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UPDATE IN THE MANAGEMENT AND TREATMENT OF ADULT ASTHMA FOR PRIMARY CARE PHYSICIANS

Asthma is a common illness; estimates are that it affects up to 18% of the global population, with rates increasing every year.^{1,2} Approximately 3.8 million Canadians have asthma,³ and these patients continue to suffer from inadequately controlled disease as well as exacerbations. Although we have more medication choice than ever, mortality rates in Canada have not declined. Our current pharmacologic strategy has been mostly unchanged for years; it starts with an anti-inflammatory medication, usually an inhaled corticosteroid (ICS) to treat the type 2 (T2) inflammation that is most common. When an ICS provides inadequate control, therapy is often stepped up to include an ICS/long-acting beta-agonist (LABA) combination and even additional therapies like leukotriene receptor antagonists or long-acting muscarinic agents (LAMAs). As patients with uncontrolled asthma are at risk for deleterious outcomes, controlling

the disease and preventing exacerbations should be the goal for all patients.⁴

Asthma Control

Our approach to asthma management should begin with assessing asthma control on every visit. The most recent Canadian Asthma guidelines recommend assessing asthma control based on the criteria identified in **Table 1**.⁵

There are validated tools for measuring asthma control, but the key is to ask questions about symptoms and limitations. Lung function should be optimized. Measurements of inflammation are not routinely done in most clinical practices.

When a patient's asthma is not controlled, the basics of asthma management should be reviewed prior to

Daytime symptoms	two or fewer occurrences per week
Nighttime symptoms	preferably none
Physical activity	not limited
Exacerbations	none
Absenteeism	none (due to asthma)
Need for a reliever	two or fewer per week, whether SABA or budesonide/formoterol
FEV1 or PEF	≥ 90% of personal best
PEF diurnal variation	≤ 10–15%
Sputum eosinophils	≤ 2–3%

Table 1: Criteria for defining asthma control; adapted from Yang et al, 2021

FEV: Forced expiratory volume; PEF: Peak expiratory flow; SABA: short-acting beta-agonist

stepping up therapy.⁶ The diagnosis of asthma should be confirmed, as often it is assumed and not objectively worked up. Lack of adherence to medication is a common issue affecting asthma control, as often patients discontinue their controller medications when they feel better. Even when patients do take their medication, they need to take it properly, or the active ingredients will not reach the site of action in the lung. Avoidable triggers of inflammation must be identified, and comorbidities that can affect control should be dealt with. Overall, it is best to take a structured approach in addressing these patients (**Table 2**).

Approach to the non-controlled asthmatic

1. Confirm the diagnosis
2. Assess medication adherence
3. Review and refine device technique
4. Avoid triggers
5. Manage comorbidities
6. Step up therapy

Table 2: Approach to the non-controlled asthmatic; adapted from Haughney et al, 2008

The diagnosis of asthma is based on a history of characteristic symptom patterns and evidence of variable expiratory airflow limitation obtained from bronchodilator reversibility testing. As asthma is a variable condition, often responsive to triggers that may not be consistent, other tests may be necessary such as a positive bronchial provocation test, excessive variability during PEF monitoring, excessive variation in FEV1 between visits, fractionated exhaled nitric oxide (FENO),⁷ or a significant increase in FEV1 after ICS treatment. It is preferable to confirm the diagnosis prior to starting controller therapy to avoid inappropriate treatment or missing other important diagnoses,⁸ and because diagnosis is often more difficult later. The results from a clinical examination, including chest auscultation, may be completely normal, but can be useful to rule out other conditions.

There are significant barriers to obtaining spirometry results in a primary care practice.⁹ These barriers include lack of access, lack of expertise in performance of spirometry, patient reluctance or delay in attending a referral centre for spirometry, lack of time during clinician appointment to perform the test and then wait for repeat spirometry after bronchodilation, low confidence in the ability to interpret spirometry results, lack of remuneration for doing the test, and more recently, infectious concerns associated with aerosol generation during the COVID-19 pandemic. Solutions to these barriers could include providing compensation for doing proper quality-controlled spirometry in primary care,^{10,11} rapid interpretative support for spirometry, centralized spirometry intake programs, and same-day spirometry in the hospital setting.

