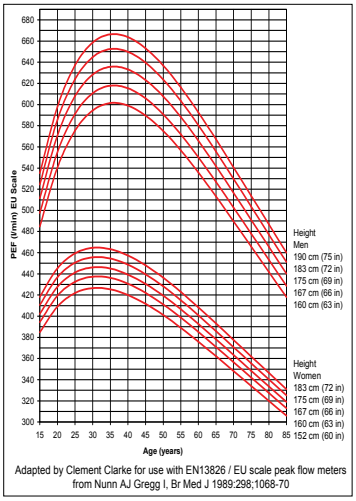
- 'Normal' (4.6–6 kPa, 35–45 mmHg) $PaCO_2$
- Severe hypoxia: PaO_2 <8 kPa (60mm Hg) irrespective of treatment with oxygen
- A low pH (or high H^+)

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

Near-fatal asthma

- Raised $PaCO_2$
- Requiring mechanical ventilation with raised inflation pressures

Peak Expiratory Flow Rate - Normal Values



Adapted by Clement Clarke for use with EN13826 / EU scale peak flow meters from Nunn AJ Gregg I, Br Med J 1989:298;1068-70

IMMEDIATE TREATMENT

- Oxygen to maintain SpO_2 94–98%
- Salbutamol 5 mg via an oxygen-driven nebuliser
- Ipratropium bromide 0.5 mg via an oxygen-driven nebuliser
- Prednisolone tablets 40–50 mg or IV hydrocortisone 100 mg
- No sedatives of any kind
- Chest X-ray if pneumothorax or consolidation are suspected or patient requires mechanical ventilation

IF LIFE-THREATENING FEATURES ARE PRESENT:

- Discuss with senior clinician and ICU team
- Consider IV magnesium sulphate 1.2–2 g infusion over 20 minutes (unless already given)
- Give nebulised β_2 agonist more frequently eg salbutamol 5 mg up to every 15-30 minutes or 10 mg per hour via continuous nebulisation (requires special nebuliser)

SUBSEQUENT MANAGEMENT

IF PATIENT IS IMPROVING continue:

- Oxygen to maintain SpO_2 94–98%
- Prednisolone 40–50mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulised β_2 agonist and ipratropium 4–6 hourly

IF PATIENT NOT IMPROVING AFTER 15–30 MINUTES:

- Continue oxygen and steroids
- Use continuous nebulisation of salbutamol at 5–10 mg/hour if an appropriate nebuliser is available. Otherwise give nebulised salbutamol 5 mg every 15–30 minutes
- Continue ipratropium 0.5 mg 4–6 hourly until patient is improving

IF PATIENT IS STILL NOT IMPROVING:

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

MONITORING

- Repeat measurement of PEF 15–30 minutes after starting treatment
- Oximetry: maintain SpO_2 >94–98%
- Repeat blood gas measurements within 1 hour of starting treatment if:
  - initial PaO_2 <8 kPa (60 mmHg) unless subsequent SpO_2 >92% or
  - $PaCO_2$ normal or raised or
  - patient deteriorates
- Chart PEF before and after giving β_2 agonists and at least 4 times daily throughout hospital stay

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

- Deteriorating PEF, worsening or persisting hypoxia, or hypercapnia
- Exhaustion, altered consciousness
- Poor respiratory effort or respiratory arrest

DISCHARGE

When discharged from hospital, patients should have:

- Been on discharge medication for 12–24 hours and have had inhaler technique checked and recorded
- PEF >75% of best or predicted and PEF diurnal variability <25% unless discharge is agreed with respiratory physician
- Treatment with **oral and inhaled steroids** in addition to bronchodilators
- Own PEF meter and **written asthma action plan**
- GP follow up arranged within **2 working days**
- Follow-up appointment in respiratory clinic **within 4 weeks**

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

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

Management of acute asthma in children in general practice

Age 2–5 years

ASSESS AND RECORD ASTHMA SEVERITY

Moderate asthma	Acute severe asthma	Life-threatening asthma
• SpO2 ≥92% • Able to talk • Heart rate ≤140/min • Respiratory rate ≤40/min	• SpO_2 <92% • Too breathless to talk • Heart rate >140/min • Respiratory rate >40/min • Use of accessory neck muscles	SpO_2 <92% plus any of: • Silent chest • Poor respiratory effort • Agitation • Confusion • Cyanosis
• β_2 agonist 2–10 puffs via spacer and facemask (given one puff at a time inhaled separately using tidal breathing) • Give one puff of β_2 agonist every 30-60 seconds up to 10 puffs according to response • Consider oral prednisolone 20 mg	• Oxygen via face mask • 10 puffs of β_2 agonist or nebulised salbutamol 2.5 mg • Oral prednisolone 20 mg **Assess response to treatment 15 mins after β_2 agonist**	• Oxygen via face mask • Nebulise every 20 minutes with: - salbutamol 2.5 mg + - ipratropium 0.25 mg • Oral prednisolone 20 mg *or* IV hydrocortisone 50 mg if vomiting
IF POOR RESPONSE ARRANGE ADMISSION	**IF POOR RESPONSE REPEAT β_2 AGONIST AND ARRANGE ADMISSION**	**REPEAT β_2 AGONIST VIA OXYGEN-DRIVEN NEBULISER WHILST ARRANGING IMMEDIATE HOSPITAL ADMISSION**

GOOD RESPONSE
- Continue β_2 agonist via spacer or nebuliser, as needed but not exceeding 4 hourly
- **If symptoms are not controlled repeat β_2 agonist and refer to hospital**
- Continue prednisolone for up to 3 days
- Arrange follow-up clinic visit within 48 hours
- Consider referral to secondary care asthma clinic if 2nd attack within 12 months.

POOR RESPONSE
- Stay with patient until ambulance arrives
- Send written assessment and referral details
- Repeat β_2 agonist via oxygen-driven nebuliser in ambulance

LOWER THRESHOLD FOR ADMISSION IF:
- Attack in late afternoon or at night
- Recent hospital admission or previous severe attack
- Concern over social circumstances or ability to cope at home

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

Age >5 years

ASSESS AND RECORD ASTHMA SEVERITY

Moderate asthma	Acute severe asthma	Life-threatening asthma
• SpO_2 ≥92% • Able to talk • Heart rate ≤125/min • Respiratory rate ≤30/min • PEF ≥50% best or predicted	• pO_2 <92% • Too breathless to talk • Heart rate >125/min • Respiratory rate >30/min • Use of accessory neck muscles • PEF 33-50% best or predicted	SpO_2 <92% plus any of: • Silent chest • Poor respiratory effort • Agitation • Confusion • Cyanosis • PEF <33% best or predicted
• β_2 agonist 2–10 puffs via spacer and mouthpiece (given one puff at a time inhaled separately using tidal breathing). • Give one puff of β_2 agonist every 30–60 seconds up to 10 puffs according to response. • Consider oral prednisolone 30–40 mg	• Oxygen via face mask • 10 puffs of β_2 agonist or nebulised salbutamol 5 mg • Oral prednisolone 30–40 mg **Assess response to treatment 15 mins after β_2 agonist**	• Oxygen via face mask • Nebulise every 20 minutes with: - salbutamol 5 mg + - ipratropium 0.25 mg • Oral prednisolone 30–40 mg *or* IV hydrocortisone 100 mg if vomiting
IF POOR RESPONSE ARRANGE ADMISSION	**IF POOR RESPONSE REPEAT β_{22} AGONIST AND ARRANGE ADMISSION**	**REPEAT β_2 AGONIST VIA OXYGEN-DRIVEN NEBULISER WHILST ARRANGING IMMEDIATE HOSPITAL ADMISSION**

GOOD RESPONSE
- Continue β_2 agonist via spacer or nebuliser, as needed but not exceeding 4 hourly
- **If symptoms are not controlled repeat β_2 agonist and refer to hospital**
- Continue prednisolone for up to 3 days
- Arrange follow-up clinic visit within 48 hours
- Consider referral to secondary care asthma clinic if 2nd attack within 12 months.

POOR RESPONSE
- Stay with patient until ambulance arrives
- Send written assessment and referral details
- Repeat β_2 agonist via oxygen-driven nebuliser in ambulance

LOWER THRESHOLD FOR ADMISSION IF:
- Attack in late afternoon or at night
- Recent hospital admission or previous severe attack
- Concern over social circumstances or ability to cope at home

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

Annex 6

Management of acute asthma in children in emergency department

Age 2–5 years

ASSESS AND RECORD ASTHMA SEVERITY

Moderate asthma	Acute severe asthma	Life-threatening asthma
• $SpO_2 \geq 92\%$ • No clinical features of severe asthma **NB: if a patient has signs and symptoms across categories, always treat according to their most severe features**	• SpO_2 <92% • Too breathless to talk or eat • Heart rate >140/min • Respiratory rate >40/min • Use of accessory neck muscles	SpO_2 <92% plus any of: • Silent chest • Poor respiratory effort • Agitation • Confusion • Cyanosis

First line treatments

Oxygen via face mask/nasal prongs to achieve SpO_2 94–98%

• β_2 agonist 2–10 puffs via spacer ± facemask (given one puff at a time inhaled separately using tidal breathing) • Give one puff of β_2 agonist every 30–60 seconds up to 10 puffs according to response • Consider oral prednisolone 20 mg	• β_2 agonist 10 puffs via spacer ± facemask or nebulised salbutamol 2.5 mg • Oral prednisolone 20 mg or IV hydrocortisone 4 mg/kg if vomiting • **If poor response** add 0.25 mg nebulised ipratropium bromide to every nebulised β_2 agonist • Repeat β_2 agonist and ipratropium up to every 20 minutes for 2 hours according to response	• Nebulised β_2 agonist: salbutamol 2.5 mg **plus** ipratropium bromide 0.25 mg nebulised • Repeat bronchodilators every 20–30 minutes • Oral prednisolone 20 mg or IV Hydrocortisone 4 mg/kg if vomiting **Discuss with senior clinician, PICU team or paediatrician**
Reassess within 1 hour		

Second line treatments

- Consider 2nd line treatments - see Annex 7
- Admit all cases if features of severe attack persist after initial treatment
- Arrange transfer to PICU/HDU if poor response to treatment as per local guidelines

DISCHARGE PLAN

- Continue β_2 agonist 4 hourly as necessary
- Consider prednisolone 20 mg daily for 3–5 days until symptoms have settled
- Advise to contact GP if not controlled on above treatment
- Provide a written asthma action plan
- Review regular treatment
- Check inhaler technique
- Arrange GP follow up within 48 hours
- Arrange hospital asthma clinic follow up in 4–6 weeks if 2nd or subsequent attack in past 12 months.

Age >5 years

ASSESS AND RECORD ASTHMA SEVERITY

Moderate asthma	Acute severe asthma	Life-threatening asthma
• $SpO_2 \geq 92\%$ • PEF ≥50% best or predicted • No clinical features of severe asthma NB: If a patient has signs and symptoms across categories, always treat according to their most severe features	• $SpO_2 < 92\%$ • PEF 33–50% best or predicted • Heart rate >125/min • Respiratory rate >30/min • Use of accessory neck	SpO_2 <92% plus any of: • PEF < 33% best or predicted • Silent chest • Poor respiratory effort • Altered consciousness

First line treatments

Oxygen via face mask/nasal prongs to achieve SpO_2 94–98%

• β_2 agonist 2–10 puffs via spacer and mouthpiece (given one puff at a time inhaled separately using tidal breathing) • Give one puff of β_2 agonist every 30–60 seconds up to 10 puffs according to response • Oral prednisolone 30–40 mg	• β_2 agonist 10 puffs via spacer or nebulised salbutamol 5 mg • Oral prednisolone 30–40 mg or IV hydrocortisone 4 mg/kg if vomiting • **If poor response** add 0.25 mg nebulised ipratropium bromide to every nebulised β_2 agonist • Repeat β_2 agonist and ipratropium up to every 20 minutes for 2 hours according to response	• Nebulised β_2 agonist: salbutamol 5 mg plus ipratropium bromide 0.25 mg nebulised • Repeat bronchodilators every 20–30 minutes • Oral prednisolone 30–40 mg or IV Hydrocortisone 4 mg/kg if vomiting **Discuss with senior clinician, PICU team or paediatrician**
Reassess within 1 hour		

Second line treatments

- Consider 2nd line treatments - see Annex 7
- Admit all cases if features of severe attack persist after initial treatment
- Arrange transfer to PICU/HDU if poor response to treatment as per local guidelines

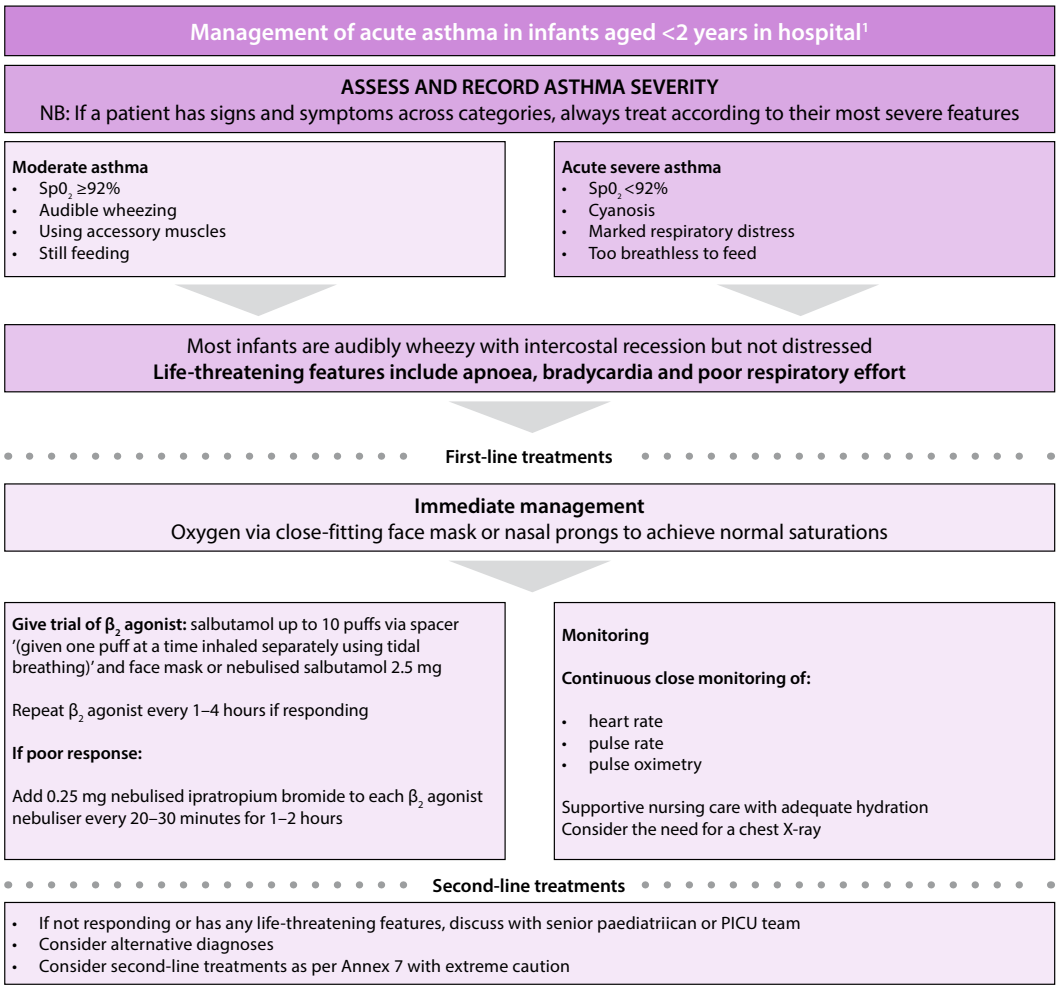
DISCHARGE PLAN

- Continue β_2 agonist 4 hourly as necessary
- Consider prednisolone 30–40 mg daily for 3–5 days until symptoms have settled
- Seek medical advice if not controlled on above treatment
- Provide a written asthma action plan
- Review regular treatment
- Check inhaler technique
- Arrange GP follow up within 48 hours
- Arrange hospital asthma clinic follow up in 4–6 weeks if 2nd or subsequent attack in past 12 months.

Annex 7

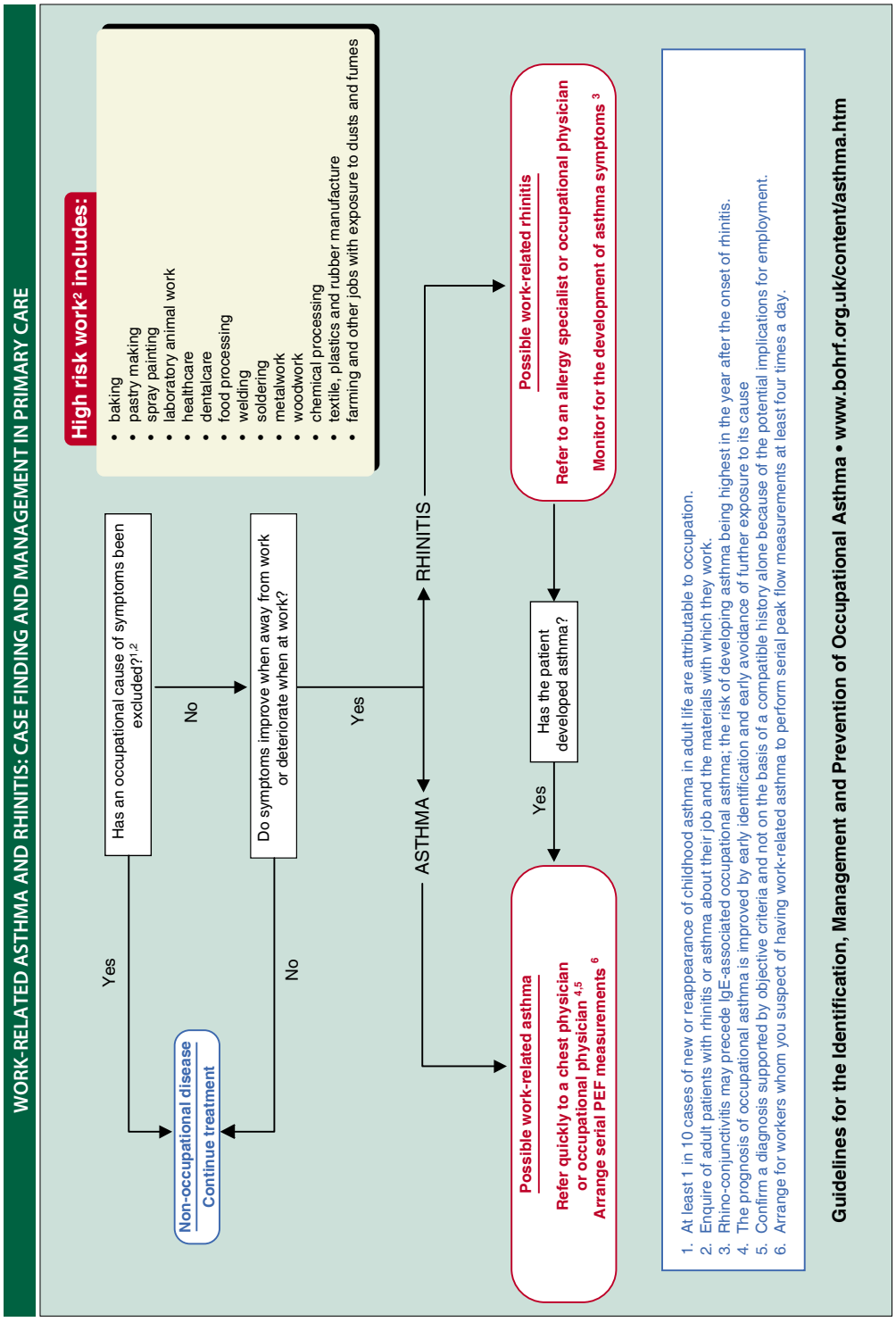
Management of acute asthma in children in hospital
Age 2–5 years
ASSESS AND RECORD ASTHMA SEVERITY
Moderate asthma
SpO2 ≥92%
No clinical features of severe asthma
NB: If a patient has signs and symptoms across categories, always treat according to their most severe features
Acute severe asthma
SpO2 <92%
Too breathless to talk or eat
Heart rate >140/min
Respiratory rate >40/min
Use of accessory neck muscles
Life-threatening asthma
SpO2 <92% plus any of:
Silent chest
Poor respiratory effort
Agitation
Confusion
Cyanosis
First-line treatments
Oxygen via face mask/nasal prongs to achieve SpO2 94–98%
β2 agonist 2–10 puffs via spacer ± facemask (given one puff at a time inhaled separately using tidal breathing)
Give one puff of β2 agonist every 30–60 seconds up to 10 puffs according to response
Consider oral prednisolone 20 mg
β2 agonist 10 puffs via spacer ± facemask or nebulised salbutamol 2.5 mg
Oral prednisolone 20 mg or IV hydrocortisone 4 mg/kg if vomiting
Repeat β2 agonist up to every 20–30 minutes according to response
If poor response add 0.25 mg nebulised ipratropium bromide to every nebulised β2 agonist every 20 minutes for 1–2 hours
Nebulised β2 agonist: salbutamol 2.5 mg plus ipratropium bromide 0.25 mg nebulised
Repeat bronchodilators every 20–30 minutes
Oral prednisolone 20mg or IV hydrocortisone 4mg/kg if vomiting
Consider adding 150 mg MgSO4 to each β2 agonist/ipratropium nebuliser in first hour
Reassess within 1 hour
Discuss with senior clinician, PICU team or paediatrician
ASSESS RESPONSE TO TREATMENT
Record respiratory rate, heart rate and oxygen saturation every 1-4 hours
Second-line treatments
RESPONDING
Continue bronchodilators 1–4 hours as necessary
Discharge when stable on 4-hourly treatment
Consider prednisolone 20 mg daily for 3–5 days or until symptoms have settled
At discharge
Ensure stable on 4-hourly inhaled treatment
Review the need for regular treatment and the use of inhaled steroids
Review inhaler technique
Provide a written asthma action plan for treating future attacks
Arrange GP follow up within 48 hours
Arrange hospital asthma clinic follow up in 4–6 weeks
NOT RESPONDING
Continue 20–30 minute nebulisers
Consider chest X-ray and blood gases
Discuss with senior clinician, paediatrician or PICU
Consider admission to HDU/PICU
Consider risks and benefits of:
Bolus IV infusion of magnesium sulphate 40 mg/kg (max 2g) over 20 minutes
Bolus IV salbutamol 15 micrograms/kg if not already given
Continuous IV salbutamol infusion 1–5 micrograms/kg/min (200 micrograms/ml solution)
IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1mg/kg/hour
Assess response before initiating each new treatment
Age >5 years
ASSESS AND RECORD ASTHMA SEVERITY
Moderate asthma
SpO2 ≥92%
PEF >50% best or predicted
No clinical features of severe asthma
NB: If a patient has signs and symptoms across categories, always treat according to their most severe features
Acute severe asthma
SpO2 <92%
PEF 33–50% best or predicted
Heart rate >125/min
Respiratory rate >30/min
Use of accessory neck muscles
Life-threatening asthma
SpO2 <92% plus any of:
PEF <33% best or predicted
Silent chest
Poor respiratory effort
Altered consciousness
Cyanosis
First-line treatments
Oxygen via face mask/nasal prongs to achieve SpO2 94–98%
β2 agonist 2–10 puffs via spacer and mouthpiece (given one puff at a time inhaled separately using tidal breathing)
Give one puff of β2 agonist every 30–60 seconds up to 10 puffs according to response
Oral prednisolone
30–40 mg
β2 agonist 10 puffs via spacer or nebulised salbutamol 5 mg
Oral prednisolone 30–40 mg or IV hydrocortisone 4 mg/kg if vomiting
Repeat β2 agonist and ipratropium up to every 20–30 minutes according to response
If poor response add 0.25 mg nebulised ipratropium bromide to every nebulised β2 agonist every 20 minutes for 1–2 hours
Nebulised β2 agonist: salbutamol 5 mg plus ipratropium bromide 0.25 mg nebulised
Repeat bronchodilators every 20–30 minutes
Oral prednisolone 30–40 mg or IV hydrocortisone 4mg/kg if vomiting
Consider adding 150 mg MgSO4 to each β2 agonist/ipratropium nebuliser in first hour
Reassess within 1 hour
Discuss with senior clinician, PICU team or paediatrician
ASSESS RESPONSE TO TREATMENT
Record respiratory rate, heart rate, oxygen saturation and PEF/FEV every 1-4 hours
Second-line treatments
RESPONDING
Continue bronchodilators 1–4 hours as necessary
Discharge when stable on 4-hourly treatment
Consider prednisolone 30–40 mg daily for 3–5 days or until symptoms have settled
At discharge
Ensure stable on 4–hourly inhaled treatment
Review the need for regular treatment and the use of inhaled steroids
Review inhaler technique
Provide a written asthma action plan for treating future attacks
Arrange GP follow up within 48 hours
Arrange hospital asthma clinic follow up in 4–6 weeks
NOT RESPONDING
Continue 20–30 minute nebulisers
Consider chest X-ray and blood gases
Discuss with senior clinician, paediatrician or PICU
Consider admission to HDU/PICU
Consider risks and benefits of:
Bolus IV infusion of magnesium sulphate 40 mg/kg (max 2g) over 20 minutes
Bolus IV salbutamol 15 micrograms/kg if not already given
Continuous IV salbutamol infusion 1–5 micrograms/kg/min (200 micrograms/ml solution)
IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1mg/kg/hour
Assess response before initiating each new treatment

