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Canadian Thoracic Society 2021 Guideline update: Diagnosis and management of asthma in preschoolers, children and adults

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Introduction

This document incorporates recommendations from the 2021 Canadian Thoracic Society (CTS) Guideline – A Focused Update on the Management of Very Mild and Mild Asthma¹ with previous statements and recommendations from the CTS 2010² and 2012³ asthma guidelines and the CTS/Canadian Pediatric Society 2015 position statement on the diagnosis and management of asthma in preschoolers.⁴ For the evidence and rationale informing those recommendations and detailed information about preschool asthma, users should refer to the original documents.¹⁻⁴ Recommendations from previous CTS guidelines were reviewed using the CTS Guideline Update Policy, the review process based on the “living guideline” concept, to determine if the information was still relevant and accurate.⁵ The recommendations from the CTS 2017 Severe Asthma Guideline⁶ have not been incorporated as severe asthma is typically managed in subspecialty clinics, but may be incorporated in future guideline updates.

Summary of new features¹ compared to the 2012 guideline³

1. **Treatment for very mild asthma.** Patients on as needed (PRN) use of a SABA with well-controlled asthma at higher risk for asthma exacerbation should have treatment escalated to daily inhaled corticosteroids (ICS) + PRN SABA (all ages) or PRN budesonide/formoterol (bud/form) (≥ 12 years of age) (Figure 3). Daily ICS (all ages) or PRN bud/form (≥ 12 years of age) are also options for patients on PRN SABA with well-controlled asthma who are not at higher risk for exacerbation, if they prefer to have better asthma control and to decrease their risk of asthma exacerbation.
Previous guidance: Patients with very mild intermittent asthma may be treated with PRN SABA. ICS should be prescribed for those with symptoms even

“less than 3 times a week,” those with mild loss of control, or those presenting with an asthma exacerbation requiring systemic steroids.

2. **Treatment for mild asthma.** Patients on PRN SABA with poorly-controlled asthma (as per updated CTS criteria) should have treatment escalated to daily ICS+PRN SABA. For individuals ≥ 12 years of age not controlled on PRN SABA who have poor adherence to daily ICS despite substantial asthma education and support, PRN bud/form is recommended over daily ICS+PRN SABA (Figure 3).

Previous guidance: Use of an ICS/LABA combination as a reliever in lieu of a fast-acting beta-agonist (FABA) alone was not recommended.

3. **Assessing risk of exacerbation in addition to asthma control.** When deciding on optimal treatment, in addition to evaluating asthma control, risk of asthma exacerbation should be assessed **based on the criteria presented in Table 3.**

Previous guidance: Exacerbations should be mild and infrequent, and some risk factors for exacerbation were included within the Asthma Control criteria.

4. **Change in control criteria for daytime symptoms and frequency of reliever need.** Those with well-controlled asthma should have daytime symptoms ≤ 2 days per week and need for reliever (SABA or PRN bud/form) ≤ 2 doses per week. For preschoolers, the frequency of symptoms has been changed from ≥ 8 days/month to >8 days/month to align with criteria for older patients.
Previous guidance: Good asthma control if <4 days per week of daytime symptoms or <4 doses per week of FABA.
5. **Clarification for criteria of mild versus severe asthma exacerbation.** A severe asthma exacerbation is one that requires either systemic steroids, an emergency department (ED) visit or hospitalization. A mild exacerbation is an increase in asthma symptoms

from baseline that does not require systemic steroids, an ED visit or a hospitalization.

Previous guidance: Severity of exacerbations was not specifically defined.

6. **Update of severity classification.** Reclassification of asthma severity to remove the very severe category to align with the Recognition and Management of Severe Asthma Position Statement,⁶ and to include other asthma therapies.

Previous guidance: Categories such as “mild intermittent” and “mild persistent” asthma were referred to in previous guidelines but are no longer used. **This terminology can lead to a misunderstanding of the underlying pathophysiology of asthma as the term “mild intermittent” may suggest to patients that there are times when they do not have asthma when in fact, asthma is a chronic condition and it is only the symptoms that can be intermittent.**

7. **Asthma continuum and ICS dosing table.** Reference ICS for dosing in the continuum has been changed to fluticasone propionate equivalents. SABA or bud/ form as needed has been extended across the bottom of the continuum (Figure 2). Dosing categories and treatments have been expanded in the continuum and ICS dosing table (Table 8) to include preschoolers.

Previous guidance: Historically asthma guidelines used beclomethasone equivalents; however, this can lead to confusion when comparing to other guidelines and

reviewing clinical trials as there are 2 forms of beclomethasone available in other countries with different potencies.

Asthma definition

It is recognized that asthma is a heterogenous disorder comprised of many different phenotypes with an increased understanding of the various endotypes or mechanistic pathways. Although some advocate viewing asthma as a component of its parts or treatable traits, outside of severe asthma, current evidence is not to the point where treatment recommendations can be based on phenotypes or endotypes, although trials utilizing this approach are being conducted.^{7,8} The definition of asthma remains unchanged from the previous CTS 2012 Asthma Guideline:

Asthma is an inflammatory disorder of the airways characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli. Inflammation and its resultant effects on airway structure and function are considered to be the main mechanisms leading to the development and maintenance of asthma.³

Asthma diagnosis

The diagnosis of asthma is based on a compatible clinical history (see previous definition) with objective evidence of reversible airflow obstruction (Table 1). In patients 6 years

Table 1. Diagnosis of asthma.

CLINICAL HISTORY COMPATIBLE WITH ASTHMA			
Paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production, and cough			
and			
CONFIRMATION OF REVERSIBLE AIRFLOW OBSTRUCTION			
Preferred	Children (1-5 years of age)	Children (6 years of age and over)	Adults (18 years of age and over)
	Documentation by trained health care provider of wheeze and other signs of airflow obstruction with documented improvement with SABA +/- oral corticosteroids	Spirometry showing reversible airflow obstruction FEV ₁ /FVC < LLN (<0.8-0.9 ^a) AND increase in FEV ₁ after a bronchodilator or after a course of controller therapy of ≥12%	Spirometry showing reversible airflow obstruction FEV ₁ /FVC < LLN (<0.75-0.8 ^a) AND increase in FEV ₁ after a bronchodilator or after a course of controller therapy of ≥12% and a minimum of ≥200mL
Alternative	Convincing caregiver report of wheezing or other symptoms of airflow obstruction with symptomatic response to a 3-month trial of a medium dose of ICS and as needed SABA or symptomatic response to SABA ^b	Peak expiratory flow ≥20% increase after a bronchodilator or after a course of controller therapy ^c	Peak expiratory flow 60L/min (minimum ≥20%) increase after a bronchodilator or after a course of controller therapy ^c OR Diurnal variation >8% ¹² based on twice daily readings; >20% based on multiple daily readings ^d
Alternative		Positive challenge test Methacholine PC ₂₀ <4 mg/ml or PD ₂₀ <0.5 μmol (100 mcg) PC ₂₀ 4-16 mg/mL or PD ₂₀ 0.2-2 μmol (100-400 mcg) is borderline PC ₂₀ >16 mg/mL or PD ₂₀ >2 μmol (>400 mcg) is negative ¹³ OR Exercise challenge with ≥10-15% decrease in FEV ₁ post-exercise	

Abbreviations: SABA, short-acting beta-agonist; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; ICS, inhaled corticosteroid; PC₂₀, provocative concentration; PD₂₀, provocative dose.

