

# SIGN 158

## British guideline on the management of asthma

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A national clinical guideline

First published 2003

Revised edition published July 2019



British  
Thoracic  
Society

**NHS**  
SCOTLAND

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## Key to evidence statements and recommendations

### Levels of evidence

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

### Grades of recommendation

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

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

### Good-practice points

- ✓ | Recommended best practice based on the clinical experience of the guideline development group.



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Scottish Intercollegiate Guidelines Network  
British Thoracic Society

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

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# Contents

|          |                                                                                    |           |
|----------|------------------------------------------------------------------------------------|-----------|
| <b>1</b> | <b>Introduction</b>                                                                | <b>1</b>  |
| 1.1      | The need for a guideline                                                           | 1         |
| 1.2      | Remit of the guideline                                                             | 1         |
| 1.3      | Statement of intent                                                                | 4         |
| <b>2</b> | <b>Key recommendations</b>                                                         | <b>6</b>  |
| 2.1      | Diagnosis                                                                          | 6         |
| 2.2      | Monitoring                                                                         | 7         |
| 2.3      | Supported self management                                                          | 7         |
| 2.4      | Non-pharmacological management                                                     | 7         |
| 2.5      | Pharmacological management                                                         | 7         |
| 2.6      | Inhaler devices                                                                    | 8         |
| 2.7      | Acute asthma                                                                       | 8         |
| 2.8      | Difficult asthma                                                                   | 9         |
| 2.9      | Asthma in pregnancy                                                                | 9         |
| 2.10     | Occupational asthma                                                                | 9         |
| <b>3</b> | <b>Diagnosis</b>                                                                   | <b>10</b> |
| 3.1      | Definition and overarching principles                                              | 10        |
| 3.2      | Predictive value of individual symptoms, signs and diagnostic tests                | 11        |
| 3.3      | Practical approach to diagnosis                                                    | 20        |
| 3.4      | Organisation of diagnostic services                                                | 28        |
| 3.5      | Wheezing in preschool children and the future risk of developing persistent asthma | 29        |
| <b>4</b> | <b>Monitoring asthma</b>                                                           | <b>30</b> |
| 4.1      | Targeting care                                                                     | 31        |
| 4.2      | Monitoring current asthma symptom control                                          | 31        |
| 4.3      | Predicting future risk of asthma attacks                                           | 32        |
| 4.4      | Physiological measures                                                             | 36        |
| 4.5      | Other approaches                                                                   | 37        |
| <b>5</b> | <b>Supported self management</b>                                                   | <b>38</b> |
| 5.1      | Effectiveness of supported self management                                         | 38        |
| 5.2      | Components of a self-management programme                                          | 38        |
| 5.3      | Self management in specific patient groups                                         | 42        |
| 5.4      | Adherence and concordance                                                          | 45        |
| 5.5      | Implementation in practice                                                         | 48        |
| <b>6</b> | <b>Non-pharmacological management</b>                                              | <b>50</b> |
| 6.1      | Primary prevention                                                                 | 50        |
| 6.2      | Secondary prevention                                                               | 55        |

---

---

|           |                                                   |            |
|-----------|---------------------------------------------------|------------|
| <b>7</b>  | <b>Pharmacological management</b>                 | <b>62</b>  |
| 7.1       | Intermittent reliever therapy                     | 63         |
| 7.2       | Regular preventer therapy                         | 63         |
| 7.3       | Initial add-on therapy                            | 70         |
| 7.4       | Additional controller therapies                   | 72         |
| 7.5       | Specialist therapies                              | 73         |
| 7.6       | Deceasing treatment                               | 82         |
| 7.7       | Specific management issues                        | 82         |
| <b>8</b>  | <b>Inhaler devices</b>                            | <b>85</b>  |
| 8.1       | Technique and training                            | 85         |
| 8.2       | $\beta_2$ agonist delivery                        | 85         |
| 8.3       | Inhaled corticosteroids for stable asthma         | 86         |
| 8.4       | Prescribing devices                               | 86         |
| 8.5       | Use and care of spacers                           | 87         |
| 8.6       | Environmental impact of metered-dose inhalers     | 87         |
| <b>9</b>  | <b>Management of acute asthma</b>                 | <b>89</b>  |
| 9.1       | Lessons from asthma deaths and near-fatal asthma  | 89         |
| 9.2       | Acute asthma in adults                            | 91         |
| 9.3       | Treatment of acute asthma in adults               | 94         |
| 9.4       | Further investigation and monitoring              | 100        |
| 9.5       | Asthma management protocols and proformas         | 100        |
| 9.6       | Hospital discharge and follow up                  | 101        |
| 9.7       | Acute asthma in children                          | 102        |
| 9.8       | Initial treatment of acute asthma in children     | 104        |
| 9.9       | Second-line treatment of acute asthma in children | 109        |
| <b>10</b> | <b>Difficult asthma</b>                           | <b>113</b> |
| 10.1      | Defining and assessing difficult asthma           | 113        |
| 10.2      | Factors contributing to difficult asthma          | 113        |
| <b>11</b> | <b>Asthma in adolescents</b>                      | <b>117</b> |
| 11.1      | Definitions                                       | 117        |
| 11.2      | Prevalence of asthma in adolescents               | 117        |
| 11.3      | Diagnosis and assessment                          | 117        |
| 11.4      | Risk factors                                      | 118        |
| 11.5      | Comorbidities and modifiable behaviours           | 119        |
| 11.6      | Asthma attacks and the risk of hospital admission | 120        |
| 11.7      | Long-term outlook and entry into the workplace    | 120        |
| 11.8      | Non-pharmacological management                    | 120        |
| 11.9      | Pharmacological management                        | 121        |
| 11.10     | Inhaler devices                                   | 121        |
| 11.11     | Organisation and delivery of care                 | 122        |
| 11.12     | Patient education and self management             | 123        |

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|                      |                                                  |            |
|----------------------|--------------------------------------------------|------------|
| <b>12</b>            | <b>Asthma in pregnancy</b>                       | <b>126</b> |
| 12.1                 | Natural history and management of stable asthma  | 126        |
| 12.2                 | Management of acute asthma in pregnancy          | 127        |
| 12.3                 | Drug therapy in pregnancy                        | 128        |
| 12.4                 | Management during labour                         | 131        |
| 12.5                 | Drug therapy for breastfeeding mothers           | 132        |
| <b>13</b>            | <b>Occupational asthma</b>                       | <b>133</b> |
| 13.1                 | Incidence                                        | 133        |
| 13.2                 | At-risk populations                              | 133        |
| 13.3                 | Diagnosis                                        | 133        |
| 13.4                 | Management of occupational asthma                | 136        |
| <b>14</b>            | <b>Organisation and delivery of care</b>         | <b>138</b> |
| 14.1                 | Care pathways                                    | 138        |
| 14.2                 | Educating clinicians                             | 138        |
| 14.3                 | Asthma clinics                                   | 139        |
| 14.4                 | Telehealthcare                                   | 140        |
| 14.5                 | School-based interventions                       | 143        |
| 14.6                 | Ethnicity/culture-based interventions            | 143        |
| 14.7                 | Lay-led interventions                            | 144        |
| 14.8                 | Pharmacist-led interventions                     | 144        |
| <b>15</b>            | <b>Provision of information</b>                  | <b>145</b> |
| 15.1                 | Checklist of information for patients and carers | 145        |
| 15.2                 | Publications from SIGN                           | 147        |
| 15.3                 | Sources of further information                   | 148        |
| <b>16</b>            | <b>The evidence base</b>                         | <b>150</b> |
| 16.1                 | Systematic literature review                     | 150        |
| 16.2                 | Recommendations for research                     | 150        |
| <b>17</b>            | <b>Development of the guideline</b>              | <b>152</b> |
| 17.1                 | Introduction                                     | 152        |
| 17.2                 | Guideline development group                      | 152        |
| 17.3                 | Acknowledgements                                 | 154        |
| 17.4                 | Consultation and peer review                     | 154        |
| <b>Abbreviations</b> |                                                  | <b>156</b> |
| <b>Annexes</b>       |                                                  | <b>158</b> |
| <b>References</b>    |                                                  | <b>172</b> |

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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 services. It is clear that much of this morbidity relates to poor management, particularly around the use of preventative medicine.

### 1.1.1 Background

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, developed using SIGN methodology<sup>1</sup> and published in 2003.<sup>2</sup>

### 1.1.2 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 2019. All updates were published on the BTS and SIGN websites. A list of the key questions addressed in this update is given in Annex 1. 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 2. 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 (*see section 16.2*).

## 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, and adolescents and children with asthma. In sections 7 and 8 on pharmacological management and inhaler devices, respectively, and in section 4.3 on predicting future risk of asthma attacks, 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 Organization)<sup>3</sup> is given in section 11.

The guideline considers diagnosis of asthma and 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 (COPD) 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.

### 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, pharmacists and other allied health professionals with an interest in respiratory care. 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

| Guideline section |                                   | Year of update                                       |
|-------------------|-----------------------------------|------------------------------------------------------|
| 2                 | Key recommendations               | 2014, 2016, 2019                                     |
| 3                 | Diagnosis                         | 2008, 2011, 2016                                     |
| 4                 | Monitoring asthma                 | 2008, 2011, 2019                                     |
| 5                 | Supported self management         | 2004, 2008, 2014, 2016, 2019                         |
| 6                 | Non-pharmacological management    | 2008, 2014, 2016, 2019                               |
| 7                 | Pharmacological management        | 2004, 2005, 2006, 2008, 2009, 2011, 2014, 2016, 2019 |
| 8                 | Inhaler devices                   | 2005, 2014, 2019                                     |
| 9                 | Management of acute asthma        | 2004, 2009, 2014, 2016, 2019                         |
| 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                                     |

### 1.2.4 Summary of updates to the 2019 edition of the guideline, by section

The table below lists all the sections and subsections of the guideline that were updated in 2019. This update includes a complete revision of the section on monitoring, and updates to sections including supported self management, non-pharmacological management of asthma, pharmacological management of asthma, inhaler devices and management of acute asthma.

| Guideline section |                                | Year of update                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2                 | Key recommendations            | Updated: 2.2 Monitoring<br>Minor update: 2.1 Diagnosis, 2.4 Non-pharmacological management, 2.10 Occupational asthma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 3                 | Diagnosis                      | Minor update: 3.3.3 Low probability of asthma based on initial structured clinical assessment, 3.4 Organisation of diagnostic services                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 4                 | Monitoring asthma              | New: Table 7, 4.1 Targeting care, 4.2 Monitoring current asthma symptom control, 4.3 Predicting future risk of asthma attacks, 4.3.1 Adults, 4.3.2 School-aged children, 4.3.3 Preschool children, 4.3.4 People with severe asthma, 4.4 Physiological measures, 4.4.1 Spirometry and peak expiratory flow, 4.4.2 Fractional exhaled nitric oxide, 4.4.3 Eosinophils, 4.5 Other approaches                                                                                                                                                                                                                                                                                                                                                                                            |
| 5                 | Supported self management      | New: 5.2.3 Increasing inhaled corticosteroids to abort an asthma attack<br>Updated: 5.4.3 Interventions to improve medication adherence<br>Minor update: 5.2.2 Personalised asthma action plans, Table 11                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 6                 | Non-pharmacological management | New: 6.2.8 Vitamin D<br>Updated: 6.2.1 House dust mite avoidance, 6.2.2 Other allergens, 6.2.3 Smoking, 6.2.4 Air pollution, 6.2.13 Air ionisers, 6.2.14 Breathing exercises                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 7                 | Pharmacological management     | Updated: 7.1.1 Frequency of dosing of inhaled SABA, Table 12 Categorisation of inhaled corticosteroids by dose – adults, Table 13 Categorisation of inhaled corticosteroids by dose – children, 7.3.5 Single combination inhaler for maintenance and reliever therapy, 7.4 Additional controller therapies, 7.5 Specialist therapies; 7.5.2 Other approaches, 7.5.3 Continuous or frequent use of oral steroids, 7.5.4 Monoclonal antibody, 7.5.6 Immunotherapy for asthma, 7.5.7 Bronchial thermoplasty, Figure 2 Summary of management in adults, Figure 3 Summary of management in children,<br>Minor updates: 7.1 Intermittent reliever therapy, 7.5.5 Other agents, 7.7.2 Exercise-induced asthma<br>Deleted: Patients on oral steroids not previously tried on inhaled therapy |
| 8                 | Inhaler devices                | New: 8.6 Environmental impact of metered-dose inhalers                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 9                 | Management of acute asthma     | Updated: 9.3.5 Magnesium sulphate, 9.3.12 Critical care settings (adults), 9.9.5 Critical care settings (children), 9.9.6 Non-invasive ventilation<br>Minor update: 9.3.2 $\beta_2$ agonist bronchodilators, 9.9.3 Intravenous magnesium sulphate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 13                | Occupational asthma            | Minor update: 13.3 Diagnosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 15                | Provision of information       | New: 15.1 Checklist of information for patients and carers, 15.2 Publications from SIGN                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 16                | The evidence base              | Updated: 16.2 Recommendations for research                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                   | Annexes                        | New: Annex 1 Key questions addressed in this update<br>Updated: Annexes 3 – 9 Management of acute asthma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

### 1.3 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at 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](http://www.sign.ac.uk)

#### 1.3.2 Patient version

Patient versions of this guideline are available from the SIGN website, [www.sign.ac.uk](http://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.<sup>4</sup>

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."<sup>4</sup>

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

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed 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](http://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.<sup>5</sup>

#### 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 technology appraisals that make recommendations on the use of new and existing medicines and treatments within the NHS in England and Wales.

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, all new formulations of existing medicines and new indications for established products, within NHSScotland.

Until 1 October 2017, Healthcare Improvement Scotland reviewed Multiple Technology Appraisals produced by NICE and provided advice about their applicability in NHSScotland. If Healthcare Improvement Scotland has advised that Multiple Technology Appraisal guidance was applicable in Scotland, NHSScotland should take account of this and ensure that recommended medicines and treatment are made available to meet clinical need where appropriate.

NICE Multiple Technology Appraisals deemed valid for NHSScotland supersede extant SMC advice as they are generally underpinned by a larger and more recent evidence base.

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.

### 2.1 Diagnosis

**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.

**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.

✓ 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<sub>1</sub> at clinic visits or by domiciliary serial peak flows to capture times with/without symptoms)
- 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.

## 2.2 Monitoring

>12 yrs   5-12 yrs   <5 yrs

|   |   |   |                                                                                                                                                                                    |
|---|---|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| D | B | D | Assess risk of future asthma attacks at every asthma review by asking about history of previous attacks, objectively assessing current asthma control, and reviewing reliever use. |
|---|---|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 2.3 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.             |

## 2.4 Non-pharmacological management

|   |                                                                                                                                                                                                                                                   |
|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| B | People with asthma and parents of children with asthma should be advised about the dangers of smoking and second-hand tobacco smoke exposure, and be offered appropriate support to stop smoking.                                                 |
| B | Weight loss interventions (including dietary and exercise-based programmes) should be considered for overweight and obese adults and children with asthma to improve asthma control.                                                              |
| A | Breathing exercise programmes (including face-to-face physiotherapist-taught methods and audiovisual programmes) can be offered to adults with asthma as an adjuvant to pharmacological treatment to improve quality of life and reduce symptoms. |

## 2.5 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 $\beta_2$ agonist, which should be considered before increasing the dose of inhaled corticosteroids.                                                                                                                                                                                                                   |
| D | D                                                                                                                                                          |   | <p>If asthma control remains suboptimal after the addition of an inhaled long-acting <math>\beta_2</math> agonist then:</p> <ul style="list-style-type: none"> <li>increase the dose of inhaled corticosteroids 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.</li> <li>consider adding a leukotriene receptor antagonist.</li> </ul> |

## 2.6 Inhaler devices

- |          |                                                                                                                                                                                                                                                                                  |   |                                                                                                                                             |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------|
| <b>B</b> | ✓                                                                                                                                                                                                                                                                                | ✓ | <b>Prescribe inhalers only after patients have received training in the use of the device and have demonstrated satisfactory technique.</b> |
| ✓        | 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 young children, a pMDI and spacer is the preferred method of delivery of $\beta_2$ 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. |   |                                                                                                                                             |

## 2.7 Acute asthma

### 2.7.1 Adults

- |          |                                                                                                                                                                                                                                                                                                                              |
|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>D</b> | <b>Refer to hospital any patients with features of acute severe or life-threatening asthma.</b>                                                                                                                                                                                                                              |
| <b>C</b> | <b>Give controlled supplementary oxygen to all hypoxaemic patients with acute severe asthma titrated to maintain an <math>\text{SpO}_2</math> level of 94–98%. Do not delay oxygen administration in the absence of pulse oximetry but commence monitoring of <math>\text{SpO}_2</math> as soon as it becomes available.</b> |
| <b>A</b> | <b>Use high-dose inhaled <math>\beta_2</math> agonists as first-line agents in patients with acute asthma and administer as early as possible. Reserve intravenous <math>\beta_2</math> agonists for those patients in whom inhaled therapy cannot be used reliably.</b>                                                     |
| <b>A</b> | <b>Give steroids in adequate doses to all patients with an acute asthma attack.</b>                                                                                                                                                                                                                                          |

### 2.7.2 Children

- |          |                                                                                                                                                                                                                 |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ✓        | Children with life-threatening asthma or $\text{SpO}_2 < 94\%$ 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%. |
| <b>A</b> | <b>Inhaled <math>\beta_2</math> agonists are the first-line treatment for acute asthma in children.</b>                                                                                                         |
| <b>A</b> | <b>Give oral steroids early in the treatment of acute asthma attacks in children.</b>                                                                                                                           |

### 2.7.3 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. |
|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 2.8 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.

## 2.9 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.

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

## 2.10 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 suspected asthma or unexplained airflow obstruction should be asked:
- Are you the same, better, or worse on days away from work?
  - Are you the same, better, or worse on holiday?
- Those with positive answers should be investigated for occupational asthma.

## 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.<sup>6</sup>

#### 3.1.2 Tests influence the probability 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',<sup>7</sup> and there is evidence that some patients shift from 'inactive' to 'active' status (and vice versa) over time.<sup>8-10</sup>

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,<sup>11-13</sup> and bronchodilator reversibility was demonstrated in only 15–17% of patients.<sup>12, 14, 15</sup> In contrast, in a population admitted to hospital with a physician-diagnosed asthma attack, 83% had obstructive lung function.<sup>16</sup> In a prospective

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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.<sup>9</sup>

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Time may, however, be used to advantage if objective signs and tests when a patient is symptomatic are compared with 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 predictive value of objective tests is often poor and 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.<sup>17</sup> 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.<sup>18-20</sup> Enquiring about the episodic nature of symptoms (for example acute attacks) as opposed to current symptoms may improve the predictive value.<sup>18, 19, 21, 22</sup>

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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.<sup>23</sup>

Wheeze heard by a healthcare professional on auscultation is an important sign that increases the probability of asthma.<sup>22</sup>

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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.<sup>18-20</sup>

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### 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.<sup>11-13</sup> 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.<sup>24</sup>

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Measuring lung function in children under five 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.<sup>25</sup> Asthma severity classified by symptoms and use of medicines correlates poorly with single measurements of forced expiratory volume in one second (FEV<sub>1</sub>) and other spirometric indices: FEV<sub>1</sub> is often normal in children with persistent asthma, and abnormal results may be seen in children with other respiratory diseases.<sup>25, 26</sup>

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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.<sup>25, 27</sup>



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

The FEV<sub>1</sub>/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.<sup>6, 28-30</sup> Detailed data about normal values for different age groups is available from the report of the European Respiratory Society Global Lung function Initiative.<sup>31</sup>

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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).

In adults with obstructive spirometry, an improvement in FEV<sub>1</sub> of 12% or more in response to either  $\beta_2$  agonists or corticosteroid treatment trials, together with an increase in volume of 200 ml or more, is regarded as a positive test,<sup>32</sup> although some people with COPD can have significant reversibility.<sup>33</sup> An improvement of greater than 400 ml in FEV<sub>1</sub> strongly suggests underlying asthma. In children, an improvement in FEV<sub>1</sub> of 12% or more is regarded as a positive test.<sup>32</sup>

**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

#### *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. The patient can be standing or sitting. Further blows should be done if the largest two PEF are not within 40 L/min.<sup>34</sup>

Peak expiratory flow 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<sup>35</sup> but the improved precision is likely to be achieved at the expense of reduced patient compliance.<sup>36</sup> 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.<sup>37</sup>

Peak expiratory flow variability is usually calculated as the difference between the highest and lowest PEF expressed as a percentage of the average PEF,<sup>38-40</sup> although one study showed that three or more days a week with significant variability was more sensitive and specific than calculating mean differences.<sup>41</sup>

The upper limit of the normal range for variability is around 20% using four or more PEF readings per day<sup>39, 40, 42</sup> but may be lower using twice-daily readings.<sup>43</sup> Studies have shown sensitivities of between 3% and 46% for identifying physician-diagnosed asthma.<sup>17, 38, 44</sup> One limitation of these epidemiological studies is that it is not always clear whether the participants were symptomatic at the time of the monitoring. Peak expiratory flow 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.<sup>38</sup>

Peak expiratory flow 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.<sup>45</sup>

In children, serial measures of peak-flow variability and FEV<sub>1</sub> show poor concordance with disease activity and do not reliably rule the diagnosis of asthma in or out.<sup>26</sup>

#### **Direct challenge tests**

The most widely-used method of measuring airway responsiveness relies on measuring response in terms of change in FEV<sub>1</sub> 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.<sup>46</sup> The response is usually quantified as the provocative concentration (PC<sub>20</sub>) or dose (PD<sub>20</sub>) of bronchoconstrictor required to cause a 20% fall in FEV<sub>1</sub> calculated by linear interpolation of the log concentration or dose response curve. A PC<sub>20</sub> of 8 mg/ml or less is regarded as positive.<sup>38, 47, 48</sup>

Two thirds, or more, of adults with a positive methacholine challenge have asthma and the false negative rate is less than 10%.<sup>17</sup> Tests of airway responsiveness are of little value in patients with established airflow obstruction as the specificity is low.<sup>49, 50</sup>

Methacholine challenge tests in schoolchildren only marginally increase the diagnostic accuracy after the symptom history is taken into account.<sup>51</sup> However, in a child, a negative methacholine test, which has a high negative predictive value, makes a diagnosis of asthma improbable.<sup>29</sup> 3

#### **Indirect challenge tests**

Other potentially helpful tests of variability in lung function include indirect challenges such as exercise and inhaled mannitol.<sup>52</sup> A positive response to these indirect stimuli, such as a fall in FEV<sub>1</sub> 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.<sup>52, 53</sup>

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%.<sup>17</sup> A negative response to an exercise challenge test is helpful in excluding asthma in children with exercise-related breathlessness.<sup>54</sup> 3

**C Referral for challenge tests should be considered in adults with no evidence of airflow obstruction on initial assessment in whom other objective tests are inconclusive but asthma remains a possibility.**

- ✓ A peak flow recorded when symptomatic (eg during the assessment of an asthma attack) may be compared with 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.<sup>28</sup> There are some important confounders.

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FeNO levels are:<sup>55-57</sup>

- 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.

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In steroid-naïve 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.<sup>32</sup>

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).<sup>17</sup> On this basis, approximately one in five people with a positive FeNO test will not have asthma (false positives), and conversely one in five people with a negative FeNO test will have asthma (false negatives). There are no data from primary care populations.

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It is feasible to measure FeNO in children from the age of three to four years.<sup>58</sup> In children, FeNO is closely linked with atopic status, age and height.<sup>59, 60</sup>

**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,<sup>61</sup> blood eosinophilia  $\geq 4\%$ ,<sup>62</sup> or a raised allergen-specific immunoglobulin E (IgE) to a range of common aeroallergens<sup>63, 64</sup> increase the probability of asthma in schoolchildren and adults.<sup>32, 61</sup> The PPV for individual tests are, however, poor (see Table 1). Non-atopic wheezing is as frequent as atopic wheezing in school-aged children.<sup>65</sup>

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**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.<sup>55, 66</sup> Sputum induction is feasible in school-aged children but is technically demanding and time consuming and remains a research tool.<sup>67, 68</sup> 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*<br>(Note that a single value indicates data from a single study) |                    |                    |                   | Comments**                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------|--------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                  |                                                                                                                                                                                                                                                                |                                                       | Sens <sup>i</sup>                                                                            | Spec <sup>ii</sup> | PPV <sup>iii</sup> | NPV <sup>iv</sup> |                                                                                                                                                                                                                                                                                                                                                                                                        |
| 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.<br>Most children with asthma have intermittent cough, wheeze and exercise-induced symptoms, but only about a quarter of children with these symptoms have asthma.<br>Note that the single study in preschool 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 <sup>20</sup>                 | 63%                                                                                          | 75%                | 14%                | 97%               |                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                  |                                                                                                                                                                                                                                                                | Wheeze in children <sup>20</sup>                      | 59%                                                                                          | 93%                | 34%                | 97%               |                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                  |                                                                                                                                                                                                                                                                | Cough in preschool children                           | 88%                                                                                          | 7%                 | 76%                | 15%               |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Wheeze in preschool children                                                                     | 54%                                                                                                                                                                                                                                                            | 57%                                                   | 80%                                                                                          | 27%                |                    |                   |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Shortness of breath in preschool children                                                        | 76%                                                                                                                                                                                                                                                            | 52%                                                   | 84%                                                                                          | 40%                |                    |                   |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Symptom variability                                                                              | Episodic symptoms in adults<br>Diurnal symptoms in adults<br>Symptoms after exercise in adults<br>Episodic symptoms in children <sup>18, 19</sup><br>Symptoms after exercise in children <sup>18, 19</sup><br>Nocturnal symptoms in children <sup>18, 19</sup> | Episodic symptoms in adults                           | 9–40%                                                                                        | 36–91%             | 14–86%             | 18–93%            | Asking about episodic symptoms improves the positive predictive values in children compared with 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 <sup>18, 19</sup>       | 36–93%                                                                                       | 35–93%             | 40–94%             | 62–90%            |                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                  |                                                                                                                                                                                                                                                                | Symptoms after exercise in children <sup>18, 19</sup> | 82–94%                                                                                       | 59–73%             | 54–86%             | 79–91%            |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Nocturnal symptoms in children <sup>18, 19</sup>                                                 | 57–84%                                                                                                                                                                                                                                                         | 58–78%                                                | 64–85%                                                                                       | 57–82%             |                    |                   |                                                                                                                                                                                                                                                                                                                                                                                                        |
| Combinations of symptoms (typically cough, wheeze, chest tightness, dyspnoea, exercise symptoms) | Symptom scores in adults<br>Symptom scores in children <sup>18–20</sup><br>Symptoms of cough and wheeze in preschool children                                                                                                                                  | Symptom scores in adults                              | 60%                                                                                          | 66%                | 44–94%             | 66–97%            | 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 <sup>18–20</sup>           | 45–83%                                                                                       | 85–97%             | 80%                | 51%               |                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                                                  |                                                                                                                                                                                                                                                                | Symptoms of cough and wheeze in preschool children    | 49%                                                                                          | 59%                |                    |                   |                                                                                                                                                                                                                                                                                                                                                                                                        |

Table 1: Summary of individual diagnostic tests (continued)

| Strategy                                                       | Description*                                                                                                                                                                          | Parameter*                                                                                                                                                   | Range of predictive values*<br>(Note that a single value indicates data from a single study) |                    |                    |                   | Comments**                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------|--------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                |                                                                                                                                                                                       |                                                                                                                                                              | Sens <sup>i</sup>                                                                            | Spec <sup>ii</sup> | PPV <sup>iii</sup> | NPV <sup>iv</sup> |                                                                                                                                                                                                                                                                          |
| Clinical assessment (continued)                                |                                                                                                                                                                                       |                                                                                                                                                              |                                                                                              |                    |                    |                   |                                                                                                                                                                                                                                                                          |
| 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 preschool 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%            |                                                                                                                                                                                                                                                                          |
| Strategies for demonstrating airway obstruction                |                                                                                                                                                                                       |                                                                                                                                                              |                                                                                              |                    |                    |                   |                                                                                                                                                                                                                                                                          |
| Spirometry                                                     | Regard a FEV <sub>1</sub> /FVC ratio of less than 70% as a positive test for obstructive airway disease.                                                                              | Obstructive spirometry in adults<br>Obstructive spirometry in children (5-18 yrs)                                                                            | 23-47%<br>52%                                                                                | 31-100%<br>73%     | 45-100%<br>75%     | 18-73%<br>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 |                                                                                                                                                                                       |                                                                                                                                                              |                                                                                              |                    |                    |                   |                                                                                                                                                                                                                                                                          |
| Bronchodilator reversibility                                   | In adults, regard an improvement in FEV <sub>1</sub> of ≥12% and ≥200 ml as a positive test.<br><br>In children regard an improvement in FEV <sub>1</sub> of ≥12% as a positive test. | Bronchodilator reversibility in adults<br>Bronchodilator reversibility in schoolchildren (using a threshold of 9% change in FEV <sub>1</sub> ) <sup>69</sup> | 17-69%<br>50%                                                                                | 55-81%<br>86%      | 53-82%             | 22-68%            | In these secondary care populations, about one in three people with a positive reversibility test will not have asthma (the cohorts all included people with COPD); and at least one in three people with a negative bronchodilator reversibility test will have asthma. |

Table 1: Summary of individual diagnostic tests (continued)

| Strategy                                                                   | Description*                                                                                                                                   | Parameter*                                                                                                                                                                                                                                                | Range of predictive values*<br>(Note that a single value indicates data from a single study) |                      |                      |                   | Comments**                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|----------------------|----------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                            |                                                                                                                                                |                                                                                                                                                                                                                                                           | Sens <sup>i</sup>                                                                            | Spec <sup>ii</sup>   | PPV <sup>iii</sup>   | NPV <sup>iv</sup> |                                                                                                                                                                                                                                                                                                    |
| Strategies for demonstrating variability in airway obstruction (continued) |                                                                                                                                                |                                                                                                                                                                                                                                                           |                                                                                              |                      |                      |                   |                                                                                                                                                                                                                                                                                                    |
| Challenge tests                                                            | Regard a PC <sub>20</sub> value of 8 mg/ml or less as a positive test.                                                                         | Methacholine challenge in adults.<br>Methacholine challenge in children <sup>29, 51, 70</sup>                                                                                                                                                             | 51–100%<br>47–86%                                                                            | 39–100%<br>36–97%    | 60–100%<br>20%       | 46–100%<br>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 antiasthma therapy)                                                                                                                 |
|                                                                            | Fall in FEV <sub>1</sub> ≥15% at cumulative dose of ≤635 mg is positive                                                                        | Mannitol in adults<br>Mannitol in children                                                                                                                                                                                                                | 56%<br>63%                                                                                   | 75%<br>81%           | 80%                  | 49%               | These data are from a single study in adults and children with symptoms of asthma on questionnaire.                                                                                                                                                                                                |
|                                                                            | Exercise challenge (range of thresholds used: 8-20% fall in FEV <sub>1</sub> )                                                                 | Exercise challenge in adults<br>Exercise challenge in children                                                                                                                                                                                            | 26–80%<br>69–72%                                                                             | 100%<br>69–72%       | 100%<br>90–99%       | 0%<br>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%).                                                                                                                                                                         |
|                                                                            | 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<br>- using mean variability of >20%<br>- using mean variability of >15%<br>- using diurnal variation >15% on >3 days/week<br>PEF charting in children<br>- using variation >12.3% (95 <sup>th</sup> centile) | 46%<br>3–5%<br>20%                                                                           | 80%<br>98–99%<br>97% | 97%<br>60–67%<br>82% | 10%<br>60%<br>64% | 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. |
| Strategies for detecting eosinophilic inflammation or atopy                |                                                                                                                                                |                                                                                                                                                                                                                                                           |                                                                                              |                      |                      |                   |                                                                                                                                                                                                                                                                                                    |
| FeNO                                                                       | Adults: Regard a FeNO level of 40 ppb or more as a positive test<br>Children 5–16yrs: regard a FeNO level of 35 ppb or more as a positive test | FeNO in adults<br>FeNO in schoolchildren                                                                                                                                                                                                                  | 43–88%<br>57%                                                                                | 60–92%<br>87%        | 54–95%<br>90%        | 65–93%<br>49%     | These studies are all in secondary care populations. Approximately one in five adults with a positive FeNO test will not have asthma (ie false positives) and one in five adults with a negative FeNO test will have asthma (ie false negatives).                                                  |

