A patient with mild asthma symptoms and a yearly flare-up

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Tom is a 24-year-old long-distance runner with a history of childhood asthma. He takes regular inhaled corticosteroid treatment. He experiences mild symptoms that are mainly exercise-induced and easily relieved with inhaled salbutamol. He has one exacerbation per year requiring a short course of oral corticosteroid, but he has had no hospitalisations in the past for asthma. How do you manage his asthma and exercise-induced symptoms?

Key points

- **People with mild asthma symptoms are still at risk of serious consequences, such as severe flare-ups, and some deaths from asthma occur in people with mild or infrequent symptoms.**
- **Overuse of short-acting bronchodilators is associated with an increased risk of exacerbations and asthma death.**
- **Taking even four to five short courses of oral corticosteroids over seven years is associated with a significantly increased incidence of osteoporosis, diabetes, pneumonia and other adverse outcomes.**
- **Inhaled corticosteroid (ICS)-containing treatments markedly reduce exacerbation risk, particularly when combination ICS-formoterol (formerly eformoterol) is taken instead of short-acting beta-2-agonist (SABA) as the patient's symptom reliever, either alone or with maintenance ICS-formoterol.**
- **As-needed low-dose budesonide-formoterol, taken for symptom relief, is a new level 2 treatment option for managing mild asthma in adults and adolescents, as an alternative to regular daily low-dose ICS plus as-needed SABA.**
- **Using SABA alone should only be considered in patients with asthma who have symptoms less than twice a month and no risk factors for exacerbations (including no exacerbation in the past year).**
- **Vocal cord dysfunction, now called inducible laryngeal obstruction, can mimic asthma or can coexist in people with asthma.**

Case scenario

Tom is a 24-year-old man with a history of childhood asthma, diagnosed at the age of four years. He is very fit, running more than 100 km a week and participating in 10 km races several times a year. He has been doing so for the last six years.

He has never had an emergency presentation or been hospitalised for asthma. His current asthma medications include budesonide-formoterol (formerly eformoterol) dry powder inhaler 200 mcg/6 mcg one puff twice daily and salbutamol as needed. He commenced this treatment in November 2019. Before that he had been on regular fluticasone propionate-salmeterol for more than 10 years. Factors that worsen his asthma control include exposure to house dust mites, and respiratory tract infections. Tom usually has three to four respiratory tract infections per year and requires about one course of prednisolone annually. He had one episode of pneumonia in 2014. There is no history of recurrent ear, sinus or pulmonary infections in childhood, and no family history of an immunodeficiency disorder.

Tom experiences typical symptoms of shortness of breath, wheeze and chest tightness about once a week and these respond well to salbutamol. He does not report cough or sputum production. Before running, he occasionally uses salbutamol pre-emptively to avoid exercise-induced symptoms. This works quite well for him.

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Table 1. Tom's lung function at first presentation and after six months

Lung function parameter	Predicted values	Lower limit of normal	Initial clinic visit			Review at six months
			Pre-bronchodilator	Post-bronchodilator	% change	Pre-bronchodilator
FEV_1 (% predicted)	4.27 L	3.45 L	4.42 L (103%)	4.46 L (104%)	+1	4.49 L (104%)
FVC (% predicted)	5.03 L	4.07 L	4.77 L (94%)	4.71 L (93%)	–1	4.86 L (95%)
FEV_1/FVC	85	74	93 (108%)	95 (111%)	+2	92 (108%)
TLC (% predicted)	6.57 L	5.17 L	6.76 L (102%)			-
RV/TLC	24	13	33 (139%)			-
DLCO corr (% predicted)	35.75 mL/min/mmHg	23.67 mL/min/mmHg	34.18 mL/min/mmHg (95%)			-
KCO (% predicted)	5.54 mL/min/mmHg	4.08 mL/min/mmHg	5.59 mL/min/mmHg (100%)			-

Abbreviations: DLCO corr = diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; KCO = carbon monoxide transfer coefficient; RV = residual volume; TLC = total lung capacity.

