

Difficult to treat asthma in adults

Graeme P Currie,¹ J Graham Douglas,¹ Liam G Heaney²

¹Aberdeen Royal Infirmary, Aberdeen AB25 2ZN

²Belfast City Hospital, Belfast BT9 7AB

Correspondence to: G P Currie Graeme.currie@nhs.net

Cite this as: *BMJ* 2009;338:b494
doi:10.1136/bmj.b494

There is no universally accepted definition of difficult asthma. However, it is reasonable to consider it present when people have persistent symptoms and frequent exacerbations, despite being treated at steps 4 or 5 of the British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN) guidelines (fig 1).¹ Such patients typically receive high dose inhaled steroids (≥ 800 μg beclometasone equivalent), a long acting β_2 agonist, plus add-on treatment. The prevalence of difficult asthma is uncertain, but it may account for 5-10% of adults with asthma.² Morbidity and health costs are disproportionately high in these patients,^{w1} and they are at greater risk of fatal and near fatal exacerbations.^{w2} In addition, frequent, intermittent, or continuous courses of oral prednisolone (plus regular high dose inhaled steroids) increase the risk of steroid related adverse effects.

Why are some people with asthma difficult to treat?

Several key questions must be considered before prescribing add-on treatments and higher doses of inhaled or oral steroids to patients with difficult to treat asthma.

Do they really have asthma?

To answer this question, the patient's history and objective support for a diagnosis of asthma need to be reviewed (boxes 1 and 2). In patients with airflow obstruction, bronchodilator reversibility to 400 μg of inhaled salbutamol should be performed. In patients without airflow obstruction, other objective ways of confirming the diagnosis—such as exercise testing, measuring exhaled nitric oxide, and bronchial challenge testing—may be necessary.¹ According to BTS-SIGN guidelines, the diagnosis should be reconsidered in patients with persistent symptoms who do not show airway hyper-responsiveness to bronchoconstrictor stimuli such as methacholine (or in the future mannitol).^{1 w3} Box 2 outlines other tests that may help establish whether asthma is present. Not all tests will be needed in each patient—this will depend on the clinical situation.

Do coexisting conditions exacerbate the asthma?

Asthma often occurs alongside other conditions. In two case series, coexisting disorders with asthma-like symptoms were found in 19%³ and 34%⁴ of patients with difficult asthma (fig 2). If coexisting conditions are correctly identified and managed, it may be possible to improve symptom control without escalating treatment. Moreover, bronchiectasis, gastro-oesophageal reflux disease, rhinosinusitis, and psychological disorders are more common in people with frequent versus infrequent severe exacerbations of asthma.^{w4} Vocal cord dysfunction (paradoxical adduction during inspiration) is an important disorder that can mimic or coexist with asthma.^{w5 w6} It may masquerade as wheeze and breathlessness, with episodes beginning and remitting abruptly (unrelated to treatment). Its prevalence is uncertain, and diagnosis requires a high index of suspicion and direct visualisation of the vocal cords when symptomatic.^{w7}

What aggravating factors might be considered?

Psychological factors

Difficult to control asthma often causes considerable psychological stress, especially if a life threatening episode has occurred; psychological factors (especially anxiety) may also worsen asthma control. Adverse psychological factors are associated with hospital

Sources and selection criteria

All authors performed a comprehensive search of articles published up to January 2009 using PubMed and Medline. Keywords and phrases used were “asthma”, “exacerbations”, “symptoms”, “difficult asthma”, “lung function”, “diagnosis”, “bronchial hyper-responsiveness”, “nitric oxide”, “sputum eosinophils”, “treatment”, “monitoring”, “inhaled steroids”, “long acting β_2 agonists”, “leukotriene receptor antagonists”, “bronchial thermoplasty”, “immunoglobulin E therapy”, and “tumour necrosis factor”.

