

Individualized treatment strategies and considerations in patients with mild asthma

Discussion of Canadian Thoracic Society guideline recommendations

Mark E. Waite MD Connie L. Yang MD MSc FRCPC

Abstract

Objective To highlight recommendations from the Canadian Thoracic Society (CTS) 2021 asthma guideline for adults and children aged 12 years and older and to address controversies related to the update.

Sources of information The CTS 2021 asthma guideline.

Main message Asthma is a common condition encountered in primary care. Poor symptom control and exacerbations contribute substantially to the burden of disease. Practice guidelines have been shifting in recent years toward more aggressive treatment of very mild and mild asthma, with goals of optimizing symptom control and reducing exacerbations. Consider underlying risk of exacerbation, extent of asthma symptoms, adherence levels, and treatment cost when choosing therapy for patients with very mild and mild asthma.

Conclusion The goal of this article is to briefly review the evidence and rationale behind treatment options in the CTS guideline to help physicians make patient-centred decisions.

Asthma affects an estimated 10.8% of all Canadians.¹ Of these, 20% to 28% rely on short-acting β -agonist (SABA) therapy alone, regardless of whether their asthma is well controlled.² Patients whose symptoms are well controlled (**Table 1**)³ by taking SABA alone are considered to have very mild asthma. In 2021 the Canadian Thoracic Society (CTS) updated its asthma guideline to review new evidence for the treatment of patients with mild and very mild asthma.^{3,4} This article explores the new recommendations for adults and children 12 years of age and older and addresses some of the controversies related to the update.

Case description

Clark is a 37-year-old man who presents to your family practice office to renew his salbutamol inhaler prescription. He had previously been prescribed an inhaled corticosteroid (ICS), which he does not use. He is mainly symptomatic in the summer when he mows the lawn and has daytime symptoms less than 3 times per week with no nocturnal symptoms and no physical activity limitations. His diagnosis of asthma was confirmed years ago by a methacholine challenge test and his recent spirometry test results showed that his forced expiratory volume in the first second (FEV₁) was within 90% of his personal best. He quit smoking 3 years ago. While upper respiratory tract infections tend to lead Clark to have a prolonged cough, he has never required oral corticosteroids to treat an exacerbation. You review his provincial electronic health record and confirm that his last refill of salbutamol was nearly 1 year ago. He does not have private coverage for his medication. Should you renew his salbutamol prescription only, educate

Editor's key points

- ▶ Individuals with well-controlled asthma symptoms can still be at risk of asthma exacerbations. Assess whether a patient is at higher risk before prescribing a short-acting β -agonist (SABA).
- ▶ For patients taking SABA with well-controlled symptoms and very mild asthma, consider the patient's underlying risk of exacerbation, the extent of their asthma symptoms, adherence levels, and treatment cost when choosing appropriate therapy.
- ▶ For patients at higher risk of exacerbation, either a daily inhaled corticosteroid plus SABA as needed or a budesonide-formoterol inhaler as needed is recommended.
- ▶ For those taking SABA but whose symptoms are not well controlled, prescribe a daily inhaled corticosteroid plus SABA as needed. However, a budesonide-formoterol inhaler is preferred for those with poor adherence to daily treatment.

him on the importance of adhering to a daily ICS, or prescribe a budesonide-formoterol inhaler instead?

Sources of information

The updated 2021 CTS guidelines were reviewed.

Main message

A major update in the 2021 guidelines focuses on how to determine whether an ICS should be recommended to patients with very mild asthma. It is now based on risk of asthma exacerbation. Patients are considered at higher risk of exacerbation if they meet any criteria in **Box 1**.⁴

Clark meets the criteria of a patient with very mild asthma at lower risk of asthma exacerbations. Options for patients like him include having him continue taking SABA as needed, starting him on a daily ICS plus SABA as needed, or discontinuing his SABA and starting him on a budesonide-formoterol inhaler as needed. There is moderate- to low-certainty evidence that a daily ICS or a budesonide-formoterol inhaler, respectively, are superior to

SABA,^{3,4} which is why a shared decision-making process that considers the impact of asthma symptoms, adherence levels, and the cost of treatments is recommended.

