Diagnosis of severe asthma

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Summary

- Patients with asthma that is uncontrolled despite high intensity medication can present in both primary and specialist care.
- An increasing number of novel (and expensive) treatments are available for patients who fail conventional asthma therapy, but these may not be appropriate for all such patients. It is essential that a rigorous evaluation process be undertaken for these patients to identify those with biologically severe asthma who will require novel therapies, and those who may improve with control of contributory factors.
- In this article, we describe three key steps in the diagnostic evaluation process for severe asthma. The first step is confirmation of asthma diagnosis with objective evidence of variable airflow obstruction. The second involves management of contributory factors such as non-adherence, poor inhaler technique, ongoing asthma triggers, and comorbidities. The third step involves phenotyping and endotyping of patients with severe asthma. We provide a practical approach to implementing these measures in both primary and secondary care.

Patients are considered to have difficult-to-treat (difficult) asthma if their asthma remains uncontrolled despite high intensity asthma therapy (ie, high dose inhaled corticosteroids plus second controller), or if high intensity therapy is required to achieve control (Box 1).[1] These patients comprise a heterogeneous group, in whom intrinsically severe asthma biology, incorrect diagnoses, patient behaviour and other contributory factors may all lead to poor asthma control.

Biologically severe asthma is a subset of difficult asthma and a diagnosis of exclusion. In international guidelines, this group of patients has been referred to as having severe asthma,[2] which should only be diagnosed if the asthma remains uncontrolled on high intensity medications after the exclusion of alternative diagnoses and optimisation of contributory factors. The distinction between difficult and severe asthma has important therapeutic implications. For example, expensive and novel therapies such as biologicals should be reserved for use in severe asthma only, and would not be appropriate for all patients with undifferentiated difficult asthma.

In the general community, a European study estimated that 17.4% of the adult asthma population had difficult asthma.[3] Of these, only 20.5% had severe asthma, accounting for 3.6% of the adult asthma population.[3]

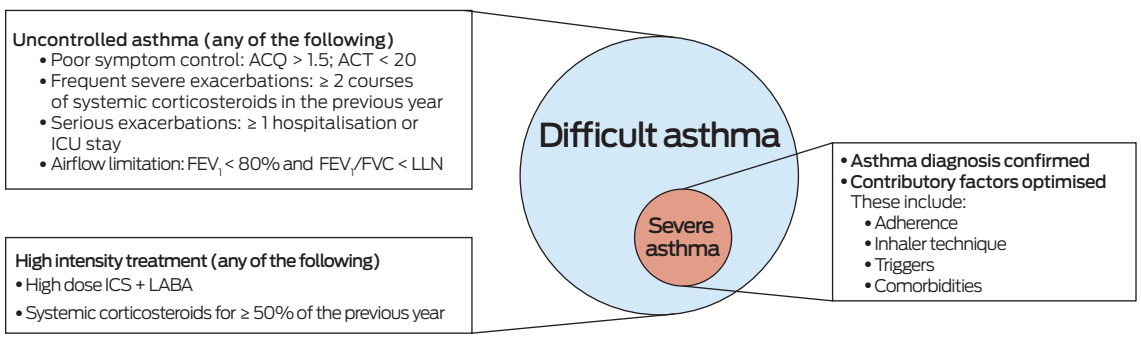
The evaluation of patients with difficult asthma can be initiated in the primary care setting, although the diagnosis of severe asthma is usually confirmed following specialist evaluation.[2,4] Box 2 outlines key elements of the diagnostic process for severe asthma; in this review, we describe each step in further detail. A glossary of key terms is provided in Box 3.

Step one: confirm asthma diagnosis

The first step in establishing a diagnosis of asthma is to stratify patients according to the likelihood of asthma based on clinical symptoms and signs.[5] Asthma usually presents with a combination of shortness of breath, wheeze, chest tightness or cough. However, various other pulmonary and non-pulmonary conditions can give rise to asthma-like symptoms; clinical clues suggesting alternative diagnoses should therefore be actively sought during clinical consultation (Box 4).

The next step is to seek evidence of variable airflow obstruction (VAO). The importance of this is emphasised in major guidelines[6,7] because diagnosis based solely on clinical impression results in substantial misdiagnosis.[8] In two different studies, one-third of patients with doctor-diagnosed asthma were found to have no evidence of asthma after objective assessment.[8,9] Misdiagnosis occurs at the specialist level as well: 5% and 12% of specialist-referred patients were found to have alternative diagnoses after difficult asthma assessment in an

1 Definition of difficult asthma and its relationship to severe asthma



ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICU = intensive care unit; ICS = inhaled corticosteroids; LABA = long-acting β-agonists; LLN = lower limit of normal.