Tom also has allergic rhinitis. He experiences postnasal drip and is currently taking an intranasal corticosteroid spray twice daily and an oral antihistamine daily. He has not had any serious sinus infections in the past. Tom's asthma worsens after taking aspirin, so he avoids it.

Tom previously lived in rural NSW but now shares an apartment with nonsmoking housemates. There is no mould in the apartment. He is undertaking university studies to become a high school teacher. He does not have any pets. Tom has never smoked cigarettes or marijuana and rarely consumes alcohol. He does not take drugs recreationally. A skin-prick test was positive to house dust mite when he was younger. He also experienced eczema when he was younger, but no longer does. He has no food allergies and no family history of asthma. He is up to date with influenza vaccination.

On examination, Tom appears well. His heart rate is 62 beats per minute and regular, and his oxygen saturation is 97% on room air. There is no digital clubbing. There is mild nasal mucosal erythema but no nasal polyps. His sinuses are not tender to palpation. His jugular venous pressure is not elevated. His heart sounds are dual with no murmurs. He has normal vesicular breath sounds with no adventitious sounds. There is no peripheral oedema.

On review of his inhaler technique, Tom does not inhale deeply and strongly, and thus has likely not been receiving the full dose of his dry powder budesonide-formoterol. He is trained in correct inhaler technique.

Tom's lung function (Table 1) shows normal expiratory spirometric values, with no airflow limitation. There is no significant increase after bronchodilator. His diffusing capacity is normal, at 95% predicted. The inspiratory loop of the flow-volume curve is flattened (Figure 1).

Commentary

In summary, Tom has a history of childhood asthma and eczema and currently has mild respiratory symptoms that occur on a weekly basis. He is on a low-dose inhaled corticosteroid (ICS)-based treatment with a combination ICS-long-acting beta-2 agonist (LABA), with as-needed salbutamol (a short-acting beta-2 agonist [SABA]) for symptom relief. He displays suboptimal inhaler technique. Tom was initially emphatic that he used his preventer twice daily and had not omitted a dose, but then he said he found it easier to remember his inhaler in the morning than in the evening. Inhaler adherence is best assessed through an empathic discussion, knowing that most patients do not take their asthma medication regularly (for suggestions for how to have a discussion about adherence to medication with patients, see https://www.asthmahandbook.org.au/management/adherence/assessing-adherence). Tom takes salbutamol

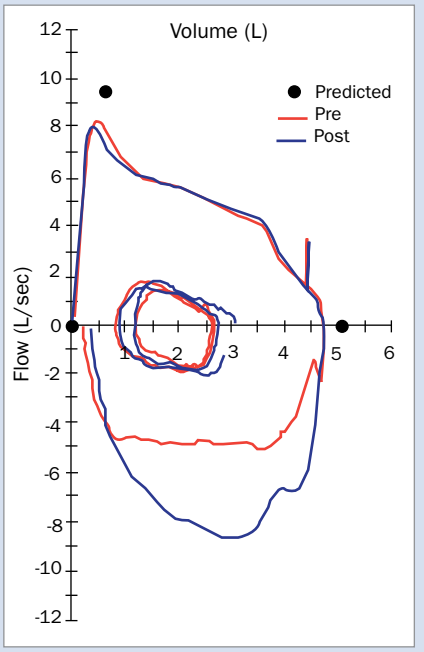

Figure 1. Tom's expiratory and inspiratory flow volume loops pre- and post-bronchodilator at his initial visit. Tom's flow volume curve revealed normal expiratory function but a flattened inspiratory loop on the pre-bronchodilator manoeuvre, which appears suspicious for vocal cord dysfunction.

pre-emptively before exercise to avoid exercise-induced symptoms. His asthma symptoms are well controlled on his current treatment, but he has one exacerbation per year requiring a course of oral prednisone. He has normal spirometry results with no evidence of significant bronchodilator reversibility today. The flow-volume loop demonstrates flattening of the inspiratory limb, which is often seen in vocal cord dysfunction (VCD), otherwise known as inducible laryngeal obstruction (ILO).

