Asthma

Alberto Papi, Christopher Brightling, Søren E Pedersen, Helen K Reddel

Asthma—one of the most common chronic, non-communicable diseases in children and adults—is characterised by variable respiratory symptoms and variable airflow limitation. Asthma is a consequence of complex gene–environment interactions, with heterogeneity in clinical presentation and the type and intensity of airway inflammation and remodelling. The goal of asthma treatment is to achieve good asthma control—ie, to minimise symptom burden and risk of exacerbations. Anti-inflammatory and bronchodilator treatments are the mainstay of asthma therapy and are used in a stepwise approach. Pharmacological treatment is based on a cycle of assessment and re-evaluation of symptom control, risk factors, comorbidities, side-effects, and patient satisfaction by means of shared decisions. Asthma is classed as severe when requiring high-intensity treatment to keep it under control, or if it remains uncontrolled despite treatment. New biological therapies for treatment of severe asthma, together with developments in biomarkers, present opportunities for phenotype-specific interventions and realisation of more personalised treatment. In this Seminar, we provide a clinically focused overview of asthma, including epidemiology, pathophysiology, clinical diagnosis, asthma phenotypes, severe asthma, acute exacerbations, and clinical management of disease in adults and children older than 5 years. Emerging therapies, controversies, and uncertainties in asthma management are also discussed.

Published **Online**
December 19, 2017
http://dx.doi.org/10.1016/S0140-6736(17)33311-1

Research Centre on Asthma and COPD, Department of Medical Sciences, University of Ferrara, Ferrara, Italy (Prof A Papi MD); **Institute for Lung Health, Leicester National Institute for Health Research Biomedical Research Centre, Department of Infection, Immunity, and Inflammation, University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, UK** (Prof C Brightling MD); **Department of Paediatrics, University of Southern Denmark, Kolding Hospital, Kolding, Denmark** (Prof S E Pedersen MD); **and Clinical Management Group and NHMRC Centre of Research Excellence in Severe Asthma, Woolcock Institute of Medical Research, University of Sydney, NSW, Australia** (Prof H K Reddel PhD)

Correspondence to: Prof Alberto Papi, Research Centre on Asthma and COPD, Department of Medical Sciences, University of Ferrara, 44121 Ferrara, Italy **ppa@unife.it**

Epidemiology

Asthma is one of the most common chronic, non-communicable diseases, and affects around 334 million people worldwide.[1] The global prevalence of self-reported, doctor-diagnosed asthma in adults is 4·3% (95% CI 4·2–4·4), with wide variation between countries. Prevalence is highest in developed countries—eg, Australia (21·0%)[2]—and lowest in developing countries—eg, China (0·2%).[2] Greater variation is seen for asthma symptoms in children, ranging from 2·8% (Indonesia) to 37·6% (Costa Rica) in children aged 6–7 years, and from 3·4% (Albania) to 31·2% (Isle of Man) in children aged 13–14 years.[3] However, prevalence is probably substantially underestimated in resource-poor countries, where basic asthma medications are not available and patients have difficulty accessing health care. Asthma prevalence is stable or decreasing in many developed countries but is increasing rapidly in developing countries as lifestyles become westernised.

Studies[4] of migration from countries with low asthma prevalence to countries with high asthma prevalence provide insight into the importance of environmental factors for these global patterns. Prevalence is lower in immigrants than in natives of the host country, rising to a similar proportion with increasing length of residence.[4] Apart from reducing maternal smoking, no specific strategies are accepted for primary prevention of asthma in children or adults.

Among children, asthma prevalence is higher in boys than in girls; however, prevalence is around 20% higher in women than men,[5] indicating a switch during puberty. Higher prevalence in boys is partly due to their smaller airways relative to lung size compared with young girls; this pattern reverses during adolescence. In a prospective study of 19-year-olds,[6] 21% of those with asthma at 7 years of age were in remission, 38% had periodic asthma, and 41% had persistent asthma. Remission was more likely in boys, but less likely in girls and patients with severe asthma or sensitisation to furred animals.[6] However, there are potential genetic and hormonal contributors, and sex differences in concomitant conditions—eg, obesity and cigarette smoking—that might increase asthma risk.[7] Asthma causes substantial disability, impaired quality of life, and avoidable deaths in children and young adults. Asthma and wheeze in preschool children were explored in a 2014 Review article,[8] and are therefore not addressed in our Seminar.

Asthma burden on patients, family, and society is disproportionately high in low-income and middle-income countries, where access to appropriate treatment is inadequate. Despite a worldwide reduction in asthma mortality in adults and children over the past 25 years, which is largely attributable to increased use of inhaled corticosteroids, a wide global disparity remains in years of life lost because of asthma (figure 1).

Pathogenesis of asthma

Asthma is a heterogeneous condition in both children and adults. Dissecting this heterogeneity is contributing to our understanding of disease pathogenesis and development of new therapeutic strategies, especially in severe disease. The observable characteristics (phenotype) of asthma—including clinical features of the disease and their underlying mechanisms (endotype)—are complex and represent a multitude of

Search strategy and selection criteria

We searched for English language articles and reviews in PubMed and Cochrane published between inception and Oct 1, 2017. The search combined the terms "Asthma" and the subheadings "epidemiology", "aetiology", "exacerbations", "pathophysiology", "innate AND adaptive immunity", "diagnosis", "therapeutics", and "prevention". We prioritised papers published from 2013 onwards. We also searched the reference lists of articles identified by this search and selected those we deemed most relevant.

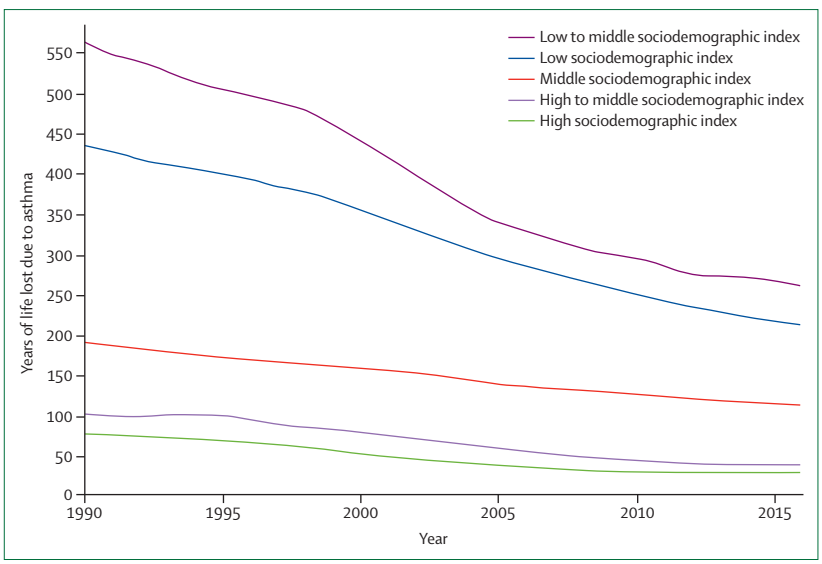

Figure 1: **Years of life lost due to asthma between 1990 and 2016, all ages, by sociodemographic index, in 195 countries**
Created with data from the Global Burden of Disease Study 2016 results.

For the **Global Burden of Disease Study 2016** see http://ghdx.healthdata.org/gbd-results-tool

host–environment interactions that occur over different spatial scales (ie, genes to cells to tissue to organ) and timescales.

Genome-wide association studies of asthma in children and adults have identified an association between polymorphisms for *IL33, IL1RL1/IL18R1, HLA-DQ, SMAD3,* and *IL2RB*[9] and the locus on chromosome 17q21 including the genes *ZPBP2*, *GSDMB*, and *ORMDL3*.[10,11] These genes implicate abnormalities in epithelial barrier function and innate and adaptive immune responses as contributing to asthma.

Progress has been made in our understanding of the heterogeneity of immunology in asthma (figure 2). Sputum cytology provides evidence of eosinophilic, neutrophilic, and mixed complex inflammation, as well as few inflammatory cells in some patients (paucigranulocytic).[13] Transcriptomic profiles of bronchoscopic samples have led to identification of molecular phenotypes consistent with high type 2 immunity and low type 2 immunity asthma, as well as others.[14,15] Because of the limitations of sampling the airway in children, particularly with invasive procedures, there is a paucity of data[16] in this age group.

Eosinophilic, high type 2 airway inflammation is present in around 50% of adults with asthma, but corticosteroid withdrawal studies often reveal eosinophilic airway inflammation, suggesting its prevalence might be underestimated.[17] Atopy is present in 50–60% of adults and children with asthma,[18] but is more common in severe asthma among children[19] and among adults with childhood-onset versus late-onset disease. Following allergic sensitisation and consequent stimulation by dendritic cells in the presence of coactivators such as epithelium-derived thymic stromal lymphopoietin, adaptive T helper 2 cells produce interleukin-5, interleukin-4, and interleukin-13. Interleukin-5 is an obligate cytokine for the survival and maturation of eosinophils. Recruitment of eosinophils to the lung mucosa is mediated via C-C motif chemokine receptor 3 chemokines and other eosinophil chemoattractants, such as mast cell-derived prostaglandin D2. Interleukin-4 drives B-cell isotype switching and IgE synthesis, which binds to mast cell high-affinity IgE receptors, leading to mast cell activation following allergen-mediated IgE cross-linking. In non-allergic eosinophilic asthma, innate lymphoid cells produce interleukin-5 and interleukin-13 in response to prostaglandin D2 and epithelium-derived alarmins interleukin-33, interleukin-25, and thymic stromal lymphopoietin released after epithelial damage by pollutants and microbes.

Non-eosinophilic asthma has been described in adults and children[19,20] but is poorly understood. Some patients have neutrophil-predominant disease with release of cytokines from T helper 1 cells, T helper 17 cells,[21] or type 3 innate lymphoid cells, with activation of macrophages and release of neutrophil chemokines such as C-X-C motif chemokine ligand 8.[22] However, with bronchiectasis as a common comorbidity of severe asthma in adults, a neutrophilic response could reflect bacterial colonisation[23] or effects of corticosteroids on promotion of neutrophil survival and suppression of type 2 immunity, leading to upregulation of type 1 or type 17 immunity.[24]

The allergic-dependent and allergic-independent mechanisms that drive eosinophilic inflammation and non-eosinophilic asthma can occur in concert, leading to mixed granulocytic inflammation or changes in the inflammatory profile over time.

Airway hyper-responsiveness is a feature present in asthma phenotypes with or without granulocytic inflammation in children and adults. In asthma, the airway smooth muscle is hypercontractile, which is amplified by co-located activated mast cells[25] and possibly by mechanotransduction[26] independent of airway inflammation.

Airway remodelling can present early in childhood, suggesting it is not simply a consequence of inflammation.[27] Remodelling is characterised by epithelial damage and cilial dysfunction, goblet cell hyperplasia, increased thickness of the lamina reticularis and reticular basement membrane,[28] increased vascularity, and increased subepithelial myofibroblasts, fibrocytes, and airway smooth muscle mass. Airway smooth muscle mass is the strongest predictor of airflow limitation.[29] These remodelling characteristics lead to thickening of the airway wall, luminal narrowing on quantitative CT,[30] and mucus plugging, with small airway obliteration.