Summary points

Difficult asthma is present when patients using treatment at steps 4 or 5 of the British Thoracic Society and Scottish Intercollegiate Guideline Network guidelines remain symptomatic and have exacerbations

Determine whether the patient truly has asthma, whether prescribed treatment is being taken, and whether an alternative or coexisting diagnosis or aggravating factors exist

After taking a detailed history and examination, further directed investigations may be needed

Assessment and further management should ideally take place within a multidisciplinary clinic setting

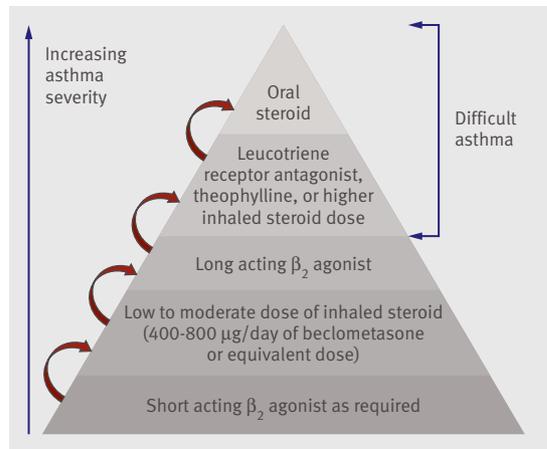


Fig 1 | Simplified diagram of the pharmacological management of chronic asthma in adults^{1 w1}

admission with acute asthma,^{w8 w9} and psychosocial morbidity has also been linked to fatal and near fatal episodes of asthma.¹ In a study where sequential patients referred to a difficult asthma service were assessed by a psychiatrist, 32 out of 65 had an ICD-10 (international classification of diseases, 10th revision) psychiatric diagnosis (usually depression).⁴ In the same study, the hospital anxiety and depression scale (HADS) had a good negative predictive value for depression. In a cohort of 56 patients, 33 had a psychiatric component to their asthma, and in 10 this was thought to be “major.”³ It is unclear whether

psychological morbidity negatively affects difficult asthma, and whether treating concomitant psychiatric morbidity improves asthma control. Although patients often identify acute stress and depression as triggers, psychological factors may cause poor adherence to treatment, rather than have a direct effect on asthma severity.

Upper airway disease

The upper and lower airways have a direct anatomical connection, share a similar epithelial lining, and release similar inflammatory mediators. Asthma and allergic rhinitis represent a continuation of the same inflammatory process so it is not surprising that they commonly coexist.⁶ Indeed, treating allergic airway inflammation in the nose can improve markers of asthma control.^{w10-w13} The allergic rhinitis and its impact upon asthma (ARIA) guidelines emphasise the importance of identifying symptoms of asthma in people with rhinitis and vice versa.⁷ Management strategies for allergic rhinitis consist of allergen avoidance, immunotherapy, intranasal steroids, and systemic or topical antihistamines.⁷

Gastro-oesophageal reflux disease

The incidence of gastro-oesophageal reflux disease is higher in patients with asthma than in the general population, although its relation to difficult asthma is not clear.^{w14 w15} A systematic review of 12 studies found no convincing evidence to support improved asthma control with treatment for gastro-oesophageal reflux disease,⁸ and in difficult asthma, identification and treatment of the disease failed to improve control.^{w16}

Adverse drug effects

Non-steroidal anti-inflammatory drugs, β blockers (including eye drops), and aspirin can exacerbate asthma. Indeed, aspirin sensitive asthma may exist in

Box 1 Important clinical aspects to cover in patients with difficult asthma

History

Details of original diagnosis: “who, when, and how,” previous demonstration of airflow obstruction, documented response to treatment

Morbidity: length of history, severity of symptoms, exacerbating factors, frequency of exacerbations, previous admissions to intensive care with abnormal airway inflation pressures

Presence of other respiratory symptoms (sputum production, chest pain, haemoptysis)

