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CLINICAL PERSPECTIVES

Overview of recent advancements in asthma management

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Abstract

Asthma is a common but complex heterogenous inflammatory airway disorder. Despite significant developments in our understanding of the pathophysiology and treatment of asthma, it remains a major cause of mortality and morbidity. Optimal management involves addressing modifiable risk factors, titration of inhaled pharmacotherapy in a stepwise approach and, in severe disease, consideration of biologic agents. Appreciation of the clinical characteristics of asthma and recognition of the immune pathways involved has allowed the development of phenotypic and endotypic subtypes of asthma to be better defined. This has revolutionised asthma management, allowing risk stratification of patients, targeted use of biologic agents to modify cytokine responses that drive asthma and improved patient outcomes. Patient education and engagement are critical to the management of this disease in an era of personalised medicine and a rapidly changing global environment.

Introduction

Asthma is one of the most common chronic diseases globally and in Australia affects 1 in 9 people.[1] It is a heterogenous respiratory disease characterised by chronic airway inflammation, variable airflow limitation and characteristic symptoms of wheeze, dyspnoea, chest tightness and/or cough that vary over time and in intensity.[2] Periods of breakthrough symptoms can develop into exacerbations, which may require hospitalisation, and in some cases are fatal.[3] While most severe exacerbations occur in patients whose disease is poorly controlled, a significant proportion of fatal asthma exacerbations occur in patients whose disease had previously been misclassified as mild.[4]

Asthma-related morbidity and deaths remain unacceptably high in Australia.[2,5,6] In 2018, there were 389 deaths caused by asthma. Per population, this is higher than comparable high-income countries such as Germany and Sweden.[5,7] Worldwide, avoidable asthma deaths are attributed to inappropriate management of asthma, including overreliance on reliever medication rather than preventer medication.[5] Up to 80% of Australian asthma hospitalisations are also considered preventable.[1] People with asthma are also more likely to report poorer quality of life than people of the same age without asthma.[1]

The significance of disease burden is particularly evident in the 10% of asthmatics who are classified as having severe asthma in Australia, with more frequent presentations to hospital, use of oral corticosteroids (OCS) with associated adverse effects, hospitalisation and death. This has implications at both the individual and healthcare system levels.[1,2]

Driven by research into severe asthma, a more complete understanding of airway inflammation, upper and

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lower airway muscles and the interaction between individuals and the environment has led to the development of highly specific biologics and other personalised therapies that have revolutionised asthma management.

Pathogenesis

The pathophysiology of asthma centres around airway inflammation. This inflammation results in airflow obstruction and hyperresponsiveness.[8] Over time, this causes increased airway wall thickness with hyperplasia of the airway smooth muscle, thickening of the lamina reticularis layer of the basement membrane, increased extracellular matrix deposition and increased submucosal glands.[8]

Despite this understanding of the pathophysiology, asthma remains a complex disease and has long been recognised to include several disease variants. The concept of an asthma 'phenotype' refers to 'clinically observable characteristics' of a disease and may relate to the presentation of asthma, triggers and treatment response. Phenotypes are useful in describing the clinically relevant properties of a disease but do not directly correlate with disease aetiology and pathophysiology. Furthermore, separating asthma into distinct phenotypes can be challenging because of the lack of specific and validated markers.[9]

A major development in our understanding of asthma pathophysiology involves defining asthma into 'endotypes' based on which immune-inflammatory pathways are involved. This endotype-driven approach allows for better diagnosis, monitoring and stratification of patients and better evaluation of treatment options, particularly in severe asthma.[10] Type 2 high (T2), type 2 low (non-T2) and mixed endotypes are described for severe asthma. Several shared pathophysiological pathways, such as genetic, epigenetic, metabolic and remodelling subtypes, are also described.[10]

Endotyping of asthma, through the use of biomarkers from body fluids or affected tissues, has the potential to individualise asthma management for patients and link the key pathogenic mechanism with a clinical asthma phenotype.[9]

By using both phenotypes and endotypes, effective targeted treatment options can be found for asthma patients, leading to significantly improved health outcomes. This has become more important with the development and widespread use of biologic agents to treat severe asthma.