^aApproximate lower limits of normal ratios for children and adults.

^bIn children with mild intermittent symptoms and mild exacerbations, the diagnosis is only suggested because the accuracy of parental report of response to treatment may be unreliable due to misperception and spontaneous improvement of symptoms, which is why confirmation of reversible obstruction by direct observation from a health care provider is preferred.

^cComparison of peak expiratory flows should be done on the same device given the variability between devices.

^dDifference between minimum AM pre-bronchodilator value in 1 week and maximum PM value as % of recent maximum.

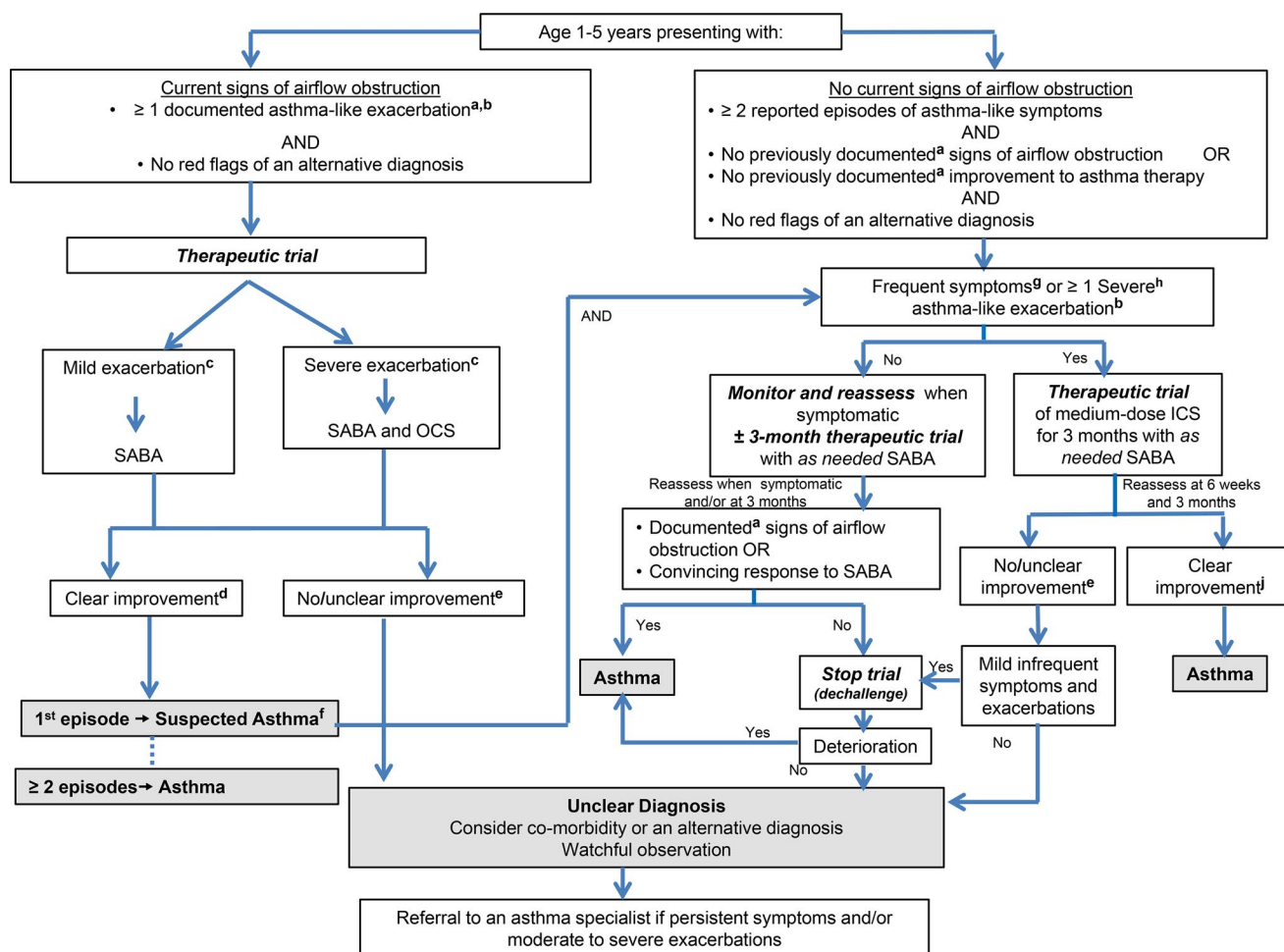


Figure 1. Diagnosis algorithm for children 1 to 5 years of age.

^aDocumentation by a physician or trained health care practitioner.

^bEpisodes of wheezing with/without difficulty breathing.

^cSeverity of an exacerbation documented by clinical assessment of signs of airflow obstruction, preferably with the addition of objective measures such as oxygen saturation and respiratory rate, and/or validated score such as the Pediatric Respiratory Assessment Measure (PRAM) score.

^dBased on marked improvement in signs of airflow obstruction before and after therapy or a reduction of ≥ 3 points on the PRAM score, recognizing the expected time response to therapy.

^eA conclusive therapeutic trial hinges on adequate dose of asthma medication, adequate inhalation technique, diligent documentation of the signs and/or symptoms, and timely medical reassessment; if these conditions are not met, consider repeating the treatment or therapeutic trial.

^fThe diagnosis of asthma is based on recurrent (≥ 2) episodes of asthma-like exacerbations (documented signs) and/or symptoms. In case of a first occurrence of exacerbation with no previous asthma-like symptoms, the diagnostic of asthma is suspected and can be confirmed with re-occurrence of asthma-like symptoms or exacerbations with response to asthma therapy.

^g >8 days/month with asthma-like symptoms.

^hSevere exacerbations require any of the following: systemic steroids, hospitalization; or an emergency department visit.

ⁱIn this age group, the diagnostic accuracy of parental report of a short-term response to as-needed short-acting β_2 -agonist (SABA) may be unreliable due to misperception and/or spontaneous improvement of another condition. Documentation of airflow obstruction and reversibility when symptomatic, by a physician or trained health care practitioner, is preferred.

^jBased on 50% fewer severe exacerbations, shorter and milder exacerbations, and fewer, milder symptoms between episodes.