Definition and clinical presentation

Asthma is a heterogeneous condition characterised by variable respiratory symptoms and variable airflow limitation. These features can be generated by a range of underlying mechanisms that are typically, but not

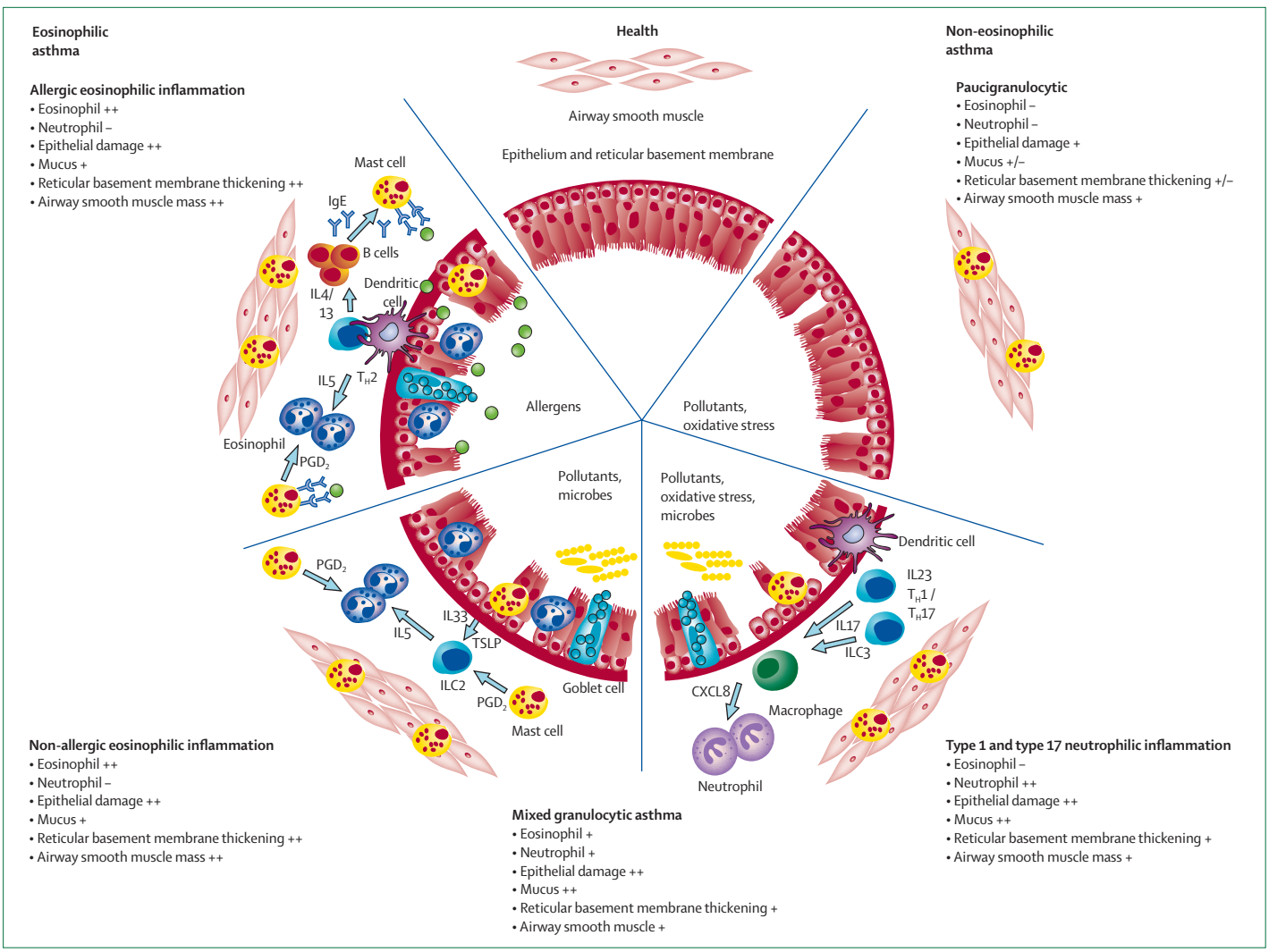

Figure 2: **Mechanisms and characteristic pathological features of asthma immunopathology**
Features are divided into eosinophilic (allergic and non-allergic), non-eosinophilic (neutrophilic type 1 and type 17 and paucigranulocytic), and mixed granulocytic inflammation. Reproduced from Russell and Brightling,[12] by permission of Portland Press. IL=interleukin. T_H=T helper. PDG_2=prostaglandin D2. TSLP=thymic stromal lymphopoietin. ILC2=type 2 innate lymphoid cells. CXCL8=C-X-C motif chemokine ligand 8. ILC2=type 3 innate lymphoid cells.

always, associated with airway inflammation and airway remodelling.

Symptoms and signs

Asthma symptoms are non-specific, and include wheezing, shortness of breath, chest tightness, and cough. The most characteristic asthma features relate to the pattern of symptoms, including symptom nature, timing, triggers, and response to treatment (appendix). Therefore, careful history taking is important to assess the probability that respiratory symptoms are due to asthma rather than a differential diagnosis or comorbidity (table 1, appendix).

Signs of asthma are few and non-specific. Expiratory wheezing might be heard on auscultation; consistent lack of wheezing during symptoms should prompt consideration of alternative diagnoses. Physical examination might reveal signs of comorbidities, such as bronchiectasis (adults) and obesity or, in atopic patients, eczema, or allergic rhinitis.

Initial clinical presentation of asthma

With diverse underlying mechanisms, some asthma phenotypes might be distinguishable at the time of initial clinical presentation, but others might not be easily distinguishable from each other.

See Online for appendix

Childhood-onset allergic asthma is commonly associated with eczema, rhinitis, or food allergy, a family history of asthma, and wheezing or coughing with, and sometimes between, viral respiratory infections. A third of wheezing children have persistent wheezing to adulthood; the probability of persistence, or later relapse, increases with early life allergen sensitisation, female sex,

	Main age group	Main clinical differences from asthma (history and examination)
Inhaled foreign body	Children, young adults	Anamnestic documented or suspected inhalation of foreign bodies; sudden onset of symptoms is common; recurrent chest infections
Congenital heart disease	Children, adolescents	Feeding problems in infancy, poor weight gain, cardiac murmurs, cyanosis, fatigue, and tiredness
Bronchopulmonary dysplasia	Children, young adults	Preterm delivery, low birthweight, required oxygen or feeding problems in infancy, symptoms already present during the neonatal period
Cystic fibrosis	Mainly children and adolescents; occasional adult diagnosis	Family history; clinical history of persistent, productive cough with acute infections, malaise, anorexia, and weight loss; concomitant gastrointestinal involvement (eg, loose fatty stools); in children, poor weight gain and reduced growth; in adults, impaired fertility
Chronic upper airway cough syndrome	Children, adolescents, adults	Nasal and sinus symptoms, sore throat, frequent throat clearing, sensation of post-nasal drip; snoring (common in children with this syndrome)
Rhinitis with or without chronic sinusitis	Children, adolescents, adults	Nasal symptoms with normal lung function, prominent nasal itching or sneezing, headache, seasonal variation, purulent rhinorrhoea; snoring (common in children); examination: nasal obstruction, hyponasal voice
Central airways stenosis, including tracheobronchomalacia	Children, older adults	Tracheal stridor (inspiratory); continuous symptoms, not responding to therapy
Vocal cord dysfunction	Children, adolescents, adults	Inspiratory (and sometimes expiratory) wheezing with or without stridor; often sudden onset; change in vocal timbre; triggered by exercise, talking on phone, strong smells; onset more sudden than with exercise-induced bronchoconstriction; can resolve rapidly; children often panic and are frightened because of the severity and sudden onset
Hyperventilation, dysfunctional breathing	Adolescents, adults, some older children	Dizziness, paraesthesia, light-headedness, peripheral tingling; possible triggers: physiological stress related, eg, to competitive exercise, musculoskeletal dysfunction, pain
Bronchiectasis	Children, adolescents, adults	Persistent sputum production, frequent lower airway infection, might have immunological disorder; examination might reveal coarse crackles
Gastro-oesophageal reflux disease	Children, adolescents, adults	Symptoms of heartburn and water brash can be triggered by posture changes and food intake; can cause nocturnal cough; physical examination usually normal
Allergic bronchopulmonary aspergillosis	Adults, adolescents, and children (including those with cystic fibrosis)	History of recurrent exacerbations, fever, malaise, expectoration of brownish mucus plugs, and, at times, haemoptysis; anamnestic exposure of atopic individuals to fungal spores or mycelial fragments; blood hypereosinophilia, fleeting pulmonary infiltrates on chest x-ray during respiratory infection episodes
Tuberculosis	Children, adolescents, adults	Haemoptysis, fever, and constitutional symptoms; fever unresponsive to common antibiotics (children)
Non-asthmatic eosinophilic bronchitis	Adults	Chronic cough, minimally productive, no breathlessness or wheeze
α1-anti-trypsin deficiency	Adults, including <40 years	Family history of emphysema; history of prolonged jaundice and poor weight gain in childhood; onset of persistent dyspnoea <40 years of age, especially with a smoking history
Pulmonary embolism	Adults	Sudden onset of dyspnoea or chest pain; might have history of deep vein thrombosis or injury or surgery
Pulmonary hypertension	Adults	Shortness of breath, fatigue, weakness, angina, or syncope, typically initially induced by exertion
Chronic obstructive pulmonary disease	Older adults	Smoking history, older age, cough with sputum, slowly progressive exertional dyspnoea with less day-to-day variability; examination not usually abnormal until airflow limitation is severe
Deconditioning	Older adults	Physiological deconditioning occurs after prolonged illness, bed rest, or a sedentary lifestyle; clinical presentation: lack of exercise and increased heart rate with standing or exercise
Interstitial lung disease	Adults	Adult onset, with or without smoking history, low symptom variability, progressive dyspnoea; wheezing is uncommon; fine crepitations might be heard
Heart diseases, including congestive cardiac failure	More common in older adults	Signs of congestion (clinical and radiological), history of cardiac events; frequent smoking history, dyspnoea on lying flat, peripheral oedema
Lung cancer	Adults, usually older	Cough, dyspnoea, and haemoptysis are the most common patient-reported symptoms in a primary care setting at onset; wheeze is less common; focal signs might be observed on physical examination
Medication-related cough	Adults, usually older	Temporal relationship of cough with initiation of medications such as angiotensin-converting enzyme inhibitors (but onset might be delayed)

Many conditions that should be considered in the differential diagnosis of asthma can also occur as comorbidities in conjunction with asthma, and contribute to respiratory symptoms or impaired quality of life. For information on investigation and treatment of comorbidities, as well as additional differential diagnoses for severe asthma, see appendix.

Table 1: **Differential diagnoses and comorbidities by main age group and disease**

and smoking.[31] Children with more severe asthma might have persistent airflow limitation in adulthood or accelerated decline in lung function.[32]

Non-allergic asthma can present at any age, including during viral respiratory infections. In children, non-allergic asthma is more likely to resolve in adolescence, particularly among boys, but in adults it is more common among women, especially with obesity.[5,33]

Exercise-induced bronchoconstriction might be the only symptom of asthma, particularly with high-intensity

aerobic exercise or exposure to cold dry air or chlorinated swimming pools.[34] Previously, when airway inflammation was considered an obligatory feature of asthma, isolated exercise-induced bronchoconstriction was distinguished from asthma. However, its variable symptoms and variable airflow limitation are compatible with the current definition of asthma itself.

