Original Article

As-Needed Use of Short-Acting β_2-Agonists Alone Versus As-Needed Use of Short-Acting β_2-Agonists Plus Inhaled Corticosteroids in Pediatric Patients with Mild Intermittent (Step 1) Asthma: A Cost-Effectiveness Analysis

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What is already known about this topic? Step 1 of the stepwise approach for managing asthma in children 5 to 11 years old is challenging, for various reasons, among them: the fact that the initial therapy in step 1 is aimed only at symptoms, despite asthma being a disease with a highly variable activity level that is driven by chronic airway inflammation.

What does this article add to our knowledge? In Colombia, a low- and middle-income country, compared with the use of albuterol alone, the use of beclomethasone dipropionate added to albuterol as needed for symptom relief is cost-effective in children 5 to 11 years old with mild intermittent (step 1) asthma, because it involves a higher probability of a lack of a requirement for prednisone for asthma exacerbation at lower total treatment costs.

How does this study impact current management guidelines? The results of this study give support to the recommendation of the Global Initiative for Asthma guidelines 2021 for the management of children 5 to 11 years old with mild intermittent asthma to allow the use of inhaled corticosteroids whenever short-acting β_2-agonist is taken (in combination or in separate inhalers) as an efficient option.

BACKGROUND: Although the efficacy of the as-needed use of short-acting β_2-agonists (SABAs) plus inhaled corticosteroids (ICS) for treating children with mild intermittent asthma has been demonstrated, evidence of its cost-effectiveness is scarce.
OBJECTIVES: The aim of the present study was to compare the cost-effectiveness of the as-needed use of SABAs alone versus the as-needed use of SABAs plus ICS in children 5 to 11 years old with mild intermittent (step 1) asthma but suffering from an exacerbation of asthma symptoms.
METHODS: A decision-analysis model was adapted. Effectiveness parameters were obtained from a randomized clinical trial. Cost data were obtained from hospital bills and from the national manual of drug prices in Colombia. The study was carried out from the perspective of the national health care system in Colombia. The main outcome of the model was a first course of prednisone for an asthma exacerbation (AE).
RESULTS: Compared with the use of SABAs alone, the as-needed use of SABAs plus ICS was associated with lower overall treatment costs (US$17.99 vs US$27.94 mean cost per patient) and a higher probability of a lack of a requirement for a first course of prednisone (0.6500 vs 0.5100), thus showing dominance.
CONCLUSIONS: In Colombia, compared with the use of albuterol alone, the use of beclomethasone dipropionate added to albuterol as needed for symptom relief is cost-effective in children 5 to 11 years old with mild intermittent (step 1) asthma, because it involves a higher probability of a lack of a requirement for prednisone for AE at lower total treatment costs. **(J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Acute asthma; Children; Cost-effectiveness; Inhaled corticosteroids*

Childhood asthma is a major public health problem in the United States as well as in many low- and middle-income countries (LMICs) such as Colombia, which has a prevalence

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Abbreviations used
AE- Asthma exacerbation
BDP- Beclomethasone dipropionate
CEA- Cost-effectiveness analysis
COPs- Colombian pesos
ED- Emergency department
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroids
LMICs- Low- and middle-income countries
MDI- Metered dose inhaler
NAEPP- National Asthma Education and Prevention Program
PSA- Probabilistic sensitivity analysis
SABAs- Short-acting β_2-agonists
TREXA- Treating Children to Prevent Exacerbations of Asthma
UI- Uncertainty intervals

estimated at 10% to 12%.[1] Asthma treatment can be adjusted in a stepwise approach to achieve good symptom control and minimize future risk of exacerbations, persistent airflow limitation, and medication side effects.[2] Step 1 of the stepwise approach for managing asthma in children 5 to 11 years old is challenging, for various reasons, among them: the fact that the initial therapy in step 1 is aimed only at symptoms, despite asthma being a disease with a highly variable activity level that is driven by chronic airway inflammation, and there being evidence that shows that overuse of short-acting β_2-agonist (SABA) is associated with increased risk of asthma-related deaths.[3] In addition, although extensive research has demonstrated the protective effect of inhaled corticosteroids (ICS) in terms of asthma-related hospitalizations and deaths,[4,5] acceptance and adherence to daily ICS therapy in patients manifesting only a few symptoms and their parents is typically low, mainly because of a lack of perceived necessity, leaving patients exposed to the risks of SABA-only treatment.[6,7]