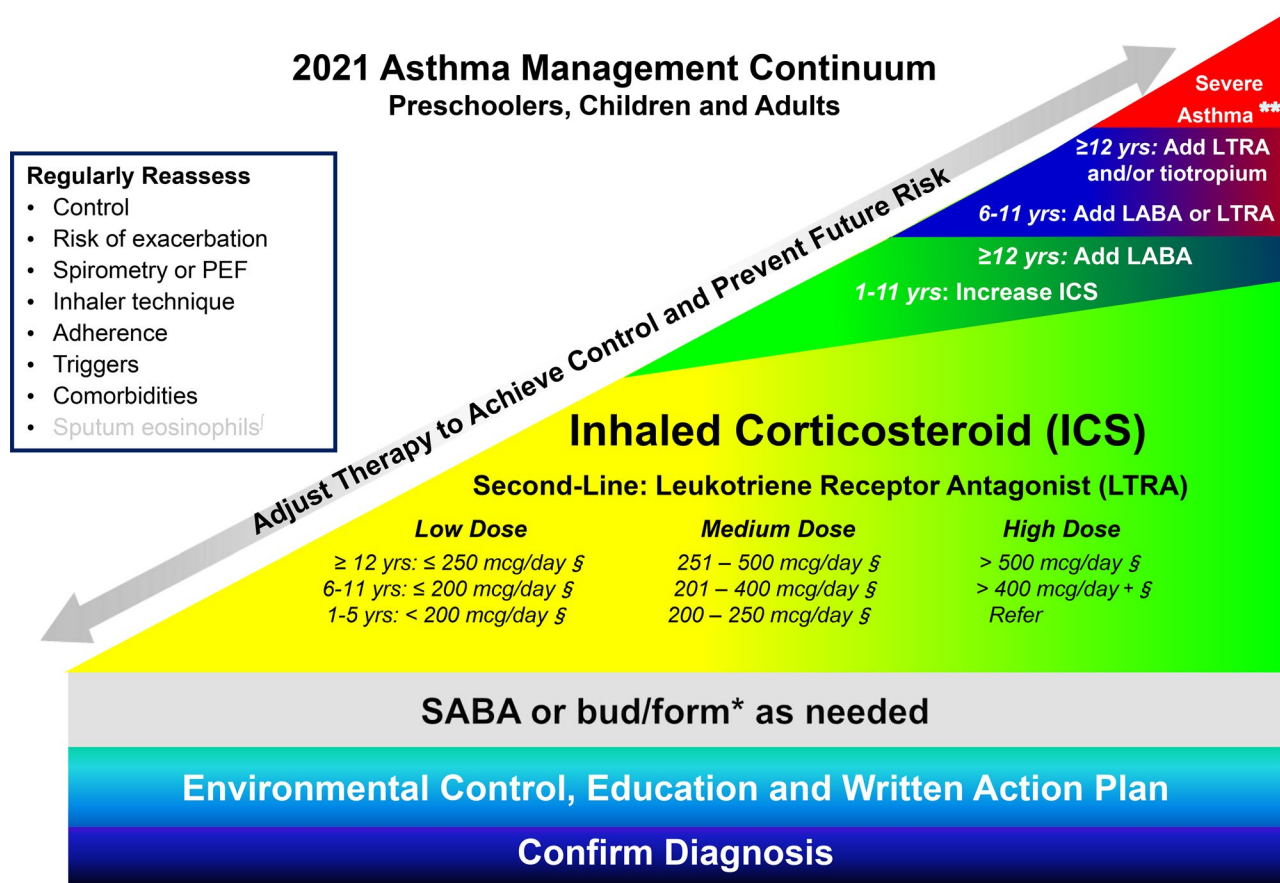
of age and over, spirometry demonstrating reversible airflow obstruction is the preferred method of confirming a diagnosis of asthma. Since spirometry has a higher specificity than sensitivity for diagnosing asthma, normal spirometry does not rule out a diagnosis of asthma.⁹

The diagnosis of asthma should be considered in children 1 to 5 years of age with recurrent asthma-like symptoms or exacerbations, even if triggered by viral infections. In children under the age of 6, a compatible clinical history, physical exam and trial of treatment are used to make a clinical diagnosis (Table 1, Figure 1). Given that up to 50% of children under the age of 6 outgrow their symptoms, a monitored

trial off medication can be attempted when asthma is well-controlled with exposure to the child's typical triggers, including no exacerbations, for at least 3-6 months.^{10,11}

Asthma management

The core components of asthma management are highlighted in the asthma management continuum (Figure 2) and include: 1) Assessing asthma control and risk of exacerbation, 2) Providing asthma self-management education including a written action plan, 3) Identifying triggers and discussing environmental control if applicable, and 4) Prescribing



* Or an alternative ICS/form preparation if another is approved for use as a reliever in the future. Bud/form is approved as a reliever for ≥12 years of age and should only be used as a reliever in individuals using it as monotherapy or in conjunction with bud/form maintenance therapy

§ HFA Fluticasone propionate or equivalent

+ Not approved for use in Canada

† In adults, 18 years of age and over with moderate to severe asthma assessed in specialist centres

** For severe asthma refer to CTS 2017 Recognition and management of Severe Asthma Position Statement

Figure 2. 2021 Asthma continuum.

Management relies on an accurate diagnosis of asthma and regular reassessment of control and risk of exacerbation. All individuals with asthma should be provided with self-management education, including a written action plan. Adherence to treatment, inhaler technique, exposure to environmental triggers, and the presence of comorbidities should be reassessed at each visit and optimized.

Individuals with well controlled asthma on no medication or PRN SABA at lower risk of exacerbation can use PRN SABA, daily ICS+PRN SABA, and if ≥ 12 years of age PRN bud/form*.

Individuals at higher risk of exacerbation even if well-controlled on PRN SABA or no medication, and those with poorly-controlled asthma on PRN SABA or no medication should be started on daily ICS+PRN SABA. In individuals ≥ 12 years old with poor adherence despite substantial asthma education and support, PRN bud/form* can be considered. LTRA are second-line monotherapy for asthma. If asthma is not adequately controlled by daily low doses of ICS with good technique and adherence, additional therapy should be considered. In children 1-11 years old, ICS should be increased to medium dose and if still not controlled in children 6-11 years old, the addition of a LABA or LTRA should be considered. In individuals 12 years of age and over, a LABA in the same inhaler as an ICS is first line adjunct therapy. If still not controlled, the addition of a LTRA or tiotropium should be considered.

In children who are not well-controlled on medium dose ICS, a referral to an asthma specialist is recommended. After achieving asthma control, including no severe exacerbations, for at least 3-6 months, medication should be reduced to the minimum necessary dose to maintain asthma control and prevent future exacerbations.

HFA, hydrofluoroalkane; SABA, short-acting beta-agonist, LABA, long-acting beta-agonist, ICS, inhaled corticosteroid, LTRA, leukotriene receptor antagonist, bud/form: budesonide-formoterol in a single inhaler

appropriate pharmacologic treatment to achieve and maintain asthma control which includes minimizing exacerbations.

Asthma control and risk of exacerbation

Asthma control (Table 2) and risk for exacerbation (Table 3) should be assessed at each clinical encounter.

The goal of asthma treatment is to have well-controlled asthma in order to minimize short- and long-term complications, morbidity and mortality.³ Asthma control is often

thought of as symptom control; however, the CTS control criteria incorporate all facets of asthma control including: 1) symptoms and impact on quality of life; 2) exacerbations; 3) lung function; and 4) inflammatory markers for adults with moderate to severe asthma. The use of the fraction of exhaled nitric oxide (FeNO) as a marker of asthma control was assessed in the CTS 2012 asthma guideline³ and was not recommended as a routine measurement.

