MANAGEMENT OF PEOPLE WITH DIFFICULT-TO-TREAT ASTHMA: A SYSTEMATIC APPROACH

Though there have been significant advances in the treatment of mild-to-moderate asthma, severe asthma that is refractory to standard treatment remains a significant health problem.\(^1,2\)

✓ Assess patients with difficult-to-treat asthma systematically to differentiate between difficult-to-treat and severe asthma (see Figure 1)\(^3\)

- **Difficult-to-treat asthma** is asthma that is uncontrolled despite high-dose ICS/LABA or OCS, or that requires such treatment to remain well controlled.\(^1\)
- **Severe asthma** is a subset of difficult-to-treat asthma and is largely a diagnosis of exclusion, that is, the exclusion of asthma that appears difficult to treat but that markedly improves after appropriate diagnosis and/or treatment of confounders.\(^2,3\)

### CASE STUDY 1: Brody presents for a review of his asthma

- 38 years old, asthma since age 8 years
- Spirometry-confirmed asthma at age 25 years

**Current history**

- Daytime symptoms 4–5 times/week for the last few months
- Needs reliever 3–4 days a week
- Symptoms affect ability to play cricket despite pre-exercise salbutamol
- ED admission last year due to flare-up not responding to salbutamol
- Two courses of OCS in the last year

**Past medical history**

- Rhinitis

**Social**

- Ex-smoker – 15 cigarettes a day since age 18, quit at age 31
- Does not drink any alcohol

**Medications**

- fluticasone propionate/salmeterol (Seretide) pMDI 250/25 micrograms, two inhalations twice daily starting 12 months ago
- salbutamol (Ventolin) pMDI 100 micrograms, 1–2 inhalations as required, repeated up to 4-hourly if needed

### CASE STUDY 2: Merindah presents to the practice, as she continues to experience poor symptom control

- 41 years old
- Spirometry-confirmed asthma at age 29 years

**Current history**

- Daytime symptoms most days for previous 3 months
- Night waking more than once a week
- Needs salbutamol at least once a day
- Admission to ICU in the last year
- Confirmed good inhaler technique, adherence, self-management and knowledge of her asthma in a previous visit
- Follows her asthma action plan

**Past medical history**

- Diabetes, HbA\(_1c\) 7.9%
- GORD

**Social**

- Never smoked, drinks alcohol occasionally
- BMI > 32 kg/m\(^2\)

**Medications**

- budesonide/formoterol (Symbicort) Turbuhaler 400/12 micrograms, two inhalations twice daily
- salbutamol (Asmol) pMDI 100 micrograms, 1–2 inhalations as required, repeated up to 4-hourly if needed
- omeprazole EC (Acimax) 20 mg, 1 tablet daily
- metformin (Diabex) 1000 mg daily

### Learning outcomes

1. Identify patients with difficult-to-treat asthma.
2. Assess asthma control, including symptom control and future risk of adverse outcomes, in patients with difficult-to-treat asthma.
3. Assess and manage factors that contribute to poor asthma control, including poor inhaler technique, poor adherence, comorbidities and triggers.
4. Identify patient characteristics for severe, high-risk and persistently difficult-to-treat asthma which may benefit from timely referral to a specialist.
5. Describe the role of biologic therapies in severe asthma and the rationale for their use.

ICS/LABA = inhaled corticosteroid/long-acting beta agonist; OCS = oral corticosteroids; pMDI = pressurised metered-dose inhaler; GORD = gastro-oesophageal reflux disease

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VENTUREWISE MANAGEMENT OF PEOPLE WITH DIFFICULT-TO-TREAT ASTHMA: A SYSTEMATIC APPROACH
Figure 1: Systematic assessment of a patient with difficult-to-treat asthma

Box 1. What is uncontrolled asthma?
Uncontrolled asthma is defined as at least one of the following:2

1. Poor symptom control: in the last 4 weeks has the patient had at least one of the following:
   - Daytime asthma symptoms more than twice per week?
   - Any night waking due to asthma?
   - Reliever needed for symptoms more than twice per week?
   - Any activity limitation due to asthma?

2. Frequent severe exacerbations: two or more courses of OCS (> 3 days each) in the previous year

3. Serious exacerbations: at least one hospitalisation, ICU stay or episode of mechanical ventilation in the previous year

4. Airflow limitation: FEV₁ < 80% predicted (after appropriate bronchodilator withheld and with reduced FEV₁/FVC).

Uncontrolled asthma is also defined as controlled asthma that worsens on tapering high doses of ICS, OCS (or biologics).2

Box 2. Tiotropium mist inhaler (Spiriva Respimat) for moderate to severe asthma
Available on the PBS general schedule as an add-on for adults with moderate to severe asthma who:

- Are on ICS ≥ 800 micrograms budesonide or equivalent per day plus a LABA, and
- Who have had one or more severe asthma exacerbations in the previous year.

Tiotropium is a LAMA that inhibits M3 receptors in the airways, resulting in relaxation of the airway smooth muscle.3,5 Compared to patients with severe asthma using ICS/LABA alone, a recent Cochrane review has found that adding tiotropium resulted in fewer exacerbations requiring OCS and is likely to have benefits on lung function and asthma control.3,5 Tiotropium should be stopped if no clinical benefit is seen.