Non-adherence is recognized as one of the main reasons for suboptimal asthma management and poor clinical outcomes.¹² Adherence issues can be divided between intentional and unintentional. A non-confrontational approach is more effective for those with intentional non-adherence. It can be helpful to frame comments with remarks such as “Many people find it difficult to take all of their medications all of the time.”¹³ Symptom-driven treatment strategies can also help correct intentional non-adherence. Unintentional non-adherence includes forgetting medications or taking them incorrectly.¹⁴ Setting reminders, placing medication near the site of a common activity, using phone apps, or simplifying a complex therapy regimen and not mixing devices can help unintentional non-adherence.^{15,16}

If the inhaled medication does not reach the lungs, it will not work. Critical errors in inhaler technique in which no medication will reach the lungs include failure to take off a device’s cap or loading it properly. Other errors can include not coordinating inhalation and device triggering or even exhaling into the device. Accurate inhaler technique is essential to asthma control, even when

adherence is otherwise perfect. As a rule, a metered dose inhaler (MDI) requires slow deep inhalations to prevent medication impacting the back of the throat, while a dry powder inhaler requires forceful inhalation for the medication to reach the lungs; yet another reason to not mix devices. The use of a valved holding chamber with an MDI can minimize upper airway side effects and improve lung deposition.¹⁷

Asthma triggers include cigarette smoking, both first- and second-hand, other inhalational activities such as vaping, cannabis and hookah use, indoor allergens such as dust mites or pet dander, and medications that increase the risk for bronchospasm, such as NSAIDs or beta-blockers.⁵ Viral infections cannot be completely avoided but vaccination for influenza, COVID-19, and pneumonia can be of value.

Key co-morbidities, including chronic rhinosinusitis with nasal polyps, allergic rhinitis, obesity,^{18,19} gastro-esophageal reflux disease (GERD), paradoxical vocal fold motion, anxiety, and depression, can contribute to or mimic the burden of lower respiratory symptoms. Clinicians may have to probe for these issues in patients who are not controlled, to provide optimal management.

Asthma Exacerbations

Exacerbations are important and occur across all levels of severity of asthma. Each episode increases the risk of unscheduled visits, hospitalizations, and mortality, as well as the loss of lung function.²⁰ As such, identification of those at high risk and the creation of preventative strategies are key. There are several factors that are clearly associated with an increased risk of asthma exacerbations (**Table 3**).²¹

- Uncontrolled asthma
- Lack of ICS due to poor adherence or poor technique
- SABA overuse
 - » Using more than two SABA cannisters per year has been associated with increased risk of exacerbations and mortality.²¹
- Comorbidities such as obesity, rhinosinusitis, GERD, food allergy and pregnancy, psychologic or socioeconomic issues, older age
- Exposures such as allergens, smoking and even air pollution
- Low lung function, especially if FEV1 < 60% predicted
- Having had a severe exacerbation in last month and last year
- History of ever needing intubation or intensive care unit admission for asthma

Table 3: Potentially modifiable risk factors for exacerbations; adapted from Reddell et al, 2021

Non-Pharmacologic Asthma Management

Asthma education should include details about asthma pathophysiology, stressing the inflammation component of the illness, defining expectations of good asthma control with recurrent assessment of such, and ensuring proper inhaler technique. Environmental assessment entails trigger identification and avoidance, which includes cessation of cigarette smoking, cannabis smoking, and inhalation of substances via other methods such as vaping and hookah, as well as identification and avoidance of allergens and irritants including potential occupational exposure. Outcomes are improved when education includes the patient's family.²² Asthma action plans have been shown to decrease exacerbations.²³ An example of an adult asthma action plan can be found at fpagc.com/tools-resources. In addition, regular exercise, nutritional optimization, social support, and vaccination to prevent respiratory infections all are key components of non-pharmacologic asthma management.