For patients with poorly-controlled asthma, potential reasons for poor control should be assessed and corrected

Table 2. Well-controlled asthma criteria.

Characteristic	Frequency or value
Daytime symptoms	≤ 2 days/week
Nighttime symptoms	< 1 night/week and mild
Physical activity	Normal
Exacerbations	Mild and infrequent*
Absence from work or school due to asthma	None
Need for a reliever (SABA or bud/form) [†]	≤ 2 doses per week
FEV ₁ or PEF	≥ 90% of personal best
PEF diurnal variation	< 10-15% [‡]
Sputum eosinophils	< 2-3% [*]

A patient who meets all of the above criteria would be considered to have well-controlled asthma.

*A mild exacerbation is an increase in asthma symptoms from baseline that does not require systemic steroids, an ED visit, or a hospitalization. "Infrequent" is not specifically defined, since the frequency of mild exacerbations that patients consider an impairment to quality of life varies. If the patient feels that the frequency of mild exacerbations is impairing their quality of life, then their asthma should be considered poorly-controlled. If a patient is having frequent mild exacerbations, they should be assessed to determine if at baseline, they have poorly-controlled asthma.

[†]There are no established criteria for control when using bud/form as a reliever; however, use of a reliever often indicates that a patient is having symptoms and is a criterion that can be objectively assessed.

[‡]Diurnal variation is calculated as the highest peak expiratory flow (PEF) minus the lowest divided by the highest peak flow multiplied by 100, for morning and night (determined over a 2-week period).

*Consider in adults ≥ 18 years of age with uncontrolled moderate to severe asthma who are assessed in specialist centers.

prior to or in conjunction with escalation of pharmacologic therapy. This includes assessment of: adherence, inhalation technique and whether they have been using an empty inhaler, environmental (including occupational) exposures and key comorbidities (eg, rhinosinusitis, gastro-esophageal reflux, paradoxical vocal fold motion, anxiety and depression).⁶

Individuals can have well-controlled asthma but still be at risk for exacerbation. Specific risk factors for severe exacerbations should be assessed at each clinical encounter (Table 3). These risk factors are particularly important when deciding on controller therapy for a patient with very mild or mild asthma.

A more complete list of risk factors for severe exacerbations (Table 4) and for near-fatal and fatal asthma (Table 5) are provided to facilitate discussion between clinicians and patients about their individual risk. Patients at risk for near fatal or fatal asthma require careful follow-up, and may benefit from a multi-disciplinary team, given that factors such as non-adherence, substance use and psychiatric illness increase their risk of death from asthma.

Asthma education and written action plan

Once a diagnosis of asthma is made, it is important that patients and families receive appropriate asthma self-management education. Key components of an asthma education program are listed in Table 6.²

Written action plan

Written asthma action plans are an important part of care for all patients with asthma.² They have been shown to decrease exacerbations in children and adults.^{21,22}

There is no clear benefit of peak-flow based action plans in comparison to symptom-based action plans.^{23,24} The choice between these 2 types of action plans can be individualized

based on patient preference and physician judgment, as there are some circumstances (eg, patients with poor symptom perception) where a peak-flow based action plan may be of benefit.

Action plans should outline recommended daily preventive management strategies to maintain control, when and how to adjust reliever therapy (and controller therapy in adults prone to exacerbations) for loss of control and provide clear instructions regarding when to seek urgent medical attention.² Treatment in the yellow zone of an action plan will be discussed in the pharmacologic treatment section. Examples of action plans for children and adults can be found on the CTS website under Guidelines and Resources at <https://cts-sct.ca/guideline-library/knowledge-tools-resources/asthma/>

Environmental control

Environmental factors that trigger a patient's asthma should be identified on history and avoided, if possible. Approximately 36% of adult-onset asthma cases are probably or possibly work-related;²⁵ therefore, it is important to perform a thorough medical and occupational history to identify work-related asthma.

Evidence for the clinical benefit of specific interventions to reduce exposure to indoor allergens in all patients with asthma is lacking.²⁶⁻²⁹ Given the expense and complexity of these interventions, these are not recommended as a general strategy; however, in patients with asthma symptoms triggered by indoor allergens, it would be prudent to minimize exposure. The current literature suggests that multi-component interventions (eg, use of two or more single-component interventions) are more effective than single-component interventions (eg, HEPA filters, cleaning products, carpet removal, pet removal).³⁰

First- or secondhand exposure to tobacco smoke is a risk factor for asthma exacerbations and counseling on smoking cessation should be provided. Smoking marijuana and vaping are increasing in prevalence, particularly among adolescents,

Table 3. Assessing risk for severe exacerbation.

Individuals with any one of these risk factors are at higher risk for asthma exacerbation:

1. any history of a previous severe asthma exacerbation (requiring any of the following: systemic steroids, ED visit, or hospitalization)
2. poorly controlled asthma as per CTS criteria
3. overuse of SABA (defined as use of more than 2 inhalers of SABA in a year)
4. current smoker

These risk factors were chosen based on OR of >1.5 for severe exacerbations, certainty of the effect and ease of use in clinical practice.^{1,14}

Table 4. Risk factors associated with severe asthma exacerbations.**Greatly increased risk (Odds Ratio (OR) > 2.5*)**

≥ 12 years of age	6-11 years of age	< 6 years of age
History of previous severe exacerbation	<ul style="list-style-type: none"> • History of previous severe exacerbation • Poorly-controlled asthma • FEV₁ < 60% predicted 	<ul style="list-style-type: none"> • History of previous severe exacerbation

Moderate increased risk (OR 1.5-2.5*)

<ul style="list-style-type: none"> • Poorly-controlled asthma • Excessive SABA use (> 2 inhalers/year¹⁶) • Current smoker** 	<ul style="list-style-type: none"> • Excessive SABA use (> 2 inhalers/year) • Comorbid atopic/allergic disease • Low socioeconomic status • Vitamin D deficiency (< 30 nmol/L) • FEV₁ 60-80% predicted
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Slightly increased risk (OR 1.1-1.5*)

<ul style="list-style-type: none"> • Older age (especially > 55 years of age) • Female sex • FEV₁ < 70% predicted • Obesity • Previous smoker** • Depression 	<ul style="list-style-type: none"> • Exposure to environmental tobacco smoke** • Younger age • Obesity • Low parental education 	<ul style="list-style-type: none"> • Comorbid atopic/allergic disease • Raised blood eosinophils (> 300/μL) • Younger age • Low socioeconomic status • Male sex • Underweight
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Note. This table is adapted from SIGN 158 - British guideline on the management of asthma by kind permission of the Scottish Intercollegiate Guidelines Network.¹⁵

*OR reported represent the OR found in the majority of studies examining the risk factor.^{14,15}

**Studies have examined the risk of tobacco smoking; however, vaping and smoking of other substances should also be considered risk factors.^{17,18}

Table 5. Risk factors associated with near-fatal or fatal asthma.^{19,20}

Any previous near-fatal asthma exacerbation (eg, previous intensive care unit (ICU) admission, ventilation, respiratory acidosis)

Recurrent hospitalizations or ED visits in last year

Severe asthma

Overuse of SABA

Poor adherence to treatment plans

Failure to attend clinic appointments

Depression, anxiety or other psychiatric illness

Alcohol or other substance use

Obesity

Severe domestic, marital, employment, local stress

Denial of illness or severity of illness

Note. This table is adapted from SIGN 158 - British guideline on the management of asthma by kind permission of the Scottish Intercollegiate Guidelines Network.¹⁵

Table 6. Components of an asthma education program.