Table 1: Summary of individual diagnostic tests (continued)

| Strategy                                                                | Description*                                                                               | Parameter*                                                                               | Range of predictive values*<br>(Note that a single value indicates data from a single study) |                    |                    |                   | Comments**                                                                                                                                                               |
|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------|--------------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                         |                                                                                            |                                                                                          | Sens <sup>i</sup>                                                                            | Spec <sup>ii</sup> | PPV <sup>iii</sup> | NPV <sup>iv</sup> |                                                                                                                                                                          |
| Strategies for detecting eosinophilic inflammation or atopy (continued) |                                                                                            |                                                                                          |                                                                                              |                    |                    |                   |                                                                                                                                                                          |
| Blood eosinophils                                                       | Suggested thresholds for blood eosinophils:<br>Adults >4.15%<br>Children ≥4% <sup>62</sup> | Blood eosinophils in adults<br>Blood eosinophils in children                             | 15–36%<br>55–62%                                                                             | 39–100%<br>67–84%  | 39–100%<br>56–69%  | 27–65%<br>73%     | Elevated blood eosinophil level is poorly predictive. The threshold varies in these studies from 4.0–6.3%.                                                               |
|                                                                         |                                                                                            |                                                                                          |                                                                                              |                    |                    |                   |                                                                                                                                                                          |
| IgE                                                                     |                                                                                            | Any allergen-specific IgE >0.35 kU/L in adults<br>Total IgE in adults >100 kU/L          | 54–93%<br>57%                                                                                | 67–73%<br>78%      | 5–14%<br>5%        | 95–99%<br>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<br>Any positive test (wheal ≥3 mm) in children | 61–62%<br>44–79%                                                                             | 63–69%<br>56–92%   | 14–81%<br>65–92%   | 39–96%<br>36–79%  |                                                                                                                                                                          |
|                                                                         |                                                                                            |                                                                                          |                                                                                              |                    |                    |                   |                                                                                                                                                                          |

**Notes:**

\* Data derived from NICE evidence tables unless otherwise specified.<sup>17</sup> 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 methacholine 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<sub>1</sub> 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,<sup>9, 12, 13, 15, 71</sup> or which compare outcomes of diagnostic tests in different settings,<sup>16, 21, 72</sup> and some potentially useful algorithms,<sup>11, 20-22, 72</sup> or symptom questionnaires in children have been derived.<sup>18, 19</sup> This section and the associated diagnostic algorithm (*see Figure 1*), therefore, represent consensus opinion, building on the overarching principles defined in section 3.1. It is further 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,<sup>72</sup> or standard morbidity questions,<sup>15, 71</sup> as the basis for the diagnostic process.<sup>11-15, 22, 71, 72</sup> A number of studies have highlighted the diagnostic significance of episodic symptoms and confirmed wheezing as important predictors of asthma.<sup>13, 16, 18-20, 22</sup> Studies also illustrate the importance of observing events over time and documenting the basis on which a diagnosis is made.<sup>9, 72</sup>

In adults, absence of smoking and young age of onset are typically included in algorithms designed to distinguish asthma from COPD.<sup>12, 14, 15, 71, 72</sup>

#### 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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Episodic symptoms</b> (see sections 3.2.1 and 3.2.2)<sup>13, 18, 19, 21, 22 62, 73, 74</sup></p> <p>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.<sup>75</sup> For example:</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> <li>• in adults, symptoms triggered by taking non-steroidal anti-inflammatory medication or beta blockers.</li> </ul> <p>An historical record of significantly lower FEV<sub>1</sub> or PEF during symptomatic episodes compared with asymptomatic periods provides objective confirmation of the obstructive nature of the episodic symptoms.</p> |
| <p><b>Wheeze confirmed by a healthcare professional on auscultation</b> (see section 3.2.1)<sup>22</sup></p> <p>It is important to distinguish wheezing from other respiratory noises, such as stridor or rattly breathing.</p> <p>Repeatedly normal examination of chest when symptomatic reduces the probability of asthma.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <p><b>Evidence of diurnal variability</b><sup>18, 19, 22, 32, 73</sup></p> <p>Symptoms which are worse at night or in the early morning.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p><b>Atopic history</b> (see section 3.2.4)<sup>17, 22, 62, 74, 76, 77</sup></p> <p>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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>Absence of symptoms, signs or clinical history to suggest alternative diagnoses</b> (including but not limited to COPD, dysfunctional breathing, obesity) (see section 3.3.3)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

**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.<sup>22</sup> 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,<sup>17</sup> and further increase the probability of asthma.<sup>20, 22, 24</sup> However, as spirometry has a false negative rate of at least 50%,<sup>17</sup> normal spirometry does not rule out asthma.<sup>24</sup> 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<sub>1</sub> at clinic visits or by domiciliary serial peak flows to capture times with/without symptoms)
  - 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, reconsidering asthma if the clinical picture changes or an alternative diagnosis is not confirmed. If reconsidering asthma, undertake or refer for further tests to investigate for a diagnosis of asthma.

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

| <b>In patients with suspected asthma</b>                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 ( <i>see sections 7.2, 8.1, 8.4</i> ) but in more acute clinical circumstances a course of oral steroids may be appropriate ( <i>see section 9.3.3</i> ). |
| 3.                                                                                                                                        | Assess the baseline status using a validated questionnaire (eg Asthma Control Questionnaire or Asthma Control Test) ( <i>see Table 8</i> ) and/or lung function tests (spirometry or peak expiratory flow) ( <i>see sections 3.2.2, 3.2.3</i> ).                                                                                                                                                               |
| 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 ( <i>see Table 8</i> ). Lung function may be monitored with FEV <sub>1</sub> at clinic visits or domiciliary serial peak flows.                                                                                                                                                                              |
| <b>If the objective response is good (ie a clinically important improvement in symptoms and/or substantial increase in lung function)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                |
| 6.                                                                                                                                        | Confirm the diagnosis of asthma and record the basis on which the diagnosis was made.                                                                                                                                                                                                                                                                                                                          |
| 7.                                                                                                                                        | Adjust the treatment according to the response (eg, 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 ( <i>see section 5.2.2</i> ) before arranging repeat prescribing so that the patient is aware of the action to take if their control deteriorates.                                                                                                                                                                                     |
| <b>If the objective response is poor or equivocal</b>                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                |
| 9.                                                                                                                                        | Discuss adherence and recheck inhaler technique as possible causes of treatment failure.                                                                                                                                                                                                                                                                                                                       |
| 10.                                                                                                                                       | Arrange further tests or consider alternative diagnoses ( <i>see section 3.3.3</i> ). It will usually be appropriate to withdraw the treatment.                                                                                                                                                                                                                                                                |

Table 4: Clinical clues to alternative diagnoses in wheezy children

| Clinical clue                                                | Possible diagnosis                                                                                                                            |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Perinatal and family history</b>                          |                                                                                                                                               |
| 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                                                                                                    |
| <b>Symptoms and signs</b>                                    |                                                                                                                                               |
| Persistent moist cough <sup>78</sup>                         | 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                                                                             |
| <b>Investigations</b>                                        |                                                                                                                                               |
| Focal or persistent radiological changes                     | Developmental lung anomaly; cystic fibrosis; postinfective disorder; recurrent aspiration; inhaled foreign body; bronchiectasis; tuberculosis |

Table 5: Clinical clues to alternative diagnoses in adults

| Clinical clue                                                                              | Possible diagnosis                                                                        |
|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>Without airflow obstruction</b>                                                         |                                                                                           |
| 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                                                                        |
| <b>With airflow obstruction</b>                                                            |                                                                                           |
| 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 bronchiolitis; 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.<sup>20, 22, 69</sup> 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.<sup>17, 79</sup>

**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 produce reliable results on testing.

***Adults and children with airways obstruction***

Asthma is 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.<sup>17, 29, 51</sup> Alternatively, a positive FeNO test indicates the presence of eosinophilic inflammation and increases the probability of asthma.<sup>17, 32, 79-82</sup> 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.<sup>17</sup> 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 aged six and under 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.<sup>83</sup>

- ✓ 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 preschool 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:

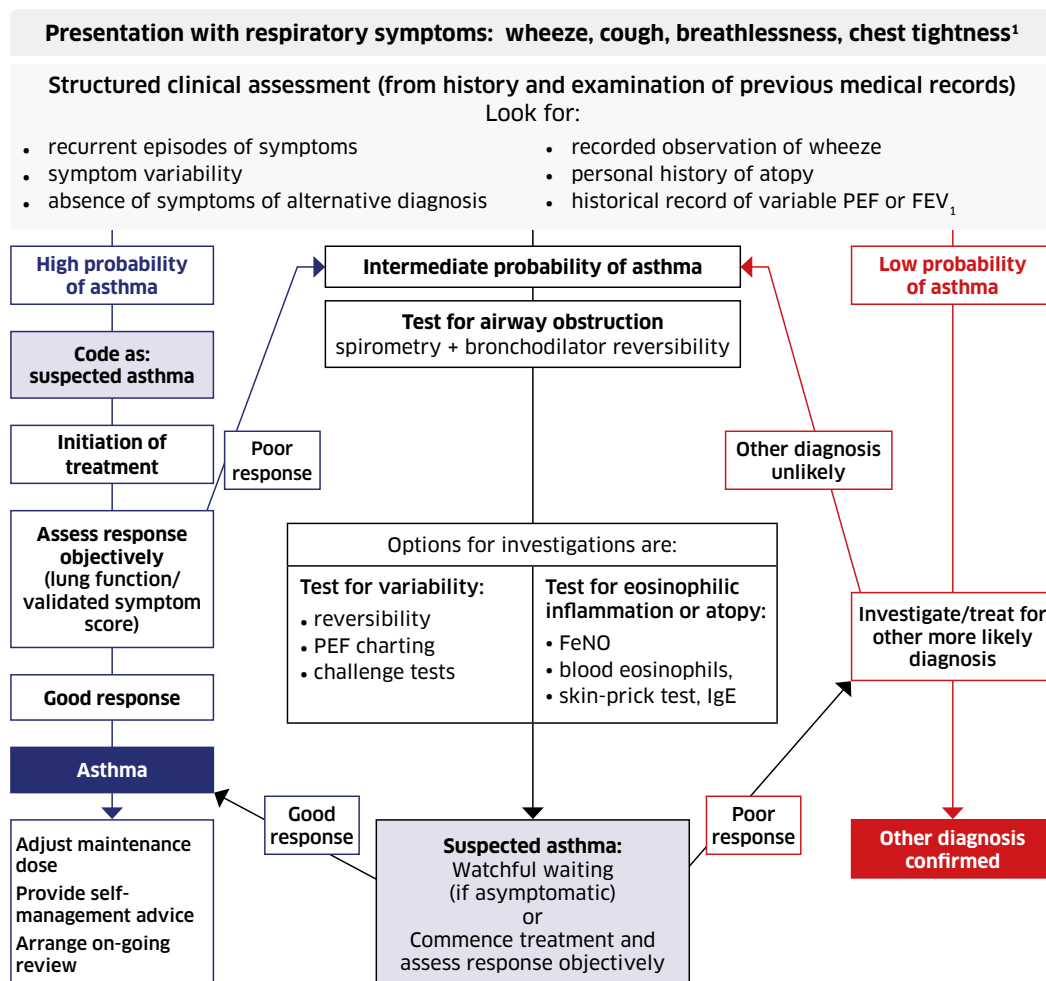
*Watchful waiting with review.* In children with mild intermittent wheeze and other respiratory symptoms that occur only with viral upper respiratory infections, it is often reasonable to give no maintenance treatment and to plan a review of the child after an interval agreed with the parents/carers.

*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 six to eight 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



<sup>1</sup> 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 probability of 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                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Referral for tests not available in primary care</b>                                                                                                  |                                                                                                       |
| 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) <sup>84</sup> |                                                                                                       |
| Poor response to asthma treatment                                                                                                                        | Poor response to monitored initiation of asthma treatment                                             |
| Severe/life-threatening asthma attack                                                                                                                    | Severe/life-threatening asthma attack                                                                 |
| <b>'Red flags' and indicators of other diagnoses</b>                                                                                                     |                                                                                                       |
| 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 possetting                                                                      |
| 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                                                                                          |
| <b>Patient or parental anxiety or need for reassurance</b>                                                                                               |                                                                                                       |

## 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.<sup>15, 71</sup>

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**C** Streamlined referral pathways should be developed for tests which are not routinely available in primary care.

### 3.5 Wheezing in preschool children and the future risk of developing persistent asthma

Several factors are associated with a risk of developing persisting wheezing or asthma through childhood.<sup>76, 85</sup> 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.<sup>86-89</sup> 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 prepubertal children. Female sex is a risk factor for the persistence of asthma in the transition from childhood to adulthood.<sup>90, 91</sup> Boys with asthma are more likely to grow out of their asthma during adolescence than girls.<sup>62, 86, 90, 92-105</sup>

#### *Severity and frequency of previous wheezing episodes*

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.<sup>74, 77, 86, 88, 94, 106-108</sup>

#### *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.<sup>109, 110</sup> 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.<sup>87, 102, 105, 111, 112</sup> 2++

#### *Abnormal lung function*

Persistent reductions in baseline airway function and increased airway responsiveness during childhood are associated with having asthma in adult life.<sup>91</sup> 3

## 4 Monitoring asthma

Regular review of people with asthma offers the opportunity to monitor current symptom control and the impact asthma is having on daily activities and quality of life, to assess future risk of asthma attacks, and to link these to management options.

Asthma is best monitored by routine clinical review on at least an annual basis by a healthcare professional with appropriate training in asthma management. The review can be undertaken in primary and/or secondary care according to clinical need and local service arrangements (*see section 14.3*). The suggested components of a review are listed in Table 7.

- ✓ The core components of an asthma review that should be assessed and recorded on at least an annual basis are current symptoms, future risk of attacks, management strategies, supported self management, and growth in children.

Table 7: Components of an asthma review

| Parameters                       | Suggested assessment                                                                                                                                                                                                                                                                                        | Further information                                                        |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| <b>Current symptom control</b>   | <ul style="list-style-type: none"> <li>• Bronchodilator use</li> <li>• Validated symptom score</li> <li>• Time off work/school due to asthma</li> </ul>                                                                                                                                                     | Section 4.2, Table 8                                                       |
| <b>Future risk of attacks</b>    | <ul style="list-style-type: none"> <li>• Past history of asthma attacks</li> <li>• Oral corticosteroid use</li> <li>• Prescription data: frequent short-acting <math>\beta_2</math> agonist (SABA) and infrequent ICS</li> <li>• Exposure to tobacco smoke</li> </ul>                                       | Section 4.3<br>Section 7.5.3<br>Sections 7.1.1, 9.1.2<br>Section 6.2.3     |
| <b>Tests/ investigations</b>     | <ul style="list-style-type: none"> <li>• Lung function (spirometry or by PEF)</li> <li>• Growth (height and weight centile) in children</li> </ul>                                                                                                                                                          | Section 4.4.1                                                              |
| <b>Management</b>                | <ul style="list-style-type: none"> <li>• Inhaler technique</li> <li>• Adherence (self report, prescription refill frequency)</li> <li>• Non-pharmacological management (trigger avoidance, breathing exercises)</li> <li>• Pharmacological management - consider multimorbidity and polypharmacy</li> </ul> | Section 8<br>Section 5.4<br>Section 6<br>Section 7<br>Sections 7.7.3–7.7.7 |
| <b>Supported self-management</b> | <ul style="list-style-type: none"> <li>• Education/discussion about self management</li> <li>• Provision/revision of a written personalised asthma action plan</li> </ul>                                                                                                                                   | Sections 5.2.1, 5.3<br>Section 5.2.2                                       |

## 4.1 Targeting care

Identifying people with poor symptom control and at future risk of asthma attacks enables targeting of care:

- at the level of the individual patient, their families and carers (eg by increasing frequency of review, commencing/increasing preventer medication, personalisation of an asthma action plan, avoiding triggers such as smoking, shifting the necessity/concerns balance for ICS treatment)
- from a public health perspective (eg addressing any inequities of care due to deprivation)
- for policy makers (ensuring access to care).

Targeting care on people/populations identified as being poorly controlled or at greater risk of asthma attacks has the potential to improve the quality of life of people with asthma and their families.

Research is needed to understand the health service impact that stepping up care for a high-risk population has on the resources available for those at lower risk. Promotion of supported self management at a policy and organisational level (*see section 5.5*) is likely to be an important strategy for ensuring the safety of all people with asthma.

## 4.2 Monitoring current asthma symptom control

When assessing asthma symptoms, a general question, such as “how is your asthma today?”, is likely to yield a non-specific answer such as, “I am OK”. Using direct questions, such as “do you use your reliever (blue inhaler) every day/or do you use it more than two times per week”, or the Royal College of Physicians’ ‘3 Questions’,<sup>113</sup> is more likely to yield useful information about current control.<sup>114</sup> Symptomatic asthma control is best measured using validated questionnaires, for example the Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) or Childhood Asthma Control Test (C-ACT) (*see Table 8*).

- ✓ When asking about asthma symptoms, use specific questions, such as the Royal College of Physicians’ ‘3 Questions’ or questions about reliever use, with positive responses prompting further assessment with a validated questionnaire to assess symptom control.
- ✓ Whenever practicable, children should be asked about their own symptoms; do not rely solely on parental report.

Table 8: Summary of tools that can be used to assess current asthma symptom control

| Measurement                                                                                                                                                                | Methodology                                                                                                                                                                | Measurement characteristics                                                                                                                        | Comments                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Royal College of Physicians '3 Questions' <sup>113</sup>                                                                                                                   | Yes/no or graded response to three questions about the impact of asthma symptoms on sleep, daytime symptoms, and activities.                                               | No to all questions consistent with controlled asthma. Any positive answers should prompt further assessment.                                      | Direct questions for use in day-to-day clinical practice, <sup>114</sup> but this is not a validated control questionnaire. |
| Asthma Control Questionnaire (ACQ) <sup>115-118</sup>                                                                                                                      | Five questions about symptoms over the preceding week plus optional reliever use and FEV <sub>1</sub> <sup>117</sup>                                                       | Well controlled $\leq 0.75$<br>Poor control $\geq 1.5$<br>Minimal important difference 0.5                                                         | Well validated in adults and children aged 5 and over.<br>Available in many languages                                       |
| Asthma Control Test (ACT) <sup>119, 120</sup> and Childhood ACT (C-ACT) for 4-11 year olds <sup>121</sup>                                                                  | ACT: five questions about symptoms, reliever use, and overall control over preceding four weeks.<br><br>C-ACT: seven questions, four for the child, three for parent/carer | Poor control $< 20$<br>Minimal important difference 3 <sup>122</sup>                                                                               | ACT well validated in adults and C-ACT in children 4-11 years                                                               |
| Mini Asthma Quality of Life Questionnaire (AQLQ) <sup>116, 123, 124</sup><br><br>Paediatric Asthma Quality of Life Questionnaire (PAQLQ) for 7-11 year olds <sup>125</sup> | 15 questions in four domains (symptoms, activity limitations, emotional function and environmental stimuli) over preceding two weeks.<br><br>The PAQLQ has 23 questions    | Mean score (between one and seven) across the four domains; higher scores indicate better quality of life.<br><br>Minimal important difference 0.5 | Mini AQLQ well validated in adults and PAQLQ in children 7-11 years.                                                        |

### 4.3 Predicting future risk of asthma attacks

Identifying future risk of asthma attacks is an important component in the delivery of personalised asthma care.<sup>126</sup>

#### 4.3.1 Adults

It is possible to identify an adult with asthma at increased risk of an asthma attack and to stratify the degree of risk associated with different markers. The factors associated with increased risk in adults are shown in Table 9.

2++  
3

Table 9: Factors associated with increased risk of future asthma attacks in adults

| Level of increased risk                        | Factor                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Greatly increased risk</b>                  | History of previous asthma attacks <sup>127-137</sup>                                                                                                                                                                                                                                                      |
| <b>Moderately increased risk</b>               | Poor control <sup>128, 131-136, 138-142</sup> (assess at every routine review using objective patient-reported control questionnaires, eg ACT <sup>129, 135, 136, 141</sup> or ACQ <sup>133, 139</sup> )<br>Inappropriate or excessive SABA use <sup>127, 132, 140, 142</sup>                              |
| <b>Slightly increased risk</b>                 | Older age <sup>127, 132, 137, 143</sup><br>Female <sup>127, 131, 132, 137, 143</sup><br>Reduced lung function <sup>127, 130, 133, 135, 142</sup><br>Obesity <sup>127, 130, 132, 143</sup><br>Smoking <sup>127, 132, 143</sup><br>Depression <sup>132, 143, 144</sup>                                       |
| <b>Unclear (evidence limited or equivocal)</b> | A history of anaphylaxis <sup>127, 132</sup><br>Comorbid gastro-oesophageal reflux <sup>127, 132</sup><br>COPD <sup>143</sup><br>Raised FeNO at routine reviews <sup>129, 138, 145, 146</sup><br>Blood eosinophilia <sup>127, 129, 132, 136, 146-148</sup><br>Poor adherence <sup>127, 136, 149, 150</sup> |

There is insufficient evidence in adults to say if the following factors are associated with an increased risk of future asthma attacks: concomitant prescription of paracetamol or non-steroidal anti-inflammatory medicines,<sup>132</sup> deprivation,<sup>143</sup> being underweight,<sup>143</sup> frequent febrile upper respiratory tract infection,<sup>137</sup> diabetes,<sup>132</sup> pollution,<sup>151</sup> black or Indian ethnicity,<sup>130, 136</sup> stepping down ICS treatment.<sup>137</sup>

#### 4.3.2 School-aged children

It is possible to identify a child (aged 5–12 years) with asthma who is at increased risk of an asthma attack and to stratify the degree of risk associated with different markers. The factors associated with an increased risk in school-aged children are shown in Table 10.<sup>152</sup>

2++

Table 10: Factors associated with an increased risk of future asthma attacks in school-aged children<sup>152</sup>

| Level of increased risk             | Factor                                                                                                                                                                                                                                                    |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Greatly increased risk</b>       | A history of previous asthma attacks<br>Persistent asthma symptoms                                                                                                                                                                                        |
| <b>Moderately increased risk</b>    | Suboptimal drug regimen (the ratio of the number of prescriptions for controller medication to total number of prescriptions for asthma medication <0.5 <sup>153</sup> )<br>Comorbid atopic/allergic disease<br>Low-income family<br>Vitamin D deficiency |
| <b>Slightly increased risk</b>      | Younger age<br>Exposure to environmental tobacco smoke<br>Obesity<br>Low parental education                                                                                                                                                               |
| <b>No increased risk</b>            | Gender<br>Urban residence                                                                                                                                                                                                                                 |
| <b>Unclear (evidence equivocal)</b> | Reduced lung function<br>Raised FeNO at routine reviews<br>Positive skin-prick tests<br>History of allergen exposure                                                                                                                                      |

There is insufficient evidence in children to say if the following factors are associated with an increased risk of future asthma attacks: serum total IgE, family history of atopy, age of onset of asthma, duration of asthma, comorbidities (gastro-oesophageal reflux disease, diabetes), special needs, parental health, parental marital status.

#### 4.3.3 Preschool children

Evidence to support risk prediction in preschool children (under 5 years of age) is limited. One large UK-based study (n=424,326; 17,320 under 5) in primary care concluded that it was possible to identify a preschool child with asthma at increased risk of an asthma attack.<sup>143</sup> Young children treated with regular preventer medication had an incremental increase in risk of an asthma attack reflecting the severity of their asthma. Other markers of slight/moderate increased risk were comorbid atopic disease, younger age, low socioeconomic status, male gender, and being overweight.

A US study of 300 preschool children measured differences in response to various treatment strategies, and concluded that those with raised blood eosinophils (>200/ $\mu$ L) and sensitisation to at least one aeroallergen had the greatest increased risk of future asthma attack but also the most favourable response to daily ICS therapy overall.<sup>154</sup>

>12 yrs   5-12 yrs   <5 yrs

|   |                                                                                                                                                                                           |   |                                                                                                                                                                                    |
|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| D | B                                                                                                                                                                                         | D | Assess risk of future asthma attacks at every asthma review by asking about history of previous attacks, objectively assessing current asthma control, and reviewing reliever use. |
|   | B                                                                                                                                                                                         | D | In children, regard comorbid atopic conditions, younger age, obesity, and exposure to environmental tobacco smoke as markers of increased risk of future asthma attacks.           |
| D |                                                                                                                                                                                           |   | In adults, regard older age, female gender, reduced lung function, obesity, smoking, and depression as markers of a slightly increased risk of future asthma attacks.              |
| ✓ | Clinicians should target care (including tailoring frequency of review, optimising pharmacological therapy, personalising supported self management) to reduce the patient's risk status. |   |                                                                                                                                                                                    |
| ✓ | Healthcare policy should target vulnerable groups, ensure equitable access to care, and promote reduction in environmental tobacco smoke.                                                 |   |                                                                                                                                                                                    |

#### 4.3.4 People with severe asthma

In children and adults with severe asthma (defined as more than two asthma attacks a year or persistent symptoms with SABA use more than twice a week despite specialist-level therapy; *see section 7.5*), evidence from observational studies shows that a history of asthma attacks, current level of symptom control and lung function provide valuable knowledge to evaluate risk of future asthma attacks. These patients will usually be under the care of a specialist asthma clinic. Predictors of future attacks were:

- previous asthma attack<sup>128, 129, 133, 142</sup>
- very poor symptom control in adults<sup>128, 133, 140, 142, 155</sup>
- greater SABA use<sup>140, 142</sup>
- lower lung function (PEF or FEV<sub>1</sub> in adults; PEF or FEV<sub>1</sub>/FVC ratio in children)<sup>133, 142</sup>
- raised FeNO.<sup>129</sup>

3

>12 yrs   5-12 yrs   <5 yrs

|   |   |  |                                                                                                                                                                                                               |
|---|---|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| D | D |  | In individuals with severe asthma, assess risk of future asthma attacks at each visit by asking structured questions about asthma control, reviewing history of previous attacks and measuring lung function. |
|---|---|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## 4.4 Physiological measures

### 4.4.1 Spirometry and peak expiratory flow

Both spirometry and PEF are widely available (*see section 3.2*). Spirometry is reproducible, demonstrates airflow obstruction and can be used in children as young as five. The lower limit of normal should be used to define obstruction rather than a fixed FEV<sub>1</sub>/FVC ratio.<sup>156, 157</sup>

In adults, there is evidence that reduced lung function (PEF or FEV<sub>1</sub>) is associated with an increased risk of acute attacks.<sup>127, 128, 130, 133, 135, 142</sup> The evidence in children is less clear,<sup>152</sup> although reduced lung function (PEF or FEV<sub>1</sub>/FVC ratio) has been identified as a risk factor in children with severe asthma (*see section 4.3*).<sup>133, 142</sup>

Some adult patients have an accelerated decline in lung function in terms of FEV<sub>1</sub>. Risk factors and treatment strategies for these patients are poorly defined and further research in this area is a priority.

### 4.4.2 Fractional exhaled nitric oxide

The evidence for use of biomarkers largely relates to fractional exhaled nitric oxide (FeNO) testing. FeNO testing is non-invasive and potentially suitable for adults and schoolchildren and is less reliant on operator skill than, for example, spirometry. Results can, however, be affected by other factors (*see section 3.2.4*) and a normal result in a person with non-eosinophilic asthma may be falsely reassuring; results must be interpreted correctly within the clinical context of each individual.

There is some evidence from systematic reviews that the use of FeNO testing to guide the management of asthma in adults and children may reduce exacerbation rates or their severity, but not have an impact on symptom control.<sup>158-160</sup> Different FeNO cut-offs and heterogeneous outcome measures and definitions amongst the included studies are reflected in inconsistent outcomes. For example, in one review, adults in the FeNO group had fewer asthma attacks than those in the control group but there was no effect on steroid courses or hospitalisations.<sup>158</sup> All the reviews concluded that, although there may be some benefit in those experiencing frequent exacerbations, there is insufficient evidence to recommend the routine use of FeNO testing for the monitoring of asthma in adults or children.

1++  
1+

**B** Except in specialist asthma clinics, the routine use of FeNO testing to monitor asthma in adults or children is not recommended.

### 4.4.3 Eosinophils

A systematic review of six RCTs (five in adults) including 374 adults and 55 children with asthma, showed that the use of sputum eosinophil analysis to guide treatment can reduce asthma exacerbation rates in adults. None of the studies, however, showed a difference in ICS use between the groups. The included studies were heterogeneous in design with different outcomes, eosinophil percentages and definitions of, for example, exacerbation, making comparison difficult. Five of the six studies did not group patients by asthma severity. There was insufficient evidence in children on which to base conclusions.<sup>161</sup>

1++

Further research is needed to determine which patients are most likely to benefit from this approach. However, the limited availability and technical demands of undertaking sputum eosinophil analysis mean it is unlikely to be a useful approach in routine clinical practice (*see section 3.2.4*).

Blood eosinophil analysis may be a useful predictor of future risk of asthma attacks in adults (*see Table 9*) but no studies were found that evaluated the use of blood eosinophil analysis for the routine monitoring of asthma.

**B The routine use of sputum eosinophilia to monitor asthma in adults or children is not recommended.**

## 4.5 Other approaches

A number of other approaches have been explored, including lung sound analysis, an index of bronchial asthma control in adults,<sup>162</sup> and exhaled breath temperature in children.<sup>163</sup> There is currently insufficient evidence on these approaches on which to base a recommendation.