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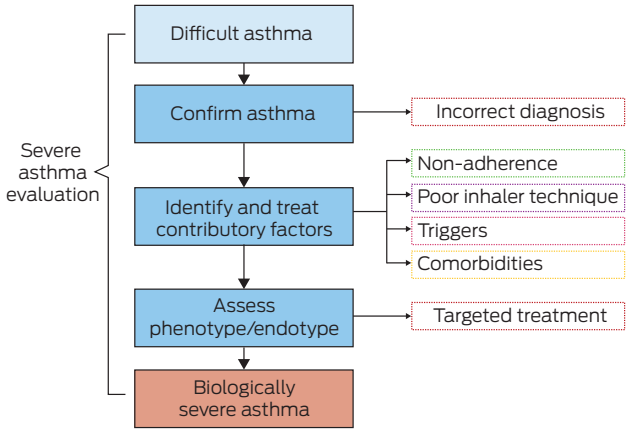
2 Diagnostic evaluation of severe asthma



Australian and a United Kingdom-based study, respectively.[10,11] Historical evidence of VAO lends support to a diagnosis of asthma, although re-evaluation should be considered if there is substantial change in asthma symptoms in the interim.

VAO is most commonly demonstrated on spirometry, with bronchodilator reversibility (BDR) of greater than 12% and 200 mL. This test can be performed in primary care clinics using a portable office spirometer, but interpretation of results requires caution as BDR lacks sensitivity (< 50%) in differentiating asthma from healthy controls,[12,13] and lacks specificity in differentiating asthma from chronic obstructive pulmonary disease.[12,14] Thus, negative BDR does not exclude a diagnosis of asthma, while positive BDR may require further evaluation to differentiate from other obstructive airway diseases. Peak flow monitoring should be performed if spirometry is not available or BDR is negative, but it is highly effort-dependent and requires greater patient engagement.[15]

When spirometry is normal without BDR, a bronchial challenge test may be undertaken to demonstrate VAO. This may be performed with agents that directly cause airway smooth muscle constriction, such as methacholine (known as direct challenge testing) or with agents that act on airway smooth muscle through the release of inflammatory mediators, such as mannitol (indirect challenge testing). Direct challenge tests have a very high sensitivity; a negative test therefore makes the diagnosis of current asthma highly unlikely.[16] A positive indirect challenge test confirms the diagnosis of asthma, and closely reflects airway inflammation and disease activity.[17]

It is increasingly acknowledged that there are limitations to using VAO to diagnose asthma.[18] In particular, irreversible airflow obstruction due to airway remodelling can develop in asthma,[19] and a distinct subset of patients with reduced lung function and negligible response to bronchodilator testing has been described.[20] Nevertheless, objective demonstration of impaired airway physiology should always be sought in patients presenting with difficult asthma.

3 Glossary

Asthma biomarker	A biological characteristic that is objectively measured and evaluated as an indicator of normal biological or pathological processes, or a response to a therapeutic intervention. Biomarkers in asthma include fractional exhaled nitric oxide, peripheral blood eosinophils and sputum eosinophils.
Asthma comorbidity	A disease that coexists with asthma, such as rhinitis or chronic rhinosinusitis.
Asthma endotype	Distinct functional or pathophysiological mechanism driving the disease process. For example, patients with aspirin-exacerbated respiratory disease have dysregulated arachidonic acid metabolism which leads to overproduction of inflammatory leukotrienes.
Asthma phenotype	Observable characteristics of a patient, such as age of asthma onset, atopy status, persistence of airflow limitation on spirometry and inflammatory cell type.
Treatable trait	A trait that can be treated based on phenotype or endotype. These traits include airflow limitation, eosinophilic airway inflammation and airway bacterial colonisation.

Step two: identify and treat contributory factors

Non-adherence, poor inhaler technique, exposure to triggers, and comorbid conditions can all contribute to poor asthma control. Evaluation of these contributory factors should be undertaken during every clinic consultation at both primary and specialist care levels.

