Asthma

Celeste Porsbjerg, Erik Melén, Lauri Lehtimäki, Dominick Shaw

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Department of Respiratory and Infectious Diseases, Bispebjerg Hospital, Copenhagen, Denmark (Prof C Porsbjerg MD PhD); Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (Prof C Porsbjerg); Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet and Sachs' Children and Youth Hospital, Stockholm, Sweden (Prof E Melén MD PhD); Allergy Centre, Tampere University Hospital, Tampere, Finland (Prof L Lehtimäki MD PhD); Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland (Prof L Lehtimäki); National Institute for Health and Care Research Nottingham Biomedical Research Centre, Division of Respiratory Medicine, School of Medicine, University of Nottingham, Nottingham, UK (Prof D Shaw MD FRCP)

Correspondence to: Dr Celeste Porsbjerg, Department of Respiratory and Infectious Diseases, Bispebjerg Hospital, Copenhagen 2400, Denmark
celeste.porsbjerg@regionh.dk

Asthma is one of the most common chronic non-communicable diseases worldwide and is characterised by variable airflow obstruction, causing dyspnoea and wheezing. Highly effective therapies are available; asthma morbidity and mortality have vastly improved in the past 15 years, and most patients can attain good asthma control. However, undertreatment is still common, and improving patient and health-care provider understanding of when and how to adjust treatment is crucial. Asthma management consists of a cycle of assessment of asthma control and risk factors and adjustment of medications accordingly. With the introduction of biological therapies, management of severe asthma has entered the precision medicine era—a shift that is driving clinical ambitions towards disease remission. Patients with severe asthma often have co-existing conditions contributing to their symptoms, mandating a multidimensional management approach. In this Seminar, we provide a clinically focused overview of asthma; epidemiology, pathophysiology, diagnosis, and management in children and adults.

Epidemiology

Asthma affects around 300 million individuals globally:[1] after having increased in prevalence for decades, the prevalence of asthma now appears to be plateauing, although there is clear regional variation with continuous increases in many low-income and middle-income countries. Estimates from publications in the past 5 years suggest a global prevalence of asthma symptoms of around 10% in children and adolescents[2,3] and 6–7% in adults, ranging from 2 to 3% in adults in some low-income countries to 10% in high-income countries.[4]

The prevalence of childhood wheeze, the hallmark of asthma in young children, varies considerably across regions and countries, with estimates of around 3–5% (in Indonesia and Albania) up to more than 20% (in New Zealand and Costa Rica).[5] By the age of 6 years, up to 50% of all children might have experienced some form of wheezing, most with a mild form of disease associated with viral infections.[6]

Risk factors associated with asthma prevalence include heredity, exposure to tobacco smoke, viral exposure, air pollution, obesity, genetic risk factors, sex (boys have a higher risk than girls before puberty) stress, some allergen exposures (eg, dust mites), urbanisation, scarcity of beneficial microbial exposures, socioeconomic status,[1] and occupational exposures in adults.[7]

Primary prevention of asthma has proven challenging, although multifaceted programmes, such as the Finnish Allergy Program 2008–2018, have shown that asthma prevention and reduced burden of disease are achievable.[8] Introduction of asthma-protective environmental microbial exposures, in the form of bacterial lysates or microbial compounds, has yielded promising results. Supplementation of some nutrients, such as fish oil during pregnancy, might decrease childhood risk of asthma.[9] Although general recommendations are given to reduce harmful exposures, such as tobacco smoke and air pollution (if possible at the individual level), targeted intervention strategies are yet to be developed and fully evaluated.

Search strategy and selection criteria

We searched for English language articles and reviews in PubMed published from database inception to June 30, 2022. The search combined the terms "asthma", and the subheadings "epidemiology", "pathophysiology", "immunology, "diagnosis", "children", "management", "severe", and "exacerbations". We prioritised papers published between Jan 1, 2018 and April 31, 2022. We also searched the reference lists of articles identified by this search and selected those we deemed most relevant.

From childhood to adulthood

Although childhood wheezing is very common, the majority of asthma has its onset in adulthood,[10] but the proportion of allergic asthma decreases with increasing age at asthma onset.[11] Conversely, there is up to a 60% chance of remission of asthma in people who develop the disease before the age of 10 years, but only 5–15% for adult-onset asthma.[12,13] Before puberty, boys are more likely to develop wheeze and asthma, whereas a sex shift occurs around the start of puberty towards a more sex-balanced onset. In adults with severe asthma, there appears to be a female predominance. Guideline recommendations about structured transitional care of adolescents and young adults with asthma are now in place and highlight the need to check that the patient is knowledgeable about their disease and compliant with their prescribed medication.[14]

Factors associated with persistence of asthma from childhood to adulthood overlap to a great extent with the general asthma risk factors (eg, heredity, polysensitisation, and obesity) but also include repeated airway infections, impaired lung function, comorbidities, and eosinophilia.[15] Asthma in childhood might impair airway development and reduce maximally attained lung function, which could persist into adulthood;[16] severe asthma during childhood has been associated with a substantially increased risk for fixed airway obstruction (in some studies classified as chronic obstructive pulmonary disease).[17]

Costs related to asthma

Expenditure related to asthma has continued to increase. In the USA, health-care costs increased from US$53 billion in 2007 to $56 billion in 2009 and $82 billion in 2013.[18] Asthma is thought to account for more than 1% of the total global disability-adjusted life-years lost.[19] The majority of costs associated with asthma care relate to emergency care and severe persistent disease.[20] In addition, indirect costs due to school absenteeism, reduced working capacity, sick leave, and disability pensions are substantial and correlate with asthma severity, but might vary across countries and health-care systems.

Pathogenesis of asthma

Asthma is an airways disease, defined by intermittent bronchospasm causing symptoms such as wheezing and dyspnoea, and characterised by airway inflammation, airway hyper-responsiveness, and mucus hypersecretion, all contributing to variable airflow obstruction, but with heterogeneous underlying inflammatory mechanisms. An improved understanding of the role of these mechanisms is leading to increasingly effective targeted treatment options.

Clinical traits and pathogenetic mechanisms

Clinical traits of asthma (ie, dyspnoea, wheezing, cough and phlegm, exacerbation tendency, loss of lung function, and asthma severity) reflect different underlying disease mechanisms, in which structural cells and immune cells interact to cause the pathogenetic features of asthma. The relative contribution of these features might vary between people who have asthma, causing heterogeneity in the clinical presentation and expression of inflammatory biomarkers (figure 1).

The immunology of asthma is heterogeneous; however, although it is well recognised that the type of airway inflammation might differ between patients (eg, eosinophilic or neutrophilic), underlying causative (endotypic) mechanisms are not understood as well, although molecular inflammatory profiling has provided better insights.[21] In early onset allergic asthma, Th2 cells are activated during allergen exposure, inducing an inflammatory cascade that results in eosinophilic airway inflammation. In the past 5 years, innate lymphoid type 2 cells (ILC2s) have been identified as possible drivers of eosinophilic airway inflammation in non-allergic asthma and have also become apparent in allergic asthma, leading to a shift in denomination from eosinophilic versus non-eosinophilic asthma to type 2 high and type-2-low asthma.[22] Clinical evidence on the exact role of ILC2 cells and other types of innate lymphoid cells in asthma is still somewhat limited.

Clinical biomarkers of type 2 inflammation include blood and airway eosinophils, which are driven mainly by IL-5, and fractional exhaled nitric oxide (FeNO), induced by IL-13. As type 2 biomarkers are suppressed by anti-inflammatory treatment, low levels do not preclude underlying type 2 inflammation in a patient on inhaled corticosteroids. Type-2-low asthma is poorly understood; the proposed potential role of neutrophils, with involvement of Th1 and Th17 cells, is increasingly debatable because attempts to targets these immune pathways have proven ineffective, and neutrophilic airway inflammation might be more of a non-specific marker of severe asthma, relating to low lung function, older age, altered airway microbiome, and high doses of inhaled corticosteroids, than a causative factor.[23] At this point, more research is needed to understand the role of Th1 and Th17 inflammation in the pathophysiology of asthma, including the potential interaction with Th2 immunity.