Does Tom have asthma?

It is important to confirm the diagnosis of asthma in Tom, despite a history consistent with childhood asthma, because his current symptoms could be due to another condition. The diagnosis of asthma can be confirmed in an individual if there are variable respiratory symptoms with variable expiratory airflow limitation. The most commonly used test for variable expiratory airflow limitation is bronchodilator responsiveness. Although the diagnosis of asthma can be confirmed by a bronchodilator response of 12% and 200 mL (or greater) improvement in forced expiratory volume in 1 second (FEV_1) and/or forced vital capacity from baseline, this is not present in many patients with asthma, particularly those who, like Tom, are already on treatment and have good symptom control.[1]

Variable expiratory airflow limitation can be documented if there is a clinically important variation. There are various ways of documenting clinically important variation, including the following:[2]

- in adults, an increase in FEV_1 of at least 200 mL and 12% from baseline 10 to 15 minutes after administration of rapid-onset bronchodilator
- a difference in FEV_1 of at least 20% when spirometry is repeated at different visits over time
- a reduction in lung function after exercise defined as a decrease in FEV_1 of at least 200 mL and 12% from baseline on spirometry, or decrease in peak expiratory flow rate by at least 20%
- an increase in lung function of at least 200 mL and 12% from baseline after a trial of ICS for 4 weeks or longer
- diurnal variability in peak expiratory flow of more than 10%
- a reduction in lung function of 15 to 20% during a test for airway hyper-responsiveness (exercise challenge test or bronchial provocation test) measured in a respiratory function laboratory.

Around 15% of deaths that occur in people with asthma are in those with apparently mild asthma

Investigations that can be performed routinely in primary care to help confirm the diagnosis include spirometry, which is the best lung function test for diagnosing asthma. Spirometry should be performed before and fifteen minutes after bronchodilator administration.[2] It is critical to obtain a reliable test, and there are two factors that impact this. First, the operator needs to fully understand the principles behind the test. Second, to ensure reliable results, spirometry equipment should be well maintained and regularly calibrated. The National Asthma Council spirometry handbook is a useful tool for learning the principles of spirometry.[3]

In a patient such as Tom, who has few respiratory symptoms, normal lung function and no variable airflow limitation on his initial spirometry, repeat bronchodilator reversibility testing can be done after withholding bronchodilator (four hours for SABA; 24 hours for twice-daily ICS-LABA such as fluticasone propionate-salmeterol; 36 hours for once-daily ICS-LABA such as fluticasone furoate-vilanterol) or when the patient is symptomatic.[4] If the diagnosis is still not confirmed, further investigations should ideally be done by a respiratory specialist, as stepping down of preventer treatment may be required. Diagnostic testing can be carried out when symptoms reappear or increase as treatment is stepped down. However, if lung function remains normal and the patient does not demonstrate worsening of symptoms, a bronchoprovocation test such as eucapnic voluntary hyperventilation challenge may be considered. A bronchoprovocation test is only considered in an individual with FEV_1 >70% predicted.[4] For an athlete, confirmation of the diagnosis of asthma is essential to allow a therapeutic use exemption for use of asthma medications, either by demonstrating significant bronchodilator reversibility (an increase in FEV_1 of ≥12% and ≥200 mL after 200 to 400 mcg of inhaled SABA) or with a bronchial provocation test such as a eucapnic voluntary hyperventilation challenge.

Reviewing Tom's asthma treatment

Asthma treatment is described as level 1 to 5 according to the Australian National Asthma Council in the *Australian Asthma Handbook* (Figure 2). The algorithm is summarised in the treatment figure for adults and adolescents, which shows (on the left) the suggested starting level based on initial symptom frequency. Asthma treatment is then stepped up or down to find the intensity of treatment (type, number and dose of medication) required to achieve optimal asthma control.

