Recent advances in the treatment and management of asthma

Neil C Thomson MD, FRCP

Despite advances in diagnosis and management of asthma many patients have poorly controlled symptoms. This article reviews recent publications on the diagnosis, assessment and management of asthma in adults, including the 2014 update of the British guideline on the management of asthma.

Asthma is a chronic inflammatory disease of the airways that affects 300 million people worldwide and 5.4 million people in the UK of whom 80 per cent are adults.1 Despite advances in the diagnosis and management of asthma,2 surveys indicate that many patients have poorly controlled symptoms and experience frequent exacerbations.3-4 Three quarters of hospital admissions and nine out of 10 deaths from asthma are likely to be preventable.1,5 The financial impact of asthma is considerable, in large part due to the cost of asthma medications, hospital admissions and time lost from work. NHS costs for asthma are estimated to be around £1 billion per year.

A systematic approach to the evaluation of patients suspected or known to have asthma is helpful and should include assessment of the diagnosis, identification of the cause(s) of persistent symptoms and development of a patient-specific management plan.

Diagnosis
An algorithm based on an assessment of the probability of asthma and a measure of airflow obstruction is recommended by the British guideline on the management of asthma in order to diagnose asthma and to direct further investigations and treatment (see Figure 1 and Table 1).2 Spirometry is the preferred lung function test to demonstrate the presence and severity of airflow obstruction, because the results are less dependent on effort and more specific for airway obstruction than peak expiratory flow (PEF).

NICE is developing guidance on diagnosing and monitoring asthma that is due to be published in late 2015 or early 2016.6 The report emphasises that asthma is often over diagnosed, resulting in unnecessary treatment. NICE recommends the measurement of fractional exhaled nitric oxide (FeNO), a biomarker associated with eosinophilic inflammation and corticosteroid responsiveness, be used to help support (FeNO level >40 ppb) or rule out a diagnosis of asthma in people who are considered...
to have an intermediate probability of asthma and normal spirometry (see Figure 1). Direct bronchial challenge tests with histamine or methacholine are advocated for cases in which the diagnosis remains uncertain. The implications of the NICE guidance on diagnosis is not clear, particularly in primary care where there is currently little access to these specialist tests.

Common conditions to be considered in the differential diagnosis in adults include COPD, bronchiectasis, heart failure and pulmonary thromboembolism, as well as vocal cord dysfunction and psychogenic breathlessness.

**Trigger factors and co-morbidities**

Several non-pharmacological management approaches targeting triggers of asthma and co-morbidities are likely to be effective in improving asthma control and quality of life, although an evidence base from clinical trials supporting the efficacy of a number of these interventions is generally weak. Avoidance of trigger factors such as allergens, NSAIDs or occupational agents in sensitive individuals, as well as exposure to environmental irritants such as second-hand smoke, is likely to prevent exacerbations.

Targeting smokers with asthma to quit smoking or patients with a high body mass index (BMI) to lose weight may result in improvements in asthma symptoms. Breathing exercise programmes improve quality of life and reduce symptoms when used as an adjunct to pharmacological treatment. Treating co-existing gastro-oesophageal reflux disease does not improve asthma symptoms.

**Self-management**

Self-management education improves asthma control and reduces emergency use of healthcare resources. The key components of an effective self-management programme are structured education and the provision of personalised asthma action plans (PAAPs). All adults with asthma should be offered self-management education and PAAPs combined with regular review by a health professional.

Non-adherence with treatment is one of the most important factors in poor asthma control. Around a quarter of exacerbations are thought to be due to non-adherence with inhaled corticosteroids (ICSs). An indication of possible non-adherence can be assessed by reviewing prescription refill frequency, including looking for overuse of short-acting bronchodilators. The ability to detect inadequate adherence based on history alone is poor though, as the patient may be collecting their ICS along with their bronchodilator but not using it. Improving adherence can be difficult and effective interventions are often complex. Strategies that may help include adequate explanation of the indications for treatment, discussion of real and perceived

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Figure 1. Diagnosis of asthma
Drug Review  | Asthma

Concerns of adverse effects of treatment (particularly ICS), simplifying drug treatment regimens, reminders and reinforcement. Shared decision-making is important as adherence is more likely when the patient and the health professional agree that the management approach is appropriate.

Around half of all patients have poor inhaler technique irrespective of the device used. Assessing inhaler technique needs to be part of routine clinical review. The choice of device is based on the drug to be administered and patient preference, as well as demonstration by the patient that they are able to use an inhaler correctly. Patients should be asked to bring their inhalers with them to each consultation. Prescribing mixed inhaler types may cause confusion and the British guideline notes that using the same type of device to deliver preventer and reliever treatments may improve outcomes.

Monitoring asthma control
Assessing asthma control should incorporate the dual components of symptom control and the future risk of exacerbations and decline in lung function.