Late-onset asthma variously refers to onset as early as 12 years of age or as late as over 65 years,[35] and is often underdiagnosed. Late-onset asthma is often non-atopic, more severe, and associated with a faster decline in lung function, particularly in patients with a smoking history.[35] Lung function is often lower at diagnosis than in early-onset asthma, suggesting more accelerated disease or prolonged asymptomatic periods. Adult-onset phenotypes include obese female preponderant asthma with persistent airflow limitation, non-atopic eosinophilic-predominant asthma with persistent airflow limitation, mild atopic asthma, and asthma in smokers.[35]

Occupational asthma (adults) is induced by occupational exposure to allergens or irritants, and is sometimes preceded by rhinitis. This form of asthma accounts for 5–20% of adult-onset asthma[36] and is often missed. Early diagnosis is essential, as ongoing exposure might cause persistent disease.[36]

Cough-variant asthma is cough with airway hyperresponsiveness, but in adults, isolated cough is more commonly due to non-asthma conditions, such as gastro-oesophageal reflux, upper airway dysfunction, upper airway cough syndrome (post-nasal drip), or eosinophilic bronchitis.[37]

For some patients, asthma initially presents with acute wheezing during respiratory infection. Viral respiratory infection is a common trigger of childhood wheeze, and exacerbations often increase in periods with high exposure to respiratory viruses, including in early autumn. For some patients with allergic rhinitis, their first asthma presentation is acutely during a thunderstorm asthma epidemic—such events are associated with high amounts of respirable allergen particles.[38] Acute presentation might also follow initiation of oral or intraocular β blockers.[39] Some patients might initially present with severe bronchospasm after taking aspirin or non-steroidal anti-inflammatory drugs. Aspirin-exacerbated respiratory disease is more common in severe asthma (15% in people with severe asthma *vs* 7% in the general population)[40] and is typically preceded by rhinitis and nasal polyposis, but is rare in children.[41]

Diagnosis of asthma

No gold standard exists for diagnosis of asthma. Diagnosis is probability-based, and considers symptoms and variable expiratory airflow limitation. Asthma is heterogeneous, and for some patients, one or both of these features might not be found.

Many features can increase or decrease the probability that symptoms are due to asthma (appendix). In children, accurate assessment of symptoms and rescue β_2 agonist use can be difficult, because most information is given by the parents, who are not always with their child and therefore might be unaware of important details. Engaging in play is important for a child's normal social and physical development, but physical activity is a substantial trigger for asthma symptoms, so children often abstain from strenuous play or exercise to avoid symptoms. Many parents and health-care personnel are unaware of this play avoidance, so a careful review of the child's daily activities, including their willingness to play and participate in sports, is essential, particularly when parents report irritability, tiredness, and mood changes as the child's main problems.

Variable expiratory airflow limitation is defined as variation that is outside the normal range for healthy individuals and is associated with a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than predicted based on age, sex, height, and race. Variable expiratory airflow can be investigated in the following ways. First, so-called bronchodilator reversibility—an increase in FEV_1 of more than 12% and greater than 200 mL (children >12% predicted) 10–15 min after administration of a rapid-acting β_2 agonist indicates variation outside the normal range. A negative test does not rule out asthma. Second, a bronchial provocation test—in children, an exercise challenge is the most commonly used provocation test. Exercise challenges are difficult to do correctly[42] in general practice, but provided the heart rate is above 180 bpm for the last 3 min of an 8-min test, most children with exercise-induced asthma symptoms will have a positive test. However, a negative test does not rule out asthma. The criteria for a positive exercise challenge are debated.[43] The 2017 Global Initiative for Asthma (GINA)[44] suggests a decrease in FEV_1 of more than 10% of the predicted value and greater than 200 mL in adults, or more than 12% of predicted in children. In adults and children, the criterion with direct challenge drugs (methacholine and histamine) is a decrease in FEV_1 of at least 20% or at least 15% for indirect challenge drugs (hypertonic saline, eucapnic hyperventilation, and mannitol), but these tests are less commonly used in children. Correct performance of any challenge test is essential, including confirmation that the FEV_1 to FVC ratio has also decreased, to avoid false positives (eg, variable inspiration or upper airway dysfunction). In addition, variable exploratory airflow can be investigated by average within-day variability of peak expiratory flow (PEF), expressed as amplitude percent mean, of more than 10% (>13% in children).[44] Less reliable tests, given that week-to-week variability in lung function is 11–12% in adults and children,[45,46] include a difference in FEV_1 of more than 12% and (in adults) greater than 200 mL between visits, or after 4 weeks of anti-inflammatory treatment.

For each test, the greater the variability or the more times variability is seen, the higher the probability of

asthma. Airflow limitation might not always be present, and the greatest chance of documenting it is during or after symptoms. Variable airflow limitation on its own is not sufficient to make an asthma diagnosis, as it might also be found in chronic obstructive pulmonary disease (COPD), and asymptomatic airway hyper-responsiveness can be found in healthy children and adults. Excessive variability might be lost in long-standing asthma in adults, but very rarely in children.[32,47]

Differential diagnosis and comorbidities

Confirmation of an asthma diagnosis requires assessment for alternative diagnoses or comorbidities (table 1, appendix). If underdiagnosed or undertreated, comorbid conditions can influence quality of life and asthma control.[48]

Rhinitis and rhinosinusitis with or without nasal polyposis (and in children rhinoconjunctivitis) are the most frequent asthma comorbidities and are often associated with uncontrolled asthma.[49]

Obesity can cause exertional dyspnoea by reducing the functional residual capacity and expiratory reserve volume. Obesity in adults, particularly women, might be associated with refractory asthma with a less eosinophilic and more neutrophilic sputum profile.[50]

Obstructive sleep apnoea is common among adults with asthma, particularly if severe. In children, tiredness, irritability, and difficulty concentrating are typical of poorly-controlled asthma,[51] but obstructive sleep apnoea should be considered if these symptoms persist despite good adherence to treatment.

Gastro-oesophageal reflux disease is found in 25–80% of adults and children with asthma. Mechanisms include increased acid reflux during exacerbations with hyperinflation, microaspirations triggering neurogenic inflammation, and β_2 agonists reducing lower oesophageal sphincter pressure. In adults, symptomatic (but not asymptomatic) gastro-oesophageal reflux disease (identified by 24-h pH monitoring) impairs quality of life,[52] but evidence in children is scarce.

Asthma–COPD overlap is an interim term for adult patients with functional and clinical features of both asthma and COPD, including persistent airflow limitation.[53] Outcomes (symptoms, quality of life, exacerbations, hospitalisations, and mortality) are worse than with asthma or COPD alone.[54] Prevalence increases with age.[54] Asthma–COPD overlap is more common in smokers, but non-smokers with asthma might have accelerated lung function decline and develop persistent airflow limitation[55] despite a typical asthma pathology profile.[54]

Mental health disorders (eg, anxiety, depression, and panic attacks) are more common in asthma of any severity,[56] and affect quality of life. Anxiety symptoms (hyperventilation, dyspnoea, and cough) can mimic asthma flare-ups. Psychological stress might contribute to poor adherence to treatment, greater airway inflammation, and worse asthma control. Depression and anxiety are commonly seen in children with asthma, and in their families.

In children, asthma is associated with a greater risk of poor health, less daily physical activity, lower fitness, avoidance of social activities, and lower mathematics and reading scores at school,[57] particularly with severe asthma and poor asthma control, although associations with school performance are less consistent. Increased school absenteeism is also well documented, but does not seem to be related to severity or amount of control.

Local side-effects of high-dose inhaled corticosteroids include oral candidiasis (around 5–10% of patients), dysphonia, and xerostomia. In adults, systemic adverse effects—such as increased risk of diabetes and poor glycaemic control, glaucoma, cataract, bruising or purpura, adrenal insufficiency, and osteoporosis—are more likely with systemic corticosteroids or long-term high-dose inhaled corticosteroids.

In children, standard recommended inhaled corticosteroid doses (table 2) are generally not associated with clinically relevant systemic adverse effects. However, use of oral or systemic corticosteroids increases the risk of fracture in a dose-dependent manner. Growth delay might be seen with higher inhaled corticosteroid doses during the first year of treatment, but is not cumulative or progressive; only one study[58] showed an effect on adult height (<0·7%). Poorly controlled asthma also affects height.[59]

Long-term management

Asthma treatment goals in children and adults are to minimise both the symptom burden (day-to-day symptoms, disturbed sleep, and activity limitation) and the risk of adverse asthma outcomes (exacerbations, persistent airflow limitation, and medication side-effects). Together, these two domains constitute asthma control. For many patients, these goals can be achieved with current treatment approaches. Patients' personal goals might differ from these medical goals, so the clinician should ask about the patient's own concerns and priorities.

Assessing asthma

In asthma, unlike many other chronic diseases, there are no objective markers of underlying disease severity. Inflammation is present even in so-called mild intermittent asthma, and severe asthma symptoms and exacerbations continue in some patients despite suppression of inflammation.[60]

Asthma symptom control can be quickly assessed at visits with questionnaires such as the Asthma Control Test (adult or paediatric)[61,62] or the Primary Care Asthma Control Screening tool (adult).[63]

Although uncontrolled symptoms increase exacerbation risk, assessing symptom control is not enough, as several other common factors are substantial risk predictors in adults and children, independent of symptoms.[44,64] These factors include short-acting β_2 agonist overuse,

not receiving inhaled corticosteroids (not prescribed, incorrect inhaler technique, or poor adherence), low lung function (adults), tobacco exposure (active or environmental), allergen exposure (if sensitised), food allergy, upper respiratory viral infections (especially if also exposed to allergen), illicit drug use (adults), psychological and socioeconomic problems, family or school problems (children), comorbidities such as rhinosinusitis or obesity, and sputum or blood eosinophilia (adults). Risk factors and comorbidities should be reviewed at least once per year.

A comprehensive approach to asthma treatment

Asthma treatment involves a personalised approach, which includes self-management education, a written asthma action plan, and inhaler training (for children, this includes parents, caregivers, and teachers), treatment of comorbidities and modifiable risk factors, non-pharmacological treatment[44] (eg, avoidance of tobacco exposure, weight loss, sublingual immunotherapy for certain patients, removal from occupational exposures, avoidance of aspirin and other non-steroidal anti-inflammatory drugs in patients with aspirin-exacerbated respiratory disease, and remediation of mould or damp), and pharmacological treatment, which can be adjusted to find each patient's minimum effective dose.

Adjustment of treatment is based on a cycle of assessment and reassessment of each patient's symptom control, risk factors, comorbidities, side-effects, and patient or parent satisfaction. Shared decision making is associated with improved patient-centred outcomes.[65]

Self-management education includes self-monitoring, a written asthma action plan so the patient (or caregiver) knows how to recognise and respond to worsening asthma, and regular clinical review. Such education is associated with a third to two-thirds reduction in urgent health-care, work or school absences, and night waking.[66,67]

Inhaler training with physical demonstration is essential, as incorrect technique is extremely common and associated with an increased risk of exacerbations.[68] In adults, regularly repeated inhaler training leads to improved asthma control.[69]

Various methods are used to treat concomitant clinical conditions such as allergic rhinitis, obesity, obstructive sleep apnoea, gastro-oesophageal reflux disease, mental disorders, and asthma-COPD overlap (appendix).