Around 15% of deaths that occur in people with asthma are in those with apparently mild asthma.[5] To reduce the risk of serious exacerbations, treatment with ICS-containing treatment is recommended for all adults and adolescents with mild asthma symptoms.[4] This should be considered even for patients with infrequent symptoms, in whom as-needed ICS-formoterol reduces the risk of severe exacerbations by two-thirds compared with SABA alone.[6-8]

Tom is currently on level 3 treatment, comprising low-dose budesonide-formoterol with as-needed salbutamol. Although Tom has good symptom control most of the time, he experiences a severe flare-up (exacerbation) requiring oral corticosteroids once a year. His inhaler technique was corrected.

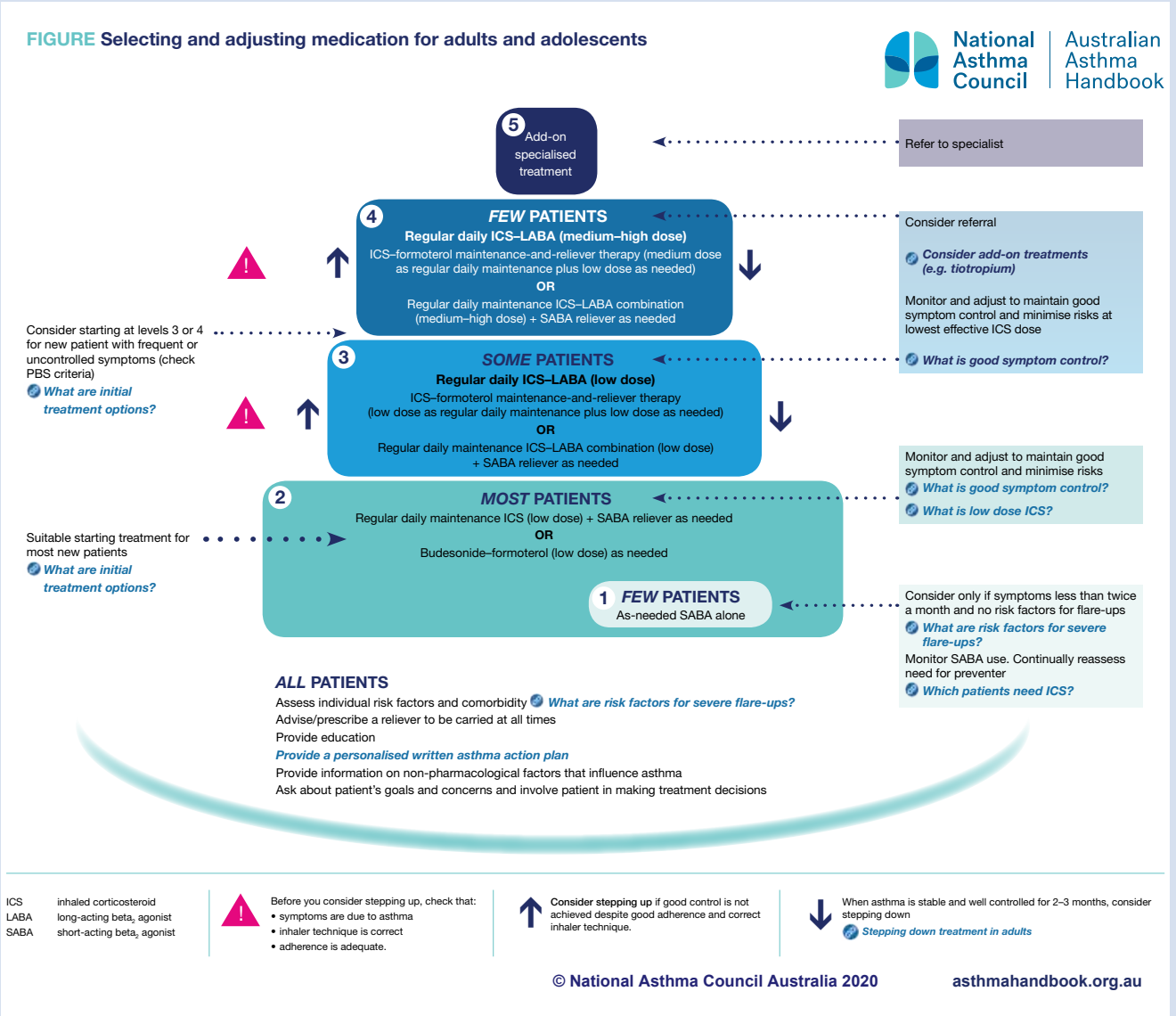

Figure 2. Selection and adjustment of asthma medications in adults and adolescents.
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The most effective strategy to reduce Tom's risk of further severe exacerbations is to switch him from a conventional maintenance combination regimen with as-needed salbutamol to MART (maintenance and reliever therapy) with low-dose budesonide-formoterol. He should continue his current low-dose budesonide-formoterol 200 mcg/6 mcg by dry powder inhaler one inhalation twice a day and use one inhalation of the same medication whenever needed for symptoms, instead of salbutamol.

Advice for patients prescribed MART

Tom was given a written asthma action plan customised to maintenance and reliever therapy. Examples of templates for action plans with either a budesonide-formoterol dry powder inhaler or budesonide-formoterol pressurised metered dose inhaler can be found on the National Asthma Council website ('Symbicort anti-inflammatory reliever +/- maintenance action plans', https://www.nationalasthma.org.au/health-professionals/asthma-action-plans/asthma-action-plan-library). Tom was advised that the maximum number of inhalations of budesonide-formoterol 200 mcg/6 mcg dry powder inhaler in any one day is a total of 12 inhalations, but that very few patients need to use this much. For patients prescribed maintenance and reliever therapy with a budesonide-formoterol pressurised metered dose inhaler 100 mcg/3 mcg, the standard dosage is two puffs twice a day plus two puffs as needed for symptoms, with a maximum total of 24 puffs in a day (Table 2).