Smoking history

Family history of respiratory disorders

Past and present occupation

Potential aggravating medical conditions (features of rhinosinusitis, nasal polyps, depression or anxiety, gastro-oesophageal reflux disease, relation to menstrual cycle)

Drugs (β blockers, aspirin, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors)

Adherence to treatment

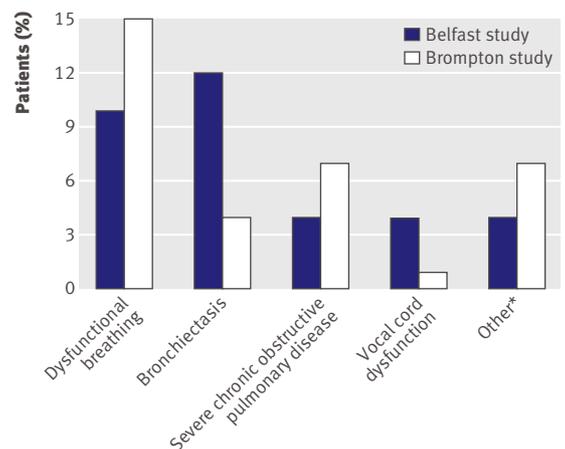
Psychosocial circumstances

Examination

Respiratory system: look for signs that may or may not be consistent with asthma

Cardiovascular system: look for signs that may indicate an alternative diagnosis

Body mass index: obesity is associated with difficult to control asthma, and uncertainty may arise in differentiating between breathlessness caused by obesity and that caused by asthma



* Other: Chronic bronchitis, IgA deficiency, cystic fibrosis, obliterative bronchiolitis, cardiomyopathy, pulmonary hypertension, hypereosinophilia, extrinsic allergic alveolitis, respiratory muscle incoordination, obstructive sleep apnoea

Fig 2 | The frequency and type of coexistent diagnoses in two studies of patients with difficult asthma. Adapted, with permission, from Heaney and Robinson⁵

Box 2 Investigations that may be needed in patients with difficult asthma**Blood tests**

Blood eosinophil count

Total serum IgE and allergen skin prick testing (or radioallergosorbent test) especially to *Aspergillus*

Blood theophylline or prednisolone concentrations (where appropriate) to support adherence

Other blood tests depending on clinical features (α_1 antitrypsin, angiotensin converting enzyme, immunoglobulins and functional antibody testing, antineutrophil cytoplasmic antibody, *Aspergillus* serology)

Pulmonary function

Spirometry

Airflow obstruction present: test for bronchodilator reversibility

Airflow obstruction absent: consider exercise test, bronchial challenge test (using inhaled methacholine or mannitol), exhaled nitric oxide (raised in eosinophilic airway inflammation), sputum eosinophil count

Flow volume loop, lung volumes, and transfer factor to identify features not consistent with asthma (where appropriate)

Radiography

Chest radiography

High resolution computed tomography of thorax (to look for bronchiectasis or interstitial lung disease)

Computed tomography of sinuses (to look for sinus disease after nasal endoscopy or a trial of nasal steroids)

Other tests (as clinically indicated)

Nasal endoscopy (to look for polyps and features of rhinosinusitis)

Bronchoscopy (to look for tumours or foreign bodies)

Laryngoscopy during symptomatic episodes (to look for vocal cord dysfunction)

Echocardiogram (where wheeze may be caused by "cardiac asthma")

Psychiatric assessment

Cardiopulmonary exercise testing

up to 20% of people with asthma.⁹ Chronic cough caused by angiotensin converting enzyme inhibitors may also mimic less well controlled asthma.