Mast cells are important effector cells, releasing bronchoconstrictive mediators, such as histamine and leukotrienes. Mast-cell infiltration of the airway smooth muscles is a feature of type-2-low asthma as well as type 2 high asthma, and hence a general driver of airway hyper-responsiveness.[24–26]

The airway epithelium is increasingly recognised as having a key role in asthma pathology with disrupted barrier function, but also an exacerbated inflammatory response to specific triggers, such as allergens, and non-specific triggers, such as virus or smoke, with increased release of thymic stromal lymphopoietin (TSLP), IL-33, and IL-25.[27,28] These epithelial cytokines (known as alarmins) then activate several immune cells, including Th2 and ILC2 cells, ultimately causing eosinophilic airway inflammation, mucus hypersecretion, and bronchospasm.[29] Additionally, TSLP and IL-33 activate mast cells directly, thereby establishing a link between the airway epithelium and mast-cell activation directly without the involvement of T2 cells, but similarly resulting in airway inflammation and airway hyper-responsiveness.[24] Consequently, alarmins have a key role in the immune hyper-responsiveness that underpins asthma exacerbations.

An aberrant innate immune memory might contribute to the increased inflammatory responses observed in asthma. Trained immunity refers to epigenetic and metabolic reprogramming of innate immune cells, resulting in an augmented secondary response to different immune triggers.[30]

In asthma, airway smooth muscle is hypertrophic, and loss of homoeostatic control causes hypercontractility with tendency to bronchospasm.[31] Airway hyper-responsiveness, the key defining pathophysiological feature of asthma, results from hypercontractile airway smooth muscle, with an increased sensitivity to the bronchoconstrictive mediators released mainly from mast cells and eosinophils in relation to airway inflammation.[32] Airway smooth muscle in asthma is thought to be affected by inflammation, rather than intrinsic abnormalities, and additionally to contribute to airway inflammation and remodelling by releasing inflammatory mediators, such as IL-5, IL-13, and IL-8.[31]

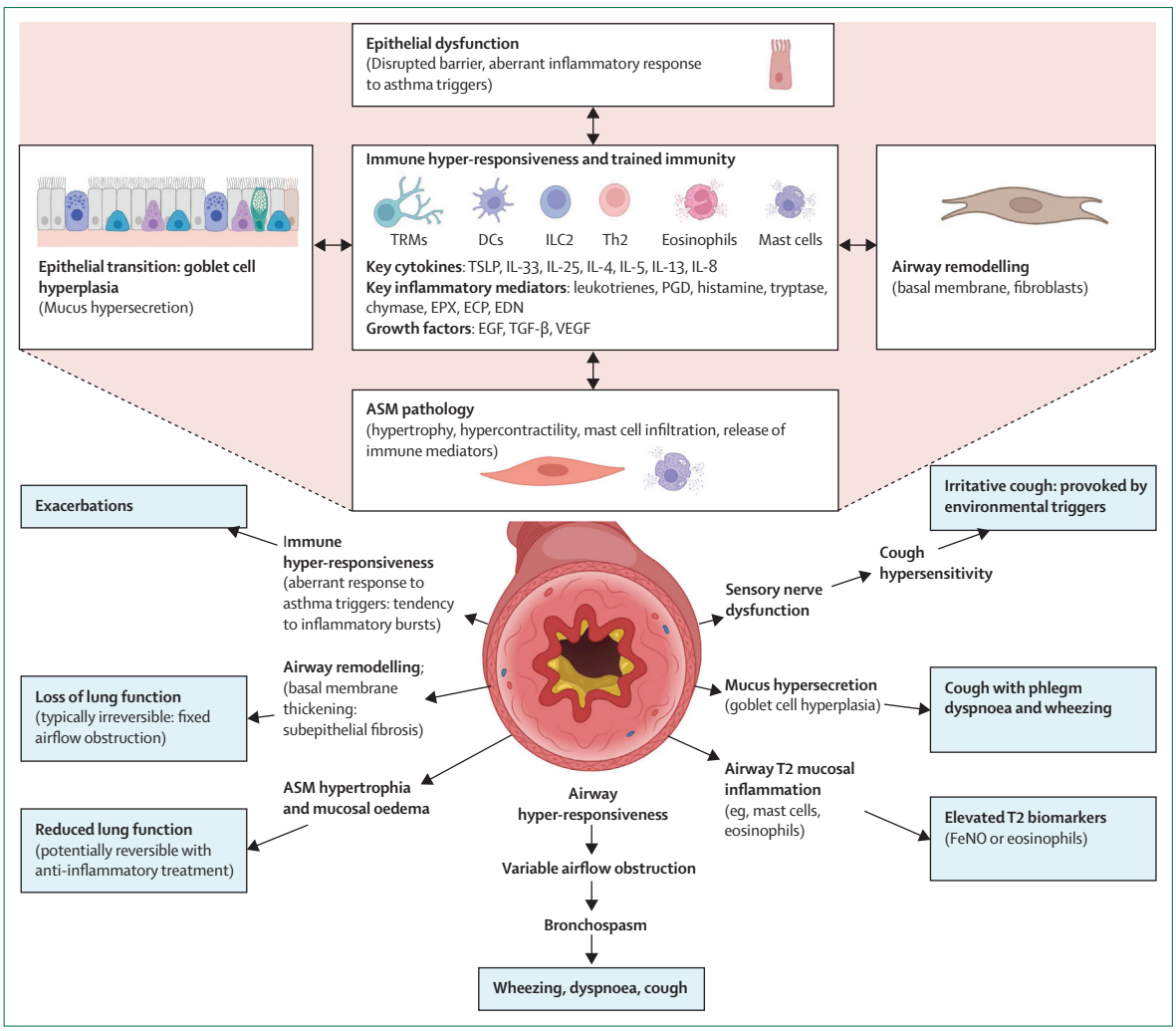


Figure 1: **Key pathophysiological mechanisms of asthma and resulting disease components and clinical features**
Bottom: dyspnoea and wheezing are caused by variable airflow obstruction, reflecting airway smooth muscle hypercontractility. Top: a range of pathophysiological mechanisms interact to cause these clinical features of asthma. These factors might interact in different manners and with variation between patients. TRM=tissue resident memory cell. DC=dendritic cell. ILC2=innate lymphoid cell. Th2=T2 helper cells. TSLP=thymic stromal lymphopoietin. PGD=prostaglandins. EPX=eosinophil peroxidase. ECP=eosinophilic cationic protein. EDN=eosinophil-derived neurotoxin. EGF=epidermal growth factors. TGF-β=tumour growth factor β. VEGF=vascular endothelial growth factor. ASM=airway smooth muscle. FeNO=fractional exhaled nitric oxide.

Sensory nerve dysfunction might cause irritative cough, but also airway hyper-responsiveness in asthma. The density of sensory nerves is increased in asthma, particularly in patients with eosinophilic airway inflammation, possibly contributing to hypersensitivity to environmental triggers and airway hyper-responsiveness.[33–35]

Airway remodelling contributes to airflow obstruction by a combination of subepithelial fibrosis, basal membrane thickening, mucosal oedema, and airway smooth muscles hypertrophy, which might to some degree be reversible with anti-inflammatory treatment but often requires longer term therapy.[36] Additionally, structural components (airway smooth muscle hypertrophy, mucosal oedema, and basal membrane thickening causing airway narrowing) also contribute to airway hyper-responsiveness.[35,37] In patients with type 2 asthma, IL-13 induces transition of the airway epithelial cells into mucus secreting phenotypes via upregulation of *MUC5AC*,[38] causing chronic mucus hypersecretion with cough and phlegm, and disrupting the epithelial barrier, potentially contributing to loss of lung function.