One potential response to these challenges is the as-needed use of an ICS plus a SABA combination as an alternative to as-needed SABA alone.[7] In this regard, there are studies showing that when compared with albuterol alone as a rescue medication, the use of ICS plus albuterol on an as-needed basis is associated with a decreased frequency of asthma exacerbations (AEs),[8] and when compared with provider-based guideline-directed adjusted asthma care (the current standard care), the use of intermittent symptom-based adjustment of ICS is similar in terms of asthma control, AEs, and measures of lung function, with lower ICS exposure.[9]

It is worth mentioning that the recommended step 1 treatment for managing asthma in children 5 to 11 years old differs between the 2 most up-to-date asthma guidelines: whereas the Global Initiative for Asthma (GINA) recommends as-needed SABA as the preferred initial treatment and includes taking ICS whenever SABA is taken (in combination or in separate inhalers) as an alternative option,[2] the 2020 focused update of the National Asthma Education and Prevention Program (NAEPP) asthma guideline recommends the use of SABA as needed for symptoms as the preferred treatment, without alternative options.[10]

Demonstrating not only effectiveness but also cost-effectiveness and cost-savings is important for advocating for a new intervention. Cost-effectiveness analysis (CEA) provides a tool that can combine the cost and the effectiveness of alternative treatments. However, studies reporting the cost-effectiveness of alternative treatment strategies in asthmatic children are scarce, and few of them have been performed in any LMIC, where the economic burden of the disease is the greatest. Furthermore, to the best of our knowledge, none of these published studies have compared the 2 above-mentioned strategies for step 1 treatment of the stepwise approach for managing asthma in children 5 to 11 years old.

Accordingly, the aim of the present study was to compare the cost-effectiveness of the as-needed use of SABAs alone versus the as-needed use of SABAs plus ICS in children 5 to 11 years old with mild intermittent (step 1) asthma living in Colombia, a South American LMIC.

METHODS

Structure of the model

To evaluate the cost-effectiveness of the as-needed use of SABAs alone versus the as-needed use of SABAs plus ICS in children 5 to 11 years old with mild intermittent (step 1) asthma, we used a decision-analysis model previously employed by our group. The model illustrates how a typical pediatric patient with mild intermittent (step 1) asthma receives treatment for his or her disease. When the patient experiences respiratory symptoms such as coughing, wheezing, underperforming due to asthma during physical activities, chest tightness, or shortness of breath, the model compares the use of 2 puffs of albuterol (180 mcg) (SABAs alone strategy) versus the use of 2 puffs of beclomethasone dipropionate (BDP) (80 mcg) added to each 2 puffs of albuterol needed for symptom relief (SABAs plus ICS strategy). For each of the 2 comparators, the model incorporates the probability of a first AE that required treatment with prednisone, after which the model incorporates the probability of a second AE that required treatment with prednisone within any 6-month period (Figure 1).

The primary outcome of the cost-effectiveness model was a clinically important outcome, that is, a first course of prednisone for AE, considering a lack of a requirement for prednisone for AE to be a success, and a requirement for prednisone for AE to be a failure. The time horizon of the CEA included the period between enrollment in the study and the follow-up within 6 months after randomization and study recruitment. Discounting of effects and costs was not relevant in this model, given the fact that the time horizon was less than 12 months.

The model evaluated direct medical costs and health outcomes from the Colombian third-party payer perspective.