Annex 8



1. Management of acute asthma in children under 1 year should be under the direction of a respiratory paediatrician.

Annex 9


WORK-RELATED ASTHMA AND RHINITIS: CASE FINDING AND MANAGEMENT IN PRIMARY CARE
Has an occupational cause of symptoms been excluded?[1,2]
Yes
No
Non-occupational disease
Continue treatment
Do symptoms improve when away from work or deteriorate when at work?
Yes
No
ASTHMA
RHINITIS
Has the patient developed asthma?
Yes
Possible work-related asthma
Refer quickly to a chest physician or occupational physician [4,5]
Arrange serial PEF measurements [6]
Possible work-related rhinitis
Refer to an allergy specialist or occupational physician
Monitor for the development of asthma symptoms [3]
High risk work[2] includes:
baking
pastry making
spray painting
laboratory animal work
healthcare
dentalcare
food processing
welding
soldering
metalwork
woodwork
chemical processing
textile, plastics and rubber manufacture
farming and other jobs with exposure to dusts and fumes
1. At least 1 in 10 cases of new or reappearance of childhood asthma in adult life are attributable to occupation.
2. Enquire of adult patients with rhinitis or asthma about their job and the materials with which they work.
3. Rhino-conjunctivitis may precede IgE-associated occupational asthma; the risk of developing asthma being highest in the year after the onset of rhinitis.
4. The prognosis of occupational asthma is improved by early identification and early avoidance of further exposure to its cause
5. Confirm a diagnosis supported by objective criteria and not on the basis of a compatible history alone because of the potential implications for employment.
6. Arrange for workers whom you suspect of having work-related asthma to perform serial peak flow measurements at least four times a day.
Guidelines for the Identification, Management and Prevention of Occupational Asthma • www.bohrf.org.uk/content/asthma.htm

My asthma triggers

Taking my asthma medicine each day will help reduce my reaction to these triggers. Avoiding them where possible will also help.

My asthma review

I should have at least one routine asthma review every year. **I will bring:**

- My action plan to see if it needs updating
- My inhaler and spacer to check I'm using them in the best way
- Any questions about my asthma and how to cope with it.

Next asthma review date: ____/____/_____

GP/asthma nurse contact

Name:
Phone number:

Out-of-hours contact number

(ask your GP surgery who to call when they are closed)

Name:
Phone number:

Get more advice & support from Asthma UK:

Speak to a specialist asthma nurse about managing your asthma on:
0300 222 5800

Get news, advice and download information packs at:
www.asthma.org.uk

Health & care information you can trust

*Adams et al; Factors associated with hospital admissions and repeat emergency department visits for adults with asthma; Thorax 2000;55:566–573

Use it, don't lose it!

Your action plan is a personal guide to help you stay on top of your asthma. Once you have created one with your GP or asthma nurse, it can help you stay as well as possible.

People who use their action plans are four times less likely to end up in hospital because of their asthma.

Your action plan will only work at its best to help keep you healthy if you:

1. **Put it somewhere easy for you and your family to find** – you could try your fridge door, the back of your front door, or your bedside table. Try taking a photo and keeping it on your mobile phone or tablet.
2. **Check in with it regularly** – put a note on your calendar, or a reminder on your mobile to read it through once a month. How are you getting along with your day-to-day asthma medicines? Are you having any asthma symptoms? Are you clear about what to do?
3. **Keep a copy near you** – save a photo on your phone or as your screensaver. Or keep a leaflet in your bag, desk or car glove box.
4. **Give a copy of your action plan or share a photo of it with a key family member or friend** – ask them to read it. Talk to them about your usual asthma symptoms so they can help you notice if they start. Help them know what to do in an emergency.
5. **Take it to every healthcare appointment – including A&E/consultant.** Ask your GP or asthma nurse to update it if any of their advice for you changes. Ask them for tips if you're finding it hard to take your medicines as prescribed.

The step-by-step guide that helps you stay on top of your asthma

Your asthma action plan

Fill this in with your GP or asthma nurse

If you use a written asthma action plan you are **four times less likely** to be admitted to hospital for your asthma.*

Name and date:

Any asthma questions?
Call our friendly helpline nurses
0300 222 5800
(9am – 5pm; Mon – Fri)
www.asthma.org.uk

Annex 10 contd.

Every day asthma care:

My personal best peak flow is: ____

My **preventer** inhaler
(insert name/colour): ____

I need to take my preventer inhaler every day even when I feel well

I take ____ puff(s) in the morning
and ____ puff(s) at night.

My **reliever** inhaler
(insert name/colour): ____

I take my reliever inhaler only if I need to

I take ____ puff(s) of my reliever inhaler
if any of these things happen:

- I'm wheezing
- My chest feels tight
- I'm finding it hard to breathe
- I'm coughing.

Other medicines I take for my asthma every day:

____

With this daily routine I should expect/aim to have no symptoms. If I haven't had any symptoms or needed my reliever inhaler for at least 12 weeks, ask my GP or asthma nurse to review my medicines in case they can reduce the dose.

People with allergies need to be extra careful as attacks can be more severe.

When I feel worse:

- **My symptoms are coming back (wheeze, tightness in my chest, feeling breathless, cough)**
- **I am waking up at night**
- **My symptoms are interfering with my usual day-to-day activities (eg at work, exercising)**
- **I am using my reliever inhaler ____ times a week or more**
- **My peak flow drops to below ____**

This is what I can do straight away to get on top of my asthma:

1 **If I haven't been using my preventer inhaler, start using it regularly again or:**

Increase my preventer inhaler dose to ____ puffs ____ times a day until my symptoms have gone and my peak flow is back to normal

Take my reliever inhaler as needed (up to ____ puffs every four hours)

URGENT! **If I don't improve within 24 hours** make an emergency appointment to see my GP or asthma nurse.

2 **If I have been given prednisolone tablets (steroid tablets) to keep at home:**

Take ____ mg of prednisolone tablets (which is ____ x 5mg) **immediately** and again every morning for ____ days or until I am fully better.

URGENT! **Contact my GP or asthma nurse today** and let them know I have started taking steroids and make an appointment to be seen within 24 hours.

In an asthma attack:

- **My reliever inhaler is not helping or I need it more than every ____ hours**
- **I find it difficult to walk or talk**
- **I find it difficult to breathe**
- **I'm wheezing a lot or I have a very tight chest or I'm coughing a lot**
- **My peak flow is below ____**

THIS IS AN EMERGENCY TAKE ACTION NOW

1. Sit up straight — don't lie down. Try to keep calm
2. Take one puff of my reliever inhaler every 30 to 60 seconds up to a maximum of 10 puffs
3. A) If I feel worse at any point while I'm using my inhaler → CALL 999
   B) If I don't feel any better after 10 puffs → CALL 999
   C) If I feel better: make an urgent same-day appointment with my GP or asthma nurse to get advice

CALL 999 → Ambulance taking longer than 15 minutes? Repeat step 2

If I feel better, and have made my urgent same-day appointment:
- Check if I've been given rescue prednisolone tablets
- If I have these I should take them as prescribed by my doctor or asthma nurse

IMPORTANT! **This asthma attack information is not designed for people on a SMART or MART medicine plan. If you're on a SMART or MART medicine plan, please speak to your GP or asthma nurse to get the correct asthma attack information.**

References

1 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003;58 Suppl 1:i1-94.

2 Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2003.

3 North of England Evidence Based Guideline Development Group. Table 16: nedocromil and sodium cromoglycate studies not included in the nedocromil meta-analysis. In: North of England Evidence Based Guideline Development Group, editor. The primary care management of asthma in adults. Newcastle: University of Newcastle upon Tyne, Centre for Health Services Research; 1999. p.46-7.

4 World Health Organization. Health topics: adolescent health. [cited 26 Jul 2016]. Available from url: http://www.who.int/topics/adolescent_health/en

5 Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. [cited 04 Mar 2015]. Available from url: http://www.medicinescomplete.com

6 Medicines and Healthcare Products Regulatory Agency. Off-label use or unlicensed medicines: prescribers' responsibilities. Drug Safety Update 2009;2(9):6-7.

7 National Institute for Health and Care Excellence (NICE). Quality standard for asthma. London: NICE; 2013. (NICE Quality Standard QS25). [cited 26 Jul 2016]. Available from url: http://www.nice.org.uk/guidance/QS25/chapter/introduction-and-overview

8 Global Initiative for Asthma. Global strategy for asthma management and prevention. [cited 26 Jul 2016]. Available from url: http://ginasthma.org/gina-reports/

9 British Medical Association (BMA), NHS Employers, NHS England. 2015/16 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF): guidance for GMS contract 2015/16. London: NHS Employers; 2015. [cited 26 Jul 2016]. Available from url: http://www.nhsemployers.org/~/media/Employers/Documents/Primary%20care%20contracts/QOF/2015%20-%2016/2015%2016%20QOF%20guidance%20for%20stakeholders.pdf

10 Waring N. Use of new asthma BTM steps in one general practice: should asthmatics no longer on treatment be followed-up? Prim Care Respir J 1997;5:28.

11 Pinnock H, Adlem L, Gaskin S, Harris J, Snellgrove C, Sheikh A. Accessibility, clinical effectiveness, and practice costs of providing a telephone option for routine asthma reviews: phase IV controlled implementation study. Br J Gen Pract 2007;57(542):714-22.

12 Schneider A, Faderl B, Schwarzbach J, Welker L, Karsch-Volk M, Jorres RA. Prognostic value of bronchial provocation and FENO measurement for asthma diagnosis: results of a delayed type of diagnostic study. Respir Med 2014;108(1):34-40.

13 Ringsberg KC, Bjarneman P, Larsson R, Wallstrom E, Lowhagen O. Diagnosis of asthma in primary health care: a pilot study. J Allergy (Cairo) 2014;2014:898965.

14 Greiver M, Lang C, Hunchuck J, Rothschild K, Lang C, Hunchuck J, et al. Improving the diagnosis of asthma in a primary care practice. Can Fam Physician 2012;58(7):773-4.

15 Melbye H, Drivenes E, Dalbak LG, Leinan T, Hoegh-Henrichsen S, Ostrem A. Asthma, chronic obstructive pulmonary disease, or both? Diagnostic labeling and spirometry in primary care patients aged 40 years or more. Int J Chron Obstruct Pulmon Dis 2011;6:597-603.

16 Metting EI, Riemersma RA, Kocks JH, Piersma-Wichers MG, Sanderman R, van der Molen T. Feasibility and effectiveness of an asthma/COPD service for primary care: a cross-sectional baseline description and longitudinal results. NPJ Primary Care Respiratory Medicine 2015;25:14101.

17 Miravitlles M, Andreu I, Romero Y, Sitjar S, Altes A. Difficulties in differential diagnosis of COPD and asthma in primary care. Br J Gen Pract 2012;62(595):e68-75.

18 Prieto Centurion V, Huang F, Naureckas ET, Camargo CA, Charbeneau J, Joo MJ, et al. Confirmatory spirometry for adults hospitalized with a diagnosis of asthma or chronic obstructive pulmonary disease exacerbation. BMC Pulm Med 2012;12:73.

19 National Institute for Health and Care Excellence (NICE). Asthma: diagnosis and monitoring of asthma in adults, children and young people - appendices A-P. London: NICE; 2015. [cited 26 Jul 2016]. Available from url: https://www.nice.org.uk/guidance/GID-CGWAVE0640/documents/asthma-diagnosis-and-monitoring-appendices2

20 Yu IT, Wong TW, Li W. Using child reported respiratory symptoms to diagnose asthma in the community. Arch Dis Child 2004;89(6):544-8.

21 Galant SP, Crawford LJ, Morphew T, Jones CA, Bassin S. Predictive value of a cross-cultural asthma case-detection tool in an elementary school population. Pediatrics 2004;114(3):e307-16.

22 Jones CA, Morphew T, Clement LT, Kimia T, Dyer M, Li M, et al. A school-based case identification process for identifying inner city children with asthma: the Breathmobile program. Chest 2004;125(3):924-34.

23 Tomita K, Sano H, Chiba Y, Sato R, Sano A, Nishiyama O, et al. A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Prim Care Respir J 2013;22(1):51-8.

24 Schneider A, Ay M, Faderl B, Linde K, Wagenpfeil S. Diagnostic accuracy of clinical symptoms in obstructive airway diseases varied within different health care sectors. J Clin Epidemiol 2012;65(8):846-54.

25 Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000;82(4):327-32.

26 Schneider A, Gindner L, Tilemann L, Schermer T, Dinant GJ, Meyer FJ, et al. Diagnostic accuracy of spirometry in primary care. BMC Pulm Med 2009;9:31.

27 Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;170(4):426-32.

28 Brouwer AF, Roorda RJ, Brand PL. Home spirometry and asthma severity in children. Eur Respir J 2006;28(6):1131-7.

29 Verini M, Peroni DG, Rossi N, Nicodemo A, De Stradis R, Spagnolo C, et al. Functional assessment of allergic asthmatic children while asymptomatic. Allergy Asthma Proc 2006;27(4):359-64.

30 Joseph-Bowen J, de Klerk NH, Firth MJ, Kendall GE, Holt PG, Sly PD. Lung function, bronchial responsiveness, and asthma in a community cohort of 6-year-old children. Am J Respir Crit Care Med 2004;169(7):850-4.

31 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948-68.

32 Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184(5):602-15.

33 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324-43.

34 National Institute for Health and Care Excellence (NICE). Asthma: diagnosis and monitoring of asthma in adults, children and young people (draft for consultation). London: NICE; 2015. [cited 26 Jul 2016]. Available from url: http://www.nice.org.uk/guidance/GID-CGWAVE0640/documents/asthma-diagnosis-and-monitoring-draft-guideline2

35 National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. [cited Available from url: http://www.nice.org.uk/guidance/cg101/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-35109323931589

36 Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000;161(1):309-29.

37 Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy 1977;7(3):235-43.

38 Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol 1992;89(1 Pt 1):23-30.

39 Higgins BG, Britton JR, Chinn S, Cooper S, Burney PG, Tattersfield AE. Comparison of bronchial reactivity and peak expiratory flow variability measurements for epidemiologic studies. Am Rev Respir Dis 1992;145(3):588-93.

40 Brand PL, Postma DS, Kerstjens HA, Koeter GH. Relationship of airway hyperresponsiveness to respiratory symptoms and diurnal peak flow variation in patients with obstructive lung disease. The Dutch CNSLD Study Group. Am Rev Respir Dis 1991;143(5 Pt 1):916-21.

41 Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Bronchial responsiveness to methacholine in chronic bronchitis: relationship to airflow obstruction and cold air responsiveness. Thorax 1984;39(12):912-8.

42 Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. Thorax 2002;57(2):120-6.

43 Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlen B, et al. Indirect airway challenges. Eur Respir J 2003;21(6):1050-68.

44 Anderton RC, Cuff MT, Frith PA, Cockcroft DW, Morse JL, Jones NL, et al. Bronchial responsiveness to inhaled histamine and exercise. J Allergy Clin Immunol 1979;63(5):315-20.

45 Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? Ann Allergy Asthma Immunol 2005;94(3):366-71.

46 Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a working party of the European Respiratory Society. Eur Respir J Suppl 1997;24:2S-8S.

47 D'Alonzo GE, Steinijans VW, Keller A. Measurements of morning and evening airflow grossly underestimate the circadian variability of FEV1 and peak expiratory flow rate in asthma. Am J Respir Crit Care Med 1995;152(3):1097-9.

48 Chowienczyk PJ, Parkin DH, Lawson CP, Cochrane GM. Do asthmatic patients correctly record home spirometry measurements? BMJ 1994;309(6969):1618.

49 Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. Thorax 2001;56(3):180-2.

50 Higgins BG, Britton JR, Chinn S, Jones TD, Jenkinson D, Burney PG, et al. The distribution of peak flow variability in a population sample. Am Rev Respir Dis 1989;140(5):1368-72.

51 Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. Relationship to symptoms and respiratory disease. Am Rev Respir Dis 1991;143(2):323-30.

52 Thiadens HA, De Bock GH, Dekker FW, Huysman JA, Van Houwelingen JC, Springer MP, et al. Value of measuring diurnal peak flow variability in the recognition of asthma: a study in general practice. Eur Respir J 1998;12(4):842-7.

53 Lebowitz MD, Krzyzanowski M, Quackenboss JJ, O'Rourke MK. Diurnal variation of PEF and its use in epidemiological studies. Eur Respir J Suppl 1997;24:49S-56S.

54 Boezen HM, Schouten JP, Postma DS, Rijcken B. Distribution of peak expiratory flow variability by age, gender and smoking habits in a random population sample aged 20-70 yrs. Eur Respir J 1994;7(10):1814-20.

55 Siersted HC, Hansen HS, Hansen NC, Hyldebrandt N, Mostgaard G, Oxhoj H. Evaluation of peak expiratory flow variability in an adolescent population sample. The Odense Schoolchild Study. Am J Respir Crit Care Med 1994;149(3 Pt 1):598-603.

56 Gannon PF, Newton DT, Belcher J, Pantin CF, Burge PS. Development of OASYS-2: a system for the analysis of serial measurement of peak expiratory flow in workers with suspected occupational asthma. Thorax 1996;51(5):484-9.

57 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171(8):912-30.

58 Alving K, Malinovschi. Basic aspects of exhaled nitric oxide. Eur Respir Monograph 2010;49:1-31.

59 Bjermer L, Alving K, Diamant Z, Magnussen H, Pavord I, Piacentini G, et al. Current evidence and future research needs for FeNO measurement in respiratory diseases. Resp Med 2014;108(6):830-41.

60 Malmberg LP, Turpeinen H, Rytila P, Sarna S, Haahtela T. Determinants of increased exhaled nitric oxide in patients with suspected asthma. Allergy 2005;60(4):464-8.

61 Barreto M, Villa MP, Monti F, Bohmerova Z, Martella S, Montesano M, et al. Additive effect of eosinophilia and atopy on exhaled nitric oxide levels in children with or without a history of respiratory symptoms. Pediatr Allergy Immunol 2005;16(1):52-8.

62 Malmberg LP, Petays T, Haahtela T, Laatikainen T, Jousilahti P, Vartiainen E, et al. Exhaled nitric oxide in healthy nonatopic school-age children: determinants and height-adjusted reference values. Pediatr Pulmonol 2006;41(7):635-42.

63 Chan EY, Dundas I, Bridge PD, Healy MJ, McKenzie SA. Skin-prick testing as a diagnostic aid for childhood asthma. Pediatr Pulmonol 2005;39(6):558-62.

64 Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162(4 Pt 1):1403-6.

65 Eysink PE, ter Riet G, Aalberse RC, van Aalderen WM, Roos CM, van der Zee JS, et al. Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. Br J Gen Pract 2005;55(511):125-31.

66 Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. J Allergy Clin Immunol 2005;116(4):744-9.

67 Pavord ID, Pizzichini MM, Pizzichini E, Hargreave FE. The use of induced sputum to investigate airway inflammation. Thorax 1997;52(6):498-501.

68 Lex C, Payne DN, Zacharasiewicz A, Li AM, Wilson NM, Hansel TT, et al. Sputum induction in children with difficult asthma: safety, feasibility, and inflammatory cell pattern. Pediatr Pulmonol 2005;39(4):318-24.

69 Rytila P, Pelkonen AS, Metso T, Nikander K, Haahtela T, Turpeinen M. Induced sputum in children with newly diagnosed mild asthma: the effect of 6 months of treatment with budesonide or disodium cromoglycate. Allergy 2004;59(8):839-44.

70 Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. Thorax 2005;60(1):13-6.

71 Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Respir Res 2009;10:4.

72 Lucas AE, Smeenk FJ, Smeele IJ, van Schayck OP. Diagnostic accuracy of primary care asthma/COPD working hypotheses, a real life study. Respir Med 2012;106(8):1158-63.

73 Buffels J, Degryse J, Liistro G, Decramer M. Differential diagnosis in a primary care population with presumed airway obstruction: a real-life study. Respiration 2012;84(1):44-54.

74 Gerald LB, Grad R, Turner-Henson A, Hains C, Tang S, Feinstein R, et al. Validation of a multistage asthma case-detection procedure for elementary school children. Pediatrics. 2004;114(4):e459-68.

75 Ly NP, Gold DR, Weiss ST, Celedon JC. Recurrent wheeze in early childhood and asthma among children at risk for atopy. Pediatrics 2006;117(6):e1132-8.

76 Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. Chest 2006;129(5):1132-41.

77 Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. Eur Respir J 2003;22(5):767-71.

78 Schonberger H, van Schayck O, Muris J, Bor H, van den Hoogen H, Knottnerus A, et al. Towards improving the accuracy of diagnosing asthma in early childhood. Eur J Gen Pract. 2004;10(4):138-45.

79 Marchant JM, Masters IB, Taylor SM, Chang AB. Utility of signs and symptoms of chronic cough in predicting specific cause in children. Thorax. 2006;61(8):694-8.