3

## 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”.<sup>164</sup> 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.<sup>165</sup>

### 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.<sup>166-187</sup> In addition, 35 RCTs provide further evidence about self management in preschool children,<sup>188-196</sup> ethnic minorities,<sup>197-208</sup> and primary care-based populations.<sup>206, 209-217</sup>

1++  
1+  
1-  
2++  
2+  
2-

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

- reduces emergency use of healthcare resources, including emergency department (ED) visits, hospital admissions and unscheduled consultations<sup>166, 168, 172-175, 177, 187</sup>
- improves markers of asthma control, including reduced symptoms and days off work, and improves quality of life.<sup>166, 168, 169, 175, 177-179</sup>

1++  
1+  
2++  
2+

Patients with all severities of asthma were included in these systematic reviews, although some focused specifically on people who had attended EDs,<sup>187</sup> or with severe or difficult asthma.<sup>172</sup> Most self-management education was delivered in healthcare settings, but some specifically evaluated school,<sup>181</sup> home,<sup>183</sup> or community-based interventions.<sup>184</sup> Typically, education was delivered by healthcare professionals either in individual consultations or group settings, but some systematic reviews included technology-based interventions,<sup>170, 171</sup> or were part of community-health interventions for deprived and/or ethnic minority groups.<sup>185, 186</sup>

### 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<sup>166, 172, 187</sup> and children.<sup>173-177</sup> There is evidence that educational interventions that were supported by a written PAAP and regular professional review were more effective than less intensive regimes.<sup>166, 169, 174, 176, 177</sup>

1++  
1+  
2++  
2+

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.<sup>170</sup>

### 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/advice/manage-your-asthma/action-plans](http://www.asthma.org.uk/advice/manage-your-asthma/action-plans)) are crucial components of effective self-management education.<sup>91, 166, 168, 178-180, 187</sup> One systematic review identified the features of PAAPs associated with beneficial outcomes (see Table 11).<sup>168</sup>

These include:

- specific advice about recognising loss of asthma control, assessed by symptoms or peak flows or both.<sup>91, 168, 169</sup> In children, symptom-based written plans are effective in reducing emergency consultations for asthma, although (in older children) plans based on peak flow may be as effective for other outcomes.<sup>178, 179</sup> 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 fourfold (as opposed to just doubling) ICS, as appropriate to clinical severity (see Table 11 for further advice).<sup>168</sup>

**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 occupational exposure to support people and their families living with asthma.
- Every opportunity should be taken to remind patients and carers of the importance of achieving a smoke-free environment.
- 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 11 Summary of the key components of a written personalised asthma action plan (adapted from Gibson et al)<sup>168</sup>

| Component of an action plan                                                                                                                         | Result                                                                                                    | Practical considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>Format of action points:</i></p> <p>Symptom v peak-flow triggered</p> <p>Standard written instructions</p> <p>Traffic light configuration</p> | <p>Similar effect</p> <p>Consistently beneficial</p> <p>Not clearly better than standard instructions</p> | <p>Asthma UK personalised asthma action plans include both symptoms and peak-flow levels at which action should be taken (<i>see <a href="http://www.asthma.org.uk/advice/manage-your-asthma/action-plans">www.asthma.org.uk/advice/manage-your-asthma/action-plans</a></i>).</p>                                                                                                                                                                                                                    |
| <p><i>Number of action points:</i></p> <p>2–3 action points</p> <p>4 action points</p>                                                              | <p>Consistently beneficial</p> <p>Not clearly better than 2–3 points</p>                                  | <p>Suggested action points in PAAPs are:</p> <p>PEF &lt;80% best: quadruple inhaled corticosteroids (<i>see section 5.2.3</i>)</p> <p>PEF &lt;60% best: commence oral steroids and seek same-day medical advice</p> <p>PEF &lt;50% best: seek urgent medical advice</p>                                                                                                                                                                                                                              |
| <p><i>Peak expiratory flow (PEF) levels:</i></p> <p>Based on percentage personal best PEF</p> <p>Based on percentage predicted PEF</p>              | <p>Consistently beneficial</p> <p>Not consistently better than usual care</p>                             | <p>Personal best should be assessed once treatment has been optimised and peak flows are stable. Best peak flow should be updated every few years in adults, and, if a peak flow is being used, more frequently in growing children.</p>                                                                                                                                                                                                                                                             |
| <p><i>Treatment instructions:</i></p> <p>Individualised using inhaled and oral steroids</p>                                                         | <p>Consistently beneficial</p>                                                                            | <p>Adults may be advised to quadruple their inhaled corticosteroid dose (<i>see section 5.2.3</i>).</p> <p>For those on maintenance and reliever therapy (MART) regimes (<i>see section 7.3.5</i>).</p> <p>Patients who have stopped medication should be reminded to restart their inhaled corticosteroids.</p> <p>Patients may safely hold an emergency supply of prednisolone tablets for use if their symptoms continue to deteriorate and/or if their peak flow falls to 60% of their best.</p> |

### 5.2.3 Increasing inhaled corticosteroids to abort an asthma attack

Regular, daily use of preventer medication is the best means of avoiding asthma attacks and the need for increased (rescue) doses of ICS. Trials of PAAPs have typically included advice to increase the dose of ICS at the start of an asthma attack in an attempt to abort the attack.

Overall, a Cochrane review including eight RCTs, five in adults (n=1,247) and three in children (n=422, age range 3–18), in people with mild to moderate asthma, showed no significant difference in the odds of requiring rescue oral corticosteroids or of having adverse events between those taking an increased dose of ICS for an exacerbation and those continuing with a stable dose, although the authors did not rule out the possibility of benefits in some patient groups.<sup>218</sup> However, the doses of ICS used during exacerbations, maintenance doses of ICS and concomitant medications varied between studies. Six of the eight studies recommended doubling ICS during attacks, four of which reported 'high' adherence (>80%) with maintenance regimes. One of the included studies reported that quadrupling ICS did not reduce the number of steroid courses, although it halved the risk of needing oral steroids in the subgroup (23%) who needed to start the increased dose. Another of the included studies reported that quintupling ICS significantly reduced the number of patients with attacks requiring steroids compared with steady low-dose ICS (18% v 38%).<sup>1++</sup>

A further pragmatic RCT in adults aged 16 and over (n=1,871) with broad inclusion criteria evaluated quadrupling the patient's usual ICS dose for up to 14 days at the start of an asthma attack as part of a personalised self-management plan. They reported 19% fewer severe asthma exacerbations in those receiving the increased dose (adjusted hazard ratio 0.81, 95% confidence interval (CI) 0.71 to 0.92), although the absolute benefit was small (proportion requiring oral steroids was 45% v 52% in the intervention and control groups, respectively). The number of hospitalisations was significantly lower in the intervention group although admissions were infrequent (0.3% v 1.9%). Local candidiasis and oral dysphonia occurred more frequently in the intervention compared with the control group (7% v 2%).<sup>219</sup><sup>1+</sup>

In contrast, an efficacy trial in children aged 5–11 years (n=254) with a reported adherence to daily ICS of 98%, evaluated quintupling a standardised dose of fluticasone for seven days at the early signs of loss of asthma control. There was no significant difference in severe attacks between those receiving the increased dose and those who continued on the lower dose. There was a non-significant trend to a lower growth rate in the intervention group.<sup>220</sup><sup>1+</sup>

It may be that highly adherent patients have little extra to gain by increasing ICS and that, in many patients, the beneficial effect arises because adherence to regular preventer therapy was poor. There is no evidence in 'real world' situations, where non-adherence is widespread, to inform recommendations in those under 16 years of age, although effective PAAPs in children have included this step.

The use of a single combination inhaler for maintenance and reliever therapy (MART) is an alternative approach to the introduction of a fixed-dose twice-daily combination inhaler which ensures an increased dosage of ICS as formoterol reliever treatment is increased (*see section 7.3.5* for a description of the MART regime). This approach might suit some individuals.

**B** In personalised asthma action plans for adults, consider advising quadrupling ICS at the onset of an asthma attack and for up to 14 days in order to reduce the risk of needing oral steroids.

- ✓ • Consider adherence before recommending increasing ICS as patients who are highly adherent (>90%) may have a ceiling effect and gain no additional benefit from increasing ICS at the onset of an attack.
- Weigh the benefit/risk ratio of recommending quadrupling ICS at the start of an asthma attack in people already on high dose ICS especially if they are experiencing frequent attacks and/or are still requiring oral steroids.

- ✓ For people on fixed-dose combination inhalers, increasing the dose of ICS may best be achieved by adding a single ICS inhaler.

### 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:

- reduce emergency use of healthcare resources, including ED attendances, hospital admissions and unscheduled consultations<sup>206, 212</sup> 1++  
1+
- improve markers of asthma control.<sup>206, 209, 210, 212-215, 221</sup>

Implementation of self-management interventions is challenging. The improved asthma control demonstrated in trials of interventions delivered by members of the research team<sup>206, 212</sup> or in a centrally administered initiative<sup>213, 214</sup> are reflected in some,<sup>209, 210, 215, 221</sup> but not all,<sup>216, 217</sup> trials in which members of the practice team are trained to deliver self-management education in routine clinical care. 1++  
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One study showed no difference in outcomes when self-management education was delivered by lay people compared with practice asthma nurses.<sup>211</sup> Studies based in the USA suggest that in deprived and/or ethnic communities the involvement of community health workers reduces ED attendance.<sup>184</sup> 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 from 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<sup>187</sup> or hospital admissions<sup>207, 222</sup> can reduce subsequent use of healthcare resources. Self-management education delivered prior to discharge can reduce readmissions and should be a core component of discharge planning (*see section 9.9.7*).<sup>223-225</sup> **1++**

One wide-reaching review of the evidence for self management in people with 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.<sup>172</sup> **2+**

**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)<sup>181</sup>
- improve markers of asthma control (number of days and nights with asthma symptoms, school absences, asthma-related quality of life).<sup>181, 182</sup>

The considerable heterogeneity in school-based interventions means it is not possible to specify which components should be included. Interventions incorporated combinations of classroom teaching for all pupils, peer support groups, individual education sessions with school nurses, interactive computer programmes, and involvement of parents.<sup>181</sup> **1+ 1-**

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

### 5.3.4 Preschool children

There is a paucity of evidence about effective self-management strategies delivered to parents of preschool children. Trials recruiting only preschool children (aged five years or under) showed no impact on emergency use of healthcare resources, including ED visits, hospital admissions and unscheduled consultations,<sup>190, 195</sup> and no<sup>190</sup> or limited<sup>195</sup> reduction in symptoms, despite increased ownership of PAAPs.<sup>195</sup>

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Other trials including preschool children and children up to the age of eight years showed only small and often transient effects of no apparent clinical significance.<sup>188, 189, 192-194</sup>

### 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,<sup>186, 197-205</sup> can:

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- reduce emergency use of healthcare resources, including ED attendances, hospital admissions and unscheduled consultations<sup>185, 186, 200, 201, 203</sup>
- improve markers of asthma control<sup>185, 186, 197, 198, 201, 203</sup>
- improve process outcomes (knowledge).<sup>185, 186, 202, 204</sup>

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 with the benefits seen in the white European population.<sup>206, 207</sup>

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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 with a white European group.<sup>206, 207</sup>

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The strategies employed in ethnic minority groups are varied and include community-based neighbourhood projects,<sup>199, 203, 204</sup> family-based education,<sup>200</sup> nurse-led home visits,<sup>198</sup> IT-based programmes,<sup>197, 201, 202</sup> and school-based educational interventions.<sup>201, 205</sup> No single 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.<sup>198, 199, 203, 204</sup> Reconfiguration of the supporting healthcare system appears to increase the impact.<sup>186</sup>

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**B**

**Culturally appropriate supported self-management education should be provided for people with asthma from 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.<sup>226</sup> Sharing decision making and achieving concordance improves, though does not guarantee, adherence.<sup>227</sup>

### 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%.<sup>228, 229</sup> The lack of evidence supporting long-term peak-flow monitoring,<sup>37, 230-232</sup> 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.<sup>232</sup> Comparison should be with the patient's best (not predicted) peak flow.<sup>168</sup>

It is estimated that between a third and a half of all medicines prescribed for long-term conditions are not taken as recommended.<sup>233</sup> Evidence in people with asthma confirms that there is widespread non-adherence to regular preventer medication<sup>234-239</sup> that increases over time.<sup>234, 236</sup> Poor adherence should always be considered when there is a failure to control asthma symptoms.

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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).<sup>233</sup>

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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.<sup>240</sup> The relative weight of these opposing arguments influences the decision to take medication (or not).<sup>241, 242</sup>

### 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<sup>233, 236, 239</sup> or dose counting.<sup>234, 235</sup> This applies both in trial populations<sup>234, 236, 239</sup> and clinical settings.<sup>235</sup> Underuse is over-reported,<sup>234-236, 239</sup> and overuse is under-reported,<sup>239</sup> reflecting socially acceptable answers.<sup>233</sup> Patients/caregivers who report missing doses or not taking medication are likely to be non-adherent,<sup>233, 235, 236</sup> though their estimate of dosages taken may still be inaccurate.<sup>233</sup> 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.<sup>233</sup> Questionnaires have been validated for use in research,<sup>240</sup> but have not been validated as a tool in clinical use.<sup>233</sup>

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#### *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 do not correlate with self-reported adherence and may be a useful strategy for opening a discussion about suspected poor adherence.<sup>241</sup> 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.<sup>237, 238, 241, 243</sup>

#### *Biomarker testing*

Biomarker testing with FeNO or biochemical urinary assays (for example for a metabolite of fluticasone propionate) may have a role in establishing (non-) adherence in people with severe/difficult asthma.<sup>244, 245</sup> 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*).<sup>244</sup>

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#### *Electronic monitoring*

Electronic monitoring is the gold standard for assessing adherence in the research context, although not normally available in routine clinical practice.<sup>236, 239</sup> Dose counting is also used as a comparator, although unlikely to be feasible in a clinical context.<sup>234, 235</sup>

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**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

Five systematic reviews were identified that evaluated interventions to improve adherence in people with asthma.<sup>246-250</sup> Multifaceted interventions have demonstrated modest improvements in adherence,<sup>249-253</sup> the clinical significance of these improvements is, however, unclear with limited, or sometimes no, observed effect on clinical outcomes.<sup>248, 250, 251, 253-255</sup>

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The observed effect was greater if the intervention:

- included behavioural components (studies were in mixed populations with chronic conditions, including asthma)<sup>256-258</sup>
- included practical facilitators (such as simplified dosage regimes),<sup>253</sup> strategies to aid integration into daily routines,<sup>259</sup> and automated reminders<sup>249, 251, 252, 254, 255, 260</sup>
- is monitored, delivered and sustained as part of a comprehensive programme of accessible proactive asthma care.<sup>249</sup>

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IT-based strategies to support adherence such as text message reminders in children and young people,<sup>251, 252, 260</sup> feedback on adherence,<sup>255</sup> and refill reminders,<sup>254</sup> showed some promise, especially if they were interactive,<sup>247, 254, 255</sup> although it is unclear how long improvements in adherence are sustained.

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The value of electronic interventions to support adherence may be diminished in patient groups who are either unable to, or lack confidence in, accessing electronic formats, for instance some older adults and those with a learning disability or cognitive impairment. The financial implications of accessing applications on mobile devices, for example for low-income families, also need to be considered. Some studies included financial incentives.

School-based interventions depend on the child actually being at school and having someone to deliver the intervention at the school in a consistent manner. This has practical implications for implementation, for example the need for training.

Overall, interventions to improve medication adherence do not clearly improve clinical outcomes, and should therefore be considered as components of, as opposed to replacement for, ongoing supportive care (*see section 14.4.1*).<sup>249</sup>

**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<sup>249</sup>
  - 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.<sup>261, 262</sup> Implementation in routine clinical practice depends as much on the context in which it is delivered as the content of the intervention. Despite the diversity of healthcare systems, 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.<sup>263</sup> In addition, 19 implementation studies from the USA,<sup>213, 216, 264-270</sup> UK,<sup>8, 217, 271, 272</sup> Scandinavia,<sup>273-275</sup> Italy,<sup>276</sup> and Brazil<sup>277, 278</sup> were identified.

### 5.5.1 Types of intervention

The interventions in the implementation studies adopted four main strategies:

- primarily professional training<sup>216, 217</sup>
- primarily organisational change<sup>8, 271, 273</sup>
- primarily patient education<sup>213, 265-268, 276</sup>
- a whole systems approach with components operating explicitly at patient, professional and organisational levels.<sup>264, 269, 270, 272, 274, 275, 277, 278</sup>

Study designs varied and included five cluster randomised trials,<sup>216, 217, 266, 267, 271</sup> a preference trial with randomised groups,<sup>213</sup> a controlled implementation study,<sup>8</sup> eight studies based on longitudinal, often large, databases,<sup>264, 265, 268-270, 274, 275, 278</sup> one control cohort,<sup>277</sup> two uncontrolled before-and-after studies,<sup>272, 276</sup> and one cross-sectional study.<sup>273</sup>

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:

- improved knowledge<sup>270</sup> and action plan ownership<sup>263, 268, 272</sup>
- reduced unscheduled care,<sup>268-270, 274, 277, 278</sup> and improved markers of control.<sup>269, 270, 274, 275</sup>

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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.<sup>216, 217</sup> Organisational change to support self management improves process outcomes such as the proportion of patients with PAAPs or achieving a review,<sup>8, 271, 273</sup> but improved asthma control in only one of the studies.<sup>273</sup> Targeting the patient with educational material,<sup>268</sup> support from pharmacists,<sup>265</sup> school,<sup>266, 276</sup> or telephone calls<sup>213, 266, 267</sup> improved medication use,<sup>213, 267</sup> knowledge<sup>266</sup> and ownership of PAAPs,<sup>265</sup> and had variable effects on clinical outcomes.

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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 prevention activities as follows:
- primary prevention – interventions introduced before the onset of disease and designed to reduce its incidence.
- 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 Monofaceted 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 there may be a role for multifaceted interventions which involve both dietary allergen reduction and environmental change to reduce exposure to inhaled allergens. Such interventions reduced the odds of a doctor diagnosing asthma later in childhood by half in those over five years of age, odds ratio (OR) 0.52, 95% CI 0.32 to 0.85.<sup>279</sup> 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.<sup>280</sup> **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.<sup>281</sup> Sensitisation to house dust mite is an important risk factor for the development of asthma,<sup>282, 283</sup> and a few studies have suggested that exposure to high levels of house dust mites early in life increases the risks of subsequent asthma.<sup>284, 285</sup> 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.<sup>286</sup>

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;<sup>287</sup> others have shown no effect on either allergic sensitisation or symptoms of allergic diseases.<sup>288</sup> 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.<sup>289</sup> Subsequent results showed a paradoxical effect with increased allergy but better lung function in the intervention group.<sup>290</sup>

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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 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.<sup>291</sup> Another concluded, in contrast, that perinatal dog exposure protects against asthma, with no effect from cats.<sup>292</sup> 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.<sup>293,</sup>

<sup>294</sup> The most methodologically sound review pooled individual participant data

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from 11 European birth cohort studies 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.<sup>294</sup> 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.

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**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.<sup>295</sup> Food allergen avoidance in pregnancy and postnatally has not been shown to prevent the later development of asthma.<sup>296</sup> Allergen avoidance during pregnancy may adversely affect maternal, and perhaps fetal, nutrition.<sup>297</sup> High-dose food allergen exposure during pregnancy may reduce subsequent sensitisation rates by inducing tolerance.<sup>298</sup>

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**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.<sup>299</sup> However, not all studies have demonstrated benefit and a large birth cohort study reported no protective effect against atopy and asthma.<sup>300</sup>

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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.<sup>301</sup> A review of the use of soy formulae found no significant effect on asthma or any other allergic disease.<sup>302</sup>

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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.<sup>303</sup> In one study late introduction of egg was associated with a non-significant increase in wheezing in preschool children.<sup>304</sup>

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.<sup>303</sup> Two RCTs 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.<sup>305</sup> 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.<sup>306</sup>

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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),<sup>307</sup> or vitamin E based on maternal pregnancy intake.<sup>308</sup> 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.<sup>303</sup> 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.<sup>309, 310</sup> A high birth weight is also associated with a higher risk of asthma.<sup>309</sup> The quality of the evidence is, however, low as there was no adjustment for confounders. 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 body mass index (BMI) increases the risk of incident asthma, with a dose-dependent relationship that was stronger in boys.<sup>311, 312</sup> 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<sup>2</sup> 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).<sup>313</sup> 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.<sup>314, 315</sup>

The concept is sometimes described as the 'microbial exposure hypothesis'. A double-blinded 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.<sup>316</sup> There remains insufficient understanding of the ecology of gut flora in infancy in relation to outcomes. Bifidobacteria may be more important than lactobacilli in reducing susceptibility to allergic disease.<sup>317</sup>

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

#### 6.1.10 Avoidance of tobacco smoke and other air pollutants

No evidence was identified 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.<sup>318–321</sup> Evidence suggests that early-life ETS exposure is associated with later persistent asthma,<sup>322, 323</sup> with a strong interaction with genetic polymorphisms which affect antioxidant activity.<sup>324</sup> 2+

**B** Current and prospective parents 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.<sup>325-327</sup> 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.<sup>328</sup> 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.<sup>329</sup>

2+

Investigation of the effects of other childhood immunisation suggests that at worst there is no influence on subsequent allergic disease and may be some protective effect against the development of asthma.<sup>330</sup>

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

## 6.2 Secondary 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 uncertainty 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 systematic review of 72 studies (64 RCTs and eight non-RCTs) included 37 studies evaluating single interventions (seven acaricides, nine air purification, one high-efficiency particulate air-filtration, 17 mattress covers, two pest-control measures, one pet removal) and 30 studies evaluating multicomponent strategies. The included studies enrolled adults, children or mixed populations. Taking a narrative approach, the review concluded that single component interventions are not effective at improving asthma control or reducing asthma attacks despite HDM levels being significantly reduced in many studies. Multicomponent interventions were found to have some clinical effects. However, the heterogeneity of interventions, how studies were combined and the small number of studies precluded definitive conclusions.<sup>331</sup> There is, therefore, continuing clinical uncertainty about which HDM avoidance measures may be clinically effective in asthma and further research is required.

1+

**B** 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) should not be routinely recommended by healthcare professionals for the management of asthma.

### 6.2.2 Other allergens

Animal allergens, particularly from cats and dogs, are potent provokers of asthma symptoms. The reported effects of removal of pets from homes are paradoxical, with either no benefit for asthma<sup>332, 333</sup> or a potential for continued high exposure to induce a degree of tolerance.<sup>334</sup> In homes where there is no cat but still detectable cat allergen, there may be a benefit from introducing additional avoidance measures such as high-efficiency vacuum cleaners for patients allergic to cats, although there is insufficient evidence on which to base a recommendation.<sup>331</sup>

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.<sup>331</sup>

Studies of individual aeroallergen avoidance strategies show that single interventions have limited or no benefit.<sup>331</sup> A multifaceted approach is more likely to be effective if it addresses all the indoor asthma triggers but there remains considerable uncertainty about which, if any, are the most effective strategies.<sup>331</sup> 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. A systematic review of this topic concluded that more research is required to determine whether this approach is effective.<sup>335</sup>

### 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.<sup>336-339</sup>

In children with asthma, exposure to environmental tobacco smoke is associated with worsening asthma symptoms.<sup>340</sup> Smoking cessation interventions aimed at families and carers have been shown to reduce childhood respiratory symptoms including those associated with asthma.<sup>341</sup> One study in adults with asthma suggested that smoking cessation improved asthma-specific quality of life, symptoms and drug requirements.<sup>342</sup>

1++  
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 children aged 14 who started to smoke (*see section 7.2.6 for the effect of smoking on treatment*).<sup>343</sup>

3

**B** People with asthma and parents/carers of children with asthma should be advised about the dangers of smoking and second-hand tobacco smoke exposure, and should 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.<sup>344, 345</sup> Time-series and other observational 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.<sup>346, 347</sup> Increased asthma symptoms in young children (mean age  $\leq 9$ ) have been linked, in observational studies, to exposure to air pollutants, including particulates, nitrogen dioxide, sulphur dioxide and ozone.<sup>340</sup> Much less attention has been focused on indoor pollutants in relation to asthma and more work is required.<sup>348, 349</sup>

Information on current levels of air pollution, recommended actions and health advice is available from The Daily Air Quality Index (available at [www.uk-air.defra.gov.uk](http://www.uk-air.defra.gov.uk)).

#### 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.<sup>350-352</sup> 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.<sup>353</sup> 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.<sup>354</sup> 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.<sup>355</sup> Studies of oral supplementation are limited and more trials are required.<sup>356-358</sup>

#### 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.<sup>359, 360</sup> 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.<sup>361</sup>

#### 6.2.7 Antioxidants

Observational studies have reported that low intakes of vitamin C, vitamin E and selenium are associated with a higher prevalence of asthma.<sup>303</sup> Intervention studies suggest that neither supplementation with vitamin C, vitamin E nor selenium is associated with clinical benefits in people with asthma.<sup>362-364</sup> 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.<sup>365-371</sup> No intervention studies evaluating the intake of fruit or vegetables and their effects on asthma have been reported.

#### 6.2.8 Vitamin D

A systematic review of nine RCTs (adults, n=658, children, n=435) examined whether administration of vitamin D reduced severe asthma exacerbations (defined as those requiring oral corticosteroids) or improved asthma symptom control. In three of the nine included trials (n=680/1093), of predominantly adults with mild to moderate asthma on treatment with ICS, vitamin D reduced the risk

1++

of severe asthma exacerbation. The number of exacerbations in children was too low to evaluate this outcome.<sup>372</sup> 1++

A further subgroup analysis reported that it was not clear whether the reduction in risk of exacerbation was confined to people with lower baseline vitamin D status. Vitamin D dosage regimes varied between trials and no evidence was provided about the optimum dose of vitamin D or circulating 25-hydroxyvitamin D concentrations. Serious adverse effects did not vary between those receiving vitamin D or placebo.<sup>373</sup> 1++

Further research is required on whether the effects of vitamin D supplementation are confined to people with lower baseline vitamin D status, and into the effects in children, and in people with frequent severe asthma attacks.

### 6.2.9 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...".<sup>374</sup> 1++

Two RCTs 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.<sup>375-377</sup> 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.<sup>375</sup> In adults, a 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.<sup>377</sup> A 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.<sup>376</sup> 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.

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

### 6.2.10 Probiotics

Studies have suggested that an imbalance in gut flora is associated with a higher risk of development of allergy.<sup>378</sup> Trials have investigated the use of probiotics in the treatment of established allergic disease with variable results.<sup>379, 380</sup> Only one study focused on asthma, finding a decrease in eosinophilia but no effect on clinical parameters.<sup>381</sup> 1+  
2+

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

#### 6.2.11 Immunisation

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.<sup>382-385</sup>

There is some discussion about whether BCG immunisation may confer protection against allergy and asthma. Research has focused on primary prophylaxis (*see section 6.1.11*), 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,<sup>386</sup> but results of trials have been disappointing.<sup>387, 388</sup> 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.<sup>389</sup> Studies in children have suggested that immunisation with the vaccine does not exacerbate asthma,<sup>390</sup> but has a small beneficial effect on quality of life in children with asthma.<sup>391</sup> The immune response to the immunisation may be adversely affected by high-dose ICS therapy and this requires further investigation.<sup>392</sup> A Cochrane review of pneumococcal vaccine found very limited evidence to support its use specifically in individuals with asthma.<sup>393</sup>

1++

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

#### 6.2.12 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 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.<sup>394</sup> A later systematic review and meta-analysis of 11 RCTs 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 publication bias in favour of positive outcome studies.<sup>395</sup> Two other trials of acupuncture in relation to induced asthma were also negative.<sup>396, 397</sup>

1+

#### 6.2.13 Air ionisers

Ionisers have been widely promoted as being of benefit for patients with asthma. A Cochrane review of six studies, five using negative ion generators and one with a positive ion generator, found no evidence that air ionisers are of benefit in reducing symptoms in patients with asthma. One of the included studies in children (n=12, age range 3–11) showed that positively-ionised air was associated with bronchoconstriction, and another (n=20, age range 9–15) showed an increase in night-time cough, although this was not statistically significant.<sup>398</sup>

1++  
1+

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

**6.2.14 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 lead to modest improvements in asthma symptoms and quality of life, and reduce bronchodilator requirement in adults with asthma, although have little effect on lung function or airway inflammation.<sup>399-402</sup> 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 than shorter courses.<sup>400</sup> They should ideally be provided as part of integrated medical care.

1++  
1+

A systematic review of inspiratory muscle training for adults with asthma (n=113), including five RCTs, reported that evidence for its use was inconclusive.<sup>403</sup>

1++

One high-quality RCT, including 655 adults with asthma and impaired asthma-related quality of life, demonstrated that breathing retraining can be successfully delivered as a self-guided audiovisual programme, leading to equivalent quality-of-life benefits, measured by the AQLQ, and likely greater cost effectiveness compared with a programme delivered face-to-face by a physiotherapist.<sup>399</sup> There were, however, clinically important improvements in AQLQ scores in a substantial proportion of the usual treatment group as well as in the two intervention groups.

1++

In a systematic review of yoga for asthma including 15 RCTs (13 in adults) and 1,048 participants (number of children not specified), meta-analysis of five of the eight studies that included quality of life as an outcome, suggested that yoga may improve quality of life,<sup>404</sup> although improvements were mostly observed in trials which did not include a sham or placebo intervention in the control arm. Furthermore, the yoga interventions studied included breathing, postures, and meditation, and results were not presented for the effects of breathing exercises alone. Although current evidence does not support yoga as a routine intervention for people with asthma, it could be considered as an additional therapy or as an alternative to other forms of breathing exercises.<sup>405</sup>

1++

There is currently insufficient evidence on breathing exercises or yoga in children and adolescents aged 12 and under on which to base a recommendation.<sup>404, 406</sup>

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

**6.2.15 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.<sup>407</sup> A more recent double-blinded placebo-controlled trial of a Chinese herb decoction (Ding Chuan Tang) showed improvement in airway hyper-responsiveness in children with stable asthma.<sup>408</sup> It is difficult to disentangle the effects of multiple ingredients; Ding Chuan Tang for example contains nine components. A second study, of 100 children with asthma, found that a five-herb mixture gave some benefits in relation to lung function and symptoms compared with placebo.<sup>409</sup>

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 controlled studies.

#### 6.2.16 Homeopathy

A Cochrane review identified only three methodologically sound RCTs, 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.<sup>410</sup> 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.<sup>411</sup>

1++  
1+

#### 6.2.17 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.<sup>412</sup>

1++

#### 6.2.18 Manual therapy including massage and spinal manipulation

A Cochrane review identified four relevant RCTs.<sup>413</sup> 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.

#### 6.2.19 Physical exercise training

A Cochrane review has shown no effect of physical training on PEF, FEV<sub>1</sub>, FVC or ventilation at maximal exercise capacity ( $V_{Emax}$ ).<sup>414</sup> 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 7.7.2*).

#### 6.2.20 Family therapy

A Cochrane review identified two trials (n=55) showing that family therapy may be a useful adjunct to medication in children with asthma.<sup>415</sup> Small study size limits the ability to form recommendations.



For those with difficult asthma in childhood, 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 used reliably to guide asthma management in children under five years of age.

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. Differences in how the doses of ICS (as well as other drug classes) are expressed (metered dose or delivered dose, ie the dose that leaves the mouthpiece), mean 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 12 and 13*). 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 | <b>1 Adults and adolescents aged over 12</b> |
|   |   |   | <b>2 Children aged 5–12 years</b>            |
|   |   |   | <b>3 Children under 5 years</b>              |

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 7.7.2.

