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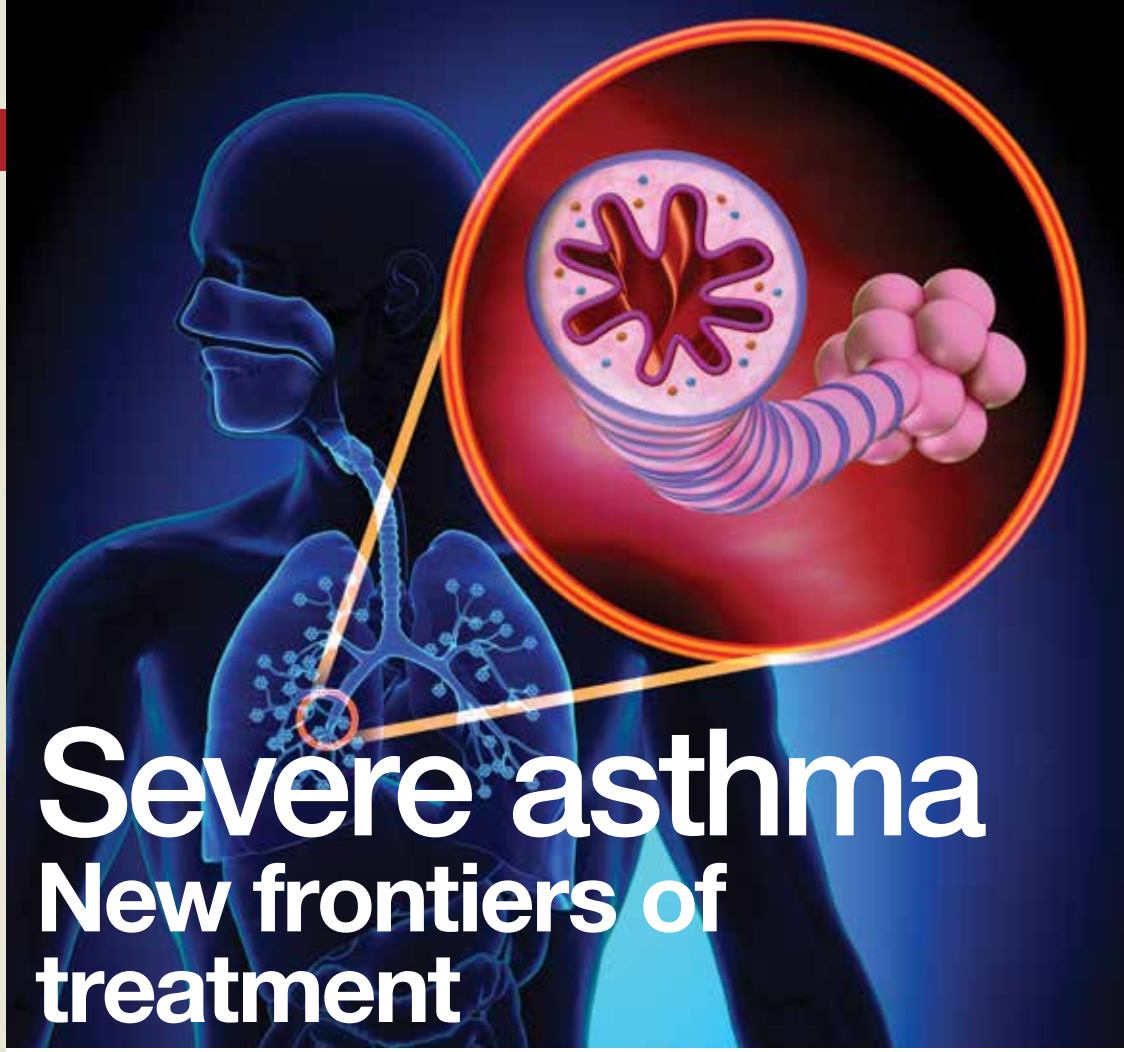
2 CPD POINTS



Severe asthma
New frontiers of treatment

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New therapies that specifically target inflammatory pathways or aberrant physiology in severe asthma offer substantial opportunities for effective treatment. Some of these therapies are available under specialist referral, and others are available in the context of clinical trials.