Non-adherence

Non-adherence is a major problem in asthma. Studies worldwide consistently show that patients often take < 30% of their daily prescribed doses of asthma controllers.[21,22] Adherence rates in patients with difficult asthma are also disappointingly low. In a Melbourne-based study, close to half of the patients with difficult asthma were non-adherent to their asthma controllers.[23] In another study following hospitalisation for a severe asthma exacerbation, patient adherence to inhaled corticosteroids (ICS) was just 50% one week after discharge.[24]

Regular use of even low dose ICS protects against asthma deaths[25] and reduces the risk of asthma exacerbations,[26] with an adherence rate of ≥ 75% giving the greatest reduction in risk of exacerbations.[22] Medication non-adherence leads to adverse clinical outcomes and is associated with asthma mortality. In patients with difficult asthma, non-adherence is an independent predictor of near-fatal asthma.[27]

Addressing medication non-adherence first requires accurate measurement, but this may be challenging in many settings. Various methods have been proposed, each with its disadvantages.[28] Patient self-report is the most convenient way to assess adherence, but this often involves over-reporting.[29,30] Pharmacy prescription refill records provide an objective way to measure adherence and have been validated for use in various centres.[31] However, prescription refill review cannot ensure that the medication is actually taken, and prescription records may not be readily accessible in all health care systems. Electronic dose monitors provide accurate recordings of the time and frequency of doses taken, and recorded data can be downloaded by the patient and clinician for review.[32] Some electronic dose monitors also come with audio-visual reminders to improve patient adherence. Their main drawbacks are cost and the lack of a suitable device for every inhaler. Fractional exhaled nitric oxide (FENO) is a biomarker measured non-invasively from a patient's exhaled breath. A high value (usually > 50 parts per billion) indicates eosinophilic inflammation and predicts response to corticosteroids. Suppression of FENO under directly observed controller therapy has been used as an indicator of ICS

4 Mimics of asthma and clinical clues for diagnosis

Conditions that can mimic asthma	Clinical clues
Non-pulmonary	
Cardiac failure	Pre-existing cardiac disease, orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema
Congenital heart disease	Cardiac murmurs
Dysfunctional breathing	Dizziness, light-headedness, peripheral tingling
Vocal cord dysfunction	Stridor, throat tightness, voice change, lack of wheezing in the chest, symptoms triggered by strong odours
Adverse drug reaction: eg, angiotensin-converting enzyme inhibitor	Prominent dry cough
Pulmonary	
Chronic obstructive pulmonary disease	History of heavy smoking or other relevant exposures
Bronchiectasis	Coarse crepitations, digital clubbing
Endobronchial lesions: eg, tumour, foreign body	Systemic symptoms: eg, weight loss, haemoptysis, choking episode, focal wheeze
Acquired tracheobronchomalacia	History of trauma: eg, intubation, history of intrathoracic tumours
Bronchiolitis obliterans	Relevant history: eg, connective tissue disease, toxin exposure, post-infectious, post-transplant
Eosinophilic granulomatosis with polyangiitis	Markedly raised peripheral blood eosinophils, sinusitis, neuropathy
Allergic bronchopulmonary aspergillosis	Markedly raised peripheral blood eosinophils and total serum IgE
Hypereosinophilic syndrome	Markedly raised peripheral blood eosinophils
Non-asthmatic eosinophilic bronchitis	Airway eosinophilia with no evidence of variable airflow obstruction

non-adherence before direct observation, although the utility of this test is limited to patients with raised baseline FENO.[33]

Interventions to address non-adherence should focus on its cause. Unintentional non-adherence may arise as a result of financial constraints, poor comprehension of the drug regimen, physical inability to manage medications, or simple forgetfulness. Measures to simplify drug regimens, such as using a single controller inhaler instead of multiple inhalers[34,35] and the use of once-daily dosing instead of twice-daily dosing,[36,37] have been shown to improve adherence. Solutions to overcome forgetfulness include using audio-visual reminders,[21] keeping the inhaler in the bathroom (not recommended for dry powder inhalers) and integrating the medication as part of a daily routine.[38]

Intentional non-adherence arises from patients' beliefs, which may be related to medication side effects, perceived necessity, medication effectiveness, and lack of motivation.[29] A shared treatment decision-making process between the clinician and patient has been shown to improve adherence and asthma outcomes.[39] This process involves sharing relevant information, expressing treatment preferences, deciding on treatment options and agreeing on treatment plans.[39] Individualised self-management education also improves long term adherence.[40]

Inhaler technique

Inhalation is the preferred route for asthma controllers because of rapid delivery to the lungs and minimisation of systemic drug effects. Unfortunately, inhaler device techniques are not intuitive and incorrect inhaler use is a common problem. In a recent systematic review of errors in inhaler use, the prevalence of correct inhaler use was only 31%.[41] The frequency of common errors was equally high for metered dose inhalers and dry powder inhalers.[41]

Initial selection of an inhaler device should take into consideration patient factors (age, comorbidities, preferences and adherence), disease-related factors (severity of airflow obstruction, which may impair inspiratory effort) and device factors (optimal inspiratory flow required).[42] Inhaler techniques are best taught using verbal or written instruction coupled with physical demonstration, rather than verbal or written instructions alone.[43] If physical demonstration is not available, instructional videos are superior to written instructions alone.[44] Checking and reinforcing patients' inhaler technique should occur at every opportunity, because inhaler technique declines over time.[43] Inhaler technique checklists and instructional videos are available on the National Asthma Council Australia website (https://www.nationalasthma.org.au/living-with-asthma/how-to-videos).