Stepwise pharmacological treatment

Recommendations for stepwise pharmacological treatment for adults and children consist of the following. First—ie, step one—as-needed short-acting β_2 agonist for quick relief of symptoms. However, short-acting β_2 agonist does not reduce the risk of flare-ups. Because of a paucity of evidence about long-term safety, GINA recommends that short-acting β_2 agonist-only treatment be restricted to patients who have symptoms less than twice per month, no waking due to asthma in the last month, and no risk factors for exacerbations.[44]

Second—ie, step two—regular low dose inhaled corticosteroids (eg, budesonide 400 µg daily [children 200 µg daily] or fluticasone 200 µg daily [children 100 µg daily]) with as-needed short-acting β_2 agonist. At these doses, inhaled corticosteroids improve symptom control, reduce exercise-induced bronchoconstriction,[43] halve the risk of asthma-related death,[70] reduce the risk of hospitalisation and rehospitalisation,[71] and reduce the decline in lung function in patients with exacerbations.[72] These doses should be considered the standard for most patients with asthma, as most of the benefit is obtained at low doses, which are effective in reducing risk of exacerbations and decline in lung function, even in patients with infrequent symptoms.[73]

However, adherence to inhaled corticosteroids is very poor in adults and children,[74] with average dispensing covering less than 25% of days. This observation is not surprising, as from the patient's perspective short-acting β_2 agonist is familiar, inexpensive, safe, and controls their asthma. However, in adults and children, poor inhaled corticosteroid adherence and over-reliance on short-acting β_2 agonists are associated with increased risk of severe exacerbations and death.[70,71] An option being investigated in adults[75,76] and adolescents[76] is to start treatment with an as-needed combination of rapid-acting β_2 agonists and inhaled corticosteroids, delivered together.[77,78]

Third—ie, step three—if symptoms or exacerbations are not well controlled[44] with low total daily doses of inhaled corticosteroids, common causes such as inhaler technique, poor adherence, comorbidities, and modifiable risk factors should be checked and addressed. If asthma remains uncontrolled, treatment can be stepped up to low-dose combination inhaled corticosteroid combined with long-acting β_2 agonist formulations; some children do better with higher doses of inhaled corticosteroids.[79] Maintenance and reliever therapy, in which a low-dose combination of inhaled corticosteroid and formoterol is used both as regular treatment and for symptom relief, is preferred over conventional maintenance inhaled corticosteroids and long-acting β_2 agonist in adults. Maintenance and reliever therapy with combination low dose inhaled corticosteroid and formoterol substantially reduces severe exacerbations with similar or better symptom control and lower inhaled corticosteroid doses than does maintenance inhaled corticosteroid combined with long-acting β_2 agonist or higher dose inhaled corticosteroid in adults[80,81] and children.[82] In adults, maintenance and reliever therapy is associated with less β_2 agonist overuse than is inhaled corticosteroid combined with long-acting β_2 agonist with as-needed short-acting β_2 agonist.[83] The effectiveness of maintenance and reliever therapy, originally shown with budesonide and formoterol in regulatory studies, has been confirmed[80] in real-life studies with electronic

	Currently recommended	Other options	Novel interventions
Step one	All ages: as-needed inhaled SABA (eg, salbutamol or terbutaline) relieves symptoms and airflow limitation for 4–6 h	All ages: consider adding regular low-dose ICS* for all patients with asthma to reduce symptoms and exercise-induced bronchoconstriction, and reduce risk of serious exacerbations and subsequent decline in lung function	Adults and adolescents: as-needed ICS and rapid-acting bronchodilator (SABA or LABA) combination—four studies in adults and adolescents with as-needed budesonide or formoterol (*vs* ICS plus SABA or SABA alone) are underway, primarily examining the risk of exacerbations; adults: sublingual allergen immunotherapy (in house dust mite-sensitised adults with comorbid allergic rhinitis and FEV_1 >70% predicted), indicated for asthma only if exacerbations persist despite ICS treatment
Step two	All ages: regular low-dose ICS* (with as-needed SABA for symptom relief) minimises symptoms and need for SABA, reduces exercise-induced bronchoconstriction, halves the risk of asthma death and reduces hospitalisations and severe exacerbations, and reduces decline in lung function in patients with exacerbations	Adults and adolescents: regular low-dose ICS and LABA* has similar symptom control and risk reduction to ICS only, higher adherence than with ICS only, higher cost than ICS only, and is not well studied in children; all ages: leukotriene receptor antagonists have similar symptom control to ICS but less exacerbation reduction, increased risk of psychiatric problems in young adults, and are in tablet form rather than an inhaler, which can be cheaper in some countries; all ages: cromones (a class of drugs that prevent and relieve swelling of the airways and build-up of mucus; not recommended because of weak efficacy and need for frequent dosing and burdensome inhaler maintenance); adults: hepatminol (not recommended because of weak efficacy and common side-effects)	Adults and adolescents: as-needed ICS and rapid-acting bronchodilator (SABA or LABA) combination as an alternative to regular daily ICS; studies with as-needed budesonide and formoterol are underway, which are examining symptom control and risk of exacerbations; adults: add-on sublingual allergen immunotherapy (in house dust mite-sensitised patients with allergic rhinitis, if FEV_1 >70% predicted)
Step three†	Adults and adolescents: low-dose ICS and LABA*, as ICS and formoterol maintenance and reliever therapy (preferred), or as maintenance ICS and LABA, with as-needed SABA reduces symptom burden, improves lung function, and reduces exacerbations (greater reduction with MART than with maintenance ICS and LABA or higher dose ICS); children: medium dose ICS* or low-dose ICS and LABA* (ICS and LABA by MART if approved, or by conventional maintenance therapy) has similar or greater reduction in exacerbations with MART than with maintenance ICS and LABA or higher dose ICS	All ages: medium-dose ICS* is less efficacious than low-dose ICS and LABA and has a greater risk of side-effects; adults: separate ICS and LABA inhalers (if no suitable combination available; avoid separate inhalers in children and adolescents),[A1] be alert to potential for selective adherence with LABA, with risk of severe exacerbations; adults: add tiotropium mist inhaler to low-dose ICS* (only in adults) as there is less evidence for exacerbation reduction by adding tiotropium rather than LABA; adults: add-on sublingual allergen immunotherapy (in house dust mite-sensitised patients with allergic rhinitis, if FEV_1 >70% predicted)	All ages: technological interventions to improve adherence, eg, inhaler reminders for missed doses, improve asthma outcomes in adults and children[A2,A3]
Step four†	Adults and adolescents: ICS and MART with more maintenance or reliever doses reduces symptoms and exacerbations; children: preferred option is to refer for expert assessment and advice, rather than stepping up dose	All ages: medium-dose* ICS and LABA with as-needed SABA needs higher doses of ICS than with MART; adults: adding tiotropium (mist inhaler) to low-dose ICS and LABA increases lung function and reduces exacerbations; adults: high-dose ICS and LABA* with as-needed SABA increases risk of side-effects and has little extra benefit; adults: dividing treatment into four daily doses might increase efficacy but reduce adherence; adults: adding leukotriene receptor antagonists or theophylline to medium-high dose ICS* has less benefit than ICS and LABA, but theophylline is not recommended for children	All ages: technological interventions to improve adherence, eg. inhaler reminders for missed doses
Step five†	Refer for further assessment and consideration of add-on therapy	See section on severe asthma	See table 3

Management strategies for patients at all stages are as follows: treat modifiable risk factors and comorbidities, including relevant non-pharmacological strategies, self-monitoring of symptoms or peak expiratory flow (for children, symptoms only), written asthma action plan, personalised to the patient's age and treatment regimen, training in inhaler technique and adherence, and regular medical review. References are listed in the appendix. SABA=short-acting β_2 agonists. ICS=inhaled corticosteroid. LABA=long-acting β_2 agonists. FEV_1=forced expiratory volume in 1 second. MART=maintenance and reliever therapy with combination low dose inhaled corticosteroid and formoterol. *ICS dose categories vary by age group. The categories refer to the range of available formulations and approved daily doses for each drug, not to their efficacy. Low dose for children aged 6–11 years corresponds to a dose of 100–200 µg/day budesonide equivalent, and for adults and adolescents, 200–400 µg/day budesonide equivalent. At the population level, these doses provide 80–90% of the maximum clinical benefit, so they should be considered the standard dose for most patients with asthma. A small proportion of patients whose asthma is not well controlled despite these doses will benefit from stepping up to higher daily doses (children >200–400 µg/day; adults >400–800 µg/day). For the very small proportion of patients with severe uncontrolled asthma despite good adherence and inhaler technique, high doses of ICS (children >400 µg/day; adults >800 µg/day budesonide equivalent) might be needed.[A4] †Before stepping up to the next level check and correct inhaler technique and adherence, check contribution of comorbidities to symptoms, and address modifiable risk factors. When choosing between options, consider individual patient features predicting risk or response to therapy.[A4]

Table 2: **Stepwise asthma treatment for adults, adolescents, and children aged at least 6 years**

monitoring of inhaler use,[83] and with a different molecule (beclometasone and formoterol).[81]

Fourth—ie, step four—if asthma remains uncontrolled, and inhaler technique, adherence, comorbidities, and modifiable risk factors have been addressed, treatment for adults can be stepped up to a medium-dose combination of inhaled corticosteroid and long-acting β_2 agonist. Lower inhaled corticosteroid doses can be used with maintenance and reliever therapy than can with conventional maintenance therapy. Add-on tiotropium is another treatment option for patients older than 12 years.[84] For children, referral to a specialist is recommended at this stage rather than increasing inhaled corticosteroid dose (table 2). Treatment controversies are described in the panel.

Severe asthma

Severe asthma is defined in the European Respiratory Society and American Thoracic Society guidelines for adults and children aged at least 6 years as asthma that

requires treatment with guidelines-suggested medication for GINA steps 4–5[44] for the past year, or systemic corticosteroids for at least 50% of the past year, to prevent it from becoming uncontrolled, or which remains uncontrolled despite therapy.[50] Uncontrolled asthma refers to poor symptom control, frequent severe exacerbations, serious exacerbations, or airflow limitation.[50] Management in dedicated severe asthma centres improves clinical outcomes.[85] Severe asthma initially requires confirmation of diagnosis, reassessment of inhaler technique and adherence, treatment of comorbidities, and identification and removal of environmental or occupational triggers whenever possible. Adherence to therapy in severe disease is suboptimal (<80%) in 65% of patients. Inbuilt electronic inhaler monitoring is likely to improve identification and facilitate management of poor adherence.[86]

Phenotypic heterogeneity is a feature of severe asthma in both adults and children, with multiple clinical phenotypes described,[50,87] including from unsupervised clustering approaches.[88–90] Thus, in severe asthma, the concept of phenotype-specific interventions toward precision medicine is increasingly important, with a need to optimise the balance between safety, efficacy, and cost for each therapeutic option. Literature on the phenotypic response in children with severe asthma is constrained by a paucity of paediatric studies, and at present, no definite individual patient phenotype recommendations are possible.[16,91]

Add-on therapy

Beyond high-dose inhaled corticosteroids and long-acting β_2 agonists,[92] add-on long-acting muscarinic antagonists (for patients aged ≥12 years), leukotriene receptor antagonists, or theophylline (adults) should also be considered before systemic corticosteroids because of more favourable side-effect profiles, although evidence for efficacy of leukotriene receptor antagonists and heptaminol acefyllinate in severe disease is scarce. Long-acting muscarinic antagonists improve lung function and increase time to first exacerbation in severe asthma, particularly in those with airflow limitation.[93] Other add-on therapies (mostly evaluated only in adults) include systemic corticosteroids, immunosuppressants, bronchial thermoplasty, and biologics.[50,94]

No randomised controlled trials of maintenance systemic corticosteroids for severe asthma exist, although the adverse effects of these drugs are well documented.[95] Small randomised studies of intramuscular depot triamcinolone in adults[96,97] and children[94] with severe asthma taking maintenance or frequent oral corticosteroids have shown fewer hospitalisations and emergency department visits, increased lung function, and reduced eosinophilic inflammation;[97] some of this benefit might result from improved treatment adherence. Biomarker-directed therapy is attractive because of the need to consider the risks and benefits of corticosteroid therapy in severe disease. Tailoring inhaled and oral

Panel: Controversies in pharmacological management of asthma

Steps one and two

Should SABA-only treatment be the initial treatment for asthma?