For pre-exercise use, Tom was told to substitute one inhalation of his 200 mcg/6 mcg

Table 2. Dosages of as-needed budesonide-formoterol* for as-needed-only or maintenance and reliever therapy (MART) according to formulation, for adults and adolescents

Formulation	Dose of maintenance treatment if prescribed	Dose of reliever treatment	Maximum dose in any one day (total of maintenance and reliever treatments)
Dry powder inhaler 200mcg budesonide/6mcg formoterol†	One inhalation twice daily OR two inhalations once daily For some patients, a maintenance dose of two inhalations twice daily may be needed. Titrate to the lowest effective dose	Patients should take one inhalation as needed in response to symptoms. If symptoms persist after a few minutes, one additional inhalation should be taken. No more than six inhalations should be taken on any single occasion	12 inhalations
Pressurised metered dose inhaler 100mcg budesonide/3mcg formoterol‡	Two inhalations twice daily OR four inhalations once daily For some patients, a maintenance dose of four inhalations twice daily may be needed. Titrate to the lowest effective dose	Patients should take two inhalations as needed in response to symptoms. If symptoms persist after a few minutes, two additional inhalations should be taken. No more than 12 inhalations should be taken on any single occasion	24 inhalations

* Formerly budesonide-eformoterol.
† Symbicort Turbuhaler approved for adults and adolescents ≥12 years, DuoResp Spiromax approved only for adults ≥18 years.
‡ Symbicort Rapihaler approved for adults and adolescents ≥12 years.

budesonide-formoterol dry powder inhaler in place of salbutamol. He was advised that he should rinse and spit out after taking his regular doses of budesonide-formoterol, but that he does not need to rinse out after as-needed doses. This advice is supported by safety data from studies in more than 30,000 patients that did not show an increased risk of a hoarse voice or candidiasis with this recommendation.[9] Most patients prescribed MART should be advised to have two of the budesonide-formoterol inhalers, one to keep at home for maintenance use, and the other in their bag or pocket for as-needed or pre-exercise use.