Asthma phenotypes

Some examples of well-recognised asthma phenotypes include:

Allergic asthma

Allergic asthma is the most common phenotype of asthma and is characterised by a personal or family history of allergic asthma and co-occurrence with allergic rhinitis and atopic dermatitis.[8] It commonly, but not exclusively, presents in childhood. High levels of allergen-specific IgE are the immunologic hallmark. Evidence of atopy through skin prick testing is key to the diagnosis, and allergic inflammation is likely to result in increased blood and sputum eosinophils.

Eosinophilic asthma

Eosinophilic asthma is an often adult-onset disease defined by high levels of eosinophilic inflammation in the absence of atopy,[8] initially recognised through elevated induced sputum eosinophils. A blood eosinophil count of ≥300 cells/μL is a useful indicator of the presence of airway inflammation. Eosinophilic asthma is generally steroid-responsive although may be refractory to inhaled therapies and may require OCS and biologic therapy to achieve control.[8]

Aspirin-exacerbated respiratory disease

Aspirin-exacerbated respiratory disease (AERD) is characterised by chronic eosinophilic rhinosinusitis, asthma, nasal polyps and aspirin sensitivity.[8,11] The latter three features are referred to as Samter triad.[11] Nonsteroidal anti-inflammatory drugs (NSAIDs) exacerbate this condition. AERD has a more treatment-refractory disease course.[11] Treatment involves optimising underlying asthma, using intranasal steroid sprays or rinses for sinus inflammation and may involve nasal polypectomy. Avoidance of NSAIDs is important and aspirin desensitisation has been employed as a therapeutic option. Leukotriene-modifying agents, such as montelukast, can be effective in some cases and anti-eosinophil agents are also effective.[12]

Neutrophilic asthma

Neutrophilic asthma is less clearly defined than other phenotypes and is difficult to diagnose given the practice of induced sputum cellular analysis is not routine in most centres.[8] Neutrophilic asthma is generally difficult to control and steroid insensitive and currently does not have a specific biologic therapy available.[8] Macrolides have been used for treatment of this group.[13]

Obesity-associated asthma

Obesity-associated asthma is a nonallergic phenotype of asthma often occurring in obese women with a later onset and disproportionately high burden of symptoms and need for hospitalisation.[14]

Exercise-induced bronchoconstriction

Although exercise is recognised as a common trigger in asthma, in some individuals exercise-induced bronchoconstriction occurs without a diagnosis of chronic asthma. Exercise challenge testing or eucapnic voluntary hyperpnoea are used for diagnosis.[15] Inhaled corticosteroid–long-acting β_2-agonist (ICS-LABA) prior to exercise provides better control than a short-acting β_2-agonist (SABA) alone.[16]

Asthma endotypes

In contrast to phenotypes, which describe clinical and morphological characteristics, endotypes are a way to group disease subtypes using pathophysiology.[9] This is conceptually important to understanding developments in targeted therapy. However, the inability to measure cytokines directly limits the clinical applications of endotypical classification.

T2 asthma

From an immune perspective, asthma is predominantly mediated by T helper 2 (Th2) cells. This can occur by at least two pathways. In susceptible individuals, allergen, pollutant or microorganism exposure causes bronchial epithelial cells to release interleukin (IL)-33 (also synthesised by airway smooth muscle and mast cells), IL-25 and thymic stromal lymphopoietin (TSLP). These promote the activation of Th2 cytokines, in particular IL-4, IL-5, IL-9 and IL-13.[10,17] A separate pathway is through cognate antigen presentation to T cells and subsequent generation of B-cell response leading to IgE production, eosinophilia and mast cell activation. IL-4 has a key role in regulating Th2 differentiation.[8] IL-5 and IL-9 are responsible for the activation of eosinophils and mast cells respectively.[18] IL-13 induces goblet cell hyperplasia, mucous hypersecretion, eosinophilia and airway hyperresponsiveness.[8,18] The common end pathway of both cognate and noncognate interactions is eosinophilic asthma.[19] The currently identified T2 asthma phenotypes are allergic asthma, eosinophilic asthma and AERD.[14]