Health care providers should be heartened to know that correcting inhaler technique improves asthma outcomes. In a randomised study conducted by community pharmacists, repeated education sessions lasting just 2.5 minutes per session carried out over 6 months markedly improved patients' inhaler techniques, with accompanying improvement in peak flow readings, asthma quality of life and perceived asthma control.[45]

Triggers

Asthma control is adversely affected by ongoing exposure to triggers such as allergens, irritants and medications (Box 5). Asthma triggers may be more common than previously thought; in an online survey conducted in Europe, 87% of participants reported more than five asthma triggers, with asthma control worsening as the number of (and exposure frequency to) triggers increased.[46] Therefore, a detailed exposure history, including work history, should always be elicited.

In many patients, allergen exposure results in sensitisation; that is, the production of allergen-specific IgE which binds to high affinity IgE receptors on mast cells and basophils. Subsequent allergen exposure cross-links these IgE molecules, triggering the

5 Potential asthma triggers

Allergens

Indoor:

- House dust mite
- Moulds: eg, *Aspergillus*
- Animal dander: eg, cat, dog
- Cockroaches

Outdoor:

- Pollen
- Moulds: eg, *Alternaria, Cladosporium*

Workplace allergens:

- High molecular weight: eg, enzymes, flour, animal proteins, latex
- Low molecular weight: eg, diisocyanates, acid anhydrides, wood dust, disinfection agents

Irritants

- Active smoking
- Second-hand smoke
- Environmental pollution
- Cleaning products
- Strong odours: eg, perfumes

Medications

- Non-steroidal anti-inflammatory drugs
- β-blockers
- Angiotensin-converting enzyme inhibitors

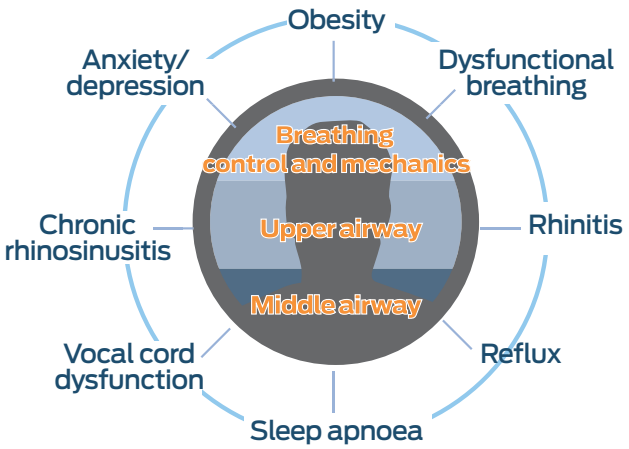
Meteorological triggers

- Cold air
- Weather changes
- Humidity
- Thunderstorms: eg, thunderstorm asthma

Miscellaneous

- Exercise
- Strong emotions
- Food and food additives: eg, sulfites

6 Extrapulmonary comorbidities in severe asthma



7 Available questionnaires for comorbidity screening

Comorbidity	Questionnaire
Sinonasal disease (includes rhinosinusitis and allergic rhinitis)	Sinonasal questionnaire[96]
Gastroesophageal reflux	Gastro-oesophageal reflux disease questionnaire[97]
Obstructive sleep apnoea	Berlin Questionnaire[98]
Vocal cord dysfunction	Pittsburgh Vocal Cord Dysfunction Index[99]
Dysfunctional breathing	Nijmegen Questionnaire[100]
Anxiety and depression	Hospital Anxiety and Depression Scale[101]

