

**TITLE:** The controversial role of as-needed short-acting  $\beta$ 2-agonist monotherapy in mild asthma: a short review of current guidelines

**Running title:** The controversial role of as-needed reliever monotherapy in mild asthma

**AUTHORS:** Simon Couillard<sup>1</sup>, MD FRCPC 0000-0002-4057-6886

Philippe Lachapelle<sup>1</sup>, MD FRCPC 0000-0001-9290-1823

Louis-Philippe Boulet<sup>2</sup>, MD FRCPC 0000-0003-3485-9393

**From :** <sup>1</sup> Faculté de médecine et des sciences de la santé, Université de Sherbrooke, 3001 12<sup>e</sup> Avenue Nord, Sherbrooke (Québec), Canada. <sup>2</sup> Centre de Recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec (Québec), Canada

**Corresponding author:** Dr Simon Couillard, Centre Hospitalier Universitaire de Sherbrooke, 3001, 12<sup>e</sup> Avenue Nord, pièce 2616, Sherbrooke (Québec), Canada, J1H 5N4 Phone: +1-819-822-6735, Fax: +1-819-822-6763, E-mail: [s.couillard@usherbrooke.ca](mailto:s.couillard@usherbrooke.ca)

**Manuscript word count:** 600/600

**Financial/nonfinancial disclosures:** This article was not sponsored nor funded. **SC:** reports grants and speaker honoraria from Sanofi-Regeneron, speaker honoraria from AstraZeneca, outside the submitted work. **PL:** reports speaker honoraria from AstraZeneca, Sanofi-Regeneron, GlaxoSmithKline and Novartis. **LP** reports research grants from Amgen, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Sanofi-Regeneron; speaker honoraria from AstraZeneca, Covis, GlaxoSmithKline, Novartis, Merck; advisory boards for AstraZeneca, Novartis, GlaxoSmithKline, Merck, Sanofi-Regeneron; Chair of the Global Initiative for Asthma Board of Directors, President of InterAsma-the Global Asthma Association, Member of the Canadian Thoracic Society Respiratory Guidelines Committee.

**Author contributions:** **SC:** is the guarantor of this publication and prepared the manuscript. **PL:** suggested the initial research question and contributed to manuscript writing. **LP:** contributed to manuscript writing. All authors reviewed and approved the final version of the manuscript.

## **KEYWORDS**

Asthma, exacerbations, risk factors, eosinophils, short-acting  $\beta$ 2-agonist, inhaled corticosteroid

## **ABBREVIATIONS**

ICS: inhaled corticosteroid

SABA: short-acting beta2-agonist

## **TWITTER SUMMARY**

The CTS 2021, EPPR4 2020, and GINA 2021 updated guidelines recommend 3 different management strategies for very mild/mild asthma. @Simcouillard et al highlight the controversy surrounding SABA monoTx in the context of increasing evidence in favour of combined ICS/reliever Tx.

The controversy surrounding short-acting  $\beta_2$ -agonist (SABA) monotherapy for very mild and mild asthma continues in guidelines<sup>1-3</sup> despite increasing evidence in favour of combined inhaled corticosteroids (ICS)/reliever therapy<sup>4</sup>.

### **Three guidelines, three management strategies in mild asthma**

A focused revision of the Canadian guideline on very mild and mild asthma was recently performed<sup>1</sup>. For mild asthma which is well-controlled, it is recommended to further stratify this group according to the risk of exacerbations (Table). In patients  $\geq 12$  years old with well-controlled mild asthma at low risk of future exacerbations, PRN SABA monotherapy, daily ICS with SABA PRN or an association of budesonide/formoterol PRN can be prescribed.

In the United-States, the 2020 EPR4 focused update on asthma management<sup>2</sup> eliminates monotherapy with SABA in mild asthma. The recommendation for patients  $\geq 12$  years old is to proceed with regular ICS plus as-needed SABA or intermittent ICS + SABA. No mention is made of an ICS/formoterol-based strategy for mild disease; its use is reserved for moderate to severe asthma.

Since 2019, the Global Initiative for Asthma Reports has eliminated SABA monotherapy and advocates ICS/reliever therapy across disease severities<sup>3</sup>. The preferred controller for mild asthma is as-needed ICS-formoterol, but SABA is still suggested as an alternative reliever treatment only when intermittent or regular ICS medication is prescribed.

### **Is SABA monotherapy safe in mild asthma?**

There is a substantial risk of harm in prescribing SABA without ICS coverage. Regular SABA intake is associated with the down-regulation of  $\beta_2$ -adrenergic receptors, a reduction in their

bronchoprotective/bronchodilator effects, and an increased response to allergens and airway eosinophilia.<sup>5</sup> Use and particularly overuse of SABA as monotherapy is associated with fatal asthma events<sup>6</sup>. Conversely, low-dose ICS decrease asthma mortality and reduce lung function decline<sup>7,8</sup>. More recently, the SABINA investigators<sup>9</sup> report that SABA overuse remains an independent risk factor for asthma attacks and asthma-related mortality. Finally, the argument of a reduced cost with SABA monotherapy does not fully apply as the average ICS doses for ICS-formoterol as-needed were relatively small in recent studies<sup>4</sup>.