Symptom control can be determined by history taking (symptoms, reliever use) and/or by the use of specific asthma control questionnaires, e.g. the Royal College of Physicians (RCP) three questions (see Table 2), asthma control questionnaire (ACQ) score or the asthma control test (ACT). The best predictors of future exacerbations are poor symptom control, a history of an exacerbation in the previous year, smoking and reduced forced expiratory volume in one second (FEV1). Excess reliever inhaler use, defined as greater than one inhaler per month is a risk factor for exacerbations and death from asthma.

For most patients symptom-based monitoring is adequate. Serial measurements of PEF are often unreliable, but can be helpful in selected patients with poor perception of asthma symptoms or with severe disease. NICE guidance on monitoring asthma does not recommend the use of FeNO to monitor asthma control, except for patients who are symptomatic despite using ICS. In primary care, monitoring of asthma is best undertaken by a routine review at least yearly. See Table 3 for Quality and Outcomes Framework (QOF) indicators in asthma. Each practice should have a named lead clinician for asthma services.

Step-wise approach
The step-wise approach to treatment should be integrated into a management plan that includes non-pharmacological management approaches where appropriate, as well as regular monitoring of symptom control and risk of future exacerbations and as well as supported self-management and assessment of adherence and inhaler technique (see Figure 2). These assessments should be undertaken prior to a step-up or step-down in treatment. Several issues concerning the efficacy and safety of commonly used drugs for asthma within the context of this approach are discussed briefly below.

ICSs
ICS is the recommended preventer for the treatment of adults with asthma. ICSs are less effective in smokers with asthma and a step-up in treatment with the addition of a long-acting beta2 agonist (LABA) may be required. Doubling the dose of ICS, from 1000 to 2000 μg/day, at the onset of an exacerbation does not reduce the risk of exacerbations requiring rescue oral corticosteroids. Once-daily ICSs include ciclesonide and mometasone.

ICS/LABA combinations
Inhaled LABA is the first choice add-on therapy for adults with poorly controlled asthma despite taking ICSs at doses of 200–800 μg beclometasone dipropionate/day. The asthma guideline recommends that LABAs should be prescribed in fixed-dose combination with an ICS to aid adherence and reduce the likelihood of LABA monotherapy.

Currently available combination products are administered twice daily, namely fluticasone propionate/salmeterol (Seretide), budesonide/formoterol (Symbicort and DuoResp Spiromax), extra-fine beclometasone/formoterol (Fostair) and fluticasone propionate/formoterol (Flutiform). A new combination multidose dry powder inhaler device (Relvar Ellipta) containing the ICS fluticasone furoate and the LABA vilanterol trifenatate (92/22 and 184/22 μg) is licensed as the first once-daily maintenance treatment for asthma. Once-daily treatment with fluticasone/
Vilanterol has the potential to improve adherence in asthma, although to date there are no published data to support improved adherence or effectiveness compared to other ICS/LABA combinations. Depending on the dose of ICS used, some alternative ICS/LABA combination inhalers are available at a lower daily cost.

The Single inhaler Maintenance And Reliever Therapy (SMART) regimen, using both budesonide and formoterol (Symbicort SMART), or the combination of inhaled extra-fine particle size beclometasone and formoterol pressurised metered dose inhaler as Maintenance And Reliever Therapy (Fostair MART) regimen for maintenance treatment and relief of symptoms, reduce the frequency of severe exacerbations compared to a fixed-dose combination plus a short-acting beta₂-agonist (SABA) as a reliever.14,15

Overall, studies indicate that the single combination inhaler approach and the fixed-dose combination strategy are both effective options for patients at Step 3 who are poorly controlled. A decision on which strategy to use is likely to be influenced by patient preference and the ability of the patient to understand the correct use of the single combination inhaler regimen.2

**Long-acting muscarinic antagonists**

Recent clinical trials have demonstrated the efficacy of the long-acting muscarinic antagonist bronchodilator tiotropium (Spiriva Respimat) in adults with asthma who have persistent airflow obstruction. Once-daily tiotropium added to medium-dose ICS reduced airflow obstruction and improved symptom control in patients with moderate symptomatic asthma16 and may be superior to doubling of the dose of ICS.17 In patients with poorly controlled asthma who have reduced lung function despite the use of combination therapy (ICS plus LABA), the addition of tiotropium increased the time to the first severe exacerbation and provided modest sustained bronchodilation.18

Tiotropium (Spiriva Respimat 5μg daily) was licensed in 2014 as an add-on maintenance bronchodilator treatment for use in adults who are currently treated with ICS (≥800μg budesonide/day or equivalent) and a LABA (Step 4 British guideline), and who experienced one or more severe exacerbations in the previous year. Tiotropium has not been compared with other add-on therapies at Step 4 eg high dose ICS or leukotriene antagonist, or in adults with asthma without persistent airflow obstruction (post-bronchodilator FEV₁ <80 per cent of predicted).

Spiriva Respimat should be used with caution in people with certain cardiac conditions, who were excluded from clinical trials of tiotropium.

