



# The importance of allergy in asthma

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## Bronchial asthma – where are we?

Asthma affects up to 10% of the UK population. Symptoms are variable and include wheeze, cough, chest tightness, and shortness of breath. Symptoms are often worse at night and in the early morning and on exertion. Asthma commonly interferes with work/school performance, leisure activities, and sleep. Commonly associated conditions include rhino conjunctivitis, atopic dermatitis (eczema), and

occasionally food allergy, all of which may have an additional impact on the quality of life for asthma sufferers and their families.

Inhaled allergens such as house dust mite, domestic pet dander, and seasonal exposure to tree and grass pollens and mould spores represent major provoking factors in many asthmatics. A major problem is the occurrence of asthma attacks triggered by common colds and other viral infections. The combination of a viral cold together with allergen exposure has been shown to be highly synergistic in provoking severe asthma exacerbations. Outdoor pollutants such as diesel particulates, nitric oxide and ozone prevalent in inner city areas are further predisposing/provoking factors.

## Modern asthma treatment is highly effective for most patients

A holistic approach is necessary to empower patients with asthma to control their own symptoms, prevent exacerbations and reduce drug side effects to a minimum. Patient education about their disease, the need to avoid/minimise provoking factors such as inhaled allergens, the need for regular 'controller' treatment, attention to inhaler technique, and recognition and treatment of co-morbidities such as rhino conjunctivitis are all important examples of this approach that is best facilitated



by the specialist practice nurse, along with a clear written personalised asthma action plan and access to regular follow up as needed. Lung function testing using portable spirometry and home monitoring by use of peak expiratory flow meters is an important aspect of care, as recently emphasised by the EAACI in their patient survey during the COVID-19 pandemic. Patient charities including Allergy UK and Asthma UK represent a major resource of information for patients with allergies and asthma with provision of dedicated helplines staffed health professionals, accessible and patient-focused websites, and supply of information leaflets on all aspects of asthma care.

Pharmacotherapy over the past 50 years has revolutionised the quality of life of asthma sufferers. Advances include the availability of long-acting as well as short-acting inhaled bronchodilators. Modern inhaled corticosteroids have reduced potential for systemic absorption and associated side effects. ‘Combination inhalers’ that include a corticosteroid that is inhaled together with a long-acting bronchodilator are highly effective and have improved asthma control and reduced exacerbations. Improvements in inhaler design together with the use of spacer devices have ensured a better drug delivery to distal airways, with reduced risk of upper airway side effects such as hoarseness and candidiasis (thrush).

**So, what’s the problem?**

Despite a holistic approach by skilled health care professionals and the availability of modern treatments, the ‘bête noir’ remains severe asthma exacerbations triggered by viruses and/or allergen exposures. Exacerbations may appear ‘out of the blue’ in patients with otherwise mild well-controlled asthma, as well as in those with more severe disease requiring high dose inhaled steroids and/or steroid tablet treatment. Although necessary for the treatment of exacerbations when prednisolone tablets are given in high doses and/or for prolonged periods of time they cause unacceptable side effects (Table 1). It should be

emphasised that inhaled corticosteroids are highly effective, the mainstay of asthma treatment, and largely free of general side effects. Inhaled corticosteroids may also cause general side effects, particularly when combined with topical corticosteroids by other routes such as nasal sprays and skin corticosteroids creams that all add to the steroid burden and this becomes particularly important in children.

**Table 1 Common corticosteroid side-effects**

- Indigestion, heartburn
- Increased appetite, weight gain
- Difficulty sleeping
- Mood changes including feeling irritable, anxious, or depressed
- Increased risk of infections
- High blood pressure
- Osteoporosis
- High blood sugar, diabetes
- Thin skin, easy bruising, and purple striae
- Cataract
- Glaucoma

**So, what’s the solution?**

*More Holistic approach!*

Happily, there often is a solution to improve asthma control and avoid drug side effects. Patients with ‘difficult asthma’ not responding to usual treatment should be referred to a specialist asthma clinic. This enables re-evaluation of the diagnosis and an opportunity to address issues that may be responsible for poor asthma control – first and foremost assess adherence to treatment and proper use of inhalers. I call this the ‘Baker’s dozen’ of causes of ‘difficult asthma’ (listed in Table 2).