1. Asthma pathophysiology: A chronic inflammatory condition in which airways are hyper-reactive (sensitive) to environmental (allergic, irritant or infectious) and/or intrinsic factors.

2. Identify triggers: Identification and avoidance of environmental triggers specific to the patients.

3. Asthma control for all patients: Asthma can be controlled and all patients with asthma can lead a normal life. Regular symptoms, poor lung function and asthma exacerbations indicate treatment failure.

4. Minimal to no exacerbations for all patients: Identify risk factors for asthma exacerbations.

5. Reliever vs. controller: The difference between reliever and controller medications and their use in the written action plan.

6. Written action plan: Provision and explanation of a written action plan comprising:

- How and how often to assess asthma control (self-monitoring)
- Instructions to maintain good control emphasizing adherence to controller medication and making specific environmental changes
- Signs and symptoms indicating poorly-controlled asthma, with instructions on what to do during loss of control (medication to add or increase, how much and how long; when and how to seek additional help (eg, when to go to the hospital or call the health care provider)

7. Medication safety and side effects: Expected onset of action and potential side effects of medications.

8. Inhaler teaching: Teaching and verification of the inhalation technique specific to the devices prescribed for the patient. Ensuring patients know how to tell when an inhaler is empty.

Table 7. Recommendations for asthma devices by age.³⁷

Age	Device	Tips for use
1-3 years old	pMDI+VHC with mask	Ensure good seal of face mask
4-6 years old	pMDI+VHC with mouthpiece	To use a VHC with mouthpiece, patient needs to form a seal around the mouthpiece and cooperate with instructions. Tidal breathing* can be used with a VHC with mouthpiece.
> 6 years old	pMDI+VHC with mouthpiece or dry powder inhaler	To use a dry powder inhaler, patient needs to be able to inhale deeply and forcefully. Breath-hold technique** with VHC with mouthpiece improves lung deposition compared to tidal breathing, and is preferred if patient is able.
>12 years old and adults	Dry powder inhaler or pMDI + VHC with mouthpiece	VHC with masks are also available for adults unable to use a dry powder inhaler or VHC with mouthpiece.

Abbreviations: pMDI, pressurized meter dose inhaler; VHC, valved holding chamber.

Age recommendations are approximate as device technique needs to be individually assessed.

*Tidal breathing: 5-10 tidal breaths per actuation.

**Breath-hold technique: Exhale slowly, actuate pMDI, slowly inhale and hold breath for 5 to 10 seconds.

and these exposures are increasingly recognized as a cause for respiratory symptoms and risk for exacerbation in patients with asthma.^{17,18,31}

Pharmacologic treatment

Inhaler device

It is important to consider the type of inhaler device that a patient prefers to use and can use properly before prescribing asthma medication, as most categories of medication come in multiple devices (eg, pressurized meter dose inhaler (pMDI), dry powder inhaler; Table 7). Poor inhaler technique is still seen in up to 70% of patients³² and is associated with poor asthma control and increased exacerbations.³³ The use of valved holding chambers with pMDIs decreases oropharyngeal deposition of medication, increases lower airway deposition and overcomes issues with actuation-inhalation coordination.³⁴ Up to 50% of patients have poor actuation-inhalation coordination with pMDIs;³² thus, valved holding chambers should be recommended for all ages of patients prescribed a pMDI, particularly with inhaled corticosteroids.³⁵ Dry powder inhalers require a minimal inspiratory pressure, which may be difficult in young children and occasionally in adult patients with low FEV₁ or other comorbid illnesses such as neuromuscular weakness,³⁶ particularly during asthma exacerbations. For resource with pictures of available asthma medication and videos on

proper inhaler technique, see <https://cts-sct.ca/guideline-library/knowledge-tools-resources/asthma/>.

Reliever therapy

All individuals with asthma should have access to a reliever for use as needed to treat acute symptoms. In Canada, SABAs (salbutamol, terbutaline), and a combination inhaler (bud/form) are approved for this indication. As needed bud/form is approved for use as a reliever in adults and children ≥12 years of age.

Bud/form is not studied and should not be used as a reliever when controller medications other than maintenance bud/form are used. The use of bud/form as a reliever in patients not on a daily controller medication (p 8), and in those on a fixed dose of bud/form for maintenance (p 8) will be discussed in the Controller Therapy section.

Regular need for a reliever (more than 2 doses per week) merits reevaluation to identify the reason(s) for poorly-controlled asthma. Frequent use of a SABA reliever is a risk factor for severe exacerbations and asthma-related death,¹⁶ and the use of more than two inhalers of SABA in a year (typically containing 200 doses each) should prompt reevaluation of asthma control.

SABAs should only be used for symptom relief and should not be regularly used “to open the airways” before daily controller therapy administration as this has been shown to increase risk of exacerbations.¹

Table 8. Comparative inhaled corticosteroids (ICS) dosing categories in preschoolers, children and adults.

Corticosteroid (tradename)	Preschoolers (1-5 years of age)		Children (6-11 years of age)			Adults and Adolescents (12 years of age and over)		
	Low	Medium	Low	Medium	High	Low	Medium	High **
Beclomethasone dipropionate HFA (QVAR)	100	200	≤ 200	201-400	> 400	≤ 200	201-500	> 500 (max 800)
Budesonide* (Pulmicort)	n/a	n/a	≤ 400	401-800	> 800	≤ 400	401-800	> 800 (max 2400)
Ciclesonide* (Alvesco)	100	200	≤ 200	201-400	> 400	≤ 200	201-400	> 400 (max 800)
Fluticasone furoate* (Arnuity)	n/a	n/a	n/a	n/a	n/a	100		200 (max 200)
Fluticasone propionate (Flovent)	< 200	200-250	≤ 200	201-400	> 400	≤ 250	251-500	> 500 (max 2000)
Mometasone furoate* (Asmanex)	n/a	n/a	100	≥ 200- < 400	≥ 400	100-200	> 200-400	> 400 (max 800)

Note. Dosing is in micrograms (mcg), dosing categories are approximate, based on a combination of approximate dose equivalency as well as safety and efficacy data.

*Licensed for once daily dosing in Canada

**Maximum (max) doses are the maximum doses approved for use in Canada.

Doses highlighted are not approved for use in Canada with the following exceptions: Beclomethasone is approved for children ≥ 5 years of age; Mometasone is approved for children ≥ 4 years of age; Maximum dose of fluticasone propionate is 200mcg/day in children 1-4 years of age (250mcg was included in this age group because the 125mcg inhaler is often used for adherence and cost), Maximum dose of fluticasone propionate is 400mcg/day in children 4-16 years of age.