Key points

- **Asthma affects about 10% of people in Australia, about 5% of whom will have severe disease.**
- **Severe asthma is asthma that is inadequately controlled despite the use of maximal doses of inhaled corticosteroids and long-acting beta-agonists or that requires additional treatment with oral corticosteroids to remain controlled.**
- **A diagnosis of asthma can be confirmed by spirometry.**
- **Patients with severe asthma or in whom the diagnosis is suspected should be referred to a specialist.**
- **New therapies for severe asthma are emerging, targeting inflammatory pathways or aberrant physiology.**
- **The monoclonal antibody omalizumab is available in Australia on specialist prescription for severe allergic asthma.**

Asthma is the most common chronic disease in Australia, affecting about one in six children and one in 10 adults. Although most patients with asthma can be controlled well with currently available inhaled preventer and reliever therapies, there remains a group of patients whose asthma is not well controlled by maximal doses of these medications. This lack of asthma control may occur in as many as one in 20 patients, and it is these patients with severe asthma who suffer most from morbidity related to their illness, including emergency presentations for asthma flare-ups, the use of oral corticosteroid medication and its side effects, hospitalisation and even death.

The significant burden of severe asthma to both individuals and the healthcare system has driven research into the condition, and the establishment of severe asthma clinics and registries has provided fertile ground for refining the diagnosis of severe asthma. More complete understanding of the underlying inflammatory basis of asthma and the role of upper and lower airway muscles has helped the development of highly specific biologics and

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1. ASTHMA MEDICATIONS[3]

Short-term medications

Relievers

- Short-acting beta$_2$-agonists (SABAs)
  - salbutamol, terbutaline sulfate
- Inhaled corticosteroid/rapid-onset long-acting beta$_2$-agonist (LABA) combinations
  - budesonide/eformoterol fumarate dihydrate*

Other short-term medicines (symptomatic and acute asthma treatment)

- Systemic corticosteroids
  - prednisolone/prednisone, methylprednisolone sodium succinate, hydrocortisone
- Anticholinergic bronchodilators (in acute asthma)
  - ipratropium
- Theophyllines (in acute asthma)
  - aminophylline, theophylline
- Magnesium sulfate (in acute asthma)

Long-term medications

Preventers

- Inhaled corticosteroids
  - beclomethasone dipropionate, budesonide, ciclesonide, fluticasone propionate
- Inhaled corticosteroid/LABA combinations
  - budesonide/eformoterol fumarate dihydrate, fluticasone furoate/vilanterol, fluticasone propionate/eformoterol fumarate dihydrate, fluticasone propionate/salmeterol xinafoate
- Leukotriene receptor antagonists
  - montelukast
- Cromones (mast cell stabilisers)
  - sodium cromoglycate, nedocromil sodium

Other long-term medicines

- Monoclonal anti-IgE antibodies†
  - omalizumab
- Anticholinergic bronchodilators
  - ipratropium bromide, tiotropium bromide
- LABAs
  - eformoterol fumarate dihydrate, salmeterol xinafoate
- Theophyllines
  - aminophylline, theophylline

Adapted from *Australian Asthma Handbook* (2014).[3]
* The budesonide/eformoterol fumarate dihydrate combination is only used as a reliever for adults and adolescents on a maintenance-and-reliever regimen.
† Monoclonal antibodies in development include an anti-interleukin (IL)-5 agent (mepolizumab) and anti-IL4 and anti-IL13 agents.

other therapies that have shown evidence of benefit in clinical trials. In Australia, the first of the biologics for severe asthma, the monoclonal antibody omalizumab, is now available on the PBS, and clinical trials of other monoclonal antibodies for severe asthma are advanced.

Severe asthma, therefore, is a condition in which recent refinements in definition, diagnosis and treatment are radically changing the clinical approach and improving patient outcomes.

WHAT IS SEVERE ASTHMA?