Evidence about maintenance and reliever therapy

MART has been recommended in Australian asthma guidelines since 2006, for patients with moderate-severe asthma. This is possible because formoterol is not only long-acting, but also has a rapid onset of action and therefore budesonide-formoterol can be used as a reliever.[10]

In addition, MART is more effective at reducing exacerbations and improving daily asthma control than the same maintenance dose of budesonide-formoterol and as-needed SABA.[11] It is also more effective than a higher dose of ICS-LABA with as-needed SABA.[12] The largest benefit of MART in reducing severe exacerbations compared with using a SABA as the reliever is seen in patients with a history of severe exacerbations, but it also reduces exacerbations in patients without such a history.[13,14]

For patients using SABA as their reliever, the risk of severe asthma exacerbations is increased if SABAs are overused because SABA alone does not treat the underlying inflammatory component that precipitates symptoms. Furthermore, regular SABA use for as little as one to two weeks leads to a reduction in bronchodilator response, increased airway hyper-responsiveness, increased mast-cell mediator release and eosinophilic inflammation.[6]

Overuse of SABA is defined as dispensing three or more canisters of salbutamol in a year (average of 1.6 or more puffs a day).[9] This is also associated with increased risk of asthma death.[15] Overuse of reliever inhalers is more common in patients using SABA reliever than those using ICS-formoterol as reliever.[16,17]

Even a single day of higher SABA use has been found to be associated with a greater short-term risk of a severe exacerbation compared with a single day of higher use of as-needed budesonide-formoterol or of as-needed SABA in patients taking budesonide maintenance. This has been observed both in patients taking MART and in patients with mild asthma taking as-needed low-dose ICS-formoterol alone.[18-20] This suggests that the timing of extra doses of both ICS and formoterol is critical in preventing asthma from worsening to an exacerbation.

Why should we be concerned about an occasional course of oral corticosteroids?

Studies have shown that even a single short course of oral corticosteroids can cause serious adverse outcomes for patients, including increased risk of thromboembolism, pneumonia and sepsis.[21] Even as few as four short courses of corticosteroids over seven years of follow up are associated with an increased risk of osteoporosis, fractures, hypertension and onset of type 2 diabetes, and they also have impacts on mental health.[22]

Exercise-induced bronchoconstriction: a change from SABA to prophylactic budesonide-formoterol

Tom takes prophylactic salbutamol before exercise to avoid symptoms of exercise-induced bronchoconstriction (EIB).

Exercise-induced bronchoconstriction is airway contraction associated with exercise.[23] In its most classic form, the patient's symptoms get worse after they stop exercising. Although EIB is markedly reduced by regular ICS, some patients still experience exercise-induced bronchoconstriction and need pre-exercise treatment. Symptoms of EIB can start during exercise, or can start within a few minutes after exercise stops, and then continue to increase for up to 20 minutes. This contrasts with conditions such as lack of fitness or vocal cord dysfunction, in which dyspnoea typically improves after the patient stops exercising.

The proposed mechanism by which bronchoconstriction occurs is cooling of the airways and heating and humidifying of air during exercise, which leads to water loss from the airway surface. The airway surface becomes hyperosmolar which provides an osmotic stimulus for water to move from cells nearby, resulting in volume loss of the cells. This leads to the release of inflammatory mediators that cause the smooth muscle to contract.[24]

In patients who experience EIB despite otherwise well-controlled asthma, the previous recommendation was to take SABAs before exercise. However, beta-2 agonists do not provide the same protection after a few weeks of continuous treatment as their effects rapidly diminish due to tachyphylaxis.[25] A study in patients with mild asthma found that a six-week treatment regimen with inhalation of low-dose combination budesonide-formoterol as required for symptom relief and before exercise was superior to as-required SABA in reducing EIB. In this study, as-needed budesonide-formoterol before exercise reduced EIB to the same extent as daily low-dose ICS (e.g. 400 mcg/day budesonide) plus as-needed SABA.[26] In patients prescribed MART, guidelines recommend that the low-dose ICS-formoterol reliever can also be used before exercise.[2] It is essential for patients to distinguish between EIB and normal breathlessness on exertion. Normal breathlessness on exertion settles once exercise stops and reduces over time with physical conditioning.