Regular SABA leads to rapid β_2 receptor tolerance, rebound bronchoconstriction, reduced response to SABA,[A5] as well as increased inflammation[A6] and responses to allergen,[A7] and there are no long-term data for safety of SABA-only treatment. Airway inflammation is present even in mild or newly diagnosed asthma. Early initiation of ICS is associated with better long-term asthma outcomes,[A8,A9] and reduced risk of exacerbations even in patients with infrequent symptoms.[A10] We therefore consider that initial treatment for asthma should include ICS, except for patients with very infrequent symptoms and no risk factors for exacerbations.[A4] However, patients are poorly adherent to regular ICS. Instead, treatment could start with as-needed ICS and rapid-acting bronchodilators (SABA or LABA), to reduce the risk of exacerbations, and avoid patients' developing reliance on SABA.[A11,A12] To this end, studies of as-needed budesonide and formoterol are underway in adults and adolescents.[A13,A14] Such studies are also needed in children with asthma, given the opportunity to prevent establishment of long-term habits that encourage reliance on SABA.

What criteria should be used for commencing ICS? Which patients will benefit?

Regular low-dose ICS halves the risk of serious exacerbations[A10] and the risk of asthma-related death,[A15] so the reverse questions are more appropriate: when is it safe to not give ICS, and what criteria should be used for withholding ICS? Existing short-term studies are not sufficient. Relevant predictive data about biomarkers could be obtained from studies in mild asthma.[A13]

Should patients with suspected asthma be started on regular ICS, as recommended in British Thoracic Society/Scottish Intercollegiate Guidelines Network 2016?[A16]

Although this approach could reduce delays in starting ICS, it could lead to overtreatment, as it is much harder to confirm an asthma diagnosis once ICS treatment has been started.

How should purely seasonal asthma be treated (in patients with no interval symptoms)?

Evidence is needed; the consensus recommendation[A4] is to immediately start ICS when symptoms commence and continue until 4 weeks after the pollen season ends. However, in allergen challenge studies, 1–2 weeks of ICS protects against allergen challenge and subsequent remodelling, with greater benefit from budesonide and formoterol.[A17] Pragmatic community-based studies are needed to identify the optimum period of ICS or ICS and LABA pretreatment.

What criteria should be used to determine when a patient should be considered for step up in treatment?

Conventional clinical criteria, supported by the results of many step-up randomised controlled trials and rigorously developed symptom control tools, include symptom frequency and reliever use at least 3 days per week and waking at night due to asthma at least 1 night per month. For patients prescribed maintenance and reliever therapy, the adjustment of ICS and formoterol dose is more pragmatic, without requiring specific control criteria. For moderate and severe asthma, sputum-guided adjustment results in better outcomes than does symptom-based adjustment.

Should there still be a black box warning for combination ICS and LABA therapy, given that the risk appears confined to patients using LABA without ICS?[A3,A18,A19]*

Published evidence from two very large safety studies in adults and adolescents[A18,A19] and one in children[A20] suggests that a black box warning is not necessary for combination ICS and LABA.

Step three

What is the preferred step-up option for children aged 6–12 years?

Some guidelines recommend moderate dose ICS, and others recommend ICS and LABA. In children, unlike adults, ICS and LABA does not reduce the risk of exacerbations compared with ICS alone,[A20] and increases in ICS dose have modest benefit. One large study found that

(Panel continues on next page)

(Continued from previous page)
children with well controlled asthma receiving ICS and LABA had a 25% lower severe asthma exacerbation rate compared with those switched to ICS alone.[A20,A21] A small crossover study in children with good adherence favoured ICS and LABA on a composite[A20] outcome that included lung function.[A22] Large pragmatic randomised controlled trials are needed to assess which children are most likely to benefit from these options.

Can we identify patients who should be fast tracked to specialist consultation, rather than going through stepwise increases in treatment?
Very limited evidence is available to date; in one study, smoking status was the only predictor of progression to severity.[A23] We recommend that baseline data should be systematically collected in patients with newly diagnosed asthma, to identify predictors of severity progression and risk of severe acute events.

Should any patients be treated with high-dose ICS (with or without LABA)?
At the group level, most benefit is obtained with low-dose ICS, with little extra benefit and a substantial increase in side-effects at higher doses.[A24] Responsiveness to ICS varies between individual patients; some might need higher ICS doses, but step up of ICS dose should only be considered after inhaler technique and adherence have been checked and corrected. Maintenance and reliever therapy studies show exacerbation risk is reduced by increasing both ICS and formoterol dose,[A25] which is generally achieved at low or medium daily doses.

Step four

Do small particle ICS achieve better outcomes than conventional ICS? In which patients?
Theoretical advantages exist with small particle formulations, including in severe asthma.[A26] However, there are few high-quality studies in which confounders have been addressed. Evidence from real-life studies is not conclusive without adjustment for clustering by prescriber.

Other

How should patients with features of both asthma and COPD (asthma-COPD overlap) be treated?
Conventional guidelines provide conflicting safety advice—asthma guidelines say that, for safety, asthma should never be treated with LABA alone without ICS, and COPD guidelines say that treatment of COPD should start with LABA alone. Patients with asthma-COPD overlap have been excluded from regulatory pharmacotherapy studies, so their treatment is an evidence-free area.[A27] We agree with the advice from the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease[A4] to treat such patients with at least low-dose ICS for safety and with bronchodilators for symptom control. Triple therapy with ICS, LABA, and LAMA should be considered if symptoms or exacerbation remain troublesome after treatment of modifiable factors. Intervention studies in this population are urgently needed.

Which patients with asthma should receive allergen immunotherapy?
Previously, there have been problems with study quality, and safety concerns about subcutaneous immunotherapy. Sublingual immunotherapy is now recommended as an add-on therapy for asthma in adults and adolescents with house dust mite allergy, allergic rhinitis, and exacerbations despite low-to-moderate dose ICS, with forced expiratory volume in 1 second more than 70% predicted.[A28,A29] Further studies are needed in broader populations with asthma, including children and adolescents, and with other allergens. Cost of treatment should be considered.

What is the role of allergen avoidance in allergic asthma?
For sensitised patients, single strategies for indoor allergens are not beneficial, but there is some evidence of benefit in children with avoidance strategies directed at house dust mites and pets. Correction of dampness and mould in homes reduces asthma symptoms and medication use in adults.[A30]

References are listed in the appendix. SABA=short-acting β_2 agonists. ICS=inhaled corticosteroids. LABA=long-acting β_2 agonists. COPD=chronic obstructive pulmonary disease. *HKR abstained from comment on this question because of her role as Chair of the Joint Data Monitoring Committee for the US Food and Drug Administration LABA safety studies.

corticosteroid dose specifically to control sputum eosinophilia in asthma showed reductions in exacerbation rates[98] and is included in guidelines for adults with severe asthma.[50]

Immunosuppressant therapies, such as ciclosporin and methotrexate, are not recommended for severe asthma, as these drugs have minor corticosteroid-sparing effects, without reductions in severe exacerbations, and cause substantial adverse effects.[50]

Omalizumab, an anti-IgE, was the first monoclonal antibody therapy for severe asthma. This drug is licensed for moderate-to-severe allergic asthma in adults and children aged at least 6 years with IgE greater than 30 IU/L. Omalizumab reduces exacerbations and hospital admissions in adults and children,[99] with response predicted by elevated high type 2 immunity biomarkers rather than IgE concentration,[100] and reduces virus-associated exacerbations.[101,102]

Mepolizumab and reslizumab are licensed neutralising antibodies that target interleukin-5. Mepolizumab consistently reduced severe asthma exacerbations by about 50%[103] (table 3), related to patients' exacerbation history and baseline blood eosinophil count,[104] with a small improvement in lung function and health status. In oral corticosteroid-dependent patients, mepolizumab reduced the need for oral corticosteroid therapy by 50% versus placebo, without loss of asthma control.[105] Phase 3 trials of intravenous reslizumab were restricted to patients with a high blood eosinophil count, and these patients showed similar reductions in exacerbation frequency, with modest effects on lung function and asthma control[106–108] (table 3). The findings from these studies support blood eosinophil count as a simple and reliable biomarker of response to anti-interleukin-5 biological therapy. However, considerable debate exists over the most appropriate cutoff point. Neither mepolizumab nor reslizumab are licensed for children. Mepolizumab is licensed for adolescents (aged 12–18 years), although very few have been included in randomised controlled trials.

Non-pharmacological strategies, such as add-on allergen immunotherapy (adults) and nocturnal temperature-controlled laminar flow (adults and children), show some benefits for reducing symptoms and corticosteroid use in mild-to-moderate atopic asthma. Results of studies[109,110] examining the effects of non-pharmacological strategies on exacerbation frequency in severe disease are awaited.

Bronchial thermoplasty is a staged bronchoscopic procedure for adults. Thermal energy is applied to conducting airways on three occasions 3–4 weeks apart. In the only sham-controlled study[111] of bronchial thermoplasty in severe asthma, respiratory adverse events during the treatment period were more likely with thermoplasty than with the sham procedure. In the post-treatment period, there was a large sham effect for quality of life, but thermoplasty-treated patients experienced fewer asthma exacerbations and emergency