Mortality due to severe asthma

Asthma control represents one of the significant public health achievements in Australia, with asthma mortality rates falling by over 60% since a peak in the late 1980s.[1] Current asthma mortality statistics indicate that asthma deaths occur at all ages but more than two-thirds of those who die from asthma are aged over 55 years.[1] Despite success in reducing asthma mortality, Australia's asthma mortality rate is one of the highest in international ratings; the USA and UK have similar rates but other European countries and Japan have substantially lower rates.[1]

Recent detailed studies of asthma mortality in Australia have revealed several features associated with death from asthma, namely social isolation, drug and alcohol dependence and poor health literacy leading to suboptimal use of currently available treatments.[2] Identification of these features, particularly cigarette smoking, may provide opportunities for treating doctors to intervene.

Asthma treatment

The currently available asthma medications are listed in Box 1. Management algorithms for asthma have been updated in the current Australian asthma guidelines, the *Australian Asthma Handbook (AAH),* and the stepped approach to adjusting asthma medication in adults recommended in these guidelines is shown in Figure 1 (*AAH* asset ID: 31; http://www.asthmahandbook.org.au/table/show/31).[3]

Asthma control is indicated by an assessment of symptoms over the preceding four weeks, with good control being determined by daytime symptoms less than twice a week, no limitation of activities and no symptoms at night or on morning waking (*AAH* asset ID: 33).[3] A high daily dose of inhaled corticosteroid is defined as being 400 µg or greater of beclomethasone dipropionate a day, 800 µg or greater of budesonide, 320 µg or greater of ciclesonide or 500 µg or

greater of fluticasone propionate (*AAH* asset ID: 22).[3]

Defining severe asthma

The definition of severe asthma has recently been updated in a joint American Thoracic Society and European Respiratory Society position paper.[4] In these guidelines, severe asthma is defined as:

- asthma that is inadequately controlled despite the use of maximal doses of inhaled medications including a corticosteroid and a long-acting beta$_2$-agonist, or
- asthma that requires treatment with oral corticosteroids in addition to maximal inhaled medications to prevent it from becoming uncontrolled.

Uncontrolled asthma in this context not only means poor symptom control but also the presence of frequent or serious (e.g. requiring intensive care admission) exacerbations, presence of comorbidities such as smoking or food allergy, and associated fixed airflow obstruction with a forced expiratory flow in one second (FEV_1) of less than 80% predicted.[5]

Most asthma care is delivered in general practice and indicators of severe or difficult asthma in this setting are poor asthma control despite the use of adequate doses of inhaled medication.

SEVERE ASTHMA: WHAT TO DO?

Once a patient's asthma appears to be uncontrolled despite maximal inhaled medication, an important question to ask is whether the patient really has severe asthma since not all asthma that is difficult to control is, in fact, severe asthma. Questions that should be asked first however are whether the patient is taking their asthma medications as prescribed and whether they actually have asthma.

Is the patient receiving their medication?

Despite a vast amount of research indicating that currently available inhaled asthma treatments are effective in gaining symptom control and reducing exacerbations, there is equally bountiful evidence, such as from prescribing data, that asthma medications are not taken as prescribed.[6] Preventer asthma treatments, including those used for maintenance and reliever regimens, should be taken regularly on a daily or twice-daily basis.