Controller therapy

The effectiveness of each treatment should be carefully evaluated for its impact on current control, future risk (in particular asthma exacerbations), and side effects.³

The safest and minimum effective ICS dose that achieves the goals of current control and eliminates exacerbations, should be prescribed to minimize side effects in all groups, particularly in children to address the concern regarding growth velocity.

Improvement in clinical symptoms occurs within 1-2 weeks of starting daily ICS,³⁸ although it can take months to see a plateau in improvement.³⁹⁻⁴¹ The dosing table provides comparative dosing for the ICS approved for use in Canada (Table 8). There is a plateau in the dose-response curve for ICS in a large number of patients who respond to daily low- to medium-dose ICS that is dose equivalent to 200-250 mcg of fluticasone propionate.^{42,43}

For patients with poorly-controlled asthma, potential reasons for poor control should be assessed and corrected prior to or in conjunction with escalation of pharmacologic therapy. This includes assessment of: adherence, inhalation technique and whether they have been using an empty inhaler, environmental (including occupational) exposures and key comorbidities (eg, rhinosinusitis, gastro-esophageal reflux, paradoxical vocal fold motion, anxiety and depression).⁶

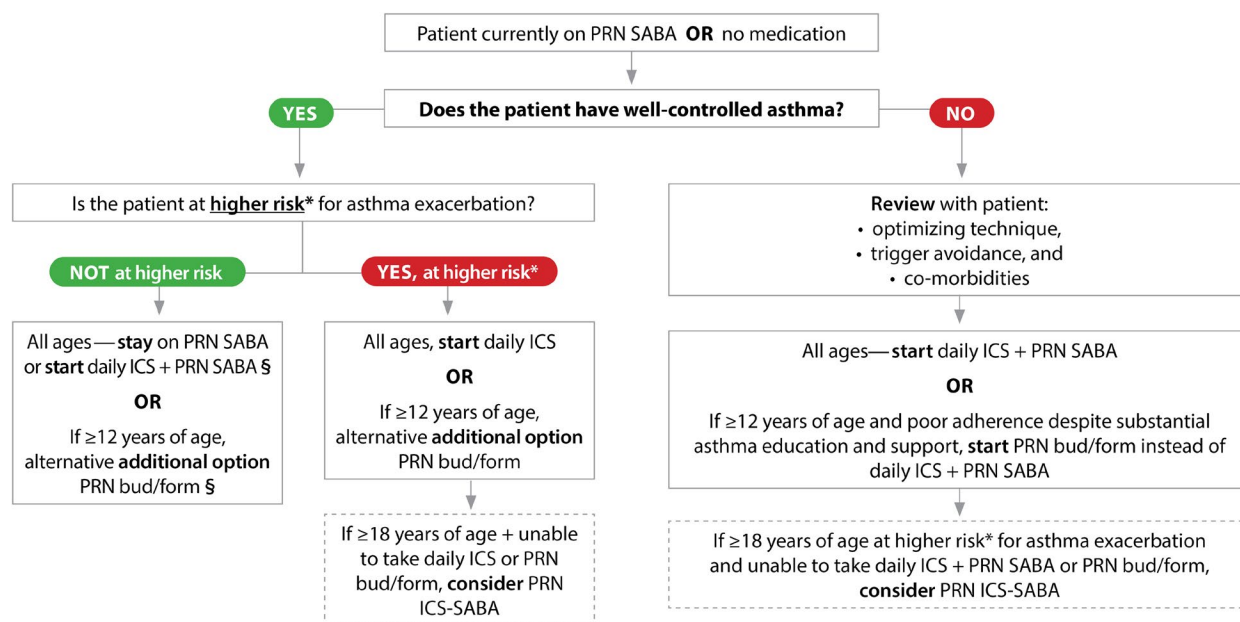
Patients not on controller therapy (Figure 3)

Patients who are well controlled on PRN SABA or no medication with a lower risk for exacerbations can continue PRN SABA or be switched to either daily ICS+PRN SABA (all ages) or PRN bud/form (≥ 12 years of age) if they prefer to have better asthma control or reduce their risk for exacerbations.¹

Patients well-controlled on PRN SABA or no medication who are at higher risk for exacerbations should not be on PRN SABA, even if they have minimal symptoms. They should be switched to daily ICS+PRN SABA (all ages) or PRN bud/form (≥ 12 years of age). Daily ICS+PRN SABA is the recommended controller therapy except for patients ≥ 12 years of age with poor adherence to daily medication despite substantial asthma education and support, for whom PRN bud/form is recommended over daily ICS+PRN SABA.¹

Patients who are not controlled on PRN SABA or no medication should be on daily ICS+PRN SABA

The strategy of taking an ICS each time a SABA is taken (PRN ICS-SABA) is not approved for use in Canada, and is only recommended as a harm reduction measure in patients ≥ 18 years of age at higher risk for exacerbations who are unable to use daily ICS+PRN SABA or PRN bud/form.¹ The clinical trial that evaluated this strategy in adults using 2 separate inhalers⁴⁴ used a regimen of beclomethasone



*Higher risk if a patient had any of the following:

- 1) any history of a previous severe asthma exacerbation requiring:
 - systemic steroids,
 - ED visit, or
 - hospitalization
- 2) poorly-controlled asthma as per CTS criteria
- 3) overuse of short-acting beta-agonist (defined as use of more than two inhalers of SABA in a year)
- 4) current smoker

§ Based on patient preference—the decision to switch from PRN SABA to daily ICS + PRN SABA or PRN bud/form is for those that want better asthma control and to decrease their risk of exacerbation

⊞ Dash boxes represent harm reduction strategy

SABA: short-acting beta-agonist; ICS: inhaled corticosteroids; bud/form: budesonide-formoterol in a single inhaler; ED: emergency department

Figure 3. Treatment approach for patients on PRN SABA or no medication.

50 mcg 2 puffs each time salbutamol 100 mcg 2 puffs was used. If clinicians recommend this strategy (off-label), we suggest that the maximum approved daily ICS dose should not be exceeded (see Table 8).

In patients of all ages, leukotriene receptor antagonists (LTRAs) are second line to daily ICS.

Patients not achieving control on low dose ICS

Children not achieving asthma control despite adherence to low dose ICS should be increased to medium dose ICS (Table 8). Children < 6 years of age, not achieving control on medium dose ICS should be referred to an asthma specialist (section Reasons for Referral).

Children 6-11 years of age not achieving control on medium dose ICS should be started on a second controller medication, either a LABA (in the same inhaler as the ICS) or LTRA. Improvement is overall more likely to be seen with the addition of a LABA; however, individual responses vary and the side effect profile of these medications should also be discussed with patients and parents when making this decision (section Safety of LABA and LTRA).⁴⁵ In children 6-11 years of age not controlled on low dose ICS, other guidelines^{46,47} recommend either increasing to medium dose ICS or adding a LABA, based on the current evidence not showing clear superiority and safety of one regimen over the other. However, the limited approval of ICS/LABA formulations in Canada for children 6-11 years of age precludes a similar recommendation at this time.

Children ≥12 years of age and adults not achieving control despite adherence to low dose ICS should be started on daily ICS/LABA. Alternative options include adding an LTRA or increasing to a medium dose of ICS.