Pharmacologic Asthma Management

The key class of therapy to treat asthma inflammation is ICS. The goal of ICS therapy is to use the lowest effective dose to achieve control while preventing exacerbations; this provides the optimal balance between efficacy and safety. When ICS are initiated, symptoms will start to improve in two weeks,²⁵ but it can often take months to achieve the full effect.²⁶ If the response is suboptimal, and all non-pharmacologic asthma management approaches have been attempted, additional therapy with a LABA is recommended rather than dose titration of the ICS, due to the plateau in the dose response curve that is seen at a daily dose equivalent to 200–250 µg of fluticasone propionate.⁵

Stepping up low-dose ICS therapy with the adjunctive use of a LABA works best in a combination inhaler to prevent the isolated use of a LABA without ICS, which has been associated with deleterious outcomes (**Figure 1**).²⁷ Further step-up therapy should be individualized to patient comorbidities and phenotypes,²⁸ and can include leukotriene receptor antagonists (LTRAs), LAMAs, and then strategies for patients with severe asthma. Immunotherapy can reduce asthma symptoms and the need for asthma medications and improve bronchial hyper-reactivity.²⁹ This can be especially useful in patients with concomitant allergic rhinitis, but the possibility of local or systemic adverse effects, such as anaphylaxis, must be considered, although they are much less likely in sublingual immunotherapy vs subcutaneous immunotherapy. LTRAs also play a role in allergic rhinitis and may have some extra benefit in obese asthmatics.¹⁷ LAMA therapy has been shown to benefit patients with respect to exacerbations and lung function and is not