The following medicines act as short-acting bronchodilators:

- inhaled short-acting  $\beta_2$  agonists<sup>416</sup>
- inhaled ipratropium bromide<sup>417</sup>
- theophyllines.<sup>416</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          | 1+            | 4           |
| 1+           | 1++           |             |
| 1++          |               |             |

Short-acting inhaled  $\beta_2$  agonists work more quickly and/or with fewer side effects than the alternatives.<sup>416</sup>

| A | B | D | Prescribe an inhaled short-acting $\beta_2$ agonist as short-term reliever therapy for all patients with symptomatic asthma. |
|---|---|---|------------------------------------------------------------------------------------------------------------------------------|
|---|---|---|------------------------------------------------------------------------------------------------------------------------------|

### 7.1.1 Frequency of dosing of inhaled short-acting $\beta_2$ agonists

Good asthma control is associated with little or no need for short-acting  $\beta_2$  agonist. Short-acting  $\beta_2$  agonists should only be used as required for the relief of symptoms.

|   |                                                                                                                                                                                                               |
|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ✓ | 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.<sup>418–421</sup> There is a body of evidence demonstrating that, at recommended doses, they are also safe and effective in children under five with asthma.<sup>422–431</sup>

| >12<br>years | 5–12<br>years | <5<br>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  $\beta_2$  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.<sup>432–436</sup>

| >12<br>years | 5–12<br>years | <5<br>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 $\beta_2$ 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 ICS and stepping down confers no benefit.<sup>437</sup>

| >12<br>years | 5–12<br>years | <5<br>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 12*) and very low dose for children (*see Table 13*).
- ✓ 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.<sup>416, 419, 434, 438, 439</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1+           | 1+            | 1+          |

There is little evidence of benefit for dosage frequency more than twice daily.<sup>419</sup>

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.<sup>440</sup>

| 1++ | 1++ |
|-----|-----|

|   |   |   |                                                                                                                          |
|---|---|---|--------------------------------------------------------------------------------------------------------------------------|
| A | A | A | <b>Give inhaled corticosteroids initially twice daily (except ciclesonide which is given once daily).</b>                |
| A | A |   | <b>Once-a-day inhaled corticosteroids at the same total daily dose can be considered if good control is established.</b> |

### 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.

Beclometasone dipropionate 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.<sup>441</sup> 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.<sup>442</sup> It is difficult to establish the exact equipotent dose of fluticasone furoate.<sup>443, 444</sup>

### 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<sup>445</sup>) 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 of ICS 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.<sup>446</sup> 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 may be associated with systemic side effects.<sup>447</sup> 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.<sup>438, 448</sup>

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  $\geq 800$  micrograms BDP per day or equivalent (medium dose ICS and above; see Table 12). 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.<sup>449, 450</sup> 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  $\beta_2$  agonists, should be actively considered.

While the use of ICS may be associated with adverse effects (including the potential to reduce 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 for acute asthma attacks.<sup>451</sup>

- ✓ 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

Current and previous smoking reduces the effect of ICS, which may be overcome with increased doses.<sup>336, 452</sup>

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

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



**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

Inhaled corticosteroids are the first choice preventer drug. There are alternative, less effective preventer therapies for patients taking short-acting  $\beta_2$  agonists alone.

- Leukotriene receptor antagonists (LTRA) have some beneficial clinical effect<sup>419, 453, 454</sup>
  - In children under five years who are unable to take ICS, leukotriene receptor antagonists may be used as an alternative preventer<sup>455, 456</sup>
- Sodium cromoglicate and nedocromil sodium
  - Sodium cromoglicate is of some benefit in adults<sup>416, 457</sup> and is effective in children aged 5-12<sup>458</sup>
  - Nedocromil sodium is of benefit in adults and children >5<sup>416, 459</sup>
  - There is no clear evidence of benefit with sodium cromoglicate in children aged <5<sup>460</sup>
- Theophyllines have some beneficial effect<sup>416, 418</sup>
- Antihistamines and ketotifen are ineffective.<sup>461</sup>

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

Table 12: Categorisation of inhaled corticosteroids by dose – adults\* (see also Figure 2)

| ICS                                                                                  | Dose                                                                        |                                                                             |                                                                               |
|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|
|                                                                                      | Low dose                                                                    | Medium dose                                                                 | High dose#                                                                    |
| <b>Pressurised metered dose inhalers (pMDI)</b>                                      |                                                                             |                                                                             |                                                                               |
| <b>Beclometasone dipropionate</b>                                                    |                                                                             |                                                                             |                                                                               |
| 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 pMDI                                                                 | 100 micrograms two puffs twice a day                                        | 200 micrograms two puffs twice a day                                        | 250 micrograms two puffs twice a day<br>250 micrograms four puffs twice a day |
| Kelhale pMDI (extrafine)                                                             | 50 micrograms two puffs twice a day                                         | 100 micrograms two puffs twice a day                                        | 100 micrograms four puffs twice a day                                         |
| Qvar pMDI (extrafine)<br>Qvar Autohaler (extrafine)<br>Qvar Easi-Breathe (extrafine) | 50 micrograms two puffs twice a day                                         | 100 micrograms two puffs twice a day                                        | 100 micrograms four puffs twice a day                                         |
| Soprobec pMDI                                                                        | 100 micrograms two puffs twice a day                                        | 200 micrograms two puffs twice a day                                        | 250 micrograms two puffs twice a day<br>250 micrograms four puffs twice a day |
| <b>Ciclesonide</b>                                                                   |                                                                             |                                                                             |                                                                               |
| Alvesco pMDI                                                                         | 80 micrograms two puffs once a day                                          | 160 micrograms two puffs once a day                                         | 160 micrograms two puffs twice a day                                          |
| <b>Fluticasone propionate</b>                                                        |                                                                             |                                                                             |                                                                               |
| Flixotide Evohaler                                                                   | 50 micrograms two puffs twice a day                                         | 125 micrograms two puffs twice a day                                        | 250 micrograms two puffs twice a day                                          |
| <b>Dry powder inhalers (DPI)</b>                                                     |                                                                             |                                                                             |                                                                               |
| <b>Beclometasone</b>                                                                 |                                                                             |                                                                             |                                                                               |
| Non-proprietary Easyhaler                                                            | 200 micrograms one puff twice a day                                         | 200 micrograms two puffs twice a day                                        | n/a                                                                           |
| <b>Budesonide</b>                                                                    |                                                                             |                                                                             |                                                                               |
| 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                                                                    | n/a                                                                         | 200 micrograms two puffs twice a day                                        | 200 micrograms four puffs twice a day                                         |
| Pulmicort Turbohaler                                                                 | 100 micrograms two puffs twice a day<br>200 micrograms one puff twice a day | 200 micrograms two puffs twice a day<br>400 micrograms one puff twice a day | 400 micrograms two puffs twice a day                                          |
| <b>Fluticasone propionate</b>                                                        |                                                                             |                                                                             |                                                                               |
| Flixotide Accuhaler                                                                  | 100 micrograms one puff twice a day                                         | 250 micrograms one puff twice a day                                         | 500 micrograms one puff twice a day                                           |
| <b>Mometasone</b>                                                                    |                                                                             |                                                                             |                                                                               |
| Asmanex Twisthaler                                                                   | 200 micrograms one puff twice a day                                         | 400 micrograms one puff twice a day                                         | n/a                                                                           |

\* Different products and doses are licensed for different age groups and some are not licensed for use in children. Prior to prescribing, the relevant summary of product characteristics (SPC) should be checked ([www.medicines.org.uk/emc](http://www.medicines.org.uk/emc)).

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

(Table 12 continues on next page)

Table 12 (continued): Categorisation of inhaled corticosteroids by dose – adults\*  
(see also Figure 2)

| ICS                                                           | Dose                                                         |                                                             |                              |
|---------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------------|------------------------------|
|                                                               | Low dose                                                     | Medium dose                                                 | High dose#                   |
| <b>Combination inhalers</b>                                   |                                                              |                                                             |                              |
| <b>Beclometasone dipropionate (extrafine) with formoterol</b> |                                                              |                                                             |                              |
| 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                                 | 200/6 two puffs twice a day  |
| <b>Budesonide with formoterol</b>                             |                                                              |                                                             |                              |
| DuoResp Spiromax                                              | 160/4.5 one puff twice a day                                 | 160/4.5 two puffs twice a day<br>320/9 one puff twice a day | 320/9 two puffs twice a day  |
| Symbicort Turbohaler                                          | 100/6 two puffs twice a day<br>200/6 one puff twice a day    | 200/6 two puffs twice a day<br>400/12 one puff twice a day  | 400/12 two puffs twice a day |
| Fobumix Easyhaler                                             | 80/4.5 two puffs twice a day<br>160/4.5 one puff twice a day | 160/4.5 two puffs twice a day<br>320/9 one puff twice a day | 320/9 two puffs twice a day  |
| <b>Fluticasone propionate with formoterol</b>                 |                                                              |                                                             |                              |
| Flutiform MDI                                                 | 50/5 two puffs twice a day                                   | 125/5 two puffs twice a day                                 | 250/10 two puffs twice a day |
| Flutiform K-haler                                             | 50/5 two puffs twice a day                                   | 125/5 two puffs twice a day                                 | n/a                          |
| <b>Fluticasone propionate with salmeterol</b>                 |                                                              |                                                             |                              |
| Aerivio Spiromax                                              | n/a                                                          | n/a                                                         | 500/50 one puff twice a day  |
| AirFluSal Forspiro                                            | n/a                                                          | n/a                                                         | 500/50 one puff twice a day  |
| AirFluSal pMDI                                                | n/a                                                          | 125/25 two puffs twice a day                                | 250/25 two puffs twice a day |
| Aloflute pMDI                                                 | n/a                                                          | 125/25 two puffs twice a day                                | 250/25 two puffs twice a day |
| Combisal pMDI                                                 | 50/25 two puffs twice a day                                  | 125/25 two puffs twice a day                                | 250/25 two puffs twice a day |
| Fusacomb Easyhaler                                            | n/a                                                          | 250/50 one puff twice a day                                 | 500/50 one puff twice a day  |
| Sereflo pMDI                                                  | n/a                                                          | 125/25 two puffs twice a day                                | 250/25 two puffs twice a day |
| 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 |
| Sirdupla pMDI                                                 | n/a                                                          | 125/25 two puffs twice a day                                | 250/25 two puffs twice a day |
| Stalpex Orbicel                                               | n/a                                                          | n/a                                                         | 500/50 one puff twice a day  |
| <b>Fluticasone furoate with vilanterol</b>                    |                                                              |                                                             |                              |
| Relvar Ellipta                                                | n/a                                                          | 92/22 one puff once a day                                   | 184/22 one puff once a day   |

\* Different products and doses are licensed for different age groups and some are not licensed for use in children. Prior to prescribing, the relevant summary of product characteristics (SPC) should be checked ([www.medicines.org.uk/emc](http://www.medicines.org.uk/emc)).

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

Table 13: Categorisation of inhaled corticosteroids by dose – children\*  
(see also Figure 3)

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

\* Different products and doses are licensed for different age groups and some are not licensed for use in children. Prior to prescribing, the relevant summary of product characteristics (SPC) should be checked ([www.medicines.org.uk/emc](http://www.medicines.org.uk/emc)).

# Medium doses (shaded boxes) should only be used after referring the patient to specialist 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

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.<sup>462–465</sup> 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.

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          | 1+            |             |

#### 7.3.2 Inhaled long-acting $\beta_2$ agonist

The addition of an inhaled long-acting  $\beta_2$  agonist (LABA) to ICS alone improves lung function and symptoms, and decreases asthma attacks in adults and children.<sup>462, 466–472</sup>

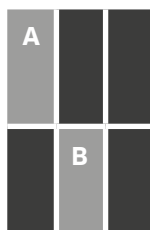
Long-acting inhaled  $\beta_2$  agonists should not be used without ICS.<sup>473</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          | 1++           |             |

Evidence to guide the choice of initial add-on therapy is stronger in adults than in children. On the basis of current evidence, LABA is the first choice initial add-on therapy in adults.

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*).<sup>472</sup> 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*).

|     |     |
|-----|-----|
| 1++ | 1++ |
|-----|-----|



**The first choice as add-on therapy to inhaled corticosteroids in adults is an inhaled long-acting  $\beta_2$  agonist, which should be considered before increasing the dose of inhaled corticosteroid.**

**In children aged five and over, an inhaled long-acting  $\beta_2$  agonist or a leukotriene receptor antagonist can be considered as initial add-on therapy.**

#### 7.3.3 Safety of long-acting $\beta_2$ agonist

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.<sup>474</sup>



Long-acting inhaled  $\beta_2$  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 $\beta_2$ agonist inhalers

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.<sup>475</sup>

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

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  $\beta_2$  agonist is not taken without inhaled corticosteroid
- improve inhaler adherence.

### 7.3.5 Single combination inhaler for maintenance and reliever therapy

The use of a single combination inhaler for maintenance and reliever therapy (MART) is an alternative approach to the introduction of a fixed-dose twice-daily combination inhaler which might suit some individuals. It relies on the rapid onset of reliever effect with formoterol and by including a dose of inhaled corticosteroid ensures that, as the need for a reliever increases, the dose of preventer medication is also increased. This underpins the self-management plan which must be provided with a MART regime. *See section 5.2.3* for a description of increasing inhaled corticosteroids at the onset of an attack. Maintenance and reliever therapy may also lower the overall dose of ICS needed to prevent asthma attacks.

A systematic review comparing a combined ICS/LABA inhaler as MART with ICS alone or with current best practice (ICS with or without LABA) showed 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.<sup>476</sup> The 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. All trials were funded by the manufacturer.

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

In a subsequent systematic review including 16 RCTs and 22,748 patients, a meta-analysis of five of the 16 studies concluded that, in patients aged 12 and over, use of MART was associated with a reduced risk of asthma attacks compared with standard ICS/LABA treatment including the same dose of ICS as the MART group (in five of the nine studies), or to standard ICS/LABA treatment including a higher dose of ICS than the MART group (in two of 16 studies). Among children aged 4-11, a subgroup analysis from a single RCT reported that MART was associated with a lower risk of asthma attacks compared with standard ICS/LABA treatment including the same dose of ICS as the MART group. There was no difference in impact on quality of life (QoL), asthma control, lung function and asthma medication use between MART and regular fixed-dose treatment regimens.<sup>477</sup> Fifteen of the 16 studies used a combination of budesonide and formoterol in a dry powder inhaler.

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

If 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 licensed for use with budesonide/formoterol or beclomethasone/formoterol. The summaries of product characteristics should be consulted for age-appropriate prescribing and maximum dosing regimens. Not all combination products are licensed for maintenance and reliever therapy. The appropriate combination inhaler should be prescribed by brand name.



**Consider the option of combined maintenance and reliever therapy in adult patients who have a history of asthma attacks on medium dose ICS or ICS/LABA.**

## 7.4 Additional controller therapies

If control remains poor on low-dose (adults) or very low-dose (children aged five and over) 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 options can be considered.

### 7.4.1 Increased dose of inhaled corticosteroids

If there is an improvement when LABA is added, but control remains suboptimal, continue with the LABA and increase the dose of ICS to medium (adults) or low dose (children 5–12 years). If there is no improvement when a LABA is added, consider stopping the LABA before increasing the dose of ICS.<sup>475</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 4            | 4             |             |

### 7.4.2 Leukotriene receptor antagonists

Evidence to support the use of 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.<sup>454, 478, 479</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          | 1++           |             |

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.<sup>472</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          | 1++           |             |

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.<sup>480</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1+           |               |             |

In adults, if there is no improvement following addition of a LABA, consider stopping the LABA and initiating a trial of LTRA.



If asthma control remains suboptimal after the addition of an inhaled long-acting  $\beta_2$  agonist then:

- increase the dose of inhaled corticosteroids 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.

or

- consider adding a leukotriene receptor antagonist.

## 7.5 Specialist therapies

In a small proportion of patients asthma is not adequately controlled on the recommended initial or additional controller therapies (see sections 7.3 and 7.4). There are very few clinical trials in this specific patient group to guide management. For this reason, these patients should be referred for specialist care.



All patients whose asthma is not adequately controlled on recommended initial or additional controller therapies should be referred for specialist care.

### 7.5.1 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.<sup>481</sup> The addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive. Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.<sup>481</sup>

| >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.<sup>482</sup> 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.<sup>483, 484</sup>

1++  
1+

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 determine if adding tiotropium to ICS ('off-label' use) is safer or more effective than increasing the dose of ICS.<sup>485</sup>

1+

### 7.5.2 Other approaches

Theophyllines may improve lung function and symptoms, but are associated with an increase in adverse events.<sup>463</sup>

| >12 years | 5–12 years | <5 years |
|-----------|------------|----------|
|-----------|------------|----------|

1+

1-

Addition of short-acting anticholinergics is generally of no value.<sup>464, 486</sup> Addition of nedocromil to ICS is of marginal benefit.<sup>457, 465</sup>

1+



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 or theophyllines.

The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone (*see sections 7.3 and 7.4*).

|          |          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>D</b> | <b>D</b> | <p><b>If asthma control remains inadequate on medium-dose (adults) or low-dose (children) of inhaled corticosteroid plus a long-acting <math>\beta_2</math> agonist or a leukotriene receptor antagonist, the following interventions can be considered:</b></p> <ul style="list-style-type: none"> <li>• <b>increase the inhaled corticosteroids to high dose (adults)/ medium dose (children 5–12 years)* <i>or</i></b></li> <li>• <b>add a leukotriene receptor antagonist (if not already trialed) <i>or</i></b></li> <li>• <b>add tiotropium (adults) <i>or</i></b></li> <li>• <b>add a theophylline.</b></li> </ul> |
|----------|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

\*at high doses of inhaled corticosteroid via a 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.

- ✓ 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).
- ✓ 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.

### 7.5.3 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 LABA, LTRA, tiotropium (adults only) or theophyllines, may require regular long-term steroid tablets. These patients should already be under the care of a specialist asthma service.

- ✓ For the small number of patients not controlled on high-dose therapies, use daily steroid tablets in the lowest dose providing adequate control.
- ✓ Patients requiring frequent or continuous use of oral corticosteroids should be under the care of a specialist asthma service.

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.<sup>449</sup> To prevent and treat steroid tablet-induced side effects:

- blood pressure should be monitored
- urine or blood sugar and cholesterol should be checked: diabetes mellitus and hyperlipidaemia may occur
- bone mineral density should be monitored in adults. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered. See also, SIGN 142 Management of osteoporosis and the prevention of fragility fractures.<sup>487</sup>

- bone mineral density should be monitored in children >5<sup>488</sup>
- growth (height and weight centile) should be monitored in children
- cataracts and glaucoma may be screened for through community optometric services.

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.

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.

#### 7.5.4 Monoclonal antibody

##### *Anti-IgE monoclonal antibody*

Omalizumab given by subcutaneous injection can reduce the steroid burden for the patient without increasing the risk of adverse events.<sup>489-491</sup> 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 or ICS.<sup>489-491</sup> These studies all reported that more patients on omalizumab compared with placebo withdrew steroids.

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

Omalizumab is given as a subcutaneous injection every two or four weeks depending on the patient's IgE level and weight. Local skin reactions may occur. Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue have been reported after administration of omalizumab occurring as early as the first dose, and as late as one year. Due to concerns about anaphylaxis, the first three doses of omalizumab should only be administered to patients in a healthcare setting under direct medical supervision.

Guidance on when to consider treatment can be found in NICE technology appraisal guidance TA278.<sup>489</sup>

##### *Anti-IL-5 monoclonal antibody*

A systematic review of anti-interleukin-5 (IL-5) monoclonal antibody therapies including trials of mepolizumab (four trials; two intravenous, one subcutaneous, one mixed), reslizumab (four trials intravenous) and benralizumab (five trials subcutaneous), and 6,000 patients aged 12 years and over, most of whom had severe eosinophilic asthma, reported reduced asthma exacerbation rates and emergency department/unscheduled care visits with mepolizumab and benralizumab, and reduced asthma exacerbation rates with reslizumab compared with placebo. No serious excess adverse events were reported although significantly more patients receiving benralizumab than placebo discontinued treatment due to adverse events and this requires further investigation.<sup>492</sup> The review did not look at the potential steroid-sparing effect of anti-IL5 therapies. Use of intravenous mepolizumab is not currently licensed.

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

An RCT of 135 patients with severe eosinophilic asthma receiving 100 mg of mepolizumab subcutaneously or placebo every four weeks, reported a significant glucocorticoid-sparing effect with mepolizumab (28% v 11%, respectively), improved secondary outcomes including fewer exacerbations and improved ACQ-5 scores, and a similar safety profile.<sup>493</sup>

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

No studies were found that directly compared omalizumab with mepolizumab. A systematic review and meta-analysis, however, concluded that mepolizumab was of equivalent benefit compared to omalizumab in patients eligible for both treatments.<sup>494</sup> A network meta-analysis comparing omalizumab with mepolizumab showed similar adverse event rates for omalizumab and intravenous mepolizumab (not a licensed route of administration) and a reduction in adverse events compared with placebo and/or baseline therapy (mean annualised asthma exacerbation rate 1.22 v 2.29 omalizumab; 1.28 v 2.56 mepolizumab).<sup>495</sup>

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

Head-to-head trials comparing omalizumab with mepolizumab and other IL-5 therapies and of different IL-5 therapies are needed to confirm the relative clinical and cost effectiveness of each approach.

Guidance on use of mepolizumab, reslizumab and benralizumab differs in England/Wales and Scotland and the relevant NICE or SMC advice should, therefore, be checked prior to considering these treatment approaches.

|   |   |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---|---|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| B | B |  | <b>Omalizumab given by subcutaneous injection may be considered in eligible patients with a high oral corticosteroid burden.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| A |   |  | <b>Mepolizumab (subcutaneous), reslizumab (intravenous) and benralizumab (subcutaneous) may be considered in eligible patients with a high oral corticosteroid burden.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| ✓ |   |  | <ul style="list-style-type: none"> <li>Patients being considered for monoclonal antibody treatment should be assessed to confirm the diagnosis of asthma, that uncontrolled asthma is the cause of their ongoing symptoms, and that they are adherent with current treatment.</li> <li>An asthma specialist with expertise in monoclonal antibody treatment should assess patients prior to undergoing treatment, and treatment should take place in a specialist centre with the appropriate resources and training, including access to an intensive care unit.</li> <li>Patients undergoing monoclonal antibody treatment should have their details entered onto the UK Severe Asthma Registry.</li> </ul> |

### 7.5.5 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.<sup>496</sup>

| >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.<sup>496</sup>

|    |  |  |
|----|--|--|
| 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.<sup>497-499</sup>

|   |   |   |
|---|---|---|
| 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.<sup>500, 501</sup>

### 7.5.6 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.

#### *Subcutaneous immunotherapy*

Trials of allergen-specific immunotherapy by subcutaneous injection of increasing doses of allergen extracts have consistently demonstrated beneficial effects compared with placebo in the management of allergic asthma. Allergens included house dust mite, grass pollen, tree pollen, cat and dog allergen and moulds. Cochrane reviews have concluded that immunotherapy reduces asthma symptoms, the use of asthma medications and improves BHR; the most recent of these 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.<sup>502</sup>

| >12 years | 5-12 years | <5 years |
|-----------|------------|----------|
|-----------|------------|----------|

|     |  |  |
|-----|--|--|
| 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.<sup>502</sup> Immunotherapy is not licensed for the treatment of asthma; the current licence is for allergic rhinitis induced by grass pollen.

|     |     |  |
|-----|-----|--|
| 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.<sup>503</sup>

|    |  |  |
|----|--|--|
| 2+ |  |  |
|----|--|--|

Immunotherapy for allergic rhinitis has been shown to have a carry-over effect after therapy has stopped.<sup>504</sup>

|   |  |  |
|---|--|--|
| 3 |  |  |
|---|--|--|



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

#### *Sublingual immunotherapy*

There has been increasing interest in the use of sublingual immunotherapy (SLIT), which is associated with fewer adverse reactions than subcutaneous immunotherapy.

A systematic review including 52 studies of SLIT in adults and children (n=5,077), most of whom had intermittent or mild asthma symptoms, showed no clear benefit of SLIT. Asthma symptoms scores were the most commonly reported outcome measure (in 42/52 studies) and although overall results were inconclusive, there was some evidence of improvements in asthma symptom scores (in nine studies) and/or medication use (in five studies). Symptom scores and medication use were, however, mostly assessed using unvalidated scales and meta-analysis was not possible. There was no evidence of improvement in lung function,

| >12 years | 5-12 years | <5 years |
|-----------|------------|----------|
|-----------|------------|----------|

|     |     |  |
|-----|-----|--|
| 1++ | 1++ |  |
|-----|-----|--|

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | >12 years | 5-12 years | <5 years |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------------|----------|
| quality of life or asthma attacks, although data on these outcomes was limited. Adverse events were significantly more common in those receiving SLIT (absolute increase 327/1,000 SLIT v 222/1,000 control) although these were mostly mild or transient. Serious adverse events were rare with only five of 22 studies reporting any events and no difference between groups in the rate of events (1.3%); all events were thought to be unrelated to treatment. <sup>505</sup> | 1++       | 1++        |          |

Despite the large volume of evidence evaluating the safety and clinical effectiveness of SLIT in adults and children, heterogeneity in studies (including in doses, allergens, treatment duration, other asthma medication and presence of asthma symptoms), together with the lack of data on its long-term effectiveness and concerns about study quality, mean there is currently insufficient evidence to recommend use of SLIT in adults or children with asthma.

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

|          |          |                                                                                                       |
|----------|----------|-------------------------------------------------------------------------------------------------------|
| <b>B</b> | <b>B</b> | <b>Sublingual immunotherapy is not recommended for the treatment of asthma in children or adults.</b> |
|----------|----------|-------------------------------------------------------------------------------------------------------|

### 7.5.7 Bronchial thermoplasty

The aim of bronchial thermoplasty is to reduce bronchial smooth muscle mass, thus reducing the capacity for bronchoconstriction. Currently only a few UK centres offer this treatment which has considerable cost and resource implications.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | >12 years | 5-12 years | <5 years |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------------|----------|
| A systematic review of three RCTs (n=429) looking at the use of bronchial thermoplasty for moderate or severe persistent asthma in adults (aged 18 and over) showed a significantly lower rate of severe asthma exacerbations at 12 months in those treated with bronchial thermoplasty in one trial that included a sham intervention in the control group. A second trial, with no sham intervention in the control group, showed a decrease in severe exacerbations in both the intervention and control groups. There were no significant differences in asthma control, lung function, changes in doses of regular medication or use of rescue medication between the intervention and control groups. A small, but statistically significant improvement in quality-of-life scores (measured using AQLQ) with bronchial thermoplasty compared with control groups was seen only in the two studies without a sham intervention. In the study with a sham intervention, QoL scores improved in both groups. <sup>506</sup> | 1++       |            |          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |     |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|--|--|
| Bronchial thermoplasty is an invasive procedure and is associated with an increased rate of adverse respiratory events in the short term. Significantly more patients receiving bronchial thermoplasty than controls were admitted to hospital because of respiratory adverse events within the first 12 weeks following treatment (8 per 100 v 2 per 100; risk ratio (RR) 3.5, 95% CI 1.26 to 9.68). By 12 months following treatment, there was no difference between groups. <sup>506</sup> | 1++ |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|--|--|

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|--|--|
| A systematic review looking at the long-term efficacy and safety of bronchial thermoplasty, including the same three RCTs, reported a significant reduction in respiratory adverse events in patients after five years compared to one year following treatment, although these results were not compared to a control group who had not received bronchial thermoplasty. There was no difference in the number of ED visits or hospitalisations for respiratory adverse events between one and five years of follow up in those treated with bronchial thermoplasty. The longer-term effects of bronchial thermoplasty, beyond five years following treatment, are not known. <sup>507</sup> | 1+ |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|--|--|

Further research is needed to identify which patients with asthma might benefit from bronchial thermoplasty. However, it is likely that patients who remain uncontrolled despite optimal medical treatment and who have been considered for biological treatments and are either unsuitable for or fail a trial of such a treatment may be an appropriate group, as other treatment options for these patients are elusive. There are no trials comparing the efficacy of bronchial thermoplasty with biological treatments for people with asthma.

**B**

**Bronchial thermoplasty may be considered for the treatment of adult patients (aged 18 and over) with severe asthma who have poorly-controlled asthma despite optimal medical therapy.**



- Patients being considered for bronchial thermoplasty should be assessed to confirm the diagnosis of asthma, that uncontrolled asthma is the cause of their ongoing symptoms, and that they are adherent with current treatment.
- An asthma specialist with expertise in bronchial thermoplasty should assess patients prior to undergoing treatment, and treatment should take place in a specialist centre with the appropriate resources and training, including access to an intensive care unit.
- Patients undergoing bronchial thermoplasty should have their details entered onto the UK Severe Asthma Registry.