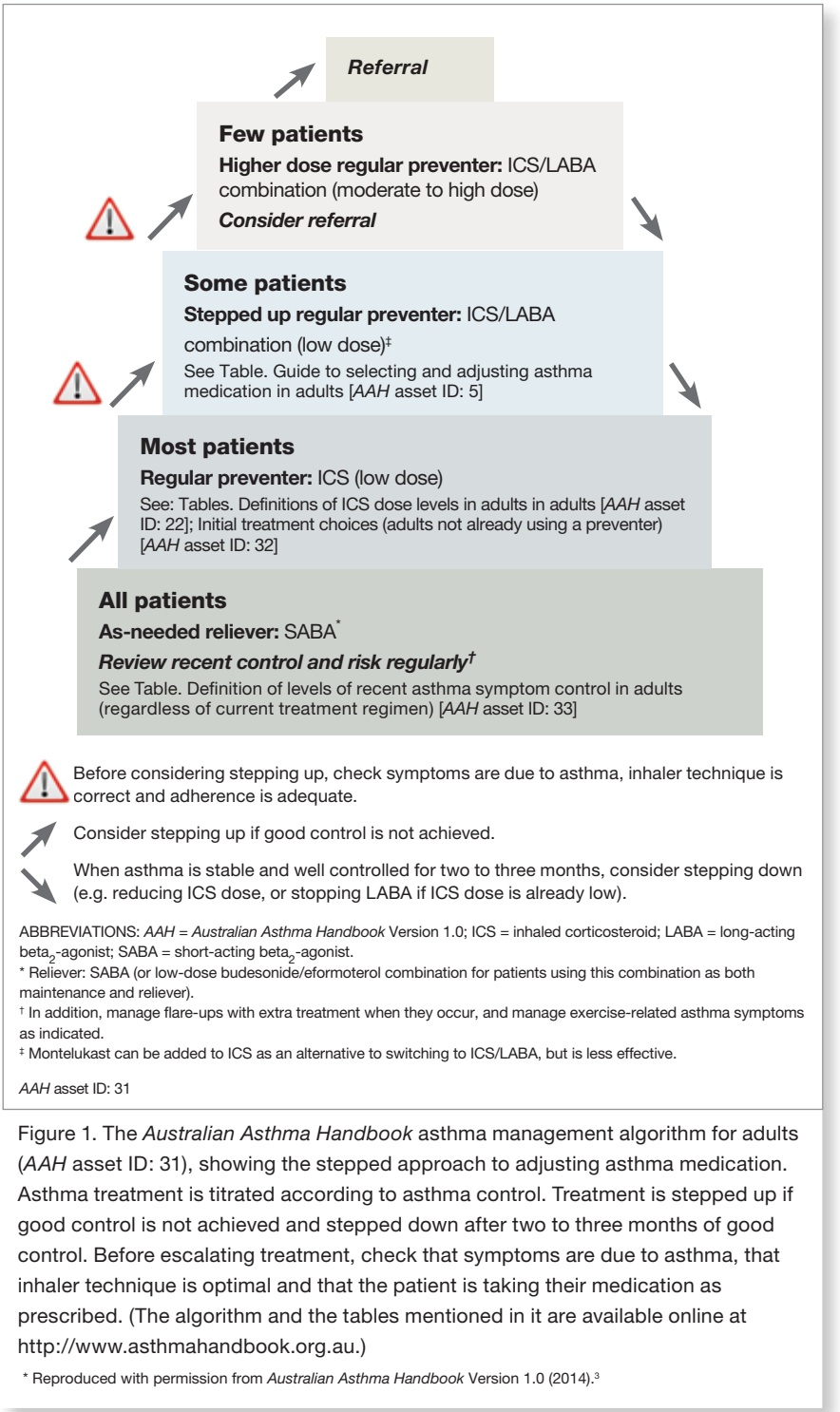


Figure 1. The *Australian Asthma Handbook* asthma management algorithm for adults (*AAH* asset ID: 31), showing the stepped approach to adjusting asthma medication. Asthma treatment is titrated according to asthma control. Treatment is stepped up if good control is not achieved and stepped down after two to three months of good control. Before escalating treatment, check that symptoms are due to asthma, that inhaler technique is optimal and that the patient is taking their medication as prescribed. (The algorithm and the tables mentioned in it are available online at http://www.asthmahandbook.org.au.)