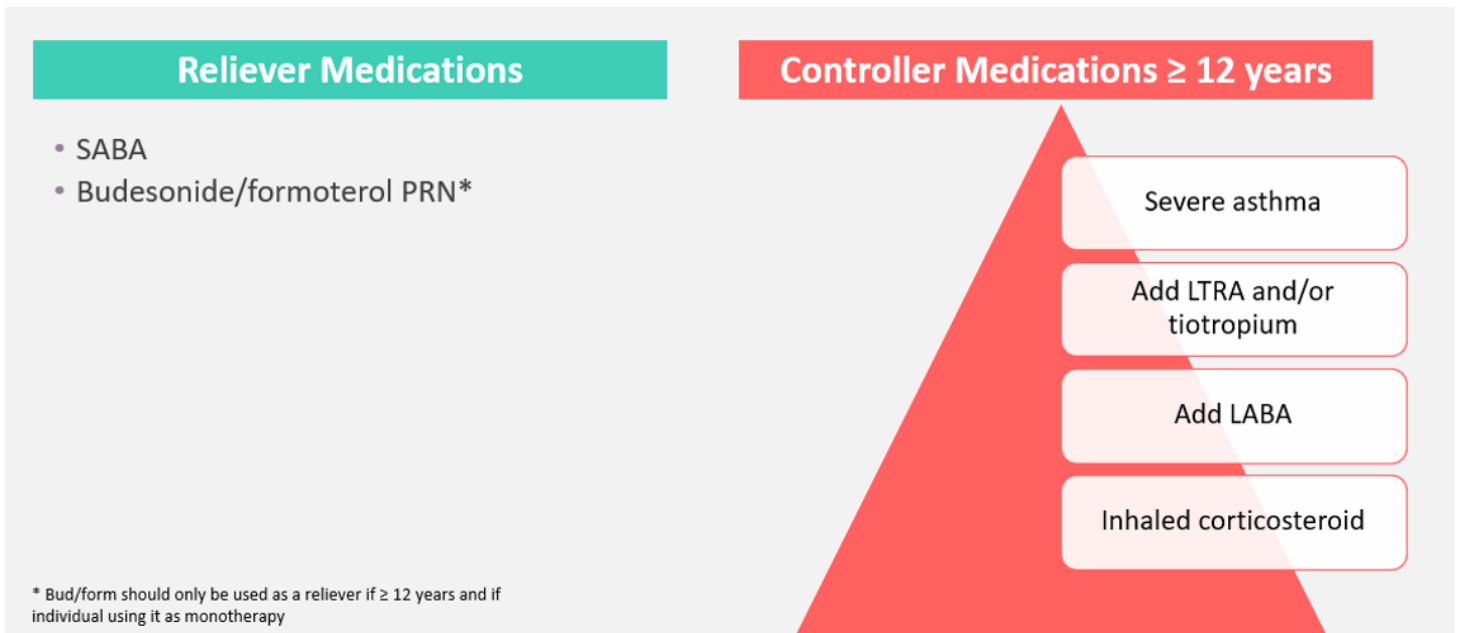


Figure 1: Recommended pharmacologic therapy adjustment steps to achieve asthma control

dependent on T2 inflammation markers.³⁰ The Canadian Thoracic Society's (CTS) asthma continuum depicts the recommended step-up algorithm for therapies.

What is New in Asthma Management

Reliever therapy

SABAs have been entrenched as reliever therapy for many years and in older clinical practice guidelines were considered the first pharmacological step for asthma management. For many years, using ICS/LABA as a rescue approach in moderate- to-severe asthmatics was both an established and preferred reliever therapy vs SABA due to reductions in exacerbations. In mild asthma, however, this changed as a result of the Global Initiative in Asthma (GINA) recommendations in 2019,³¹ which highlighted that:

- SABA overreliance was dangerous and associated with exacerbations and mortality
- SABA did not treat inflammation and therefore did not treat the underlying issue
- Monotherapy with SABA was not recommended

GINA recommended use of a reliever that contained ICS to ensure that the inflammation treatment was escalated at the time of the worsening. The data at the time supported the use of ICS/formoterol as this reliever showed improved control vs SABA alone and reduced exacerbations.³² Formoterol, despite being a long-acting beta agonist, is also a fast-acting beta agonist and therefore can be used as a reliever. In Canada, the only medication approved for this strategy is budesonide/formoterol. While regular ICS treatment and an asthma

action plan would likely out-perform the p.r.n. use of ICS/formoterol in mild asthma, symptom-based therapy with ICS/formoterol is superior in patients with adherence issues as it addresses the patient's inclination to take medication when they need it. There are also combination therapies with ICS/SABA that are not available in Canada.^{33,34}

The CTS guidelines continue to recommend SABA in addition to regular ICS therapy for mild asthma, but recognize that in those who are less adherent, ICS/formoterol would be preferable. In addition, the guidelines support the use of SABA monotherapy in very mild asthmatics, but only for those at low risk of exacerbations including:

- Having good asthma control
- No history of exacerbations, especially in the last year
- Using two or less SABA per year
- Not being a smoker

In summary, SABA therapy may be used adjunctively with ICS monotherapy, with ICS/LABA controller therapy other than budesonide/formoterol, or on top of triple therapy. However, monotherapy with SABA is not recommended.

Triple Therapy

Stepping up to triple therapy should be considered for those patients who are not controlled on dual therapy and have been shown to improve lung function and reduce exacerbations.³⁵ As discussed, ensure that the diagnosis has been properly made, review the basics such as adherence, technique, comorbidities, and triggers. This

is a step that can and should be done in primary care, but perhaps should get the clinician to consider that if they need such aggressive therapy, they are beginning to meet the criteria for severe asthma, and a biologic referral may be appropriate (see the severe asthma section below).

There are now two single inhaler triple therapies (SITT) for asthma available in Canada. Clinicians may also consider adding a LAMA to an ICS/LABA, which would be a multiple inhaler triple therapy (MITT). There is also good evidence that SITT outperforms MITT with respect to medication persistence rates, lung function,³⁶ and health status.³⁷ The two SITTs available in Canada are indacaterol (as acetate) / glycopyrronium (as bromide) / mometasone furoate inhalation powder hard capsules and fluticasone furoate, umeclidinium and vilanterol dry powder for oral inhalation.