Figure 2: Summary of management in adults

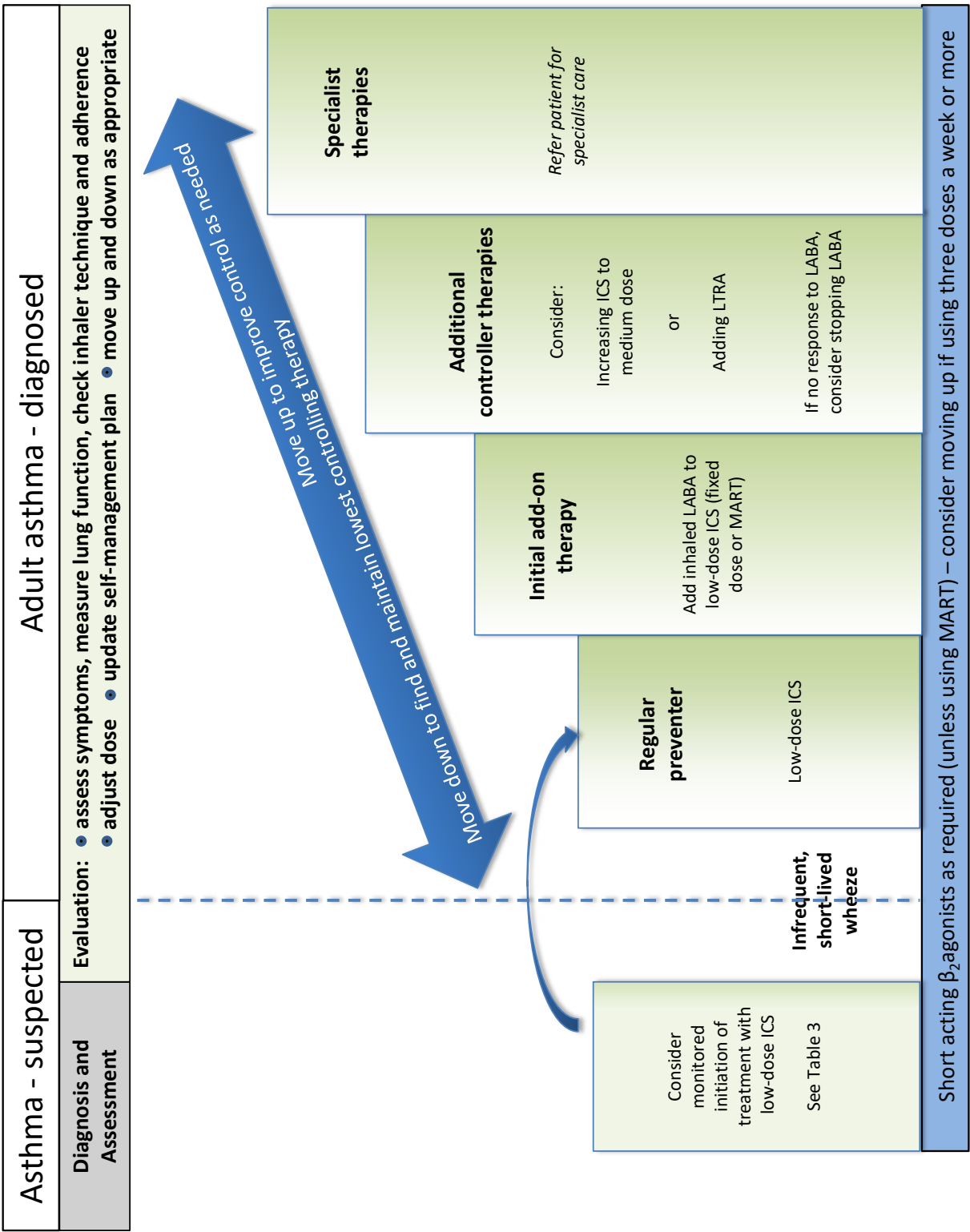
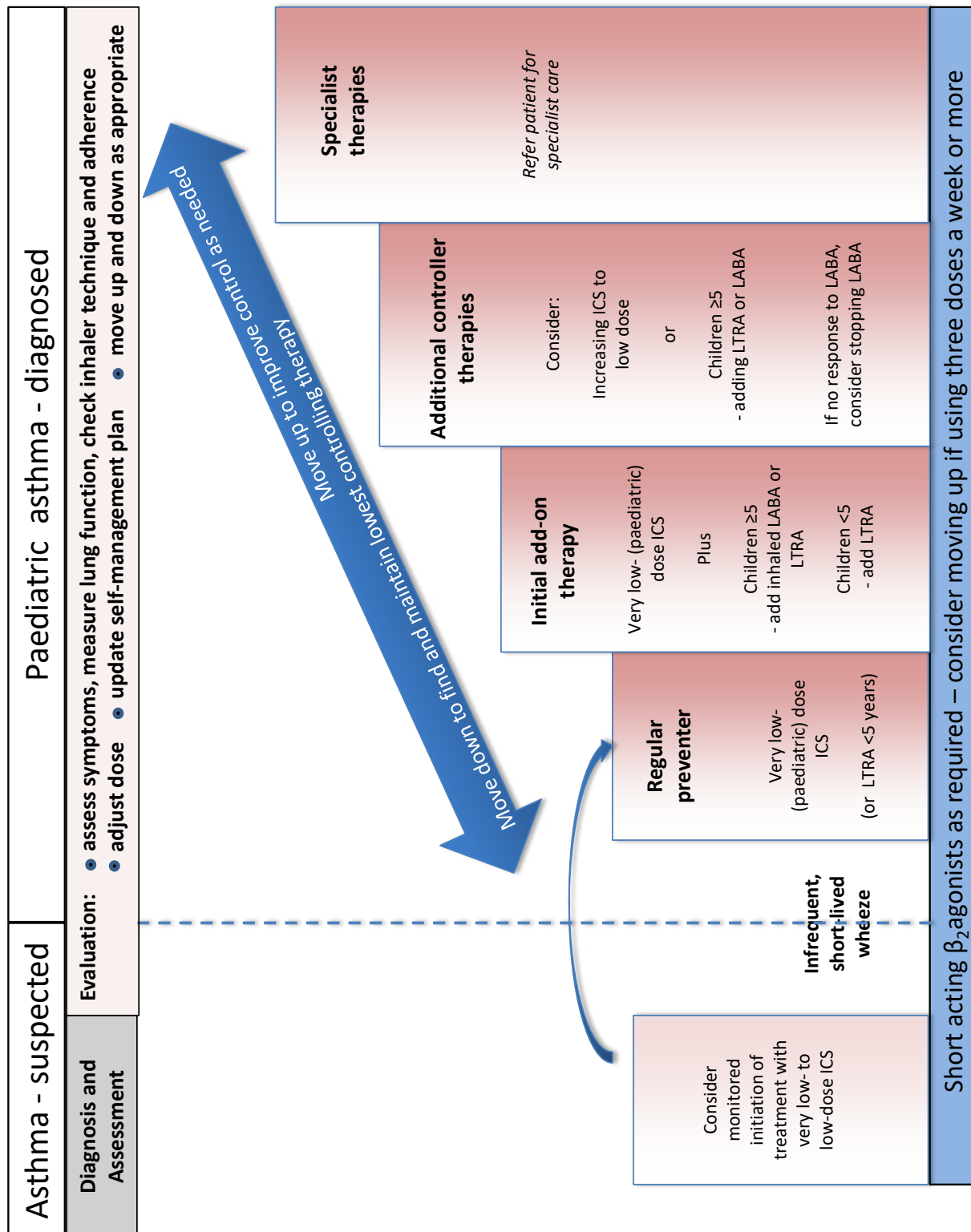


Figure 3: Summary of management in children



## 7.6 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.<sup>501</sup>

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.

## 7.7 Specific management issues

### 7.7.1 Asthma attacks

There is some limited evidence that LTRA 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.<sup>508</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
|              | 1+            | 1+          |

### 7.7.2 Exercise-induced asthma

The following medicines have been shown to give protection against exercise-induced asthma:

- inhaled corticosteroids<sup>420, 509, 510</sup>
- short-acting  $\beta_2$  agonists<sup>416, 511</sup>
- long-acting  $\beta_2$  agonists<sup>512</sup>
- theophyllines<sup>513, 514</sup>
- leukotriene receptor antagonists<sup>515</sup>
- sodium cromoglicate or nedocromil sodium.<sup>516</sup>

| >12<br>years   | 5–12<br>years | <5<br>years |
|----------------|---------------|-------------|
| 1++            | 1++           |             |
| 1++            | 1++           |             |
| 1++            | 1++           |             |
| 1 <sup>-</sup> | 2+            |             |
| 1++            | 2+            |             |
| 1++            | 2+            |             |

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

- anticholinergics<sup>517</sup>
- ketotifen<sup>518</sup>
- antihistamine.<sup>519</sup>

|     |     |
|-----|-----|
| 1+  | 1+  |
| 1+  | 1+  |
| 1++ | 1++ |

Long-acting  $\beta_2$  agonists and LTRA provide more prolonged protection than SABA, but a degree of tolerance develops with LABA particularly with respect to duration of action. No tolerance has been demonstrated with LTRA.<sup>514, 515, 520</sup>

|     |     |
|-----|-----|
| 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 $\beta_2$ agonists           |
| C | C |  | • sodium cromoglicate or nedocromil sodium |
| C | C |  | • theophyllines.                           |

Immediately prior to exercise, inhaled SABA are the drug of choice.<sup>416, 511</sup>

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

|   |   |  |                                                                                                                  |
|---|---|--|------------------------------------------------------------------------------------------------------------------|
| A | A |  | <b>Immediately prior to exercise, inhaled short-acting <math>\beta_2</math> agonists are the drug of choice.</b> |
|---|---|--|------------------------------------------------------------------------------------------------------------------|

### 7.7.3 Comorbid rhinitis

Patients with asthma often have rhinitis. The most effective therapy for rhinitis is intranasal steroids.<sup>521, 522</sup> Treatment of allergic rhinitis with intranasal steroids has not been shown, in double-blinded placebo-controlled trials, to improve asthma control.

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

### 7.7.4 Allergic bronchopulmonary aspergillosis

In adult patients with allergic bronchopulmonary aspergillosis, itraconazole may decrease steroid tablet dose and improve asthma control.<sup>523</sup>

|              |               |             |
|--------------|---------------|-------------|
| >12<br>years | 5-12<br>years | <5<br>years |
| 2+           |               |             |

|   |  |  |                                                                                                                                 |
|---|--|--|---------------------------------------------------------------------------------------------------------------------------------|
| C |  |  | <b>In adult patients with allergic bronchopulmonary aspergillosis, a four-month trial of itraconazole should be considered.</b> |
|---|--|--|---------------------------------------------------------------------------------------------------------------------------------|

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

### 7.7.5 Aspirin-intolerant asthma

There are theoretical reasons to suggest that LTRA 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.<sup>524, 525</sup>

### 7.7.6 Comorbid gastro-oesophageal reflux

A Cochrane review of twelve double-blinded controlled trials found that treatment of gastro-oesophageal reflux disease (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.<sup>526, 527</sup>

A systematic review identified a single RCT which found that proton-pump inhibitors did not improve asthma symptoms in children with GORD.<sup>528</sup>

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | >12<br>years | 5-12<br>years | <5<br>years |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|---------------|-------------|
| 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 with controls, but no differences in asthma symptom score, Asthma Quality of Life Questionnaire score, evening PEF, FEV <sub>1</sub> 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. <sup>529</sup> | 1++          |               |             |

7.7.7 Beta blockers

Beta blockers, including eye drops, are contraindicated in patients with asthma. Current guidance can be found in the British National Formulary.<sup>4</sup>

## 8 Inhaler devices

### 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 pMDI, 53–59% for 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.<sup>530</sup>

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).<sup>530</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          |               |             |



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

### 8.2 $\beta_2$ 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.<sup>531–534</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
| 1++          | 1++           |             |



**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 insufficient 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 with other inhalers and the data are insufficiently extensive or robust to draw conclusions for pMDI compared with 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 with a Turbohaler is the only difference with regard to side effects. Patients have been shown to prefer a Turbohaler to a pMDI.<sup>530, 535, 536</sup>

| >12<br>years | 5–12<br>years | <5<br>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.

For the delivery of ICS in children aged 5–12 years with stable asthma, a pMDI is as effective as a Clickhaler.<sup>537, 538</sup> No significant clinical difference was found between a pMDI and a Turbohaler at half the dose for the same drug (budesonide).<sup>530, 539</sup> This comparison cannot necessarily be made against other ICS/device combinations.

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. 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.<sup>530, 539</sup>

| >12<br>years | 5–12<br>years | <5<br>years |
|--------------|---------------|-------------|
|              |               |             |
| 1++          | 1++           |             |



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

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

No recommendation can be given for nebulised therapy in children aged 5–12 years and there is no evidence relating to children aged 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 the 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 young children, a pMDI and spacer is the preferred method of delivery of  $\beta_2$  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 use of different devices for preventer and reliever treatments with use of 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).<sup>540, 541</sup>

| >12<br>years | 5-12<br>years | <5<br>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 6 months.

## 8.6 Environmental impact of metered dose inhalers

Metered dose inhalers contain propellants which are liquefied, compressed gases used as a driving force and an energy source for atomisation of the drug. Chlorofluorocarbons (CFCs), which were used originally, are potent greenhouse gases and ozone-depleting substances, and were phased out under the Montreal Protocol. They have been replaced by two hydrofluoroalkane (HFA) propellants: 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227ea), identified as having a high global-warming potential.<sup>542</sup> As a result of this change, MDIs currently contribute an estimated 3.5% of the carbon footprint of the NHS in the UK.<sup>543</sup> The UK has a high proportion of MDI use (70%) compared with the rest of Europe (< 50%) and Scandinavia (10–30%).<sup>544</sup>

- ✓ Prescribers, pharmacists and patients should be aware that there are significant differences in the global-warming potential of different MDIs and that inhalers with low global-warming potential should be used when they are likely to be equally effective. Where there is no alternative to MDIs, lower volume HFA134a inhalers should be used in preference to large volume or HFA227ea inhalers.
- ✓ Patients should be encouraged to ask the pharmacy they use if they can recycle their used inhalers.

## 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.<sup>545-549</sup> The report of the UK-wide National Review of Asthma Deaths (NRAD) in 2014 reiterates many of the findings from earlier studies.<sup>550</sup>

#### 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.<sup>545-549, 551</sup> **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 SABA therapy was associated with asthma death.<sup>545-549, 552, 553</sup> The NRAD report recommended that prescription of more than 12 SABA inhalers a year should prompt review of a patient's management.<sup>550</sup> **2++**

Deaths continue to be reported following inappropriate prescription of beta blockers and non-steroidal anti-inflammatory drugs; all asthma patients should be asked about past reactions to these agents (*see sections 7.7.7 and 7.7.5*).

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*).<sup>551</sup>

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*).<sup>550</sup>

#### 9.1.3 Adverse psychosocial and behavioural factors

Behavioural and adverse psychosocial factors were recorded in the majority of patients who died of asthma.<sup>545-549</sup> The most important of these are shown in Table 14.

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.<sup>554, 555</sup> **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 14: Patients at risk of developing near-fatal or fatal asthma<sup>545-549, 552, 553</sup>

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>A combination of severe asthma recognised by one or more of:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• previous near-fatal asthma, eg previous ventilation or respiratory acidosis</li> <li>• previous admission for asthma, especially if in the last year</li> <li>• requiring three or more classes of asthma medication</li> <li>• heavy use of <math>\beta_2</math> agonist</li> <li>• repeated attendances at ED for asthma care, especially if in the last year.</li> </ul>                                                                                                                                                                                                                                                |
| <b>AND adverse behavioural or psychosocial features recognised by one or more of:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li>• non-adherence with treatment or monitoring</li> <li>• failure to attend appointments</li> <li>• fewer GP contacts</li> <li>• frequent home visits</li> <li>• self discharge from hospital</li> <li>• psychosis, depression, other psychiatric illness or deliberate self harm</li> <li>• current or recent major tranquilliser use</li> <li>• denial</li> <li>• alcohol or drug abuse</li> <li>• obesity</li> <li>• learning difficulties</li> <li>• employment problems</li> <li>• income problems</li> <li>• social isolation</li> <li>• childhood abuse</li> <li>• severe domestic, marital or legal stress.</li> </ul> |

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 14, and that these contribute to the near-fatal asthma attack.<sup>556-558</sup> 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 more likely to have ready access to acute medical care, and are less likely to have concurrent medical conditions or to experience delay in receiving 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 July and August in people aged up to 44 years and in December and January in older people.<sup>556, 559</sup>

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.<sup>560-565</sup> 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 3-5 contain algorithms summarising the recommended treatment for patients presenting with moderate, acute severe or life-threatening asthma in general practice (*see Annex 3*), the ED (*see Annex 4*), and hospital (*see Annex 5*).

### 9.2.1 Recognition of acute asthma

Definitions of increasing levels of severity of acute asthma attacks are provided in Table 15.<sup>566-571</sup> Predicted PEF values should be used only if the recent best PEF (within two years) is unknown.<sup>572</sup> **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,<sup>166</sup> and deaths from asthma (*see section 5.3.2*).<sup>573</sup>

### 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 are at risk of becoming seriously unwell very quickly. Such patients should have immediate access to a healthcare professional trained in the emergency treatment of asthma. 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 15 and 16. It may be helpful to use a systematic recording process. Proformas have proved useful in the ED setting.<sup>574</sup>

Table 15: Levels of severity of acute asthma attacks in adults<sup>566-571</sup>

|                                |                                                                                                                                                         |                                          |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| <b>Moderate acute asthma</b>   | Increasing symptoms<br>PEF >50–75% best or predicted<br>No features of acute severe asthma                                                              |                                          |
| <b>Acute severe asthma</b>     | Any one of:<br>- PEF 33–50% best or predicted<br>- respiratory rate ≥25/min<br>- heart rate ≥110/min<br>- inability to complete sentences in one breath |                                          |
| <b>Life-threatening asthma</b> | Any one of the following in a patient with severe asthma:                                                                                               |                                          |
|                                | <b>Clinical signs</b>                                                                                                                                   | <b>Measurements</b>                      |
|                                | Altered conscious level                                                                                                                                 | PEF <33% best or predicted               |
|                                | Exhaustion                                                                                                                                              | SpO <sub>2</sub> <92%                    |
|                                | Arrhythmia                                                                                                                                              | PaO <sub>2</sub> <8 kPa                  |
|                                | Hypotension                                                                                                                                             | 'normal' PaCO <sub>2</sub> (4.6–6.0 kPa) |
|                                | Cyanosis                                                                                                                                                |                                          |
|                                | Silent chest                                                                                                                                            |                                          |
|                                | Poor respiratory effort                                                                                                                                 |                                          |
| <b>Near-fatal asthma</b>       | Raised PaCO <sub>2</sub> and/or requiring mechanical ventilation with raised inflation pressures <sup>555-557</sup>                                     |                                          |

SpO<sub>2</sub>: oxygen saturation measured by a pulse oximeter

PaO<sub>2</sub>: partial arterial pressure of oxygen

kPa: kilopascals

PaCO<sub>2</sub>: 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 16: Initial assessment of symptoms, signs and measurements

|                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| <b>Clinical features</b>      | <p>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.<sup>566-571, 575</sup></p> <p>None of these singly or together is specific. Their absence does not exclude a severe attack.</p>                                                                                                                                                                                                                                                                     | 2+      |
| <b>PEF or FEV<sub>1</sub></b> | <p>Measurements of airway calibre improve recognition of the degree of severity, the appropriateness or intensity of therapy, and decisions about management in hospital or at home.<sup>576, 577</sup></p> <p>PEF or FEV<sub>1</sub> 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.</p> | 2+      |
| <b>Pulse oximetry</b>         | <p>Measure oxygen saturation (SpO<sub>2</sub>) with a pulse oximeter to determine the adequacy of oxygen therapy and the need for arterial blood gas measurement. The aim of oxygen therapy is to maintain SpO<sub>2</sub> 94-98%.<sup>578</sup></p>                                                                                                                                                                                                                                                                                                                                                                                                                       |         |
| <b>Blood gases</b>            | <p>Patients with SpO<sub>2</sub> &lt;92% (irrespective of whether the patient is on air or oxygen) or other features of life-threatening asthma require arterial blood gas measurement.<sup>566-569, 571, 579</sup> SpO<sub>2</sub> &lt;92% is associated with a risk of hypercapnia. Hypercapnia is not detected by pulse oximetry.<sup>579</sup> In contrast, the risk of hypercapnia with SpO<sub>2</sub> &gt;92% is much less.<sup>578</sup></p>                                                                                                                                                                                                                       | 2+<br>4 |
| <b>Chest X-ray</b>            | <p>Chest X-ray is not routinely recommended in the absence of:</p> <ul style="list-style-type: none"> <li>- suspected pneumomediastinum or pneumothorax</li> <li>- suspected consolidation</li> <li>- life-threatening asthma</li> <li>- failure to respond to treatment satisfactorily</li> <li>- requirement for ventilation.</li> </ul>                                                                                                                                                                                                                                                                                                                                 | 4       |
| <b>Systolic paradox</b>       | <p>Systolic paradox (<i>pulsus paradoxus</i>) is an inadequate indicator of the severity of an attack and should not be used.<sup>566-571, 580</sup></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 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).<sup>556, 558, 566-571</sup>

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 of oral corticosteroid 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.<sup>581-584</sup> 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<sub>2</sub> of 94–98%,<sup>578</sup> taking care to avoid overoxygenation which may be detrimental.<sup>585</sup>

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<sub>2</sub> level of 94–98%. Do not delay oxygen administration in the absence of pulse oximetry but commence monitoring of SpO<sub>2</sub> as soon as it becomes available.**

### 9.3.2 $\beta_2$ agonist bronchodilators

In most cases inhaled  $\beta_2$  agonists given in high doses act quickly to relieve bronchospasm with few side effects.<sup>586-588</sup> There is no evidence for any difference in efficacy between salbutamol and terbutaline. Nebulised adrenaline (epinephrine), a non-selective  $\beta_2$  agonist, does not have significant benefit over salbutamol or terbutaline.<sup>589</sup>

1++  
1+

In patients with mild to moderate asthma attacks,  $\beta_2$  agonists can be administered by repeated activations of a pMDI via an appropriate large volume spacer. There are insufficient data on which to make a recommendation about the use of metered dose inhalers with spacers in acute-severe or life-threatening asthma. In such patients,  $\beta_2$  agonists should be administered by wet nebulisation driven by oxygen, if available.<sup>531</sup> Inhaled  $\beta_2$  agonists are as efficacious and preferable to intravenous  $\beta_2$  agonists (meta-analysis has excluded subcutaneous trials) in adult acute asthma in the majority of cases.<sup>590</sup> If intravenous  $\beta_2$  agonists are used, consider monitoring serum lactate.<sup>591</sup>

1++  
3

**A Use high-dose inhaled  $\beta_2$  agonists as first-line agents in patients with acute asthma and administer as early as possible. Reserve intravenous  $\beta_2$  agonists for those patients in whom inhaled therapy cannot be used reliably.**

✓ If intravenous  $\beta_2$  agonists are used, consider monitoring serum lactate to monitor for toxicity.

Oxygen-driven nebulisers are preferred for nebulising  $\beta_2$  agonist bronchodilators because of the risk of oxygen desaturation while using air-driven compressors.<sup>531, 566, 592</sup>

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.<sup>578</sup>

4

The absence of supplemental oxygen should not prevent nebulised therapy from being administered when appropriate.<sup>593</sup>

4

**A In hospital, ambulance and primary care, nebulisers for giving  $\beta_2$  agonist bronchodilators should preferably be driven by oxygen.**

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

Parenteral  $\beta_2$  agonists, in addition to inhaled  $\beta_2$  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  $\beta_2$  agonists. Continuous nebulisation of  $\beta_2$  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.<sup>594-597</sup>

1+

**A In patients with severe asthma that is poorly responsive to an initial bolus dose of  $\beta_2$  agonist, consider continuous nebulisation with an appropriate nebuliser.**

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

Repeat doses of  $\beta_2$  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  $\beta_2$  agonist therapy. The earlier they are given in the acute attack the better the outcome.<sup>598, 599</sup> **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.<sup>598</sup> Prednisolone 40–50 mg daily or parenteral hydrocortisone 400 mg daily (100 mg six hourly) are as effective as higher doses.<sup>600</sup> 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.<sup>601</sup> **1++**

✓ Continue prednisolone (40–50 mg daily) until recovery (minimum 5 days).

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).<sup>602, 603</sup> **1+**

It is not known if ICS provide further benefit in addition to systemic steroids.<sup>604, 605</sup> **1+**

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

### 9.3.4 Ipratropium bromide

Combining nebulised ipratropium bromide with a nebulised  $\beta_2$  agonist produces significantly greater bronchodilation than  $\beta_2$  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.<sup>606–608</sup> **1++**

**B Add nebulised ipratropium bromide (0.5 mg 4–6 hourly) to  $\beta_2$  agonist treatment for patients with acute severe or life-threatening asthma or those with a poor initial response to  $\beta_2$  agonist therapy.**

### 9.3.5 Magnesium sulphate

A systematic review of 25 RCTs (13 including adults) involving 2,907 patients with asthma showed that nebulised magnesium sulphate when used in addition to nebulised  $\beta_2$  agonist (with or without nebulised ipratropium) provided no benefit in terms of lung function or need for hospital admission.<sup>609</sup> Subgroup analysis of the most severe patients was not possible due to heterogeneity in studies and the use of multiple different end-points. Some smaller studies noted modest improvements in lung function with nebulised magnesium in the most severe subgroup (presenting  $FEV_1 < 50\%$ ), but the results were not significant. **1++**

A double-blinded, 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 or nebulised magnesium or to placebo.<sup>610</sup> 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 intravenous magnesium sulphate is safe **1++**  
**1+**

and may improve lung function and reduce intubation rates in patients with acute severe asthma.<sup>355, 611-613</sup> 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 intravenous magnesium was given in relation to standard treatment limit the conclusions that can be drawn.<sup>613</sup>

1++  
1+

The safety and efficacy of repeated intravenous (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 intravenous 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 with standard care with inhaled bronchodilators and steroids. Side effects such as arrhythmias and vomiting are increased if IV aminophylline is used.<sup>614</sup>

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 were not identified in a meta-analysis of trials.<sup>614</sup> 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.<sup>615</sup> 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.<sup>616</sup> Decision making regarding the use of antibiotics in patients with acute asthma should be guided by objective measures including procalcitonin where available.<sup>617, 618</sup>

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.<sup>619, 620</sup> 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.<sup>621, 622</sup> 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  $\beta_2$  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  $\beta_2$  agonists.<sup>623</sup>

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:<sup>566, 567</sup>

- 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.<sup>624</sup>

2-

**Extracorporeal membrane oxygenation**

Extracorporeal membrane oxygenation (ECMO) is thought to help to provide adequate gas exchange whilst helping to prevent the barotraumas caused by aggressive mechanical ventilation. Currently, there are five centres in the UK with ECMO facilities for adults (Glenfield Hospital, Leicester; Papworth Hospital, Cambridge; Wythenshawe Hospital, Manchester; Guy's & St Thomas' Hospital, London; Royal Brompton & Harefield Hospital, London).

An international retrospective registry study of 272 adult patients with near-fatal asthma most of whom were put on venovenous ECMO showed a survival rate to hospital discharge of 83.5%. The rate of in-hospital complications was high (65.1%), the most common of which was haemorrhage (28.3%), most commonly at a manageable cannulation site (13.1%); only 1.5% died as a result of the haemorrhage. Other complications were renal (26.8%), cardiovascular (26.1%), mechanical (24.6%), metabolic (22.4%), infection (16.5%), neurologic (4.8%), and limb ischemia (2.6%). The most common cause of death was organ failure (37.8%, 17/45 complications). Long-term complications of ECMO were not considered.<sup>625</sup>

3

Although it is unclear which patients would benefit the most from venovenous ECMO, survivors were younger (34.7  $\nu$  43.4,  $p=0.001$ ), had a lower mean pH (7.1  $\nu$  7.2,  $p=0.045$ ), higher oxygen saturation (92.3  $\nu$  85.2,  $p=0.03$ ) and lower positive end-expiratory pressure (7.8  $\nu$  11.5,  $p=0.002$ ) than those who died.

Limitations of the registry include the lack of selection criteria for inclusion, and consequent lack of clarity about whether patients were on optimal or even similar ventilator settings, and the voluntary nature of reporting of cases which may lead to reporting bias. Despite these limitations, the use of ECMO provides a potential rescue therapy in patients with near-fatal asthma refractory to conventional ventilator treatment.

**D** Where available, extracorporeal membrane oxygenation may be considered in adults with near-fatal asthma refractory to conventional ventilator treatment.

**Recombinant human deoxyribonuclease**

A pilot RCT of the use of recombinant human deoxyribonuclease in severely ill, non-intubated adults with asthma refractory to bronchodilators reported no benefit from its use in this patient group.<sup>626</sup>

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.<sup>566, 567</sup>

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.<sup>627</sup>

4

Evidence to support the use of NIV in adults is limited and inconclusive. A Cochrane review found only one trial of NIV, with 30 patients, which showed improvement in hospitalisation rates, discharge from emergency departments and lung function.<sup>628</sup> 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.<sup>629, 630</sup>

1++  
1+  
2-

Larger RCTs are needed to determine the role of NIV in treating patients with acute asthma.<sup>628</sup> 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  $\beta_2$  agonist.
- Record oxygen saturation by oximetry and maintain arterial  $\text{SpO}_2$  at 94–98%.
- Repeat measurements of blood gas tensions within one hour of starting treatment if:
  - the initial  $\text{PaO}_2$  is  $<8$  kPa unless  $\text{SpO}_2$  is  $>92\%$ ; or
  - the initial  $\text{PaCO}_2$  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.<sup>574, 631, 632</sup>

2++

## 9.6 Hospital discharge and follow up

Annex 5 summarises management of acute asthma in hospital.

An asthma care bundle developed by the BTS is also available from the BTS website ([www.brit-thoracic.org.uk](http://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  $\beta_2$  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.<sup>633, 634</sup>

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.<sup>635</sup>

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.<sup>636</sup>

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.<sup>187</sup>

1++

For the above groups there is a role for a trained asthma liaison nurse based in, or associated with, the emergency department.<sup>187</sup>

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.<sup>637</sup> 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.<sup>638</sup> 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.

## 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 17 details criteria for assessment of severity of acute asthma attacks in children.

Annexes 6–9 contain algorithms summarising the recommended treatments for children presenting with acute or uncontrolled asthma in general practice (*see Annex 6*), the ED (*see Annex 7*), and hospital (*see Annexes 8 and 9*).

Table 17: Levels of severity of acute asthma attacks in children<sup>639</sup>

|                                |                                                                                                                                                                                                                                                                                                                                                              |                                       |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| <b>Moderate acute asthma</b>   | Able to talk in sentences<br>$\text{SpO}_2 \geq 92\%$<br>$\text{PEF} \geq 50\%$ best or predicted<br>Heart rate $\leq 140/\text{min}$ in children aged 1–5 years<br>$\leq 125/\text{min}$ in children >5 years<br>Respiratory rate $\leq 40/\text{min}$ in children aged 1–5 years<br>$\leq 30/\text{min}$ in children >5 years                              |                                       |
| <b>Acute severe asthma</b>     | Can't complete sentences in one breath or too breathless to talk or feed<br>$\text{SpO}_2 < 92\%$<br>$\text{PEF}$ 33–50% best or predicted<br>Heart rate $> 140/\text{min}$ in children aged 1–5 years<br>$> 125/\text{min}$ in children >5 years<br>Respiratory rate $> 40/\text{min}$ in children aged 1–5 years<br>$> 30/\text{min}$ in children >5 years |                                       |
| <b>Life-threatening asthma</b> | Any one of the following in a child with severe asthma:                                                                                                                                                                                                                                                                                                      |                                       |
|                                | <b>Clinical signs</b>                                                                                                                                                                                                                                                                                                                                        | <b>Measurements</b>                   |
|                                | Exhaustion                                                                                                                                                                                                                                                                                                                                                   | $\text{PEF} < 33\%$ best or predicted |
|                                | Hypotension                                                                                                                                                                                                                                                                                                                                                  | $\text{SpO}_2 < 92\%$                 |
|                                | Cyanosis                                                                                                                                                                                                                                                                                                                                                     |                                       |
|                                | Silent chest                                                                                                                                                                                                                                                                                                                                                 |                                       |
|                                | Poor respiratory effort                                                                                                                                                                                                                                                                                                                                      |                                       |
|                                | 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 preterminal 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.<sup>640-643</sup> 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.<sup>640, 643</sup> **2++**

- B** Consider intensive inpatient treatment of children with SpO<sub>2</sub> <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<sub>1</sub> 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.<sup>644, 645</sup>

- ✓ 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<sub>2</sub>.<sup>578</sup> If ear lobe sampling is not practicable a finger prick sample can be an alternative. Normal or raised PaCO<sub>2</sub> levels are indicative of worsening asthma. A more easily obtained free flowing venous blood PaCO<sub>2</sub> measurement of <6 kPa (45 millimetres of mercury) excludes hypercapnia.<sup>578</sup> **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.

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.<sup>646</sup>

4

**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  $\text{SpO}_2 < 94\%$  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 $\beta_2$ agonists

Inhaled  $\beta_2$  agonists are the first-line treatment for acute asthma in children aged two years and over.<sup>647-650</sup> Assessment of response should be based on accurately recorded clinical observations and repeat measurements of oxygenation ( $\text{SpO}_2$ ) (see Table 17). 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.<sup>531</sup> In children under two who have a poor initial response to  $\beta_2$  agonists administered with adequate technique, consider an alternative diagnosis and other treatment options.

1+

**A Inhaled  $\beta_2$  agonists are the first-line treatment for acute asthma in children.**

✓ Discontinue long-acting  $\beta_2$  agonists when short-acting  $\beta_2$  agonists are required more often than four hourly.