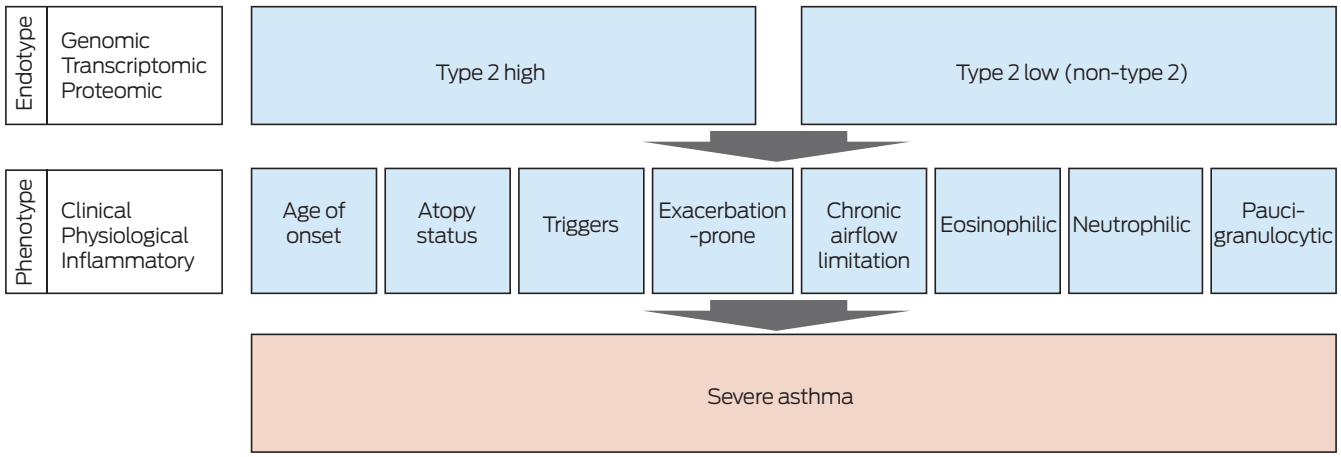
release of inflammatory mediators. In severe asthma cohorts, up to 80% of patients are sensitised to aeroallergens.[20,47] However, allergen sensitisation based on skin prick testing or enzyme-linked immunosorbent assays does not always mean that atopy is the main driver of disease severity.[48] Other useful indicators of allergy-driven asthma include early disease onset and the presence of other atopic comorbidities, such as allergic rhinitis and atopic dermatitis. Common allergens include house dust mite, moulds, animal dander, and pollen. Complete avoidance of sensitising allergens has been shown to improve asthma outcomes,[49] but measures aimed at reducing indoor allergens have so far been ineffective.[50]

Commonly reported irritants include smoking and environmental pollution.[46] Current smokers should be counselled about smoking cessation because they experience more asthma symptoms than never-smokers and ex-smokers.[51,52] Environmental tobacco smoke and outdoor air pollution are also associated with poorer asthma control.[53,54] Environmental tobacco smoke has been shown to worsen lung function, decrease quality of life, increase health care utilisation,[55] and has even been implicated in an acute asthma death in the United States.[56]

Medications such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) and β-blockers may trigger asthma symptoms in susceptible patients. Between 14% and 30% of patients with severe asthma are reported to be aspirin intolerant.[57,58] Patients with aspirin-exacerbated respiratory disease usually present in the third or fourth decade of life with asthma, chronic rhinosinusitis and nasal polyps. Exposure to NSAIDs also results in nasal symptoms along with wheeze and chest tightness. Severe asthma may persist despite the avoidance of NSAIDs,[59,60] and both patients and physicians should be cognisant that non-oral NSAID exposure (eg, via topical routes) may also trigger asthma symptoms.[61,62] Diagnosis of aspirin-exacerbated respiratory disease is often suspected based on patients' reports of previous asthma exacerbations after NSAID exposure, although not all patients with aspirin-exacerbated respiratory disease have a history of NSAID reaction.[63] This condition should be considered in all patients with chronic sinusitis, nasal polyps and asthma. The diagnosis of aspirin-exacerbated respiratory disease is confirmed with a single-blind, placebo-controlled challenge using oral aspirin, bronchial L-lysine–aspirin or nasal L-lysine–aspirin, although challenge tests are generally discouraged in patients with poor lung function (forced expiratory volume in 1 second < 70% predicted).[64]

Non-selective β-blockers (eg, propranolol) should be avoided in asthma, although cardioselective β-blockers (eg, bisoprolol, atenolol) may still be used in patients with cardiovascular indications. Non-selective β-blockers have been shown to

8 Relationship between phenotypes and endotypes in severe asthma



reduce lung function to a greater extent than cardioselective β-blockers[65] as well as increase the risk of exacerbations in high doses.[66] Clinicians and patients should also be aware that topical administration of non-selective β-blocker eye drops for glaucoma has similar detrimental effects on lung function.[67]

Work-related asthma comprises both occupational asthma and work-exacerbated asthma and is an important diagnosis to consider in all working asthma patients. In occupational asthma, there is a causal relationship between workplace factors and asthma, such as an allergen in the workplace; 10–25% of new onset asthma in adults[68,69] may be attributable to occupational asthma. In work-exacerbated asthma, asthma onset precedes workplace exposure but is aggravated by work-related factors such as irritant exposure.[70] Work-exacerbated asthma is present in 14% of patients with asthma.[71,72] An extensive list of occupational asthma and work-exacerbated asthma workplace triggers has been published.[71,73,74] Early identification of work triggers is important because persistent exposure to triggers leads to greater lung function decline.[75] Evaluation of suspected work-related asthma involves: confirming a diagnosis of asthma; determining whether asthma symptoms are work-related; identifying workplace triggers; and differentiating occupational asthma from work-exacerbated asthma.[76]