Common causes of worsening asthma include environmental allergen exposures. Perennial mite and domestic pet exposures commonly underly perennial asthma. Tree and grass pollen commonly cause hay fever in more than 1 in 4 asthmatics, may exacerbate asthma and requires

**Table 2 ‘Baker’s dozen’ (What to do when asthma does not respond to treatment!)**

- Wrong diagnosis (or additional diagnoses)
- Nonadherence to treatment (not taken regularly, poor inhaler technique)
- Undiagnosed allergies (e.g. pets, moulds, occupational allergens, food)
- Psychosocial problems (Family, home, work/school bullying, separation, bereavement)
- Laryngeal/vocal fold dysfunction
- Rhinosinusitis with/without nasal polyps
- Gastroesophageal reflux (although correction often improves reflux but not the asthma)
- Hormonal changes (pregnancy, menstrual cycle, menopause, thyroid dysfunction)
- Allergic bronchopulmonary aspergillosis (bronchial inflammation due to aspergillus mould)
- Drug side effects (aspirin, beta-blockers)
- Vasculitis (organ damage due to eosinophilic granulomatous inflammation)
- Corticosteroid resistance (rare, only to be diagnosed when 1-11 excluded!)
- ‘Other’ – we should always be on the lookout for other reversible causes

separate recognition and treatment. Frequently unrecognised occupational causes include catalysts used in resin manufacture and two-part paint systems and varnishes, colophony in electronic solders and small animal exposure in laboratory animal workers (and rarely, exposure to flour in bakers!).

Psychosocial factors include abusive behaviour towards both children and adults, bereavement, parental separation, and financial difficulties. Laryngeal dysfunction is a common accompaniment of asthma and may be the sole cause of airway obstruction, requiring the attention of an expert speech therapist for diagnosing and treating the condition.

Obesity is an increasing problem in the UK and may be exacerbated by corticosteroid use. Excess fat tissue releases inflammatory mediators that may worsen asthma, and lack of exercise may result in deconditioning. An obese neck may compress the upper airway and cause obstructive sleep apnoea that can mimic asthma, and when recognised may respond extremely well to assisted ventilation using continuous positive airway pressure devices at night.

Other causes include rhinosinusitis, acid reflux, hormonal influences, drug-induced asthma such as aspirin intolerance, and rare causes such as allergic aspergillosis and serious vasculitic disorders that may be life-threatening if not diagnosed and treated.

Why the Baker’s dozen? Because the baker’s tray accommodates pastry for baking 12 pies and there is always a bit left to roll up and make a 13th. This reminds us that even having identified and resolved the 12 common causes, we should remain alert to look for that ‘other’ 13th cause not listed that may be an important asthma provoker for our individual patient. Attention to these factors may avoid the need for escalation of asthma medication and may even allow dose reduction.

**Monoclonal antibody therapies**

Having confirmed the diagnosis and after attending to items above and listed in table 2, there remains a small proportion of patients with confirmed eosinophilic asthma, so-called ‘type 2’ asthma, in whom the recent availability of monoclonal antibody therapies has represented a major advance in treatment.

Monoclonal antibodies include anti-IgE (Xolair), ‘anti-Th2’ cytokines such as anti-IL-5 (Mepolizumab), anti-TSLP (Tezepelumab), and anti-Th2 receptors (Reslizumab, and Dupilumab). Monoclonal antibodies target the so-called ‘Th2’ pathway that is the major driver of asthma for many patients including atopic allergic asthma as

well as 'late onset' eosinophilic asthma that may be associated with nasal polyps and sensitivity to aspirin-like drugs. Monoclonal antibodies have replaced immunosuppressive drugs such as cyclosporin and methotrexate that were previously used (and often ineffective) to treat the most severe confirmed asthma cases. In rigorous controlled clinical trials, monoclonal antibody therapies have been shown to prevent exacerbations and to reduce the need for 'rescue' high dose corticosteroids as well as reduce dependence and/or the dose of long-term maintenance prednisolone tablets and attendant side effects (Table 1).