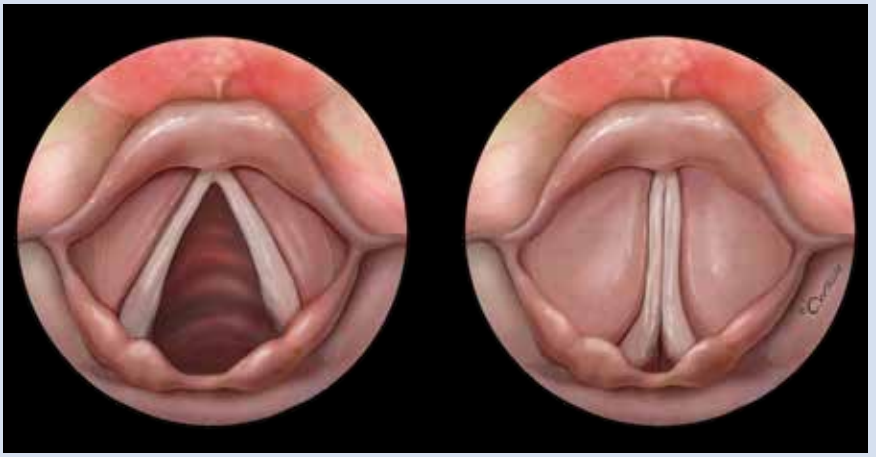

Figure 3. The vocal cords. a (left). Normal vocal cords. b (right). Vocal cord dysfunction is characterised by abnormal adduction of the vocal cords.

Tom's progress

Tom returned for follow up after six months. He reported a recent respiratory infection for which he had appropriately increased his as-needed doses of budesonide-formoterol at the time. He did not require prednisone. He now reports an inspiratory discomfort which he describes as a 'freezing' sensation when he inspires. This is not related to exertion. He states he takes an additional puff of budesonide-formoterol for this sensation, with no relief in symptoms. He does not report cough, wheeze or sinus symptoms. His allergic rhinitis is treated with intranasal corticosteroid and antihistamine, and he has minimal symptoms from that. He does not report symptoms that suggest gastroesophageal reflux disease. He was still able to run ninety kilometres last week but described dyspnoea during inspiration when running, which did not resolve despite taking an inhalation of budesonide-formoterol before and during exercise. On examination, his oxygen saturation was 99% on room air, and heart rate 73 beats per minute. His lungs were clear on auscultation, and cardiovascular examination was unremarkable. Spirometry results on this occasion were normal (Table 1), but flow volume demonstrated a flattened inspiratory limb (Figure 1).

What is the differential diagnosis of these new symptoms?

The main differential diagnosis here is VCD. VCD refers to involuntary adduction of the vocal cords during inspiration (Figure 3), and may mimic asthma or coexist with asthma.[27] The prevalence of VCD is unknown but has been estimated at 4 to 6% with the use of a postal questionnaire survey.[28] VCD is now included under the broader heading of ILO, as similar symptoms can be found without vocal cord adduction (e.g. from supraglottic muscle squeeze).[29] The most common symptoms are shortness of breath, cough and wheeze, which may be precipitated by exercise, stress or irritant chemicals such as gastric acid.[30] Patients with exercise-induced dyspnoea have been shown to have a higher frequency of VCD-like symptoms. Exercise-induced laryngeal obstruction (EILO) occurs most commonly in adolescents and young adults, with estimated prevalence ranging from 5.7 to 7.5%.[31,32] In the past, there has been emphasis on an emotional component associated with VCD, although it is not the primary trigger for athletes.[33] If a patient reports dyspnoea, shortness of breath, stridor or wheeze during exercise and medications prescribed to relieve the symptoms are not effective, VCD should be considered as a coexisting diagnosis. A flattened inspiratory limb on flow-volume loops is suggestive of upper extrathoracic airway obstruction, as can be seen in VCD, although this may not always be seen.[34] Dysphonia occurring during these symptoms is also a suggestive clinical feature. The diagnosis should be confirmed with visualisation of the vocal cords via