Features suggesting work-related symptoms include an improvement in symptoms away from work and worsening of symptoms at work, although the diagnostic accuracy of work-related symptoms is poor.[77,78] Objective tests include serial measurements of peak flow, serial measurements of non-specific bronchial hyper-responsiveness, detection of specific IgE to occupational allergens, and specific inhalational challenge.[70]

Comorbidities

Extra-pulmonary comorbidities are common in asthma and even more frequent in difficult asthma.[79,80] In a difficult asthma cohort in Melbourne, 80% of patients had two or more extra-pulmonary comorbidities.[10] These comorbidities may be classified into those involving breathing control and lung mechanics, the upper airway, and the middle airway (Box 6). They include dysfunctional breathing, anxiety and depression, obesity, rhinitis, chronic rhinosinusitis, gastro-oesophageal reflux disease, obstructive sleep apnoea, and vocal cord dysfunction. The detection of these comorbidities is an essential part of difficult asthma assessment, because they may both mimic asthma and worsen asthma control. Some comorbidities even contribute to phenotypes of severe asthma, as with obesity or chronic rhinosinusitis with nasal polyps.[81]

Vocal cord dysfunction, dysfunctional breathing and exertional dyspnoea due to obesity may all be misdiagnosed as asthma. Patients with vocal cord dysfunction can present with asthma-like symptoms such as wheezing and dyspnoea. A delay in diagnosis results in unnecessary treatment with high dose corticosteroids.[82,83] Vocal cord dysfunction often also coexists with severe asthma and may be present in up to 50% of these patients.[84] Dysfunctional breathing is a breathing pattern disorder, the most commonly recognised pattern being hyperventilation. About 1–2% of patients seen in difficult asthma clinics had symptoms attributable to dysfunctional breathing without objective evidence of asthma.[10,79] Dysfunctional breathing also coexists with asthma in 30–64% of patients with difficult asthma, resulting in increased symptoms and health care utilisation.[85,86] Obesity is a risk factor for wheeze and dyspnoea, but not airflow obstruction or airway hyper-responsiveness.[87,88] Obese individuals are more likely to be incorrectly diagnosed as having asthma when they present acutely with respiratory symptoms, compared with non-obese individuals.[89] Nevertheless, obesity is highly prevalent in patients with severe asthma, affecting 30–39% of patients,[47,80] and also contributes to asthma symptoms and exacerbations.[90,91]

All the comorbidities discussed above can increase asthma symptoms or exacerbations, leading to worse asthma control. Rhinitis,[47,86] chronic rhinosinusitis,[20,86] gastro-oesophageal reflux disease,[80,92] obstructive sleep apnoea[86] and anxiety and depression[93] are present in > 30% of patients with severe asthma. Many studies have shown a beneficial impact of comorbidity treatment on asthma outcomes, although the majority of studies were observational in nature.[80,81,94]

Despite their clinical importance, comorbidities are commonly under-recognised in difficult asthma. Clinicians, including asthma specialists, are prone to overlook sinonasal disease, obstructive sleep apnoea, vocal cord dysfunction and dysfunctional breathing.[95] Diagnosis of comorbidities in difficult asthma inevitably requires thorough systematic evaluation, which can be achieved through exhaustive assessment by various specialists, as is performed in certain centres.[96] This method is resource intensive and not feasible in most health care settings. A more affordable approach is to screen for comorbidities using validated screening questionnaires (Box 7),[97-102] followed by

9 Severe asthma diagnostic evaluation at primary care and specialist care

	Primary care management	Specialist management
Confirm asthma diagnosis	Chest x-ray Electrocardiography Office spirometry Peak flow meter	Spirometry (pre/post bronchodilator) Bronchial challenge test Ancillary tests to exclude alternative diagnoses: eg, computed tomography thorax, 2-dimensional echocardiography
Identify and treat contributory factors		
Non-adherence	Assess based on patient report	Electronic dose monitors Fractional exhaled nitric oxide suppression test
Poor inhaler technique	Education and reassessment	Education and reassessment
Triggers	Smoking cessation General advice about allergen/irritant avoidance Check for potential medication triggers	Work-related asthma assessment Aspirin desensitisation
Comorbidities	Initiate treatment for rhinitis, chronic rhinosinusitis, gastro-oesophageal reflux disease, obesity	Referral to other departments Subspecialty evaluation for vocal cord dysfunction and dysfunctional breathing
Assess phenotype/ endotype	Blood eosinophil Serum specific IgE Total serum IgE	Skin prick test Serum specific IgE Total serum IgE Fractional exhaled nitric oxide Blood eosinophil Sputum inflammometry

confirmatory clinical consultation and targeted multidisciplinary evaluation as needed.[81] In difficult asthma, this bespoke approach has been shown to improve both comorbidity control and asthma outcomes.[94]