Non-T2 asthma

Non-T2 asthma, often referred to as noneosinophilic asthma, includes both inflammatory endotypes (where non-T2 cytokines are involved in driving asthma) and noninflammatory endotypes (where structural abnormalities and neuroinflammation are present). Sputum cytometry can help to differentiate subendotypes.[10] Neutrophilic, paucigranulocytic (absence of airway eosinophilia and neutrophilia) and obesity-associated asthma are currently defined non-T2 phenotypes. Key cytokines in neutrophilic asthma are IL-17, IL-8 and IL-6, whereas paucigranulocytic asthma is characterised by the absence of airway inflammation (eosinophilia and neutrophilia) with persistent symptoms of asthma and evidence of airway hyperresponsiveness.[10] Paucigranulocytic asthma may also reflect well-treated asthma.[20]

Noninvasive biomarkers

Induced sputum is the gold standard approach to the noninvasive study of airway inflammation and can also be used to study infective agents in the airway. The differential cell counts obtained are relevant in characterising asthma (Fig. 1). Sputum eosinophil counts correlate well with more invasive testing through bronchoalveolar lavage or bronchial biopsies.[20]

A noninvasive method that acts as a surrogate marker of eosinophilic airway inflammation is the measurement of fractional exhaled nitric oxide (FeNO). FeNO is often elevated in patients with eosinophilic asthma[2,21] and can be used to predict steroid responsiveness. It is a breath test of submaximal effort, which is quicker than spirometry and can be performed by the bedside. Although not diagnostic, FeNO correlates with sputum eosinophils, and a high FeNO is supportive of a diagnosis of allergic or eosinophilic airway inflammation.[22]

Diagnosis

The diagnosis of asthma is made based on two criteria:

1 history of characteristic respiratory symptoms that vary over time and in intensity; and
2 confirmed variable airflow limitation.

The characteristic symptoms of asthma include cough, wheeze and chest tightness. Symptoms are commonly worse at night and in the early morning. Patients may have variable triggers but common triggers are cold or changing weather, exercise, viral infections, strong emotion and allergen exposure.[2]

Variable airflow limitation, or obstruction, is most accurately measured with spirometry. Obstruction on spirometry is diagnosed with a reduced forced expiratory volume in the first second of expiration (FEV_1)/forced vital capacity ratio of <0.7 or below the predicted value for the patient's age, sex and ethnicity.[2] Peak expiratory flow (PEF) is a convenient measure of airflow obstruction that the patient can self-perform; however, being effort-dependent, it is associated with less reliable results than in-laboratory spirometry.[2]

Variability in airflow limitation can be demonstrated by reversible airway obstruction on spirometry: a change