Study population of reference

Patient characteristics and details of interventions administered in the Treating Children to Prevent Exacerbations of Asthma (TREXA) study[8] defined our reference population. Specifically, the TREXA study analyzed children 6 to 18 years old with a history of mild persistent asthma during the previous 2 years and qualified for interruption or discontinuation of controller treatment because their illness was well controlled (as defined in US NAEPP asthma care guidelines). The eligibility criteria for inclusion in the study were children who were naive to controller treatment and who had a history of 1 to 2 exacerbations in the previous year, children who were treated for the previous 8 weeks with a monotherapy other than ICS, or children whose disease was controlled for the previous 8 weeks on low-dose corticosteroids as monotherapy ($\leq$160 mcg daily with a BDP equivalent). Participants were excluded from the study if they had a prebronchodilator forced expiratory volume of 1 s of less

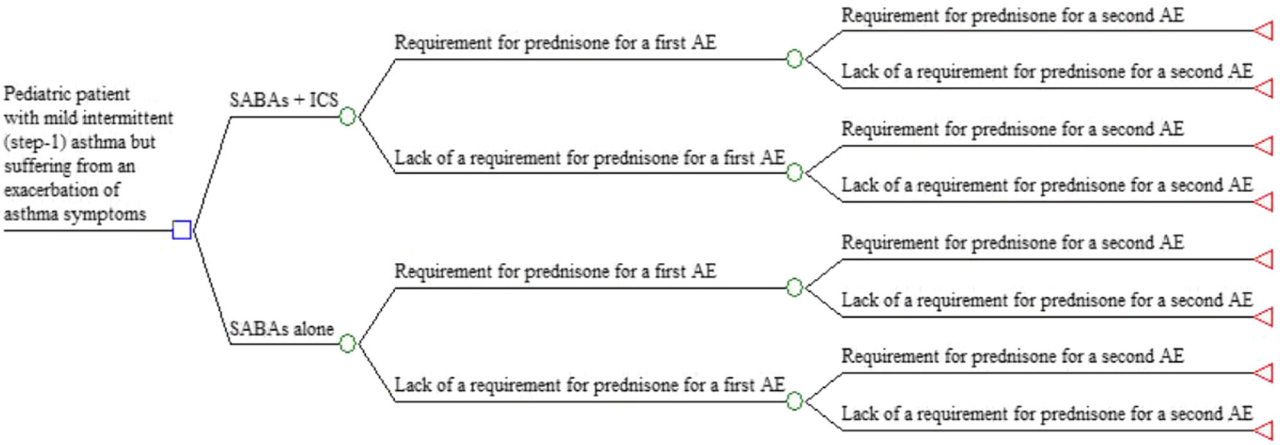

FIGURE 1. Diagram of cost-effectiveness model for each treatment option. *AE*, Asthma exacerbation; *ICS*, inhaled corticosteroids; *SABAs*, short-acting β_2-agonists.

TABLE I. Baseline and range values of parameters included in the model

Cost items	Base-case value	Lower value	Higher value
Probability of a first AE that required treatment with prednisone with SABAs alone[8]	0.49	0.37	0.61
Probability of a first AE that required treatment with prednisone with SABAs + ICS[8]	0.35	0.24	0.47
Probability of a second AE that required treatment with prednisone with SABAs alone[8]	0.23	0.14	0.34
Probability of a second AE that required treatment with prednisone with SABAs + ICS[8]	0.085	0.02	0.15
Cost of BDP MDI × 50 mcg[11]	2.74	2.19	5.04
Cost of Pred tablets × 5 mg[11]	0.034	0.001	0.17
Cost of ED AE[12]	38.8	21.1	64.1

Values used in the deterministic sensitivity analyses were based on plausible ranges, including 95% confidence intervals when available.
AE, Asthma exacerbation; *BDP*, beclomethasone dipropionate; *ED*, emergency department; *ICS*, inhaled corticosteroids; *MDI*, metered dose inhaler; *SABAs*, short-acting β_2-agonists.

than 60% of that predicted at the first visit, were admitted to hospital for asthma during the previous year, had an AE during the previous 3 months or more than 2 AEs during the previous year, and had a history of life-threatening AEs that required intubation or mechanical ventilation or that resulted in a hypoxic seizure.[8]

Source of data

Disease outcomes and probabilities. Clinical outcomes associated with the use of either of the 2 strategies, namely, the probability of a first AE that required treatment with prednisone and the probability of a second AE that required treatment with prednisone, were extracted from the above-mentioned TREXA study.[8]

Resource utilization and costs. Because a third-party payer perspective was used for the CEA, direct costs were the only costs considered in the model.