* Reproduced with permission from *Australian Asthma Handbook* Version 1.0 (2014).[3]

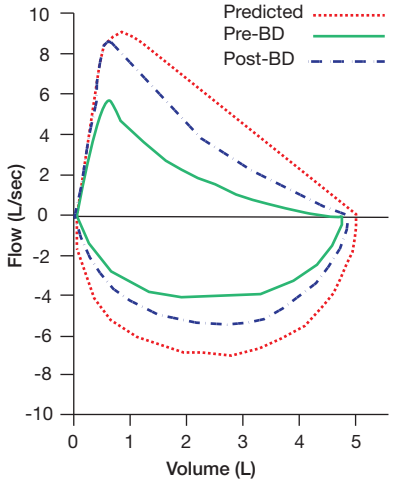


Figure 2. Example of a spirometry flow–volume loop for a 20-year-old man with asthma. There is a significant improvement in FEV_1 of more than 12% following bronchodilator, which is diagnostic. (BD = bronchodilator.)

COURTESY OF DR DAVID JOHNS, UNIVERSITY OF TASMANIA, HOBART, TAS.

Nonadherence to a medication plan can be both intentional and nonintentional. Intentional nonadherence involves patients undertaking a 'risk–benefit' analysis when considering using asthma medication, by weighing up the cost, inconvenience and perceived side effects of asthma treatment against the potential benefits. As studies of patient attitudes to asthma treatment have revealed significant patient concerns regarding side effects, these need to be specifically addressed in the consultation.[7] Patients may also 'ration' their asthma medications (i.e. use less than prescribed), especially those patients for whom the financial burden of treatment is likely to be significant.

To address intentional nonadherence, doctors need to be specific regarding the potential benefits of treatment and to relate these in terms that are meaningful to the patient. For example, preventing future exacerbations may mean little to a teenager with asthma but being able to keep up with peers during sporting activities is a specific goal that is more likely to have currency for a young person with sporting interests. In contrast, prevention of exacerbations may be a reasonable goal of treatment for older people with asthma, who are likely to be worried about flare-ups of their asthma.[8]

Nonintentional nonadherence is when medication is forgotten or overlooked, or is not taken as prescribed because of difficulty handling the administering device. For some individuals with chaotic lifestyles such as homelessness, drug dependence or mental illness, this represents a very real challenge. For some, reminders such as setting a mobile phone alert or putting the medication somewhere very accessible, such as in a handbag, may improve adherence. Inhaler device technique is also an important factor in poorly controlled asthma, and education can significantly and durably improve this component of effective asthma care.[9]

Primary care physicians are the first and often most trusted source of advice for asthma care for most patients. Outlining the reasons for the choice of medication, its anticipated benefit and its treatment regimen can make a significant difference to patient outcomes. But effective asthma education can be time-consuming and so may benefit from specialist input. The use of trained asthma educators can improve asthma outcomes, and general practice incentive programs can facilitate such consultations.

Is it really asthma?

Confirmation that a patient has asthma can often be gained by the presence of reversible airway obstruction on spirometry (Figure 2). Variability in peak flow of more than 15% between the two highest and two lowest readings over a two-week period can also provide a concrete diagnosis of asthma by demonstrating airway reversibility. However, because asthma is episodic, normal lung function does not entirely exclude asthma. Challenge or other testing may therefore be appropriate in patients with indicative symptoms but normal resting spirometry.

Some individuals will have fixed airflow obstruction on spirometry, which can also be a feature of chronic obstructive pulmonary disease (COPD). A history of cigarette smoking tends to indicate COPD is more likely, but a component of fixed airflow obstruction can also be a feature of severe asthma, or there may be an overlap of the two conditions (currently designated 'ACOS', or asthma COPD overlap syndrome). The presence of any fixed component of airflow obstruction in an individual with asthma confers a diagnosis of severe asthma and is an indication for specialist referral.

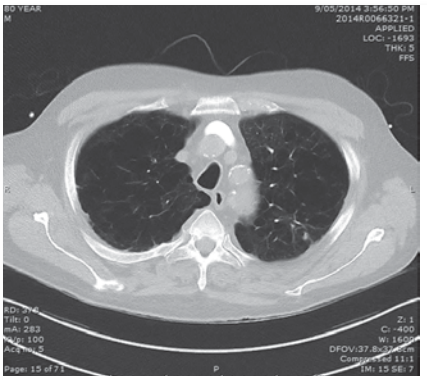
Chest imaging is not diagnostic in asthma. Chest x-rays in patients with asthma may be normal, may reveal hyperexpansion suggestive of gas rapping or may show atelectasis due to mucus impaction. Optimal resolution of the airways and lung parenchyma can be obtained with a high-resolution CT scan of the chest and may reveal evidence of other diagnoses such as emphysema, bronchiectasis or an interstitial lung disease (Figures 3a and 3b). In this context detailed lung function testing, including a gas transfer measurement, can be very informative.