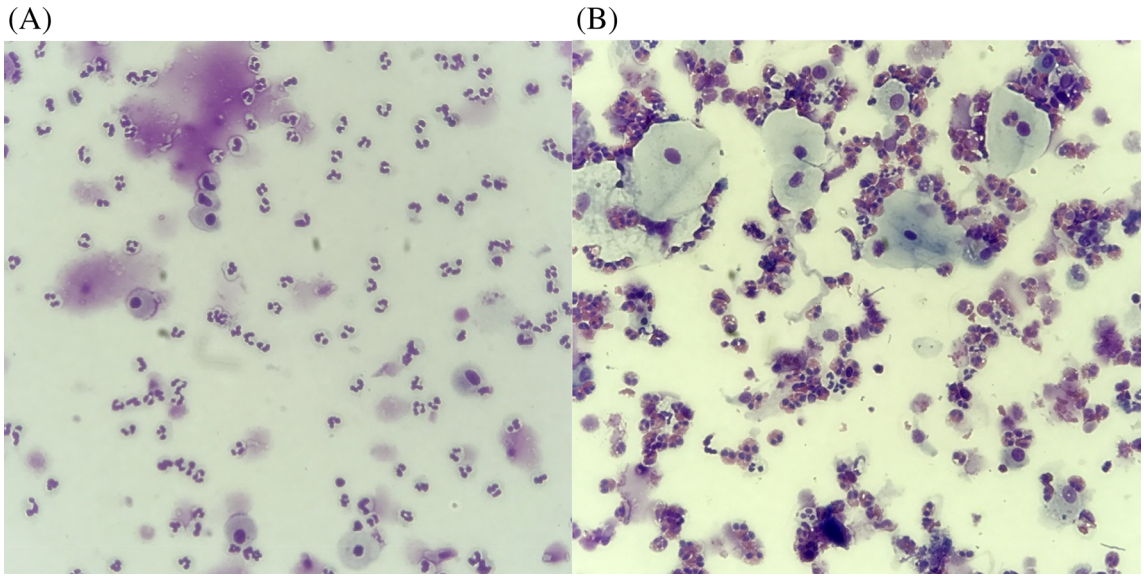

Figure 1 Induced sputum from a patient with neutrophilic asthma (A) and eosinophilic asthma (B).

in FEV_1 of >12% and >200 mL is consistent with asthma.[2] Using PEF, definitions vary; however, the National Institute for Health and Care Excellence reported that diurnal variability of 15% over four or more days had 97% specificity for diagnosing asthma in people with respiratory signs and symptoms.[23] These measures are not only important in diagnosis but in monitoring asthma treatment. Handheld spirometers are increasingly accessible and affordable and can be used to document variability in settings where it may otherwise be challenging, such as in exercise-induced asthma.

In patients with normal spirometry, bronchial provocation testing can be performed to document variable airflow limitation. Although bronchial provocation testing may not be necessary to make a diagnosis of asthma for the majority of patients, it is an option for atypical presentations, where the diagnosis is uncertain, and for those in whom a definitive diagnosis is important. A fall in FEV_1 of 20% with methacholine or 15% with mannitol is consistent with a diagnosis of asthma.[2]

Severity

Recent changes to the Global Initiative for Asthma (GINA) recommendations mean severe asthma is now defined without reference to GINA Steps (Fig. 2), and asthma severity is assessed based on the treatment required to control the patient's symptoms. Thus, severe asthma is defined as asthma that is uncontrolled despite high-dose ICS-LABA or that requires high-dose ICS-LABA to remain controlled.[2]

Risk factors

Uncontrolled asthma symptoms are the most important predictor of exacerbation risk; however, the risk factors outlined in Table 1 increase the risk of exacerbations independent of symptoms and require individual attention and treatment.[2]

Treatable traits

A newer paradigm in understanding factors that can contribute to asthma symptoms takes into consideration:

1 overlapping disorders that can present with symptoms that are indistinguishable from asthma, for example, chronic obstructive pulmonary disease, bronchiectasis and inducible laryngeal obstruction.
2 Comorbidities that may contribute to poor asthma control, for example, gastro-oesophageal reflux, obesity, depression and treatment side effects.
3 Lifestyle or environmental factors, for example, cigarette smoke, indoor/outdoor pollution and workplace exposures.
4 Behavioural factors, for example, symptom perception, inhaler device polypharmacy, treatment adherence, inhaler technique and family and social support.

Investigation and management of these 'treatable traits' represent personalised management where the various components causing poor asthma control can be identified and optimised for each individual.[24] This concept is also reflected in the 2021 GINA recommendations where assessment of correct inhaler technique,