The costs of using bronchodilators with either strategy were not included in the cost analysis, because although albuterol use increased in all participants during the course of the TREXA study, there was no difference in increase between treatment groups. Nevertheless, the cost of using bronchodilators was taken into account in the cost analysis of AEs.

Calculation of the costs of the as-needed use of SABAs plus ICS strategy was based on the estimated use of BDP added to each 2 puffs of albuterol needed for symptom relief, according to the Drug Price Information System,[11] an official database provided by the Colombian Ministry of Health and Social Protection, which constitutes an important and representative primary source of medication prices in the country, and the available concentrations of the medication according to current market research. Because BDP metered dose inhaler (MDI) canisters are not transferable or reusable between patients, the cost of MDI delivery of BDP was calculated by using the cost of 1 MDI canister per patient.

Direct medical costs of pediatric AEs (unit costs and resource utilization data) were obtained from a recent study aimed at evaluating the direct medical costs associated with pediatric acute asthma in Bogota, Colombia.[12] Only costs for patients admitted to the emergency department (ED) were considered in this study, because the model assumed that all patients having an AE required only ED attendance. This assumption was made because the primary outcome of the TREXA study was the time to first exacerbation that required treatment with prednisone without a specific mention of the setting of the attendance and because in Colombia, as well as in other LMICs, unscheduled health care visits for pediatric asthma almost always occur in the ED setting.[13] In addition, a recent

TABLE II. Base-case cost-effectiveness analysis of the as-needed use of SABAs alone versus the as-needed use of SABAs plus ICS in children 5 to 11 years old with mild intermittent (step 1) asthma

All patients

Category	Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness (avoidance of asthma exacerbation)	Incremental effectiveness (avoidance of asthma exacerbation)	Cost-effectiveness
Undominated	SABAs + ICS	17.99	–	0.6500	–	27.67
Absolutely dominated	SABAs alone	27.94	9.95	0.5100	−0.1400	54.77

ICS, Inhaled corticosteroids; *SABAs*, short-acting β_2-agonists.

TABLE III. Parameter distributions used in the probabilistic sensitivity analysis

Probability distribution	Distribution parameters	Distribution parameters
Beta distribution	**Alpha**	**Beta**
Probability of a first AE that required treatment with prednisone with SABAs alone	33.52417	34.8925
Probability of a first AE that required treatment with prednisone with SABAs + ICS	23.73318	44.0759
Probability of a second AE that required treatment with prednisone with SABAs alone	16.0632	53.7768
Probability of a second AE that required treatment with prednisone with SABAs + ICS	6.173817	66.45932
Gamma distribution	**Alpha**	**Lambda**
Cost of BDP MDI × 50 mcg	14.78	5.39
Cost of Pred tablets × 5 mg	0.64	19.04
Cost of ED AE	13.03	0.34

AE, Asthma exacerbation; *BDP*, beclomethasone dipropionate; *ED*, emergency department; *ICS*, inhaled corticosteroids; *MDI*, metered dose inhaler; *SABAs*, short-acting β_2-agonists.

Cochrane systematic review with meta-analysis concluded that there is currently no evidence from randomized trials to inform the use of patient- or parent-initiated oral corticosteroids in people with asthma.[14]

Specifically, the costs of medications (albuterol, prednisone), as well as other consumables (fluids, supplies, and oxygen treatment), medical and therapy services (including respiratory therapy), diagnostics tests and procedures (white blood cell count, C-reactive protein, and chest X-ray studies), and hotel services (hospital stay), when appropriate, were included.[12]

All calculated costs were as close to reimbursement or true costs as possible (Table I). Costs were calculated in Colombian pesos (COPs) and converted to dollars (US$) based on the average exchange rate for 2018 (1 US$ 2000.68 COPs).[15] All the costs were adjusted to 2018 COPs before converting them to US$. The study protocol was approved by the local ethics board.