Oral Corticosteroid (OCS) Dangers

While exacerbations are harmful, the impact of short courses of OCS for exacerbations is underestimated,³⁸ they are associated with adverse events such as psychiatric effects, osteoporosis, fracture, diabetes, glaucoma, cataracts, atypical infections and even mortality.³⁹ This risk is magnified in patients on long-term OCS, which have been used to achieve control in patients with more severe asthma. It is important to keep track of those short courses of OCS for exacerbations, as even two courses per year can lead to significant patient risk.

Severe Asthma

Severe asthma is defined as asthma requiring high-dose ICS plus a second controller medication.⁴⁰ The prevalence of persistent and severe asthma is between 5–10% of all patients with asthma, with these patients consuming a proportionally large amount of all asthma resources.⁴¹ In primary care, it is important to identify those patients who are at risk of poor outcomes (**Table 3**) and to identify those patients that require reassessment if not referral. The ReferID tool shown in **Figure 2** provides a quick method to assess patients in-office.⁴² The criteria for reassessing patients with this tool to evaluate for severe asthma include having two or more exacerbations per year, use of OCS twice per year or in a maintenance fashion, a history of having been admitted to an ICU or intubated and using three or more SABA per year. The primary care practitioner (PCP) is not expected to be involved in choosing or monitoring biologic therapy for asthma, but the PCP should identify those who would benefit from consideration of these therapies and make the appropriate referral. Biologics are currently divided into four classes: anti-IgE therapy, anti IL-5 therapy, anti-IL4/13 therapy, and anti-TSLP treatment. Treatments are chosen based on patient history, lung function, and

biomarkers including allergy testing, serum IgE levels, blood eosinophil levels, and FENO levels. These biologic medications are very safe and do not affect immune function in the same way as biologics used for other conditions like colitis, rheumatoid arthritis, and psoriasis.

Conclusion

Most of the patients seen in primary care with asthma have mild disease. The basics of asthma care, include confirming a diagnosis, ensuring adherence to therapy and proper inhaler technique, avoidance of triggers, and the treatment of comorbidities, which will allow your patients to have good asthma control and prevent exacerbations. New relievers that also treat the inflammation, such as ICS/formoterol (currently indicated in Canada), can also help prevent exacerbations and avoid overreliance on SABA monotherapy, which does not treat the underlying condition. Stepping up therapy from ICS to ICS/LABA to triple therapy and referring patients for consideration for biologic therapy gives clinicians a tremendous array of therapeutic options to keep patients well-controlled in the primary care setting.

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Asthma ReferID

Use this conversation guide to quickly identify the adult asthma patient whose **asthma is uncontrolled** and requires **urgent attention and possible referral**.


If the patient answers 'yes' to any of the questions:

If the patient is uncontrolled, **re-assess** for asthma control, treatment options, adherence, inhaler technique and co-morbidities (see section 2 of this tool).


If the patient remains uncontrolled (the answer is still yes to any of the below questions), this patient would benefit from **review by a specialist**.

1 


Has the patient used **2 or more courses of systemic corticosteroids (SCS) and/or is using maintenance SCS therapy over the past 12 months?**

2 

Has the patient had **2 or more emergency attendances /unscheduled visits due to asthma over the past 12 months?**

3 

Has the patient ever been **intubated or admitted to an ICU (intensive care unit) or high dependency unit due to their asthma?**

4 

Has the patient used **3 or more SABA (short-acting beta2-agonist) inhalers in the past 12 months?**

This Refer ID guide has been developed by the PRECISION program of AstraZeneca in collaboration with five asthma experts: Dr. D. Jackson, Dr. J.W.H. Kocks, M. Al-Ahmad, MD, R. del Olmo, MD and Dr. Tan Tze Lee. The content in this guide is based on the 2019-2021 Global Strategy For Asthma Management and Prevention reports: <http://ginasthma.org>. Veeva ID: 24-22623. Date of preparation: March 2020; Updated May 2021. Date of expiry: 31 March 2022.

Figure 2: Refer ID asthma severity and control assessment tool

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