Allergy

Increased sensitisation to aeroallergens has been associated with greater airway hyper-responsiveness,^{10 w17} and sensitisation to fungal allergens has been linked to life threatening asthma.^{w18} However, little evidence

Box 3 Potential reasons for patients not adhering to treatment

Treatment considered unnecessary, ineffective, or dangerous

Lack of immediate effect after taking inhaled steroids

Poor understanding of the treatment regimen

Poor inhaler technique

Resentment about the need for treatment

Economic restriction on access to health care and drugs

Demographic factors such as sex and ethnicity

Forgetfulness and stress

Secondary gain from persistent symptoms

exists to suggest that reducing exposure to house dust mite and other ubiquitous allergens reduces symptom scores and exacerbations or improves peak expiratory flow.¹¹

Occupational factors

Many patients with difficult asthma may have stopped work because of symptoms. Because occupational asthma may account for as much as 10-15% of adult onset disease,¹ questioning patients about occupational exposure to airway irritants may uncover a trigger. Those who are better on days away from work or when on holiday should be investigated for occupational asthma.

Cigarette smoking

Cigarette smoking is associated with persistent asthma, an accelerated decline in lung function, and higher mortality after admission with an episode of near fatal asthma.^{w19-w21} People who currently smoke or previously smoked have reduced airway sensitivity to the effects of inhaled steroids compared with non-smokers.^{12 13}

Obesity

Accumulating data associate obesity with persistent asthma and asthma related visits to the emergency department, and obese women seem to have an increased risk of having asthma.¹⁴ Although the association between asthma and obesity is not fully understood, weight loss should be encouraged.

Are patients taking their treatment?

In a cross sectional observational study of non-adherence in difficult asthma (n=182), 34% of people were collecting less than 50% of their prescriptions for inhaled combination therapy.^{w22} In a case series, 50% of patients prescribed oral steroids were found to be non-adherent when assessed by plasma prednisolone and cortisol concentrations.³ Thus, despite persistent symptoms, many patients choose not to take their prescribed treatment and reasons for this need to be explored (box 3).

Should you refer a patient with difficult asthma?

Patients who are refractory to guideline based treatment should be referred to a specialised clinic. This is important if the diagnosis is in doubt or when excessive amounts of drugs, especially oral steroids, are used. Ideally, referring doctors should have access to a multidisciplinary clinic where experienced personnel (respiratory physicians, psychologists, and specialist nurses) have the necessary tools (such as bronchial challenge test kits and fiberoptic nasoendoscopy) and infrastructure available for assessment. However, a UK postal questionnaire sent to more than 600 consultant members of the BTS (50% response rate) found that only 23% of responding respiratory physicians had a dedicated difficult asthma clinic in their hospital.¹⁵

Asthma control test²⁰

Questions and answers	Score				
	1	2	3	4	5
Question 1	How much of the time did your asthma keep you from getting as much done at work, school, or home?				
Answers	All the time	Most of the time	Some of the time	A little of the time	None of the time
Question 2	How often have you had shortness of breath?				
Answers	More than once a day	Once a day	3-6 times a week	Once or twice a week	Not at all
Question 3	How often did your asthma symptoms wake you up at night or earlier than usual in the morning?				
Answers	≥4 nights a week	2-3 nights a week	Once a week	Once or twice	Not at all
Question 4	How often have you used your rescue inhaler or nebulised drug?				
Answers	≥3 times a day	1-2 times a day	2-3 times a week	At least once a week	Not at all
Question 5	How would you rate your asthma control?				
Answers	Not at all controlled	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled

The five questions refer to the past 4 weeks. A total score of 25 indicates perfect control; 20-24 indicates that asthma may be well controlled, although further advice should be obtained; and <20 indicates that further recommendations regarding management should be made by a nurse or doctor.

What new approaches are available?