### **Can we predict the risk of an asthma attack in mild asthma?**

Selecting patients at low enough risk for SABA monotherapy is a difficult task and there is a lack of data supporting the efficacy and safety of this approach. Despite this, it is now recommended that risk assessment for mild disease – most of which will inevitably be left to primary care – should be based on what may be considered a complex list of clinical risk factors. Furthermore, the list does not include a common risk factor which also implies ICS responsiveness: the type-2 inflammatory phenotype<sup>10</sup>.

Indeed, the pre-specified subgroup analysis of Novel START<sup>11</sup> showed that the incidence of severe exacerbations in the salbutamol-only group was five times greater for patients with a baseline blood eosinophil count  $\geq 0.3 \times 10^9/L$  than those with eosinophils  $< 0.15 \times 10^9/L$ . Importantly, this biomarker-dependent excess risk was removed by ICS exposure: the odds ratios for treatment effect were 0.11 and 0.15 in the ICS/reliever regimens arms when blood eosinophils were  $\geq 0.3 \times 10^9/L$  at baseline.

Furthermore, a second overlooked treatable trait is atopy. The 2016 thunderstorm asthma event in Australia documented that nearly all patients hospitalised for an asthma attack were allergic to

grass; only 26% of these were previously on ICS.<sup>12</sup> This type of event is unusual but highlights that one of the main triggers of exacerbations in allergic asthma is exposure to various allergens and these last can also contribute to virus-induced exacerbations. We may therefore consider that atopic patients need access to an ICS. It has long been suggested to provide a written action plan in case of exacerbations in asthma but unfortunately, these are insufficiently offered to asthmatic patients<sup>13</sup>.

## **Conclusion**

SABA monotherapy in mild/very mild asthma is increasingly eliminated from guidelines. However, if the clinician decides to recommend SABA monotherapy in a given patient, current asthma control and the risk of asthma attacks should be carefully evaluated. We suggest that this process should also include looking for blood eosinophilia and atopy to determine if a more effective option including ICS is required. Furthermore, if the strategy of prescribing a regular ICS plus as-needed SABA in these mild patients is selected, careful repeated check for adherence to treatment is mandatory as it is often poor. The as-needed ICS/formoterol therapy for mild (and very mild asthma) is a major change in paradigm: its benefits are nevertheless supported by evidence.

## REFERENCES

1. Yang CL, Hicks EA, Mitchell P, 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*. February 2021;1-41. doi:10.1080/24745332.2021.1877043
2. Cloutier MM, Baptist AP, Blake K V., et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217-1270. doi:10.1016/j.jaci.2020.10.003
3. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention (2021 Update)*.; 2021. <https://ginasthma.org/>.
4. Satia I, Cusack RP, O’Byrne PM. Paradigm shift in the management of mild asthma: Focus toward a patient centered approach. *Can J Respir Crit Care, Sleep Med*. 2020;4(1):55-60. doi:10.1080/24745332.2020.1722976
5. Cockcroft DW. Clinical concerns with inhaled  $\beta_2$ -agonists: Adult asthma. *Clin Rev Allergy Immunol*. 2006;31(2-3):197-207. doi:10.1385/CRIAI:31:2:197
6. Speizer FE, Doll R, Heaf P, Strang LB. Investigation into Use of Drugs Preceding Death from Asthma. *Br Med J*. 1968;1(5588):339-343. doi:10.1136/bmj.1.5588.339
7. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343(5):332-336. doi:10.1056/NEJM200008033430504

8. HK R, WW B, S P, et al. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet (London, England)*. 2017;389(10065):157-166.  
doi:10.1016/S0140-6736(16)31399-X
9. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting  $\beta$ 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).  
doi:10.1183/13993003.01872-2019
10. Couillard S, Laugerud A, Jabeen M, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax*. 2021.  
doi:10.1136/thoraxjnl-2021-217325
11. Pavord ID, Holliday M, Reddel HK, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med*. 2020;8(7):671-680. doi:10.1016/S2213-2600(20)30053-9
12. Harun N-S, Lachapelle P, Bowatte G, et al. 2016 Thunderstorm-asthma epidemic in Melbourne, Australia: An analysis of patient characteristics associated with hospitalization. *Can J Respir Crit Care, Sleep Med*. March 2020:1-7.  
doi:10.1080/24745332.2020.1727301
13. Boulet L-P, Bourbeau J, Skomro R, Gupta S. Major care gaps in asthma, sleep and chronic obstructive pulmonary disease: A road map for knowledge translation. *Can Respir J*.



2013;20(4):265. doi:10.1155/2013/496923

**TABLE**

**Risk factors for asthma exacerbations in Canadian guidelines – with proposed additions**

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

- Any history of previous severe asthma exacerbation requiring systemic steroids, emergency department visit, or hospitalisation;
- Poorly-controlled asthma as per Canadian Thoracic Society criteria
- Reliever overuse (defined as used of more than two salbutamol inhalers per year)
- Current smoker

**Proposed additional risk factors which also predict ICS-responsiveness**

- Blood eosinophil count  $\geq 0.3 \times 10^9/L$
- Atopy (clinically diagnosed or documented sensitisation to airborne allergen)

ICS, inhaled corticosteroid