Sensitivity analyses

To assess the robustness of the model, 1-, 2-, and multiway deterministic sensitivity analyses were performed using plausible variations in key model parameters. Values used in the deterministic sensitivity analyses were based on plausible ranges, including 95% confidence intervals when available. In addition, a probabilistic sensitivity analysis (PSA) using a second-order Monte Carlo simulation with 10,000 iterations (assigning uncertainty distributions to input parameters in the model and sampling a random value from each distribution simultaneously) was used to deal with parameter uncertainty. On the basis of the PSA results, we calculated 95% uncertainty intervals (UI) for costs and effects and generated a cost-effectiveness plane (to show the estimated joint distribution of incremental costs vs incremental effects). All analyses were performed using TreeAgePro 2016 software (TreeAge Software, Williamstown, Mass).

RESULTS

Baseline and range values of parameters included in the model

Baseline and high and low values of each key variable included in the model, including unit costs of resources, costs of medications, the probability of a first AE that required treatment with prednisone, and the probability of a second AE that required treatment with prednisone, along with their respective sources, are shown in Table I.

Base-case analysis

The base-case analysis showed that compared with the use of SABAs alone, the as-needed use of SABAs plus ICS was associated with lower overall treatment costs (US$17.99 vs US$27.94 mean cost per patient) and a higher probability of a lack of a requirement for a first course of prednisone for AE (0.6500 vs 0.5100), thus showing dominance. A position of dominance negates the need to calculate an incremental cost-effectiveness ratio (Table II).

Sensitivity analyses

In the deterministic sensitivity analyses, our base-case results were robust to variations of all assumptions and parameters. Parameter distributions used in the PSA are shown in Table III. Beta distribution was used to model probabilities, and gamma distribution was used to model costs. The results of the PSA are graphically represented as a scatter plot in Figure 2. This scatter plot shows that compared with the use of SABAs alone, the as-needed use of SABAs plus ICS tends to be associated with lower costs and higher probability of a lack of a requirement for a first course of prednisone for AE. Based on the results from this simulation, the 95% UI for cost per patient treated with SABAs alone and with a combination of SABAs and ICS were US$13.98 to $46.58 and US$9.24 to $30.18, respectively. The 95% UI for the avoidance of hospitalization were 0.3954 to 0.6248 and 0.5331 to 0.7562, respectively. In 95.2% of the iterations, treatment with a combination of SABAs and ICS was associated with a higher probability of a lack of a requirement for a first course of prednisone for AE and lower costs compared with treatment with SABAs alone.