80 Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. Am J Respir Crit Care Med 2004;169(4):473-8. (34 ref).

81 Goldstein MF, Veza BA, Dunsky EH, Dvorin DJ, Belecanech GA, Haralabatos IC. Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV(1) responses, and methacholine inhalation challenges in the evaluation of suspected asthma. Chest 2001;119(4):1001-10.

82 Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. Chest 2002;121(4):1051-7.

83 Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med 2005;172(4):453-9.

84 Hederos CA, Janson S, Andersson H, Hedlin G. Chest X-ray investigation in newly discovered asthma. Pediatr Allergy Immunol 2004;15(2):163-5.

85 Kurukulaaratchy RJ, Matthews S, Arshad SH. Relationship between childhood atopy and wheeze: what mediates wheezing in atopic phenotypes? Ann Allergy Asthma Immunol 2006;97(1):84-91.

86 Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ 1994;309(6947):90-3.

87 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133-8.

88 Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood: a birth cohort study. Arch Dis Child 1991;66(9):1050-3.

89 Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312(7040):1195-9.

90 Aberg N, Engstrom I. Natural history of allergic diseases in children. Acta Paediatr Scand 1990;79(2):206-11.

91 Toelle BG, Xuan W, Peat JK, Marks GB. Childhood factors that predict asthma in young adulthood. Eur Respir J 2004;23(1):66-70.

92 Anderson HR, Pottier AC, Strachan DP. Asthma from birth to age 23: incidence and relation to prior and concurrent atopic disease. Thorax 1992;47(7):537-42.

93 Barbee RA, Murphy S. The natural history of asthma. J Allergy Clin Immunol 1998;102(4 Pt 2):S65-72.

94 Blair H. Natural history of childhood asthma. 20-year follow-up. Arch Dis Child 1977;52(8):613-9.

95 Johnstone DE. A study of the natural history of bronchial asthma in children. Am J Dis Child 1968;115(2):213-6.

96 Laor A, Cohen L, Danon YL. Effects of time, sex, ethnic origin, and area of residence on prevalence of asthma in Israeli adolescents. BMJ 1993;307(6908):841-4.

97 Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax 2003;58(7):561-6.

98 Luyt DK, Burton PR, Simpson H. Epidemiological study of wheeze, doctor diagnosed asthma, and cough in preschool children in Leicestershire. BMJ 1993;306(6889):1386-90.

99 Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. Br Med J 1980;280(6229):1397-400.

100 Robertson CF, Heycock E, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. BMJ 1991;302(6785):1116-8.

101 Roorda RJ. Prognostic factors for the outcome of childhood asthma in adolescence. Thorax 1996;51(Suppl 1):S7-12.

102 Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. Arch Dis Child 1996;75(5):392-8.

103 Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. Am J Epidemiol 1990;132(1):83-95.

104 Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. Pediatrics 1995;95(4):500-5.

105 Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. J Allergy Clin Immunol 1998;101(5):587-93.

106 Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? Am J Respir Crit Care Med 1999;160(5 Pt 1):1473-80.

107 Dodge R, Martinez FD, Cline MG, Lebowitz MD, Burrows B. Early childhood respiratory symptoms and the subsequent diagnosis of asthma. J Allergy Clin Immunol 1996;98(1):48-54.

108 Reijonen TM, Kotaniemi-Syrjanen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. Pediatrics 2000;106(6):1406-12.

109 Kotaniemi-Syrjanen A, Reijonen TM, Romppanen J, Korhonen K, Savolainen K, Korppi M. Allergen-specific immunoglobulin E antibodies in wheezing infants: the risk for asthma in later childhood. Pediatrics 2003;111(3):e255-61.

110 Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA. The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy 1989;19(4):419-24.

111 Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. J Allergy Clin Immunol 1997;99(4):454-60.

112 Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, et al. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. Am J Respir Crit Care Med 1999;160(5 Pt 1)):1617-22.

113 Wensley D, Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. Am J Respir Crit Care Med 2004;170(6):606-12.

114 Burkhart PV, Rayens MK, Revelette WR, Ohlmann A. Improved health outcomes with peak flow monitoring for children with asthma. J Asthma 2007;44(2):137-42.

115 McCoy K, Shade DM, Irvin CG, Mastronarde JG, Hanania NA, Castro M, et al. Predicting episodes of poor asthma control in treated patients with asthma. J Allergy Clin Immunol 2006;118(6):1226-33.

116 Nuijsink M, Hop WC, Sterk PJ, Duiverman EJ, de Jongste JC. Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial. Eur Respir J 2007;30(3):457-66.

117 de Jongste JC, Carraro S, Hop WC, CHARISM Study Group, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. Am J Resp Crit Care Med 2009;179(2):93-7.

118 Fritsch M, Uxa S, Horak F Jr, Putschoegl B, Dehlink E, Szepfalusi Z, et al. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. Pediatr Pulmonol 2006;41(9):855-62.

119 Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. Thorax 2005;60(3):215-8.

120 Szefler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. Lancet 2008;372(9643):1065-72.

121 Covar RA, Szefler SJ, Zeiger RS, Sorkness CA, Moss M, Mauger DT, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. J Allergy Clin Immunol 2008;122(4):741-7.

122 Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD, CAMP Research Group. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. Pediatrics 2006;118(2):e347-55.

123 Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. Am J Respir Crit Care Med 2005;171(10):1077-82.

124 Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 2004;170(8):836-44.

125 Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360(9347):1715-21.

126 Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005;352(21):2163-73.

127 Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. Eur Respir J 2006;27(3):483-94.

128 Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. Am J Respir Crit Care Med 1999;159(4 Pt 1):1043-51.

129 Pearson MG, Bucknall CE, editors. Measuring clinical outcome in asthma : a patient-focused approach. London: Royal College of Physicians of London; 1999.

130 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-38.

131 Tweeddale PM, Alexander F, McHardy GJ. Short term variability in FEV1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. Thorax 1987;42(7):487-90.

132 Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. Thorax 1992;47(3):162-6.

133 Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100(4):616-21.

134 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14(4):902-7.

135 Juniper EF, Svensson K, Mork AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;99(5):553-8.

136 Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J 2010;36(6):1410-6.

137 Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113(1):59-65.

138 Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117(3):549-56.

139 Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147(4):832-8.

140 Bacharier LB, Guilbert TW, Zeiger RS, Strunk RC, Morgan WJ, Lemanske RF Jr, et al. Patient characteristics associated with improved outcomes with use of an inhaled corticosteroid in preschool children at risk for asthma. J Allergy Clin Immunol 2009;123(5):1077-82.

141 Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. Eur Respir J 2003;21(3):433-8.

142 Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. Clin Exp Allergy 2005;35(9):1175-9.

143 Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. Lancet 1999;353(9171):2213-4.

144 Belda J, Leigh R, Parameswaran K, O'Byrne PM, Sears MR, Hargreave FE. Induced sputum cell counts in healthy adults. Am J Respir Crit Care Med 2000;161(2 Pt 1):475-8.

145 Djukanovic R, Sterk PJ, Fahy JV, Hargreave FE. Standardised methodology of sputum induction and processing. Eur Respir J Suppl 2002;37:1s-2s.

146 Institute of Medicine of the National Academies. The 1st Annual Crossing the Quality Chasm Summit: a focus on communities. Washington D.C.: The National Academic Press; 2004.

147 Ring N, Jepson R, Hoskins G, Wilson C, Pinnock H, Sheikh A, et al. Understanding what helps or hinders asthma action plan use: a systematic review and synthesis of the qualitative literature. Patient Educ Couns 2011;85(2):e131-43.

148 Gibson PG, Powell H, Coughlan J, Wilson A, Abramson MJ, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database of Systematic Reviews 2002, Issue 1.

149 Lefevre F, Piper M, Weiss K, Mark D, Clark N, Aronson N. Do written action plans improve patient outcomes in asthma? An evidence-based analysis. J Fam Pract 2002;51(10):842-8.

150 Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. Thorax 2004;59(2):94-9.

151 Powell H, Gibson PG. Options for self-management education for adults with asthma Cochrane Database of Systematic Reviews 2002, Issue 1.

152 Bussey-Smith KL, Rossen RD. A systematic review of randomized control trials evaluating the effectiveness of interactive computerized asthma patient education programs. Ann Allergy Asthma Immunol 2007;98(6):507-16.

153 de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. Cochrane Database of Systematic Reviews 2012, Issue 12.

154 Smith JR, Mugford M, Holland R, Noble MJ, Harrison BD. Psycho-educational interventions for adults with severe or difficult asthma: a systematic review. J Asthma 2007;44(3):219-41.

155 Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. Cochrane Database of Systematic Reviews 2009, Issue 2.

156 Coffman JM, Cabana MD, Halpin HA, Yelin EH. Effects of asthma education on children's use of acute care services: a meta-analysis. Pediatrics 2008;121(3):575-86.

157 Wolf F, Guevara JP, Grum CM, Clark NM, Cates CJ. Educational interventions for asthma in children. Cochrane Database of Systematic Reviews 2002, Issue 4.

158 Clarke SA, Calam R. The effectiveness of psychosocial interventions designed to improve health-related quality of life (HRQOL) amongst asthmatic children and their families: a systematic review. Qual Life Res 2012;21(5):747-64.

159 Bravata DM, Gienger AL, Holty JE, Sundaram V, Khazeni N, Wise PH, et al. Quality improvement strategies for children with asthma: a systematic review. Arch Pediatr Adolesc Med 2009;163(6):572-81.

160 Bhogal SK, Zemek RL, Ducharme F. Written action plans for asthma in children. Cochrane Database of Systematic Reviews 2006, Issue 3.

161 Zemek RL, Bhogal SK, Ducharme FM. Systematic review of randomized controlled trials examining written action plans in children: what is the plan? Arch Pediatr Adolesc Med 2008;162(2):157-63.

162 Kessler KR. Relationship between the use of asthma action plans and asthma exacerbations in children with asthma: a systematic review. J Asthma Allergy Educ 2011;2(1):11-21.

163 Coffman JM, Cabana MD, Yelin EH. Do school-based asthma education programs improve self-management and health outcomes? Pediatrics 2009;124(2):729-42.

164 Ahmad E, Grimes DE. The effects of self-management education for school-age children on asthma morbidity: a systematic review. J Sch Nurs 2011;27(4):282-92.

165 Welsh EJ, Hasan M, Li P. Home-based educational interventions for children with asthma. Cochrane Database of Systematic Reviews 2011, Issue 10.

166 Viswanathan M, Kraschnewski J, Nishikawa B, Morgan LC, Thieda P, Honeycutt A, et al. Outcomes of community health worker interventions. USA: AHRQ; 2009. (Evidence Report/Technology Assessment No. 181). [cited 28 Jul 2016]. Available from url: http://www.ncbi.nlm.nih.gov/books/NBK44601/pdf/Bookshelf_NBK44601.pdf

167 Bailey EJ, Cates CJ, Kruske SG, Morris PS, Brown N, Chang AB. Culture-specific programs for children and adults from minority groups who have asthma. Cochrane Database of Systematic Reviews 2009, Issue 2.

168 Press VG, Pappalardo AA, Conwell WD, Pincavage AT, Prochaska MH, Arora VM. Interventions to improve outcomes for minority adults with asthma: a systematic review. J Gen Intern Med 2012;27(8):1001-15.

169 Tapp S, Lasserson TJ, Rowe BH. Education interventions for adults who attend the emergency room for acute asthma. Cochrane Database of Systematic Reviews 2007, Issue 3.

170 Wilson SR, Latini D, Starr NJ, Fish L, Loes LM, Page A, et al. Education of parents of infants and very young children with asthma: a developmental evaluation of the Wee Wheezers program. J Asthma 1996;33(4):239-54.

171 Clark NM, Gong M, Schork MA, Evans D, Roloff D, Hurwitz M, et al. Impact of education for physicians on patient outcomes. Pediatrics 1998;101(5):831-6.

172 Stevens CA, Wesseldine LJ, Couriel JM, Dyer AJ, Osman LM, Silverman M. Parental education and guided self-management of asthma and wheezing in the pre-school child: a randomised controlled trial. Thorax 2002;57(1):39-44.

173 Butz AM, Malveaux FJ, Eggleston PA, Thompson L, Huss K, Rand CS. A review of community-based asthma interventions for inner-city children. Pediatr Asthma Allergy Immunol 2009;8(3):149-56.

174 Eakin MN, Rand CS, Bilderback A, Bollinger ME, Butz A, Kandasamy V, et al. Asthma in Head Start children: effects of the Breathmobile program and family communication on asthma outcomes. J Allergy Clin Immunol 2012;129(3):664-70.

175 Hederos CA, Janson S, Hedlin G. Group discussions with parents have long-term positive effects on the management of asthma with good cost-benefit. Acta Paediatr 2005;94(5):602-8.

176 Hederos CA, Janson S, Hedlin G. Six-year follow-up of an intervention to improve the management of preschool children with asthma. Acta Paediatr 2009;98(12):1939-44.

177 Szczepanski R, Jaeschke R, Spindler T, Ihorst G, Forster J, ASEV Study Group. Preschoolers' and parents' asthma education trial (P2AET): a randomized controlled study. Eur J Pediatr 2010;169(9):1051-60.

178 Warschburger P, von Schwerin AD, Buchholz HT, Petermann F. An educational program for parents of asthmatic preschool children: short- and medium-term effects. Patient Educ Couns 2003;51(1):83-91.

179 Bartholomew LK, Gold RS, Parcel GS, Czyzewski DI, Sockrider MM, Fernandez M, et al. Watch, Discover, Think, and Act: evaluation of computer-assisted instruction to improve asthma self-management in inner-city children. Patient Educ Couns 2000;39(2-3):269-80.

180 Brown JV, Bakeman R, Celano MP, Demi AS, Kobrynski L, Wilson SR. Home-based asthma education of young low-income children and their families. J Pediatr Psychol 2002;27(8):677-88.

181 Fisher EB, Strunk RC, Sussman LK, Sykes RK, Walker MS. Community organization to reduce the need for acute care for asthma among African American children in low-income neighborhoods: the Neighborhood Asthma Coalition. Pediatrics 2004;114(1):116-23.

182 La Roche MJ, Koinis-Mitchell D, Gualdron L. A culturally competent asthma management intervention: a randomized controlled pilot study. Ann Allergy Asthma Immunol 2006;96(1):80-5.

183 Joseph CL, Peterson E, Havstad S, Johnson CC, Hoerauf S, Stringer S, et al. A web-based, tailored asthma management program for urban African-American high school students. Am J Respir Crit Care Med 2007;175(9):888-95.

184 Mosnaim GS, Cohen MS, Rhoads CH, Rittner SS, Powell LH. Use of MP3 players to increase asthma knowledge in inner-city African-American adolescents. Int J Behav Med 2008;15(4):341-6.

185 Flores G, Bridon C, Torres S, Perez R, Walter T, Brotanek J, et al. Improving asthma outcomes in minority children: a randomized, controlled trial of parent mentors. Pediatrics 2009;124(6):1522-32.

186 Martin MA, Catrambone CD, Kee RA, Evans AT, Sharp LK, Lyttle C, et al. Improving asthma self-efficacy: developing and testing a pilot community-based asthma intervention for African American adults. J Allergy Clin Immunol 2009;123(1):153-9.e3.

187 Velsor-Friedrich B, Militello LK, Richards MH, Harrison PR, Gross IM, Romero E, et al. Effects of coping-skills training in low-income urban African-American adolescents with asthma. J Asthma 2012;49(4):372-9.

188 Moudgil H, Marshall T, Honeybourne D. Asthma education and quality of life in the community: a randomised controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. Thorax 2000;55(3):177-83.

189 Griffiths C, Foster G, Barnes N, Eldridge S, Tate H, Begum S, et al. Specialist nurse intervention to reduce unscheduled asthma care in a deprived multiethnic area: the east London randomised controlled trial for high risk asthma (ELECTRA). BMJ 2004;328(7432):144.

190 Poureslami I, Nimmon L, Doyle-Waters M, Rootman I, Schulzer M, Kuramoto L, et al. Effectiveness of educational interventions on asthma self-management in Punjabi and Chinese asthma patients: a randomized controlled trial. J Asthma 2012;49(5):542-51.

191 Barbanel D, Eldridge S, Griffiths C. Can a self-management programme delivered by a community pharmacist improve asthma control? A randomised trial. Thorax 2003;58(10):851-4.

192 Nokela M, Arnlind MH, Ehrs PO, Krakau I, Forslund L, Jonsson EW. The influence of structured information and monitoring on the outcome of asthma treatment in primary care: a cluster randomized study. Respiration 2010;79(5):388-94.

193 Partridge MR, Caress AL, Brown C, Hennings J, Luker K, Woodcock A, et al. Can lay people deliver asthma self-management education as effectively as primary care based practice nurses? Thorax 2008;63(9):778-83.

194 Guendelman S, Meade K, Benson M, Chen YQ, Samuels S. Improving asthma outcomes and self-management behaviors of inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary. Arch Pediatr Adolesc Med 2002;156(2):114-20.

195 Delaronde S, Peruccio DL, Bauer BJ. Improving asthma treatment in a managed care population. Am J Manag Care. 2005;11(6):361-8.

196 Feifer RA, Verbrugge RR, Khalid M, Levin R, O'Keefe GB, Aubert RE. Improvements in asthma pharmacotherapy and self-management: an example of a population-based disease management program. Dis Manag Health Outcomes 2004;12(2):93-102.

197 Glasgow NJ, Ponsonby AL, Yates R, Beilby J, Dugdale P. Proactive asthma care in childhood: general practice based randomised controlled trial. BMJ 2003;327(7416):659.

198 Homer CJ, Forbes P, Horvitz L, Peterson LE, Wypij D, Heinrich P. Impact of a quality improvement program on care and outcomes for children with asthma. Arch Pediatr Adolesc Med 2005;159(5):464-9.

199 Cleland JA, Hall S, Price D, Lee AJ. An exploratory, pragmatic, cluster randomised trial of practice nurse training in the use of asthma action plans. Prim Care Respir J 2007;16(5):311-8.

200 Heard AR, Richards IJ, Alpers JH, Pilotto LS, Smith BJ, Black JA. Randomised controlled trial of general practice based asthma clinics. Med J Aust 1999;171(2):68-71.

201 Thoonen BP, Schermer TR, Van Den Boom G, Molema J, Folgering H, Akkermans RP, et al. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. Thorax 2003;58(1):30-6.

202 Osman LM, Abdalla MI, Beattie JA, Ross SJ, Russell IT, Friend JA, et al. Reducing hospital admission through computer supported education for asthma patients. BMJ 1994;308(6928):568-71.

203 Osman LM, Calder C, Godden DJ, Friend JA, McKenzie L, Legge JS, et al. A randomised trial of self-management planning for adult patients admitted to hospital with acute asthma. Thorax. 2002;57(10):869-74.

204 Yoon R, McKenzie DK, Bauman A, Miles DA. Controlled trial evaluation of an asthma education programme for adults. Thorax 1993;48(11):1110-6.

205 Madge P, McColl J, Paton J. Impact of a nurse-led home management training programme in children admitted to hospital with acute asthma: a randomised controlled study. Thorax 1997;52(3):223-8.

206 Royal Pharmaceutical Society of Great Britain. From compliance to concordance: achieving shared goals in medicine taking. London: Royal Pharmaceutical Society of Great Britain; 1997.

207 Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med 2010;181(6):566-77.

208 Garrett J, Fenwick JM, Taylor G, Mitchell E, Rea H. Peak expiratory flow meters (PEFMs): who uses them and how and does education affect the pattern of utilisation? Aust N Z J Med 1994;24(5):521-9.

209 Redline S, Wright EC, Kattan M, Kercsmar C, Weiss K. Short-term compliance with peak flow monitoring: results from a study of inner city children with asthma. Pediatr Pulmonol 1996;21(4):203-10.

210 Effectiveness of routine self monitoring of peak flow in patients with asthma. Grampian Asthma Study of Integrated Care (GRASSIC). BMJ 1994;308(6928):564-7.

211 Burkhart PV, Dunbar-Jacob JM, Fireman P, Rohay J. Children's adherence to recommended asthma self-management. Pediatr Nurs 2002;28(4):409-14.

212 Yoos HL, Kitzman H, McMullen A, Henderson C, Sidora K. Symptom monitoring in childhood asthma: a randomized clinical trial comparing peak expiratory flow rate with symptom monitoring. Ann Allergy Asthma Immunol 2002;88(3):283-91.

213 National Collaborating Centre for Primary Care. Clinical guidelines and evidence review for medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: NICE; 2009. (NICE guideline CG76). [cited 10 Jul 2014]. Available from url: http://www.nice.org.uk/Guidance/CG76

214 Krishnan JA, Bender BG, Wamboldt FS, Szefler SJ, Adkinson NF, Zeiger RS, et al. Adherence to inhaled corticosteroids: an ancillary study of the Childhood Asthma Management Program clinical trial. J Allergy Clin Immunol 2012;129(1):112-8.

215 Reznik M, Ozuah PO. Measurement of inhaled corticosteroid adherence in inner-city, minority children with persistent asthma by parental report and integrated dose counter. J Allergy (Cairo) 2012;2012:570850.

216 Schultz A, Sly PD, Zhang G, Venter A, Devadason SG, le Souef PN. Usefulness of parental response to questions about adherence to prescribed inhaled corticosteroids in young children. Arch Dis Child 2012;97(12):1092-6.

217 Blais L, Kettani FZ, Beauchesne MF, Lemiere C, Perreault S, Forget A. New measure of adherence adjusted for prescription patterns: the case of adults with asthma treated with inhaled corticosteroid monotherapy. Ann Pharmacother 2011;45(3):335-41.

218 Taylor A, Chen LC, Smith MD. Adherence to inhaled corticosteroids by asthmatic patients: measurement and modelling. Int J Clin Pharm 2014;36(1):112-9.

219 Patel M, Perrin K, Pritchard A, Williams M, Wijesinghe M, Weatherall M, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. Respirology 2013;18(3):546-52.

220 Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health 1999;14(1):1-24.

221 Van Steenis M, Driesenaar J, Bensing J, Van Hulten R, Souverein P, Van Dijk L, et al. Relationship between medication beliefs, self-reported and refill adherence, and symptoms in patients with asthma using inhaled corticosteroids. Patient Prefer Adherence 2014;8:83-91.

222 Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One 2013;8(12):e80633.

223 Vollmer WM, Xu M, Feldstein A, Smith D, Waterbury A, Rand C. Comparison of pharmacy-based measures of medication adherence. BMC Health Serv Res 2012; 12: 155.

224 McNicholl DM, Stevenson M, McGarvey LP, Heaney LG. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. Am J Respir Crit Care Med 2012;186(11):1102-8.

225 Hagan JB, Netzel BC, Matthews MR, Korpi-Steiner NL, Singh RJ. Urinary fluticasone propionate-17beta-carboxylic acid to assess asthma therapy adherence. Allergy Asthma Proc 2012;33(4):e35-9.

226 Moullec G, Gour-Provencal G, Bacon SL, Campbell TS, Lavoie KL. Efficacy of interventions to improve adherence to inhaled corticosteroids in adult asthmatics: Impact of using components of the chronic care model. Respir Med 2012;106(9):1211-25.

227 Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews 2008, Issue 2.

