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

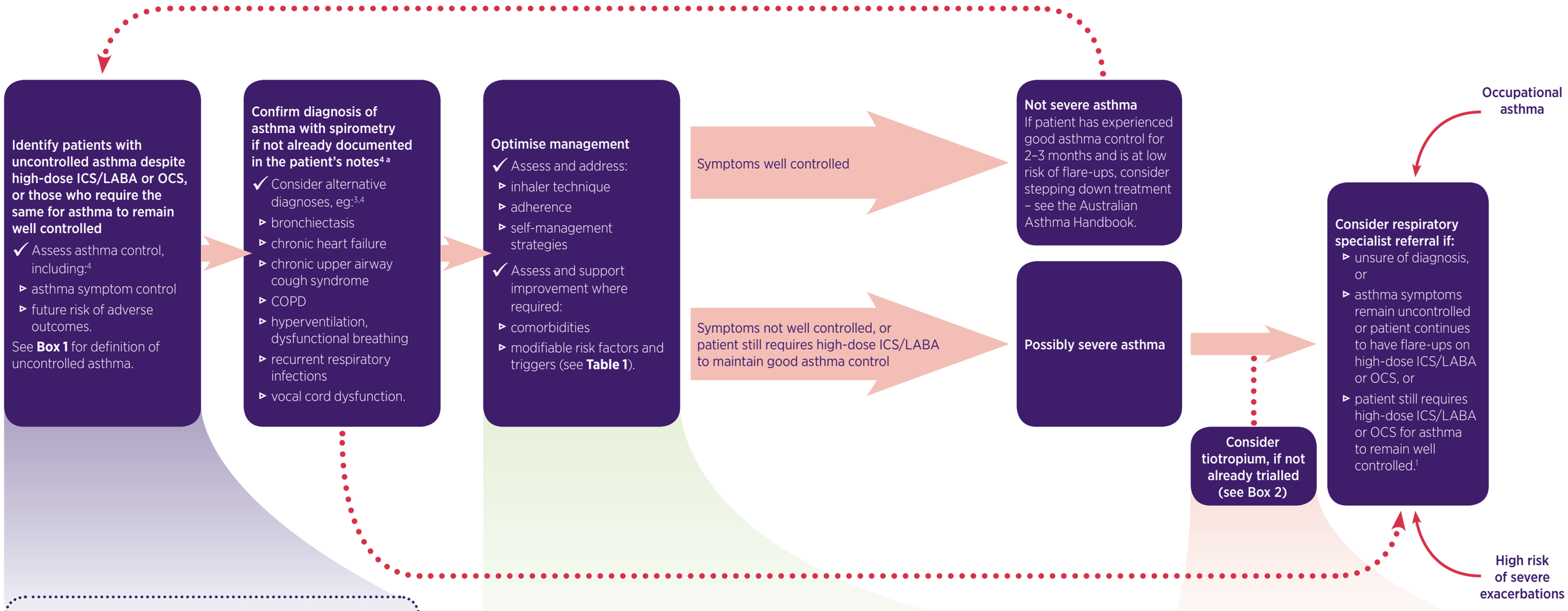
- budesonide/formoterol (Symbicort) Turbuhaler 400/12 micrograms, two inhalations twice daily
- salbutamol (Asmol) pMDI 100 micrograms, 1–2 inhalations as required, repeated up to 4-hourly if needed
- omeprazole EC (Acimax) 20 mg, 1 tablet daily
- metformin (Diabex) 1000 mg daily

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 $beta_2$ agonist; OCS = oral corticosteroids; pMDI = pressurised metered-dose inhaler; GORD = gastro-oesophageal reflux disease

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: FEV_1 < 80% predicted (after appropriate bronchodilator withheld and with reduced FEV_1/FVC).

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

TABLE 1 Modifiable factors that may contribute to poor symptom control

Modifying the comorbidities in **bold** can particularly improve asthma control.

Medicines and related	Exposures	Comorbidities
▹ High SABA use	▹ Allergen exposure in sensitised patients (house dust mite, cat, mould, cockroach)	▹ Allergic bronchopulmonary aspergillosis
▹ Incorrect inhaler technique	▹ Confirmed food allergy	▹ Anxiety, depression
▹ Medicines that may exacerbate asthma	▹ Indoor or outdoor air pollution, extreme weather	▹ COPD
▹ Poor adherence with preventer therapy	▹ Occupational exposure to allergens or irritants	▹ Bronchiectasis
	▹ Respiratory viruses	▹ GORD
	▹ **Smoking or environmental tobacco smoke**, biomass fuel exposure	▹ **Obesity**
		▹ Rhinosinusitis ± nasal polyposis
		▹ Vocal cord dysfunction
		▹ Pregnancy

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[5] 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.[6]

Tiotropium is a LAMA that inhibits M3 receptors in the airways, resulting in relaxation of the airway smooth muscle.[7]

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.[6]

Tiotropium should be stopped if no clinical benefit is seen.

a. Diagnosis is confirmed by compatible history, objective demonstration of variable expiratory airway obstruction using change in FEV_1, either spontaneously over time, before and after bronchodilator, or in response to a bronchial provocation agent (when baseline FEV_1 is normal).[5]

COPD = chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; SABA = short-acting $beta_2$ agonist; LAMA = long-acting muscarinic antagonist

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.[8,9]

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

Laboratory markers and treatment associated with pathobiological characteristics of severe asthma in patients using high-dose ICS, according to inflammatory phenotype[1,10]

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

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

TABLE 3

PBS-subsidised biologic therapy

	OMALIZUMAB (XOLAIR)	MEPOLIZUMAB (NUCALA)
PBS indication[c]	Uncontrolled severe allergic asthma	Uncontrolled severe eosinophilic asthma
Mechanism of action	Monoclonal antibody that selectively binds to human IgE and limits the availability of mediators involved in the allergic cascade[11]	Monoclonal antibody directed against human IL-5, the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils[12]
Benefits	▸ Reduced asthma exacerbations ▸ Reduced need for ICS ▸ Improvement in asthma symptom control ▸ Improvement in quality of life[4]	▸ Reduced asthma exacerbations ▸ Oral-steroid sparing effect ▸ Improvement in quality of life[13–15]
Common side effects	▸ Injection-site reactions ▸ Anaphylaxis	▸ Injection-site reactions ▸ Headache
Administration	▸ Subcutaneous injection every 2–4 weeks[11] ▸ The patient should remain for 2 hours under direct staff observation after the first three doses; and 30 minutes for subsequent doses[16]	▸ Subcutaneous injection every 4 weeks[12] ▸ The patient should remain for 1 hour under direct staff observation after the first dose; and 30 minutes for subsequent doses[17]

c. Authority Required: Refer to PBS Schedule for full authority information. Information current at 9 January 2018.

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

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

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