Individuals ≥12 years of age and adults on an ICS/LABA with poor control or who are prone to exacerbations can

be switched to bud/form maintenance and reliever therapy at the same maintenance ICS dose.

Patients not achieving control on moderate dose ICS+second controller medication

Health care providers are referred to the CTS 2017 position statement on the Recognition and Management of Severe Asthma⁶ for further recommendations on assessment and management.

Safety of LABA and LTRA

The safety of LABA **taken in conjunction with ICS** has been demonstrated in large trials,⁴⁸ and there is no longer a black box warning on LABA medications. They are still, however, not to be used as monotherapy. A new black box warning has been issued for LTRAs due to neuropsychiatric side effects, most commonly irritability, aggressiveness, anxiety and sleep disturbance including suicidal thoughts or actions.⁴⁹ These side effects have been reported in up to 16% of pediatric asthma patients started on montelukast and typically occurred within 2 weeks of initiation.^{50,51}

Yellow zone management (Table 9)

It is not recommended that children and adults on maintenance ICS double the dose of their ICS with acute loss of asthma control given the lack of benefit of this approach.

In children (<16 years of age and older) it is not recommended that the ICS dose be increased by 4-fold or more given the lack of benefit of this approach. This was recently confirmed in a trial of 5 to 11 year olds examining fluticasone 200 mcg/day versus 1000 mcg/day in the yellow zone, which did not find any decrease in exacerbations.⁵²

Table 9. Yellow Zone action plan recommendations based on age and maintenance controller therapy.

Maintenance therapy	Recommended controller step-up therapy
Preschoolers (under 6 years of age) and children (6 to 11 years of age)	
No maintenance	<ul style="list-style-type: none"> No step up in controller medication Consider starting regular controller therapy
ICS or LTRA or ICS/LABA**	<ul style="list-style-type: none"> No step up in controller medication In children with a history of severe exacerbation in last year and who fail to respond to SABA, consider prednisone/prednisolone 1 mg/kg x 3-5 days*
Adults (12 years of age and older)	
No maintenance	<ul style="list-style-type: none"> No step up in controller Consider starting regular controller therapy or PRN bud/form
As needed bud/form	<ul style="list-style-type: none"> Increase bud/form to a maximum of 8 inhalations per day
Daily ICS or LTRA	<p>In individuals ≥16 years of age and older with a history of a severe exacerbation in the last year:</p> <ul style="list-style-type: none"> 1st choice: trial of ≥4 fold increase in ICS for 7 to 14 days 2nd choice: Prednisone 30-50 mg for at least 5 days* <p>Otherwise no step up in controller medication.</p>
Daily bud/form	<ul style="list-style-type: none"> 1st choice: Increase bud/form to a maximum of 4 inhalations twice daily for 7 to 14 days (≥16 years of age and older) or use bud/form as reliever and a controller (maximum 8 inhalations per day) (≥12 years of age and older) 2nd choice: Prednisone 30-50 mg for at least 5 days*
Daily fluticasone propionate/salmeterol, mometasone/formoterol, fluticasone furoate/vilanterol	<p>In individuals ≥16 years of age with a history of a severe exacerbation in the last year:</p> <ul style="list-style-type: none"> 1st choice: trial of ≥4 fold increase in ICS (higher ICS strength of ICS/LABA combination or extra ICS) for 7 to 14 days 2nd choice: Prednisone 30-50 mg for at least 5 days* <p>Otherwise no step up in controller medication.</p>

*If regular need for step up therapy or need for a course of systemic steroids, address reasons for poor control and reassess/initiate controller therapy.

**Does not apply to preschoolers.

In adults (≥ 16 years of age) with a history of a severe exacerbation in the last year, a trial of a 4 or 5-fold increase in maintenance ICS dose for 7-14 days is suggested. A pragmatic trial of adults (16 years of age and older) compared quadrupling the dose of ICS in the yellow zone to maintaining the same baseline dose and found a modest improvement in severe exacerbations (45% in the quadrupling group vs 52% in the control group, hazard ratio for time to first exacerbation 0.81, 95% confidence interval 0.71-0.92, $p=0.002$) at the expense of increased dysphonia and oral candidiasis in the quadrupling group.⁵³

In adults (≥ 16 years of age) on daily bud/form, it is suggested that the dose be increased to a maximum of 4 inhalations twice daily for 7-14 days, as this has been shown to decrease severe exacerbations.³

Evidence for increasing doses for other ICS/LABA formulations is lacking, and for adult patients on daily ICS/LABA other than bud/form, a 4-fold or greater increase in ICS dose for 7-14 days or a course of systemic steroids is only suggested for adults that are exacerbation prone. Health care providers should be aware of the maximum daily LABA dose approved for adult use in Canada (salmeterol 100 mcg, formoterol 48 mcg, vilanterol 25 mcg). A tool to assist clinicians prescribe increased doses of ICS or ICS/LABA in the yellow zone is available in the Guidelines and Resources section of the CTS website at <https://cts-sct.ca/guideline-library/knowledge-tools-resources/asthma/>.

It is not recommended to routinely add oral corticosteroids as part of a written action plan in children or adults except in patients with recent severe exacerbations who fail to respond to inhaled SABA as part of their written action plan.

Prednisone dose and duration in adults should be individualized based on previous or current response. A dose of 30 to 50 mg/day for at least 5 days is suggested. For

children suggested dose is 1 mg/kg/day (maximum 50 mg) for at least 3 days.

Any severe exacerbation (requiring use of systemic steroids, ED visit or hospitalization) is an indication to start a controller therapy for patients only on PRN SABA (see Figure 3) and for all patients is an indication for a reassessment of asthma management. Frequent courses of oral corticosteroid should prompt referral to a specialist (see the Reasons for referral section).

Asthma severity

Asthma severity is defined by the intensity of medication required to **maintain** asthma control. Given that it can only be determined once asthma control is achieved, categorization of asthma severity is not useful to guide treatment decisions except when a patient meets the criteria for severe asthma and other therapeutic options are available.⁶ This classification (Table 10) is an update to the 1999 criteria and is provided to standardize terminology. It is important to highlight that even those with very mild or mild asthma are at risk for asthma-related morbidity, including exacerbations and mortality.¹⁹

Reasons for referral

A referral to an asthma specialist for consultation or co-management is recommended for the following reasons:

- Diagnostic uncertainty
- Children not controlled on moderate dose ICS with correct inhaler technique and appropriate medication adherence
- Suspected or confirmed severe asthma
- Life-threatening event such as an admission to the ICU for asthma

Table 10. Severity classification.

Asthma severity	Treatment required 1999	Treatment required 2021
Very mild	Well-controlled on no medication or inhaled SABA rarely	Well-controlled on PRN SABA
Mild	Well-controlled on SABA (occasionally) and low dose ICS	Well-controlled on: Low dose ICS (or LTRA) and PRN SABA or PRN bud/form
Moderate	Well-controlled on SABA and low to moderate dose ICS +/- additional therapy	Well-controlled on: Low dose ICS + second controller and PRN SABA or Moderate doses of ICS +/- second controller medication and PRN SABA or Low-moderate dose bud/form + PRN bud/form
Severe	Well-controlled on SABA and high dose ICS + additional therapy	High doses of ICS + second controller for the previous year or systemic steroids for 50% of the previous year to prevent it from becoming uncontrolled, or is uncontrolled despite this therapy
Very severe	Well- or poorly-controlled on SABA and high dose ICS + additional therapy + oral steroids	Category removed

Abbreviations: SABA, short-acting beta-agonist; PRN, as needed; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonists; bud/form, budesonide/formoterol.