Genetics and epigenetics

Estimates from twin studies show a very strong hereditary effect with up to 80% or more of disease occurrence (ie, heritability) explained by genetic factors.[39] Yet the influence of genetic factors needs to be considered in an environmental context with multiple factors influencing disease risk. Overall, the genetic influence appears to be stronger for child-onset asthma than adult-onset asthma, although many risk loci are common for both children

and adults (eg, *IL18R1, HLA* genes, and *TSLP*).[40,41] There is no gene that alone might cause asthma, but for childhood asthma, genes at the 17q12-21 locus (including gasdermin-B [*GSDMB*] and ORMDL sphingolipid biosynthesis regulator 3 [*ORMDL3*]) appear particularly important. There is strong evidence for gene–environment interaction effects between these 17q12-21 variants and early life exposures such as viral infections, tobacco smoke, and farming lifestyle.[42] This evidence highlights the joint effect of genetic and environmental effects in asthma. Expression analyses of key genes at this locus also direct attention to airway epithelial function and crosstalk with the immune system. Other well known asthma genes, such as *IL33* and *TSLP,* also seem to exert their effect primarily on the epithelium.[43]

Evidence from the past 5 years suggests that epigenetic mechanisms are central for the regulation of airway epithelial cells and immune responses (eg, eosinophil activation) in asthma in both children and adults.[44] Epigenetics refers to chemical modifications of the DNA, without any change in the underlying nucleotide sequence but causing alterations in the translation into mRNA and proteins, and is influenced by a whole range of factors, from genetics, host factors, and ageing to environmental exposures (eg, smoking, air pollution, and viral infections) and disease processes.[44]

Clinical presentation and diagnosis of asthma

Asthma is characterised by intermittent and variable symptoms of bronchospasm and airway inflammation (ie, dyspnoea, tightness of the chest, wheezing, cough, and phlegm), which occur either spontaneously or in response to triggers such as exercise or cold air. Some patients might experience asthma attacks (exacerbations) with more pronounced and persistent symptoms, such as after a viral infection. Asthma is a heterogeneous condition and might present differently in terms of the age at onset, the severity of asthma, and the clinical presentation.

Essentially, a diagnosis of asthma is based on a combination of a relevant history and demonstration of variable airflow obstruction. Diagnosing asthma might be challenging; due to its variable nature, objective signs of asthma might be absent at the time of assessment, and the diagnostic process consists of assessing the likelihood of asthma based on symptoms, objective tests, and response to treatment (figure 2).[46] In addition, markers of asthma phenotypes might aid in guiding management. A key part of the diagnostic testing of asthma is also considering differential diagnoses and determining the presence of comorbidities and other potentially treatable traits (figure 3).[47]

Taking a history from a patient assesses the likelihood of asthma; typical asthma symptoms such as wheezing and tightness of chest that vary over time, and are triggered by exercise, allergen exposure, or viral infections highly increase the pre-test likelihood of asthma, whereas atypical symptoms such as monosymptomatic cough, upper chest wheeze (eg, laryngeal obstruction), or dyspnoea on exertion without variability make asthma less likely.

The diagnosis of asthma is ideally confirmed objectively by showing variable airflow obstruction:[46] reversibility testing and peak expiratory flow (PEF) diaries are the most widely available tests, but also have a limited sensitivity, and bronchial challenge testing might be necessary. The results of objective asthma tests should also be interpreted in the context of the symptoms. For a patient in whom there is a suspicion of asthma based on the history (ie, a high pre-test likelihood of asthma), a trial of treatment with inhaled steroid might be considered, if bronchial challenge tests are unavailable.

Bronchodilator reversibility testing assesses the increase in the forced expiratory volume in 1 s (FEV_1) after inhalation of a rapid-acting bronchodilator; an increase of 12% and at least 200 mL after 15 min is considered clinically significant (in children: >12% FEV_1 increase only). The sensitivity of the test is, however, poor,[48,49] particularly in patients with normal lung function,[50,51] and a negative test does not rule out asthma.

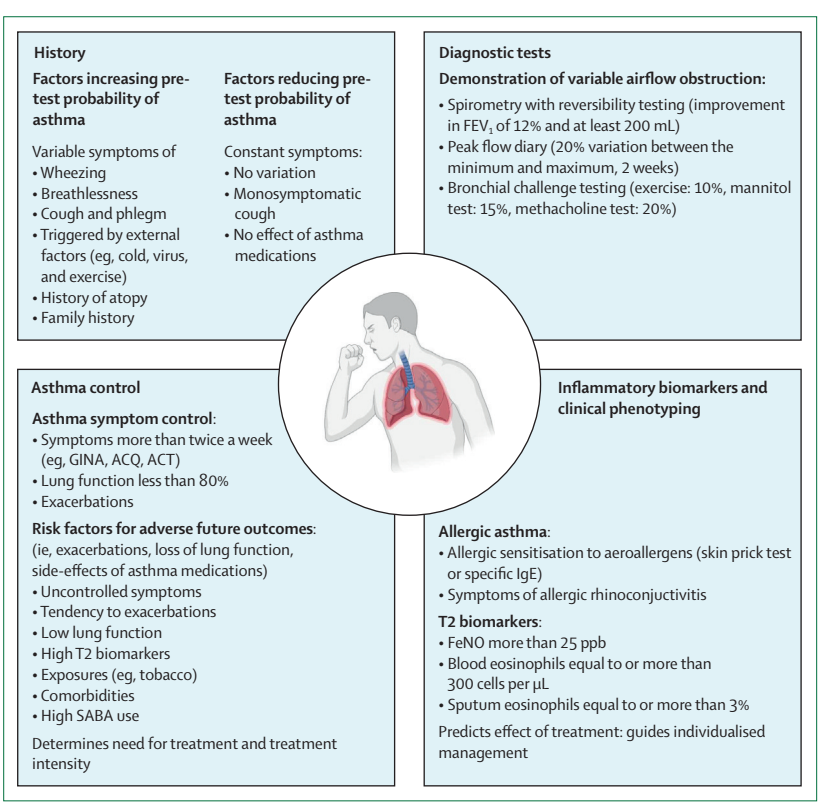


Figure 2: **Diagnostic assessment of asthma: history taking, diagnostic tests, assessment of asthma control and phenotyping**

Asthma is ideally diagnosed on the basis of a history of classic symptoms and objective signs of variable airflow limitation. Symptoms might vary over time; during stable periods, asthma might be difficult to detect. Assessment of asthma control guides the level of treatment, and asthma phenotyping guides individualised management strategies. In children, no reference values for peak flow variation exist.[45] ACQ=Asthma Control Questionnaire. ACT=Asthma Control Test. FeNO=fractional exhaled nitric oxide. FEV_1=forced expiratory volume in 1 s. GINA=Global Initiative for Asthma. SABA=short-acting β_2 agonists. T2=type 2.

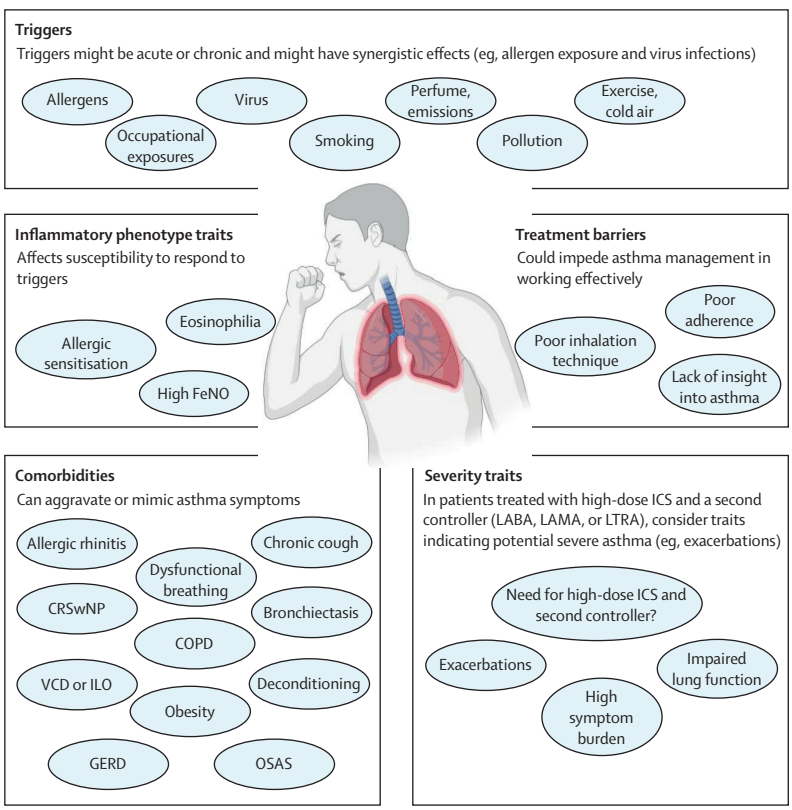


Figure 3: **Factors contributing to poor asthma control**
Many factors could contribute to poor asthma control: symptoms, need for SABA, reduced lung function, and exacerbations. As part of the diagnostic evaluation and management of asthma, these factors should be assessed, and potential treatable traits be addressed. COPD=chronic obstructive pulmonary disease. CRSwNP=chronic rhinosinusitis with nasal polyps. FeNO=fractional exhaled nitric oxide. GERD=gastro-oesophageal reflux. ICS=inhaled corticosteroids. ILO=inducible laryngeal obstruction. LABA=long-acting β_2 agonists. LAMA=long-acting muscarinic antagonists. LTRA=leukotriene receptor antagonists. OSAS=obstructive sleep apnoea. SABA=short-acting β_2 agonists. VCD=vocal cord dysfunction.