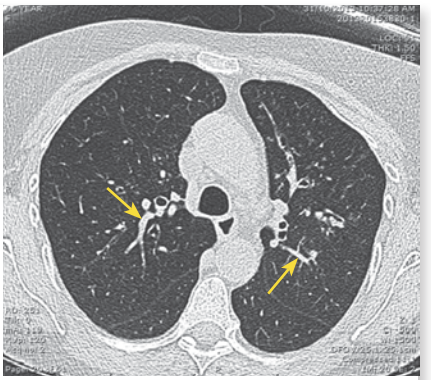
Alternative diagnoses to consider in a patient with supposed asthma are listed in Box 2.

Are there nasal symptoms?

For some patients, their complaints of airway obstruction and cough are due to rhinitis and associated airway irritation.

Symptoms of nasal discharge, nasal obstruction and ocular symptoms may suggest an allergic cause, either seasonal as in hayfever or at any time following exposure to a known allergic trigger. In patients with allergic rhinitis and asthma, the addition of a topical nasal corticosteroid can significantly reduce asthma exacerbations.[10] Meta-analyses also support the effectiveness of subcutaneous and sublingual allergen immunotherapy in reducing asthma exacerbations or





Figures 3a and b. CT imaging showing alternative diagnoses to asthma.
a (left). CT scan of a patient with emphysema; note the large bullae. b (right). CT scan of a patient with bronchiectasis; note the increased airways size and large airways (arrows) captured in this slice.

2. DIFFERENTIAL DIAGNOSES FOR ASTHMA*

- Chronic obstructive pulmonary disease
- Chronic cough
- Vocal cord dysfunction
- Gastro-oesophageal reflux
- Obesity
- Pulmonary hypertension (characterised by a low gas transfer measurement)
- Emphysema
- Interstitial lung disease
- Allergic bronchopulmonary aspergillosis
- Bronchiectasis
- Rhinitis
- Nasal polyposis

* Listed in order of most likely to least likely.

asthma symptoms.[11,12] A specialist in allergy should initiate allergen immunotherapy, especially in patients with asthma, because despite the benefits of the therapy, unstable asthma is a relative contraindication.

Nasal polyps characteristically cause anosmia and nasal obstruction. Although topical corticosteroids can be effective for nasal disease, surgery is often required. Nasal polyps, asthma and aspirin sensitivity form a triad of symptoms typically associated with nonallergic respiratory disease and severe asthma, and often asthma is difficult to control in these patients. Newer monoclonal antibody therapies targeting eosinophils offer major opportunities for improved treatment in this group.

Are there specific asthma triggers?

Some people with asthma that is difficult to control may be exposed to specific triggers for their asthma. Exposure to occupational asthma allergens such as animal antigens, wood dust, wheat flour or spray paints can render asthma difficult to control in sensitised individuals. A history of asthma that flares in the workplace can provide a clue, and specific testing may be required to confirm the diagnosis.

Tobacco smoking is also an important trigger of asthma symptoms. A recent study has shown that current smoking increases the risk of uncontrolled asthma compared with never-smoking, and that former smokers also had an increased risk of uncontrolled asthma compared with never-smokers.[13]

Is it severe asthma?

Having addressed medication adherence and confirmed a definite diagnosis of asthma, the criteria for severe asthma are met if the patient is not well controlled despite optimised medication.

Patients who truly meet criteria for severe asthma, or in whom the diagnosis is being considered, should be referred to a physician with specific expertise in the area. Clinical practice in the domain of severe asthma is rapidly advancing, and new therapeutic options are available that can be life-changing for some patients.