	Intervention and duration	Patients	Results	
			Primary outcomes	Secondary outcomes
Hanania et al 2016; LAVOLTA I and II, phase 3[A31]	Lebrikizumab; anti-interleukin-13; 52 weeks, n=1081 (LAVOLTA I), n=1067 (LAVOLTA II)	Adults (18–75 years); prebronchodilator FEV_1 40–80%; bronchodilator response >12%; background therapy (500–2000 µg/day fluticasone propionate or equivalent) for 6 months and an additional controller medication	Exacerbation rate in periostin^{high} or eosinophil^{high}: significant decrease in exacerbation by about 50% (LAVOLTA I); non-significant change in exacerbation (LAVOLTA II)	Significant increase in FEV_1 (by around 100 mL); non-significant change in ACQ, non-significant change in AQLQ
Brightling et al 2015; phase 2b[A32]	Tralokinumab; anti-interleukin-13; 52 weeks, n=452	Adults (18–75 years); prebronchodilator FEV_1 40–80%; background therapy (>500 µg/day fluticasone propionate or equivalent) for >1 month and LABA; ≥2 but ≤6 exacerbations in the previous year	Exacerbation rate: non-significant change in exacerbation rate	Significant increase in FEV_1 (by about 130 mL); non-significant change in ACQ; non-significant AQLQ
Wenzel et al 2016; phase 2b[A33]	Dupilumab; anti-interleukin-Rα; 24 weeks, n=769	Adults (aged ≥18 years); prebronchodilator FEV_1 40–80%; bronchodilator response >12%; background therapy (≥500 µg/day fluticasone propionate or equivalent) for >1 month and LABA; ≥1 exacerbation in last year; ACQ ≥1·5	FEV_1 at week 12 in eosinophil^{high}: significant increase in FEV_1 (by around 210 mL)	Significant decrease in exacerbation rate by 60–80%; significant decrease in ACQ (by about 0·5), significant increase in AQLQ (by about 0·6)
Bel et al 2014; SIRIUS phase 3[A34]	Mepolizumab; anti-interleukin-5; 20 weeks, n=135	Age range 16–74 years; background therapy (5–35 mg/day of prednisone or equivalent) for >6 months; blood eosinophil count ≥150 cells per µL at screening or ≥300 cells per µL in the previous year	Oral corticosteroid use: significant decrease in oral corticosteroid use (by about 50%)	Significant decrease in exacerbation rate by around 32%; significant decrease in ACQ (by about 0·52)
Ortega et al 2014; MENSA phase 3[A35]	Mepolizumab; anti-interleukin-5; 32 weeks, n=576	Adults and children (aged ≥12 years); background therapy (≥880 µg/day fluticasone propionate or equivalent) for >3 months and an additional controller; ≥2 exacerbations in the previous year; blood eosinophil count ≥150 cells per µL at screening or ≥300 cells per µL in the last year	Exacerbation rate: significant decrease in exacerbation rate by around 50%	Significant increase in FEV_1 (by 100 mL); significant decrease in ACQ (by around 0·43); significant decrease in SGRQ (by around 7)
Castro et al 2015; phase 3[A36]	Reslizumab; anti-interleukin-5; 52 weeks, n=953 (study 1 n=489, study 2 n=464)	Adults and children (12–75 years); bronchodilator response >12%; ACQ ≥1·5; background therapy (≥440 µg/day fluticasone propionate or equivalent) for >1 month and an additional controller; ≥1 exacerbation in last year; blood eosinophil count ≥400 cells per µL	Exacerbation rate (eosinophil^{high} only recruited >400 cells per µL): significant decrease in exacerbation rate by 60–80%	Significant increase in FEV_1 (by 100 mL); significant decrease in ACQ (by about 0·25); significant increase in AQLQ (by about 0·23)
Corren et al 2016[A37]	Reslizumab; anti-interleukin-5; 16 weeks, n=492	Adults and children (12–65 years); bronchodilator response >12%; background therapy (≥440 µg/day fluticasone propionate or equivalent) for >1 month and an additional controller; ACQ ≥1·5	FEV_1 at week 16 non-significant change	Eosinophil^{high}: significant increase in FEV_1 (by 270 mL); significant decrease in ACQ (by 0·49); no benefits in eosinophil^{low} group
Bjermer et al 2016[A38]	Reslizumab; anti-interleukin-5; 16 weeks, n=315	Adults and children (12–75 years); background therapy (≥440 µg/day fluticasone propionate or equivalent) for >1 month and an additional controller; blood eosinophil count ≥400 cells per µL; ACQ ≥1·5	FEV_1 at week 16 in eosinophil^{high}: significant increase in FEV_1 (by about 140 mL)	Significant decrease in ACQ (by around 0·3); significant increase in AQLQ (by around 0·3)
Bleecker et al 2016; SIROCCO phase 3[A39]	Benralizumab; anti-interleukin-5R; 48 weeks, n=1205	Adults and children (12–75 years); prebronchodilator FEV_1 <80% (adults), <90% (children); bronchodilator response >12%; background therapy ICS plus LABA for ≥1 year before enrolment (high-dose ICS in adults and moderate-to-high in children) and another controller; ≥2 exacerbations in the previous year; ACQ ≥1·5	Exacerbation rate in eosinophil^{high}: significant decrease in exacerbation rate (by around 50%)	Significant increase in FEV_1 (by 110 mL); significant decrease in ACQ (by about 0·25); significant increase in AQLQ (by around 0·25)
FitzGerald et al 2016; CALIMA phase 3[A40]	Benralizumab; anti-interleukin-5R; 56 weeks, n=306	As per SIROCCO	Exacerbation rate in eosinophil^{high}: significant decrease in exacerbation rate (by around 30%)	Significant increase in FEV_1 (by about 120 mL); significant decrease in ACQ (by around 0·2); significant increase in AQLQ (by 0·2)
Nair et al 2017; ZONDA phase 3[A41]	Benralizumab; anti-interleukin-5R; 28 weeks, n=220	Adults >18 years; background therapy (7–40 mg/day of prednisone or equivalent) for >6 months in addition to ICS and LABA; blood eosinophil count ≥150 cells per µL at screening	Oral corticosteroid use: significant decrease in oral corticosteroid use (by around 75%)	Significant decrease in exacerbation rate by about 60%
Gonem et al 2016; phase 2a[A42]	Fevipiprant; anti-DP2; 12 weeks, n=61	Adults (≥18 years); background therapy (low-dose to high-dose ICS); sputum eosinophil count ≥2% at screening; ACQ ≥1·5 or ≥1 exacerbation in last year	Significant decrease in sputum eosinophils	Significant increase in FEV_1 (by 160 mL); significant decrease in ACQ (by 0·56); significant increase in AQLQ (by 0·59)
Corren et al 2017; phase 2b[A43]	Tezepelumab; anti-TSLP; 52 weeks, n=584	Adults (≥18 years); background therapy ICS (moderate-to-high dose) plus LABA; bronchodilator response >12%; ACQ ≥1·5; ≥2 exacerbations in last year	Significant decrease in exacerbation rate (by around 65%)	Significant increase in FEV_1 (by 130 mL); significant decrease in ACQ (by 0·3); significant increase in AQLQ (by 0·4)
Castro et al 2010; phase 3[A44]	Thermoplasty; 52 weeks three-stage procedure, n=288	Adults (18–65 years); prebronchodilator FEV_1 ≥60%; bronchodilator response >12%; background therapy (≥500 µg/day fluticasone propionate or equivalent) and an additional controller; AQLQ <6·26	Significant increase in AQLQ (by 0·19)	Significant decrease in exacerbation rate (by around 30%)

The table shows results since 2010 of phase 3 trials (or latest phase 2 clinical trials for ongoing phase 3 programmes). References are listed in the appendix. FEV_1=forced expiratory volume in 1 second. ACQ=asthma control questionnaire. AQLQ=asthma-quality-of-life-questionnaire. LABA=long-acting β_2 agonist. SGRQ=St George's chronic respiratory questionnaire. ICS=inhaled corticosteroid.

Table 3: **New treatments developed for moderate-to-severe asthma**

department visits.[111] The reduction in exacerbations was maintained at 5 years,[112] but no long-term lung function comparison has been performed. Guidelines recommend that bronchial thermoplasty should only be undertaken within research trials or national registries to enable further evaluation of efficacy and safety.

Macrolide antibiotics reduce exacerbation frequency in bronchiectasis and COPD by either their antibiotic or anti-inflammatory effects. In severe asthma, the role of macrolide antibiotics is uncertain.[50] Early evidence in a small study[113] suggested benefits of macrolide antibiotics might be restricted to those with non-eosinophilic inflammation. However, in a large randomised placebo-controlled study[114] of 420 adults with persistent uncontrolled moderate-to-severe asthma, oral azithromycin decreased the frequency of moderate and severe asthma exacerbations. People with eosinophilic inflammation had a marginally greater benefit than those with non-eosinophilic inflammation, although the greatest benefit was in those with positive bacterial culture.[114] Use of long-term macrolides is not recommended at present and use should be cognisant of potential implications for antibiotic stewardship to minimise widespread antibiotic resistance.

Although antifungal therapy is recommended for allergic bronchopulmonary aspergillosis in severe asthma,[50] it has not shown a clear benefit in the absence of allergic bronchopulmonary aspergillosis.[115]

Emerging therapies

Emerging therapies targeting type 2-mediated immunity have shown the greatest promise (table 3). Benralizumab targets the α chain of the interleukin-5 receptor and has shown reductions in exacerbation frequency and improvements in lung function and asthma control similar to those of interleukin-5 neutralising antibodies (table 3).[116,117] Anti-interleukin-13 neutralising antibody lebrikizumab showed initial promise in phase 2 studies, but results for exacerbations in phase 3 studies were inconsistent.[118] Tralokinumab, another interleukin-13 neutralising antibody, also did not show a reduction in exacerbations.[119] The disappointing response to anti-interleukin-13 thus far might be a consequence of overlapping effects of interleukin-4 and interleukin-13. Dupilumab, a monoclonal antibody that targets the α subunit of the interleukin-4 receptor, and therefore blocks both the interleukin-4 and interleukin-13 pathways, has shown striking benefits in lung function, symptom and exacerbation reduction.[120] In a single-centre study[121] of moderate-to-severe asthma, fevipiprant, an anti-prostaglandin D2 type 2 receptor, reduced sputum and tissue eosinophils and epithelial damage, and improved lung function, symptom control, and health status. Other targets upstream of type 2-mediated immunity, such as interleukin-33 and thymic stromal lymphopoietin, might have broader effects. Indeed, tezepelumab anti-thymic stromal lymphopoietin reduced exacerbation frequency and improved lung function in patients with or without an elevated blood eosinophil count.[122,123]

Targeting beyond type 2 immunity has been disappointing. Early studies targeting TNF α showed benefits which were not supported by later phase trials and were overshadowed by safety concerns related to increased risk of infection and cancer.[124] Anti-C-X-C motif chemokine receptor 2 had no effect on asthma exacerbations nor symptoms[125] and early studies of interleukin-17 have not shown benefits. Findings from other programmes targeting interleukin-17 and interleukin-23 are awaited. None of these new drugs have yet been studied in children younger than 12 years.

Within the next 3 years there might be three or four classes of type 2 directed therapy, including biologics and small molecule therapies. A need exists to identify the most appropriate patients for these treatments and to better understand how to measure response as treatments move more towards precision medicine for severe asthma.[126]

Asthma exacerbations

Acute or subacute episodes of increased symptoms—known as exacerbations, asthma attacks, or flare-ups—punctuate the natural course of asthma and require a change in treatment. Exacerbations are characterised by progressively increasing shortness of breath, cough, wheezing or chest tightness, and decreasing lung function. Onset is usually rapid in children, but can develop over a week or more in adults. Exacerbations account for a substantial portion of asthma-related expenditure; they affect quality of life[127] and can sometimes be fatal, even in apparently mild asthma.[128] Overall, deaths due to asthma are decreasing,[129] possibly because of increased use of asthma control medications.

Clinical assessment of exacerbations

Clinical assessment of exacerbations requires immediate recognition of the potential risk of asthma-related death if the patient is drowsy, confused, or has a silent chest (ie, no wheezing on auscultation and attenuated respiratory sounds). Risk factors for asthma-related death include a history of emergency department visits or hospitalisations, particularly with admission to an intensive care unit or need for mechanical ventilation.[130] Overuse of short-acting β_2 agonists, absence of (or poor adherence to) inhaled corticosteroid maintenance treatment, withdrawal of systemic corticosteroids, psychiatric disorders, food allergy, and illicit drug use are additional major risk factors.[130] Children from dysfunctional family settings are also at greater risk of asthma-related death.[131]

Initial assessment of exacerbations includes differential diagnosis for acute breathlessness or wheeze in an adult or child, even if they have a known asthma diagnosis. Differential diagnosis includes acute bronchitis, epiglottitis, vocal cord dysfunction (adults and adolescents),