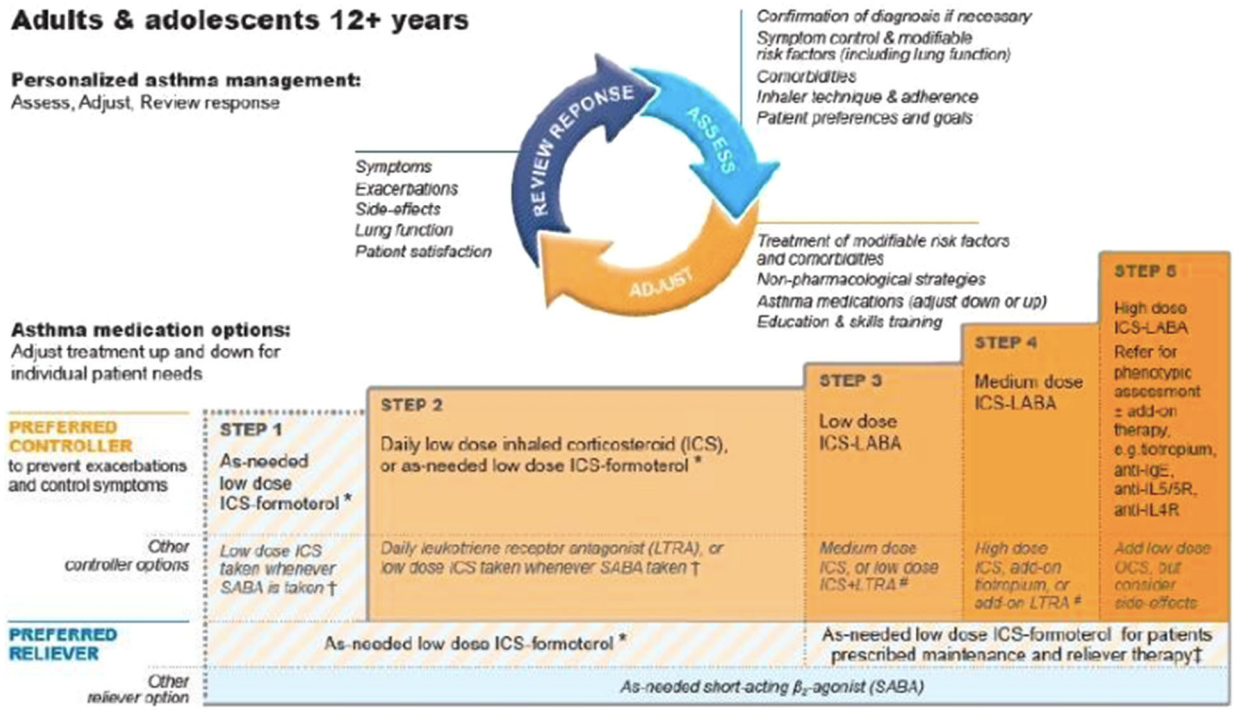

Figure 2 Stepwise titration of asthma treatment. Reproduced with permission from Global Strategy for Asthma Management and Prevention, 2021. Available from URL: www.ginasthma.org[2]. HDM SLIT, house dust mite sublingual immunotherapy; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor agonist; SABA, short-acting β_2-agonist.

medication adherence, modifiable risk factors and comorbidities occur prior to stepping up therapy (Fig. 2).[2]

Management

Asthma management aims to control symptoms, prevent exacerbations and minimise the risk of persistent airflow limitation and asthma-related death.[2]

Control-based asthma management uses the presence of symptoms to guide adjustments to therapy and is shown to improve outcomes on a population level.[2] Several validated asthma control questionnaires are available and can be used serially to monitor objectively patient symptoms and control. Examples include the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ-5). The latter uses five items to assess daytime and nighttime symptoms, activity limitation and reliever medication use over the past week as reported by the patient.[25]

All patients should be trained in correct inhaler technique, as incorrect technique is frequent and impacts optimal drug delivery.[26] In addition, assessment of symptoms, adherence, triggers and optimisation of comorbidities and risk factors should occur at each clinical review as standard of care and as part of personalised asthma management.[26] Poor adherence to pharmacotherapy is common and associated with poor outcomes.[27] Given the inaccuracies of self-reported adherence, monitoring of prescription filling and electronic inhaler monitors are potential options for more accurate assessment of adherence; however, these are not available to all practitioners.[27]

Table 1 Risk factors for asthma exacerbations

Patient comorbidities	Chronic rhinosinusitis, gastro-oesophageal reflux disease, obesity, pregnancy, major psychosocial affliction, inducible laryngeal obstruction
Physiological factors	Decreased FEV_1 (particularly <60% predicted), high bronchodilator reversibility, peripheral eosinophilia, elevated FeNO despite ICS
Exposures	Smoking, pollution, allergens sensitised to including food allergens
Medication factors	High short-acting β_2-agonist use, inadequate or no ICS, poor adherence, incorrect inhaler technique
Previous exacerbation	Ever intubated or required admission to intensive care, >1 severe exacerbation in the past 12 months

Abbreviations: FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second of expiration; ICS, inhaled corticosteroid.