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

Children under 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  $\beta_2$  agonists are safe for the treatment of acute asthma,<sup>647-649</sup> although children with mild symptoms benefit from lower doses.<sup>650</sup>

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 ( $\text{SpO}_2 < 92\%$ ) 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  $\beta_2$  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  $\beta_2$  agonists are of no greater benefit than the use of frequent intermittent doses in the same total hourly dosage.<sup>651, 652</sup> 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  $\beta_2$  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  $\beta_2$  agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients.<sup>653</sup>

1+

**A If symptoms are refractory to initial  $\beta_2$  agonist treatment, add ipratropium bromide (250 micrograms/dose mixed with the nebulised  $\beta_2$  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  $\beta_2$  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.<sup>598, 599</sup> 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.<sup>654-656</sup>

1+  
1-

A large UK study of preschool 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 preschool 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.<sup>657</sup>

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 two 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 five years.

Oral and intravenous steroids are of similar efficacy.<sup>600, 658, 659</sup> 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.<sup>660</sup> There is no need to taper the dose of steroid tablets at the end of treatment.<sup>602, 603</sup>

2+

- ✓ • Use a dose of 10 mg prednisolone for children under two years of age, 20 mg for children aged 2–5 years and 30–40 mg for children older than five years. Those already receiving maintenance steroid tablets should receive 2 mg/kg prednisolone up to a maximum dose of 60 mg.
- Repeat the dose of prednisolone in children who vomit and consider intravenous steroids in those who are unable to retain orally ingested medication.
- Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery. 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.<sup>604, 661-668</sup>

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, but the majority of acute asthma attacks are triggered by viral infection.<sup>458</sup>

✓ 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.<sup>508, 669</sup> Current evidence shows no benefit for the addition of leukotriene receptor antagonists to standard asthma treatment for moderate to severe asthma attacks.<sup>615</sup>

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  $\beta_2$  agonists, in children with mild to moderate asthma.<sup>609</sup> A subgroup analysis from a large RCT suggests a possible role in children with more severe asthma attacks ( $\text{SpO}_2 < 92\%$ ) or with short duration of deterioration. Further studies are required to evaluate which clinical groups would benefit the most from this intervention.<sup>670</sup>

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  $\text{SpO}_2 < 92\%$ .**

## 9.9 Second-line treatment of acute asthma in children

Children with continuing severe asthma despite optimal first-line treatments, frequent nebulised  $\beta_2$  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  $\beta_2$  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.<sup>671</sup> 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.<sup>672</sup>

1++  
1+

### 9.9.1 Intravenous salbutamol

The role of intravenous  $\beta_2$  agonists in addition to nebulised treatment remains unclear.<sup>590</sup> 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.<sup>590</sup>

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  $\beta_2$  agonists and should be replaced.

✓ If intravenous  $\beta_2$  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.<sup>612, 614, 673, 674</sup> One well-conducted study has shown evidence of benefit in children with acute severe asthma unresponsive to multiple doses of  $\beta_2$  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.<sup>675</sup>

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.<sup>676</sup> Doses of up to 75 mg/kg/day (maximum 2 g) have been used. One additional trial (n=34 receiving magnesium sulphate) reported that the potential side effect of hypotension with a single dose of IV magnesium sulphate is rare.<sup>671</sup>

1++  
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.

### 9.9.5 Critical care settings

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.<sup>677</sup>

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<sub>2</sub> and provides clinical improvement in mechanically ventilated children.<sup>678</sup> Use of this agent is, however, limited to areas with appropriate scavenging facilities to extract gas in order to protect healthcare staff.

3

**Extracorporeal membrane oxygenation**

There is no good quality evidence on the use of ECMO in children, probably reflecting, in part, the low number of children who would be suitable for this approach. Extracorporeal membrane oxygenation has, however, been used successfully in other forms of critical respiratory failure in children for a number of years and there are four paediatric ECMO centres in the UK that would consider treating children with near-fatal asthma who are not responding to conventional treatment (Glenfield Hospital, Leicester; The Freeman Hospital, Newcastle; The Royal Hospital for Children, Glasgow; and Great Ormond Street Hospital, London).

**Recombinant human deoxyribonuclease**

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



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**

A systematic review of NIV for acute asthma in children included two RCTs (n=40) comparing NIV as add-on therapy to usual care versus usual care in children under 18 years of age hospitalised for an acute asthma attack. Both included studies used bilevel positive airway pressure only. Both included studies reported improvements in asthma symptom scores. This finding is, however, based on a small number of participants and on trials assessed as having a high risk of bias.<sup>679</sup>

1++

A further, observational, study reported that NIV is feasible in children with severe asthma within the paediatric intensive care unit setting, but did not include a control group for comparison of clinical outcomes.<sup>680</sup>

3

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.

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.<sup>681</sup> Peak expiratory flow and/or FEV<sub>1</sub> should be >75% of best or predicted and SpO<sub>2</sub> >94%. An asthma care bundle developed by BTS is also available from the BTS website ([www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)). Adult studies show that optimal care comprising self monitoring, regular review and a written PAAP can improve outcomes.<sup>166</sup> 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 at about one month after admission
- 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.



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.

## 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 definition of difficult asthma in children or adults that is universally agreed, 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, or have stipulated a treatment level equivalent to at least high-dose ICS (adults) or medium-dose ICS (children) plus a LABA or LTRA before labelling as 'difficult'.<sup>682, 683</sup>

In this guideline difficult asthma is defined as persistent symptoms and/or frequent asthma attacks despite treatment with high-dose ICS (adults) or medium-dose ICS (children) plus a LABA (age 5 and over) or LTRA; or medium-dose ICS (adults) or low-dose ICS (children) plus a LABA (age 5 and over) or LTRA and an appropriate additional therapy (*see section 7.5.2*); or continuous or frequent use of oral steroids (*see section 7.5.3*).

Observational uncontrolled studies in participants with difficult asthma, using multidisciplinary assessment models have identified high rates of alternative or coexistent diagnoses and psychological comorbidity.<sup>97, 684-686</sup> 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.

**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

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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.<sup>687</sup> In another study, 75 of 115 (65%) 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.<sup>688</sup> A study of 71 school-aged children with persistent symptoms, 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.<sup>689</sup> 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.<sup>690</sup> 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.<sup>685</sup>

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There is a need to identify patients who have poor control solely as a result of poor adherence to simple therapies that are currently available. 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.<sup>691</sup> 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.<sup>234</sup> 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.<sup>244</sup> Some other objective measures such as prescription filling are problematical because patients may fill prescriptions but not take the medication.

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**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<sup>97, 685, 692–695</sup> and a case-control study<sup>696</sup> in patients with difficult asthma have also suggested a high level of psychological morbidity, though this observation has not been universal.<sup>697, 698</sup>

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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.<sup>699</sup> 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 patients with difficult asthma are of benefit. A small proof of concept study targeting treatment of depression demonstrated a reduction in oral steroid use,<sup>700</sup> 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.<sup>701</sup> However, a non-blinded randomised intervention study in adults with difficult asthma showed no benefit from a six-month nurse-delivered psychoeducational programme.<sup>702</sup> 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.<sup>703</sup> 1+  
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**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. The dysfunctional breathing may cause symptoms that mimic asthma or coexist with asthma, worsening symptoms.<sup>97, 685</sup> It remains unclear what is the best mechanism for identifying and managing this problem. 3

**D Dysfunctional breathing should be considered as part of the assessment of patients with difficult asthma.**

### 10.2.4 Allergy

Acute asthma has been associated with IgE-dependent sensitisation to indoor allergens.<sup>704</sup> In case-control studies, mould sensitisation has been associated with recurrent admission to hospital and oral steroid use<sup>705, 706</sup> and with intensive care unit admissions and respiratory arrest.<sup>707, 708</sup> There is no published evidence of any intervention study in this patient group. Research in this area is required. 2++  
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**C In patients with difficult asthma and recurrent hospital admission, allergen testing to moulds should be performed.**

10.2.5 Monitoring airway response

Two blinded RCTs 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.<sup>709-711</sup> 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.<sup>709</sup> Case series have suggested that sputum induction is safe in patients with difficult to control asthma.<sup>67, 712-715</sup>

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Controlled studies using FeNO to target treatment have not specifically targeted adults or children with difficult asthma.<sup>716, 717</sup>

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**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.<sup>3</sup>

There is international agreement on best practice for working with adolescents with health problems outlined in consensus publications.<sup>718-720</sup> Key elements of working effectively with adolescents in the transition to adulthood include:<sup>721</sup>

- 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%.<sup>722</sup> For more severe asthma (defined as  $\geq 4$  attacks of wheeze or  $\geq 1$  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.<sup>722-725</sup> This has been attributed to under reporting of symptoms. A number of risk factors have been independently 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.<sup>725</sup> Children with undiagnosed frequent wheezing do not receive adequate healthcare for their illness<sup>725</sup> and the health consequences of not being diagnosed with asthma are substantial.<sup>726, 727</sup>

Although feasible, there is insufficient evidence to support screening for asthma in adolescents.<sup>728, 729</sup>



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

## 11.3 Diagnosis and assessment

### 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.<sup>730</sup> 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.<sup>54</sup>

Most exercise-related wheezing in adolescents can be diagnosed and managed by careful clinical assessment.<sup>731</sup> The absence of other features of asthma and an absent response to pretreatment with  $\beta_2$  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.<sup>54</sup>

### 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.<sup>732</sup>

In one study in adolescents, internet and written questionnaires about asthma provided equivalent results.<sup>733</sup> The ACQ and the ACT have been validated in adolescents with asthma (see Table 8).<sup>118</sup>

### 11.3.3 Quality of life measures

Quality of life scales (such as AQLQ12+) can be used in adolescents.<sup>734, 735</sup>

### 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.<sup>736</sup>

A negative response to an exercise test is helpful in excluding asthma in children with exercise-related breathlessness.<sup>54</sup>

## 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.<sup>737-740</sup>

### 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.<sup>741</sup>

Frequent or severe episodes of wheezing in childhood are associated with recurrent wheeze that persists into adolescence.<sup>74, 77, 86, 88, 94, 106-108, 740</sup>

#### 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.<sup>742</sup> 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.<sup>743</sup> This phenomenon has been attributed to a greater incidence of asthma among teenage girls.<sup>744</sup>

#### 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.<sup>745</sup> Such associations were not found among adolescents without atopy or in those who attended copper-silver sanitised pools.<sup>746</sup>

### 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.<sup>747</sup> In young people with asthma, the presence of an anxiety or depressive disorder is highly associated with increased asthma symptom burden.<sup>748</sup> 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.<sup>749</sup>

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.<sup>750</sup>

Brief screening questionnaires for anxiety and depression suitable for use in adolescents are available and may help identify those with significant anxiety and depression.<sup>751</sup>

#### 11.5.2 Obesity

The evidence on whether asthma is more common in overweight and obese adolescents with asthma is conflicting.<sup>737, 752-754</sup> 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.<sup>755</sup> 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.<sup>756</sup> There is no evidence that treatment for GORD improves asthma symptoms in children and adolescents with GORD and asthma.<sup>527, 528</sup>

## 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.<sup>757</sup>

## 11.7 Long-term outlook and entry into the workplace

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.<sup>758</sup> 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 GP. 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 ( $p\leq 0.001$ ) reported in the next 12 months, as well as fewer episodes of poor asthma control ( $p=0.042$ ).<sup>759</sup>

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.<sup>760</sup>

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Among adolescents, smoking is a risk factor for asthma.<sup>738, 761-763</sup> 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.<sup>764</sup>

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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 of Italian teenagers, 16% of those included had used complementary and alternative medicine (CAM) (homeopathy, acupuncture, herbal medicines).<sup>765</sup> 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.<sup>766</sup> While most adolescents used CAM with conventional asthma therapy, 27% reported they used it instead of prescribed therapy<sup>766</sup> suggesting that CAM use may be a marker of non-adherence to prescribed asthma treatment.

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- ✓ Healthcare professionals should be aware that complementary and 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.<sup>767, 768</sup> There were no differences between the two inhaler devices in terms of symptoms or lung function but patients preferred the DPI.

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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.<sup>769, 770</sup>

- ✓ 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.<sup>684</sup>

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### 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 (*see section 14.5*). One focus has been on healthcare delivery, such as school-based clinics. Evidence from a single cluster RCT suggests that school-based, nurse-led asthma clinics increase the uptake of asthma reviews in adolescents from 51% in practice care to 91%.<sup>771</sup> 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.<sup>772</sup> 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.<sup>201</sup>

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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.<sup>773</sup>

**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 services

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.<sup>718-720</sup>

It is important that the process of transition is co-ordinated and 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.<sup>774, 775</sup>

- ✓ 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.<sup>774</sup> It should begin early, be planned, involve the young person, and be both age and developmentally appropriate.<sup>774</sup>

- 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 supported self management, including 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 negotiate the health system effectively. 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. The specific knowledge, attitudes and skills that underpin independent self-management practices in adolescents with asthma are that they can:<sup>776</sup>

- name and explain their condition
- list their medications, treatments or other management practices (eg special diet)
- explain why each medication or management practice is necessary
- remember to take their medications most of the time
- answer questions asked of them by doctors or other healthcare professionals
- ask questions of their doctor or other healthcare professional
- arrange (and cancel) appointments
- consult with a doctor or other healthcare professional without a parent/carer
- remember to order more medication before it runs out
- have prescriptions filled at the pharmacy
- develop the desire for their healthcare to be independent of their parents/carers
- 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.<sup>777, 778</sup>

Studies of adolescents with chronic illness (including asthma) have highlighted factors that adolescents feel are important in delivering education about self management to them.<sup>779</sup> 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.

**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.<sup>780</sup>

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).<sup>770, 781</sup> 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.<sup>782</sup>

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.<sup>783</sup> 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.<sup>784</sup> Clinical tools such as the Home, Education/Employment, Activities, Drugs, Sexuality, Suicide/depression adolescent health screen provide practitioners with an easily usable psychosocial screen.<sup>785</sup>

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.<sup>786</sup> One study found that once-daily supervised asthma preventer therapy at school improved asthma control and quality of life.<sup>787</sup>

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## 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%.<sup>788</sup> A prospective cohort study of 1,739 pregnant women showed an overall improvement in 23% and deterioration in 30.3%.<sup>789</sup> 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.<sup>790</sup> There is also some evidence that the course of asthma is similar in successive pregnancies.<sup>788, 791</sup> A systematic review showed no effect of pregnancy or stage of pregnancy on FEV<sub>1</sub>.<sup>792</sup>

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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.<sup>793, 794</sup> Severe asthma is more likely to worsen during pregnancy than mild asthma,<sup>788</sup> 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.<sup>789</sup> The corresponding rates of hospitalisation were 2%, 7% and 27%.

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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.<sup>791</sup> In a large cohort study, the most severe symptoms were experienced by patients between the 24<sup>th</sup> and 36<sup>th</sup> week of pregnancy. Thereafter symptoms decreased significantly in the last four weeks and 90% of patients had no asthma symptoms during labour or delivery. Of those who did, only two patients required anything more than inhaled bronchodilators.<sup>788</sup> A further study has confirmed that patients are least likely to have an asthma attack in the last month of pregnancy.<sup>795</sup>

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#### 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.<sup>796</sup> 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.<sup>797</sup>

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Uncontrolled asthma is associated with many maternal and fetal complications, including hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, complicated labour, fetal growth restriction, preterm birth, increased perinatal mortality, and neonatal hypoxia.<sup>789, 798-801</sup> A large Swedish population-based study using record linkage data demonstrated increased risks for preterm birth, low birth weight, perinatal mortality and pre-eclampsia in women with asthma. The risks for preterm delivery and low birth weight were higher in women with more severe asthma necessitating admission.<sup>802</sup>

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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).<sup>789</sup> Logistic regression analysis of the severe group showed an increased risk of gestational diabetes (adjusted odds ratio (AOR) 3.0, 95% CI 1.2 to 7.8) and preterm 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 preterm delivery but oral steroids increased the rate of preterm delivery and reduced gestation by 2.2 weeks (AOR 1.05, 95% CI 1.01 to 1.09).<sup>803</sup> 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.<sup>804</sup> The RR was 2.54 (95% CI 1.52 to 4.25) compared with women without asthma. In a large cohort study of 2,123 women with asthma, there was an association of both mean FEV<sub>1</sub> and mean FEV<sub>1</sub> <80% predicted with gestational hypertension, preterm delivery <37 weeks and <32 weeks, and low birth weight.<sup>805</sup>

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In contrast, if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications.<sup>788, 793</sup> Pregnancy should therefore be an indication to optimise therapy and maximise lung function in order to reduce the risk of acute asthma attacks.

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**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.<sup>806</sup> 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 five confidential enquiries into maternal deaths in the UK (covering

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1994–2008) there were 22 deaths from asthma.<sup>807–811</sup> A 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.<sup>812</sup>

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Oxygen should be delivered to maintain saturation 94–98% in order to prevent maternal and fetal hypoxia.<sup>578</sup> 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<sub>2</sub><sup>813, 814</sup> but oxygen saturations are unaltered.<sup>815</sup> Acidosis is poorly tolerated by the fetus.

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Drug therapy should be given as for a non-pregnant patient with acute asthma, including nebulised  $\beta_2$  agonists and early administration of steroid tablets (*see section 9*).<sup>788, 794, 795, 798, 799</sup> In severe cases, intravenous  $\beta_2$  agonists, aminophylline or intravenous bolus magnesium sulphate can be used as indicated.<sup>816</sup>

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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.<sup>817</sup> Pregnant women may be more difficult to intubate due to anatomical changes especially if they have pre-eclampsia.<sup>818</sup>

**C** In pregnant patients, give drug therapy for acute asthma as for non-pregnant patients including systemic steroids and magnesium sulphate.

**D** In pregnant patients with acute asthma, 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 whose asthma is poorly controlled 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.<sup>819, 820</sup> 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.<sup>821</sup> The risk of harm to the fetus from severe or chronically undertreated asthma outweighs any small risk from the medications used to control asthma.

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

12.3.1  $\beta_2$  agonists

No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to short-acting  $\beta_2$  agonists.<sup>819-823</sup> 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.<sup>824</sup> A case-control study including 2,460 infants exposed to short-acting  $\beta_2$  agonists found no increased risk of congenital malformations in exposed infants.<sup>789</sup>

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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.<sup>825, 826</sup> A systematic review of studies including 190 exposures to LABA demonstrated no increased risk of congenital malformations, preterm delivery or pre-eclampsia.<sup>827</sup> A case-control study including 156 infants exposed to LABA found no increased risk of major congenital malformations.<sup>821</sup> As in other settings, LABAs should be used with an ICS, ideally as a combination product.<sup>828</sup>

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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.<sup>829</sup>

**C Use short-acting  $\beta_2$  agonists as normal during pregnancy.**

**C Use long-acting  $\beta_2$  agonists 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.<sup>819, 821, 827, 830-838</sup> 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.<sup>839</sup> The UK case-control study included 1,429 infants exposed to ICSs and found no increased risk of major congenital malformations.<sup>821</sup>

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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.<sup>794, 795</sup> A randomised placebo-controlled trial of inhaled beclometasone compared with 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.<sup>789</sup>

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**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.<sup>819, 840</sup>

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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.<sup>841</sup>

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**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,<sup>819</sup> 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.<sup>842, 843</sup> One case-control study, however, found a significant association, although this increase is not significant if only paired controls are considered.<sup>844</sup> Although one meta-analysis reported an increased risk, a prospective study by the same group found no difference in the rate of major birth defects in prednisolone-exposed and control babies.<sup>845</sup> A further 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.<sup>846</sup> Another case-control study including 262 exposed infants found no such association, although this was not limited to first trimester exposure.<sup>821</sup>

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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.<sup>800, 813</sup> 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.

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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.<sup>806</sup> Failure to administer steroid tablets when indicated increases the risk of ongoing asthma attacks and therefore the risk to the mother and her fetus.

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Some studies have found an association between steroid tablet use and pregnancy-induced hypertension or pre-eclampsia, preterm labour<sup>797</sup> and fetal growth but severe asthma may be a confounding variable.<sup>847</sup>

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**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  $\beta_2$  agonists.<sup>847</sup> A systematic review found no increased risk of malformations or preterm delivery in nine exposed women.<sup>803, 827</sup> Three studies looking at infant outcomes in women exposed to LTRAs (two in women taking montelukast) showed no increased risk of congenital malformations.<sup>848-850</sup>

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**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.<sup>819, 827, 847</sup>

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**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,<sup>797, 851, 852</sup> 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.<sup>795</sup> 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).<sup>789</sup>

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Data suggest that the risk of postpartum asthma attacks is increased in women having Caesarean sections.<sup>851</sup> 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.<sup>841</sup> Prostaglandin F2 $\alpha$  (carboprost/hemobate®) used to treat postpartum haemorrhage due to uterine atony may cause bronchospasm.<sup>841</sup> Although ergometrine may cause bronchospasm particularly in association with general anaesthesia,<sup>841</sup> this is not a problem encountered when syntometrine (syntocinon/ergometrine) is used for postpartum haemorrhage prophylaxis.

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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.<sup>853</sup>

- ✓ 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.
- ✓ If anaesthesia is required, regional blockade is preferable to general anaesthesia in women with asthma due to the potential risk of bronchospasm with certain inhaled anaesthetic agents.
- ✓ 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.<sup>854</sup> There is less experience with newer agents. Less than 1% of the maternal dose of theophylline is excreted into breast milk.<sup>854</sup> 2+

Prednisolone is secreted in breast milk, but milk concentrations of prednisolone are only 5–25% of those in serum.<sup>527</sup> The proportion of an oral or intravenous dose of prednisolone recovered in breast milk is less than 0.1%.<sup>855–857</sup> 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.<sup>855–857</sup> 2+  
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- 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.<sup>858-860</sup> It is now the commonest industrial lung disease in the developed world with over 400 reported causes.<sup>861-863</sup> **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.<sup>864-872</sup> **2++**

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.<sup>864, 865, 867, 869-875</sup> **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.<sup>876-879</sup> **2+**

### 13.3 Diagnosis

Occupational asthma should be considered in all workers with symptoms of airflow limitation (*see Annex 10*). 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. The use of non-leading questions is advocated.<sup>880</sup> 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 45–100%, with wheeze and shortness of breath the symptoms most commonly reported.<sup>881</sup> 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.<sup>881</sup> **4**

One study notes a relatively low positive predictive value of work related symptoms.<sup>882</sup> 3

- ✓ Adults with suspected asthma or unexplained airways obstruction should be asked:
- Are you the same, better, or worse on days away from work?
  - Are you the same, better, or worse 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.<sup>883-890</sup> 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.<sup>891</sup> 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.<sup>890</sup> 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).<sup>892</sup>

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.<sup>893</sup> A statistical method using the addition of timepoint analysis requires the waking time to be similar on rest and work days.<sup>894</sup> 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](http://www.occupationalasthma.com)

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

### 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".<sup>881</sup> 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.<sup>881</sup> 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.<sup>881</sup>

**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.<sup>881, 895</sup>

**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.<sup>896</sup> When carrying out specific challenge testing, an increased duration of allergen exposure may increase the overall diagnostic sensitivity of the tests.<sup>897</sup>

A positive SIC is one in which the FEV<sub>1</sub> falls by  $\geq 15\%$  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.<sup>898</sup> Equivocal reactions can sometimes be clarified by finding changes in non-specific bronchial responsiveness, sputum eosinophils or exhaled nitric oxide. Specific inhalation challenge is generally a safe procedure; excessive reactions are rare with <3% of patients needing repeated doses of a bronchodilator and steroid treatment.

The sensitivity and specificity of SIC are high but not easily quantified as the method is usually used as the reference standard for the diagnosis of occupational asthma. False negative tests also occur, and SIC testing may be of less value where complex workplace exposures cannot be replicated in the laboratory. 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.<sup>881, 895, 899</sup> 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.<sup>881</sup> In the clinical setting the absence of sputum eosinophilia does not exclude a diagnosis of occupational asthma.<sup>881</sup>

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### 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". The review concluded that the role of exhaled nitric oxide measurements in the diagnosis of occupational asthma in this setting is not established.<sup>881</sup>

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### 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.<sup>900, 901</sup>

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## 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.<sup>885, 902-910</sup>

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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.<sup>911-913</sup>

**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.<sup>914-916</sup> The risk of unemployment may fall with increasing time after diagnosis.<sup>917</sup> 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.<sup>915, 916</sup> Approximately one third of workers with occupational asthma have been shown to be unemployed up to six years after diagnosis.<sup>913-921</sup>

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## 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.”<sup>922</sup>

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.<sup>923, 924</sup> Pathways for inpatient care can improve processes of care, such as prescription of oral prednisolone and use of written asthma action plans in children,<sup>925</sup> and can reduce length of stay for children,<sup>646, 926</sup> but have not improved follow up in general practice after discharge.<sup>927</sup>

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Further well-conducted studies are needed to define the benefits of care pathways for asthma. These should include large studies suitably powered 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<sup>928</sup>
- mixed interactive and didactic education is more effective than either alone.<sup>929</sup>

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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,<sup>189, 930</sup> or adaptations of it for Australian and UK practice,<sup>217, 931</sup> and have shown reductions in ED visits,<sup>930</sup> improved symptom control,<sup>217</sup> and increased use of written asthma action plans.<sup>931</sup> The PACE intervention has not been tested for adult populations and there is little experience of its use in the UK.

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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.<sup>932</sup> 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

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for their physician colleagues and feedback on their colleagues' performance along with monthly support from a nurse co-ordinator. 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.

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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.<sup>933-936</sup>

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Remote IT educational interventions, such as remote spirometry training,<sup>937</sup> 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.<sup>166</sup> Benefits include reduced school or work absence, reduced asthma attack rate, improved symptom control and reduced attendance at the emergency department.<sup>938, 939</sup> Proactive structured review, as opposed to opportunistic or unscheduled review, is associated with reduced rates of asthma attack and days lost from normal activity.<sup>940-942</sup> 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.<sup>941, 943, 944</sup>

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**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 (for example GP clinic) which occupies a defined and often regular clinical session for the routine review of patients with asthma".<sup>945</sup>

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.<sup>945</sup> 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.<sup>172</sup> The review focused on psychoeducational interventions mostly for adults and adolescents (age 16 or older) 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

Telehealthcare is evolving rapidly and terminology 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,<sup>946</sup> educational games to improve knowledge<sup>170, 181, 266, 947</sup> or effect behavioural change,<sup>201, 948, 949</sup> and telemonitoring with various levels of professional oversight to support self management.<sup>212, 950-955</sup> These functions may use different IT modalities (text messaging,<sup>171, 956</sup> automated telephone calls,<sup>267</sup> 'apps',<sup>953</sup> computer games,<sup>170, 181, 266</sup> cloud-based electronic health records,<sup>953-955</sup>) and may be delivered in different contexts (primary/community care,<sup>212, 267, 952, 953</sup> hospital outpatients,<sup>947</sup> school based<sup>181, 201, 266, 949</sup>) 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.<sup>946</sup> As part of more complex telehealthcare interventions, reminders may contribute to improved adherence to monitoring or medication use.<sup>171, 954-956</sup>

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,<sup>170, 181, 266</sup> and children attending a UK outpatients clinic.<sup>947</sup> The latter study showed reduced school absenteeism and the number of steroid courses,<sup>947</sup> but overall there is an inconsistent effect on clinical outcomes,<sup>170, 181, 266</sup> and no impact on use of healthcare resources.<sup>181, 266, 947</sup>

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. 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.<sup>201, 949</sup>

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,<sup>952, 955</sup> lung function,<sup>212</sup> quality of life, reduced risk of activity limitation,<sup>212</sup> and school absenteeism, exacerbations, and use of unscheduled care.<sup>212</sup> Other trials, however, have shown no impact on asthma control or use of healthcare resources.<sup>951, 953</sup>

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<sup>212, 952</sup>), and the level of professional support provided (frequency of monitoring,<sup>212, 954</sup> personalisation of feedback,<sup>954</sup> access to case-management support<sup>952</sup>). People with poorly-controlled asthma have the potential to gain more by engaging with telemonitoring than those whose control is already optimal.<sup>955</sup> Telehealthcare-supported self management offered no clinical benefits over care delivered in traditional ways that was already guideline standard.<sup>953</sup>

1++  
1+

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

- can improve process outcomes, such as knowledge,<sup>170, 181, 957</sup> adherence to monitoring,<sup>171</sup> self-efficacy/self-management skills,<sup>181, 948, 957</sup> and increased use of preventer medication,<sup>946, 956, 957</sup> at least in the short term<sup>946</sup>
- has an inconsistent effect on clinical outcomes, such as symptoms,<sup>170, 171, 181, 948, 950, 951, 956, 957</sup> SABA use,<sup>170</sup> lung function,<sup>170, 171, 950, 956, 957</sup> school absenteeism,<sup>181, 957</sup> activity limitation,<sup>950, 957</sup> quality of life,<sup>181, 950, 951, 957</sup> and oral steroid courses<sup>948</sup>
- generally has no effect on unscheduled use of healthcare resources (such as hospitalisations and ED attendances),<sup>170, 951, 956, 957</sup> out-of-hours consultations,<sup>951</sup> and GP consultations<sup>951, 957</sup>

1++  
1-  
2++  
2+  
2-

- has cost implications relating to providing and supporting telehealthcare services<sup>171, 951</sup> | 1++  
1-
- 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. | 2++  
2+  
2-

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. Information technology-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 other studies, most of them observational, included only four studies addressing asthma, two of them RCTs, one of which was of poor quality.<sup>958, 959</sup> Although both reviews suggest that asynchronous telehealthcare 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,<sup>213, 267, 960, 961</sup> two were considered to be of low methodological quality.<sup>213, 267</sup> There is some evidence to suggest that synchronous consulting can lead to improvements in parental QoL,<sup>960</sup> and equivalent health status to people reviewed in 'traditional' face-to-face consultations.<sup>961</sup> | 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.<sup>962</sup> | 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 | 1++

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.<sup>963</sup> 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.<sup>181</sup> Other approaches include peer education, whereby students are trained and then, in turn, train their peers,<sup>772, 964</sup> web-based programmes,<sup>201</sup> or directly-observed therapy with ICS medication,<sup>787</sup> which may additionally include education of parents (*see section 11.11.2*).<sup>965</sup> One study tested a multifaceted intervention combining education of schoolchildren with additional training of their doctor, including provision of self-management plans.<sup>966</sup> 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.<sup>181</sup> Peer education was effective for adolescents<sup>772</sup> but not preteens.<sup>964</sup> In two studies, directly observed therapy improved symptom control.<sup>787, 965</sup> 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.<sup>966</sup> 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.<sup>186</sup> Interventions were usually intensive, multisession clinic-based programmes. They were nurse led or used experts including pharmacists or allergy specialists.<sup>186</sup> These findings mirror the little work published in the UK, which showed that a clinic based in primary care was ineffective,<sup>206</sup> 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.<sup>207</sup> 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 RCTs of lay-led self-management education programmes was identified.<sup>967</sup> 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.<sup>968, 969</sup>

Interventions generally involved educating community pharmacists to, in turn, educate patients.<sup>970-972</sup> Other models or elements included follow-up reviews for newly prescribed medication,<sup>973</sup> identifying those with poor control by using questionnaires such as the Asthma Control Test,<sup>972</sup> searching prescribing databases for patients using large numbers of reliever inhalers,<sup>974</sup> and targeting reviews or referral to general practitioners.

Overall, the most consistent improvements in outcomes were seen in inhaler technique,<sup>970-972</sup> with a few studies showing improvements in reduced dispensing of, or need for, reliever inhalers.<sup>972, 974</sup> There was no convincing evidence of reduction in healthcare use.

