Optimizing Asthma Management in Pediatric Patients:
Daily vs. Intermittent Inhaled Corticosteroids

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Background

Asthma represents a significant public health challenge globally as it exerts a substantial economic pressure on healthcare systems and societies as one of the most prevalent chronic respiratory diseases worldwide. Healthcare costs associated with asthma management encompass everything from direct medical expenditures to indirect costs related to lost productivity and diminished quality of life for patients. These costs are largely in part due to the fact that asthma remains a complex and challenging condition to treat effectively, despite advancements in pharmacological treatments and the dissemination of clinical guidelines for diagnosis and management, especially in developing nations.[1]

In Colombia, asthma prevalence among school-age children is of particular concern. A study conducted in six Colombian cities found asthma symptoms among 12% of children within a 5-year time frame.[2] This indicates a significant escalation in childhood asthma burden, amplifying the urgency for effective interventions and healthcare strategies to mitigate its impact on both individuals and the healthcare system.

Treatment Options

Currently, inhaled corticosteroids (ICS) are considered the cornerstone of anti-inflammatory therapy for asthma, worldwide, showcasing efficacy in reducing symptom severity, emergency department visits, and hospitalizations related to disease exacerbations. Despite the well-established benefits of continuous ICS treatment for asthma, various factors contribute to its intermittent use. Most common is a "steroid phobia" among patients and physicians, driven by concerns about systemic effects. Along the same lines, intermittent ICS usage is also seen as a strategy to reduce cumulative corticosteroid exposure and minimize adverse events. Furthermore, inadequate asthma education often leads to the perception of asthma as an episodic disease managed only during symptomatic periods, promoting intermittent rather than continuous treatment. Moreover, the rapid anti-inflammatory action of ICS, coupled with challenges in adherence to daily inhalers, has led to consideration of intermittent ICS as an alternative strategy. Lastly, the high cost and limited availability of essential asthma medications in low- and middle-income countries pose significant barriers to daily use.[3]

These factors have prompted the development of an approach involving intermittent ICS treatment alongside short-acting beta2 agonists.[4,5] As mentioned above, daily ICS aims for consistent control of airway inflammation, helping reduce symptoms, exacerbation risk, and long-term complications.[6] It offers stable disease control and may prevent the progression of asthma, potentially improving long-term outcomes. In contrast, intermittent therapy relies on using ICS only as needed, which may lead to an increased risk of exacerbations during

asymptomatic periods. [7] While intermittent therapy minimizes corticosteroid exposure, it may not adequately manage inflammation and allow the disease to worsen over time.

Taking into account the seemingly conflicting views between medical and patients on the benefits of the two approaches, it is a fruitful task to evaluate which therapy is optimal. Through a series of simulations that partially replicate "Cost-utility analysis of daily versus intermittent inhaled corticosteroids in mild-persistent asthma", we aim to conduct a preliminary assessment of the optimal ICS treatment strategy for asthma - daily or intermittent among school-age children. [8]

The Model

Asthma exhibits a fluctuating pattern of symptom severity, with patients transitioning between states of adequate control and symptomatic periods that do not necessitate healthcare intervention. This dynamic nature of the disease lends itself well to modeling using discrete health states, such as those defined in a Markov framework (Figure 1). [9]

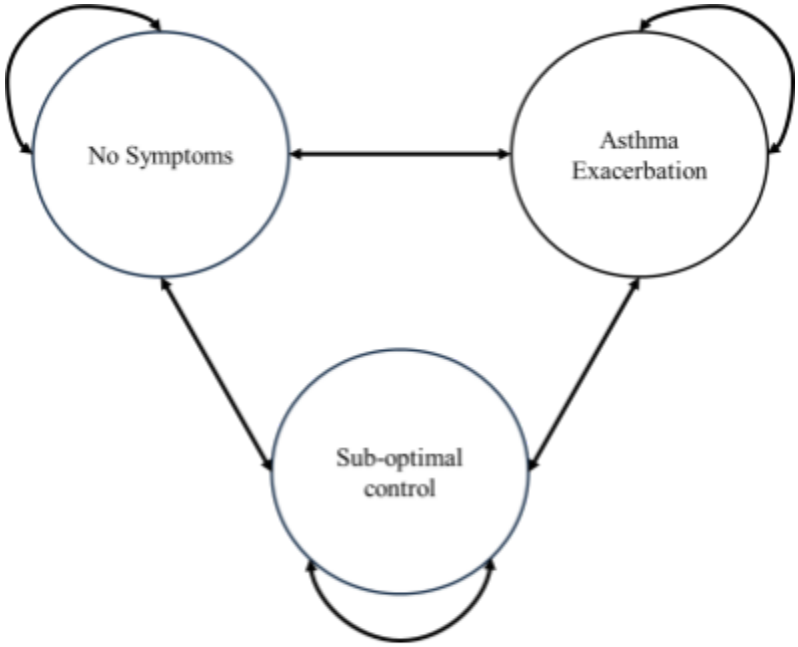

Figure 1: Markov Model with Each Health State

Patients often experience periods of relative wellness between attacks or manage mild symptoms independently. However, asthma exacerbations, particularly those necessitating hospitalization, pose significant clinical and economic burdens. These exacerbations incur substantial healthcare costs and indicate poor disease control, impacting patients' quality of life beyond the acute event itself. [9]