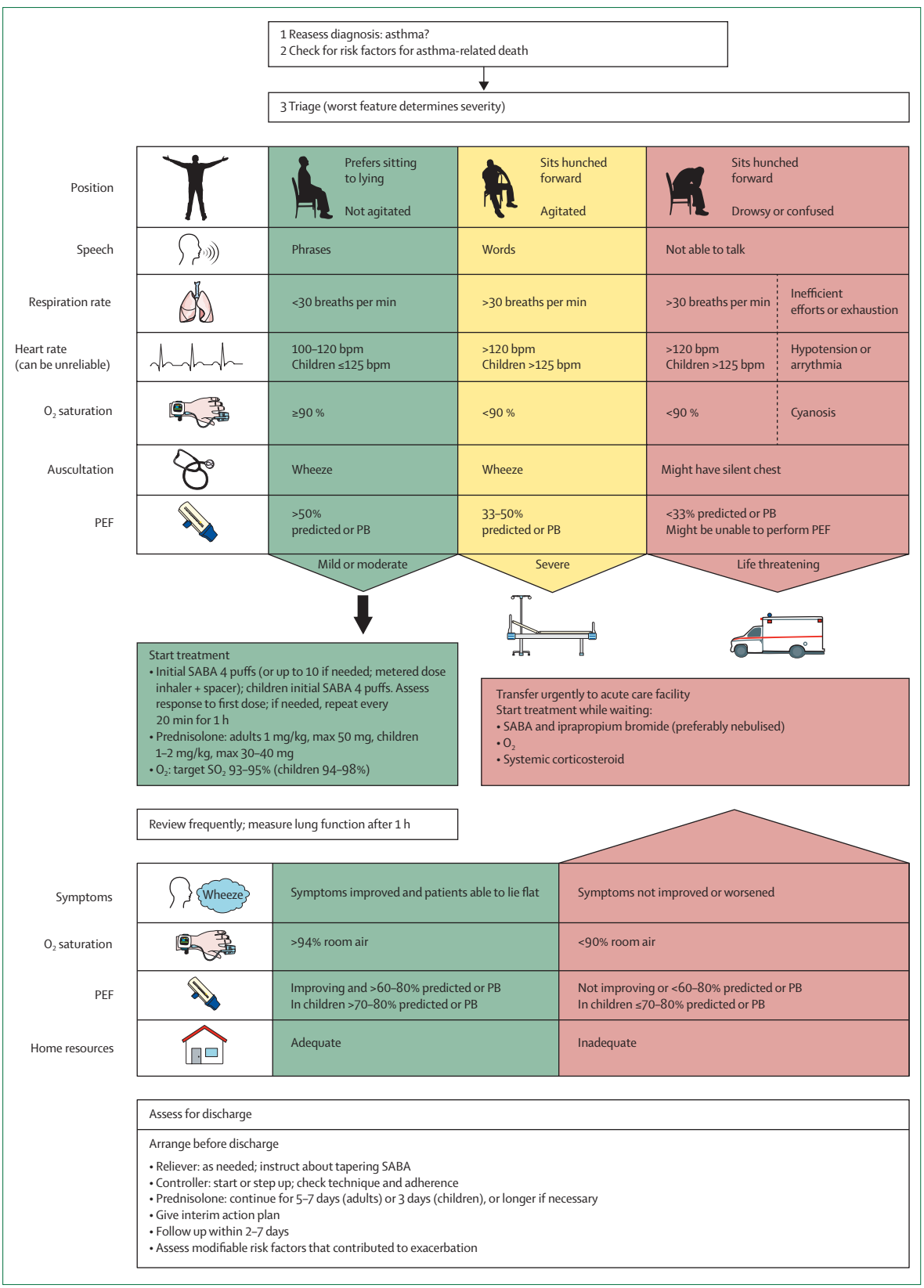

Figure 3: **Management of asthma exacerbation in primary care (adults and children older than 5 years)**
See appendix for additional description of treatment doses and management of asthma exacerbations in acute care facilities. PEF=peak expiratory flow. PB=personal best. SABA=short-acting β_2 agonist.

foreign body inhalation, tracheal obstruction, hyperventilation syndrome, and, in adults, pulmonary oedema, pneumonia, pulmonary embolism, and exacerbations of other chronic respiratory conditions, such as COPD and bronchiectasis.[44,130,132]

In acute asthma, if measurement of lung function (FEV_1 or PEF) is obtainable this can provide reliable information about the severity of the exacerbation and, later, about the patient's response to therapy. Standard blood tests, chest x-ray, and arterial blood gas analyses are not routinely necessary, but arterial blood gases should be performed in patients with any sign of a severe exacerbation or if peripheral capillary oxygen saturation is 90–92% or lower.

Symptoms of severe exacerbation include chest tightness, cough, sensation of air hunger, inability to speak because of laboured breathing, inability to lie down, and fatigue (figure 3, appendix). Signs of severe exacerbation include use of accessory muscles of respiration, tachypnoea, tachycardia, wheezing (or disappearance of wheezing as a sign of severe airflow limitation), diaphoresis, cyanosis, obtundation, and altered mental status, which indicate the requirement for immediate emergency care. The most common abnormalities in arterial blood gases during severe exacerbations are hypoxaemia and hypocapnia. A normal concentration of partial pressure of carbon dioxide is a danger sign, indicating decreasing alveolar ventilation and potential development of respiratory failure.

For examples of written **asthma action plans for adults and children** see https://www.nationalasthma.org.au/health-professionals/asthma-action-plans and https://www.asthma.org.uk/advice/manage-your-asthma/action-plan/#

In children, the cause, duration, and intensity of the exacerbation, as well as the child's maintenance treatment and the history of any previous exacerbations, should be explored and assessed. Lung function measurement might add information about the severity of the exacerbation and the response to treatment; however, many children are not familiar with lung function measurements, so the severity of exacerbations often has to be based on clinical assessment. These assessments include vital signs (pulse and respiratory rates) and use of accessory respiratory muscles, pallor or cyanosis, degree of fatigue, and ability to speak in complete sentences.

Pathology and pathophysiology

The pathology of exacerbations has not been adequately investigated, even in adults, because of the difficulty in performing invasive manoeuvres in symptomatic patients. Non-invasive assessments during exacerbation have revealed sputum eosinophilia, particularly in subjects with eosinophilic inflammation in a stable state; however, many exacerbations have low or moderate sputum eosinophils.[133]

Studies of fatal or near fatal asthma in adults and children show pronounced airway wall thickening (including smooth muscle and mucus glands), oedema, lumen occlusion by mucus plugs, and predominantly eosinophilic infiltration.[134,135] Fast onset deaths (<3 h) are associated with more mast cell degranulation and less eosinophilic inflammation than are slower onset deaths.[136] Airway obstruction is the primary pathophysiological consequence of these processes, leading to pulmonary hyperinflation and disordered gas exchange.

In adults and children, about 80% of asthma exacerbations are caused by respiratory virus infections, most commonly rhinovirus, although all respiratory viruses can also have this effect (eg, during influenza outbreaks).[137,138]

Multiple factors are commonly involved in triggering asthma exacerbations (infections, allergens or atopy, pollution, environment, and comorbidities) and are related to the immune responses of asthmatic patients (appendix).

Exacerbation treatment and management

Written personalised asthma action plans show patients how to recognise and respond to worsening asthma with appropriate short-term changes to their treatment, and how and when to seek medical care.[44,139] Self-management education that includes a written personalised action plan, self-monitoring of symptoms or PEF, and regular medical review, effectively reduces use of health-care resources, including emergency department visits, hospital admissions, and unscheduled consultations, and improves asthma control.[67]

An effective written personalised asthma action plan[44,132,140] should include specific advice about recognising worsening symptoms or a decrease in PEF (if available) and sequential actions to take if asthma worsens. Patients should be instructed to increase the use of reliever and controller medications. Oral corticosteroids should be started promptly if needed, and medical care should be sought if symptoms fail to respond to treatment.

Once medical care is sought, management will differ depending on the clinical presentation, context of evaluation, and response to treatment. Less urgent conditions can be managed in a primary care setting with modification of the patient's maintenance and reliever medications and with a short course of oral steroids. More serious conditions need to be managed in acute care facilities or a respiratory intensive care unit for close monitoring of patients' parameters and for the possibility of requirement of mechanical ventilation (appendix). Various controversies exist regarding asthma exacerbtions and treatment (appendix).

A randomised controlled trial[141] assessed the efficacy of 2 weeks of inhaled interferon β after onset of cold symptoms in adults with asthma with a history of cold-associated exacerbations. Acute augmentation of interferon β decreased virus-induced deterioration of asthma in the subgroup with more severe disease. Inhaled interferon β activated local antiviral defences and attenuated proinflammatory responses.[141]

A single dose of benralizumab (interleukin-5 receptor antibody) given after patients were discharged from the emergency department reduced asthma exacerbations requiring hospitalisation in the subsequent 12 weeks.[142]

Contributors

All authors participated in the development and review of the manuscript and gave approval to submit for publication.

Declaration of interests

AP reports grants, personal fees, and travel expenses reimbursement from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Takeda, Mundipharma, and TEVA; personal fees and travel expenses reimbursement from Menarini, Novartis, and Zambon; and grants from Sanofi. HKR reports grants, personal fees and nonfinancial support from GlaxoSmithKline; grants and personal fees from AstraZeneca; and personal fees from Merck, Novartis, Teva, Mundipharma, and Boehringer Ingelheim. HKR is Chair of Global Initiative for Asthma Scientific Committee. CB has received grants and consultancies paid to his institution from GlaxoSmithKline, AstraZeneca/MedImmune, Roche/Genentech, Boehringer Ingelheim, Chiesi, Novartis, Pfizer, Prep, Vectura, Teva, Sanofi/Regeneron, Gilead, and Mologic. SP reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, and Sandoz.

Acknowledgments

We acknowledge Federico Bellini, Irene Marchi, Luca Morandi and Alessia Pauletti (University of Ferrara, Ferrara, Italy) for revising the manuscript and conceiving some of the original figures, and Ruth Saunders and Fay Hollins (Leicester National Institute for Health Research Biomedical Research Centre, Leicester) who helped with the immunopathology figure. We also thank Mary McKenney (Menominee, MI, USA) and Elisa Veratelli (University of Ferrara, Ferrara, Italy) for scientific editorial assistance in the preparation of the manuscript.

References

1 Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2163–96.

2 To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 2012; **12:** 204.

3 Asher MI, Montefort S, Björksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368:** 733–43.

4 Cabieses B, Uphoff E, Pinart M, Antó JM, Wright J. A systematic review on the development of asthma and allergic diseases in relation to international immigration: the leading role of the environment confirmed. *PLoS One* 2014; **9:** e105347.

5 Leynaert B, Sunyer J, Garcia-Esteban R, et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. *Thorax* 2012; **67:** 625–31.

6 Andersson M, Hedman L, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Remission and persistence of asthma followed from 7 to 19 years of age. *Pediatrics* 2013; **132:** e435–42.

7 Raghavan D, Jain R. Increasing awareness of sex differences in airway diseases. *Respirology* 2016; **21:** 449–59.

8 Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet* 2014; **383:** 1593–604.

9 Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010; **363:** 1211–21.

10 Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007; **448:** 470–73.

11 Portelli MA, Hodge E, Sayers I. Genetic risk factors for the development of allergic disease identified by genome-wide association. *Clin Exp Allergy* 2015; **45:** 21–31.

12 Russell RJ, Brightling C. Pathogenesis of asthma: implications for precision medicine. *Clin Sci (Lond)* 2017; **131:** 1723–35.

13 Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 2006; **11:** 54–61.

14 Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; **180:** 388–95.

15 Kuo CS, Pavlidis S, Loza M, et al. A transcriptome-driven analysis of epithelial brushings and bronchial biopsies to define asthma phenotypes in U-BIOPRED. *Am J Respir Crit Care Med* 2016; **195:** 443–55.

16 Mokhallati N, Guilbert TW. Moving towards precision care for childhood asthma. *Curr Opin Pediatr* 2016; **28:** 331–38.

17 Kulkarni NS, Hollins F, Sutcliffe A, et al. Eosinophil protein in airway macrophages: a novel biomarker of eosinophilic inflammation in patients with asthma. *J Allergy Clin Immunol* 2010; **126:** 61–99.

18 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; **54:** 268–72.

19 Del Giacco SR, Bakirtas A, Bel E, et al. Allergy in severe asthma. *Allergy* 2017; **72:** 207–20.

20 Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002; **57:** 875–79.

21 Doe C, Bafadhel M, Siddiqui S, et al. Expression of the T helper 17-associated cytokines IL-17A and IL-17F in asthma and COPD. *Chest* 2010; **138:** 1140–47.

22 Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015; **16:** 45–56.

23 Gupta S, Siddiqui S, Haldar P, et al. Qualitative analysis of high-resolution CT scans in severe asthma. *Chest* 2009; **136:** 1521–28.

24 Choy DF, Hart KM, Borthwick LA, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma. *Sci Transl Med* 2015; **7:** 301ra129.