Anti-immunoglobulin E

Many people with asthma are atopic, with the consequence that aeroallergens interact with IgE and cause the release of inflammatory mediators.^{w23} Omalizumab is a humanised monoclonal antibody that can be given subcutaneously; its dose is determined by baseline IgE and body weight. Omalizumab cannot be given if the total IgE is more than 700 IU/l, which effectively excludes highly atopic patients. A randomised controlled trial evaluated the addition of omalizumab in people with severe asthma who had persistent symptoms despite using inhaled steroids and long acting β₂ agonists.¹⁶ The clinically significant asthma exacerbation rate was 0.68 with omalizumab and 0.91 with placebo over 28 weeks (P=0.042), and compared with placebo, active treatment significantly reduced severe asthma exacerbation rates (0.24 v 0.48; P=0.002) and emergency visit rates (0.24 v 0.43; P=0.038). The National Institute for Health and Clinical Excellence advises that omalizumab should

be considered only for patients who have had at least two severe exacerbations requiring hospital admission within the previous year, whereas the Scottish Medicines Consortium advises its restriction to patients requiring maintenance oral steroids when all other treatments have failed.

Other biological treatments

Tumour necrosis factor α is thought to have a role in some chronic inflammatory conditions. Despite initial promise, however, a randomised double blind study evaluating etanercept (a tumour necrosis factor antagonist) over 12 weeks found no significant improvement in major outcomes in patients with steroid dependent asthma.¹⁷ Moreover, a trial of 24 weeks' treatment with gomalumab (a humanised monoclonal antibody against tumour necrosis factor) also found no important differences in asthma outcome. The trial was stopped early because of the significantly increased numbers of infections and incidence of malignancies in the active treatment arm.¹⁸ Whether other biological agents such as anti-interleukin 13 antibody or anti-neutrophilic strategies such as anti-CXCR1/R2 will be beneficial in refractory asthma remains to be seen.

Other drugs

Various drugs such as ciclosporin, methotrexate, gold, and subcutaneous terbutaline have been tried with various degrees of success in difficult asthma. These agents are not in widespread use but may be considered under specialist supervision.

Bronchial thermoplasty

An increase in airway smooth muscle mass is thought to be an important factor in severe or fatal asthma.^{w24 w25} Bronchial thermoplasty—where controlled thermal energy is delivered to the airway wall during several bronchoscopy procedures—results in prolonged reduction of smooth muscle mass. In people with moderate to severe asthma, this procedure reduces symptoms, use of relievers, and exacerbations, and it improves quality of life and lung function.¹⁹ Larger

Additional educational resources

Additional educational resources for healthcare professionals

- British Thoracic Society (www.brit-thoracic.org.uk)—The main UK respiratory society for clinicians
- Lung and Asthma Information Agency (www.laia.ac.uk)—Gives epidemiological data on asthma, allergy, and other respiratory conditions
- National Heart, Lung, and Blood Institute (www.nhlbi.nih.gov/health/public/lung/index.htm)—Gives information on lung diseases such as asthma
- Oasys and Occupational Asthma (www.occupationalasthma.com/)—Provides information on occupational asthma
- Dendrite Clinical Systems Ltd (<http://host.e-dendrite.com/csp/asthma/FrontPages/asthmafront.csp>)—British Thoracic Society difficult asthma registry

Additional educational resources for patients

- Asthma UK (www.asthma.org.uk)—A leading UK asthma charity organisation
- British Lung Foundation (www.lunguk.org)—A leading UK charity helping those with respiratory disorders
- ASH (www.ash.org.uk)—A public health charity dedicated to limiting harm caused by smoking

Tips for non-specialists

Always check that the diagnosis of asthma is correct
 Consider further tests to help confirm the diagnosis; refer to a specialist if the diagnosis remains questionable
 Always ask about adherence to treatment
 Assess inhaler technique at every opportunity
 Always encourage smoking cessation and weight reduction

long term studies are needed to evaluate this new technique fully.

How should patients with difficult asthma be monitored?

It is unclear how best to monitor patients in the community, although regular follow-up by doctors and nurses trained in asthma management may be beneficial. This also provides an opportunity to assess inhaler technique and switch to a more efficient device if necessary or one that the patient can use more easily. Non-specific questions tend to underestimate symptoms,²⁰ but asthma control can be assessed by well validated questions, such as those in the asthma control test (table).