Practice points

- Confirm the diagnosis of asthma, if possible before starting treatment.
- Dispensing of three or more canisters of short-acting beta-2 agonist (SABA) in a year is associated with a higher risk of asthma exacerbations and death.
- A single day of higher use of SABA is associated with increased short-term risk of severe exacerbations, including in patients with apparently mild asthma. Monitoring of SABA use is advised, to alert patients to worsening asthma.
- All patients with asthma should have a written action plan, to reduce exacerbations and reduce the need for oral corticosteroids.
- An inhaled corticosteroid-containing regimen markedly reduces the risk of severe exacerbations compared with as-needed salbutamol alone.
- For adults and adolescents with infrequent symptoms of asthma, as-needed budesonide-formoterol (formerly eformoterol) taken instead of SABA for relief of symptoms may be used in place of regular daily inhaled corticosteroid plus as-needed SABA.
- Starting asthma treatment with as-needed budesonide-formoterol may help reinforce to the patient that an anti-inflammatory preventer is crucial in their long-term management, and may help to avoid over-reliance on SABA.
- As-needed budesonide-formoterol can be used instead of a SABA before, during or after exercise to reduce exercise-induced bronchoconstriction.
- Early recognition and correct diagnosis of vocal cord dysfunction (VCD) is necessary. VCD may mimic or coexist with asthma and it can be difficult to distinguish from asthma. This may lead to overtreatment with corticosteroids. If suspected, consider referral to a voice clinic or ENT specialist for functional laryngoscopy. Do not omit inhaled corticosteroid treatment if the patient also has asthma.

functional fibreoptic rhinolaryngoscopy, which is usually performed by an ear, nose and throat specialist with an interest in voice problems, or at a voice clinic. Management of VCD includes training by a speech pathologist, which consists of learning exercises to facilitate laryngeal relaxation including using diaphragmatic breathing.[33]

Given Tom's history of respiratory tract infections, it is important to evaluate his risk factors, such as establishing his burden of sinus disease or allergic rhinitis, and optimise treatment. If he continues to have respiratory infections, further investigations with a high-resolution CT chest scan may be considered to look for bronchiectasis along with a referral to a specialist respiratory physician for an evaluation.

Can Tom's asthma treatment be stepped down?

Good asthma pharmacotherapy management includes finding each patient's minimum effective medication dose by gradually stepping down therapy after their asthma is well-controlled for two to three months. For people with asthma who take low-dose ICS alone plus as-needed SABA reliever, treatment can either be maintained long-term or switched to as-needed low dose budesonide-formoterol. For patients whose asthma is well-controlled on level 3 MART treatment (low-dose budesonide-formoterol maintenance treatment with as-needed doses of the same medication for symptom relief), the logical level 2 treatment would be to drop the maintenance doses and continue on as-needed low-dose budesonide-formoterol alone. Previously for level 2 treatment, the only treatment option was daily maintenance low-dose ICS plus as-needed SABA. Updated Australian asthma guidelines published in 2020 incorporated as-needed low-dose budesonide-formoterol as an alternative level 2 treatment option for managing mild asthma in adults and adolescents.[2,9] Level 1 treatment in Australian guidelines is as-needed SABA, but only for patients who experience symptoms less than twice a month and have no risk factors for exacerbations, including no exacerbation in the previous year.

Before stepping down treatment, it is important to assess how often a patient takes their preventer medication, and if inhaler technique is correct. It is also important that each patient has a written asthma action plain that explains what to do if they experience an increase in symptoms. After stepping down, if the patient experiences an increase in asthma symptoms or lung function falls, the patient should resume their previous dose. Complete cessation of ICS is not advised as this increases the risk of severe exacerbations.[35] **RMT**

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A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

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