Adjustments to management are made according to response and patient preference and goals (Fig. 2). Patient education and engagement are paramount.

If safe and possible to do so, evidence of an asthma diagnosis through spirometry, which may include bronchoprovocation, should be recorded prior to commencement of pharmacotherapy. In the case of difficult to manage or control asthma, spirometry is a vital step in establishing the correct diagnosis.

Pharmacological management

ICS are the backbone of asthma management and should be initiated as soon as possible after a diagnosis of asthma is made.[28]

Pharmacotherapy for asthma can be divided into three categories:

1 *preventer medication*, which controls symptoms, reduces risk of exacerbation and prevents the sequelae of chronic inflammation.
2 *Reliever medication*, which is taken as required for symptoms.
3 *Add-on therapies*, including biologic agents, for severe disease.

There has been a significant change to the management of asthma following the release of the 2019 GINA recommendations. SABA-only treatment is no longer recommended for the treatment of asthma in any adult, given strong evidence that SABA-only treatment increases the risk of severe exacerbations and asthma-related death.[29]

Initial therapy

For most patients with infrequent and mild symptoms, the initial recommended therapy is as-needed, low-dose ICS-formoterol.[30] It is important to note that formoterol is specifically chosen as the LABA in this situation because of its rapid onset of action compared with other β_2-agonists. In trials, as-needed ICS-formoterol reduced exacerbations when compared with as-needed SABA alone, and may have advantages in treatment adherence compared with continuous preventive treatment.[31] The alternative initial therapy is a daily low-dose ICS preventer and SABA, which is shown to improve lung function and asthma control compared with as- needed ICS-formoterol with equivalent outcomes regarding exacerbations, and may be a more affordable option, especially in lower-income settings.[32] For patients whose symptoms are frequent enough that they would require a reliever medication more than twice a month, a daily low-dose ICS preventer is the recommended initial therapy.[2]

Patients whose initial presentation of asthma is that of a severe exacerbation should be prescribed a short course of OCS in conjunction with an ICS-containing preventer that should remain long-term.

Pharmacotherapy should be uptitrated in a stepwise approach, individualised to the patient's symptoms. Monitoring of side effects, barriers to compliance such as financial limitations and patient expectations should be considered. Once daily, inhaler regimens may improve compliance, but not necessarily clinical outcomes.[33]

Table 2 Add-on therapy

Add-on therapy	Comment
Increased ICS dose	Increasing the ICS dose provides little additional benefit at this step[34,35] but is associated with an increased side-effect profile.
Long-acting muscarinic antagonists	Tiotropium is shown to improve moderately lung function and increase the time to severe exacerbation. Tiotropium inhibits muscarinic M3 receptors preferentially and reduces AHR in asthma patients and may act by targeting mast cells.[10]
Macrolides	Macrolides possess antimicrobial as well as immunomodulatory properties. Azithromycin taken three times weekly is shown to reduce exacerbations and improve asthma-related quality of life.[13]
Leukotriene receptor antagonists	Montelukast improves asthma control when added to ICS monotherapy, but ICS-montelukast was inferior to ICS-LABA. It may have some use in exercise-induced asthma and AERD.[36]
Low-dose oral corticosteroids	In patients with severe, uncontrolled disease despite appropriate stepwise management, regular OCS or frequent bursts of OCS may be required.[2,37] Continuous OCS should be used at the lowest possible dose and be considered a temporary therapy only until specialist referral, where transitioning to steroid-sparing agents (such as biologics), should be considered. This is separate from management of asthma exacerbations where a short (3- to 5-day) course of OCS is routinely recommended.[2] Corticosteroid use is associated with a significant adverse-effect profile including osteoporosis and bone fractures, weight gain, mood disorders and hyperglycaemia.[37] It should also be noted that repeated short courses of OCS reach a cumulative toxic dose that can result in the above adverse effects.[27]

Abbreviations: AERD, aspirin-exacerbated respiratory disease; AHR, airway hyperreactivity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OCS, oral corticosteroid.