**Severe asthma**

For the 5–10 per cent of patients with severe asthma, there are limited treatment options (Steps 4 and 5, see Figure 2).19,20 These patients often have poorly controlled asthma despite treatment with high-dose ICS and LABAs plus other add-on therapies and, at Step 5, oral corticosteroids.

Omalizumab, a humanised monoclonal antibody that binds circulating IgE antibody, is indicated for patients with severe allergic asthma (see Table 4). Its use is associated with improvements in asthma control.21

### Table 2. The RCP “three questions” for determining asthma control

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No or Don’t Know</th>
<th>Don’t Know or Don’t know Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last month/week have you had difficulty sleeping due to your asthma (including cough symptoms)?</td>
<td>1 “yes” indicates medium morbidity and 2 or 3 “yes” answers indicate high morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had your usual asthma symptoms (eg cough, wheeze, chest tightness, shortness of breath) during the day?</td>
<td>1 “yes” indicates medium morbidity and 2 or 3 “yes” answers indicate high morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has your asthma interfered with your usual daily activities (eg school, work, housework)?</td>
<td>1 “yes” indicates medium morbidity and 2 or 3 “yes” answers indicate high morbidity</td>
<td></td>
<td></td>
</tr>
</tbody>
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**Table 3. 2015–2016 QOF indicators for asthma**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Points</th>
<th>Achievement thresholds</th>
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</thead>
<tbody>
<tr>
<td>Records AST001. The contractor establishes and maintains a register of patients with asthma, excluding patients with asthma who have been prescribed no asthma-related drugs in the preceding 12 months</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Initial diagnosis AST002. The percentage of patients aged 8 or over with asthma (diagnosed on or after 1 April 2006), on the register, with measures of variability or reversibility recorded between 3 months before or any time after diagnosis</td>
<td>15</td>
<td>45–80%</td>
</tr>
<tr>
<td>Ongoing treatment AST003. The percentage of patients with asthma, on the register, who have had asthma review in the preceding 12 months that includes an assessment of asthma control using the 3 RCP questions (NICE 2011 menu ID: NM23)</td>
<td>20</td>
<td>45–70%</td>
</tr>
<tr>
<td>AST004. The percentage of patients with asthma aged 14 or over and who have not attained the age of 20, on the register, in whom there is a record of smoking status in the preceding 12 months</td>
<td>6</td>
<td>45–80%</td>
</tr>
</tbody>
</table>
Figure 2. Step-wise approach to the management of asthma in adults, in children aged 5–12 years and in children less than 5 years.

**Step 1**
Mild intermittent asthma

Adults and children >12 years

Inhaled SABA as required

**Step 2**
Regular preventer therapy

Children 5–12 years

Add inhaled steroid 200–800μg per day*

Children <5 years

Add inhaled steroid 200–400μg per day*

Consider other preventer drug such as LTRA if steroid cannot be used

**Step 3**
Initial add-on therapy

*Refers to beclometasone or budesonide; equivalent dosages for fluticasone and mometasone should be halved; ciclesonide is also more potent although its precise equivalence to beclometasone is unclear

**Step 4**
Persistent poor control

In children taking inhaled steroid 200–400μg per day,* consider adding LTRA

**Step 5**
Continuous or frequent oral steroid

In children taking LTRA alone, reconsider adding inhaled steroid 200–400μg per day*

In children <2 years old consider proceeding to Step 4

**At each step check:**
- Current symptoms
- Risk of exacerbation
- Adherence
- Inhaler technique
- Triggers
- Co-morbidities
- Consider nonpharmacological approaches
- Action plan
- Need for specialist referral (particularly at steps 4 and 5)

SABA: short-acting beta₂-agonist; LABA: long-acting beta₂-agonist; LTRA: leukotriene receptor antagonist; SR: slow release

*Refers to beclometasone or budesonide; equivalent dosages for fluticasone and mometasone should be halved; ciclesonide is also more potent although its precise equivalence to beclometasone is unclear

**Figure 2.** Step-wise approach to the management of asthma in adults, in children aged 5–12 years and in children less than 5 years.
The best predictors of future exacerbations are poor symptom control, and the yearly cost per patient is considerable. Bronchial thermoplasty, which involves the delivery of radiofrequency energy to the airways to reduce airway smooth muscle mass has been shown to improve quality of life and reduce exacerbation in severe asthma. The asthma guidelines advise that bronchial thermoplasty may be considered for the treatment of moderate to severe asthma in patients who have poorly controlled asthma despite maximal therapy. The procedure is available in several specialist centres in the UK. Biological agents targeting proinflammatory cytokines such as interleukin-5 and interleukin-13 are under development for severe asthma.

**Conclusion**

The diagnosis of asthma is based on an assessment of the probability of asthma and evidence of variable airflow obstruction. The step-wise approach to drug treatment should be integrated into a patient-centered management plan that includes: non-pharmacological management approaches where appropriate; regular monitoring of symptom control and risk of future exacerbations; supported self-management; and assessment of adherence and inhaler technique. Better therapies are required for the 5–10 per cent of people with severe asthma.

**References**


**Declaration of interests**

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