### TABLE 1: Modifiable factors that may contribute to poor symptom control

<table>
<thead>
<tr>
<th>Medicines and related</th>
<th>Exposures</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>High SABA use</td>
<td>Allergen exposure in sensitised patients (house dust mite, cat, mould, cockroach)</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Incorrect inhaler technique</td>
<td>Confirmed food allergy</td>
<td>Anorexia, depression</td>
</tr>
<tr>
<td>Medicines that may exacerbate asthma</td>
<td>Indoor or outdoor air pollution, extreme weather</td>
<td>COPD</td>
</tr>
<tr>
<td>Poor adherence with preventer therapy</td>
<td>Occupational exposure to allergens or irritants</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>Smoking or environmental tobacco smoke, biomass fuel exposure</td>
<td>GORD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obesity</td>
</tr>
</tbody>
</table>

**Symptoms well controlled**
- Assess and support improvement where required
- Comorbidities
- Modifiable risk factors and triggers (see Table 1)
- Consider alternative diagnoses, eg:
  - Bronchectasis
  - Chronic heart failure
  - Chronic upper airway cough syndrome
  - COPD
  - Hyperventilation, dysfunctional breathing
  - Recurrent respiratory infections
  - Vocal cord dysfunction

**Symptoms not well controlled, or patient still requires high-dose ICS/LABA to maintain good asthma control**
- Assess and support improvement where required
- Comorbidities
- Modifiable risk factors and triggers (see Table 1)
- Consider alternative diagnoses, eg:
  - Bronchectasis
  - Chronic heart failure
  - Chronic upper airway cough syndrome
  - COPD
  - Hyperventilation, dysfunctional breathing
  - Recurrent respiratory infections
  - Vocal cord dysfunction

**Not severe asthma**
If patient has experienced good asthma control for 2–3 months and is at low risk of flare-ups, consider stepping down treatment – see the Australian Asthma Handbook.

**Possibly severe asthma**
- Identify patients with uncontrolled asthma despite high-dose ICS/LABA or OCS, or those who require the same for asthma to remain well controlled
  - Assess asthma control, including:
    - Asthma symptom control
    - Future risk of adverse outcomes
  - See Box 1 for definition of uncontrolled asthma.
Collaborate with respiratory specialists for patient-centred care

- Consider referral for patients with severe or persistently difficult-to-treat asthma to improve quality of life and allow timely access to specialist treatment options available for this patient population.\(^1\)
- To be eligible for PBS-subsidised biologic therapy, patients must be under the care of a specialist experienced in the management of severe asthma for at least 12 months.\(^6,9\)

Phenotyping and targeted treatments

- The respiratory specialist assesses and tailors treatment for patients with severe asthma based on inflammatory phenotypes.
- Three recognised clinical and inflammatory phenotypes are eosinophilic, allergic and non-eosinophilic asthma, and targeted treatments are now available for patients with severe asthma and an allergic or eosinophilic phenotype.\(^1,10\)
- After initiation of biologic therapy by a specialist, the primary care prescriber facilitates the ongoing treatment in collaboration with the specialist.

### TABLE 2

<table>
<thead>
<tr>
<th>ALLENGIC AIRWAY INFLAMMATION</th>
<th>EOSINOPHILIC AIRWAY INFLAMMATION</th>
<th>NEUTROPHILIC AIRWAY INFLAMMATION</th>
<th>MIXED INFLAMMATION</th>
<th>PAUCIGRANULOCYTIC ASTHMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers in patients using high-dose ICS</strong></td>
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</tr>
<tr>
<td>Total serum IgE</td>
<td>Blood eosinophil count ≥ 0.3 cells x10^9/L, FeNO ≥ 20 ppb, sputum eosinophils ≥ 2%, low neutrophil percentage</td>
<td>≥ 40–60% polymorphonuclear neutrophils in sputum, low eosinophil percentage</td>
<td>High type 2 (eosinophilic) and neutrophilic markers</td>
<td>No elevation of type 2 (eosinophilic) markers and ≤ 40–60% sputum polymorphonuclear neutrophils</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Omalizumab + OCS</td>
<td>Mepolizumab + OCS</td>
<td>LABA, LAMA, ?macrolide(^b)</td>
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</tr>
</tbody>
</table>

b. Macrolides are not currently approved in Australia for long-term management of asthma

### TABLE 3

**PBS-subsidised biologic therapy**

<table>
<thead>
<tr>
<th>OMAZILUMAB (XOLAIR)</th>
<th>MEPOLIZUMAB (NUCALA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PBS indication</strong></td>
<td>Uncontrolled severe allergic asthma</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Monoclonal antibody that selectively binds to human IgE and limits the availability of mediators involved in the allergic cascade(^11)</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>Reduced asthma exacerbations</td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td>Injection-site reactions</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Subcutaneous injection every 2–4 weeks(^16)</td>
</tr>
</tbody>
</table>

**References available online at:** nps.org.au/asthma-card-refs

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ppb = parts per billion; IgE = immunoglobulin E; FeNO = fractional exhaled nitric oxide; IL-5 = interleukin 5