Table 3 Biologic drugs currently available in Australia

Immunological target	Biologic Agent	Mechanism of action	Outcomes	Administration
IgE	Omalizumab	Monoclonal antibody that binds Fc portion of IgE, inhibiting binding to masts cells and instead forming omalizumab-IgE complexes.[8,38]	In patients with severe allergic asthma, omalizumab reduced exacerbations by 25% at 12 months. Symptomatic onset of efficacy of omalizumab is at 12–16 weeks with stabilisation of peak flow and symptoms.[39]	2–4 weekly
IL-5	Mepolizumab	Monoclonal antibody that blocks binding of IL-5 to the α chain of IL-5 receptor, inhibiting eosinophilic inflammation.[8,38,40]	In patients with severe eosinophilic asthma, mepolizumab reduced exacerbation rate by 53% at 12 months, and a clinically significant reduction in symptoms.[40]	4 weekly
IL-5R	Benralizumab	Fucosylated monoclonal antibody that acts on IL-5Rα on eosinophils and basophils, inducing antibody mediated cytotoxicity and rapid eosinophil depletion.[8,38,41]	In patients with severe eosinophilic asthma, benralizumab reduced exacerbations by 51% at 12 months, reduced serum eosinophil counts and improved symptom control.[41]	4 weekly for first 3 doses, then 8 weekly dosing interval recommended.
IL-4Rα	Dupilumab	Monoclonal antibody to the IL-4Rα subunit that inhibits IL-4 and IL-13.[8,38]	In moderate–severe asthma, dupilumab reduced exacerbations in severe asthma by 47% and improved lung function and symptoms.[42]	2 weekly

Abbreviations: IL, interleukin.

If symptoms occur less than twice per month and there are no exacerbation risk factors, the patient commences at step 1. If symptoms occur more than twice per month and/or exacerbation risk factors are present, the patient commences at step 2 (Fig. 2).

Add-on pharmacotherapies

In patients whose asthma is not controlled on moderate- to high-dose ICS-LABA, phenotypic and endotypic assessment for consideration of biologic drugs should occur. Additional therapies (Table 2) can be considered at this step. Moderate doses of ICS are defined as >400 mcg budesonide, >160 mcg ciclesonide, >250 mcg fluticasone or equivalent.[2]

Stepping down

Once the patient achieves good control as defined by symptom measurement and exacerbations, treatment should be reduced, aiming to find the lowest effective dose of ICS. Each reduction should be seen as a therapeutic trial and the patient should be educated to recommence their previous dose if symptoms worsen.[2]

Self-management education

All patients, regardless of asthma severity, should have a personalised 'Asthma Action Plan' – a document that details what symptoms indicate worsening control or an exacerbation and how to manage these – as part of self-management education. The addition of peak flow values may be helpful in some patients, such as those who are poor perceivers of symptoms.[2,37] Patients with education on self-management were hospitalised 36% less often than those without.[37]

Biologic drugs

Biologic agents for asthma target endotypical inflammatory pathways and are delivered as subcutaneous injections in either a hospital setting, through a general

Table 4 Indications for referral to a specialist asthma clinic

1 Two or more courses of oral corticosteroids in the past 12 months, or maintenance oral corticosteroids.
2 Exacerbation requiring hospitalisation in the past 12 months.
3 Persistent symptoms despite Global Initiative for Asthma Step 4 (medium-dose ICS-LABA) treatment.
4 Uncertainty about asthma diagnosis.
5 Suspected occupational asthma.

practitioner or self-administered by the patient at home. Available biologic drugs are listed in Table 3.