PEF monitoring might be useful in patients with a normal lung function. Different calculations might be applied; the percentage amplitude highest PEF ([(highest PEF−lowest PEF)/highest PEF]×100) with a cutoff of more than 20%, is considered accurate and does not require calculating the daily mean PEF.[46]

Bronchial challenge tests for airway hyper-responsiveness have the highest sensitivity for detecting asthma (60–80%)[52] but are mainly restricted to specialist settings; exercise testing might be difficult to perform correctly; and in adults, inhalation challenge tests such as the direct methacholine test or the indirect mannitol or hypertonic saline tests are more commonly used. Direct challenge tests act directly on the airway smooth muscle, making them the most sensitive tests but also less specific, with false-positive tests in patients with chronic cough or patients who smoke.[52] Indirect tests act via inflammatory cells—mainly mast cells releasing broncho-constricting mediators in response to an increase in airways osmolarity (eg, exposure to mannitol, hypertonic saline, or exercise).[53] The indirect tests are hence more specific, reflecting airway hyper-responsiveness caused by airway inflammation, but are less sensitive because a specific level of inflammation is required to be present at the time of the test.

See Online for appendix

Specific considerations in children

In preschool children (younger than 5 years), asthma might be challenging to diagnose due to a wide spectrum of disease symptoms and scarcity of objective airway or lung function measures, and because many children might have a virally induced wheezing phenotype rather than asthma, which might not become evident until later in life. Several wheezing phenotypes have also been identified, each with a specific set of clinical characteristics and pathophysiological features.[54] A history of recurrent symptoms such as wheezing, coughing, chest tightness, and trouble breathing constitutes the basis for diagnosis (figure 1; appendix p 1). Information on symptom triggers, symptom duration and severity, effect of asthma medications, family history, and other allergic manifestation is used for the diagnosis. In school-age children (potentially from age 5 years) and older, the use of objective tools to show airflow obstruction or airway inflammation (spirometry, bronchodilator reversibility testing, and FeNO), in addition to disease history, are strongly encouraged for a correct diagnosis.[55] Many adolescents might have asthma-like symptoms during exercise, and for these patients exercise testing may be useful.

Phenotyping and endotyping asthma

Asthma can be divided into phenotypes by observable disease manifestations and endotypes by inflammatory mechanisms, which is increasingly important with the advent of more targeted treatments: allergy to aeroallergens is diagnosed on the basis of allergic sensitisation (ie, skin prick test or specific IgE) in combination with symptoms in relation to a relevant exposure. Clinical biomarkers of type 2 inflammation include blood eosinophils (>300 cells per µL) and FeNO (>25 ppb) for differentiation of type 2 high versus type-2-low asthma.[56–58]

Although the gold standard for assessing airway inflammation is induced sputum, blood eosinophil measurements are more feasible, although with a moderate sensitivity, and low blood eosinophils do not preclude eosinophilic airway inflammation.[59,60] Additionally, as steroid treatment suppresses type 2 inflammation, type 2 biomarkers and their variation over time should be evaluated in the context of ongoing treatment. Over half of people with asthma are likely to have an eosinophilic disease, and the proportion is higher in more severe asthma.[61]

Differential diagnosis and comorbidities

Many conditions might resemble asthma, some of which might also co-exist with asthma as a comorbidity and could contribute to poor asthma control if not managed (appendix pp 1–4).

Allergic rhinitis is the most frequent comorbidity in asthma, particularly in children, and a common cause of poorly controlled asthma.[62] Chronic rhinosinusitis with or without nasal polyposis is characterised by recurrent episodes of sinus or facial pain, nasal stenosis, post-nasal drip, and loss of sense of smell, mostly occurring in adults, and might be associated with aspirin intolerance.[63,64]

Dysfunctional breathing is very common in asthma and can mimic symptoms similar to asthma:[65] patients with a chronic hyperventilation pattern might also have dizziness, numbness, tingling around the mouth, fingers, and toes, tiredness, and difficulty concentrating.

Mental health disorders are common in asthma, and—similar to dysfunctional breathing—the direction of causality might be difficult to establish, particularly in patients with anxiety or depression.[66] Psychological stress might contribute to poor symptom control and trigger airway inflammation, particularly in allergic and eosinophilic asthma.[67,68]

Obesity is associated with worse asthma control and increased risk of exacerbations. Additionally, comorbidities associated with obesity (ie, gastroesophageal reflux disease and obstructive sleep apnoea syndrome) often contribute to poor asthma control.[69]

Inducible laryngeal obstruction can mimic or co-exist with asthma, but causes sudden onset of symptoms in response to triggers such as strong smells or exercise.[70] Due to the sudden onset and often profound nature, this acute laryngeal obstruction can be very frightening for people with asthma and can lead to repeated acute hospitalisations.

Overlap of asthma and chronic obstructive pulmonary disease (COPD) can reflect several situations; incomplete development of lung function during childhood resulting in reduced FEV_1/forced vital capacity (FVC) ratio,[16] irreversible loss of lung function in asthma due to remodelling, and development of COPD in an asthma patient who smokes.[71]

Chronic cough with cough hypersensitivity to a range of triggers is now recognised as a disease entity, rather than a non-specific symptom, but might also co-exist with asthma.[72] Differentiating chronic cough from cough-variant asthma can be difficult; a trial of treatment with inhaled steroids might be necessary. Eosinophilic bronchitis is a rare but important differential diagnosis that is treated similarly to asthma.[73]

Assessing asthma control and factors contributing to poor asthma control

Asthma symptom control and the presence of risk factors associated with future adverse events inform the management strategy (figure 2) and form the basis for a dialogue with the patient to set shared treatment goals.

Adverse future outcomes include recurrent exacerbations (asthma attacks), accelerated decline in lung function, and treatment-related comorbidities.[58,74–76] Additionally, considering factors that could contribute to poor asthma control is important: exposure to triggers, treatment barriers, comorbidities, inflammatory phenotype traits, and asthma severity traits (figure 3).

Long-term management of non-severe asthma

Once the diagnosis has been established, and factors contributing to symptoms and future risks of exacerbations and loss of lung function have been assessed, a management plan addressing these factors can be made, including appropriate pharmacological management.

Non-pharmacological management of asthma includes advice on avoidance of exposures such as allergens (when relevant and feasible), smoking and occupational exposures, and appropriate management of comorbidities contributing to poor asthma control (figure 4). Providing adequate education information to patients (and families) on their disease and management is key to achieving positive long-term outcomes. Teaching inhalation technique by physical demonstration of the device is important to prevent treatment failure due to poor inhalation technique, and in patients with known asthma, inhalation technique and adherence should be assessed at every clinical control.

Pharmacological treatment regimens

Traditionally mild asthma was treated with short-acting β_2 agonists (SABA) alone and an inhaled corticosteroid was added in when symptoms were not adequately controlled. Asthma was then treated in a stepwise manner, in which the dose of inhaled corticosteroids was increased, or second controllers (ie, long-acting β_2 agonists [LABA] and leukotriene receptor antagonists [LTRA]) were added, until asthma became controlled, and subsequently adjusted according to the level of asthma control.