- Need for allergy testing to assess the possible role of environmental allergens in those with a suggestive clinical history
- Confirmed or suspected work-related asthma or
- Any asthma hospitalization (all ages), ≥ 2 ED visits (all ages) or ≥ 2 courses of systemic steroids (children)

An asthma specialist includes specialists in asthma, general respirology, pediatrics, and/or allergy/immunology who have access to lung function, certified asthma/respiratory educators/nurse clinicians +/- FeNO, induced sputum analysis.⁶

Questions for future guidelines to address

These topics were identified during the update of this guideline as areas where there is differing recommendations in international and national guidelines, or where a specific clinical question has not been addressed in the past or requires updating.

- Sensitivity and specificity of peak flow change after bronchodilator or trial of controller medication for the diagnosis of asthma
- Sensitivity and specificity of exhaled nitric oxide for the diagnosis of asthma
- Sensitivity and specificity of different challenge tests for the diagnosis of asthma
- Sensitivity and specificity of different diagnostic algorithms for the diagnosis of asthma
- Contribution of diurnal variation in assessing asthma control
- 90% of personal best FEV₁ for cut-off to define well-controlled asthma
- Safety and efficacy of ICS-LABA medication in children 6-11years of age compared to moderate dose ICS
- Safety and efficacy of daily seasonal use of asthma controller therapy versus daily use year-round in those with seasonal triggers
- Safety and efficacy of sublingual or subcutaneous immunotherapy for the treatment of asthma
- Safety and efficacy of combination ICS/LABA/LAMA (long-acting muscarinic antagonists) for the treatment of asthma
- Safety and efficacy of combination ICS/LAMA for the treatment of asthma

Performance metrics for monitoring practice concordance with guideline recommendations

Health care providers wishing to monitor adherence to the key recommendations in this guideline may use the following parameters:

- Patients 1-5 years of age with suspected asthma who have documentation by trained health care provider of wheeze or other signs of airflow obstruction and improvement with SABA or documentation of caregiver report of response to 3-month trial of medium

- dose ICS or SABA (numerator) among patients 1-5 years of age with suspected asthma (denominator)
- Patients 6 years of age and older with suspected asthma who have spirometry as part of diagnostic workup for asthma (numerator) among patients 6 years of age and older with suspected asthma
- Number of clinic visits for asthma where asthma control and risk for exacerbation are assessed (numerator) among total clinic visits for asthma (denominator)
- Number of patients with poorly-controlled asthma who have medication adherence and inhalation technique assessed (numerator) among patients with poor asthma control (denominator)
- Number of patients with poorly-controlled asthma provided with asthma education (numerator) among patients with poor asthma control (denominator)
- Number of patients with asthma referred for spirometry as part of asthma control assessment (numerator) among total number of asthma patients (denominator)
- Patients with well-controlled asthma at high risk for exacerbation or patients with poorly-controlled asthma prescribed a controller medication (numerator) among patients with well-controlled asthma at high risk for exacerbation or patients with poorly controlled asthma (denominator)
- Patients with asthma prescribed a reliever medication (SABA or bud/form) (numerator) among patients with asthma (denominator)
- Patients prescribed short courses of ICS (numerator) among patients with asthma (denominator) (practice should not occur)
- Adults with one asthma hospitalization or ≥ 2 ED Visits seen by asthma specialist (numerator) among adults with one asthma hospitalization or ≥ 2 ED visits for asthma (denominator)
- Children with one asthma hospitalization or ≥ 2 ED Visits or ≥ 2 courses of systemic steroids seen by asthma specialist (numerator) among children with one asthma hospitalization or ≥ 2 ED Visits or ≥ 2 courses of systemic steroids (denominator)
- Children with uncontrolled asthma on moderate dose ICS (with good technique and adherence) seen by asthma specialist (numerator) among children uncontrolled on moderate dose ICS (denominator)
- Children or adults with suspected or confirmed severe asthma seen by asthma specialist (numerator) among children or adults with suspected or confirmed severe asthma (denominator)

Definitions

Preschool = refers to children ≥ 1 year of age to 5 years of age

Children = refers to children ≥ 6 years of age to 11 years of age

Adult = refers to individuals ≥ 12 years of age unless otherwise specified, individuals 12-18 years of age are included in this category because medication

approval is often for patients ≥ 12 years of age, however, patients 12 to 18 years of age (particularly those who are pre-pubertal) are at higher risk for some medication side-effects such as growth suppression and should be monitored similarly to children

Controller = A medication taken daily to decrease airway inflammation, maintain asthma control and prevent exacerbations

Reliever = A medication taken only as needed for quick relief of symptoms (eg, SABA, bud/form); use of > 2 doses of reliever medication in a week is a sign of poorly-controlled asthma (the number of actuations in a dose is variable depending on the reliever medication but is often 1-2 actuations)

SABA = Short-acting beta-agonist (eg, salbutamol, terbutaline)

LABA = Long-acting beta-agonist (e.g., salmeterol, formoterol, vilanterol)

FABA = Fast-acting beta-agonist which can either be a short-acting beta-agonist or a long-acting beta-agonist with rapid onset of action. In Canada, formoterol in a single inhaler with budesonide is approved for use as a fast-acting beta-agonist. The term is used in this document in reference to previous CTS guidelines, however for clarity the terms SABA and bud/form will be used when appropriate

LTRA = Leukotriene receptor antagonist

LAMA = Long-acting muscarinic antagonist

bud/form = Single inhaler of budesonide and formoterol

PRN ICS-SABA = As needed use of an inhaled corticosteroid each time a short-acting beta-agonist is taken; in Canada, this would be in 2 separate inhalers as there is not currently a single inhaler containing ICS and SABA

Severe exacerbation: an exacerbation requiring any of the following:

1. systemic steroids
2. emergency department visit; or
3. hospitalization

Mild exacerbation: an increase in asthma symptoms from baseline that does not require systemic steroids, an emergency department visit or a hospitalization. Differentiating this from chronic poorly-controlled asthma may only occur retrospectively.

Higher risk of exacerbation is defined by presence of any of the following:

1. any history of a previous severe asthma exacerbation (requiring either systemic steroids, ED visit or hospitalization);

2. poorly-controlled asthma as per CTS criteria;
3. overuse of SABA (using more than 2 inhalers of SABA in 1 year); or
4. being a current smoker.

Individuals without any of these features have a lower risk of exacerbation.

Well-controlled asthma: Asthma in which all criteria for well-controlled asthma are met (Table 3)

Poorly-controlled asthma: Asthma in which any one of the criteria for well-controlled are not met (Table 3).

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Disclosure statement

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