Newer biologic agents currently under investigation

Anti-TSLP (tezepelumab)

Tezepelumab, an anti-TSLP monoclonal antibody, reduced exacerbations and improved lung function, asthma control and quality of life in moderate–severe asthma.[43]

Anti–IL-33 (astegolimab)

Astegolimab is a monoclonal antibody that targets IL-33 and decreases exacerbations in adult patients with severe asthma regardless of blood eosinophils.[10]

Bronchial thermoplasty. Bronchoscopic thermoablation of the smooth muscle in the airways is an option available in some severe asthma centres. In some studies, bronchial thermoplasty (BT) improved symptom control and decreased exacerbations; however, there was a considerable response seen in the placebo group.[44] BT remains a subject of debate because of short-term complications from the procedure, such as asthma exacerbation, and uncertain long-term outcomes. BT has not been recommended in international guidelines outside of clinical trials or registry studies.[45]

Immunotherapy. In selected patients with allergic asthma, there may be a role for immunotherapy, which is the administration, either subcutaneously or sublingually (SLIT), of an exogenous aeroallergen to which a person has demonstrated sensitisation in order to reduce the IgE-mediated allergic responses associated with asthma and rhinitis.[45] Registered therapies in Australia that have efficacy in asthma include house dust mite and grass pollen SLIT,[46,47] with choice of therapy often guided by the allergy specialist.[45] Immunotherapy has the potential to worsen asthma symptoms, so should be administered under supervision in patients whose asthma control is optimised.[45]

Referral to a specialist asthma clinic

Indications for referral to a specialist asthma clinic are listed in Table 4.[2,46]

Personalised asthma management

Asthma management should be personalised and stratified, especially in severe asthma. Concepts of shared decision-making between patient and clinician in setting treatment goals, practical use of pharmacotherapy, such as as-needed preventer medication, considering 'treatable traits' of asthma and phenotyping and endotyping of severe asthma form the basis of a patient-focussed strategy informed by an understanding of inflammatory pathways rather than a 'one-size-fits-all' approach.

Asthma, the environment and thunderstorm asthma

The impact of pollution and environmental exposures on the clinical presentation and pathophysiology of asthma is an increasingly recognised and important phenomenon. Wildfires are increasing in frequency and severity and have adverse effects on respiratory health associated with fine particulate matter PM 2.5.[10] Climate change can alter the duration and intensity of pollen season and pollen allergy worldwide, and thus the risks of severe episodic thunderstorm asthma especially in people with allergic rhinitis.[10,48] Mould proliferation can cause similar presentations. Enhancing environmental health literacy is key to managing these disparate asthma triggers. Optimising asthma control and adherence to ICS, treatment of allergic rhinitis and recognition of asthma symptoms especially during 'at-risk' days are the mainstay of treatment of thunderstorm asthma.[48,49]

COVID-19

Given the known correlation between asthma and influenza A disease severity, there were concerns early in the coronavirus disease 2019 (COVID-19) pandemic about the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with asthma. Asthma is not an independent risk factor for either SARS-CoV-2 infection or disease severity. Asthma phenotypes with high peripheral eosinophils may be associated with reduced mortality, which is postulated to be attributable to the role of eosinophils in viral infections.[50] ICS decreases the expression of pulmonary angiotensin-converting enzyme-2, the receptor through which SARS-CoV-2 enters host cells, which may further explain the apparent protectiveness of asthma against severe disease. However, in post-acute COVID-19 syndrome, or long COVID, a history of asthma has been demonstrated to be a risk factor.[51]

Conclusion

Asthma is a complex disease for which optimal management requires an understanding of the varied drivers of immune pathways, as well as stepwise titration of

medications tailored for the individual patient and their symptoms. Phenotyping and endotyping asthma with the assistance of biomarkers, and the development of biologic agents that target specific immune pathways, has led to significant advances in the control of severe disease and contains exciting potential for future therapeutics. Significant changes to recommended management have occurred in recent years and a more personalised approach to asthma therapy has revolutionised the field in a rapidly changing global environment.

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