In the UK these drugs have received regulatory approval and have been included in international guidelines, including the recently 2021 GINA guideline (Fig.1) at step 4/5 of asthma therapy. There are two caveats – firstly, in view of very high cost to the NHS, they should be reserved for those patients who have been through the above rigorous review in a specialist asthma clinic registered to prescribe them. Secondly, although of proven value in this carefully selected group of 'type 2' asthmatics, nonetheless, they represent a symptomatic treatment as with other anti-asthma drugs, with no disease modification and with relapse as soon as they are discontinued, hence the need for their continuous long-term prescription and adherence to treatment in order to maintain asthma control.

### Anything else?

Well, there is actually. I think quite exciting. A theme in this short communication has been the impact of allergen exposure as well as viruses in inducing exacerbations of asthma, even today a cause of occasional asthma fatalities. Also, the need to treat co-morbidities such as allergic rhinitis in order to improve the quality of life of asthma sufferers whether, or not there is an impact on their asthma control per se (which remains nonproven).

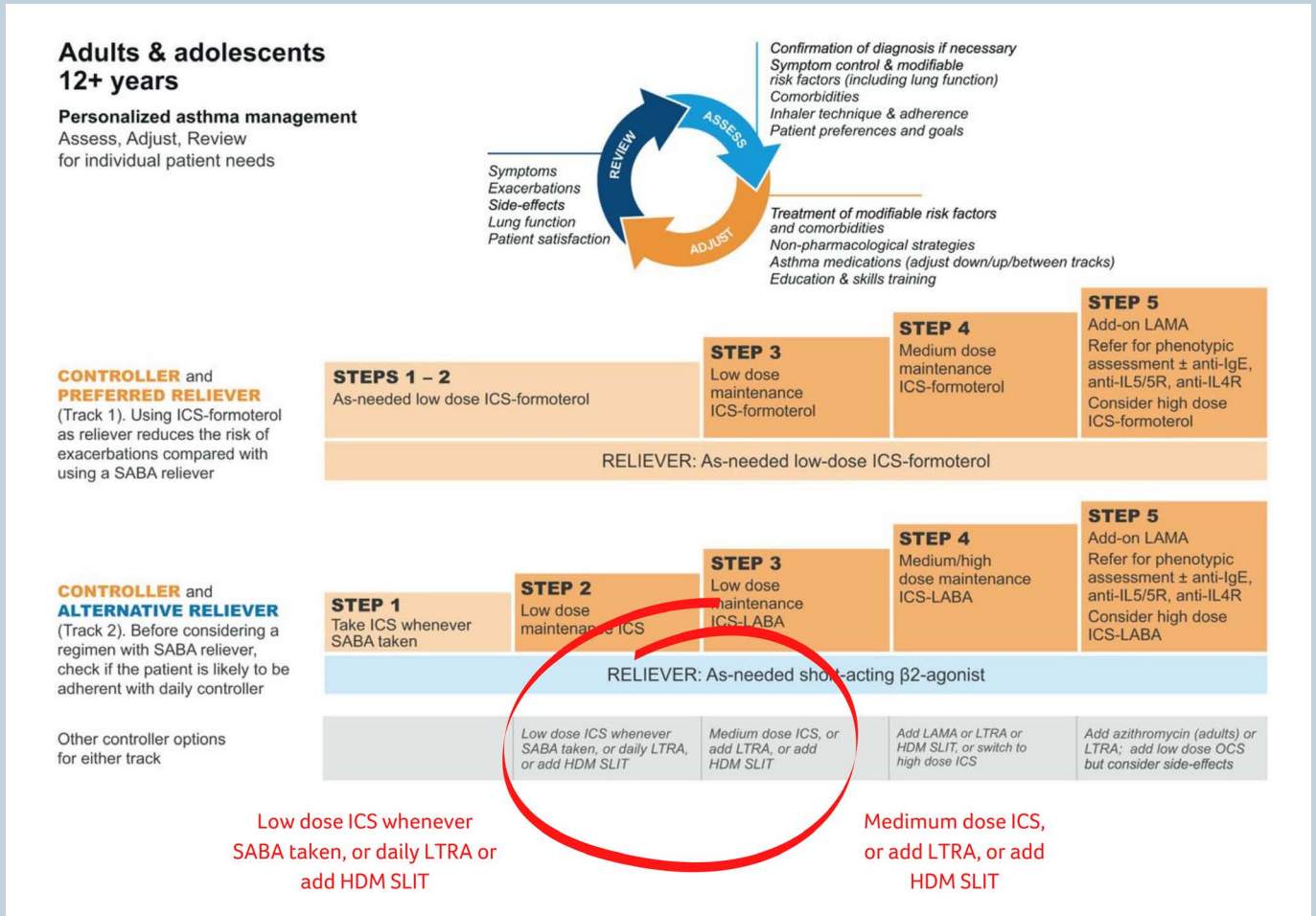
Asthma patients are rightly concerned about the