Controversy. In 2019 the Global Initiative for Asthma recommended that ICS-formoterol as needed replace SABA as the preferred reliever therapy for all patients with asthma,⁵ leaving many to debate whether patients with very mild asthma should still be given the option of SABA monotherapy. Overuse of SABA is associated with worse outcomes,⁵ either due to tachyphylaxis from SABA or due to SABA overuse being a surrogate marker for poorly controlled asthma. A study published in 2020 showed that use of more than 2 SABA inhalers in a year is associated with increased risk of exacerbation and death in a dose-dependent manner.⁶ There is also well-established evidence that use of ICS reduces the risk of asthma exacerbations.³ However, after reviewing the evidence and finding no trials (ie, those comparing ICS or ICS and long-acting β -agonists with SABA monotherapy) studying patients with very mild asthma, the CTS elected to keep SABA as needed on the continuum of possible therapies. Patients with symptoms less than twice per week can still be at increased risk of asthma exacerbations and, theoretically, would benefit from a greater absolute risk reduction of exacerbations with an ICS. As such, the CTS recommendation is to assess a patient's individual risk using the criteria in **Box 1**.⁴

The CTS elected to keep SABA as an option in carefully selected patients owing to the greater cost of ICS-based therapy, the higher number needed to treat to prevent an exacerbation in patients at lower risk, the absence of a cost-effectiveness analysis comparing ICS with SABA monotherapy in patients with very mild asthma at lower risk of exacerbations, and the underrepresentation of these patients in clinical trials.³

Table 1. 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 budesonide-formoterol) [†]	≤ 2 doses per week
FEV ₁ or PEF	$\geq 90\%$ 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	

ED—emergency department, FEV₁—forced expiratory volume in the first second, PEF—peak expiratory flow, SABA—short-acting β -agonist.
*A mild exacerbation is an increase in asthma symptoms from baseline that does not require systemic steroids, an ED visit, or 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 budesonide-formoterol 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 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 centres.
This table was reproduced from the Canadian Thoracic Society (CTS) guideline on the management of very mild and mild asthma by kind permission of CTS.³

Box 1. Assessing risk of severe exacerbation

Individuals with any one of these risk factors are at higher risk of severe 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

CTS—Canadian Thoracic Society, ED—emergency department, OR—odds ratio, SABA—short-acting β -agonist.
*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. Adapted from the CTS 2021 guideline update on the diagnosis and management of asthma in preschoolers, children and adults with kind permission of the CTS.⁴

Back to Clark

After you discuss treatment options with Clark, he chooses to remain on SABA due to lower cost. You prescribe him 1 inhaler with 1 refill.

Clark returns to your office 8 months later to have his SABA prescription refilled. He is going through a divorce and recently started smoking again to help deal with the stress. He feels that his asthma is well controlled, but you learn that he now wakes up at night with a cough and has symptoms of shortness of breath on average 3 times per week that he sometimes uses his SABA to remedy. His recent spirometry test results continue to show that his FEV₁ is within 90% of his personal best, but when reviewing his electronic health record you find that he has recently filled 2 other prescriptions for SABA inhalers from a walk-in clinic, on top of the inhalers you had prescribed him. Should you have him continue with SABA as needed, both prescribe daily ICS and recommend taking SABA first to open up the lungs, prescribe daily ICS with SABA as needed, or prescribe a budesonide-formoterol inhaler as needed?

Prescribing a daily ICS with SABA as needed or prescribing a budesonide-formoterol inhaler as needed are acceptable approaches. The first option is not recommended for Clark as he has poorly controlled asthma (Table 1)³ and is at higher risk of exacerbation (Box 1).⁴ The second option is also not recommended because routine use of SABA prior to scheduled ICS increases the risk of exacerbations.

Recent studies continue to show that although most Canadians consider their asthma to be well controlled, 53% to 90% of Canadians meet 1 or more criteria for poorly controlled asthma.^{7,8} Furthermore, it is possible that these “well-controlled” symptoms are the result of SABA overuse. In response to this issue, guidelines are now focusing more on exacerbation prevention as opposed to simply treating symptoms, even in those patients whose symptoms are well controlled. Clark has 3 major exacerbation risk factors: He has poorly controlled asthma, he smokes, and he overuses his SABA.

Should you prescribe a daily ICS with SABA as needed or a budesonide-formoterol inhaler as needed? Evidence from randomized clinical trials show similar rates of exacerbation with a daily ICS and ICS-formoterol as needed, better symptom control with a daily ICS, and small but statistically significantly greater improvements in FEV₁ in the daily budesonide groups compared with the ICS-formoterol groups (mean difference=32.6 mL [95% CI 11.4 to 53.7 mL]).^{9,10} It is important to note that adherence rates to daily budesonide in these studies were 62.8% and 78.9%, respectively. It is unclear if better adherence would have led to better results for participants in the daily ICS group; nevertheless, low adherence to prescribed therapies is a reality of clinical practice. In a pragmatic open-label trial

where adherence to daily ICS was only 56%, although the relative rate of exacerbations among patients in the budesonide-formoterol group did not differ significantly from that of patients in the daily ICS group (1.12; 95% CI 0.70 to 1.79; $P=.65$), there were fewer severe exacerbations among patients in the budesonide-formoterol as-needed group compared with those in the daily ICS group (9 vs 21; relative risk=0.44; 95% CI 0.20 to 0.96).¹¹

In terms of cost-effectiveness, as-needed budesonide-formoterol inhalers appear to be superior to daily ICS plus SABA as needed at a population-wide level in Canada, with incremental cost savings estimated at \$9882 per patient over 50 years; however, for individual patients the up-front cost of budesonide-formoterol inhalers is approximately \$47 higher.¹²

For prevention of exacerbations, a daily ICS and budesonide-formoterol as needed are equally effective, and the CTS does not recommend one over the other for patients with well-controlled asthma symptoms. Due to improved symptom control with daily ICS use, the CTS recommendation for a patient like Clark would be daily ICS plus SABA as needed. If he did not adhere to a daily ICS treatment despite adequate asthma education and support, then a budesonide-formoterol inhaler would be the preferred option, regardless of symptom control.