MONOCLONAL ANTIBODIES FOR SEVERE ASTHMA

Omalizumab was the first monoclonal antibody to be widely marketed for severe asthma and in Australia is subsidised for eligible patients through the PBS. It is a monoclonal anti-IgE antibody that binds circulating IgE and thereby prevents it binding to mast cells and basophils, leading to a reduction in allergic responses (Figure 4).

Omalizumab is TGA-indicated for individuals aged 12 years and older with allergic asthma, usually characterised by evidence of IgE sensitisation to one or more perennial inhaled allergens, and is given monthly or fortnightly by subcutaneous injection. The major benefit of omalizumab in large trials is a reduction in exacerbation rates to nearly half that of control groups of patients.[14] Clinical experience shows that it can be life-changing for some patients in whom allergy is the major trigger for disease. Specialist referral is required to access this treatment.

Several other monoclonal antibodies for asthma treatment are in development. The most well-studied of these is mepolizumab, a monoclonal antibody against interleukin-5 (IL5; a cellular mediator that drives the growth, proliferation and activation of eosinophils). Studies on the effects of anti-IL5 agents have only shown benefit where the patients have underlying eosinophilic asthma, where a halving of the exacerbation rate has been found in patients receiving maximal treatment and then treated with mepolizumab, compared with placebo.[15]

Studies analysing the inflammatory

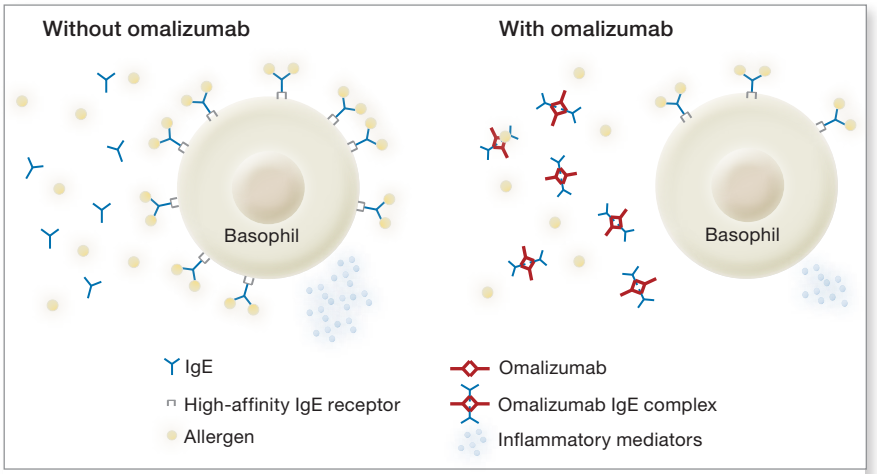


Figure 4. Action of omalizumab. The monoclonal antibody binds to IgE and thereby reduces the reactivity of basophils.

nature of asthma have shown that asthma has inflammatory endotypes that can be determined by measuring sputum cellularity (Figures 5a and b). Induced sputum samples can reveal eosinophilic, neutrophilic or paucigranulocytic inflammation. Although the analysis of airway inflammation through induced sputum analysis has been used in the research setting for some time, this technique has not found widespread application in the clinical setting. Recent trials have therefore used blood eosinophil counts of greater than 0.3×10^9/L as an indicator of eosinophilic airway disease.