228 Knight KM, McGowan L, Dickens C, Bundy C. A systematic review of motivational interviewing in physical health care settings. Br J Health Psychol 2006;11(Pt 2):319-32.

229 Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Arch Intern Med 2007;167(6):540-50.

230 Kahana S, Drotar D, Frazier T. Meta-analysis of psychological interventions to promote adherence to treatment in pediatric chronic health conditions. J Pediatr Psychol 2008;33(6):590-611.

231 Oake N, Jennings A, Van Walraven C, Forster AJ. Interactive voice response systems for improving delivery of ambulatory care. Am J Manag Care 2009;15(6):383-91.

232 Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med 2012;157(11):785-95.

233 Wu YP, Pai AL. Health care provider-delivered adherence promotion interventions: a meta-analysis. Pediatrics 2014;133(6):e1698-707.

234 Tran N, Coffman JM, Sumino K, Cabana MD. Patient reminder systems and asthma medication adherence: a systematic review. J Asthma 2014;51(5):536-43.

235 Bender BG, Cvietusa PJ, Goodrich GK, Lowe R, Nuanes HA, Rand C, et al. Pragmatic trial of health care technologies to improve adherence to pediatric asthma treatment: a randomized clinical trial. JAMA Pediatr 2015;169(4):317-23.

236 Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. J Allergy Clin Immunol 2014;134(6):1260-8.e3.

237 Wells KE, Peterson EL, Ahmedani BK, Williams LK. Real-world effects of once vs greater daily inhaled corticosteroid dosing on medication adherence. Ann Allergy Asthma Immunol 2013;111(3):216-20.

238 Brooks TL, Leventhal H, Wolf MS, O'Conor R, Morillo J, Martynenko M, et al. Strategies used by older adults with asthma for adherence to inhaled corticosteroids. J Gen Intern Med 2014;29(11):1506-12.

239 Wiener-Ogilvie S, Pinnock H, Huby G, Sheikh A, Partridge MR, Gillies J. Do practices comply with key recommendations of the British Asthma Guideline? If not, why not? Prim Care Respir J 2007;16(6):369-77.

240 Asthma UK. Compare your care. [cited 10 Jul 2014]. Available from url: http://www.asthma.org.uk/compareyourcare

241 Ring N, Malcolm C, Wyke S, Macgillivray S, Dixon D, Hoskins G, et al. Promoting the use of Personal Asthma Action Plans: a systematic review. Prim Care Respir J 2007;16(5):271-83.

242 Bunik M, Federico MJ, Beaty B, Rannie M, Olin JT, Kempe A. Quality improvement for asthma care within a hospital-based teaching clinic. Acad Pediatr 2011;11(1):58-65.

243 Bunting BA, Cranor CW. The Asheville Project: long-term clinical, humanistic, and economic outcomes of a community-based medication therapy management program for asthma. J Am Pharm Assoc (2003) 2006;46(2):133-47.

244 Gerald LB, Redden D, Wittich AR, Hains C, Turner-Henson A, Hemstreet MP, et al. Outcomes for a comprehensive school-based asthma management program. J Sch Health 2006;76(6):291-6.

245 Vollmer WM, Kirshner M, Peters D, Drane A, Stibolt T, Hickey T, et al. Use and impact of an automated telephone outreach system for asthma in a managed care setting. Am J Manag Care 2006;12(12):725-33.

246 Forshee JD, Whalen EB, Hackel R, Butt LT, Smeltzer PA, Martin J, et al. The effectiveness of one-on-one nurse education on the outcomes of high-risk adult and pediatric patients with asthma. Manag Care Interface 1998;11(12):82-92.

247 Findley SE, Thomas G, Madera-Reese R, McLeod N, Kintala S, Andres Martinez R, et al. A community-based strategy for improving asthma management and outcomes for preschoolers. J Urban Health 2011;88(Suppl 1):85-99.

248 Polivka BJ, Chaudry RV, Crawford J, Bouton P, Sweet L. Impact of an urban healthy homes intervention. J Environ Health 2011;73(9):16-20.

249 Kemple T, Rogers C. A mailed personalised self-management plan improves attendance and increases patients' understanding of asthma. Prim Care Respir J 2003;12(4):110-4.

250 Swanson V, Wright S, Power KG, Duncan B, Morgan J, Turner E, et al. The impact of a structured programme of asthma care in general practice. Int J Clin Pract 2000;54(9):573-80.

251 Lindberg M, Ahlner J, Ekstrom T, Jonsson D, Moller M. Asthma nurse practice improves outcomes and reduces costs in primary health care. Scand J Caring Sci 2002;16(1):73-8.

252 Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, et al. A 10 year asthma programme in Finland: major change for the better. Thorax 2006;61(8):663-70.

253 Kauppi P, Linna M, Martikainen J, Makela MJ, Haahtela T. Follow-up of the Finnish Asthma Programme 2000-2010: reduction of hospital burden needs risk group rethinking. Thorax 2013;68(3):292-3.

254 Chini L, Iannini R, Chianca M, Corrente S, Graziani S, La Rocca M, et al. Happy air®, a successful school-based asthma educational and interventional program for primary school children. J Asthma 2011;48(4):419-26.

255 Andrade WC, Camargos P, Lasmar L, Bousquet J. A pediatric asthma management program in a low-income setting resulting in reduced use of health service for acute asthma. Allergy 2010;65(11):1472-7.

256 Souza-Machado C, Souza-Machado A, Franco R, Ponte EV, Barreto ML, Rodrigues LC, et al. Rapid reduction in hospitalisations after an intervention to manage severe asthma. Eur Respir J 2010;35(3):515-21.

257 Maas T, Dompeling E, Muris J, Wesseling G, Knottnerus J, van Schayck OC. Prevention of asthma in genetically susceptible children: a multifaceted intervention trial focussed on feasibility in general practice. Pediatr Allergy Immunol 2011;22(8):794-802.

258 Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. J Allergy Clin Immunol 1997;99(6 Pt 1):763-9.

259 Corver K, Kerkhof M, Brussee JE, Brunekreef B, van Strien RT, Vos AP, et al. House dust mite allergen reduction and allergy at 4 yr: follow up of the PIAMA-study. Pediatr Allergy Immunol 2006;17(5):329-36.

260 Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. Lancet 2000;356(9239):1392-7.

261 Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. Thorax 2003;58(6):489-93.

262 Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med 1990;323(8):502-7.

263 Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. Thorax 2004;59(10):855-61.

264 Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. J Allergy Clin Immunol 2005;116(1):49-55.

265 Horak F Jr, Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study: 24 months results of the Study of Prevention of Allergy in Children in Europe. Clin Exp Allergy 2004;34(8):1220-5.

266 Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during the first year of life: a randomised trial. Lancet 2001;358(9277):188-93.

267 Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. Am J Respir Crit Care Med 2004;170(4):433-9.

268 Takkouche B, Gonzalez-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. Allergy 2008;63(7):857-64.

269 Lodge CJ, Allen KJ, Lowe AJ, Hill DJ, Hosking CS, Abramson MJ, et al. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. Clin Dev Immunol 2012;2012:176484.

270 Chen CM, Tischer C, Schnappinger M, Heinrich J. The role of cats and dogs in asthma and allergy: a systematic review. Int J Hyg Environ Health 2010;213(1):1-31.

271 Lødrup Carlsen KC, Roll S, Carlsen K, Mowinckel P, Wijga A, Brunekreef B, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. PLoS ONE 2012;7(8):e43214.

272 Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. Pediatr Allergy Immunol 2004;15(2):103-11.

273 Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. Pediatr Allergy Immunol 2004;15(4):291-307.

274 Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database of Systematic Reviews 2012, Issue 9.

275 Vance GH, Grimshaw KE, Briggs R, Lewis SA, Mullee MA, Thornton CA, et al. Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy. Clin Exp Allergy 2004;34(12):1855-61.

276 van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, et al. Breast feeding and allergic disease: a multi-disciplinary review of the literature (1996-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003;58(9):833-43.

277 Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet 2002;360(9337):901-7.

278 Osborn DA, Sinn JKH. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database of Systematic Reviews 2006, Issue 4.

279 Osborn DA, Sinn JKH. Soy formula for prevention of allergy and food intolerance in infants. Cochrane Database of Systematic Reviews 2006, Issue 4.

280 Tricon S, Willers S, Smit HA, Burney PG, Devereux G, Frew AJ, et al. Nutrition and allergic disease. Clin Exp Allergy Rev 2006;6(5):117-88.

281 Zutavern A, von Mutius E, Harris J, Mills P, Moffatt S, White C, et al. The introduction of solids in relation to asthma and eczema. Arch Dis Child 2004;89(4):303-8.

282 Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol 2003;112(6):1178-84.

283 Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM, et al. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. Pediatr Allergy Immunol 2004;15(6):517-22.

284 Shaheen SO, Newson RB, Henderson AJ, Emmett PM, Sherriff A, Cooke M, et al. Umbilical cord trace elements and minerals and risk of early childhood wheezing and eczema. Eur Respir J 2004;24(2):292-7.

285 Devereux G, Turner SW, Craig LC, McNeill G, Martindale S, Harbour PJ, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. Am J Respir Crit Care Med 2006;174(5):499-507.

286 Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. Arch Dis Child 2006;91(4):334-9.

287 Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007;175(7):661-6.

288 Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. Obes Rev 2013;14(3):222-31.

289 Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. BMC Pediatr 2013;13:121.

290 Forno E, Young OM, Kumar R, Simhan H, Celedon JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. Pediatrics 2014;134(2):e535-46.

291 Holt PG, Sly PD, Bjorksten B. Atopic versus infectious diseases in childhood: a question of balance? Pediatr Allergy Immunol 1997;8(2):53-8.

292 Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55(Suppl 1):S2-10.

293 Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001;357(9262):1076-9.

294 Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child 2006;91(10):814-9.

295 Cook DG, Strachan DP. Health effects of passive smoking-10: summary of effects of parental smoking on the respiratory health of children and implications for research. Thorax 1999;54(4):357-66.

296 Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. Am J Respir Crit Care Med 1999;159(2):403-10.

297 Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax 2000;55(4):271-6.

298 Lodrup Carlsen KC, Carlsen KH, Nafstad P, Bakketeig L. Perinatal risk factors for recurrent wheeze in early life. Pediatr Allergy Immunol 1999;10(2):89-95.

299 Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. Chest 2005;127(2):502-8.

300 Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 2004;94(1):136-40.

301 Kabesch M, Hoefler C, Carr D, Leupold W, Weiland SK, von Mutius E. Glutathione S transferase deficiency and passive smoking increase childhood asthma. Thorax 2004;59(7):569-73.

302 Belanger K, Beckett W, Triche E, Bracken MB, Holford T, Ren P, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. Am J Epidemiol 2003;158(3):195-202.

303 Lee YL, Lin YC, Lee YC, Wang JY, Hsiue TR, Guo YL. Glutathione S-transferase P1 gene polymorphism and air pollution as interactive risk factors for childhood asthma. Clin Exp Allergy 2004;34(11):1707-13.

304 Miller RL, Garfinkel R, Horton M, Camann D, Perera FP, Whyatt RM, et al. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. Chest 2004;126(4):1071-8.

305 Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Estela del Rio-Navarro B, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. Thorax 2004;59(1):8-10.

306 Kemp A, Bjorksten B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. Pediatr Allergy Immunol 2003;14(2):74-80.

307 Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? Pediatr Allergy Immunol 2005;16(3):193-200.

308 Gotzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database of Systematic Reviews 2008, Issue 2.

309 Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 1989;83(4):730-4.

310 Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158(1):115-20.

311 Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001;357(9258):752-6.

312 Francis H, Fletcher G, Anthony C, Pickering C, Oldham L, Hadley E, et al. Clinical effects of air filters in homes of asthmatic adults sensitized and exposed to pet allergens. Clin Exp Allergy 2003;33(1):101-5.

313 Popplewell EJ, Innes VA, Lloyd-Hughes S, Jenkins EL, Khdir K, Bryant TN, et al. The effect of high-efficiency and standard vacuum-cleaners on mite, cat and dog allergen levels and clinical progress. Pediatr Allergy Immunol 2000;11(3):142-8.

314 Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. J Allergy Clin Immunol 2001;108(5):732-7.

315 Krieger JW, Takaro TK, Song L, Weaver M. The Seattle-King County Healthy Homes Project: a randomized, controlled trial of a community health worker intervention to decrease exposure to indoor asthma triggers. Am J Public Health. 2005;95(4):652-9.

316 Warner JA, Frederick JM, Bryant TN, Weich C, Raw GJ, Hunter C, et al. Mechanical ventilation and high-efficiency vacuum cleaning: a combined strategy of mite and mite allergen reduction in the control of mite-sensitive asthma. J Allergy Clin Immunol 2000;105(1 Pt 1):75-82.

317 Singh M, Bara A, Gibson P. Humidity control for chronic asthma. Cochrane Database of Systematic Reviews 2002, Issue 2.

318 Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 2002;57(3):226-30.

319 Ehrlich R, Jordaan E, Du Toit D, Potter P, Volmink J, Zwarenstein M, et al. Household smoking and bronchial hyperresponsiveness in children with asthma. J Asthma 2001;38(3):239-51.

320 Gallefoss F, Bakke PS. Does smoking affect the outcome of patient education and self-management in asthmatics? Patient Educ Couns 2003;49(1):91-7.

321 Mannino DM, Homa DM, Redd SC. Involuntary smoking and asthma severity in children: data from the Third National Health and Nutrition Examination Survey. Chest 2002;122(2):409-15.

322 Murray AB, Morrison BJ. The decrease in severity of asthma in children of parents who smoke since the parents have been exposing them to less cigarette smoke. J Allergy Clin Immunol 1993;91(1 Pt 1):102-10.

323 Wilson SR, Yamada EG, Sudhakar R, Roberto L, Mannino D, Mejia C, et al. A controlled trial of an environmental tobacco smoke reduction intervention in low-income children with asthma. Chest 2001;120(5):1709-22.

324 Tonnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin A, et al. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res 2005;7(1):139-48.

325 Wakefield M, Banham D, McCaul K, Martin J, Ruffin R, Badcock N, et al. Effect of feedback regarding urinary cotinine and brief tailored advice on home smoking restrictions among low-income parents of children with asthma: a controlled trial. Prev Med 2002;34(1):58-65.

326 Irvine L, Crombie IK, Clark RA, Slane PW, Feyerabend C, Goodman KE, et al. Advising parents of asthmatic children on passive smoking: randomised controlled trial. BMJ 1999;318(7196):1456-9.

327 Hovell MF, Meltzer SB, Wahlgren DR, Matt GE, Hofstetter CR, Jones JA, et al. Asthma management and environmental tobacco smoke exposure reduction in Latino children: a controlled trial. Pediatrics 2002;110(5):946-56.

328 Rasmussen F, Siersted HC, Lambrechtsen J, Hansen HS, Hansen NC. Impact of airway lability, atopy, and tobacco smoking on the development of asthma-like symptoms in asymptomatic teenagers. Chest 2000;117(5):1330-5.

329 Devalia JL, Rusznak C, Herdman MJ, Trigg CJ, Tarraf H, Davies RJ. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. Lancet 1994;344(8938):1668-71.

330 Molfino NA, Wright SC, Katz I, Tarlo S, Silverman F, McClean PA, et al. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. Lancet 1991;338(8761):199-203.

331 Department of Health, Committee on the Medical Effects of Air Pollutants. Asthma and outdoor air pollution. London: HMSO; 1995.

332 Lin M, Chen Y, Burnett RT, Villeneuve PJ, Krewski D. Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: a bi-directional case-crossover analysis. J Epidemiol Community Health 2003;57(1):50-5.

333 Norbäck D, Björnsson E, Janson C, Widstrom J, Boman G. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. Occup Environ Med 1995;52(6):388-95.

334 Tunnicliffe WS, Burge PS, Ayres JG. Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. Lancet 1994;344(8939-40):1733-6.

335 Burney P. A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. Chest 1987;91(6 Suppl):143S-8S.

336 Burney PG. The causes of asthma: does salt potentiate bronchial activity? Discussion paper. J R Soc Med 1987;80(6):364-7.

337 Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusion capacity in exercise-induced asthma. Med Sci Sports Exerc 2005;37(6):904-14.

338 Ardern KD, Ram FS. Dietary salt reduction or exclusion for allergic asthma. Cochrane Database of Systematic Reviews 2001, Issue 4.

339 Britton J, Pavord I, Richards K, Wisniewski A, Knox A, Lewis S, et al. Dietary magnesium, lung function, wheezing, and airway hyperreactivity in a random adult population sample. Lancet 1994;344(8919):357-62.

340 Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database of Systematic Reviews 2005, Issue 2.

341 Bede O, Suranyi A, Pinter K, Szlavik M, Gyurkovits K. Urinary magnesium excretion in asthmatic children receiving magnesium supplementation: a randomized, placebo-controlled, double-blind study. Magnes Res 2003;16(4):262-70.

342 Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. Clin Exp Allergy 2003;33(10):1355-9.

343 Hill J. Magnesium and airway reactivity. Clin Sci (Lon) 1998;95(2):111-2.

344 Prescott SL, Calder PC. N-3 polyunsaturated fatty acids and allergic disease. Curr Opin Clin Nutr Metab Care 2004;7(2):123-9.

345 Stephensen CB. Fish oil and inflammatory disease: is asthma the next target for n-3 fatty acid supplements? Nutr Rev 2004;62(12):486-9.

346 Thien FCK, De Luca S, Woods RK, Abramson MJ. Dietary marine fatty acids (fish oil) for asthma in adults and children. Cochrane Database of Systematic Reviews 2002, Issue 2.

347 Allam MF, Lucena RA. Selenium supplementation for asthma. Cochrane Database of Systematic Reviews 2004, Issue 2.

348 Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. Thorax 2004;59(8):652-6.

349 Ram FS, Rowe BH, Kaur B. Vitamin C supplementation for asthma. Cochrane Database of Systematic Reviews 2004, Issue 3.

350 Butland BK, Strachan DP, Anderson HR. Fresh fruit intake and asthma symptoms in young British adults: confounding or effect modification by smoking? Eur Respir J 1999;13(4):744-50.

351 Carey IM, Strachan DP, Cook DG. Effects of changes in fresh fruit consumption on ventilatory function in healthy British adults. Am J Respir Crit Care Med 1998;158(3):728-33.

352 Cook DG, Carey IM, Whincup PH, Papacosta O, Chirico S, Bruckdorfer KR, et al. Effect of fresh fruit consumption on lung function and wheeze in children. Thorax 1997;52(7):628-33.

353 Ellwood P, Asher MI, Bjorksten B, Burr M, Pearce N, Robertson CF. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. Eur Respir J 2001;17(3):436-43.

354 Gilliland FD, Berhane KT, Li YF, Gauderman WJ, McConnell R, Peters J. Children's lung function and antioxidant vitamin, fruit, juice, and vegetable intake. Am J Epidemiol 2003;158(6):576-84.

355 Heinrich J, Holscher B, Bolte G, Winkler G. Allergic sensitization and diet: ecological analysis in selected European cities. Eur Respir J 2001;17(3):395-402.

356 Strachan DP, Cox BD, Erzinclioglu SW, Walters DE, Whichelow MJ. Ventilatory function and winter fresh fruit consumption in a random sample of British adults. Thorax 1991;46(9):624-9.

357 Adeniyi FB, Young T. Weight loss interventions for chronic asthma. Cochrane Database of Systematic Reviews 2012, Issue 7.

358 Scottish Intercollegiate Guidelines Network (SIGN). Management of obesity. Edinburgh: SIGN; 2010. (SIGN publication no. 115). [cited 26 Jul 2016]. Available from url: http://www.sign.ac.uk/guidelines/fulltext/115/index.html

359 Jensen ME, Gibson PG, Collins CE, Hilton JM, Wood LG. Diet-induced weight loss in obese children with asthma: a randomized controlled trial. Clin Exp Allergy 2013;43(7):775-84.

360 Ma J, Strub P, Xiao L, Lavori PW, Camargo CA, Wilson SR, et al. Behavioral weight loss and physical activity intervention in obese adults with asthma. A randomized trial. Ann Am Thorac Soc 2015;12(1):1-11.

361 Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. Clin Exp Allergy 2013;43(1):36-49.

362 Bjorksten B, Sepp E, Julge K, Voor T, Mikelsaar M. Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol 2001;108(4):516-20.

363 Helin T, Haahtela S, Haahtela T. No effect of oral treatment with an intestinal bacterial strain, Lactobacillus rhamnosus (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. Allergy 2002;57(3):243-6.

364 Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy 2000;30(11):1604-10.

365 Wheeler JG, Shema SJ, Bogle ML, Shirrell MA, Burks AW, Pittler A, et al. Immune and clinical impact of Lactobacillus acidophilus on asthma. Ann Allergy Asthma Immunol 1997;79(3):229-33.

366 Gruber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. Pediatrics 2003;111(3):e282-8.

367 Gruber C, Meinlschmidt G, Bergmann R, Wahn U, Stark K. Is early BCG vaccination associated with less atopic disease? An epidemiological study in German preschool children with different ethnic backgrounds. Pediatr Allergy Immunol 2002;13(3):177-81.

368 Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. BMJ 1999;318(7192):1173-6.

369 Nilsson L, Kjellman NI, Bjorksten B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. Arch Pediatr Adolesc Med 1998;152(8):734-8.

370 Choi IS, Koh YI. Therapeutic effects of BCG vaccination in adult asthmatic patients: a randomized, controlled trial. Ann Allergy Asthma Immunol 2002;88(6):584-91.

371 Arikan C, Bahceciler NN, Deniz G, Akdis M, Akkoc T, Akdis CA, et al. Bacillus Calmette-Guerin-induced interleukin-12 did not additionally improve clinical and immunologic parameters in asthmatic children treated with sublingual immunotherapy. Clin Exp Allergy 2004;34(3):398-405.

372 Tsai JJ, Peng HJ, Shen HD. Therapeutic effect of Bacillus Calmette-Guerin with allergen on human allergic asthmatic patients. J Microbiol Immunol Infect 2002;35(2):99-102.

373 Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, Wiselka MJ, Leese J, Ayres J, et al. Randomised placebo-controlled crossover trial on effect of inactivated influenza vaccine on pulmonary function in asthma. Lancet 1998;351(9099):326-31.

374 Bueving HJ, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus AD, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. Am J Respir Crit Care Med 2004;169(4):488-93.

375 Bueving HJ, van der Wouden JC, Raat H, Bernsen RM, de Jongste JC, van Suijlekom-Smit LW, et al. Influenza vaccination in asthmatic children: effects on quality of life and symptoms. Eur Respir J 2004;24(6):925-31.

376 Hanania NA, Sockrider M, Castro M, Holbrook JT, Tonascia J, Wise R, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. J Allergy Clin Immunol 2004;113(4):717-24.

377 Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma. Cochrane Database of Systematic Reviews 2002, Issue 1.

378 Linde K, Jobst K, Panton J. Acupuncture for chronic asthma. Cochrane Database of Systematic Reviews 2000, Issue 2.

379 Martin J, Donaldson AN, Villarroel R, Parmar MK, Ernst E, Higginson IJ. Efficacy of acupuncture in asthma: systematic review and meta-analysis of published data from 11 randomised controlled trials. Eur Respir J 2002;20(4):846-52.