Whenever an ICS is recommended, it is important for clinicians to promote adherence to therapy and to educate patients on the rationale for its use. If patients treated with ICS maintenance therapy are nonadherent despite adequate education, changing their reliever inhalers to a combination of an ICS and formoterol is an excellent strategy to ensure patients receive sufficient doses of ICS while preventing SABA overuse.

Case resolution

You opt to start Clark on low-dose daily budesonide and continue his SABA as needed. You counsel him on smoking cessation and discuss the possibility of stepping down on therapy as an incentive to quit. You book a follow-up appointment in 1 month to reassess his symptoms and his adherence to treatment.

Conclusion

Treatment and prevention in those with very mild and mild asthma require open communication and shared decision making between patients and providers. When considering treatment for patients who have well-controlled symptoms and very mild asthma, make sure to assess their underlying risk of exacerbation, the extent of their asthma symptoms, and treatment cost. 🌿

Dr Mark E. Waite is a family physician at the Moncton Hospital in New Brunswick.

Dr Connie L. Yang is Investigator and Pediatric Respiriologist at BC Children's Hospital in Vancouver and Clinical Associate Professor in the Division of Respiratory Medicine and Department of Pediatrics at the University of British Columbia.

Contributors

All authors contributed to conducting the literature review and to preparing the manuscript for submission.

Competing interests

Drs Mark E. Waite and **Connie L. Yang** were part of the Canadian Thoracic Society Guidelines Committee for mild asthma. **Dr Mark E. Waite** has previously received a consulting fee from Sanofi Pasteur. **Dr Connie L. Yang** is a clinical investigator in studies sponsored by GSK and Boehringer Ingelheim.

Correspondence

Dr Mark E. Waite; email drwaite@protonmail.com

References

- Public Health Agency of Canada. *Asthma in Canada*. Ottawa, ON: Government of Canada; 2018. Available from: <https://health-infobase.canada.ca/datalab/asthma-blog.html>. Accessed 2023 Nov 1.
- Ungar WJ, Chapman KR, Santos MT. Assessment of a medication-based asthma index for population research. *Am J Respir Crit Care Med* 2002;165(2):190-4.
- Yang CL, Hicks EA, Mitchell P, Reisman J, Podgers D, Hayward KM, et al. 2021 Canadian Thoracic Society guideline—a focused update on the management of very mild and mild asthma. *Can J Respir Crit Care Sleep Med* 2021;5(4):205-45.
- Yang CL, Hicks EA, Mitchell P, Reisman J, Podgers D, Hayward KM, et al. Canadian Thoracic Society 2021 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can J Respir Crit Care Sleep Med* 2021;5(6):348-61.
- Global strategy for asthma management and prevention*. Fontana, WI: Global Initiative for Asthma; 2019. Available from: <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-june-2019-wms.pdf>. Accessed 2023 Jan 10.
- Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2 -agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* 2020;55(4):1901872.
- FitzGerald JM, Boulet LP, McIvor RA, Zimmerman S, Chapman KR. Asthma control in Canada remains suboptimal: The Reality of Asthma Control (TRAC) study. *Can Respir J* 2006;13(5):253-9.
- Survey: asthma not well-controlled for most Canadians* [news release]. Ottawa, ON: Canadian Lung Association; 2016. Available from: <https://www.lung.ca/survey-asthma-not-well-controlled-most-canadians>. Accessed 2023 Nov 9.
- Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378(20):1877-87.
- O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378(20):1865-76.
- Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019;380(21):2020-30. Epub 2019 May 19.
- Sadatsafavi M, FitzGerald JM, O'Byrne PM, Soliman M, Sriskandarajah N, Vicente C, et al. The cost-effectiveness of as-needed budesonide-formoterol versus low-dose inhaled corticosteroid maintenance therapy in patients with mild asthma in Canada. *Allergy Asthma Clin Immunol* 2021;17(1):108.

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to <https://www.cfp.ca> and click on the Mainpro+ link.

This article has been peer reviewed.

Can Fam Physician 2023;69:829-32 (Eng), 833-6 (Fr).

DOI: 10.46747/cfp.6912829

Cet article se trouve aussi en français à la page 833.