1+

1-



**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 11*) 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](http://www.sign.ac.uk), (*see section 15.2*) 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 15.3*).

### 15.1 Checklist of information for patients and carers

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

#### Assessment and diagnosis

- Fully explain symptoms and triggers, giving examples to help. Ask the patient questions to ensure they understand.
- Explain to the patient that diagnosing and managing asthma is not straightforward, and that they might be trying a few different tests and medicines. Explain to the patient that the results of tests or medicine trials may mean more tests and trying different medicines.
- Explain the different tests using clear, concise, jargon-free language. Show the materials that will be used in these tests, for example a spirometer.
- Ensure patients are kept informed about which tests will be performed, when they are likely to be carried out, and what the results mean.
- Explain and show equipment (inhalers and spacers), how it is used, how often the patient should use it, where they will get these from.
- Encourage patients and their families to discuss their questions and concerns during appointments and reviews. This will help patients to get the most from their appointments or reviews.

**Ongoing care (monitoring)**

- Advise patients and their families of the need to work in partnership with them to allow a holistic approach to managing their asthma.
- Ensure the patient is aware that they do not have to wait until their regular review if they have concerns that they need to discuss with their healthcare professional sooner.
- Encourage people to take a notebook to appointments to allow them to record key information.
- Offer a summary of discussions at the end of every appointment and check the patient's understanding.
- Ensure appropriate information is given to patients to encourage them to take responsibility for their asthma, for example making sure that they are familiar with personal asthma action plans and filling these in with them if they do not have one.
- Be sensitive to and aware of how culture and beliefs affect a patient's asthma and lifestyle. For example offer action plans in different language as appropriate.
- Listen carefully to the needs and priorities of patients and carers.
- Explain what happens if the patient reaches a crisis point of an asthma attack.

**Medicines (pharmacological management)**

- Inform patients of side effects from medication when prescribing and reviewing medication and reassure them that these are normal. Listen to any concerns.
- Explain in clear, jargon-free language, any new medicines, and reasons for changing medicines.
- Check and optimise inhaler technique.

**Non-pharmacological management**

- Remain open minded and open to discussing things that may help manage symptoms alongside medicines. Different things might help different people.

**Self management**

- Ask patients to think about asthma triggers, for example perfumes, cleaning products, smoke, etc.
- Ask patients what they do to help them to manage their asthma, for example do they keep a diary, notebook, use an app, peak-flow meter, etc.
- Provide and explain a personal asthma action plan (PAAP).

**Asthma attacks**

- Introduce yourself.
- Discuss with the patient their personal asthma action plan before they leave hospital.
- Discuss with the patient and their family or carer what happens after they leave the hospital, for example explain that they need to make an appointment with their doctor or asthma nurse.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Asthma in pregnancy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>• Communicate with the labour team to ensure they are aware of any at-risk patients.</li> <li>• Discuss with the patient any changes to their asthma action plan and make sure the patient understands any changes.</li> </ul>                                                                                                                                                                                                                                                             |
| <b>Asthma in young people</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>• Involve children and young people from the start and encourage them to take responsibility for managing their asthma. Listen to and address their needs fully and ask children and young people the following questions. <ul style="list-style-type: none"> <li>- Have you had any asthma attacks? What were you doing at the time?</li> <li>- Have you been breathless?</li> <li>- Have you been taking your medication? If not, what were the reasons for this?</li> </ul> </li> </ul> |
| <b>Work-related asthma</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>• Explain that people may find they have issues at work, for example triggers may be present.</li> <li>• Discuss what can be done to help at work.</li> </ul>                                                                                                                                                                                                                                                                                                                              |

## 15.2 Publications from SIGN

SIGN patient versions of guidelines are documents that 'translate' guideline recommendations and their rationales, originally developed for healthcare professionals, into a form that is more easily understood and used by patients and the public. They are intended to:

- help patients and carers understand what the latest evidence supports around diagnosis, treatment and self care
- empower patients to participate fully in decisions around management of their condition in discussion with healthcare professionals
- highlight for patients where there are areas of uncertainty.

The following SIGN patient versions for asthma can be accessed at:  
[www.sign.ac.uk/patient-publications.html](http://www.sign.ac.uk/patient-publications.html)

- Managing asthma in adults: a booklet for adults, partners, friends, family members and carers. (SIGN 2019)
- Managing asthma in children: a booklet for parents, carers and family members. (SIGN 2019)
- Asthma in pregnancy: a booklet for women, partners, friends, family members and carers. (SIGN 2019)

## 15.3 Sources of further information

### 15.3.1 National organisations for people who have asthma

#### **Asthma UK**

18 Mansell Street, London, E11 8AA

Asthma UK's Helpline: 0300 222 5800 (9am-5pm, Mon-Fri) – nurses provide advice for people with asthma and for healthcare professionals.

General enquiries: [info@asthma.org.uk](mailto:info@asthma.org.uk)

Tel: 0300 222 5800

[www.asthma.org.uk](http://www.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

Helpline: 08458 50 50 20

Tel: 020 7688 5555

[www.blf.org.uk](http://www.blf.org.uk)

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.

### 15.3.2 Other organisations

#### **Allergy UK**

Planwell House, Lefa Business Park, Edginton Way, Sidcup, Kent, DA14 5BH

Helpline: 01322 619898

[www.allergyuk.org](http://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](http://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.scot](http://www.nhs24.scot)

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](http://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. 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 2 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 update of the guideline (*see Annex 1*). The following areas for further research have been identified:

- Clinical prediction models for quantifying risk need to be developed and prospectively validated in adults, children aged 5–12 and children under five years of age. Does risk assessment based on these factors improve outcomes when used prospectively in routine clinical practice?
- In monitoring asthma, what level of risk is associated with factors where evidence is currently limited or equivocal (*see Tables 9 and 10*)?
- Does incorporation of assessment of risk of future asthma attacks (potentially using a risk score) into routine care improve outcomes?
- What is the utility of FeNO measurement in guiding asthma treatment to improve asthma outcomes, such as reduced asthma attacks or increased asthma control, in different patient groups?
- What is the impact of poverty, urban/rural living and ethnicity on asthma outcomes in the UK setting?
- In children under five years of age, what factors are associated with increased risk of acute asthma/wheezing attacks? Do risk factors in this age group differ from those in older children?
- What features of available apps lead to improvements in adherence to medication and which have any impact on clinical outcomes?
- Which approaches to improving medication adherence are most effective and sustainable in patients with asthma?
- How effective are house dust mite and other allergen reduction measures in asthma? A systematic review/meta-analysis is required including only high-quality trials that i) use interventions that are documented to reduce allergen exposure, ii) follow up participants for a sufficient time for important clinical

outcomes to become apparent, iii) provides separate analyses for children and adults, and iv) accounts for any changes in asthma medication over the course of the trial.

- What are the potential beneficial effects of vitamin D supplementation in people with asthma, particularly children and people with frequent severe asthma exacerbations, with different baseline vitamin D levels?
- How effective are breathing exercises in children with asthma?
- What components of individualised multicomponent allergen reduction strategies are effective at improving asthma control and reducing exacerbations?
- Do strategies to reduce environmental allergens improve asthma control and reduce exacerbations in specific subgroups of people with asthma, eg children?
- How effective is montelukast in patients without allergic rhinitis and/or atopic dermatitis?
- Development of an agreed universal definition of 'asthma exacerbation' to allow comparison of this outcome between studies.
- Classification of asthma-related and non-asthma related adverse events to allow comparison of adverse events between studies.
- Which, if any, subgroups of children benefit most from addition of LTRA as compared with LABA as additional add-on therapy to ICS alone?
- What are the short- and long-term steroid-sparing effects of monoclonal antibody therapies in adults and children on different treatment regimens?
- Does the effectiveness of treatment with monoclonal antibodies decrease over time and/or does clinically relevant antibody sensitisation occur, and if so, at what point does/do these occur?
- What markers of response are there to enable targeting of monoclonal antibody therapy?
- Does suppression of IgE or IL-5 have any long-term effects on the recipient's immune function?
- What is the short- and long-term effectiveness and safety of subcutaneous and sublingual immunotherapy in asthma in studies with optimal design and patient-centric endpoints, such as asthma control and exacerbations? Does effectiveness differ between different products or between patients with different characteristics?
- Which patients with asthma might benefit most from bronchial thermoplasty and what are the long-term outcomes and safety of this treatment?
- What is the place of bronchial thermoplasty in the management of severe asthma compared with other options such as biological treatments?
- What is the relative clinical effectiveness and safety of bronchial thermoplasty compared with monoclonal antibody treatments?
- What is the role of non-invasive ventilation and high-flow oxygen therapy in treating children with severe exacerbations of asthma, and what is their effect on measurable outcomes including respiratory parameters, physiological variables and blood gases?
- In considering treatment with extracorporeal membrane oxygenation (ECMO) what is the definition of life-threatening or standard care?
- What is the clinical effectiveness and safety of ECMO treatment in patients with asthma taking anticoagulants?

## 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](http://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 Board of Trustees, are in place. These arrangements cover production of each update and appointment of members to the overall Guideline Development Group.

### 17.2 Guideline development group

|                              |                                                                                                                                                                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dr James Paton<br>(Co-chair) | Clinical Reader and Honorary Consultant<br>Paediatrician, Royal Hospital for Children, Glasgow                                                                                                                                        |
| Dr John White<br>(Co-chair)  | Consultant Respiratory Physician,<br>York District Hospital                                                                                                                                                                           |
| Mr Joe Annandale             | Respiratory Nurse Specialist, Prince Philip<br>Hospital, Llanelli                                                                                                                                                                     |
| Dr Anne Boyter               | Senior Lecturer, Strathclyde Institute of Pharmacy<br>and Biomedical Sciences, Glasgow                                                                                                                                                |
| Ms Juliet Brown              | Evidence and Information Scientist, Healthcare<br>Improvement Scotland                                                                                                                                                                |
| Ms Beatrice Cant             | Programme Manager, SIGN Executive                                                                                                                                                                                                     |
| Dr Toby Capstick             | Consultant Pharmacist, St James' University<br>Hospital, Leeds                                                                                                                                                                        |
| Dr Richard Chavasse          | Consultant in Respiratory Paediatrics, St George's<br>Hospital, London                                                                                                                                                                |
| Dr Luke Daines               | Academic Clinical Fellow, Asthma UK Centre for<br>Applied Research, Usher Institute of Population<br>Health Sciences and Informatics, University of<br>Edinburgh, and General Practitioner, Craiglockhart<br>Medical Group, Edinburgh |
| Dr Andrew Deacon             | ST4 Adult Respiratory Medicine, Manchester<br>Royal Infirmary                                                                                                                                                                         |
| Dr Rebecca Devaney           | ST6 Paediatric Respiratory Medicine, Queen's<br>Medical Centre, Nottingham                                                                                                                                                            |
| Dr Sinan Eccles              | Consultant Adult Respiratory Medicine, Royal<br>Glamorgan Hospital, Pontyclun                                                                                                                                                         |

|                           |                                                                                                                                                                                                                                            |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Professor David Fishwick  | Consultant Respiratory Physician, Brearley Chest Clinic, Northern General Hospital, Sheffield                                                                                                                                              |
| Ms Karen Gibson           | Asthma Nurse Specialist, Norfolk and Norwich University Hospital, Norwich                                                                                                                                                                  |
| Mrs Toni Gibson           | Lay Representative                                                                                                                                                                                                                         |
| Professor Chris Griffiths | Professor of Primary Care, Centre for Primary Care and Public Health, London                                                                                                                                                               |
| Dr Nicola Littlewood      | Consultant in Emergency Medicine, Queen Elizabeth University Hospital, Glasgow                                                                                                                                                             |
| Dr David Lo               | ST8 Paediatric Respiratory Medicine, Leicester Royal Infirmary                                                                                                                                                                             |
| Dr Kenneth MacLeod        | Consultant in Paediatric Respiratory Medicine, Royal Hospital for Sick Children, Edinburgh                                                                                                                                                 |
| Dr Alexander Mathioudakis | NIHR Academic Clinical Fellow and Honorary Lecturer in Respiratory Medicine, University of Manchester                                                                                                                                      |
| Ms Tina Morrow            | Lay representative                                                                                                                                                                                                                         |
| Dr Rob Niven              | Senior Lecturer in Respiratory Medicine, Withenshaw Hospital, Manchester                                                                                                                                                                   |
| Dr Rebecca Normansell     | Joint Co-ordinating Editor Cochrane Airways, Population Health Research Institute, St George's, University of London                                                                                                                       |
| Professor Hilary Pinnock  | Professor of Primary Care Respiratory Medicine, Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, and General Practitioner, Whitstable Medical Practice, Kent |
| Professor Graham Roberts  | Professor and Honorary Consultant Paediatrician, University of Southampton                                                                                                                                                                 |
| Dr Stephen Scott          | Consultant in Respiratory Medicine, Countess of Chester Hospital, Chester                                                                                                                                                                  |
| Dr Diana Slim             | Respiratory Registrar, Bristol Royal Infirmary                                                                                                                                                                                             |
| Mrs Lynne Smith           | Evidence and Information Scientist, Healthcare Improvement Scotland                                                                                                                                                                        |
| Dr Fatimazahra Tharoo     | General Practitioner, Birmingham                                                                                                                                                                                                           |
| Professor Steve Turner    | Professor and Honorary Consultant Paediatrician, Department of Child Health, University of Aberdeen                                                                                                                                        |
| Ms Sally Welham           | Deputy Chief Executive, British Thoracic Society                                                                                                                                                                                           |
| Dr Sarah Winfield         | Consultant Obstetrician, Leeds Teaching Hospitals NHS Trust                                                                                                                                                                                |
| Mr Alex Woodward          | Respiratory Physiotherapist, Leicestershire Partnership NHS Trust                                                                                                                                                                          |

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](http://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](http://www.sign.ac.uk)

|                 |                             |
|-----------------|-----------------------------|
| Euan Bremner    | Project Officer             |
| Karen Graham    | Patient Involvement Advisor |
| Kirsty Allan    | Administration Officer      |
| Domenico Romano | Publications Designer       |
| Gaynor Rattray  | Guideline Co-ordinator      |

### 17.3 Acknowledgements

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 153: British guideline on the management of asthma, on which this guideline is based.

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.

### 17.4 Consultation and peer review

#### 17.4.1 Consultation

Selected changes to this guideline were presented for discussion in draft form at the Winter Meeting of the British Thoracic Society in December 2018. All questions and comments raised at the meeting were addressed on the day and were also summarised and considered separately by the guideline development group. The draft guideline was also available on the SIGN and BTS websites for five weeks to allow all interested parties to comment. A total of eighteen organisations and seven individuals submitted formal responses as part of the open consultation. 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.

### 17.4.2 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 BTS are very grateful to these experts for their contribution to the guideline.

|                           |                                                                                                                                                                   |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dr Bernard Higgins        | Consultant Respiratory Physician, Newcastle Upon Tyne Hospitals NHS Trust                                                                                         |
| Professor Richard Beasley | Director, Medical Research Institute of New Zealand and Adjunct Professor, University of Otago and Physician, Capital and Coast District Health Board, Wellington |

### 17.4.3 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 BTS/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 the editorial group made declarations of interest and further details of these are available on request from the SIGN executive.

|                    |                                                                    |
|--------------------|--------------------------------------------------------------------|
| Mrs Sheila Edwards | Chief Executive, British Thoracic Society                          |
| Dr Luke Howard     | Chair, BTS Standards of Care Committee                             |
| Dr Roberta James   | Programme Lead, SIGN                                               |
| Dr Karen Ritchie   | Head of Knowledge and Information, Healthcare Improvement Scotland |
| Ms Sally Welham    | Deputy Chief Executive, British Thoracic Society                   |

## Abbreviations

|                        |                                                                                                                           |
|------------------------|---------------------------------------------------------------------------------------------------------------------------|
| <b>ACT</b>             | Asthma Control Test                                                                                                       |
| <b>ACQ</b>             | Asthma Control Questionnaire                                                                                              |
| <b>AOR</b>             | adjusted odds ratio                                                                                                       |
| <b>Apgar score</b>     | A number expressing the physical condition of a newborn infant (a score of ten representing the best possible condition). |
| <b>AQLQ</b>            | Asthma Quality of Life Questionnaire                                                                                      |
| <b>BCG</b>             | Bacillus Calmette-Guérin                                                                                                  |
| <b>BDP</b>             | beclometasone dipropionate                                                                                                |
| <b>BHR</b>             | bronchial hyper-reactivity                                                                                                |
| <b>BMI</b>             | body mass index                                                                                                           |
| <b>BNF</b>             | British National Formulary                                                                                                |
| <b>BTS</b>             | British Thoracic Society                                                                                                  |
| <b>CAM</b>             | complementary and alternative medicine                                                                                    |
| <b>CDSS</b>            | computerised decision support systems                                                                                     |
| <b>CFC</b>             | chlorofluorocarbon                                                                                                        |
| <b>C-ACT</b>           | Childhood Asthma Control Test                                                                                             |
| <b>CI</b>              | confidence interval                                                                                                       |
| <b>COPD</b>            | chronic obstructive pulmonary disease                                                                                     |
| <b>DPI</b>             | dry powder inhaler                                                                                                        |
| <b>ECG</b>             | electrocardiogram                                                                                                         |
| <b>ECMO</b>            | extracorporeal membrane oxygenation                                                                                       |
| <b>ED</b>              | emergency department                                                                                                      |
| <b>ETS</b>             | environmental tobacco smoke                                                                                               |
| <b>FeNO</b>            | fractional exhaled nitric oxide                                                                                           |
| <b>FEV<sub>1</sub></b> | forced expiratory volume in one second                                                                                    |
| <b>FVC</b>             | forced vital capacity                                                                                                     |
| <b>GMC</b>             | General Medical Council                                                                                                   |
| <b>GORD</b>            | gastro-oesophageal reflux disease                                                                                         |
| <b>GP</b>              | general practitioner                                                                                                      |
| <b>HbA1c</b>           | glycated haemoglobin                                                                                                      |
| <b>HDM</b>             | house dust mite                                                                                                           |
| <b>HFA</b>             | hydrofluoroalkane                                                                                                         |
| <b>ICS</b>             | inhaled corticosteroids                                                                                                   |
| <b>ICU</b>             | intensive care unit                                                                                                       |
| <b>IgE</b>             | immunoglobulin E                                                                                                          |
| <b>IL5</b>             | interleukin-5                                                                                                             |
| <b>IM</b>              | intramuscular                                                                                                             |
| <b>IT</b>              | information technology                                                                                                    |
| <b>IU</b>              | international unit                                                                                                        |

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|                         |                                                                                                                        |
|-------------------------|------------------------------------------------------------------------------------------------------------------------|
| <b>IV</b>               | intravenous                                                                                                            |
| <b>kU/L</b>             | kilounits of antibody per litre                                                                                        |
| <b>kPa</b>              | kilopascals                                                                                                            |
| <b>LABA</b>             | long-acting $\beta_2$ agonist                                                                                          |
| <b>LAMA</b>             | long-acting muscarinic antagonist                                                                                      |
| <b>LTRA</b>             | leukotriene receptor antagonists                                                                                       |
| <b>MA</b>               | marketing authorisation                                                                                                |
| <b>MART</b>             | maintenance and reliever therapy                                                                                       |
| <b>MDI</b>              | metered dose inhaler                                                                                                   |
| <b>MHRA</b>             | Medicines and Healthcare products Regulatory Agency                                                                    |
| <b>n-3PUFA</b>          | omega-3 polyunsaturated fatty acid                                                                                     |
| <b>NICE</b>             | National Institute for Health and Care Excellence                                                                      |
| <b>NIV</b>              | non-invasive ventilation                                                                                               |
| <b>NPV</b>              | negative predictive value                                                                                              |
| <b>NRAD</b>             | National Review of Asthma Deaths                                                                                       |
| <b>OR</b>               | odds ratio                                                                                                             |
| <b>PAAP</b>             | personalised asthma action plan                                                                                        |
| <b>PACE</b>             | Physician Asthma Care Education                                                                                        |
| <b>PaCO<sub>2</sub></b> | partial arterial pressure of carbon dioxide                                                                            |
| <b>PaO<sub>2</sub></b>  | partial arterial pressure of oxygen                                                                                    |
| <b>PAQLQ</b>            | Paediatric Asthma Quality of Life Questionnaire                                                                        |
| <b>PC<sub>20</sub></b>  | the provocative concentration of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV <sub>1</sub> |
| <b>PD<sub>20</sub></b>  | the provocative dose of bronchoconstrictor (eg methacholine) required to cause a 20% fall in FEV <sub>1</sub>          |
| <b>PEF</b>              | peak expiratory flow                                                                                                   |
| <b>pMDI</b>             | pressurised metered dose inhaler                                                                                       |
| <b>ppb</b>              | parts per billion                                                                                                      |
| <b>PPV</b>              | positive predictive value                                                                                              |
| <b>QoL</b>              | quality of life                                                                                                        |
| <b>RCT</b>              | randomised controlled trial                                                                                            |
| <b>RR</b>               | risk ratio                                                                                                             |
| <b>SABA</b>             | short-acting $\beta_2$ agonist                                                                                         |
| <b>SCIT</b>             | subcutaneous immunotherapy                                                                                             |
| <b>SIC</b>              | specific inhalation challenge                                                                                          |
| <b>SIGN</b>             | Scottish Intercollegiate Guidelines Network                                                                            |
| <b>SLIT</b>             | sublingual immunotherapy                                                                                               |
| <b>SMC</b>              | Scottish Medicines Consortium                                                                                          |
| <b>SpO<sub>2</sub></b>  | oxygen saturation measured by a pulse oximeter                                                                         |
| <b>TNF</b>              | tumour necrosis factor                                                                                                 |
| <b>V<sub>E</sub>max</b> | ventilation at maximal exercise capacity                                                                               |

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# Annex 1

## Key questions addressed in this update

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.

| Section  | Key question                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4.2, 4.4 | <p><b>1. In people with asthma (&lt;5, 5–12, &gt;12) which marker/s is/are most effective for monitoring current asthma control?</b></p> <p>Population: people with asthma</p> <p>Interventions: symptom scores, physiological measurements (lung function tests, bronchial reactivity/airway challenge), other markers: exhaled air (eg FeNO), sputum, blood (eg eosinophil count), periostin</p> <p>Comparisons: as for interventions</p> <p>Outcomes: current asthma control</p>                                                                                                                                         |
| 4.3      | <p><b>2. In people with asthma (&lt;5, 5–12, &gt;12), which individual, or combination of, characteristic/s effectively predict/s future loss of control and/or future risk of attacks?</b></p> <p>Population: people with asthma</p> <p>Interventions: symptom pattern, asthma control, asthma severity, previous history of attacks, atopy (including sensitisation, comorbid allergic conditions, family history), treatment adherence, behaviours (including smoking), social deprivation, biomarkers, polypharmacy</p> <p>Comparisons: none</p> <p>Outcomes: number of asthma attacks, frequency of asthma attacks</p> |
| 5.2.3    | <p><b>3. In people with asthma, at the onset of an asthma attack and as part of a self-management plan, does increasing the dose of ICS or adding an LTRA, compared to usual care, reduce the severity of or abort the asthma attack or improve symptom scores?</b></p> <p>Population: people with asthma</p> <p>Interventions: increasing ICS above current dose, adding LTRA</p> <p>Comparisons: usual care</p> <p>Outcomes: change in asthma control, aborting asthma attack, change in severity of asthma attack, avoidance of need for oral steroids</p>                                                               |

|          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6.2      | <p><b>4. What interventions (avoidance or reduction of exposure to environmental factors) in the home/school/outdoor environment improve asthma control and prevent or reduce severity of asthma attacks?</b></p> <p>Population: people with asthma</p> <p>Interventions: avoidance of exposure to environmental factors, reduction of exposure to environmental factors, eg use of mattress covers for house dust mites</p> <p>Comparisons: no intervention to reduce exposure to environmental factors.</p> <p>Outcomes: asthma symptom control, number of asthma attacks, severity of asthma attacks</p>                                                                                                                                                                                                                                                                                                                   |
| 6.2.14   | <p><b>5. In people aged 12 and over with asthma, is breathing training in addition to usual care effective at reducing asthma attacks, improving symptoms, reducing side effects, improving treatment adherence or improving lung function?</b></p> <p>Population: people with asthma aged 12 and over</p> <p>Interventions: breathing training</p> <p>Comparisons: no breathing training (ie usual care)</p> <p>Outcomes: asthma attacks, asthma symptom control, adverse side effects, treatment adherence, lung function</p>                                                                                                                                                                                                                                                                                                                                                                                               |
| 7.3      | <p><b>6. In people with asthma whose symptoms are not adequately controlled (poor control and/or frequent attacks) by low-dose (&gt;12 years) or very low-dose (&lt;5, 5–12 years) ICS, which initial add-on therapy is most effective at reducing asthma attacks, improving symptoms, reducing side effects, improving treatment adherence or improving lung function?</b></p> <p>Population: people with asthma taking low-dose (&gt;12 years) or very low-dose (&lt;5, 5–12 years) ICS</p> <p>Interventions: increasing ICS above low/very-low dose, LABA, LTRA, LAMA, theophylline, slow-release <math>\beta_2</math> agonist tablets</p> <p>Comparisons: increasing ICS above low/very-low dose, LABA, LTRA, LAMA, theophylline, slow-release <math>\beta_2</math> agonist tablets</p> <p>Outcomes: asthma attacks, asthma symptom control, adverse side effects, treatment adherence, lung function</p>                 |
| 7.4, 7.5 | <p><b>7. In people with asthma whose symptoms are not adequately controlled by low-dose (&gt;12 years) or very low-dose (&lt;5, 5–12 years) ICS plus a LABA, is adding an LTRA, LAMA, theophylline or slow-release <math>\beta_2</math> agonist tablets, more effective than increasing the dose of ICS at reducing asthma attacks, improving symptoms, reducing side effects, improving treatment adherence or improving pulmonary/lung function?</b></p> <p>Population: people with asthma taking low-dose (&gt;12 years) or very low-dose (&lt;5, 5–12 years) ICS plus a LABA</p> <p>Interventions: LTRA, LAMA, theophylline, slow-release <math>\beta_2</math> agonist tablets</p> <p>Comparisons: increasing ICS dose above low-dose (&gt;12 years) or very low-dose (&lt;5, 5–12 years)</p> <p>Outcomes: asthma attacks, asthma symptom control, adverse side-effects, treatment adherence, pulmonary/lung function</p> |

|       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7.5.4 | <p><b>8. In people with asthma who are not adequately controlled on high-dose ICS plus LABA or on oral corticosteroids, does addition of monoclonal antibodies (eg omalizumab, mepolizumab, reslizumab) reduce use of oral steroids, unscheduled care, side effects, or improve symptoms, treatment adherence or lung function?</b></p>                                                                                                                                                                                                                              |
|       | <p>Population: people with asthma inadequately controlled on high-dose ICS plus a LABA or on oral corticosteroids</p> <p>Interventions: monoclonal antibodies (including omalizumab, mepolizumab, reslizumab, etc)</p> <p>Comparisons: no use of monoclonal antibodies</p> <p>Outcomes: reduction in unscheduled care (reduced asthma attacks, reduced steroid courses, reduced unplanned hospital/GP visits), adverse side effects, asthma symptom control, lung function, treatment adherence, reductions in treatment (ICS reduction, oral steroid reduction)</p> |
| 7.5.7 | <p><b>9. In people with asthma who are not adequately controlled on high-dose ICS plus a LABA or oral corticosteroids, does addition of bronchial thermoplasty reduce use of oral steroids, unscheduled care, side effects, or improve symptoms, treatment adherence or lung function?</b></p>                                                                                                                                                                                                                                                                       |
|       | <p>Population: people with asthma inadequately controlled on high-dose ICS plus a LABA or on oral corticosteroids</p> <p>Interventions: bronchial thermoplasty</p> <p>Comparisons: no bronchial thermoplasty</p> <p>Outcomes: reduction in unscheduled care (reduced asthma attacks, reduced steroid courses, reduced unplanned hospital/GP visits), adverse side effects, asthma symptom control, lung function, treatment adherence, reductions in treatment (ICS reduction, oral steroid reduction)</p>                                                           |
| 7.5.6 | <p><b>10. In people with asthma who are poly- or mono-sensitised, is sublingual immunotherapy compared to standard therapy effective at reducing asthma attacks, improving asthma control, improving treatment adherence or improving lung function?</b></p>                                                                                                                                                                                                                                                                                                         |
|       | <p>Population: people with asthma mono- or poly-sensitised</p> <p>Interventions: sublingual immunotherapy (SLIT)</p> <p>Comparisons: standard therapy</p> <p>Outcomes: asthma attacks, asthma symptom control, treatment adherence, lung function</p>                                                                                                                                                                                                                                                                                                                |
| 5.4.3 | <p><b>11. What interventions in the home or workplace/school improve adherence with asthma treatments?</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|       | <p>Population: people with asthma</p> <p>Interventions: inhaler timers, inhaler alarms, directly observed therapy (by video, at school, in primary/secondary care settings)</p> <p>Comparisons: usual care</p> <p>Outcomes: asthma symptom control, number of asthma attacks, severity of asthma attacks</p>                                                                                                                                                                                                                                                         |

|                  |                                                                                                                                                                                                                                                              |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9.3.12,<br>9.9.5 | <b>12. In the immediate treatment of people with life-threatening or near-fatal asthma, does extracorporeal membrane oxygenation (ECMO) or other potentially life-saving therapies, compared to usual care, improve patient survival or other outcomes?</b>  |
|                  | <p>Population: people experiencing a life-threatening or near-fatal asthma attack</p> <p>Interventions: extracorporeal membrane oxygenation (ECMO), ketamine, other rescue therapies</p> <p>Comparisons: usual care</p> <p>Outcomes: survival, morbidity</p> |
| 6.2.8            | <b>13. In people with asthma, is supplementation with vitamin D compared to placebo effective at reducing asthma attacks, reducing side effects or improving lung function?</b>                                                                              |
|                  | <p>Population: people with asthma</p> <p>Interventions: vitamin D supplementation</p> <p>Comparisons: usual care</p> <p>Outcomes: asthma attacks, side effects, lung function</p>                                                                            |

## Annex 2

### 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 2019 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 published between 2012 and March 2018. 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 4 Monitoring asthma**

##### *Monitoring current asthma symptom control*

A broad search was carried out in May 2018 covering 2014–2018. No study design filter was applied.

##### *Predicting future risk of asthma attacks*

A broad search was carried out in May 2018 with no date limit. No study design filter was applied.

#### **Section 5 Supported self management**

##### *Components of a self-management programme*

A broad search was carried out in April 2018 with no date limit to identify studies which looked at people with asthma increasing the dose of ICS or adding an LTRA, compared to usual care, at the onset of an asthma attack and as part of a self-management plan. No study design filter was applied.

#### **Section 6 Non-pharmacological management**

##### *Secondary non-pharmacological prevention*

A broad search was carried out to identify studies which looked at what interventions (avoidance or reduction of exposure to environmental factors) in the home/school/outdoor environment improve asthma control and prevent or reduce severity of asthma attacks. The search covered 2014–2018 on Medline. No study design filter was applied.

A search was conducted in April 2018 to identify studies on breathing training. The search covered 2013–2018 in Medline, Embase, the Cochrane Library and CINAHL. An RCT filter was applied.