380 Gruber W, Eber E, Malle-Scheid D, Pfleger A, Weinhandl E, Dorfer L, et al. Laser acupuncture in children and adolescents with exercise induced asthma. Thorax. 2002;57(3):222-5.

381 Malmstrom M, Ahlner J, Carlsson C, Schmekel B. No effect of chinese acupuncture on isocapnic hyperventilation with cold air in asthmatics, measured with impulse oscillometry. Acupunct Med 2002;20(2-3):66-73.

382 Blackhall K, Appleton S, Cates CJ. Ionisers for chronic asthma. Cochrane Database of Systematic Reviews 2003, Issue 3.

383 Warner JA, Marchant JL, Warner JO. A double blind trial of ionisers in children with asthma sensitive to the house dust mite. Thorax 1993;48(4):330-3.

384 O'Connor E, Patnode CD, Burda BU, Buckley DI, Whitlock EP. Breathing exercises and/or retraining techniques in the treatment of asthma: comparative effectiveness. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012. (Comparative effectiveness review no. 71). [cited 26 Jul 2016]. Available from url: https://effectivehealthcare.ahrq.gov/ehc/products/222/1251/CER71_BreathingExercises_FinalReport_20120905.pdf

385 Huntley A, Ernst E. Herbal medicines for asthma: a systematic review. Thorax 2000;55(11):925-9.

386 Chan CK, Kuo ML, Shen JJ, See LC, Chang HH, Huang JL. Ding Chuan Tang, a Chinese herb decoction, could improve airway hyper-responsiveness in stabilized asthmatic children: a randomized, double-blind clinical trial. Pediatr Allergy Immunol 2006;17(5):316-22.

387 Hsu CH, Lu CM, Chang TT. Efficacy and safety of modified Mai-Men-Dong-Tang for treatment of allergic asthma. Pediatr Allergy Immunol 2005;16(1):76-81.

388 Linde K, Jobst KA. Homeopathy for chronic asthma. Cochrane Database of Systematic Reviews 2000, Issue 2.

389 White A, Slade P, Hunt C, Hart A, Ernst E. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial. Thorax 2003;58(4):317-21.

390 Huntley A, White AR, Ernst E. Relaxation therapies for asthma: a systematic review. Thorax 2002;57(2):127-31.

391 Hondras MA, Linde K, Jones AP. Manual therapy for asthma. Cochrane Database of Systematic Reviews 2001, Issue 1.

392 Holloway E, Ram FS. Breathing exercises for asthma. Cochrane Database of Systematic Reviews 2004, Issue 1.

393 Panton J, Barley EA. Family therapy for asthma in children. Cochrane Database of Systematic Reviews 2000, Issue 2.

394 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.2: ipratopium bromide. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.2.html

395 Dennis SM, Sharp SJ, Vickers MR, Frost CD, Crompton GK, Barnes PJ, et al. Regular inhaled salbutamol and asthma control: the TRUST randomised trial. Therapy Working Group of the National Asthma Task Force and the MRC General Practice Research Framework. Lancet 2000;355(9216):1675-9.

396 Walters EH, Walters JAE, Gibson PG, Jones P. Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Cochrane Database of Systematic Reviews 2003, Issue 1.

397 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.4a: inhaled corticosteroid vs theophylline. [cited 10 July 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.4a.html

398 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.4c: inhaled corticosteroid vs leukotriene receptor antagonists. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.4c.html

399 Adams N, Bestall J, Jones P.W. Inhaled fluticasone propionate for chronic asthma. Cochrane Database of Systematic Reviews 2000, Issue 2.

400 Adams NP, Bestall JC, Malouf R, Lasserson TJ, Jones P. Beclomethasone versus placebo for chronic asthma. Cochrane Database of Systematic Reviews 2005, Issue 1.

401 Calpin C, Macarthur C, Stephens D, Feldman W, Parkin PC. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. J Allergy Clin Immunol 1997;100(4):452-7.

402 Carlsen KC, Stick S, Kamin W, Cirule I, Hughes S, Wixon C. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. Respir Med 2005;99(11):1393-402.

403 Teper AM, Colom AJ, Kofman CD, Maffey AF, Vidaurreta SM, Bergada I. Effects of inhaled fluticasone propionate in children less than 2 years old with recurrent wheezing. Pediatr Pulmonol 2004;37(2):111-5.

404 Teper AM, Kofman CD, Szulman GA, Vidaurreta SM, Maffey AF. Fluticasone improves pulmonary function in children under 2 years old with risk factors for asthma. Am J Respir Crit Care Med 2005;171(6):587-90.

405 Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. Pediatrics 2004;113(2):e87-94.

406 Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, et al. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy Clin Immunol 2008;121(5):1167-74.

407 Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. Pediatrics 2009;123(3):e519-25.

408 Kerwin EM, Pearlman DS, de Guia T, Carlsson LG, Gillen M, Uryniak T, et al. Evaluation of efficacy and safety of budesonide delivered via two dry powder inhalers. Curr Med Res Opin 2008;24(5):1497-510.

409 Knuffman JE, Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Martinez FD, et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. J Allergy Clin Immunol 2009;123(2):411-6.

410 Kooi EM, Schokker S, Marike Boezen H, de Vries TW, Vaessen-Verberne AA, van der Molen T, et al. Fluticasone or montelukast for preschool children with asthma-like symptoms: randomized controlled trial. Pulm Pharmacol Ther 2008;21(5):798-804.

411 Papi A, Nicolini G, Baraldi E, Boner AL, Cutrera R, Rossi GA, et al. Regular vs prn nebulized treatment in wheeze preschool children. Allergy 2009;64(10):1463-71.

412 Rachelefsky G. Inhaled corticosteroids and asthma control in children: assessing impairment and risk. Pediatrics 2009;123(1):353-66.

413 O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. Am J Respir Crit Care Med 2001;164(8 Pt 1):1392-7.

414 Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361(9363):1071-6.

415 Berger WE. Budesonide inhalation suspension for the treatment of asthma in infants and children. Drugs 2005;65(14):1973-89.

416 Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol 2007;119(1):64-72.

417 Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol 2007;120(5):1043-50.

418 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.7: high dose step down. [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.7.html

419 Hodges IG, Netherway TA. Once-daily fluticasone propionate is as effective as twice-daily treatment in stable, mild-to-moderate childhood asthma. Clin Drug Investig 2005;25(1):13-22.

420 Chen YZ, Busse WW, Pedersen S, Tan W, Lamm CJ, O'Byrne PM. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. Pediatr Allergy Immunol 2006;17(Suppl 17):7-13.

421 Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF, Mauger DT, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 2011;377(9766):650-7.

422 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.25: budesonide vs beclometasone. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.25.html

423 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.15: mometasone furoate dry powder inhalation. [cited 10 July 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.15.html

424 Woodcock A, Bateman ED, Busse WW, Lotvall J, Snowise NG, Forth R, et al. Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial. Respir Res 2011;12:132.

425 Woodcock A, Bleecker ER, Busse WW, Lotvall J, Snowise NG, Frith L, et al. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. Respir Res 2011;12:160.

426 London Respiratory Team. Inhaled corticosteroid safety information for adults. London: NHS London; c2012. [cited 29 Jul 2016]. Available from url: https://www.networks.nhs.uk/nhs-networks/london-respiratory-network/key-documents/responsible-respiratory-prescribing/LRT%20Inhaled%20steroid%20safety%20card.pdf

427 Fay JK, Jones A, Ram FS. Primary care based clinics for asthma. Cochrane Database of Systematic Reviews 2002, Issue 1.

428 Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics 2000;106(1):E8.

429 Dunlop KA, Carson DJ, Steen HJ, McGovern V, McNaboe J, Shields MD. Monitoring growth in asthmatic children treated with high dose inhaled glucocorticoids does not predict adrenal suppression. Arch Dis Child 2004;89(8):713-6.

430 Covar RA, Spahn JD, Martin RJ, Silkoff PE, Sundstrom DA, Murphy J, et al. Safety and application of induced sputum analysis in childhood asthma. J Allergy Clin Immunol 2004;114(3):575-82.

431 Bernstein DI, Allen DB. Evaluation of tests of hypothalamic-pituitary-adrenal axis function used to measure effects of inhaled corticosteroids. Ann Allergy Asthma Immunol 2007;98(2):118-27.

432 Kelly A, Tang R, Becker S, Stanley CA. Poor specificity of low growth hormone and cortisol levels during fasting hypoglycemia for the diagnoses of growth hormone deficiency and adrenal insufficiency. Pediatrics 2008;122(3):e522-8.

433 Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 2005;60(4):282-7.

434 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.4d: leukotriene receptor antagonists with short-acting beta-agonists. [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.4d.html

435 Ducharme FM. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systematic review of current evidence. BMJ 2003;326(7390):621.

436 Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001;108(3):E48.

437 Valovirta E, Boza ML, Robertson CF, Verbruggen N, Smugar SS, Nelsen LM, et al. Intermittent or daily montelukast versus placebo for episodic asthma in children. Ann Allergy Asthma Immunol 2011;106(6):518-26.

438 Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Respir J 1993;6(1):35-41.

439 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.24a: other preventer therapies - chromones in children aged 5-12. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/index.html

440 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.4j: do chromones works as first line preventor in children >5 years? [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.4j.html

441 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.24b: other preventer therapies - chromones in children aged <5. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.24b.html

442 Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. Eur Respir J 1997;10(10):2216-24.

443 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.11b: add-on drugs for inhaled steroids - long acting or oral B2 agonists. [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.11b.html

444 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.11d: add-on drugs for inhaled steroids - theophylline, beclometasone diproponate, budesonide. [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.11d.html

445 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.11c: add-on drugs for inhaled steroids - anticholinergics. [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.11c.html

446 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.11a: add on drugs for inhaled steroids - chromones. [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.11a.html

447 Becker AB, Simons FE. Formoterol, a new long-acting selective beta 2-adrenergic receptor agonist: double-blind comparison with salbutamol and placebo in children with asthma. J Allergy Clin Immunol 1989;84(6 Pt 1):891-5.

448 Kips JC, Pauwels RA. Long-acting inhaled beta(2)-agonist therapy in asthma. Am J Respir Crit Care Med 2001;164(6):923-32.

449 de Blic J, Ogorodova L, Klink R, Sidorenko I, Valiulis A, Hofman J, et al. Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children. Pediatr Allergy Immunol 2009;20(8):763-71.

450 Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Strater C, Steinkamp G, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatr Pulmonol 2009;44(11):1132-42.

451 Morice AH, Peterson S, Beckman O, Kukova Z. Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: a superiority and therapeutic equivalence study. Pulm Pharmacol Ther 2008;21(1):152-9.

452 Pearlman D, Qaqundah P, Matz J, Yancey SW, Stempel DA, Ortega HG. Fluticasone propionate/salmeterol and exercise-induced asthma in children with persistent asthma. Pediatr Pulmonol 2009;44(5):429-35.

453 Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database of Systematic Reviews 2014, Issue 1.

454 Medicines and Healthcare products Regulatory Agency. Salmeterol (Severant) and formoterol (Oxis) in asthma management. London: MHRA; 2003. [cited 11 Jul 2014]. Available from url: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007449

455 Medicines and Healthcare products Regulatory Agency. Long-acting β2-agonists: reminder for use in children and adults. Drug Safety Update 2010;4(2):H2.

456 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.22: combined therapy of inhaled steroids and long acting B2 agonists. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.22.html

457 Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;61(5):725-36.

458 O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. Am J Respir Crit Care Med 2005;171(2):129-36.

459 Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368(9537):744-53.

460 Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. Curr Med Res Opin 2004;20(9):1403-18.

461 Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? Eur Respir J 2005;26(5):819-28.

462 Kew KM, Karner C, Mindus SM, Ferrara G. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2013, Issue 12.

463 Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2013, Issue 4.

464 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.8c: children with poor asthma control on ICS - is addition of leukotriene receptor antagonists helpful? [cited 11 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.8c.html

465 Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax 2008;63(5):453-62.

466 Cao Y, Wang J, Bunjhoo H, Xie M, Xu Y, Fang H. Comparison of leukotriene receptor antagonists in addition to inhaled corticosteroid and inhaled corticosteroid alone in the treatment of adolescents and adults with bronchial asthma: a meta-analysis. Asian Pac J Allergy Immunol 2012;30(2):130-8.

467 Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database of Systematic Reviews 2016, Issue 1.

468 Kew KM, Evans DJW, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma. 2015. (Cochrane Database of Systematic Reviews 2015, Issue 6). [cited 26 Jul 2016]. Available from url: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011438.pub2/pdf

469 Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. 2015. (Cochrane Database of Systematic Reviews 2015, Issue 8). [cited 5 Nov 2015]. Available from url: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011397.pub2/pdf

470 Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. J Allergy Clin Immunol 2011;128(2):315-22.

471 Evans DJW, Kew KM, Anderson DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma. 2015. (Cochrane Database of Systematic Reviews 2015, Issue 7). [cited 5 Nov 2015]. Available from url: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011437.pub2/pdf

472 Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. Cochrane Database of Systematic Reviews 2004, Issue 3.

473 National Osteoporosis Society. Guidance on the prevention and management of corticosteroid induced osteoporosis. Bath: National Osteoporosis Society; 1998.

474 Bachrach LK, Sills IN. Clinical report: bone densitometry in children and adolescents. Pediatrics 2011;127(1):189-94.

475 Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 2005;60(3):302-8.

476 Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy 2004;34(4):632-8.

477 Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol 2009;124(6):1210-6.

478 Norman G, Faria R, Paton F, Llewellyn A, Fox D, Palmer S, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Health Technol Assess 2013;17(52):1-342.

479 Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database of Systematic Reviews 2014, Issue 1.

480 Rodrigo GJ, Neffen H, Castro-Rodriguez JA, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. Chest 2011;139(1):28-35.

481 Powell C, Milan SJ, Dwan K, Bax L, Walters N. Mepolizumab versus placebo for asthma. Cochrane Database of Systematic Reviews 2015, Issue 7.

482 Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371(13):1189-97.

483 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.13a: immunosuppresive agents. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.13a.html

484 O'Driscoll BR, Ruffles SP, Ayres JG, Cochrane GM. Long term treatment of severe asthma with subcutaneous terbutaline. Br J Dis Chest 1988;82(4):360-7.

485 Payne DN, Balfour-Lynn IM, Biggart EA, Bush A, Rosenthal M. Subcutaneous terbutaline in children with chronic severe asthma. Pediatr Pulmonol 2002;33(5):356-61.

486 Bremont F, Moisan V, Dutau G. Continuous subcutaneous infusion of beta 2-agonists in infantile asthma. Pediatr Pulmonol 1992;12(2):81-3.

487 Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med 2006;354(7):697-708.

488 Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. BMJ 2003;326(7399):1115.

489 Kew KM, Undela K, Kotortsi I, Ferrara G. Macrolides for chronic asthma. 2015. (Cochrane Database of Systematic Reviews 2015, Issue 9). [cited 5 Nov 2015]. Available from url: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002997.pub4/pdf

490 Nassif EG, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. N Engl J Med 1981;304(2):71-5.

491 Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews 2010, Issue 8.

492 Shaikh WA. Immunotherapy vs inhaled budesonide in bronchial asthma: an open, parallel, comparative trial. Clin Exp Allergy 1997;27(11):1279-84.

493 Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341(7):468-75.

494 Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006;61(10):1162-72.

495 Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. J Allergy Clin Immunol 2009;124(1):157-61.e1-32.

496 Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. Allergy 2009;64(11):1570-9.

497 Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med 2010;181(2):116-24.

498 Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, et al. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol 2013;132(6):1295-302.

499 Wu Q, Xing Y, Zhou X, Wang D. Meta-analysis of the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma. J Int Med Res 2011;39(1):10-22.

500 Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med 2007;356(13):1327-37.

501 Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med 2007;176(12):1185-91.

502 Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, Olivenstein R, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. BMC Pulm Med 2011;11:8.

503 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.9: exacerbation. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.9.html

504 Quon BS, FitzGerald JM, Lemière C, Shahidi N, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2010, Issue 12.

505 Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial Am J Resp Crit Care Med 2007;175(4):323-9.

506 Henriksen JM, Agertoft L, Pedersen S. Protective effect and duration of action of inhaled formoterol and salbutamol on exercise-induced asthma in children. J Allergy Clin Immunol 1992;89(6):1176-82.

507 Raissy HH, Harkins M, Kelly F, Kelly HW. Pretreatment with albuterol versus montelukast for exercise-induced bronchospasm in children. Pharmacotherapy 2008;28(3):287-94.

508 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3a: long acting B2 agonists in exercise induced asthma. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3a.html

509 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3c: theophyllines in exercise-induced asthma. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3c.html

510 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3d: leukotriene receptor antagonists in exercise induced asthma. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3d.html

511 Kelly K, Spooner CH, Rowe BH. Nedocromil sodium vs. sodium cromoglycate for preventing exercise-induced bronchoconstriction in asthmatics. Cochrane Database of Systematic Reviews 2000, Issue 4.

512 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3g: oral B2 agonists for exercise induced asthma. [cited 14th Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3g.html

513 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3f: anticholinergic therapy for exercise-induced asthma. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3f.html

514 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3b: ketotifen for exercise-induced asthma. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3b.html

515 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.3e: antihistamines for exercise-induced asthma. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.3e.html

516 Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. J Allergy Clin Immunol 2008;121(2):383-9.

517 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.10: rhinitis. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.10.html

518 Pedroletti C, Lundahl J, Alving K, Hedlin G. Effect of nasal steroid treatment on airway inflammation determined by exhaled nitric oxide in allergic schoolchildren with perennial rhinitis and asthma. Pediatr Allergy Immunol 2008;19(3):219-26.

519 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.19: allergic bronchopulmonary aspergillosis. [cited 14 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.19.html

520 Wark PA, Gibson PG, Wilson A. Azoles for allergic bronchopulmonary aspergillosis associated with asthma Cochrane Database of Systematic Reviews 2004, Issue 3.

521 Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of asthma. Evidence table 4.21: aspirin intolerant asthma. [cited 10 Jul 2014]. Available from url: http://www.sign.ac.uk/guidelines/published/support/guideline63/table4.21.html

522 Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. Thorax 2001;56(3):198-204.

523 Gibson PG, Henry R, Coughlan JJL. Gastro-oesophageal reflux treatment for asthma in adults and children. Cochrane Database of Systematic Reviews 2003, Issue 1.

524 Sopo SM, Radzik D, Calvani M. Does treatment with proton pump inhibitors for gastroesophageal reflux disease (GERD) improve asthma symptoms in children with asthma and GERD? A systematic review. J Investig Allergol Clin Immunol 2009;19(1):1-5.

525 Chan WW, Chiou E, Obstein KL, Tignor AS, Whitlock TL. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. Arch Intern Med 2011;171(7):620-9.

526 Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess 2001;5(26):1-149.

527 Cates CJ, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database of Systematic Reviews 2000, Issue 2.

528 Leversha AM, Campanella SG, Aickin RP, Asher MI. Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. J Pediatr 2000;136(4):497-502.

529 Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C. Efficacy of bronchodilators administered by nebulizers versus spacer devices in infants with acute wheezing. Pediatr Pulmonol 1998;26(5):344-8.

530 Delgado A, Chou KJ, Silver EJ, Crain EF. Nebulizers vs metered-dose inhalers with spacers for bronchodilator therapy to treat wheezing in children aged 2 to 24 months in a pediatric emergency department. Arch Pediatr Adolesc Med 2003;157(1):76-80.

531 Ram FS, Wright J, Brocklebank D, White JE. Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering beta(2) agonists bronchodilators in asthma. BMJ 2001;323(7318):901-5.

532 Broeders ME, Molema J, Hop WC, Vermue NA, Folgering HT. Does the inhalation device affect the bronchodilatory dose response curve of salbutamol in asthma and chronic obstructive pulmonary disease patients? Eur J Clin Pharmacol 2003;59(5-6):449-55.

533 Hughes DA, Woodcock A, Walley T. Review of therapeutically equivalent alternatives to short acting beta(2) adrenoceptor agonists delivered via chlorofluorocarbon-containing inhalers. Thorax 1999;54(12):1087-92.

534 Farmer IS, Middle M, Savic J, Perri VL, Herdman MJ. Therapeutic equivalence of inhaled beclomethasone dipropionate with CFC and non-CFC (HFA 134a) propellants both delivered via the Easibreathe inhaler for the treatment of paediatric asthma. Respir Med 2000;94(1):57-63.

535 Cates CJ, Adams N, Bestall J. Holding chambers versus nebulisers for inhaled steroids in chronic asthma. Cochrane Database of Systematic Reviews 2001, Issue 2.

536 Alotaibi S, Hassan WM, Alhashimi H. Concurrent use of metered dose inhalers without spacer and dry powder inhalers by asthmatic children adversely affect proper inhalation technique. Internet J Pediatr Neonatol 2011;13(1):pii.29.

537 van der Palen J, Klein JJ, van Herwaarden CL, Zielhuis GA, Seydel ER. Multiple inhalers confuse asthma patients. Eur Respir J 1999;14(5):1034-7.

538 Accuracy of death certificates in bronchial asthma. Accuracy of certification procedures during the confidential inquiry by the British Thoracic Association. A subcommittee of the BTA Research Committee. Thorax 1984;39(7):505-9.

539 Bucknall CE, Slack R, Godley CC, Mackay TW, Wright SC. Scottish Confidential Inquiry into Asthma Deaths (SCIAD), 1994-6. Thorax 1999;54(11):978-84.

540 Burr ML, Davies BH, Hoare A, Jones A, Williamson IJ, Holgate SK, et al. A confidential inquiry into asthma deaths in Wales. Thorax 1999;54(11):985-9.

541 Mohan G, Harrison BD, Badminton RM, Mildenhall S, Wareham NJ. A confidential enquiry into deaths caused by asthma in an English health region: implications for general practice. Br J Gen Pract 1996;46(410):529-32.

542 Wareham NJ, Harrison BD, Jenkins PF, Nicholls J, Stableforth DE. A district confidential enquiry into deaths due to asthma. Thorax 1993;48(11):1117-20.

543 Royal College of Physicians. Why asthma still kills: the national review of asthma deaths (NRAD). Confidential enquiry report 2014. [cited 26 Jul 2016]. Available from url: https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills

544 Harrison B, Slack R, Berrill WT, Burr ML, Stableforth DE, Wright SC. Results of a national confidential enquiry into asthma deaths. Asthma J 2000;5(4):180-6.

545 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 1992;326(8):501-6.

546 Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. Eur Respir J 1994;7(9):1602-9.

547 Jalaludin BB, Smith MA, Chey T, Orr NJ, Smith WT, Leeder SR. Risk factors for asthma deaths: a population-based, case-control study. Aust N Z J Public Health 1999;23(6):595-600.

548 Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. Thorax 1986;41(11):833-9.

549 Campbell MJ, Cogman GR, Holgate ST, Johnston SL. Age specific trends in asthma mortality in England and Wales, 1983-95: results of an observational study. BMJ 1997;314(7092):1439-41.

550 Richards GN, Kolbe J, Fenwick J, Rea HH. Demographic characteristics of patients with severe life threatening asthma: comparison with asthma deaths. Thorax 1993;48(11):1105-9.

551 Innes NJ, Reid A, Halstead J, Watkin SW, Harrison BD. Psychosocial risk factors in near-fatal asthma and in asthma deaths. J R Coll Physicians Lond 1998;32(5):430-4.