This treatment approach has changed because of several linked issues. Data suggested SABA overuse and ICS underuse were associated with a higher risk of exacerbation or even death,[77] and that compliance with inhaled medication in patients with asthma has consistently been poor, even when patients have symptoms of asthma. A study of rapidly increasing inhaled steroid dose at the onset of worsening asthma control showed fewer severe asthma exacerbations, supporting the idea that increasing doses of inhaled steroids before exacerbation onset improves the outcome.

Based on these factors and several large studies,[77,78] the Global Initiative for Asthma (GINA) now recommends two different tracks for adults and adolescents (ie, aged 12 years and older) and for children (aged 6–11 years), with very similar regimens (figure 4). Track 1 is based on a combination of inhaled corticosteroid and formoterol (a fast onset but long-acting bronchodilator) in a single inhaler used as a reliever, and the more traditional Track 2 has a SABA prescribed as a reliever, alongside intermittent or regular inhaled corticosteroids.

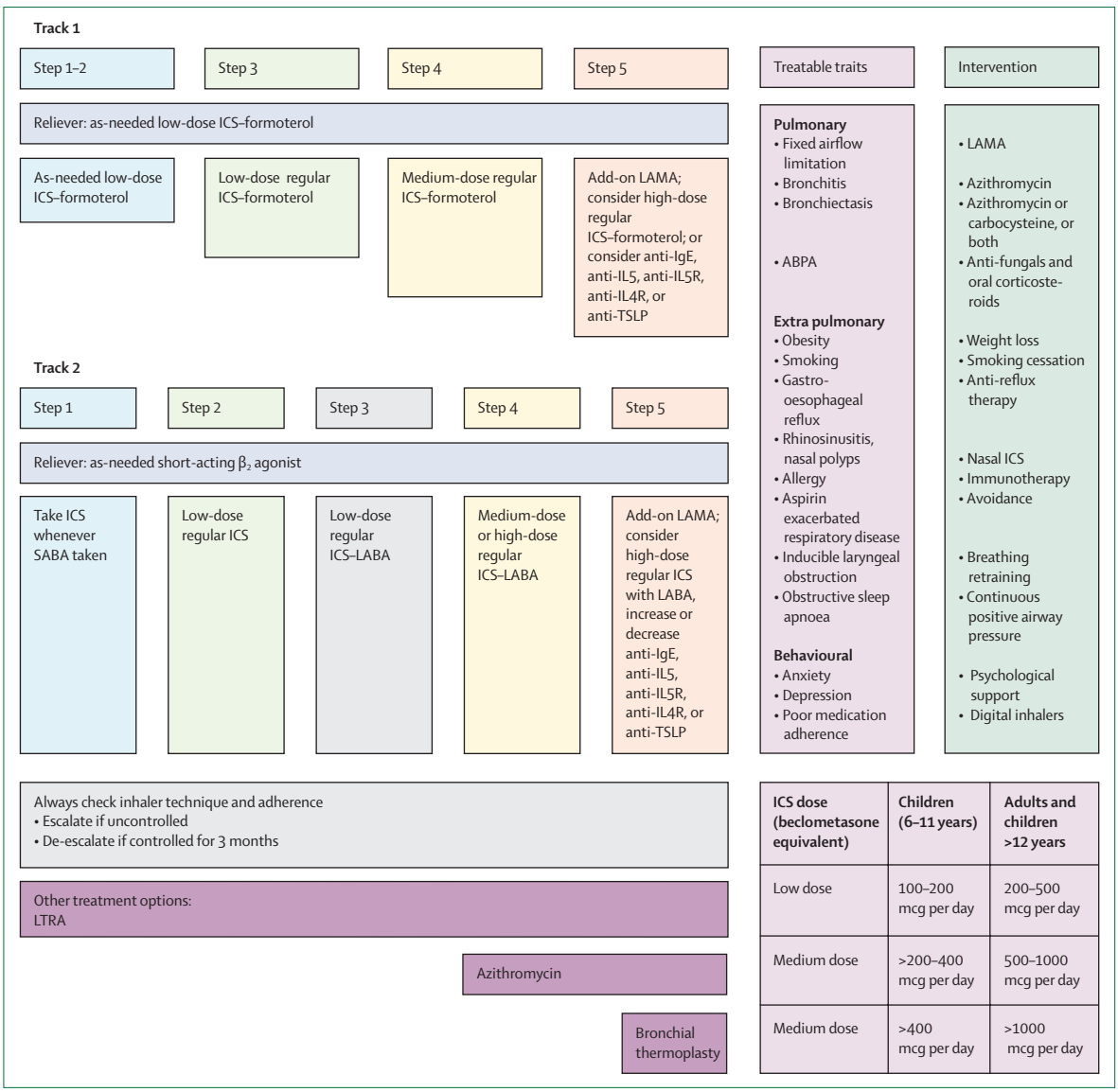


Figure 4: **Long-term management of asthma in adults and adolescents older than 12 years**
ABPA=allergic bronchopulmonary aspergillosis. ICS=inhaled corticosteroids. LABA=long-acting β_2 agonists. LAMA=long-acting muscarinic antagonists. LTRA=leukotriene receptor antagonists. SABA=short-acting β_2 agonists. TSLP=thymic stromal lymphopoietin.

These recommendations are based on data suggesting that SABA overuse is associated with a worse outcome.[77] However, it is difficult to establish from studies whether SABA overuse per se or relative under-use of inhaled corticosteroids is the main driver for the poorer outcomes, or a marker of more severe disease, because the same association is observed in patients on high-dose inhaled corticosteroids with a high use of prescribed as-needed SABA.[79] Importantly, the use of monotherapy with a single inhaled corticosteroid and formoterol inhaler in mild asthma is not licensed or approved in all countries, or by the US Food and Drug Administration or European Medicines Agency, although its use is becoming more widespread globally.

For more on the **types of asthma drugs and inhalers** see www.rightbreathe.com

For children aged 0–5 years, SABA as needed can be recommended for mild wheeze only, although short-course inhaled corticosteroids at symptom onset (GINA Step 1) or daily low-dose inhaled corticosteroids (or LTRA; Step 2) should be considered when symptoms become frequent or more severe. For Step 3 and 4, inhaled corticosteroids dose is increased and LTRA added. If asthma is still not well controlled at Step 4, refer for specialist assessment (panel 1).

A stepwise approach based on increasing the dose of inhaled corticosteroids at each step forms the foundation of many national and international asthma guidelines (figure 4). The dose administered depends not only on the formulation but also particle size and type of inhaler.

Panel 1: **Controversies in pharmacological management of asthma: Global Initiative for Asthma (GINA) Track 1 *vs* Track 2**

The GINA guidance is based on a series of studies summarised in a meta-analysis[80] that found as-required long-acting β_2 agonists (LABA) with inhaled corticosteroids are effective in adults and adolescents with mild asthma. Compared with short-acting β_2 agonists (SABA) alone, combined LABA and inhaled corticosteroids reduced exacerbations, hospital admissions, and oral corticosteroid use. Compared with regular inhaled corticosteroids with rescue SABA, as-required LABA with inhaled corticosteroids was more effective at reducing hospitalisations and emergency department visits, with reduced overall exposure to inhaled corticosteroids.

Outside of the published studies, there are clear benefits to adopting combined inhaled corticosteroids and LABA monotherapy as initial treatment in mild asthma. These benefits include medication use being more consistent up the steps, potentially increasing adherence, use of a single type of reliever or maintenance inhaler, with the added advantage of only having to learn one inhaler technique; and not relying on SABA monotherapy during an exacerbation.

Potential downsides are that symptoms and exacerbation risk might not be closely linked in individual patients,[81] leading to over-use of inhaled corticosteroids with LABA; symptoms of asthma and other diseases, such as inducible laryngeal obstruction, dysfunctional breathing, and cough reflex hypersensitivity, can often overlap, potentially leading to over-use of inhaled corticosteroids with LABA; and reports of some primary care doctors refusing to prescribe rescue SABA in patients known to be compliant with inhaled corticosteroids, but still symptomatic, can lead to confusion. In mild to moderate asthma on GINA step 2, regular use of maintenance inhaled corticosteroids led to better symptom control and lung function than as-needed combined inhaled corticosteroids and formoterol.[82,83] This outcome is understandable since an inherent part of the as-needed strategy is to react to symptoms instead of preventing symptoms by regular medication. Therefore, as-needed use of asthma medication might work best in the mildest forms of asthma with infrequent symptoms and normal lung function.