need to identify and treat the underlying causes of their condition, rather than just symptomatic treatment. For allergic asthma, there is the need to avoid provoking allergens to which they have established sensitivity. For example, avoidance of animals to which they are sensitive, effective treatment for their hay fever during the pollen season where pollen exposure is unavoidable (and too restrictive). House dust mite avoidance methods using hard flooring, mite-proof mattress/duvet/pillow covers and regular vacuum cleaning (by someone else!) have not been proved to be efficacious in adults whereas there has been some success in mite-allergic asthmatic children.

### *What about allergen immunotherapy?*

In patients with seasonal allergic rhinitis, (hay fever) with/without allergic asthma, over the past 110 years, and initially preceding the availability of antihistamines and nasal steroid sprays, allergen immunotherapy (desensitisation) has been shown to be very effective. After an initial up dosing phase, this took the form of repeated monthly injections into the subcutaneous tissue of grass pollen or tree pollen extracts and house dust mite or animal dander extracts. Although effective, subcutaneous immunotherapy requires specialist supervision and there is the risk of allergic side effects, including anaphylaxis following injections. In contrast, use of sublingual immunotherapy for seasonal pollens has proved highly effective and safe and able to be self-administered in the patients' home environment. This involves placing a concentrated high-dose allergen solution in the form of drops, or more recently, in the form of a tablet under the tongue. When taken 4 months before the pollen season, this has been shown for both grass pollen and tree pollen to be highly effective, and moreover, if taken daily as a fast-dissolving grass pollen or tree pollen tablet daily for 3 years, to be able not only improve seasonal symptoms but modify the course of the disease with the persistence of clinical benefit (long-term tolerance) for several years after its discontinuation.

**Figure 1 – Reproduced with permission by Global Initiative for Asthma**  
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 Available from www.ginasthma.org)



Interestingly, studies of a house dust mite tablet from 2 independent manufacturers have also been shown to be effective for perennial allergic rhinitis due to house dust mite. Further, the fast-dissolving freeze-dried tablet has been shown to be effective in reducing required maintenance doses of inhaled corticosteroids and to prevent asthma exacerbations in house dust mite allergic adult asthmatics who had partially controlled asthma. In the UK and Europe, the tablet now has regulatory approval to treat house dust mite-driven asthma associated with allergic rhinitis. In the recent GINA 2021 Guideline, SLIT fast-dissolving house dust mite tablets have an indication for use in patients with house dust mite allergic asthma and associated rhinitis at step 2-4 on the asthma treatment pathway (Fig.1). This is at the step prior to consideration of monoclonal

antibody treatment (step 4-5) that is indicated in more severe asthma as a symptomatic treatment. So, the good news is that we have a disease-modifying treatment for both seasonal rhinitis to tree and grass pollens and for carefully selected patients with moderate perennial house dust mite-driven asthma, with the potential to reduce exacerbations, reduce steroid burden and as proven for seasonal pollen allergy, likely induce long-term clinical benefits and remission, although the long-term effects for house dust mite tablet immunotherapy remain to be established in long-term trials.

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