Screening and management of some comorbidities can be performed even in primary care. Rhinitis, chronic rhinosinusitis, gastro-oesophageal reflux disease and obesity are readily identified based on history and physical examination, and treatment can be comfortably initiated by most primary care physicians.

Step three: establish asthma phenotype

Clinical and inflammatory phenotypes

Severe asthma can be considered a syndrome, analogous to anaemia or arthritis, with contributions by various disease entities arising as a result of multiple pathophysiological mechanisms. The impetus in recent asthma research has been to differentiate patients according to their observable traits, in order to tailor therapy appropriately. The process of characterising observable traits is termed phenotyping.[103]

Asthma phenotypes have been described since the early 20th century. Rackeman first observed differences in the clinical characteristics of asthmatics in the 1920s and introduced the terms "extrinsic" and "intrinsic" asthma to differentiate patients with and without identifiable environmental triggers, respectively.[104] An increasing understanding of airway inflammation in asthma led to the distinction between various inflammatory phenotypes. The importance of airway eosinophilia in asthma was noted by Brown in the 1950s.[105] Other researchers subsequently demonstrated that severe asthma could be divided into eosinophilic and non-eosinophilic phenotypes, with distinct accompanying clinical and physiological characteristics.[106,107] We now know that inflammation in asthma can be further divided into eosinophilic, neutrophilic, mixed and pauci-granulocytic based on sputum[108] and blood profiles.[109]

Patients have traditionally been phenotyped based on characteristics such as age of asthma onset, atopy status, presence of chronic airflow limitation and eosinophilic inflammation[103] (Box 8). However, phenotyping based on individual predefined characteristics is subjective and obscures less evident patterns. Cluster analysis is an unbiased statistical method used to identify homogeneous groups. Using cluster analysis, the following phenotypes have been repeatedly identified in various severe asthma cohorts: early onset atopic,[110,111] late onset severe eosinophilic,[110] obese non-eosinophilic,[110,111] and chronic airflow limitation.[112-114]

The early onset atopic phenotype describes asthma starting in childhood.[110] In the Severe Asthma Research Program cohort, daily symptoms and rescue bronchodilator use predominated over exacerbations.[111] The late onset eosinophilic phenotype is of adult onset and found mainly in patients with severe asthma.[110] These patients are older and have poorer lung function.[110,114,115] Patients also commonly have severe sinusitis and nasal polyposis.[114] Concomitant neutrophilic airway inflammation has been observed in some of these patients.[113,115] Patients with the obese non-eosinophilic phenotype are usually female and less likely to be atopic.[110,111] Despite minimal airway inflammation, they are highly symptomatic with frequent health care utilisation.[110,112] Age of asthma onset is not a constant feature in this phenotype.[110,112,114] The chronic airflow limitation phenotype fits the current definition of chronic obstructive pulmonary disease and is in itself heterogeneous. It has been associated with both eosinophilic and neutrophilic inflammation,[112,113] as well as early and late onset asthma.[116] This phenotype is likely influenced by various factors including childhood lung function trajectory, smoking and airway inflammation.[117,118]

Endotypes

Clinical phenotypes highlight the heterogeneity of severe asthma but do not necessarily reflect the underlying disease process. With greater understanding of asthma immunology and the advent of -omics biology (genomics, transcriptomics, proteomics), researchers are now starting to discover various asthma endotypes. Endotypes refer to disease subgroups with distinct underlying biological mechanisms. Deconstructing asthma into aetiological and pathophysiological mechanisms assists in identifying targets for treatment[119] (Box 8).