Inhaled corticosteroids are not without risk. Inhaled corticosteroids have been linked to a risk of pneumonia in both asthma and chronic obstructive pulmonary disease,[84] and osteoporosis,[76,85] all in a dose-dependent manner, and high-dose inhaled corticosteroids (>1600 beclometasone equivalent) are equivalent to a systemic dose of prednisolone of 5–8 mg.[86] High-dose inhaled corticosteroid use has also been linked to adrenal suppression, particularly in children,[87] so the addition of a second controller rather than an increase in inhaled corticosteroids dose is often initially preferred. Occurrence of growth suppression has been observed in children with regular use of inhaled corticosteroids, in particular during the first year, but catch-up is possible and the overall effect on growth is considered very small (around 1 cm difference in adult height).[88] Growth should, however, be monitored regularly in all children.

Of note, 80–90% of the maximum obtainable benefit in the long-term treatment of asthma in adults occurs when taking less than 500 µg beclometasone equivalent daily.

Stepping up therapy depends on the level of asthma control. In people who take inhaled corticosteroids with LABA as a reliever, the number of as-needed doses can be adjusted day-to-day according to symptoms. For people with asthma taking maintenance inhaled corticosteroids, the dose can be increased for between one and two weeks during periods of worsening asthma control (eg, due to a viral infection or seasonal allergen exposure). If asthma control is persistently poor, there should be a step up to the next level.

If people with asthma are still symptomatic despite a low-dose combination of inhaled corticosteroids with LABA (step 2 and 3) or medium or high-dose inhaled corticosteroids with LABA (steps 3 and 4), GINA advises addition of a long-acting muscarinic antagonist (LAMA) or LTRA as of May, 2022. The combination of inhaled corticosteroids, LABA, and LAMA is referred to as triple therapy. Addition of LAMA has been shown to reduce time to exacerbation in moderate to severe asthma, with modest improvements in asthma control and lung function,[89] without substantial differences in quality of life or mortality, when compared with inhaled corticosteroids with LABA therapy. Triple therapy is associated with an increased risk of dry mouth and dysphonia.[90]

Aside from increases in inhaled corticosteroid dose, other options are available to improve asthma control. In the UK, the addition of an LTRA such as montelukast is recommended as the next addition after the initial use of low-dose inhaled corticosteroids, rather than adding LABA.[91] GINA suggests LTRA can be given as a treatment trial at any step to improve symptom control.

Most guidelines suggest stepping down the inhaled corticosteroids dose by 25–50% or removing any additional controller medication if the patient is controlled for at least 3 months. GINA states that treatment should be stepped down when asthma symptoms have been well controlled and lung function has been stable for a minimum of 3 months. This decision needs to be balanced against the risk of future exacerbations or persistent airflow limitation.

Because of the plateau effect on lung function and symptoms, at an inhaled corticosteroid dose of around 500 µg beclometasone equivalent, the GINA step 4 to 5 might be better served by an assessment of airway inflammation status and targeting an increased dose of inhaled corticosteroids at persistent airway inflammation

(after showing the patient is compliant—ie, using their inhalers as prescribed and with proper technique).[47] Biomarker-directed therapy with higher dose treatment in patients with persistent type 2 inflammation improved outcomes in the CAPTAIN[92] study; this was an approach taken in the RASP-UK study, in which FeNO measurement was used to down-titrate and up-titrate the dose of inhaled corticosteroids.

One potential obstacle to moving towards a fully biomarker-directed therapy approach is the commonly held view that asthma symptoms are closely linked to risk of asthma exacerbation. The events around the epidemic thunderstorm event in Melbourne, VIC, Australia,[93] where more than 3000 emergency asthma admissions occurred in 24 h, with only 28% of patients having a formal asthma diagnosis, and many of the patients with asthma having few symptoms preceding the event, showed us that even patients with minimal symptoms can be at risk of an exacerbation if exposed to an antigen or virus. Conversely, patients with poorly controlled asthma and daily symptoms might not necessarily be at an increased risk of an asthma exacerbation.[94] Using biomarkers to both stratify risk and guide therapy gives the potential to both target treatment and reduce exacerbations,[95] but more randomised controlled studies are needed.

Allergen immunotherapy

Allergic asthma is often associated with allergic rhinitis. Allergen immunotherapy is widely used and recommended to treat allergic rhinitis, and although its role in treating allergic asthma is less established, allergen immunotherapy has the potential of being a disease-modifying treatment in mild to moderate asthma; however, caution is needed if used in severe asthma. Subcutaneous immunotherapy with various allergens has been found to reduce asthma symptoms, the need for asthma medication, and airway hyper-responsiveness, but there is no consistent effect on exacerbations.[96] However, some evidence suggests that sublingual immunotherapy with house-dust-mite allergen could decrease exacerbations and the need for asthma medication.[97,98]

Panel 2: Digital inhalers and focus on sustainable inhalers

Digital inhalers, with embedded technology enabling the measurement of the number of puffs, inhaler technique, and inspiratory flow are now offered by several companies. The use of connected digital devices is quite new but studies to date have consistently found that their use is associated with an improvement in adherence (at least in the short term), although this does not always translate to improved clinical outcomes.[117] Connected inhaler systems are now being used routinely in some severe asthma services, along with monitoring of fractional exhaled nitric oxide or forced expiratory volume in 1 s, to establish whether patients with poor control either need adherence reinforcement or increased doses of inhaled corticosteroids.[118]

The carbon footprint of inhalers continues to rise as global use increases. A study estimated that in 2018, 800 million hydrofluoroalkane (HFA)-propellant-based metered-dose inhalers were manufactured worldwide, using approximately 11 500 tonnes of hydrofluorocarbons, predominantly HFA-134a.[119] Most of these HFAs are contained in salbutamol metered-dose inhalers. HFAs are strong greenhouse gases and contribute to global warming; every puff of salbutamol is estimated to be approximately equivalent to a mile travelled in a petrol car in terms of global warming. Consequently, the use of dry powder inhalers that do not contain propellants is now encouraged. Three companies have announced programmes to implement propellants with a lower global warming potential using HFA-152a or HFA-1234ze, with the first products potentially available from 2025. Disappointingly, the ability to recycle inhalers is still limited globally and the majority still end up in landfill.

Biomarkers to guide therapy

The use of type 2 biomarkers in guiding therapy is important in severe asthma, but their use in mild and moderate asthma is more contentious. FeNO measurement has been studied for different indications, including asthma diagnosis,[99] predicting the response to inhaled corticosteroids,[100] dose titration of inhaled corticosteroids,[101,102] and adherence monitoring of inhaled corticosteroids.[103–105]

The recent American Thoracic Society Clinical Practice Guideline[106] stated that measuring FeNO is beneficial and should be used in addition to usual care, although gave a conditional recommendation. The guidance recommended that an individual's FeNO level should be interpreted in conjunction with clinical judgements based on the perceived probability of benefit, including reducing exacerbation risk. The group concluded that there were not enough data to recommend specific cutoff points associated with specific actions, such as starting or increasing the dose of an inhaled corticosteroid, but recognised that initial guidelines stated that a low FeNO value of 25 ppb in adults (20 ppb in children) was considered evidence that a response to the corticosteroids was unlikely, and a high FeNO value above 50 ppb in adults (35 ppb in children) was considered evidence of a likely corticosteroid response, with response between these two boundaries unpredictable. A similar conclusion was reached in a systematic review[107] of 22 studies that suggested using a strategy based on FeNO to reduce asthma exacerbations in both children and adults; however, a more recent study[108] in children found that adding FeNO to symptom-guided treatment did not reduce exacerbations. These findings might reflect the problem of using group mean cutoff points to guide individual therapy with FeNO. GINA now recommends repeated assessments of type 2 biomarkers (blood eosinophils and FeNO) at the time of asthma worsenings and a lowest possible level of inhaled corticosteroids before assuming asthma is type-2-low.

In a clinical context, elevated FeNO in a patient given inhaled corticosteroids should lead to consideration of poor adherence; it also supports increasing the dose of inhaled corticosteroids, when compared with adding a second controller, if the patient is poorly controlled.