A search was conducted in May 2018 to identify studies on vitamin D supplementation. The search covered 2016–2018 in Medline, Embase, the Cochrane Library and CINAHL. An RCT filter was applied.

### **Section 7 Pharmacological management**

The 2019 revision updated searches for inhaled steroids, long-acting  $\beta_2$  agonists, theophyllines, leukotriene receptor antagonists, frequency and dose of inhaled steroids, monoclonal antibodies, sublingual immunotherapy and bronchial thermoplasty.

The Cochrane Library, Medline and Embase were searched from 2012–2018. SIGN systematic review and RCT filters were applied.

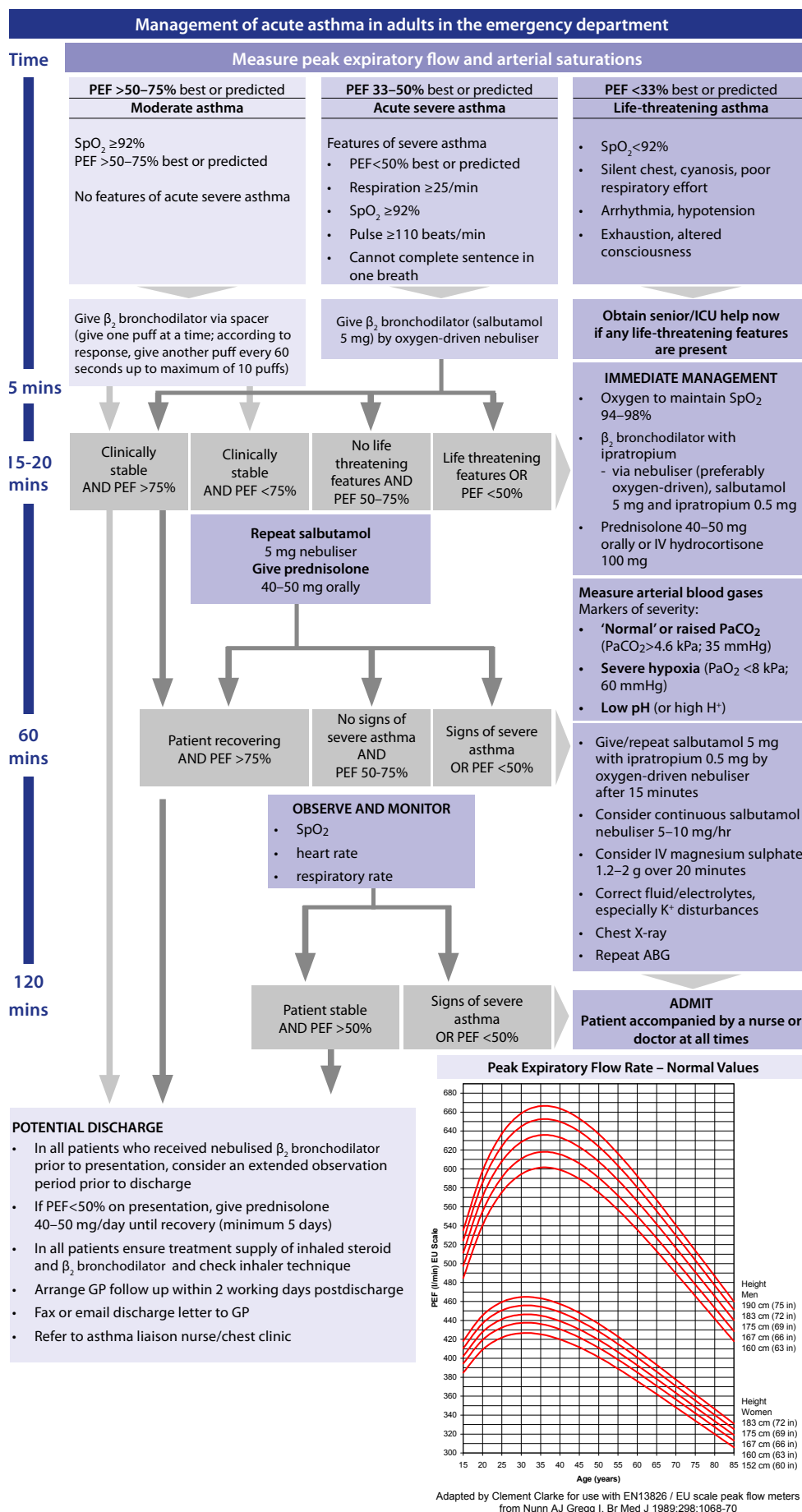
### **Section 9 Management of acute asthma**

Broad searches were carried out in May/June 2018 with no date limit to identify studies which looked at extracorporeal membrane oxygenation (ECMO) or other potentially life-saving therapies for people with life-threatening or near-fatal asthma. No study design filter was applied.

## Annex 3

| Management of acute asthma in adults in general practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Many deaths from asthma are preventable. Delay can be fatal. Factors leading to poor outcome include:</b></p> <ul style="list-style-type: none"> <li>Clinical staff failing to assess severity by objective measurement</li> <li>Patients or relatives failing to appreciate severity</li> <li>Under use of corticosteroids</li> </ul> <p>Regard each emergency asthma consultation as for acute severe asthma until shown otherwise.</p>                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <p><b>Assess and record:</b></p> <ul style="list-style-type: none"> <li>Peak expiratory flow (PEF)</li> <li>Symptoms and response to self treatment</li> <li>Heart and respiratory rates</li> <li>Oxygen saturation (by pulse oximetry)</li> </ul> <p><b>Caution:</b> 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.</p>                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>SpO<sub>2</sub> ≥92%</li> <li>Speech normal</li> <li>Respiration &lt;25 breaths/min</li> <li>Pulse &lt;110 beats/min</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                             | <ul style="list-style-type: none"> <li>SpO<sub>2</sub> ≥92%</li> <li>Can't complete sentences</li> <li>Respiration ≥25 breaths/min</li> <li>Pulse ≥110 beats/min</li> </ul>                                                                                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>SpO<sub>2</sub> &lt;92%</li> <li>Silent chest, cyanosis or poor respiratory effort</li> <li>Arrhythmia or hypotension</li> <li>Exhaustion, altered consciousness</li> </ul>                                                                                                                                                                                                                                                                           |
| MANAGEMENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Treat at home or in surgery and ASSESS RESPONSE TO TREATMENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Consider admission                                                                                                                                                                                                                                                                                                                                                                                                                                     | Arrange immediate ADMISSION                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| TREATMENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>β<sub>2</sub> bronchodilator:               <ul style="list-style-type: none"> <li>via spacer*</li> </ul> </li> </ul> <p>If no improvement:</p> <ul style="list-style-type: none"> <li>via nebuliser (preferably oxygen-driven), salbutamol 5 mg</li> <li>Give prednisolone 40–50 mg</li> <li>Continue or increase usual treatment</li> </ul> <p>If good response to first treatment (symptoms improved, respiration and pulse settling and PEF &gt;50%) continue or increase usual treatment and continue prednisolone</p> | <ul style="list-style-type: none"> <li>Oxygen to maintain SpO<sub>2</sub> 94–98% if available</li> <li>β<sub>2</sub> bronchodilator:               <ul style="list-style-type: none"> <li>via nebuliser (preferably oxygen-driven), salbutamol 5 mg</li> <li>or if nebuliser not available, via spacer*</li> </ul> </li> <li>Prednisolone 40–50 mg or IV hydrocortisone 100 mg</li> <li><b>If no response in acute severe asthma: ADMIT</b></li> </ul> | <ul style="list-style-type: none"> <li>Oxygen to maintain SpO<sub>2</sub> 94–98%</li> <li>β<sub>2</sub> bronchodilator with ipratropium:               <ul style="list-style-type: none"> <li>via nebuliser (preferably oxygen-driven), salbutamol 5 mg and ipratropium 0.5mg</li> <li>or if nebuliser and ipratropium not available, β<sub>2</sub> bronchodilator via spacer*</li> </ul> </li> <li>Prednisolone 40–50 mg or IV hydrocortisone 100 mg immediately</li> </ul>                 |
| <p><b>Admit to hospital if any:</b></p> <ul style="list-style-type: none"> <li>Life-threatening features</li> <li>Features of acute severe asthma present after initial treatment</li> <li>Previous near-fatal asthma</li> </ul> <p>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</p>                                                                                                       | <p><b>If admitting the patient to hospital:</b></p> <ul style="list-style-type: none"> <li>Stay with patient until ambulance arrives</li> <li>Send written assessment and referral details to hospital</li> <li>β<sub>2</sub> bronchodilator via oxygen-driven nebuliser in ambulance</li> </ul>                                                                                                                                                       | <p><b>Follow up after treatment or discharge from hospital:</b></p> <ul style="list-style-type: none"> <li>Continue prednisolone until recovery (minimum 5 days)</li> <li><b>GP review within 2 working days</b></li> <li>Monitor symptoms and PEF</li> <li>Check inhaler technique</li> <li><b>Written asthma action plan</b></li> <li>Modify treatment according to guidelines for chronic persistent asthma</li> <li>Address potentially preventable contributors to admission</li> </ul> |
| <p>* β<sub>2</sub> bronchodilator via spacer given one puff at a time, inhaled separately using tidal breathing; according to response, give another puff every 60 seconds up to a maximum of 10 puffs</p>                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

## Annex 4



## Annex 5

## Management of acute 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  $\geq 25$  breaths/min
- Pulse  $\geq 110$  beats/min

## Life-threatening features

- PEF  $< 33\%$  of best or predicted
- SpO<sub>2</sub>  $< 92\%$
- Silent chest, cyanosis, or poor 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:

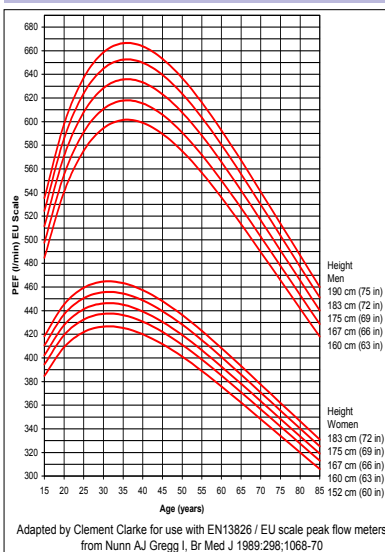
- 'Normal' (4.6–6 kPa, 35–45 mmHg) PaCO<sub>2</sub>
- Severe hypoxia: PaO<sub>2</sub>  $< 8$  kPa (60 mmHg) irrespective of treatment with oxygen
- A low pH (or high H<sup>+</sup>)

**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<sub>2</sub>
- Requiring mechanical ventilation with raised inflation pressures

## Peak Expiratory Flow Rate - Normal Values



## IMMEDIATE TREATMENT

- Oxygen to maintain SpO<sub>2</sub> 94–98%
- $\beta_2$  bronchodilator (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  $\beta_2$  bronchodilator 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<sub>2</sub> 94–98%
- Prednisolone 40–50 mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulised  $\beta_2$  bronchodilator with 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  $\beta_2$  bronchodilator or IV aminophylline or progression to mechanical ventilation

## MONITORING

- Repeat measurement of PEF 15–30 minutes after starting treatment
- Oximetry: maintain SpO<sub>2</sub>  $> 94$ –98%
- Repeat blood gas measurements within 1 hour of starting treatment if:
  - initial PaO<sub>2</sub>  $< 8$  kPa (60 mmHg) unless subsequent SpO<sub>2</sub>  $> 92\%$  or
  - PaCO<sub>2</sub> normal or raised or
  - patient deteriorates
- Chart PEF before and after giving  $\beta_2$  bronchodilator 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 steroids (prednisolone 40–50 mg until recovery - minimum 5 days) 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

## Annex 6

## Management of acute asthma in children in general practice

## Age 2–5 years

## ASSESS AND RECORD ASTHMA SEVERITY

## Moderate asthma

- SpO<sub>2</sub> ≥92%
- Able to talk
- Heart rate ≤140/min
- Respiratory rate ≤40/min

## Acute severe asthma

- SpO<sub>2</sub> <92%
- Too breathless to talk
- Heart rate >140/min
- Respiratory rate >40/min
- Use of accessory neck muscles

## Life-threatening asthma

- SpO<sub>2</sub> <92% plus any of:
- Silent chest
- Poor respiratory effort
- Agitation
- Confusion
- Cyanosis

- β<sub>2</sub> bronchodilator:  
- via spacer ± facemask\*
- Consider oral prednisolone 20 mg

- Oxygen via facemask to maintain SpO<sub>2</sub> 94–98% if available

- β<sub>2</sub> bronchodilator  
- via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg  
- or, if nebuliser not available, via spacer\*
- Oral prednisolone 20 mg

- β<sub>2</sub> bronchodilator with ipratropium:  
- via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg and ipratropium 0.25 mg every 20 minutes  
- or, if nebuliser and ipratropium not available, β<sub>2</sub> bronchodilator via spacer\*
- Oral prednisolone 20 mg or IV hydrocortisone 50 mg if vomiting

**Assess response to treatment 15 mins after β<sub>2</sub> bronchodilator**

## IF POOR RESPONSE ARRANGE ADMISSION

IF POOR RESPONSE REPEAT β<sub>2</sub> BRONCHODILATOR AND ARRANGE ADMISSION

**REPEAT β<sub>2</sub> BRONCHODILATOR VIA OXYGEN-DRIVEN NEBULISER WHILST ARRANGING IMMEDIATE HOSPITAL ADMISSION**

## GOOD RESPONSE

- Continue β<sub>2</sub> bronchodilator via spacer or nebuliser, as needed but not exceeding 4 hourly
- If symptoms are not controlled repeat β<sub>2</sub> bronchodilator and refer to hospital
- Continue prednisolone until recovery (minimum 3–5 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<sub>2</sub> bronchodilator 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**

\* β<sub>2</sub> bronchodilator via spacer given one puff at a time, inhaled separately using tidal breathing, according to response, give another puff every 60 seconds up to a maximum of 10 puffs

## Age &gt;5 years

## ASSESS AND RECORD ASTHMA SEVERITY

## Moderate asthma

- SpO<sub>2</sub> ≥92%
- Able to talk
- Heart rate ≤125/min
- Respiratory rate ≤30/min
- PEF ≥50% best or predicted

## Acute severe asthma

- SpO<sub>2</sub> <92%
- Too breathless to talk
- Heart rate >125/min
- Respiratory rate >30/min
- Use of accessory neck muscles
- PEF 33–50% best or predicted

## Life-threatening asthma

- SpO<sub>2</sub> <92% plus any of:
- Silent chest
- Poor respiratory effort
- Agitation
- Confusion
- Cyanosis
- PEF <33% best or predicted

- β<sub>2</sub> bronchodilator:  
- via spacer\*
- Consider oral prednisolone 30–40 mg

- Oxygen via facemask to maintain SpO<sub>2</sub> 94–98% if available

- β<sub>2</sub> bronchodilator  
- via nebuliser (preferably oxygen-driven), salbutamol 5 mg  
- or, if nebuliser not available, via spacer\*
- Oral prednisolone 30–40 mg

- β<sub>2</sub> bronchodilator with ipratropium:  
- via nebuliser (preferably oxygen-driven), salbutamol 5 mg and ipratropium 0.25 mg every 20 minutes  
- or, if nebuliser and ipratropium not available, β<sub>2</sub> bronchodilator via spacer\*
- Oral prednisolone 30–40 mg or IV hydrocortisone 100 mg if vomiting

**Assess response to treatment 15 mins after β<sub>2</sub> bronchodilator**

## IF POOR RESPONSE ARRANGE ADMISSION

IF POOR RESPONSE REPEAT β<sub>2</sub> BRONCHODILATOR AND ARRANGE ADMISSION

**REPEAT β<sub>2</sub> BRONCHODILATOR VIA OXYGEN-DRIVEN NEBULISER WHILST ARRANGING IMMEDIATE HOSPITAL ADMISSION**

## GOOD RESPONSE

- Continue β<sub>2</sub> bronchodilator via spacer or nebuliser, as needed but not exceeding 4 hourly
- If symptoms are not controlled repeat β<sub>2</sub> bronchodilator and refer to hospital
- Continue prednisolone until recovery (minimum 3–5 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<sub>2</sub> bronchodilator 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 7

## Management of acute asthma in children in emergency department

## Age 2–5 years

## ASSESS AND RECORD ASTHMA SEVERITY

**Moderate asthma**

- SpO<sub>2</sub> ≥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**

- SpO<sub>2</sub> <92%
- Too breathless to talk or eat
- Heart rate >140/min
- Respiratory rate >40/min
- Use of accessory neck muscles

**Life-threatening asthma**

SpO<sub>2</sub> <92% plus any of:

- Silent chest
- Poor respiratory effort
- Agitation
- Confusion
- Cyanosis

## First line treatments

Oxygen via face mask/nasal prongs to achieve SpO<sub>2</sub> 94–98%

- β<sub>2</sub> bronchodilator:
  - via spacer ± facemask\*
- Consider oral prednisolone 20 mg

β<sub>2</sub> bronchodilator

- via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg
- or, if nebuliser not available, via spacer\*
- 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<sub>2</sub> bronchodilator and repeat every 20 minutes for 2 hours according to response

Reassess within 1 hour

## First line treatments

Oxygen via face mask/nasal prongs to achieve SpO<sub>2</sub> 94–98%

- β<sub>2</sub> bronchodilator with ipratropium:
  - via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg and ipratropium 0.25 mg
  - 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

## Age &gt;5 years

## ASSESS AND RECORD ASTHMA SEVERITY

**Moderate asthma**

- SpO<sub>2</sub> ≥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**

- SpO<sub>2</sub> <92%
- PEF 33–50% best or predicted
- Heart rate >125/min
- Respiratory rate >30/min
- Use of accessory neck muscles

**Life-threatening asthma**

SpO<sub>2</sub> <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 SpO<sub>2</sub> 94–98%

- β<sub>2</sub> bronchodilator:
  - via spacer\*
- Oral prednisolone 30–40 mg

β<sub>2</sub> bronchodilator

- via nebuliser (preferably oxygen-driven), salbutamol 5 mg
- or, if nebuliser not available, via spacer\*
- 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<sub>2</sub> bronchodilator and repeat every 20 minutes for 2 hours according to response

Reassess within 1 hour

## First line treatments

Oxygen via face mask/nasal prongs to achieve SpO<sub>2</sub> 94–98%

- β<sub>2</sub> bronchodilator with ipratropium:
  - via nebuliser (preferably oxygen-driven), salbutamol 5 mg and ipratropium 0.25 mg
  - 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

## Second line treatments

- Consider 2nd line treatments – see Annex 8
- 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<sub>2</sub> bronchodilator 4 hourly as necessary
- Continue prednisolone 20 mg daily until recovery (minimum 3–5 days)
- 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.

## Second line treatments

**DISCHARGE PLAN**

- Continue β<sub>2</sub> bronchodilator 4 hourly as necessary
- Continue prednisolone 30–40 mg daily until recovery (minimum 3–5 days)
- 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.

- Consider 2nd line treatments – see Annex 8
- 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

\* β<sub>2</sub> bronchodilator via spacer given one puff at a time, inhaled separately using tidal breathing; according to response, give another puff every 60 seconds up to a maximum of 10 puffs

## Annex 8

## Management of acute asthma in children in hospital

## Age 2–5 years

## Age &gt;5 years

## ASSESS AND RECORD ASTHMA SEVERITY

## ASSESS AND RECORD ASTHMA SEVERITY

**Moderate 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**

**Acute severe asthma**

- $SpO_2 < 92\%$
- Too breathless to talk or eat
- Heart rate  $> 140/\text{min}$
- Respiratory rate  $> 40/\text{min}$
- Use of accessory neck muscles

**Life-threatening asthma**

$SpO_2 < 92\%$  plus any of:

- Silent chest
- Poor respiratory effort
- Agitation
- Confusion
- Cyanosis

**Moderate 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**

**Acute severe asthma**

- $SpO_2 < 92\%$
- $PEF 33\text{--}50\%$  best or predicted
- Heart rate  $> 125/\text{min}$
- Respiratory rate  $> 30/\text{min}$
- Use of accessory neck muscles

**Life-threatening asthma**

$SpO_2 < 92\%$  plus any of:

- $PEF < 33\%$  best or predicted
- Silent chest
- Poor respiratory effort
- Confusion
- Cyanosis

## First-line treatments

## First-line treatments

Oxygen via face mask/nasal prongs to achieve  $SpO_2$  94–98%

Oxygen via face mask/nasal prongs to achieve  $SpO_2$  94–98%

•  $\beta_2$  bronchodilator:  
- via spacer  $\pm$  facemask\*

• Consider oral prednisolone 20 mg

•  $\beta_2$  bronchodilator  
- via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg  
- or, if nebuliser not available, via spacer\*

• Oral prednisolone 20 mg or IV hydrocortisone 4 mg/kg if vomiting

• Repeat  $\beta_2$  bronchodilator up to every 20–30 minutes according to response

• **If poor response** add 0.25 mg nebulised ipratropium bromide to every nebulised  $\beta_2$  bronchodilator every 20 minutes for 1–2 hours

•  $\beta_2$  bronchodilator with ipratropium:  
- via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg and ipratropium 0.25 mg

• Repeat bronchodilators every 20–30 minutes

• Oral prednisolone 20mg or IV hydrocortisone 4mg/kg if vomiting

• Consider adding 150 mg magnesium sulphate to each  $\beta_2$  bronchodilator/ipratropium nebuliser in first hour

**Discuss with senior clinician, PICU team or paediatrician**

•  $\beta_2$  bronchodilator:  
- via spacer\*

• Oral prednisolone 30–40 mg

•  $\beta_2$  bronchodilator  
- via nebuliser (preferably oxygen-driven), salbutamol 5 mg  
- or, if nebuliser not available, via spacer\*

• Oral prednisolone 30–40 mg or IV hydrocortisone 4 mg/kg if vomiting

• Repeat  $\beta_2$  bronchodilator up to every 20–30 minutes according to response

• **If poor response** add 0.25 mg nebulised ipratropium bromide to every nebulised  $\beta_2$  bronchodilator every 20 minutes for 1–2 hours

•  $\beta_2$  bronchodilator with ipratropium:  
- via nebuliser (preferably oxygen-driven), salbutamol 5 mg and ipratropium 0.25 mg

• Repeat bronchodilators every 20–30 minutes

• Oral prednisolone 30–40 mg or IV hydrocortisone 4mg/kg if vomiting

• Consider adding 150 mg magnesium sulphate to each  $\beta_2$  bronchodilator/ipratropium nebuliser in first hour

**Discuss with senior clinician, PICU team or paediatrician**

## Reassess within 1 hour

## Reassess within 1 hour

Record respiratory rate, heart rate and oxygen saturation every 1–4 hours

Record respiratory rate, heart rate, oxygen saturation and  $PEF/FEV$  every 1–4 hours

Second-line treatments

Second-line treatments

## RESPONDING

• Continue bronchodilators 1–4 hours as necessary

• Discharge when stable on 4-hourly treatment

• Continue prednisolone 20 mg daily until recovery (minimum 3–5 days)

**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

## RESPONDING

• Continue bronchodilators 1–4 hours as necessary

• Discharge when stable on 4-hourly treatment

• Continue prednisolone 30–40 mg daily until recovery (minimum 3–5 days)

**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

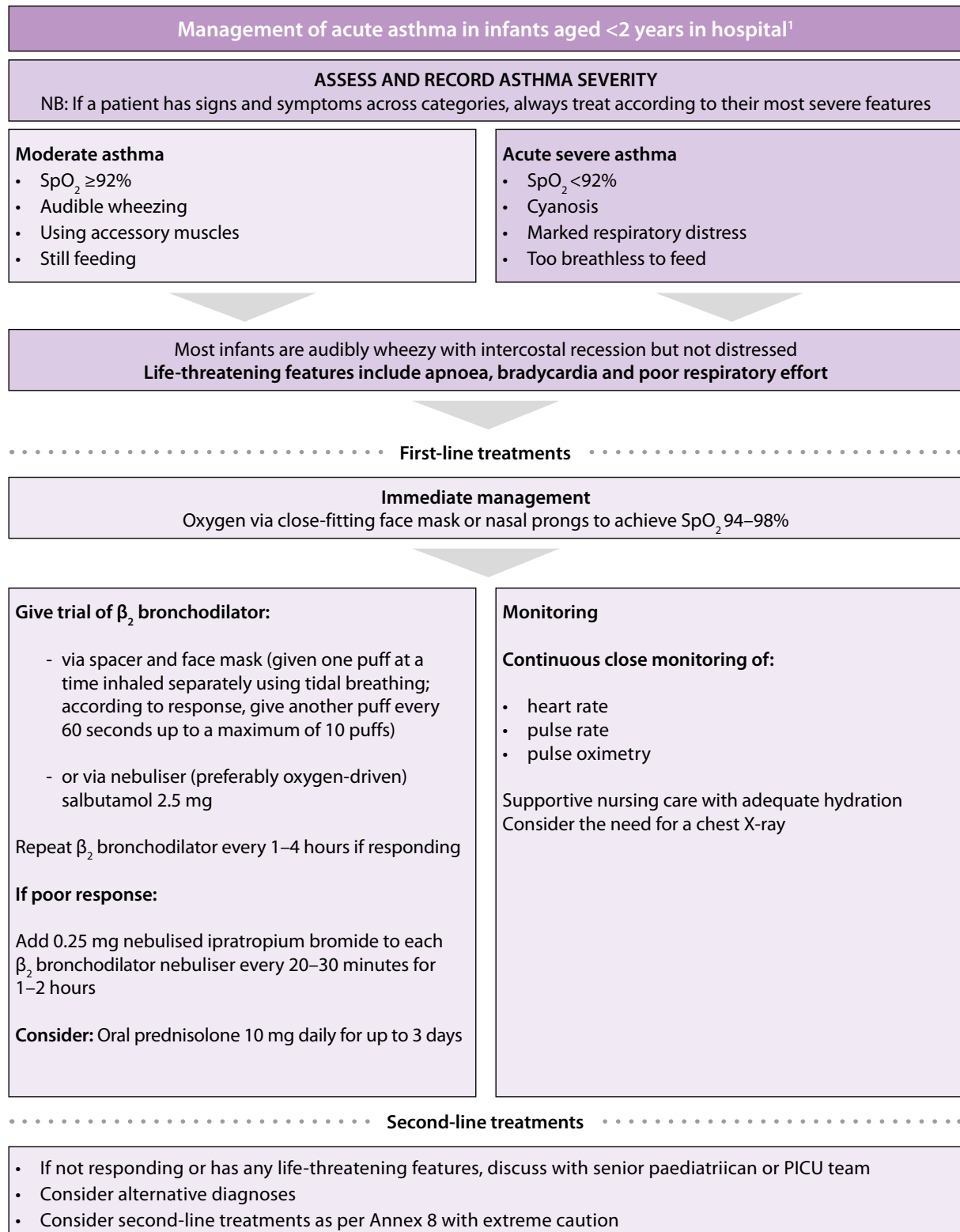
Consider risks and benefits of:

- **Bolus IV infusion of magnesium sulphate** 40 mg/kg (max 2 g) 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

\*  $\beta_2$  bronchodilator via spacer given one puff at a time, inhaled separately using tidal breathing; according to response, give another puff every 60 seconds up to a maximum of 10 puffs

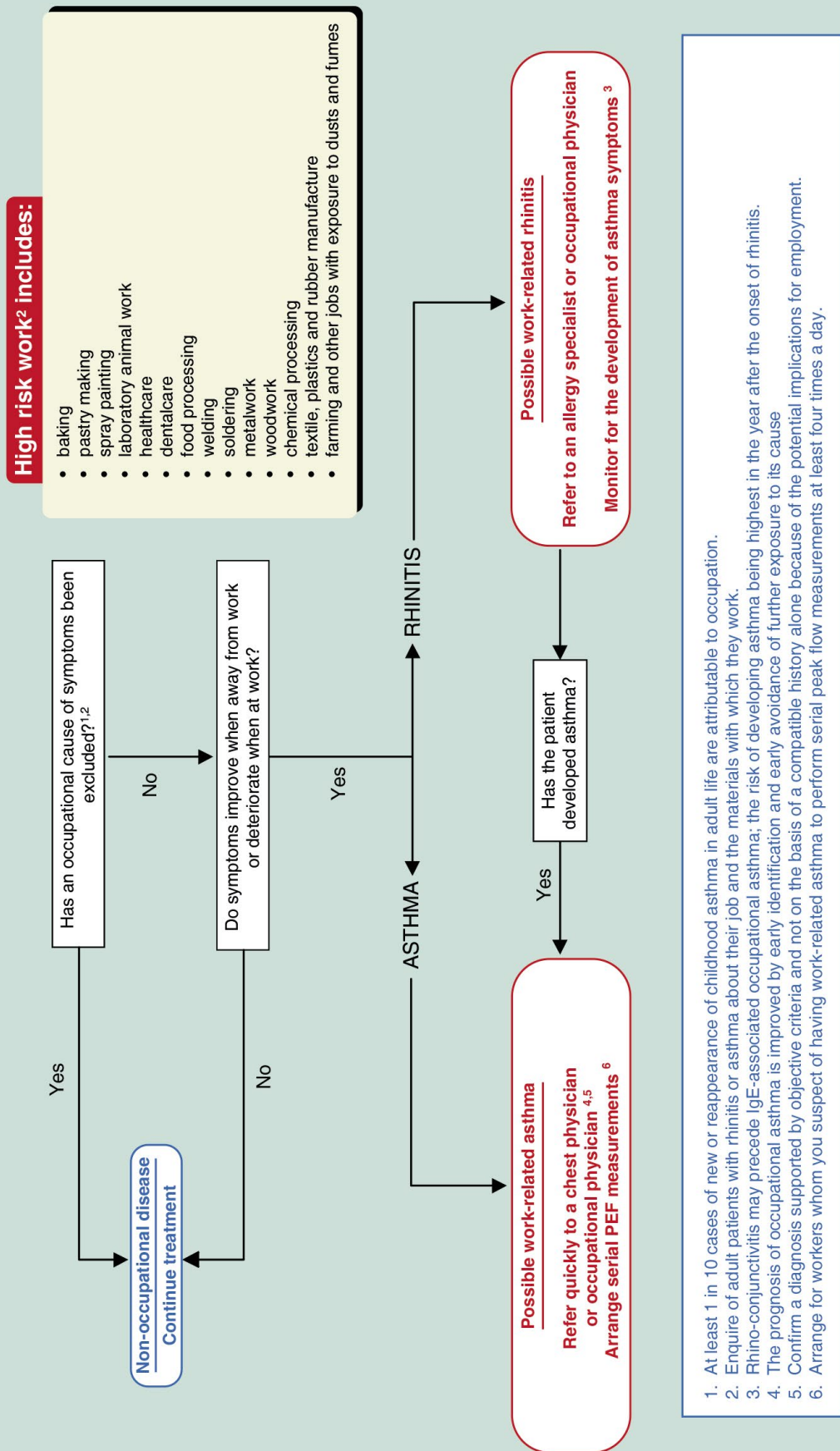
## Annex 9



<sup>1</sup> Management of acute asthma in children under 1 year should be under the direction of a respiratory paediatrician.

## Annex 10

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

Guidelines for the identification, Management and Prevention of Occupational Asthma | [www.bohrf.org.uk/projects/asthma.html](http://www.bohrf.org.uk/projects/asthma.html)

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