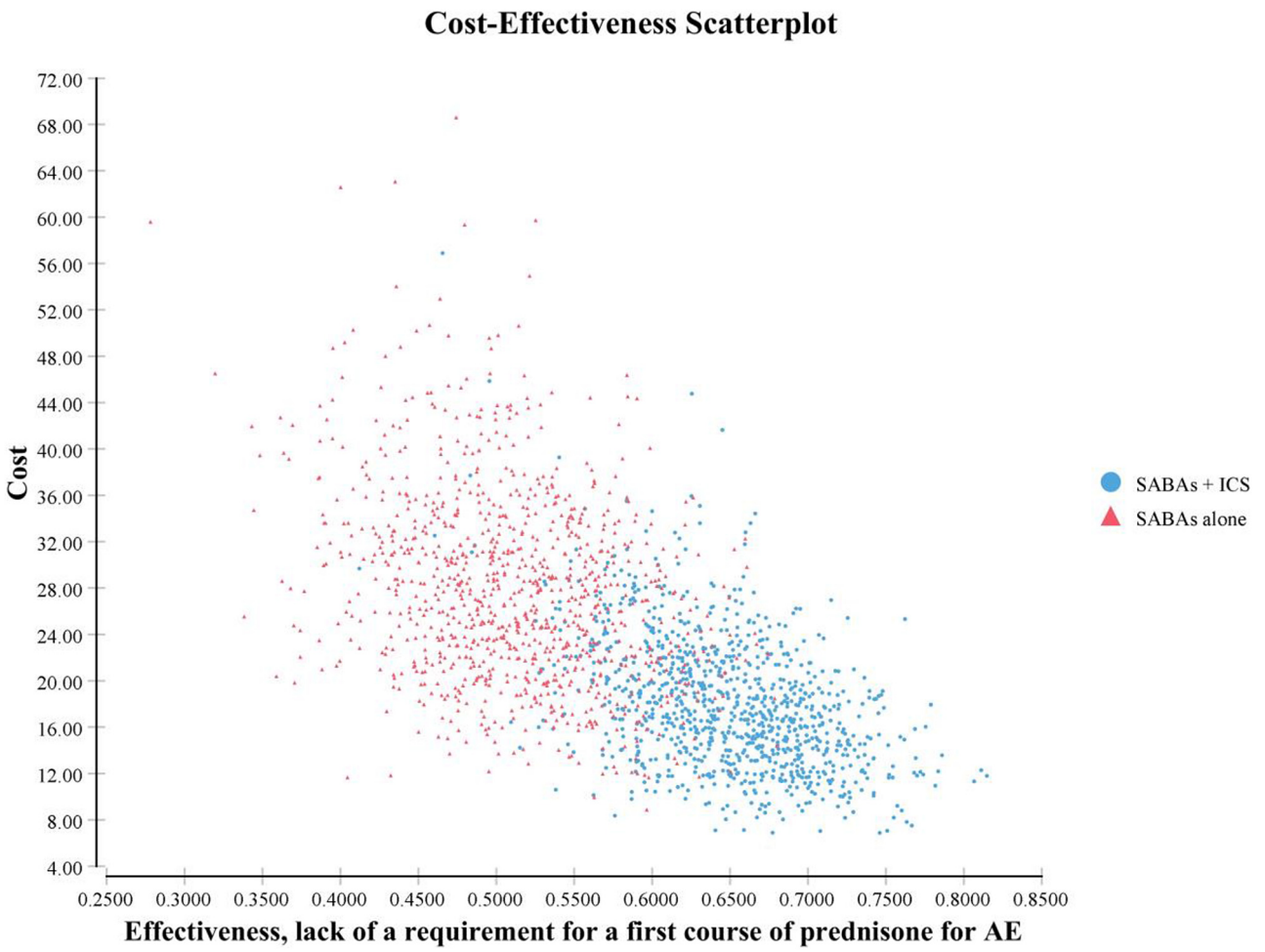

FIGURE 2. Scatter plot of each iteration's cost and effectiveness values for each strategy in pediatric mild intermittent asthma. The *X*-axis shows the effectiveness, measured as lack of a requirement for a first course of prednisone for AE; the *Y*-axis shows the costs measured in dollars (US$, 2018). Each point represents one of the 10,000 trial runs, where each input was assigned a random value according to its probability density function. *AE*, Asthma exacerbation; *ICS*, inhaled corticosteroids; *SABAs*, short-acting β_2-agonists.

DISCUSSION

The present study shows that in Colombia, an LMIC, compared with the use of albuterol alone, the use of BDP added to albuterol as needed for symptom relief is cost-effective in children 5 to 11 years old with mild intermittent (step 1) asthma, because it involves a higher probability of a lack of a requirement for a first course of prednisone for AE at lower total treatment costs. The base-case results were robust to variations of all assumptions and parameters. In addition, the PSA showed that there is a more than 95% probability that therapy with a combination of albuterol and BDP is more cost-effective than therapy with albuterol alone.

These results offer crucial evidence supporting the recommendation of the GINA asthma guidelines 2021 on the management of children 5 to 11 years old with mild intermittent asthma to allow the use of ICS whenever SABA is taken (in combination or separate inhalers) as a valid option.[2] The use of BDP added to albuterol as needed for symptom relief could help to ensure more efficient management of asthma in children 5 to 11 years old with mild intermittent asthma. Although demonstrating the cost-effectiveness of an intervention for treating asthma in pediatric patients is certainly important, it is even more so in LMICs, given the greater clinical and economic burden of the pediatric asthma in LMICs when compared with high-income countries.