552 Khot A, Evans N, Lenney W. Seasonal trends in childhood asthma in south east England. Br Med J (Clin Res Ed) 1983;287(6401):1257-8.

553 Barr RG, Woodruff PG, Clark S, Camargo CA Jr. Sudden-onset asthma exacerbations: clinical features, response to therapy, and 2-week follow-up. Multicenter Airway Research Collaboration (MARC) investigators. Eur Respir J 2000;15(2):266-73.

554 Kolbe J, Fergusson W, Garrett J. Rapid onset asthma: a severe but uncommon manifestation. Thorax 1998;53(4):241-7.

555 Kolbe J, Fergusson W, Vamos M, Garrett J. Case-control study of severe life threatening asthma (SLTA) in adults: demographics, health care, and management of the acute attack. Thorax 2000;55(12):1007-15.

556 Rodrigo GJ, Rodrigo C. Rapid-onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. Chest 2000;118(6):1547-52.

557 Turner MO, Noertjojo K, Vedal S, Bai T, Crump S, Fitzgerald JM. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 1998;157(6 Pt 1):1804-9.

558 Woodruff PG, Emond SD, Singh AK, Camargo CA Jr. Sudden-onset severe acute asthma: clinical features and response to therapy. Acad Emerg Med 1998;5(7):695-701.

559 British Thoracic Society, National Asthma Campaign, Royal College of Physicians of London in association with the General Practitioner in Asthma Group, The British Association of Accident and Emergency Medicine, The British Paediatric Respiratory Society, Royal College of Paediatrics and Child Health. The British guidelines on asthma management 1995 review and position statement. Thorax 1997;52(Suppl 1):S1-S21.

560 Scottish Intercollegiate Guidelines Network (SIGN). Emergency management of acute asthma. Edinburgh: SIGN; 1999. (SIGN publication no. 38).

561 International consensus report on the diagnosis and treatment of asthma. National Heart, Lung, and Blood Institute, National Institutes of Health. Bethesda, Maryland 20892. Publication no. 92-3091, March 1992. Eur Respir J 1992;5(5):601-41.

562 Neville E, Gribbin H, Harrison BD. Acute severe asthma. Respir Med 1991;85(6):463-74.

563 Brenner B, Kohn MS. The acute asthmatic patient in the ED: to admit or discharge. Am J Emerg Med 1998;16(1):69-75.

564 Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian asthma consensus report, 1999. Canadian asthma consensus group. CMAJ 1999;161(11 Suppl):S1-61.

565 Nunn AJ, Gregg I. New regression equations for predicting peak expiratory flow in adults. BMJ 1989;298(6680):1068-70.

566 Abramson MJ, Bailey MJ, Couper FJ, Driver JS, Drummer OH, Forbes AB, et al. Are asthma medications and management related to deaths from asthma? Am J Respir Crit Care Med 2001;163(1):12-8.

567 Robinson SM, Harrison BD, Lambert MA. Effect of a preprinted form on the management of acute asthma in an accident and emergency department. J Accid Emerg Med 1996;13(2):93-7.

568 Arnold DH, Gebretsadik T, Minton PA, Higgins S, Hartert TV. Clinical measures associated with FEV1 in persons with asthma requiring hospital admission. Am J Emerg Med 2007;25(4):425-9.

569 Shim CS, Williams MH Jr. Evaluation of the severity of asthma: patients versus physicians. Am J Med 1980;68(1):11-3.

570 Emerman CL, Cydulka RK. Effect of pulmonary function testing on the management of acute asthma. Arch Intern Med 1995;155(20):2225-8.

571 O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63(Suppl 6):vi1-68.

572 Carruthers DM, Harrison BD. Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma? Thorax 1995;50(2):186-8.

573 Pearson MG, Spence DP, Ryland I, Harrison BD. Value of pulsus paradoxus in assessing acute severe asthma. British Thoracic Society Standards of Care Committee. BMJ 1993;307(6905):659.

574 McFadden ER Jr, Lyons HA. Arterial-blood gas tension in asthma. N Engl J Med 1968;278(19):1027-32.

575 Rebuck AS, Read J. Assessment and management of severe asthma. Am J Med 1971;51(6):788-98.

576 Jenkins PF, Benfield GF, Smith AP. Predicting recovery from acute severe asthma. Thorax 1981;36(11):835-41.

577 Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. N Engl J Med 1991;324(5):285-8.

578 Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax 2011;66(11):937-41.

579 McFadden ER Jr. Critical appraisal of the therapy of asthma: an idea whose time has come. Am Rev Respir Dis 1986;133(5):723-4.

580 Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122(3):365-71.

581 Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132(2):283-6.

582 Rodrigo GJ, Nannini LJ. Comparison between nebulized adrenaline and beta2 agonists for the treatment of acute asthma. A meta-analysis of randomized trials. Am J Emerg Med 2006;24(2):217-22.

583 Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database of Systematic Reviews 2006, Issue 2.

584 Travers AA, Jones AP, Kelly KD, Camargo CA, Barker SJ, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2001, Issue 1.

585 Lewis L, Ferguson I, House SL, Aubuchon K, Schneider J, Johnson K, et al. Albuterol administration is commonly associated with increases in serum lactate in patients with asthma treated for acute exacerbation of asthma. Chest 2014(1):53-9.

586 Gleeson JG, Green S, Price JF. Air or oxygen as driving gas for nebulised salbutamol. Arch Dis Child 1988;63(8):900-4.

587 Douglas JG, Rafferty P, Fergusson RJ, Prescott RJ, Crompton GK, Grant IW. Nebulised salbutamol without oxygen in severe acute asthma: how effective and how safe? Thorax 1985;40(3):180-3.

588 Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. Ann Emerg Med 1993;22(12):1847-53.

589 Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. Ann Emerg Med 1993;22(12):1842-6.

590 Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous vs intermittent albuterol, at high and low doses, in the treatment of severe acute asthma in adults. Chest 1996;110(1):42-7.

591 Camargo CA Jr, Spooner C, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. Cochrane Database of Systematic Reviews 2003, Issue 4.

592 Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews 2001, Issue 1.

593 Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database of Systematic Reviews 2007, Issue 3.

594 Manser R, Reid D, Abramson MJ. Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database of Systematic Reviews 2001, Issue 1.

595 Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. Chest 2004;126(2):362-8.

596 Hatton MQ, Vathenen AS, Allen MJ, Davies S, Cooke NJ. A comparison of 'abruptly stopping' with 'tailing off' oral corticosteroids in acute asthma. Respir Med 1995;89(2):101-4.

597 O'Driscoll BR, Kalra S, Wilson M, Pickering CA, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. Lancet 1993;341(8841):324-7.

598 Edmonds ML, Camargo CA, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database of Systematic Reviews 2003, Issue 3.

599 Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation. Chest 2006;130(5):1301-11.

600 Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998;114(2):365-72.

601 Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999;107(4):363-70.

602 Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. Ann Emerg Med 1999;34(1):8-18.

603 Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J 2007;24(12):823-30.

604 Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database of Systematic Reviews 2012, Issue 12.

605 Goodacre S, Cohen J, Bradburn M, Gray A, Benger J, Coats T, et al. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial. Lancet Respir Med 2013;1(4):293-300.

606 Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, et al. Aerosolized magnesium sulfate for acute asthma: a systematic review. Chest 2005;128(1):337-44.

607 Rowe BH, Bretzlaff J, Bourdon C, Bota G, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2000, Issue 1.

608 Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2014, Issue 5.

609 Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database of Systematic Reviews 2000, Issue 4.

610 Watts K, Chavasse RJPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. Cochrane Database of Systematic Reviews 2012, Issue 5.

611 Graham VA, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. Lancet 1982;1(8269):418-20.

612 Long W, Li LJ, Huang GZ, Zhang XM, Zhang YC, Tang JG, et al. Procalcitonin guidance for reduction of antibiotic use in patients hospitalized with severe acute exacerbations of asthma: a randomized controlled study with 12-month follow-up. Crit Care 2014;18(5):471.

613 Tang J, Long W, Yan L, Zhang Y, Xie J, Lu G, et al. Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: a randomized controlled trial. BMC Infect Dis 2013;13:596.

614 Kass JE, Terregino CA. The effect of heliox in acute severe asthma: a randomized controlled trial. Chest 1999;116(2):296-300.

615 Henderson SO, Acharya P, Kilaghbian T, Perez J, Korn CS, Chan LS. Use of heliox-driven nebulizer therapy in the treatment of acute asthma. Ann Emerg Med 1999;33(2):141-6.

616 Rodrigo GJ, Pollack CV, Rodrigo C, Rowe BH. Heliox for non-intubated acute asthma patients. Cochrane Database of Systematic Reviews 2006, Issue 4.

617 Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of helium-oxygen mixtures in the treatment of acute asthma: a systematic review. Chest 2003;123(3):891-6.

618 Yen ZS, Chen SC. Best evidence topic report. Nebulised furosemide in acute adult asthma. Emerg Med J 2005;22(9):654-5.

619 Goyal S, Agrawal A. Ketamine in status asthmaticus: a review. Indian J Crit Care Med 2013;17(3):154-61.

620 Silverman RA, Foley F, Dalipi R, Kline M, Lesser M. The use of rhDNAse in severely ill, non-intubated adult asthmatics refractory to bronchodilators: a pilot study. Respir Med 2012;106(8):1096-102.

621 Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. Chest 1996;110(3):767-74.

622 Lim WJ, Mohammed Akram R, Carson KV, Mysore S, Labiszewski NA, Wedzicha JA, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database of Systematic Reviews 2012, Issue 12.

623 Galindo-Filho VC, Brandao DC, Ferreira Rde C, Menezes MJ, Almeida-Filho P, Parreira VF, et al. Noninvasive ventilation coupled with nebulization during asthma crises: a randomized controlled trial. Respir Care 2013;58(2):241-9.

624 Pallin M, Hew M, Naughton MT. Is non-invasive ventilation safe in acute severe asthma? Respirology 2015;20(2):251-7.

625 Lim KL, Harrison BD. A criterion based audit of inpatient asthma care. Closing the feedback loop. J R Coll Physicians Lond 1992;26(1):71-5.

626 Goldberg R, Chan L, Haley P, Harmata-Booth J, Bass G. Critical pathway for the emergency department management of acute asthma: effect on resource utilization. Ann Emerg Med 1998;31(5):562-7.

627 Udwadia ZF, Harrison BD. An attempt to determine the optimal duration of hospital stay following a severe attack of asthma. J R Coll Physicians Lond 1990;24(2):112-4.

628 Pearson MG, Ryland I, Harrison BD. National audit of acute severe asthma in adults admitted to hospital. Standards of Care Committee, British Thoracic Society. Qual Health Care 1995;4(1):24-30.

629 Emerman CL, Woodruff PG, Cydulka RK, Gibbs MA, Pollack CV Jr, Camargo CA Jr. Prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. MARC investigators. Multicenter Asthma Research Collaboration. Chest 1999;115(4):919-27.

630 Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. Chest 1997;112(6):1534-8.

631 Nathan JA, Pearce L, Field C, Dotesio-Eyres N, Sharples LD, Cafferty F, et al. A randomized controlled trial of follow-up of patients discharged from the hospital following acute asthma: best performed by specialist nurse or doctor? Chest 2006;130(1):51-7.

632 Baren JM, Boudreaux ED, Brenner BE, Cydulka RK, Rowe BH, Clark S, et al. Randomized controlled trial of emergency department interventions to improve primary care follow-up for patients with acute asthma. Chest 2006;129(2):257-65.

633 Davies G, Paton JY, Beaton SJ, Young D, Lenney W. Children admitted with acute wheeze/asthma during November 1998-2005: a national UK audit. Arch Dis Child 2008 93(11):952-8.

634 Connett GJ, Lenney W. Use of pulse oximetry in the hospital management of acute asthma in childhood. Pediatr Pulmonol 1993;15(6):345-9.

635 Geelhoed GC, Landau LI, Le Souef PN. Evaluation of SaO2 as a predictor of outcome in 280 children presenting with acute asthma. Ann Emerg Med 1994;23(6):1236-41.

636 Schuh S, Johnson D, Stephens D, Callahan S, Canny G. Hospitalization patterns in severe acute asthma in children. Pediatr Pulmonol 1997;23(3):184-92.

637 Wright RO, Santucci KA, Jay GD, Steele DW. Evaluation of pre- and posttreatment pulse oximetry in acute childhood asthma. Acad Emerg Med 1997;4(2):114-7.

638 Brooks LJ, Cloutier MM, Afshani E. Significance of roentgenographic abnormalities in children hospitalized for asthma. Chest 1982;82(3):315-8.

639 Gershel JC, Goldman HS, Stein RE, Shelov SP, Ziprkowski M. The usefulness of chest radiographs in first asthma attacks. N Engl J Med 1983;309(6):336-9.

640 Cunningham S, Logan C, Lockerbie L, Dunn MJ, McMurray A, Prescott RJ. Effect of an integrated care pathway on acute asthma/wheeze in children attending hospital: cluster randomized trial. J Pediatr 2008;152(3):315-20.

641 Schuh S, Parkin P, Rajan A, Canny G, Healy R, Rieder M, et al. High-versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. Pediatrics 1989;83(4):513-8.

642 Schuh S, Reider MJ, Canny G, Pender E, Forbes T, Tan YK, et al. Nebulized albuterol in acute childhood asthma: comparison of two doses. Pediatrics 1990;86(4):509-13.

643 Robertson CF, Smith F, Beck R, Levison H. Response to frequent low doses of nebulized salbutamol in acute asthma. J Pediatr 1985;106(4):672-4.

644 Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma. J Pediatr 1999;135(1):22-7.

645 Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. Acad Emerg Med 1996;3(11):1019-24.

646 Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med 1993;21(10):1479-86.

647 Plotnick LH, Ducharme FM. Combined inhaled anticholinergic agents and beta-2-agonists for initial treatment of acute asthma in children. Cochrane Database of Systematic Reviews 2000, Issue 2.

648 Altamimi S, Robertson G, Jastaniah W, Davey A, Dehghani N, Chen R, et al. Single-dose oral dexamethasone in the emergency management of children with exacerbations of mild to moderate asthma. Pediatr Emerg Care 2006;22(12):786-93.

649 Gordon S, Tompkins T, Dayan PS. Randomized trial of single-dose intramuscular dexamethasone compared with prednisolone for children with acute asthma. Pediatr Emerg Care 2007;23(8):521-7.

650 Greenberg RA, Kerby G, Roosevelt GE. A comparison of oral dexamethasone with oral prednisone in pediatric asthma exacerbations treated in the emergency department. Clin Pediatr 2008;47(8):817-23.

651 Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. N Engl J Med 2009;360(4):329-38.

652 Becker JM, Arora A, Scarfone RJ, Spector ND, Fontana-Penn ME, Gracely E, et al. Oral versus intravenous corticosteroids in children hospitalized with asthma. J Allergy Clin Immunol 1999;103(4):586-90.

653 Barnett PL, Caputo GL, Baskin M, Kuppermann N. Intravenous versus oral corticosteroids in the management of acute asthma in children. Ann Emerg Med 1997;29(2):212-7.

654 Langton Hewer S, Hobbs J, Reid F, Lenney W. Prednisolone in acute childhood asthma: clinical responses to three dosages. Respir Med 1998;92(3):541-6.

655 Edmonds ML, Brenner BE, Camargo CA, Rowe BH. Inhaled steroids in acute asthma following emergency department discharge. Cochrane Database of Systematic Reviews 2000, Issue 3.

656 McKean MC, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. Cochrane Database of Systematic Reviews 2000, Issue 1.

657 Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, et al. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. N Engl J Med 2000;343(10):689-94.

658 Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 2009;360(4):339-53.

659 Papi A, Nicolini G, Boner AL, Baraldi E, Cutrera R, Fabbri LM, et al. Short term efficacy of nebulized beclomethasone in mild-to-moderate wheezing episodes in pre-school children. Ital J Pediatr 2011;37:39.

660 Schuh S, Dick PT, Stephens D, Hartley M, Khaikin S, Rodrigues L, et al. High-dose inhaled fluticasone does not replace oral prednisolone in children with mild to moderate acute asthma. Pediatrics 2006;118(2):644-50.

661 Upham BD, Mollen CJ, Scarfone RJ, Seiden J, Chew A, Zorc JJ. Nebulized budesonide added to standard pediatric emergency department treatment of acute asthma: a randomized, double-blind trial. Acad Emerg Med 2011;18(7):665-73.

662 Volovitz B, Bilavsky E, Nussinovitch M. Effectiveness of high repeated doses of inhaled budesonide or fluticasone in controlling acute asthma exacerbations in young children. J Asthma 2008;45(7):561-7.

663 Harmanci K, Bakirtas A, Turktas I, Degim T. Oral montelukast treatment of preschool-aged children with acute asthma. Ann Allergy Asthma Immunol 2006;96(5):731-5.

664 Powell C, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I, et al. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. Lancet 2013;1(4):301-8.

665 Singhi S, Grover S, Bansal A, Chopra K. Randomised comparison of intravenous magnesium sulphate, terbutaline and aminophylline for children with acute severe asthma. Acta Paediatr 2014;103(12):1301-6.

666 Travers AH, Jones AP, Camargo CA, Milan SJ, Rowe BH. Intravenous beta2-agonists versus intravenous aminophylline for acute asthma. Cochrane Database of Systematic Reviews 2012, Issue 12.

667 Goodman DC, Littenberg B, O'Connor GT, Brooks JG. Theophylline in acute childhood asthma: a meta-analysis of its efficacy. Pediatr Pulmonol 1996;21(4):211-8.

668 Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child 1998;79(5):405-10.

669 Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. Arch Pediatr Adolesc Med 2000;154(10):979-83.

670 Jat KR, Chawla D. Ketamine for management of acute exacerbations of asthma in children. Cochrane Database of Systematic Reviews 2012, Issue 11.

671 Schutte D, Zwitserloot AM, Houmes R, de Hoog M, Draaisma JM, Lemson J. Sevoflurane therapy for life-threatening asthma in children. Br J Anaesth 2013;111(6):967-70.

672 Basnet S, Mander G, Andoh J, Klaska H, Verhulst S, Koirala J. Safety, efficacy, and tolerability of early initiation of noninvasive positive pressure ventilation in pediatric patients admitted with status asthmaticus: a pilot study. Pediatr Crit Care Med 2012;13(4):393-8.

673 Mayordomo-Colunga J, Medina A, Rey C, Concha A, Menendez S, Arcos ML, et al. Non-invasive ventilation in pediatric status asthmaticus: a prospective observational study. Pediatr Pulmonol 2011;46(10):949-55.

674 Stormon MO, Mellis CM, Van Asperen PP, Kilham HA. Outcome evaluation of early discharge of asthmatic children from hospital: a randomized control trial. J Qual Clin Pract 1999;19(3):149-54.

675 Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. Eur Respir J 1999;13(5):1198-208.

676 Prys-Picard CO, Campbell SM, Ayres JG, Miles JF, Niven RM, Consensus on Difficult Asthma Consortium UK (CODAC-UK). Defining and investigating difficult asthma: developing quality indicators. Respir Med 2006;100(7):1254-61.

677 Bratton DL, Price M, Gavin L, Glenn K, Brenner M, Gelfand EW, et al. Impact of a multidisciplinary day program on disease and healthcare costs in children and adolescents with severe asthma: a two-year follow-up study. Pediatr Pulmonol 2001;31(3):177-89.

678 Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, et al. Systematic assessment of difficult-to-treat asthma. Eur Respir J 2003;22(3):478-83.

679 Weinstein AG, McKee L, Stapleford J, Faust D. An economic evaluation of short-term inpatient rehabilitation for children with severe asthma. J Allergy Clin Immunol 1996;98(2):264-73.

680 Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. Am J Respir Crit Care Med 2009;180(9):817-22.

681 Murphy AC, Proeschal A, Brightling CE, Wardlaw AJ, Pavord I, Bradding P, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. Thorax 2012;67(8):751-3.

682 Bracken M, Fleming L, Hall P, Van Stiphout N, Bossley C, Biggart E, et al. The importance of nurse-led home visits in the assessment of children with problematic asthma. Arch Dis Child 2009;94(10):780-4.

683 Ranganathan SC, Payne DN, Jaffe A, McKenzie SA. Difficult asthma: defining the problems. Pediatr Pulmonol 2001;31(2):114-20.

684 Apter AJ, Wang X, Bogen DK, Rand CS, McElligott S, Polsky D, et al. Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial. J Allergy Clin Immunol 2011;128(3):516-23.e1-5.

685 Vamos M, Kolbe J. Psychological factors in severe chronic asthma. Aust N Z J Psychiatry 1999;33(4):538-44.

686 Vila G, Nollet-Clemencon C, de Blic J, Mouren-Simeoni MC, Scheinmann P. Asthma severity and psychopathology in a tertiary care department for children and adolescent. Eur Child Adolesc Psychiatry 1998;7(3):137-44.

687 Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. Allergy 2007;62(5):554-60.

688 Wamboldt MZ, Weintraub P, Krafchick D, Wamboldt FS. Psychiatric family history in adolescents with severe asthma. J Am Acad Child Adolesc Psychiatry 1996;35(8):1042-9.

689 Miles JF, Garden GM, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. Clin Exp Allergy 1997;27(10):1151-9.

690 ten Brinke A, Ouwerkerk ME, Bel EH, Spinhoven P. Similar psychological characteristics in mild and severe asthma. J Psychosom Res 2001;50(1):7-10.

691 Wamboldt MZ, Fritz G, Mansell A, McQuaid EL, Klein RB. Relationship of asthma severity and psychological problems in children. J Am Acad Child Adolesc Psychiatry 1998;37(9):943-50.

692 McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. J Dev Behav Pediatr 2001;22(6):430-9.

693 Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. Biol Psychiatry 2005;58(11):865-70.

694 Godding V, Kruth M, Jamart J. Joint consultation for high-risk asthmatic children and their families, with pediatrician and child psychiatrist as co-therapists: model and evaluation. Fam Process 1997;36(3):265-80.

695 Smith JR, Mildenhall S, Noble MJ, Shepstone L, Koutantji M, Mugford M, et al. The Coping with Asthma Study: a randomised controlled trial of a home based, nurse led psychoeducational intervention for adults at risk of adverse asthma outcomes. Thorax 2005;60(12):1003-11.

696 Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BD, et al. A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma. Health Technol Assess 2005;9(23):iii-iv,1-167.

697 Position statement. Environmental allergen avoidance in allergic asthma. Ad Hoc Working Group on Environmental Allergens and Asthma. J Allergy Clin Immunol 1999;103(2 Pt 1):203-5.

698 O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. BMC Pulm Med 2005;5:4.

699 Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F, et al. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. BMJ 2002;325(7361):411-4.

700 Black PN, Udy AA, Brodie SM. Sensitivity to fungal allergens is a risk factor for life-threatening asthma. Allergy 2000;55(5):501-4.

701 O'Hollaren MT, Yunginger JW, Offord KP, Somers MJ, O'Connell EJ, Ballard DJ, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324(6):359-63.

702 Chlumsky J, Striz I, Terl M, Vondracek J. Strategy aimed at reduction of sputum eosinophils decreases exacerbation rate in patients with asthma. J Int Med Res 2006;34(2):129-39.