Taking all of this into account, the simulation model used contained the following health states:

1. No Symptoms: This state reflects optimal asthma control according to predefined criteria, based on the Global Initiative for Asthma (GINA) guidelines. It encompasses periods without nighttime waking due to asthma, no emergency hospital visits, absence of exacerbations, minimal rescue bronchodilator use, and normal peak expiratory flow (PEF) values.
2. Asthma Exacerbation: In this state, patients experience asthma exacerbations necessitating either primary-care or hospital treatment. The exacerbation management may occur entirely in outpatient settings, the emergency room or require inpatient care, depending on the severity of symptoms.
3. Sub-Optimal Control: Individuals in this state experience asthma symptoms below acceptable levels of control, yet not severe enough to warrant immediate healthcare intervention. Despite experiencing symptoms, they do not meet the criteria for exacerbations or require emergency care.

Determining the length of each cycle in a Markov model is crucial for accurately capturing the progression of a disease. Asthma's nature requires shorter cycles to reflect changes in a patient's condition over time. A weekly cycle was chosen for this model because longer cycles might miss important changes occurring within a week, while shorter cycles might not capture the full duration of severe exacerbations. In other words, a weekly cycle allows for a thorough assessment of treatment effectiveness and disease management outcomes, ensuring that important events within the week are captured.[8, 9]

In conducting the analysis, certain simplifying assumptions were made:

- 52-week period: The analysis only covered a 52 week (1-year) period instead of a lifetime, as this was deemed sufficient to assess the major health and economic impacts of using inhaled corticosteroids in pediatric asthma treatment based on previous studies.[10, 11]
- Mutually Exclusive Health States: The model assumes that individuals can only occupy one health state at a time. This simplification allows for clear delineation between different states, such as "no symptoms," "suboptimal control, no exacerbation," and "asthma exacerbation."
- No Treatment Adherence Variability: The model does not explicitly incorporate variability in treatment adherence over time. Issues of incomplete or failing adherence to therapy were not considered as denoted by the absence of an absorption state.
- Homogeneous Patient Population: The model assumes a homogeneous patient population in terms of disease severity, treatment response, and resource utilization. In reality, patients may exhibit variability in these factors, which could impact outcomes.
- No Discounting of Costs and Effects: The model does not discount costs and effects over time as the simulation length was 52 weeks.
- Linear Relationship Between Resource Utilization and Health States: The model assumes a linear relationship between resource utilization and health states. For example, the cost

of asthma exacerbation is assumed to be proportional to the severity of the exacerbation, without considering potential nonlinearities.

- Constant Transition Probabilities: The model assumes constant transition probabilities between health states over time. This assumption may not capture changes in transition probabilities due to factors such as disease progression or changes in treatment efficacy.
- Homogeneous Treatment Effects: The model assumes homogeneous treatment effects across all patients. It does not explicitly account for variability in treatment response based on individual characteristics or comorbidities.

Model Sources and Validation

Transition probabilities between the three health states were derived from data obtained through systematic reviews of published randomized clinical trials (RCTs), ensuring a robust foundation for the model. Furthermore, health outcomes were assessed using health utilities or quality-adjusted life-years (QALYs), offering a comprehensive measure of disease burden that considers both quality and quantity of life lived. The model also integrated cost data from the perspective of the national healthcare system, providing insights into the economic implications of different therapeutic strategies. Sensitivity analyses were conducted to evaluate the robustness of the findings, considering uncertainties in parameter estimates and alternative model specifications. [9]

The data collection stemmed from a systematic review of published randomized clinical trials (RCTs). Through extensive searches of databases like MEDLINE, EMBASE, and CENTRAL, alongside published literature, the authors identified potential studies. This approach led to 185 citations, of which 33 studies underwent full-text examination. For inclusion, studies had to: (a) be randomized control trials of parallel-group design, involving patients under 18 years old with recurrent wheezing or mild persistent asthma and (b) compare daily versus intermittent ICS, initiated only during exacerbations, and report at least one of the following outcomes: percentage of symptom-free days or probability of asthma exacerbation during the observation period.[4, 5, 7, 12] Based on this criteria, data from four publications was utilized consisting of a total of 259 school children.