Although the present analysis is based on the TREXA study, in which ICS were given whenever albuterol was needed in children with mild persistent asthma as a step-down strategy for children whose asthma is well controlled with low-dose ICS as monotherapy, demonstrating that the cost-effectiveness of this treatment strategy could help to promote its use in all pediatric patients with mild asthma (although this would need to be further supported by a body of clinical evidence). This is because the results of the present analysis provide evidence for the efficiency of the use of ICS as an "anti-inflammatory reliever"[16] during times of acute illness in school children, an age at which exacerbations play a major part in asthma morbidity.[17] The reason for this is that in addition to the well-known anti-inflammatory effects of ICS carried out through 3 genomically independent mechanisms by binding to a cytoplasmic

glucocorticoid receptor, ICS cause immediate local bronchial mucosal vasoconstriction and inhibition of edema formation mediated by nongenomic mechanisms.[18,19]

It is worth mentioning that the use of ICS as an "anti-inflammatory reliever" could help to deal with the many challenges in the current treatment of asthma in children, which often lead to poor disease control.[7] These challenges include the learned overuse or over-reliance on SABAs and underuse of ICS, which typically occurs in patients with poor adherence to ICS therapy; parents' and caregivers' safety concerns regarding regular use of ICS; the long-standing recommendation in the initial phase of the stepwise asthma management to use SABA alone on an as-needed basis during times of acute illness instead of an anti-inflammatory medication such as an ICS, despite evidence showing the presence of underlying airway inflammation of asthma even in patients with infrequent or recent-onset asthma symptoms; the highly variable activity level of pediatric asthma; the adjustments in medications occurring after a review of symptoms in a previous period of time rather than from the first onset of symptoms;[20] and other factors that have been associated with suboptimal adherence to inhaled controller therapy, such as the typical episodic nature of pediatric asthma, a lack of perceived necessity (especially in patients with infrequent symptoms), and perceived and actual side effects.[7]

The results of the present study are in good agreement with previously published studies in the literature reporting not only the efficacy but also the cost-effectiveness of the use of ICS on an intermittent or as-needed basis.[9,10,21-29] The use of ICS on an intermittent or as-needed basis does not refer to a single strategy, but rather includes heterogeneous strategies with different criteria for initiating ICS therapy (at the first sign of an upper respiratory tract infection, when signs and symptoms of an AE are already evident, or when a SABA is needed), with or without ICS use during stable periods of the disease. These strategies have been given various names in the literature: "symptom-driven," "symptom-based," "on demand," and "rescue treatment."[9,10,21-30]

We are aware that our research may have at least 4 limitations. First, cost data were obtained from a single clinical center and may not be representative of the whole country. However, these data were obtained from a pediatric clinic that receives patients from the most representative medical insurance companies in the city. Moreover, costs were subjected to wide sensitivity analyses. Second, the model assumed that all patients having an AE required only ED attendance. However, we consider that this is a conservative approach, because the exclusion of costs of attendance in the pediatric ward, in the pediatric intermediate care unit, and in the pediatric intensive care unit may be biased against the SABAs plus ICS strategy, and their inclusion would be likely to further increase the difference in costs between the 2 treatment strategies. Third, although we could have used economic modeling techniques to extend the analysis beyond the length of time of the TREXA study, we considered that using a time horizon of 6 months it was possible to assess the most important clinical events and costs of each of the 2 therapeutic strategies without unrealistically simplifying the assumptions. Finally, although it would be interesting to analyze the number of AEs that occur during a certain fixed period of time with each of the 2 strategies, in the present study we modeled only the first 2 exacerbations that occurred after the start of therapies. This is because we judged that the first 2 exacerbations, as evaluated in the TREXA study, are enough to determine the major health and economic consequences of the 2 strategies analyzed.

In conclusion, the results of the present analysis show that in Colombia, an LMIC, compared with the use of albuterol alone, the use of BDP added to albuterol as needed for symptom relief is cost-effective in children 5 to 11 years old with mild intermittent asthma, because it involves a higher probability of a lack of a requirement for a first course of prednisone for AE at lower total treatment costs. These results give support to the recommendation of the GINA asthma guidelines 2021 for the management of children 5 to 11 years old with mild intermittent asthma to allow the use of ICS whenever SABA is taken (in combination or in separate inhalers) as an efficient option.

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