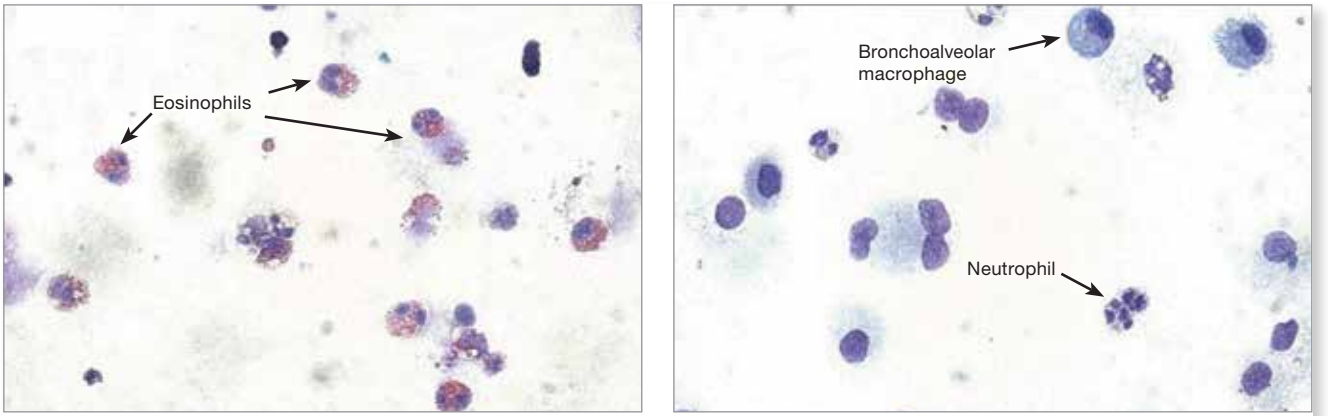
The growing number of monoclonal antibodies showing efficacy in asthma will require that diagnostic phenotyping be performed to identify the most important inflammatory pathways for a particular patient's asthma. Other cytokine antagonists with evidence of efficacy in asthma include an anti-IL4 agent and an anti-IL13 agent.[16,17] With the large numbers of clinical trials currently being conducted in Australia, there are opportunities for patients with severe asthma to participate.

TREATING MUSCLES IN ASTHMA

A different paradigm in the treatment of patients with severe asthma is that of medical procedural interventions targeted at airway muscle for patients refractory to usual treatments.

Bronchial thermoplasty, in which radiofrequency energy (heat) applied to visible proximal airways via bronchoscopy selectively ablates airway smooth muscle, has been trialled in patients with asthma. It is the first nonpharmacological intervention therapy approved by the US Food and Drug Administration for severe asthma. A recent systematic review of the evidence included three trials and revealed modest clinical benefit in quality of life and lower rates of asthma exacerbations, but no significant difference in asthma control scores or lung function testing parameters.[18] The studies have generated much controversy, and have been criticised for significant biases in methodology.[5,19,20] Despite five-year post-thermoplasty safety and efficacy data now being available, the true effectiveness of the procedure remains uncertain.[21,22] Current recommendations from American Thoracic Society/European Respiratory Society guidelines are that bronchial thermoplasty be performed in adults with severe asthma only, in the context of an Institutional Review Board-approved independent systematic registry or a clinical study.[5]

Vocal cord dysfunction can often mimic or coexist with asthma.[2,23] A recent observational study used local injection of botulinum toxin into laryngeal tissues



Figures 5a and b. Induced sputum analysis in a patient with asthma, showing eosinophilic inflammation (a, left) and neutrophilic inflammation (b, right).

Reproduced with permission from a BMedSc thesis (Chua J. Monash University, 2010).

unilaterally to treat abnormal vocal cord movement via temporary paralysis of muscle in an attempt to improve asthma control.[23] There was suggestion that asthma control test scores were improved and airway calibre was widened, but spirometry was unchanged and overall no firm conclusions on efficacy can be drawn.

Further research to better understand the mechanism of action of bronchial thermoplasty and botulinum toxin injection and the potential effects on different asthma phenotypes are required before their widespread use can be recommended.

CONCLUSION

Severe asthma places an enormous burden upon patients. New therapies targeting inflammatory pathways or aberrant physiology in severe asthma offer substantial opportunities for effective treatment. Some of these therapies are available under the referral of a specialist, and others are available in the context of clinical trials. It is evident, however, that the era of personalised medicine provides tangible opportunities to significantly improve patient outcomes in this difficult group. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: Professor Douglass has received honoraria for delivering lectures or serving on Advisory Boards from GlaxoSmithKline, AstraZeneca, Mundipharma, Novartis and Stallergenes. In the past five years she has conducted investigator-initiated research supported by Novartis and commercial clinical trials for GlaxoSmithKline and AstraZeneca.
Dr Harun: None.

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