Other factors

Prescribing an inhaler if the patient cannot or will not use it correctly has little benefit. Unfortunately, issues of poor

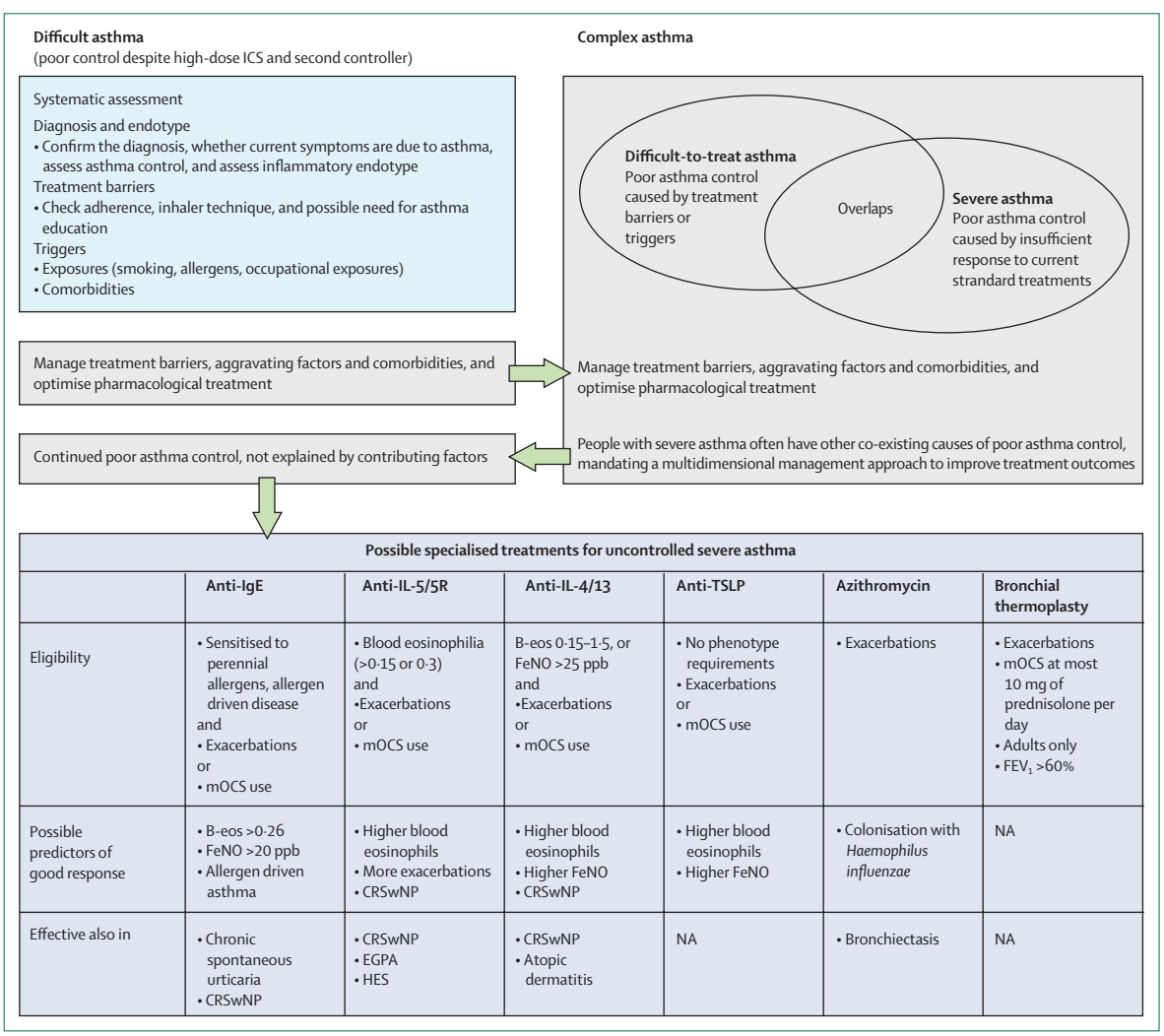
technique or adherence persist,[109,110] and both should be assessed at every opportunity. The plethora of drug–device combinations available (eg, single, double, triple, metered-dose inhaler, dry powder, and soft mist) probably exacerbates the issue. Poor adherence is often linked to socioeconomic disadvantage and psychological comorbidity.[111,112]

The use of written personalised asthma action plans, describing how to recognise and respond to worsening symptoms, has consistently been associated with reduced use of health-care resources, emergency department visits, hospital admissions, and unscheduled consultations, and better asthma control.[113] Understanding when to increase reliever medication, when to take rescue oral corticosteroids, and when to seek medical advice is crucial. Although guidelines recommend a structured transitional care for adolescents with asthma and highlight the need to check self-management and compliance with their medication,[114] real-life data suggest that health-care consultations decrease after the transition to adult asthma care.[115] Influenza vaccination should be offered annually to both children and adults with asthma. Data are scarce but a systematic review[116] concluded that the vaccination might reduce asthma exacerbations (panel 2).

Severe asthma

Severe asthma is defined as "asthma that is uncontrolled, despite adherence with maximal optimised high-dose inhaled corticosteroids with LABA treatment and management of contributory factors, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations".[120] Whereas GINA guidelines define high-dose inhaled corticosteroids as more than 800 µg beclometasone, American Thoracic

For **examples of personalised asthma action plans** see https://www.asthma.org.uk/advice/manage-your-asthma/action-plan/



Possible specialised treatments for uncontrolled severe asthma

	Anti-IgE	Anti-IL-5/5R	Anti-IL-4/13	Anti-TSLP	Azithromycin	Bronchial thermoplasty
Eligibility	• Sensitised to perennial allergens, allergen driven disease and • Exacerbations or • mOCS use	• Blood eosinophilia (>0·15 or 0·3) and •Exacerbations or • mOCS use	B-eos 0·15–1·5, or FeNO >25 ppb and •Exacerbations or • mOCS use	• No phenotype requirements • Exacerbations or • mOCS use	• Exacerbations	• Exacerbations • mOCS at most 10 mg of prednisolone per day • Adults only • FEV_1 >60%
Possible predictors of good response	• B-eos >0·26 • FeNO >20 ppb • Allergen driven asthma	• Higher blood eosinophils • More exacerbations • CRSwNP	• Higher blood eosinophils • Higher FeNO • CRSwNP	• Higher blood eosinophils • Higher FeNO	• Colonisation with *Haemophilus influenzae*	NA
Effective also in	• Chronic spontaneous urticaria • CRSwNP	• CRSwNP • EGPA • HES	• CRSwNP • Atopic dermatitis	NA	• Bronchiectasis	NA

Figure 5: **Assessment and treatment of severe asthma**
B-eos=blood eosinophils. CRSwNP=chronic rhinosinusitis with nasal polyps. EGPA=eosinophilic granulomatosis with polyangiitis. FEV_1=forced expiratory volume in 1 s. HES=hypereosinophilic syndrome. ICS=inhaled corticosteroids. FeNO=fractional exhaled nitric oxide. mOCS=maintenance oral corticosteroids. NA=not applicable. TSLP=thymic stromal lymphopoietin.

Society and European Respiratory Society guidelines set the cutoff at more than 1600 µg beclometasone, which is the most widely used definition in setting the indication for biological therapies. About 5–10% of asthmatics have severe asthma, often with frequent exacerbations and requiring maintenance oral corticosteroids, and severe asthma drives most costs associated with the health care of asthma.

Difficult-to-treat asthma and systematic assessment

Most people referred to specialist care for uncontrolled asthma despite taking high-dose treatment do not have severe asthma, but have other causes of poor asthma control, such as treatment barriers, exposures to allergens or smoking, or asthma triggers caused by comorbidities. Hence, to make a diagnosis of severe asthma, a systematic assessment is mandated, to identify and manage these factors, before considering a biological treatment (figure 5).

Panel 3: **Controversies in severe asthma**

The definition of severe asthma might bias our perception of severe asthma towards a mainly type-2-inflammation-driven disease, because the definition is based on the intensity of the anti-inflammatory treatment, rather than biological characteristics of the disease process. People with asthma who have low type 2 biomarkers, have tried high-dose inhaled corticosteroids without effect, and have been down-titrated again, do not fulfill current definitions of severe asthma, even if they have a substantial burden of symptoms, reduced lung function, and exacerbations.