703 Fahy JV, Boushey HA, Lazarus SC, Mauger EA, Cherniack RM, Chinchilli VM, et al. Safety and reproducibility of sputum induction in asthmatic subjects in a multicenter study. Am J Respir Crit Care Med. 2001;163(6):1470-5.

704 Grootendorst DC, van den Bos JW, Romeijn JJ, Veselic-Charvat M, Duiverman EJ, Vrijlandt EJ, et al. Induced sputum in adolescents with severe stable asthma. Safety and the relationship of cell counts and eosinophil cationic protein to clinical severity. Eur Respir J 1999;13(3):647-53.

705 Loh LC, Kanabar V, D'Amato M, Barnes NC, O'Connor BJ. Sputum induction in corticosteroid-dependant asthmatics: risks and airway cellular profile. Asian Pac J Allergy Immunol 2005;23(4):189-96.

706 Tarodo de la Fuente P, Romagnoli M, Carlsson L, Godard P, Bousquet J, Chanez P. Eosinophilic inflammation assessed by induced sputum in corticosteroid-dependent asthma. Respir Med 1999;93(3):183-9.

707 English A, Park MJ, Shafer MA, Kreipe RE, D'Angelo LJ. Health care reform and adolescents-an agenda for the lifespan: a position paper of the Society for Adolescent Medicine. J Adolesc Health 2009;45(3):310-5.

708 Royal Australasian College of Physicians. National standards for the care of children and adolescents. Sydney: RACP; 2008. [cited 02 Jul 2014]. Available from url: http://www.racp.edu.au/index.cfm?objectid=393E4ADA-CDAA-D1AF-0D543B5DC13C7B46

709 Royal College of Paediatrics and Child Health. Bridging the gaps: health care for adolescents. London: Royal College of Paediatrics and Child Health; 2003. [cited 02 Jul 2014]. Available from url: http://www.rcpsych.ac.uk/files/pdfversion/cr114.pdf

710 Royal Australasian College of Physicians Joint Adolescent Health Committee. Confidential health care for adolescents and young people. Sydney: RACP; 2010. [cited 11th April 2011]. Available from url: http://www.racp.edu.au/index.cfm?objectid=655B70C1-A0F2-D4A4-6DB6505DCA1AB937

711 Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009;64(6):476-83.

712 Siersted HC, Boldsen J, Hansen HS, Mostgaard G, Hyldebrandt N. Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study. BMJ 1998;316(7132):651-5.

713 Yeatts KB, Shy CM. Prevalence and consequences of asthma and wheezing in African-American and white adolescents. J Adolesc Health 2001;29(5):314-9.

714 Yeatts K, Davis KJ, Sotir M, Herget C, Shy C. Who gets diagnosed with asthma? Frequent wheeze among adolescents with and without a diagnosis of asthma. Pediatrics 2003;111(5 Pt 1):1046-54.

715 Yeatts K, Johnston Davis K, Peden D, Shy C. Health consequences associated with frequent wheezing in adolescents without asthma diagnosis. Eur Respir J 2003;22(5):781-6.

716 Yeatts K, Shy C, Sotir M, Music S, Herget C. Health consequences for children with undiagnosed asthma-like symptoms. Arch Pediatr Adolesc Med 2003;157(6):540-4.

717 Abramson JM, Wollan P, Kurland M, Yawn BP. Feasibility of school-based spirometry screening for asthma. J Sch Health 2003;73(4):150-3.

718 Yawn BP. Asthma screening, case identification and treatment in school-based programs. Curr Opin Pulm Med 2006;12(1):23-7.

719 Henriksen AH, Tveit KH, Holmen TL, Sue-Chu M, Bjermer L. A study of the association between exercise-induced wheeze and exercise versus methacholine-induced bronchoconstriction in adolescents. Pediatr Allergy Immunol 2002;13(3):203-8.

720 Seear M, Wensley D, West N. How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren? Arch Dis Child 2005;90(9):898-902.

721 Mallol J, Castro-Rodriguez JA. Differences in prevalence of asthma, rhinitis, and eczema between parental and self-completed questionnaires in adolescents. Pediatr Pulmonol 2006;41(5):482-7.

722 Raat H, Mangunkusumo RT, Mohangoo AD, Juniper EF, Van Der Lei J. Internet and written respiratory questionnaires yield equivalent results for adolescents. Pediatr Pulmonol 2007;42(4):357-61.

723 Juniper EF, Svensson K, Mork AC, Stahl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes 2005;3:58.

724 Burkhart PV, Svavarsdottir EK, Rayens MK, Oakley MG, Orlygsdottir B. Adolescents with asthma: predictors of quality of life. J Adv Nurs 2009;65(4):860-6.

725 Obase Y, Shimoda T, Kawano T, Saeki S, Tomari S, Izaki K, et al. Bronchial hyperresponsiveness and airway inflammation in adolescents with asymptomatic childhood asthma. Allergy 2003;58(3):213-20.

726 Rodriguez MA, Winkleby MA, Ahn D, Sundquist J, Kraemer HC. Identification of population subgroups of children and adolescents with high asthma prevalence: findings from the Third National Health and Nutrition Examination Survey. Arch Pediatr Adolesc Med 2002;156(3):269-75.

727 Duse M, Donato F, Porteri V, Pirali F, Spinoni V, Tosoni C, et al. High prevalence of atopy, but not of asthma, among children in an industrialized area in North Italy: the role of familial and environmental factors - a population-based study. Pediatr Allergy Immunol 2007;18(3):201-8.

728 Del-Rio-Navarro B, Berber A, Blandon-Vijil V, Ramirez-Aguilar M, Romieu I, Ramirez-Chanona N, et al. Identification of asthma risk factors in Mexico City in an International Study of Asthma and Allergy in Childhood survey. Allergy Asthma Proc 2006;27(4):325-33.

729 Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. Pediatr Pulmonol 2005;40(4):316-23.

730 Anand D, Stevenson CJ, West CR, Pharoah PO. Lung function and respiratory health in adolescents of very low birth weight. Arch Dis Child 2003;88(2):135-8.

731 Fagan JK, Scheff PA, Hryhorczuk D, Ramakrishnan V, Ross M, Persky V. Prevalence of asthma and other allergic diseases in an adolescent population: association with gender and race. Ann Allergy Asthma Immunol 2001;86(2):177-84.

732 Debley JS, Redding GJ, Critchlow CW. Impact of adolescence and gender on asthma hospitalization: a population-based birth cohort study. Pediatr Pulmonol 2004;38(6):443-50.

733 Nicolai T, Pereszlenyiova-Bliznakova L, Illi S, Reinhardt D, von Mutius E. Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls. Pediatr Allergy Immunol 2003;14(4):280-3.

734 Bernard A, Nickmilder M, Voisin C. Outdoor swimming pools and the risks of asthma and allergies during adolescence. Eur Respir J 2008;32(4):979-88.

735 Bernard A, Carbonnelle S, de Burbure C, Michel O, Nickmilder M. Chlorinated pool attendance, atopy, and the risk of asthma during childhood. Environ Health Perspect 2006;114(10):1567-73.

736 Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. Psychol Med 2004;34(8):1465-74.

737 Richardson LP, Lozano P, Russo J, McCauley E, Bush T, Katon W. Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. Pediatrics 2006;118(3):1042-51.

738 Hommel KA, Chaney JM, Wagner JL, McLaughlin MS. Asthma-specific quality of life in older adolescents and young adults with long-standing asthma: the role of anxiety and depression. J Clin Psychol Med Settings 2002;9(3):185-92.

739 Powell C, Brazier A. Psychological approaches to the management of respiratory symptoms in children and adolescents. Paediatr Respir Rev 2004;5(3):214-24.

740 Katon W, Russo J, Richardson L, McCauley E, Lozano P. Anxiety and depression screening for youth in a primary care population. Ambul Pediatr 2008;8(3):182-8.

741 Brenner JS, Kelly CS, Wenger AD, Brich SM, Morrow AL. Asthma and obesity in adolescents: is there an association? J Asthma 2001;38(6):509-15.

742 Mai XM, Nilsson L, Axelson O, Braback L, Sandin A, Kjellman NI, et al. High body mass index, asthma and allergy in Swedish schoolchildren participating in the International Study of Asthma and Allergies in Childhood: Phase II. Acta Paediatr 2003;92(10):1144-8.

743 Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, et al. Obesity and the risk of newly diagnosed asthma in school-age children. Am J Epidemiol 2003;158(5):406-15.

744 Debley JS, Carter ER, Redding GJ. Prevalence and impact of gastroesophageal reflux in adolescents with asthma: a population-based study. Pediatr Pulmonol 2006;41(5):475-81.

745 Thakkar K, Boatright RO, Gilger MA, El-Serag HB. Gastroesophageal reflux and asthma in children: a systematic review. Pediatrics 2010;125(4):e925-30.

746 Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, et al. Outcome in adulthood of asymptomatic airway hyperresponsiveness in childhood: a longitudinal population study. Pediatr Pulmonol 2002;34(3):164-71.

747 Orbon KH, van der Gulden JW, Schermer TR, van den Nieuwenhof L, Boot CR, van den Hoogen H, et al. Vocational and working career of asthmatic adolescents is only slightly affected. Respir Med 2006;100(7):1163-73.

748 Gerald LB, Gerald JK, Gibson L, Patel K, Zhang S, McClure LA. Changes in environmental tobacco smoke exposure and asthma morbidity among urban school children. Chest 2009;135(4):911-6.

749 Precht DH, Keiding L, Madsen M. Smoking patterns among adolescents with asthma attending upper secondary schools: a community-based study. Pediatrics. 2003;111(5 Pt 1):e562-8.

750 Annesi-Maesano I, Oryszczyn MP, Raherison C, Kopferschmitt C, Pauli G, Taytard A, et al. Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? Clin Exp Allergy 2004;34(7):1017-23.

751 Genuneit J, Weinmayr G, Radon K, Dressel H, Windstetter D, Rzehak P, et al. Smoking and the incidence of asthma during adolescence: results of a large cohort study in Germany. Thorax 2006;61(7):572-8.

752 Larsson L. Incidence of asthma in Swedish teenagers: relation to sex and smoking habits. Thorax 1995;50(3):260-4.

753 Hedman L, Bjerg A, Sundberg S, Forsberg B, Ronmark E. Both environmental tobacco smoke and personal smoking is related to asthma and wheeze in teenagers. Thorax 2011;66(1):20-5.

754 Lombardi C, Gani F, Landi M, Boner A, Canonica GW, Passalacqua G. Clinical and therapeutic aspects of allergic asthma in adolescents. Pediatr Allergy Immunol 2003;14(6):453-7.

755 Reznik M, Ozuah PO, Franco K, Cohen R, Motlow F. Use of complementary therapy by adolescents with asthma. Arch Pediatr Adolesc Med 2002;156(10):1042-4.

756 Juntunen-Backman K, Kajosaari M, Laurikainen K, Malinen A, Kaila M, Mustala L, et al. Comparison of Easyhaler(R) metered-dose, dry powder inhaler and a pressurised metered-dose inhaler plus spacer in the treatment of asthma in children. Clin Drug Invest 2002;22(12):827-35.

757 Adler LM, Anand C, de L Wright FG, Barret CF, McKeith D, Clark WIC, et al. Efficacy and tolerability of beclomethasone dipropionate delivered by a novel multidose dry powder inhaler (Clickhaler®) versus a metered-dose inhaler in children with asthma. Curr Ther Res 2001;62(11):758-69.

758 Brennan VK, Osman LM, Graham H, Critchlow A, Everard ML. True device compliance: the need to consider both competence and contrivance. Respir Med 2005;99(1):97-102.

759 Edgecombe K, Latter S, Peters S, Roberts G. Health experiences of adolescents with uncontrolled severe asthma. Arch Dis Child 2010;95(12):985-91.

760 Salisbury C, Francis C, Rogers C, Parry K, Thomas H, Chadwick S, et al. A randomised controlled trial of clinics in secondary schools for adolescents with asthma. Br J Gen Pract 2002;52(485):988-96.

761 Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, et al. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial. BMJ 2001;322(7286):583-5.

762 Henry RL, Lough S, Mellis C, Australasian Paediatric Respiratory Group. National policy on asthma management for schools. J Paediatr Child Health 2006;42(9):491-5.

763 Royal College of Physicians of Edinburgh Transition Steering Group. Think transition: developing the essential link between paediatric and adult care. Edinburgh: Royal College of Physicians of Edinburgh; 2008. [cited 26 Jul 2016]. Available from url: http://www.cen.scot.nhs.uk/files/16o-think-transition-edinburgh.pdf

764 Scal P, Davern M, Ireland M, Park K. Transition to adulthood: delays and unmet needs among adolescents and young adults with asthma. J Pediatr 2008;152(4):471-5.

765 Sawyer S, Drew S, Duncan R. Adolescents with chronic disease: the double whammy. Aust Fam Physician 2007;36(8):622-7.

766 Cordina M, Hughes CM, McElnay JC. Health-related issues of importance to school children with asthma: a qualitative study. J Soc Adm Pharm 2002;19(5):162-70.

767 Cohen R, Franco K, Motlow F, Reznik M, Ozuah PO. Perceptions and attitudes of adolescents with asthma. J Asthma 2003;40(2):207-11.

768 Kyngas H. Patient education: perspective of adolescents with a chronic disease. J Clin Nurs 2003;12(5):744-51.

769 Bender BG, Rankin A, Tran ZV, Wamboldt FS. Brief-interval telephone surveys of medication adherence and asthma symptoms in the Childhood Asthma Management Program Continuation Study. Ann Allergy Asthma Immunol 2008;101(4):382-6.

770 Buston KM, Wood SF. Non-compliance amongst adolescents with asthma: listening to what they tell us about self-management. Fam Pract 2000;17(2):134-8.

771 Kyngas HA. Compliance of adolescents with asthma. Nurs Health Sci 1999;1(3):195-202.

772 Bender BG. Risk taking, depression, adherence, and symptom control in adolescents and young adults with asthma. Am J Respir Crit Care Med 2006;173(9):953-7.

773 Sawyer S, Bowes G. Caring for adolescents with asthma: do we know how to? Med J Aust 1996;165(9):463-4.

774 Goldenring JM, Cohen E. Getting into adolescent heads. Contemp Pediatr 1988;5(7):75-90.

775 Kyngas HA, Kroll T, Duffy ME. Compliance in adolescents with chronic diseases: a review. J Adolesc Health 2000;26(6):379-88.

776 Gerald LB, McClure LA, Mangan JM, Harrington KF, Gibson L, Erwin S, et al. Increasing adherence to inhaled steroid therapy among schoolchildren: randomized, controlled trial of school-based supervised asthma therapy. Pediatrics 2009;123(2):466-74.

777 Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988;81(3):509-17.

778 Dombrowski MP, Schatz M, Wise R, Momirova V, Landon M, Mabie W, et al. Asthma during pregnancy. Obstet Gynecol 2004;103(1):5-12.

779 Juniper EF, Newhouse MT. Effect of pregnancy on asthma: a systematic review and meta-analysis. In: Schatz M, Zeiger RS, Claman HN, editors. Asthma and immunological diseases in pregnancy and early infancy. New York: Marcel Dekker; 1998. p.401-25.

780 Gluck JC, Gluck PA. The effect of pregnancy on the course of asthma. Immunol Allergy Clin North Am 2006;26(1):63-80.

781 Kwon HL, Belanger K, Bracken MB. Effect of pregnancy and stage of pregnancy on asthma severity: a systematic review. Am J Obstet Gynecol 2004;190(5):1201-10.

782 Schatz M, Zeiger RS, Hoffman CP, Harden K, Forsythe A, Chilingar L, et al. Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. Am J Respir Crit Care Med 1995;151(4):1170-4.

783 Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. Am J Obstet Gynecol 1996;175(1):150-4.

784 Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. Thorax 1996;51(4):411-4.

785 Schatz M. Interrelationships between asthma and pregnancy: a literature review. J Allergy Clin Immunol 1999;103(2 Pt 2):S330-6.

786 Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. Thorax 1988;43(1):12-8.

787 Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. J Allergy Clin Immunol 1986;78(2):349-53.

788 Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. Am J Obstet Gynecol 1992;167(4 Pt 1):963-7.

789 Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. Chest 1990;98(2):389-92.

790 Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med 1998;158(4):1091-5.

791 Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy: a population based study. Eur J Epidemiol 2000;16(2):167-71.

792 Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol 2003;102(4):739-52.

793 Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax 2006;61(2):169-76.

794 Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. Am J Obstet Gynecol 2006;194(1):120-6.

795 Cydulka RK, Emerman CL, Schreiber D, Molander KH, Woodruff PG, Camargo CA Jr. Acute asthma among pregnant women presenting to the emergency department. Am J Respir Crit Care Med 1999;160(3):887-92.

796 Department of Health. Why mothers die: report on confidential enquiries into maternal deaths in the United Kingdom 1994-1996. London: Stationery Office; 1998.

797 Lewis G, Drife J. Why mothers die, 1997-1999. The fifth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. London: RCOG Press; 2001.

798 Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Why mothers die: the sixth report of the confidential enquiries into maternal deaths in the UK. London: RCOG Press; 2004.

799 Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003-2005. The seventh report on confidential enquiries into maternal deaths in the UK. London: CEMACH; 2007.

800 Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The eighth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011;118(Suppl 1):1-203.

801 Intensive Care National Audit and Research Centre. Female admissions (aged 16-50 years) to adult, general critical care units in England, Wales and Northern Ireland reported as 'currently pregnant' or 'recently pregnant'. London: ICNARC; 2013. [cited 09 Jul 2014]. Available from url: http://www.oaa-anaes.ac.uk/assets/_managed/cms/files/Obstetric%20admissions%20to%20critical%20care%202009-2012%20-%20FINAL.pdf

802 Campbell LA, Klocke RA. Implications for the pregnant patient. Am J Respir Crit Care Med 2001;163(5):1051-4.

803 Templeton A, Kelman GR. Maternal blood-gases, (PAo2--Pao2), physiological shunt and VD/VT in normal pregnancy. Br J Anaesth 1976;48(10):1001-4.

804 Van Hook JW, Harvey CJ, Anderson GD. Effect of pregnancy on maternal oxygen saturation values: use of reflectance pulse oximetry during pregnancy. South Med J 1996;89(12):1188-92.

805 Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie trial: a randomised placebo-controlled trial. Lancet 2002;359(9321):1877-90.

806 Gee JB, Packer BS, Millen JE, Robin ED. Pulmonary mechanics during pregnancy. J Clin Invest. 1967;46(6):945-52.

807 Izci B, Riha RL, Martin SE, Vennelle M, Liston WA, Dundas KC, et al. The upper airway in pregnancy and pre-eclampsia. Am J Respir Crit Care Med 2003;167(2):137-40.

808 Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997;100(3):301-6.

809 Chambers C. Safety of asthma and allergy medications in pregnancy. Immunol Allergy Clin North Am 2006;26(1):13-28.

810 Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. Thorax 2008;63(11):981-7.

811 Rayburn WF, Atkinson BD, Gilbert K, Turnbull GL. Short-term effects of inhaled albuterol on maternal and fetal circulations. Am J Obstet Gynecol 1994;171(3):770-3.

812 Schatz M, Dombrowski MP, Wise R, Momirova V, Landon M, Mabie W, et al. The relationship of asthma medication use to perinatal outcomes. J Allergy Clin Immunol 2004;113(6):1040-5.

813 Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chilingar LM, et al. The safety of inhaled beta-agonist bronchodilators during pregnancy. J Allergy Clin Immunol 1988;82(4):686-95.

814 Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol 1996;49(2):247-50.

815 Wilton LV, Shakir SA. A post-marketing surveillance study of formoterol (Foradil): its use in general practice in England. Drug Saf 2002;25(3):213-23.

816 Gluck JC, Gluck PA. Asthma controller therapy during pregnancy. Am J Obstet Gynecol 2005;192(2):369-80.

817 Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129(1):15-26

818 Perrio MJ, Wilton LV, Shakir SA. A modified prescription-event monitoring study to assess the introduction of Seretide Evohaler in England: an example of studying risk monitoring in pharmacovigilance. Drug Saf 2007;30(8):681-95.

819 Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983;98(4):478-80.

820 Dombrowski M, Thom E, McNellis D. Maternal-Fetal Medicine Units (MFMU) studies of inhaled corticosteroids during pregnancy. J Allergy Clin Immunol 1999;103(2 Pt 2):S356-9.

821 Dombrowski MP, Brown CL, Berry SM. Preliminary experience with triamcinolone acetonide during pregnancy. J Matern Fetal Med 1996;5(6):310-3.

822 Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999;93(3):392-5.

823 Silverman M, Sheffer A, Diaz PV, Lindmark B, Radner F, Broddene M, et al. Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. Ann Allergy Asthma Immunol 2005;95(6):566-70.

824 Christensson C, Thoren A, Lindberg B. Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. Drug Saf 2008;31(11):965-88.

825 Lim A, Stewart K, Konig K, George J. Systematic review of the safety of regular preventive asthma medications during pregnancy. Ann Pharmacother 2011;45(7-8):931-45.

826 Breton MC, Beauchesne MF, Lemire C, Rey E, Forget A, Blais L. Risk of perinatal mortality associated with inhaled corticosteroid use for the treatment of asthma during pregnancy. J Allergy Clin Immunol 2010;126(4):772-7.e2.

827 Lin S, Munsie JP, Herdt-Losavio ML, Druschel CM, Campbell K, Browne ML, et al. Maternal asthma medication use and the risk of selected birth defects. Pediatrics 2012;129(2):e317-24.

828 Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Hum Exp Toxicol 2006;25(8):447-52.

829 Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. Chest 1995;107(3):642-7.

830 Schatz M. Asthma during pregnancy: interrelationships and management. Ann Allergy 1992;68(2):123-33.

831 Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997;56(5):335-40.

832 Källén B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. Cleft Palate Craniofac J 2003;40(6):624-8.

833 Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998;58(1):2-5.

834 Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62(6):385-92.

835 Carmichael SL, Shaw GM, Ma C, Werler MM, Rasmussen SA, Lammer EJ, et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007;197(6):585.e1-7;discussion 683-4,e1-7.

836 Bakhireva LN, Schatz M, Chambers CD. Effect of maternal asthma and gestational asthma therapy on fetal growth. J Asthma 2007;44(2):71-6.

837 Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen HS, Johnson D, Slymen DJ, et al. Safety of leukotriene receptor antagonists in pregnancy. J Allergy Clin Immunol 2007;119(3):618-25.

838 Nelsen LM, Shields KE, Cunningham ML, Stoler JM, Bamshad MJ, Eng PM, et al. Congenital malformations among infants born to women receiving montelukast, inhaled corticosteroids, and other asthma medications. J Allergy Clin Immunol 2012;129(1):251-4.e1-6.

839 Sarkar M, Koren G, Kalra S, Ying A, Smorlesi C, De Santis M, et al. Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes. Eur J Clin Pharmacol 2009;65(12):1259-64.

840 Mabie WC, Barton JR, Wasserstrum N, Sibai BM. Clinical observations on asthma in pregnancy. J Matern Fetal Med 1992;1(1):45-50.

841 Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. Eur J Obstet Gynecol Reprod Biol 1990;35(2-3):183-90.

842 Arad I, Landau H. Adrenocortical reserve of neonates born of long-term, steroid-treated mothers. Eur J Pediatr 1984;142(4):279-80.