It is difficult to assess adherence to inhaled drugs, although surrogate markers such as prescription filling of maintenance inhalers may be helpful. Direct measurements such as plasma theophylline concentrations or plasma prednisolone and cortisol measurements can provide supportive evidence.

In the future it may be increasingly important to monitor disease activity—and thereby titrate treatment—using surrogate inflammatory biomarkers; examples of these include airway hyper-responsiveness (using indirect challenge tests such as mannitol), induced sputum eosinophil counts, and exhaled nitric oxide.²¹ Indeed, asthma control may be improved when a surrogate inflammatory biomarker is incorporated into algorithms (along with conventional measures of asthma control) by which treatment is altered.²²⁻²⁴ However, in one study, the use of exhaled nitric oxide as an indicator of asthma control resulted in higher doses of inhaled steroids being used, without a clinically important reduction in symptoms.²⁵

Conclusions

Managing asthma that is refractory to usual treatment requires a systematic approach to ensure a correct diagnosis, identify coexisting disorders, tailor treatment, and evaluate adherence. The BTS has established UK registries of adults and children with difficult to control asthma to standardise and optimise assessment protocols across UK centres. In the future, this may facilitate research into severe asthma phenotypes and disease mechanisms in an attempt to define best practice.

Contributors: GPC had the original idea for the manuscript and wrote it along with JGD and LGH; GPC is guarantor.

Competing interests: GPC has received funding and honorariums from AstraZeneca, Merck Sharp and Dohme, and GlaxoSmithKline; JGD from GlaxoSmithKline, AstraZeneca, and Novartis; and LGH from AstraZeneca, Merck Sharp and Dohme, Novartis, and GlaxoSmithKline for attending postgraduate educational meetings and giving talks.

Provenance and peer review: Commissioned; externally peer reviewed.

- 1 British Thoracic Society and Scottish Intercollegiate Guideline Network. British guideline on the management of asthma. *Thorax* 2008;63(suppl 4):iv1-121.
- 2 Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J* 1998;12:1209-18.
- 3 Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003;22:478-83.
- 4 Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax* 2003;58:561-6.
- 5 Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. *Lancet* 2005;365:974-6.
- 6 Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997;99:5781-6.
- 7 Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-334.
- 8 Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. *Thorax* 2001;56:198-204.
- 9 Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004;328:434.
- 10 Currie GP, Jackson CM, Lee DK, Lipworth BJ. Allergen sensitization and bronchial hyper-responsiveness to adenosine monophosphate in asthmatic patients. *Clin Exp Allergy* 2003;33:1405-8.
- 11 Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003;349:225-36.
- 12 Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;60:282-7.
- 13 Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004;24:822-33.
- 14 Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. *Thorax* 2008;63:1018-23.
- 15 Roberts NJ, Robinson DS, Partridge MR. How is difficult asthma managed? *Eur Respir J* 2006;28:968-73.
- 16 Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309-16.
- 17 Morjaria JB, Chauhan AJ, Babu KS, Polosa R, Davies DE, Holgate ST. The role of a soluble TNFalpha receptor fusion protein (etanercept) in corticosteroid refractory asthma: a double blind, randomised, placebo controlled trial. *Thorax* 2008;63:584-91.
- 18 Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlen SE, et al. A randomized, double-blind, placebo-controlled study of TNF- α blockade in severe persistent asthma. *Am J Respir Crit Care Med* 2009 Jan 8 (Epub ahead of print).
- 19 Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007;356:1327-37.
- 20 Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.
- 21 Currie GP, Fardon TC, Lee DK. The role of measuring airway hyperresponsiveness and inflammatory biomarkers in asthma. *Ther Clin Risk Manag* 2005;1:83-92.
- 22 Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352:2163-73.
- 23 Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
- 24 Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med* 1999;159:1043-51.
- 25 Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;372:1065-72.