The aetiologies and exact mechanisms underlying severe and non-severe asthma are still poorly understood, but can be simplistically divided into type 2 high and type 2 low (non-type 2) inflammatory processes.[120] Type 2 high inflammation features the prominent secretion of cytokines that are typically produced by type 2 helper (Th2) lymphocyte cells (interleukin [IL]-4, IL-5 and IL-13). Type 2 high inflammation may drive both allergic and non-allergic eosinophilic airway responses.[121] In allergic asthma, exposure to an allergen results in production of IL-4 and IL-13 by Th2 cells. These cytokines stimulate B cells to produce IgE that drives the allergic cascade. Th2 cells also produce IL-5, which increases the production, differentiation, maturation and activation of eosinophils. In non-allergic eosinophilic asthma, type 2 innate lymphoid cells appear responsible for the production of type 2 cytokines IL-5 and IL-13.[120] Much less is known about type 2 low inflammation, which includes pauci-granulocytic and neutrophilic subtypes.[122]

Biomarkers

Sputum eosinophils, blood eosinophils, FENO and serum periostin are biomarkers available clinically to diagnose type 2 inflammation. These biomarkers are also used to predict responses to treatment. In the UK Refractory Asthma Stratification Programme, a composite of blood eosinophil, serum periostin and FENO will be used to optimise corticosteroids in severe asthma.[123] Likewise, these biomarkers have been shown to predict treatment response to monoclonal antibodies. More recently, sputum gene signatures have been found to predict response to oral corticosteroids better than sputum and blood eosinophils.[124] Newer diagnostic and predictive biomarkers will be needed to guide the selection of increasing numbers of biologicals.

Targeted therapies

Phenotyping allows clinicians to select patients who are most likely to respond to novel targeted therapies. Assessment of a patient's atopy status and peripheral blood eosinophil counts can aid in determining the most appropriate biological for targeted treatment. In the US for example, the anti-IgE monoclonal antibody omalizumab and the anti-eosinophilic biologicals mepolizumab, benralizumab and reslizumab are all approved by the Food and Drug Administration. In Australia, only omalizumab and mepolizumab are approved by the Therapeutic Goods Administration and funded under the Pharmaceutical Benefits Scheme. An in-depth discussion of biological therapy is provided by Upham and Chung in this supplement.[125]

Integrating diagnostic evaluation across primary and specialist care

Diagnosis and management of patients with severe asthma require coordinated efforts between primary care and specialist care (Box 9). This framework of care often involves bidirectional referrals between general practitioners and specialists to tap each level's expertise.

In primary care, apart from taking a relevant history and examination, relatively accessible investigations such as chest radiography and electrocardiography can be performed in patients with persistent asthma symptoms to exclude asthma mimics. GPs with office spirometers or peak flow meters should also use these to look for evidence of variable airflow obstruction. Repeated evaluation of adherence, education and reinforcement of inhaler technique, management of asthma triggers (especially active smoking), treatment of comorbidities such as rhinitis, chronic rhinosinusitis and gastro-oesophageal reflux disease, as well as weight management advice for obese patients, can be instituted in primary care.[79,126,127]

In addition, patients with more complex comorbidities who have already been evaluated by specialists may also benefit from a primary care management plan and a multidisciplinary team care arrangement. This enables the patient to access government-subsidised allied health interventions. This is particularly important for patients who live in regional areas who may not have regular or convenient access to allied health professionals in tertiary centres. These include a referral to a dietitian for patients who are obese, psychology support for patients with mental health disorders, a speech therapist for patients diagnosed with vocal cord dysfunction, and a respiratory physiotherapist for patients diagnosed with dysfunctional breathing.

When patients continue to have uncontrolled asthma on Global Initiative for Asthma treatment step 4 (high dose ICS plus an additional controller) despite the above, or if there are doubts about asthma diagnosis or suspicion of occupational asthma, referral to a specialist should be considered.[126] Specialist physicians are better equipped to manage patients with severe asthma, although subspecialised care may be required for a proportion of patients. Patients with suspected work-related asthma may need referral to an occupational medicine specialist. Comorbidities such as vocal cord dysfunction and dysfunctional breathing often require multidisciplinary input.[79,127] Phenotyping using skin prick testing, serum-specific IgE, blood eosinophils and FENO are available in most specialist clinics but more advanced phenotyping methods (eg, sputum inflammometry) are only performed in a few research centres.

Conclusion

The diagnostic evaluation for severe asthma outlined in this article should be undertaken for patients presenting with difficult asthma. The exploration of asthma diagnosis and contributory factors can be readily initiated in community primary care, and completed in specialist secondary care. Further detailed endotyping of severe asthma, and initiation of phenotype-targeted treatment, may only be possible in specialised centres. Importantly, many gaps remain at each step of the evaluation process for severe asthma, and the development of new systems of care may be needed to fully address these shortcomings.

Competing interests: Joy Lee has delivered educational talks for GlaxoSmithKline and AstraZeneca. Mark Hew has undertaken contracted research for AstraZeneca, Sanofi, Novartis and GlaxoSmithKline; delivered educational talks for GlaxoSmithKline, AstraZeneca and Novartis; and participated on advisory boards/consultancies for AstraZeneca, GlaxoSmithKline and Seqirus; his employer (Alfred Health) has been reimbursed for all of these.

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