25 Brightling CE, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID, Bradding P. Interleukin-4 and -13 expression is co-localized to mast cells within the airway smooth muscle in asthma. *Clin Exp Allergy* 2003; **33:** 1711–16.

26 Park JA, Sharif AS, Tschumperlin DJ, et al. Tissue factor-bearing exosome secretion from human mechanically stimulated bronchial epithelial cells in vitro and in vivo. *J Allergy Clin Immunol* 2012; **130:** 1375–83.

27 O'Reilly R, Ullmann N, Irving S, et al. Increased airway smooth muscle in preschool wheezers who have asthma at school age. *J Allergy Clin Immunol* 2013; **131:** 1024–32.

28 Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Eng J Med* 2002; **346:** 1699–705.

29 Brightling CE, Gupta S, Gonem S, Siddiqui S. Lung damage and airway remodelling in severe asthma. *Clin Exp Allergy* 2012; **42:** 638–49.

30 Hartley RA, Barker BL, Newby C, et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: a single-center study. *J Allergy Clin Immunol* 2016; **137:** 1413–22.

31 Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004; **5:** 155–61.

32 McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016; **374:** 1842–52.

33 Crane J, Lampshire P, Wickens K, et al. Asthma, atopy and exhaled nitric oxide in a cohort of 6-yr-old New Zealand children. *Pediatr Allergy Immunol* 2012; **23:** 59–64.

34 Smoliga JM, Weiss P, Rundell KW. Exercise induced bronchoconstriction in adults: evidence based diagnosis and management. *BMJ* 2016; **352:** h6951.

35 de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Rev* 2013; **22:** 44–52.

36 Baur X, Sigsgaard T, Aasen TB, et al. Guidelines for the management of work-related asthma. *Eur Respir J* 2012; **39:** 529–45.

37 Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129** (suppl 1): 116–21.

38 Marks GB, Colquhoun JR, Girgis ST, et al. Thunderstorm outflows preceding epidemics of asthma during spring and summer. *Thorax* 2001; **56:** 468–71.

39 Covar RA, Macomber BA, Szefler SJ. Medications as asthma triggers. *Immunol Allergy Clin North Am* 2005; **25:** 169–90.

40 Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: a meta-analysis of the literature. *J Allergy Clin Immunol* 2015; **135:** 676–81.

41 Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; **328:** 434.

42 Joos GF, O'Connor B, Anderson SD, et al. Indirect airway challenges. *Eur Respir J* 2003; **21:** 1050–68.

43 Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013; **187:** 1016–27.

44 Global Initiative for Asthma. 2017 GINA Report, Global Strategy for Asthma Management and Prevention. 2017. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/ (accessed June 6, 2017).

45 Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005; **26:** 948–68.

46 Brouwer AFJ, Roorda RJ, Duiverman EJ, Brand PLP. Reference values for peak flow and FEV1 variation in healthy schoolchildren using home spirometry. *Eur Respir J* 2008; **32:** 1262–68.

47 Vonk JM, Jongepier H, Panhuysen CI, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003; **58:** 322–27.

48 Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J* 2009; **33:** 897–906.

49 Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Irvin CG. Allergic rhinitis and sinusitis in asthma: differential effects on symptoms and pulmonary function. *Chest* 2006; **130:** 429–35.

50 Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; **43:** 343–73.

51 van Maanen A, Wijga AH, Gehring U, et al. Sleep in children with asthma: results of the PIAMA study. *Eur Respir J* 2013; **41:** 832–37.

52 Parsons JP, Mastronarde JG. Gastroesophageal reflux disease and asthma. *Curr Opin Pulm Med* 2010; **16:** 60–63.

53 Global Initiative for Asthma and Global Initiative for Chronic Obstructive Pulmonary Disease. Diagnosis and initial treatment of asthma, COPD and asthma-COPD overlap. http://ginasthma.org/download/824/ (accessed Nov 29, 2017).

54 Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *Lancet Respir Med* 2015; **3:** 719–28.

55 Contoli M, Baraldo S, Marku B, et al. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol* 2010; **125:** 830–37.

56 ten Brinke A, Ouwerkerk ME, Bel EH, Spinhoven P. Similar psychological characteristics in mild and severe asthma. *J Psychosom Res* 2001; **50:** 7–10.

57 O'Byrne PM, Pedersen S, Schatz M, et al. The poorly explored impact of uncontrolled asthma. *Chest* 2013; **143:** 511–23.

58 Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012; **367:** 904–12.

59 Pedersen S. Do inhaled corticosteroids inhibit growth in children? *Am J Respir Crit Care Med* 2001; **164:** 521–35.

60 Wilson SJ, Ward JA, Sousa AR, et al. Severe asthma exists despite suppressed tissue inflammation: findings of the U-BIOPRED study. *Eur Respir J* 2016; **48:** 1307–19.

61 Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007; **119:** 817–25.

62 Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; **117:** 549–56.

63 LeMay KS, Armour CL, Reddel HK. Performance of a brief asthma control screening tool in community pharmacy: a cross-sectional and prospective longitudinal analysis. *Prim Care Respir J* 2014; **23:** 79–84.

64 Loymans RJB, Gemperli A, Cohen J, et al. Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. *BMJ* 2014; **348:** g3009.

65 Shay LA, Lafata JE. Where is the evidence? A systematic review of shared decision making and patient outcomes. *Med Decis Making* 2015; **35:** 114–31.

66 Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. *Cochrane Database Syst Rev* 2009; **2:** CD001290.

67 Pinnock H, Parke HL, Panagioti M, et al. Systematic meta-review of supported self-management for asthma: a healthcare perspective. *BMC Med* 2017; **15:** 64.

68 Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; **105:** 930–38.

69 Basheti IA, Armour CL, Bosnic-Anticevich SZ, Reddel HK. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Patient Educ Couns* 2008; **72:** 26–33.

70 Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; **343:** 332–36.

71 Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002; **57:** 880–84.

72 O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009; **179:** 19–24.

73 Reddel HK, Busse WW, Pedersen S, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet* 2017; **389:** 157–66.

74 Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med* 2012; **33:** 405–17.

75 Beasley R, Pavord I, Papi A, et al. Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma. *Eur Respir J* 2016; **47:** 981–84.

76 O'Byrne PM, FitzGerald JM, Zhong N, et al. The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: study protocols for two randomised controlled trials. *Trials* 2017; **18:** 12.

77 Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377:** 650–57.

78 Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; **356:** 2040–52.

79 Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010; **362:** 975–85.

80 Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013; **4:** CD007313.

81 Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013; **1:** 23–31.

82 Bisgaard H, Le Roux P, Bjåmer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006; **130:** 1733–43.

83 Patel M, Pilcher J, Pritchard A, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; **1:** 32–42.

84 Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting β2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Syst Rev* 2016; **1:** CD011721.

85 Gibeon D, Heaney LG, Brightling CE, et al. Dedicated severe asthma services improve health-care use and quality of life. *Chest* 2015; **148:** 870–76.

86 Lindsay JT, Heaney LG. Non-adherence in difficult asthma and advances in detection. *Expert Rev Respir Med* 2013; **7:** 607–14.

87 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; **18:** 716–25.

88 Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; **181:** 315–23.

89 Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; **178:** 218–24.

90 Fitzpatrick AM, Teague WG, Meyers DA, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011; **127:** 382–89.

91 Schatz M, Hsu JW, Zeiger RS, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014; **133:** 1549–56.

92 Sweeney J, Brightling CE, Menzies-Gow A, Niven R, Patterson CC, Heaney LG. Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2012; **67:** 754–56.

93 Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; **367:** 1198–207.

94 Bush A, Pedersen S, Hedlin G, et al. Pharmacological treatment of severe, therapy-resistant asthma in children: what can we learn from where? *Eur Respir J* 2011; **38:** 947–58.

95 Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015; **136:** 1488–95.

96 Mancinelli L, Navarro L, Sharma OP. Intramuscular high-dose triamcinolone acetonide in the treatment of severe chronic asthma. *West J Med* 1997; **167:** 322–29.

97 ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Crit Care Med* 2004; **170:** 601–05.

98 Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; **360:** 1715–21.

99 Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014; **1:** CD003559.

100 Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013; **187:** 804–11.

101 Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; **364:** 1005–15.

102 Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015; **136:** 1476–85.

103 Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371:** 1198–207.

104 Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016; **4:** 549–56.

105 Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; **371:** 1189–97.

106 Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest* 2016; **150:** 789–98.

107 Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; **3:** 355–66.

108 Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest* 2016; **150:** 799–810.

109 Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev* 2015; **8:** CD011293.

110 Boyle RJ, Pedroletti C, Wickman M, et al. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax* 2012; **67:** 215–21.

111 Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010; **181:** 116–24.

112 Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol* 2013; **132:** 1295–302.

113 Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013; **68:** 322–39.

114 Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **390:** 659–68.

115 Agbetile J, Bourne M, Fairs A, et al. Effectiveness of voriconazole in the treatment of *Aspergillus fumigatus*-associated asthma (EVITA3 study). *J Allergy Clin Immunol* 2014; **134:** 33–39.

116 Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; **388:** 2115–27.

117 Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; **376:** 2448–58.

118 Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016; **4:** 781–96.

119 Stinson SE, Amrani Y, Brightling CE. D prostanoid receptor 2 (chemoattractant receptor-homologous molecule expressed on T_H2 cells) protein expression in asthmatic patients and its effects on bronchial epithelial cells. *J Allergy Clin Immunol* 2015; **135:** 395–406.

120 Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016; **388:** 31–44.

121 Gonem S, Berair R, Singapuri A, et al. Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2016; **4:** 699–707.

122 Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017; **377:** 936–46.

123 Gauvreau GM, O'Byrne PM, Boulet LP, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014; **370:** 2102–10.

124 Brightling C, Berry M, Amrani Y. Targeting TNF-α: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–12.

125 O'Byrne PM, Metev H, Puu M, et al. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2016; **4:** 797–806.

126 Brightling CE. Clinical trial research in focus: do trials prepare us to deliver precision medicine in those with severe asthma? *Lancet Respir Med* 2017; **5:** 92–95.

127 Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Ann Am Thorac Soc* 2015; **12** (suppl 2)**:** S144–49.

128 Dusser D, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007; **62:** 591–604.

129 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2013; **380:** 2095–128.

130 Fergeson JE, Patel SS, Lockey RF. Acute asthma, prognosis, and treatment. *J Allergy Clin Immunol* 2017; **139:** 438–47.

131 Anagnostou K, Harrison B, Iles R, Nasser S. Risk factors for childhood asthma deaths from the UK Eastern Region Confidential Enquiry 2001–2006. *Prim Care Respir J* 2012; **21:** 71–77.

132 British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. A national clinical guideline. September 2016. https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/ (accessed Dec 1, 2016).

133 Jayaram L, Pizzichini MM, Cook RJ, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006; **27:** 483–94.

134 Fabbri L, Beghe B, Caramori G, Papi A, Saetta M. Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease. *Thorax* 1998; **53:** 803–08.

135 Wark PA, Gibson PG. Asthma exacerbations. 3: pathogenesis. *Thorax* 2006; **61:** 909–15.

136 Elliot JG, Abramson MJ, Drummer OH, Walters EH, James AL. Time to death and mast cell degranulation in fatal asthma. *Respirology* 2009; **14:** 808–13.

137 Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; **310:** 1225–29.

138 Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ* 1993; **307:** 982–86.

139 National Asthma Council Australia. Australian Asthma Handbook. Version 1.2. Melbourne: National Asthma Council Australia, 2016.

140 Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax* 2004; **59:** 94–99.

141 Djukanović R, Harrison T, Johnston SL, et al. The effect of inhaled IFN-β on worsening of asthma symptoms caused by viral infections. A randomized trial. *Am J Respir Crit Care Med* 2014; **190:** 145–54.

142 Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma. *Am J Emerg Med* 2015; **33:** 14–20.