843 Turner ES, Greenberger PA, Patterson R. Management of the pregnant asthmatic patient. Ann Intern Med 1980;93(6):905-18.

844 Ost L, Wettrell G, Bjorkhem I, Rane A. Prednisolone excretion in human milk. J Pediatr 1985;106(6):1008-11.

845 McKenzie SA, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. Arch Dis Child 1975;50(11):894-6.

846 Greenberger PA, Odeh YK, Frederiksen MC, Atkinson AJ Jr. Pharmacokinetics of prednisolone transfer to breast milk. Clin Pharmacol Ther 1993;53(3):324-8.

847 Meredith S, Nordman H. Occupational asthma: measures of frequency from four countries. Thorax 1996;51(4):435-40.

848 Blanc PD, Toren K. How much adult asthma can be attributed to occupational factors? Am J Med 1999;107(6):580-7.

849 Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003;167(5):787-97.

850 Ross DJ. Ten years of the SWORD project. Surveillance of Work-related and Occupational Respiratory Disease. Clin Exp Allergy 1999;29(6):750-3.

851 Hendrick DJ, Burge PS. Asthma. In: Hendrick DJ, Beckett W, Burge PS, Churg A, editors. Occupational disorders of the lung. Recognition, management and prevention. London: WB Saunders; 2002. p.33-76.

852 Banks DE, Wang ML. Occupational asthma: "the big picture". Occup Med 2000;15(2):335-58.

853 Ameille J, Pauli G, Calastreng-Crinquand A, Vervloet D, Iwatsubo Y, Popin E, et al. Reported incidence of occupational asthma in France, 1996-99: the ONAP programme. Occup Environ Med 2003;60(2):136-41.

854 Brhel P. Occupational respiratory diseases in the Czech Republic. Ind Health 2003;41(2):121-3.

855 Cortona G, Pisati G, Dellabianca A, Moscato G. Respiratory occupational allergies: the experience of the Hospital Operative Unit of Occupational Medicine in Lombardy from 1990 to 1998 [Italian]. G Ital Med Lav Ergon 2001;23(1):64-70.

856 Gannon PF, Burge PS. The SHIELD scheme in the West Midlands Region, United Kingdom. Midland Thoracic Society Research Group. Br J Ind Med 1993;50(9):791-6.

857 Hnizdo E, Esterhuizen TM, Rees D, Lalloo UG. Occupational asthma as identified by the Surveillance of Work-related and Occupational Respiratory Diseases programme in South Africa. Clin Exp Allergy 2001;31(1):32-9.

858 McDonald JC, Keynes HL, Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989-97. Occup Environ Med 2000;57(12):823-9.

859 Meyer JD, Holt DL, Cherry NM, McDonald JC. SWORD '98: surveillance of work-related and occupational respiratory disease in the UK. Occup Med (Lond) 1999;49(8):485-9.

860 Sallie BA, Ross DJ, Meredith SK, McDonald JC. SWORD '93. Surveillance of work-related and occupational respiratory disease in the UK. Occup Med (Lond) 1994;44(4):177-82.

861 Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. Scand J Work Environ Health 1999;25(5):430-5.

862 Meredith SK, Taylor VM, McDonald JC. Occupational respiratory disease in the United Kingdom 1989: a report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. Br J Ind Med 1991;48(5):292-8.

863 Karjalainen A, Kurppa K, Martikainen R, Karjalainen J, Klaukka T. Exploration of asthma risk by occupation: extended analysis of an incidence study of the Finnish population. Scand J Work Environ Health 2002;28(1):49-57.

864 Reijula K, Haahtela T, Klaukka T, Rantanen J. Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. Chest 1996;110(1):58-61.

865 Jaakkola JJ, Piipari R, Jaakkola MS. Occupation and asthma: a population-based incident case-control study. Am J Epidemiol 2003;158(10):981-7.

866 Johnson AR, Dimich-Ward HD, Manfreda J, Becklake MR, Ernst P, Sears MR, et al. Occupational asthma in adults in six Canadian communities. Am J Respir Crit Care Med 2000;162(6):2058-62.

867 Kogevinas M, Anto JM, Soriano JB, Tobias A, Burney P. The risk of asthma attributable to occupational exposures. A population-based study in Spain. Spanish Group of the European Asthma Study. Am J Respir Crit Care Med 1996;154(1):137-43.

868 Kogevinas M, Anto JM, Sunyer J, Tobias A, Kromhout H, Burney P. Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. Lancet 1999;353(9166):1750-4.

869 Nicholson P J, Cullinan P, Burge P S, Boyle C. Occupational asthma: prevention, identification & management. London: British Occupational Health Research Foundation; 2010. [cited 26 Jul 2016]. Available from url: http://www.bohrf.org.uk/downloads/OccupationalAsthmaEvidenceReview-Mar2010.pdf

870 Chiry S, Boulet L-P, Lepage J, Forget A, Begin D, Chaboillez S, et al. Frequency of work-related respiratory symptoms in workers without asthma. Am J Ind Med 2009;52(6):447-54.

871 Burge PS, Pantin CF, Newton DT, Gannon PF, Bright P, Belcher J, et al. Development of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma. Midlands Thoracic Society Research Group. Occup Environ Med 1999;56(11):758-64.

872 Bright P, Newton DT, Gannon PF, Pantin CF, Burge PS. OASYS-3: improved analysis of serial peak expiratory flow in suspected occupational asthma. Monaldi Arch Chest Dis 2001;56(3):281-8.

873 Burge PS. Occupational asthma in electronics workers caused by colophony fumes: follow-up of affected workers. Thorax 1982;37(5):348-53.

874 Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC20 and peak expiratory flow rate in cedar asthma. J Allergy Clin Immunol 1990;85(3):592-8.

875 Leroyer C, Perfetti L, Trudeau C, L'Archeveque J, Chan-Yeung M, Malo JL. Comparison of serial monitoring of peak expiratory flow and FEV1 in the diagnosis of occupational asthma. Am J Respir Crit Care Med 1998;158(3):827-32.

876 Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. Chest 1991;100(1):63-9.

877 Malo JL, Cote J, Cartier A, Boulet LP, L'Archeveque J, Chan-Yeung M. How many times per day should peak expiratory flow rates be assessed when investigating occupational asthma? Thorax 1993;48(12):1211-7.

878 Moore VC, Jaakkola MS, Burge PS. A systematic review of serial peak expiratory flow measurements in the diagnosis of occupational asthma. Ann Respir Med 2009;1(1):31-44.

879 Malo JL, Ghezzo H, L'Archeveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? Am Rev Respir Dis 1991;143(3):528-32.

880 Anees W, Gannon PF, Huggins V, Pantin CF, Burge PS. Effect of peak expiratory flow data quantity on diagnostic sensitivity and specificity in occupational asthma. Eur Respir J 2004;23(5):730-4.

881 Moore VC, Jaakkola MS, Burge CB, Pantin CF, Robertson AS, Vellore AD, et al. PEF analysis requiring shorter records for occupational asthma diagnosis. Occup Med (Lond) 2009;59(6):413-7.

882 Burge CB, Moore VC, Pantin CF, Robertson AS, Burge PS. Diagnosis of occupational asthma from time point differences in serial PEF measurements. Thorax 2009;64(12):1032-6.

883 Malo JL, Cardinal S, Ghezzo H, L'Archeveque J, Castellanos L, Maghni K. Association of bronchial reactivity to occupational agents with methacholine reactivity, sputum cells and immunoglobulin E-mediated reactivity. Clin Exp Allergy 2011;41(4):497-504.

884 Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. Eur Respir J 2014;43(6):1573-87.

885 D'Alpaos V, Vandenplas O, Evrard G, Jamart J. Inhalation challenges with occupational agents: threshold duration of exposure. Respir Med 2013;107(5):739-44.

886 Stenton SC, Avery AJ, Walters EH, Hendrick DJ. Statistical approaches to the identification of late asthmatic reactions. Eur Respir J 1994;7(4):806-12.

887 Vandenplas O, D'Alpaos V, Heymans J, Jamart J, Thimpont J, Huaux F, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. Allergy 2009;64(5):754-61.

888 Munoz X, Velasco MI, Culebras M, Roca O, Morell F, Cruz MJ. Utility of exhaled breath condensate pH for diagnosing occupational asthma. Int Arch Allergy Immunol 2012;159(3):313-20.

889 Sanchez-Vidaurre S, Cruz MJ, Gomez-Olles S, Morell F, Munoz X. Diagnostic utility of exhaled breath condensate analysis in conjunction with specific inhalation challenge in individuals with suspected work-related asthma. Ann Allergy Asthma Immunol 2012;108(3):151-6.

890 Chan-Yeung M, Lam S, Koener S. Clinical features and natural history of occupational asthma due to western red cedar (Thuja plicata). Am J Med 1982;72(3):411-5.

891 Merget R, Schulte A, Gebler A, Breitstadt R, Kulzer R, Berndt ED, et al. Outcome of occupational asthma due to platinum salts after transferral to low-exposure areas. Int Arch Occup Environ Health 1999;72(1):33-9.

892 Moscato G, Dellabianca A, Perfetti L, Brame B, Galdi E, Niniano R, et al. Occupational asthma: a longitudinal study on the clinical and socioeconomic outcome after diagnosis. Chest 1999;115(1):249-56.

893 Pisati G, Baruffini A, Zedda S. Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure. Br J Ind Med 1993;50(1):60-4.

894 Rosenberg N, Garnier R, Rousselin X, Mertz R, Gervais P. Clinical and socio-professional fate of isocyanate-induced asthma. Clin Allergy 1987;17(1):55-61.

895 Tarlo SM, Banks D, Liss G, Broder I. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. Occup Environ Med 1997;54(10):756-61.

896 Valentino M, Pizzichini MA, Monaco F, Governa M. Latex-induced asthma in four healthcare workers in a regional hospital. Occup Med (Lond) 1994;44(3):161-4.

897 Valentino M, Rapisarda V. Course of isocyanate-induced asthma in relation to exposure cessation: longitudinal study of 50 subjects [Italian]. G Ital Med Lav Ergon 2002;24(1):26-31.

898 Vandenplas O, Delwiche JP, Depelchin S, Sibille Y, Vande Weyer R, Delaunois L. Latex gloves with a lower protein content reduce bronchial reactions in subjects with occupational asthma caused by latex. Am J Respir Crit Care Med 1995;151(3 Pt 1):887-91.

899 Chan-Yeung M, MacLean L, Paggiaro PL. Follow-up study of 232 patients with occupational asthma caused by western red cedar (Thuja plicata). J Allergy Clin Immunol 1987;79(5):792-6.

900 Malo JL, Cartier A, Ghezzo H, Lafrance M, McCants M, Lehrer SB. Patterns of improvement in spirometry, bronchial hyperresponsiveness, and specific IgE antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. Am Rev Respir Dis 1988;138(4):807-12.

901 Gannon PF, Weir DC, Robertson AS, Burge PS. Health, employment, and financial outcomes in workers with occupational asthma. Brit J Ind Med 1993;50(6):491-6.

902 Axon EJ, Beach JR, Burge PS. A comparison of some of the characteristics of patients with occupational and non-occupational asthma. Occup Med (Lond) 1995;45(2):109-11.

903 Cannon J, Cullinan P, Newman Taylor A. Consequences of occupational asthma. BMJ 1995;311(7005):602-3.

904 Larbanois A, Jamart J, Delwiche JP, Vandenplas O. Socioeconomic outcome of subjects experiencing asthma symptoms at work. Eur Respir J 2002;19(6):1107-13.

905 Ross DJ, McDonald JC. Health and employment after a diagnosis of occupational asthma: a descriptive study. Occup Med (Lond) 1998;48(4):219-25.

906 Ameille J, Pairon JC, Bayeux MC, Brochard P, Choudat D, Conso F, et al. Consequences of occupational asthma on employment and financial status: a follow-up study. Eur Respir J 1997;10(1):55-8.

907 Marabini A, Dimich-Ward H, Kwan SY, Kennedy SM, Waxler-Morrison N, Chan-Yeung M. Clinical and socioeconomic features of subjects with red cedar asthma. A follow-up study. Chest 1993;104(3):821-4.

908 Vandenplas O, Jamart J, Delwiche JP, Evrard G, Larbanois A. Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. J Allergy Clin Immunol 2002;109(1):125-30.

909 Venables KM, Davison AG, Newman Taylor AJ. Consequences of occupational asthma. Respir Med 1989;83(5):437-40.

910 Rotter T, Kinsman L, James EL, Machotta A, Gothe H, Willis J, et al. Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. Cochrane Database of Systematic Reviews 2010, Issue 3.

911 Smith JR, Noble MJ, Musgrave S, Murdoch J, Price GM, Barton GR, et al. The at-risk registers in severe asthma (ARRISA) study: a cluster-randomised controlled trial examining effectiveness and costs in primary care. Thorax 2012;67(12):1052-60.

912 Mitchell EA, Didsbury PB, Kruithof N, Robinson E, Milmine M, Barry M, et al. A randomized controlled trial of an asthma clinical pathway for children in general practice. Acta Pediatr 2005;94(2):226-33.

913 Doherty SR, Jones PD. Use of an 'evidence-based implementation' strategy to implement evidence-based care of asthma into rural district hospital emergency departments. Rural Remote Health 2006;6(1):529.

914 Johnson KB, Blaisdell CJ, Walker A, Eggleston P. Effectiveness of a clinical pathway for inpatient asthma management. Pediatrics 2000;106(5):1006-12.

915 Zorc JJ, Chew A, Allen JL, Shaw K. Beliefs and barriers to follow-up after an emergency department asthma visit: a randomized trial. Pediatrics 2009;124(4):1135-42.

916 O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, et al. Educational outreach visits: effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews 2007, Issue 4.

917 Forsetlund L, Bjørndal A, Rashidian A, Jamtvedt G, O'Brien MA, Wolf FM, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews 2009, Issue 2.

918 Cabana MD, Slish KK, Evans D, Mellins RB, Brown RW, Lin X, et al. Impact of physician asthma care education on patient outcomes. Pediatrics 2006;117(6):2149-57.

919 Shah S, Sawyer SM, Toelle BG, Mellis CM, Peat JK, Lagleva M, et al. Improving paediatric asthma outcomes in primary health care: a randomised controlled trial. Med J Austr 2011;195(7):405-9.

920 Lozano P, Finkelstein JA, Carey VJ, Wagner EH, Inui TS, Fuhlbrigge AL, et al. A multisite randomized trial of the effects of physician education and organizational change in chronic-asthma care: health outcomes of the Pediatric Asthma Care Patient Outcomes Research Team II Study. Arch Pediatr Adolesc Med 2004;158(9):875-83.

921 Smeele IJ, Grol RP, van Schayck CP, van den Bosch WJ, van den Hoogen HJ, Muris JW. Can small group education and peer review improve care for patients with asthma/chronic obstructive pulmonary disease? Qual Health Care 1999;8(2):92-8.

922 Witt K, Knudsen E, Ditlevsen S, Hollnagel H. Academic detailing has no effect on prescribing of asthma medication in Danish general practice: a 3-year randomized controlled trial with 12-monthly follow-ups. Fam Pract 2004;21(3):248-53.

923 Liaw ST, Sulaiman ND, Barton CA, Chondros P, Harris CA, Sawyer S, et al. An interactive workshop plus locally adapted guidelines can improve general practitioners asthma management and knowledge: a cluster randomised trial in the Australian setting. BMC Fam Pract 2008;9:22.

924 Goeman DP, Sanci LA, Scharf SL, Bailey M, O'Hehir RE, Jenkins CR, et al. Improving general practice consultations for older people with asthma: a cluster randomised control trial. Med J Aust 2009;191(2):113-7.

925 Stout JW, Smith K, Zhou C, Solomon C, Dozor AJ, Garrison MM, et al. Learning from a distance: Effectiveness of online spirometry training in improving asthma care. Acad Pediatr 2012;12(2):88-95.

926 Charlton I, Charlton G, Broomfield J, Mullee MA. Audit of the effect of a nurse run asthma clinic on workload and patient morbidity in a general practice. Br J Gen Pract 1991;41(347):227-31.

927 Hoskins G, Neville R, Smith B, Clark RA. The link between nurse training and asthma outcomes. Br J Comm Nursing 1999;4(5):222-8.

928 Feder G, Griffiths C, Highton C, Eldridge S, Spena M, Southgate L. Do clinical guidelines introduced with practice based education improve care of asthmatic and diabetic patients? A randomised controlled trial in general practitioners in east London. BMJ 1995;311(7018):1473-8.

929 Bryce FP, Neville RG, Crombie IK, Clark RA, McKenzie P. Controlled trial of an audit facilitator in diagnosis and treatment of childhood asthma in general practice. BMJ 1995;310(6983):838-42.

930 Dickinson J, Hutton S, Atkin A, Jones K. Reducing asthma morbidity in the community: the effect of a targeted nurse-run asthma clinic in an English general practice. Respir Med 1997;91(10):634-40.

931 Lindberg M, Ahlner J, Moller M, Ekstrom T. Asthma nurse practice: a resource-effective approach in asthma management. Respir Med 1999;93(8):584-8.

932 Baishnab E, Karner C. Primary care based clinics for asthma. Cochrane Database of Systematic Reviews 2012, Issue 4.

933 McPherson AC, Glazebrook C, Forster D, James C, Smyth A. A randomized, controlled trial of an interactive educational computer package for children with asthma. Pediatrics 2006;117(4):1046-54.

934 Hieftje K, Edelman EJ, Camenga DR, Fiellin LE. Electronic media-based health interventions promoting behavior change in youth: a systematic review. JAMA Pediatr 2013;167(6):574-80.

935 Joseph CL, Ownby DR, Havstad SL, Saltzgaber J, Considine S, Johnson D, et al. Evaluation of a web-based asthma management intervention program for urban teenagers: reaching the hard to reach. J Adolesc Health 2013;52(4):419-26.

936 Pare G, Moqadem K, Pineau G, St-Hilaire C. Clinical effects of home telemonitoring in the context of diabetes, asthma, heart failure and hypertension: a systematic review. J Med Internet Res 2010;12(2):e21.

937 Marcano Belisario JS, Huckvale K, Greenfield G, Car J, Gunn LH. Smartphone and tablet self management apps for asthma. Cochrane Database of Systematic Reviews 2013, Issue 11.

938 Gustafson D, Wise M, Bhattacharya A, Pulvermacher A, Shanovich K, Phillips B, et al. The effects of combining web-based eHealth with telephone nurse case management for pediatric asthma control: a randomized controlled trial. J Med Internet Res 2012;14(4):e101.

939 Ryan D, Price D, Musgrave SD, Malhotra S, Lee AJ, Ayansina D, et al. Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. BMJ 2012;344:e1756.

940 van der Meer V, Bakker MJ, van den Hout WB, Rabe KF, Sterk PJ, Kievit J, et al. Internet-based self-management plus education compared with usual care in asthma: a randomized trial. Ann Intern Med 2009;151(2):110-20.

941 van der Meer V, van Stel HF, Bakker MJ, Roldaan AC, Assendelft WJ, Sterk PJ, et al. Weekly self-monitoring and treatment adjustment benefit patients with partly controlled and uncontrolled asthma: an analysis of the SMASHING study. Respir Res 2010;11:74.

942 DiBello K, Boyar K, Abrenica S, Worral PS. The effectiveness of text messaging programs on adherence to treatment regimens among adults aged 18 to 45 years diagnosed with asthma: a systematic review. JBI Database of Systematic Reviews and Implementation Reports 2014;12(1):485-532.

943 Morrison D, Wyke S, Agur K, Cameron EJ, Docking RI, Mackenzie AM, et al. Digital asthma self-management interventions: a systematic review. J Med Internet Res 2014;16(2):e51.

944 de Jong CC, Ros WJ, Schrijvers G. The effects on health behavior and health outcomes of Internet-based asynchronous communication between health providers and patients with a chronic condition: a systematic review. J Med Internet Res 2014;16(1):e19.

945 Deshpande A, Khoja S, Lorca J, McKibbon A, Rizo C, Husereau D, et al. Asynchronous telehealth: a scoping review of analytic studies. Open Med 2009;3(2):e69-91.

946 Garbutt JM, Banister C, Highstein G, Sterkel R, Epstein J, Bruns J, et al. Telephone coaching for parents of children with asthma: impact and lessons learned. Arch Pediatr Adolesc Med 2010;164(7):625-30.

947 Pinnock H, Bawden R, Proctor S, Wolfe S, Scullion J, Price D, et al. Accessibility, acceptability, and effectiveness in primary care of routine telephone review of asthma: pragmatic, randomised controlled trial. BMJ 2003;326(7387):477-9.

948 Matui P, Wyatt JC, Pinnock H, Sheikh A, McLean S. Computer decision support systems for asthma: a systematic review. NPJ Primary Care Respiratory Medicine 2014;24:14005.

949 Fathima M, Peiris D, Naik-Panvelkar P, Saini B, Armour CL. Effectiveness of computerized clinical decision support systems for asthma and chronic obstructive pulmonary disease in primary care: a systematic review. BMC Pulm Med 2014;14:189.

950 Clark NM, Shah S, Dodge JA, Thomas LJ, Andridge RR, Little RJ. An evaluation of asthma interventions for preteen students. J Sch Health 2010;80(2):80-7.

951 Halterman JS, Szilagyi PG, Fisher SG, Fagnano M, Tremblay P, Conn KM, et al. Randomized controlled trial to improve care for urban children with asthma: results of the School-Based Asthma Therapy trial. Arch Pediatr Adolesc Med 2011;165(3):262-8.

952 Bruzzese JM, Sheares BJ, Vincent EJ, Du Y, Sadeghi H, Levison MJ, et al. Effects of a school-based intervention for urban adolescents with asthma. A controlled trial. Am J Respir Crit Care Med 2011;183(8):998-1006.

953 Foster G, Taylor SJC, Eldridge S, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. Cochrane Database of Systematic Reviews 2007, Issue 4.

954 Pande S, Hiller JE, Nkansah N, Bero L. The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries. Cochrane Database of Systematic Reviews 2013, Issue 2.

955 Benavides S, Rodriguez JC, Maniscalco-Feichtl M. Pharmacist involvement in improving asthma outcomes in various healthcare settings: 1997 to present. Ann Pharmacother 2009;43(1):85-97.

956 Basheti IA, Armour CL, Bosnic-Anticevich SZ, Reddel HK. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. Patient Educ Couns 2008;72(1):26-33.

957 Hammerlein A, Muller U, Schulz M. Pharmacist-led intervention study to improve inhalation technique in asthma and COPD patients. J Eval Clin Pract 2011;17(1):61-70.

958 Mehuys E, Van Bortel L, De Bolle L, Van Tongelen I, Annemans L, Remon JP, et al. Effectiveness of pharmacist intervention for asthma control improvement. Eur Respir J 2008;31(4):790-9.

959 Elliott RA, Barber N, Clifford S, Horne R, Hartley E. The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines. Pharm World Sci 2008;30(1):17-23.

960 Bereznicki BJ, Peterson G, Jackson S, Walters EH, George J, Stewart K, et al. Uptake and effectiveness of a community pharmacy intervention programme to improve asthma management. J Clin Pharm Ther 2013;38(3):212-8.

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