Furthermore, the terminology on severe asthma assumes that we can always differentiate between the truly severe asthma and people with other causes of poor asthma control (ie, the difficult-to-treat asthma). The reality is that many patients with severe asthma also have many other contributing factors, in particular comorbidities that might not be modifiable.

Hence, severe asthma needs to be redefined into a definition that reflects the complexity of this group of people, who often require the multidimensional and multidisciplinary approach offered in severe asthma clinics to improve asthma control.

Novel biological treatments targeting the inflammatory cascade in asthma more upstream (ie, at the initiation of the inflammtory response, at the epithelial level) could potentially make it possible to begin inducing asthma remission. More research is needed to understand what immune remission of asthma is and how it can be achieved.

We do not know what triggers asthma to become severe and what the typical trajectories in the development of severe asthma are. Improved knowledge on the triggers and mechanisms of severe asthma would allow more precise treatment and possibly also prevention in the future.

Systematic assessment consists of confirming the diagnosis with objective tests, and assessing phenotype, treatment barriers, triggers, and comorbidities,[120,121] and requires a highly specialised and multidisciplinary setup to adequately identify and manage all treatable traits. Importantly, a multidimensional management approach of patients who have poorly controlled asthma despite high-dose treatment has been shown to improve asthma control.[122] Asthma associated with factors other than severe asthma is termed difficult-to-treat asthma. Recognising that there is a substantial overlap of severe asthma and difficult-to-treat asthma both in children and adults is important,[123,124] because patients with truly severe asthma often have comorbidities that are not fully or easily modifiable, such as obesity and gastroesophageal reflux disease. Perhaps these patients should be considered as having complex asthma, rather than difficult-to-treat or severe asthma (ie, having several contributors to their symptom burden that need to be taken into consideration in a situation of loss of symptom control and managed appropriately).

Pharmacological treatment of severe asthma

Besides the described standard asthma therapies, there are several biological therapies available for severe asthma, but until the introduction of tezepelumab, therapies were mostly directed against type 2 inflammation (panel 3).

In general, the main effects of biological therapies are a reduction in exacerbations and the need for maintenance oral corticosteroids, and these two traits of severe asthma set the indication for starting a biological therapy in most countries, which is important to take into account when considering referral of a patient to a severe asthma center.[125] People with asthma might also experience substantial improvements in symptom control and lung function; generally, these effects have been moderate in phase 3 studies on biological therapies, mainly due to substantial improvements in the placebo groups, reflecting the importance of general asthma care in severe asthma as well. Subsequent real-life studies show more consistent effects on symptoms and lung function, which might reflect a better selection of patients through systematic assessment in the severe asthma clinics.

Most current biological therapies in severe asthma are directed towards mediators of type 2 inflammation, but recently a novel biological therapy targeting TSLP (tezepelumab) has been approved.[126] Although most effective in eosinophilic asthma, tezepelumab has also shown efficiency in patients with low biomarkers of type 2 inflammation.[127] The mode of action in these patients is unclear, but might reflect effects via mast cells or directly on the airway smooth muscle, both of which are activated by TSLP.

Other treatment options for severe asthma

Regular long-term use of azithromycin has been shown to decrease asthma exacerbations regardless of inflammatory

endotype,[128] but it might be even more effective in people with *Haemophilus influenzae* colonisation of the airways.[129] Gastrointestinal-tract related side effects are sometimes encountered with regular use of azithromycin, and macrolide resistance, potential reversible hearing loss, and long QT time are other factors to consider.

Bronchial thermoplasty is a procedure in which radiofrequency energy is applied to the bronchial wall, which has been shown to decrease asthma exacerbations. The precise mode of action is not fully understood; bronchial thermoplasty reduces airway smooth muscle mass but also appears to improve the ability of the airway epithelium to regenerate and affects afferent nerves of the airways.[130,131] However, studies are unclear on what type of patients would benefit most from bronchial thermoplasty.

Choosing between treatment modalities in severe asthma

There are several options for the treatment of severe asthma, particularly in a patient with type 2 high severe asthma, and treatment regimens should be selected with a precision medicine approach (ie, the right treatment for the right patient). Some of the current biological therapies for severe asthma are also licensed for the treatment of common comorbidities, such as atopic dermatitis or chronic rhinosinusitis with nasal polyposis, which might guide the choice of treatment (figure 5).

Severe asthma from a paediatric perspective

Severe asthma in children and adolescents is fortunately a rather rare condition. Estimates suggest that 2–10% of children with asthma of school-age and older have chronic symptoms or severe exacerbations despite treatment with several drugs.[132] However, most children and adolescents with asthma improve their asthma control once modifiable factors have been addressed (ie, difficult-to-treat asthma), and only a small remaining group can be classified as having severe therapy-resistant asthma. Type-2 high asthma constitutes a well defined endotype that is also found in children and adolescents, which is possible to treat with available biological drugs.

Asthma exacerbations

Asthma exacerbations are episodes of worsening symptoms that do not respond to rescue β_2 agonist treatment and require a change in therapy to resolve,[133] often including a short course of oral corticosteroids. Asthma exacerbations can be life threatening and are not always preceded by poor symptom control, either because of differences in perception of dyspnoea,[134] or because day to day symptoms reflect more than just airway inflammation.[135] Attempts to predict asthma exacerbations with risk stratification have yet to be implemented into mainstream clinical care.[136–138]

Asthma exacerbations are most prevalent in young children before school-age and are associated with many factors, including seasonal change (representing increased exposure to viruses or allergens), previous exacerbations, gastroesophageal reflux, obesity, low socioeconomic status, and comorbid diseases, including allergic rhinitis or chronic rhinosinusitis.[139,140] Several treatable traits are associated with an increased risk of asthma exacerbation and need to be assessed in clinic. Over-reliance on SABA (eg, salbutamol) has long been known to be associated with asthma exacerbations.[77,141] In Sweden, a third of adults with asthma were high-users of SABA (defined as three or more canisters per year), of whom 28% had no collection of anti-inflammatory drugs,[78] which suggests undertreatment of asthma and lack of inhaled corticosteroids to be the underlying cause of the increased exacerbation risk in people with asthma with a high SABA use; data are similar in the UK.[142] Elevated blood eosinophil counts are also associated with an increased risk of asthma exacerbation,[143,144] and are used as one variable to identify patients who might benefit from monoclonal antibody therapy. Poor adherence is often overlooked but is an important risk factor for exacerbations; the highest reduction in the odds of exacerbation is found in patients achieving 80% or more adherence with their inhaled corticosteroids.[145]

Clinical assessment and management of exacerbations

Asthma exacerbations cause acute shortness of breath and wheeze. Most exacerbations can be managed in the community with bronchodilators and often a short course of oral prednisolone (or betamethasone). More severe exacerbations require hospital admissions. Patients with asthma exacerbations can deteriorate rapidly; regular assessment via peak flow and patient examination is required. Oxygen saturations should be monitored by pulse oximetry (appendix p 5).[146,147]

Care after an exacerbation

Before discharge from hospital, patients should not have had any troublesome asthma symptoms for at least 24 h and should ideally have a PEF rate of more than 75% predicted (or best) at 1 h after treatment and have had their inhaler technique checked and asthma triggers identified. A written personalised asthma action plan explaining when and how medications should be changed, when to seek help, and future ongoing management, along with a PEF meter (or personal spirometer), should be administered. Follow-up should be arranged with a health-care professional in the near future.

Future directions

Asthma is one of the chronic inflammatory conditions for which we have the best insights into underlying immunological disease mechanisms, which has enabled the development of very targeted and hence safe and effective treatments. With this development, ambitions for achieving even better outcomes, such as the

prevention of asthma, but also inducing remission of asthma, have grown.[148] In the next few years, we can expect to learn much more about how to reach these ambitious goals, such as earlier intervention in at-risk individuals, but we must also aim for a future in which long-term oral steroids are not needed and admissions to intensive care units and asthma deaths are a thing of the past.

Contributors

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