Using the four publications, transition probabilities were computed. To calculate transition probabilities from the "sub-optimal control, no exacerbation" to "asthma exacerbation" states, for each treatment option, a weighted average of the probability of "time to first exacerbation" based on Kaplan–Meier curves was determined. For "sub-optimal control, no exacerbation" to the "no symptoms" state, a weighted average of "symptom-free days" was calculated. Transition probabilities from "no symptoms" to both "no symptoms" and "asthma exacerbation" states were computed based on the probability of "symptom-free days" and "time to first exacerbation," respectively, in patients with more than 80 percent of symptom-free days in the included studies. Transition probabilities from "asthma exacerbation" to "no symptoms" states were used from a previous model developed by the study authors.[8] To calculate transition probabilities from

"asthma exacerbation" to "asthma exacerbation" states, values were assumed to be 10% greater than transition probabilities from "sub-optimal control, no exacerbation" to "asthma exacerbation" states for each alternative. Finally, to complete the transitional probability matrix, the difference of one minus the sum of the probabilities in the same row was calculated, ensuring the sum of probabilities for each row equaled one.[8]

Adjustments were made for studies with different time frames by calculating 1-week probabilities of the events based on instantaneous rates derived for these events.

Utility values for the three health states included in the model were based on a utility valuation survey of 76 parents of children (28 preschool children) with asthma in Colombia using a standard gambling methodology. Parents were chosen as respondents on the basis that many children with asthma would be too young to provide reliable responses.[13]

Each health state in the Markov model was associated with a specific cost, assessed from the perspective of the national healthcare system in Colombia. Unit costs of medications were sourced from the Drug Price Information System (SISMED, 2011), [14,] an official database provided by the Colombian Ministry of Health and Social Protection.

To determine costs attributed to daily and intermittent ICS therapy, the authors utilized the costs of beclomethasone dipropionate (BDP), considering it was the ICS used in two of the four included studies, and that all ICS at equipotent doses generally provide a similar level of asthma control. Utilization rates of health resources and events for each health state were determined through literature review, expert consensus, and administrative data from care providers. Costs were calculated in Colombian pesos (COP) and converted to US dollars (US$) based on the average exchange rate for 2011.[5, 7]

Cost-Effectiveness Using Baseline Model

A baseline model was established using the transition probabilities in Table 1 as well as health costs in Table 2. Health states corresponding to “no symptoms,” “sub-optimal control, no exacerbation,” and “asthma exacerbation” had utility values of 0.989, 0.705, and 0.275. A population size of 10,000 was used with 52 week length simulation length and an alpha of 0.05. As mentioned earlier, no discounting to health costs was done due to a 52 week or 1-year simulation length.

Table 1. Transition Probabilities for Pediatric Patients with Recurrent Wheezing and Mild Persistent Asthma Treated with Daily and Intermittent Inhaled Corticosteroids

Transition from	**Transition to:**

	No symptoms	Sub-optimal control, no exacerbation	Asthma exacerbation
No symptoms			
Daily therapy	0.933	0.058	0.009
Intermittent therapy	0.858	0.132	0.010
Sub-optimal control, no exacerbation			
Daily therapy	0.887	0.097	0.016
Intermittent therapy	0.817	0.16	0.023
Asthma exacerbation			
Daily therapy	0.255	0.733	0.012
Intermittent therapy	0.105	0.878	0.017

Table 2. Resource Use and Costs Associated with Model Health States (US$, 2011)

Health state	**Resources costed**[8]	**Weekly cost per patient**	**Weekly cost per patient**
		Daily ICS	**Intermittent ICS**
No symptoms	GPa consultation, pediatrician consultation, spirometry, BDPb via pMDIc × 250 mcg	2.51	2.11

Sub-optimal control, no exacerbation	GP consultation, pediatrician consultation, spirometry, albuterol via pMDI, BDP via pMDI × 250 mcg	33.23	32.83
Asthma exacerbation	GP consultation, pediatrician consultation, spirometry, albuterol via pMDI, treatment in the EDd, hospitalization for asthma exacerbation, prednisolone × 5 mg, others (radiology procedures, laboratory tests, ambulance), BDP via pMDI × 250 mcg	397.40	397.40

a GP consultation, consultation with general practitioners.
b BDP, beclomethasone dipropionate.
c pMDI, pressurized metered-dose inhaler.
d ED, emergency department.

The model showed that compared to intermittent ICS, daily therapy with ICS had lower costs (US$433 vs. 585 average cost per patient over 12 months) and utilities (0.9632 vs 0.9398 average utility per patient). These results were in line with the results from the original paper (Table 4).

Table 4. Baseline Cost-Utility Analysis of Daily Therapy vs. Intermittent Therapy with Inhaled Corticosteroids for Pediatric Patients with Recurrent Wheezing and Mild Persistent Asthma

Category	Strategy	Cost (US$)	Incremental cost	Utility	Incremental utility	Cost/utility
A. Original Paper[8]						
Undominated	Daily ICS	437.02	—	0.9629	—	453.86
Absolutely dominated	Intermittent ICS	585.03	148.01	0.9392	−0.0237	622.90
B.Our Model						
Undominated	Daily ICS	433	—	0.9632	—	449.51

Absolutely dominated	Intermitte nt ICS	585	152	0.939 8	−0.0234	622.47

Due to the daily therapy dominating and a relatively small sample size, the incremental effect and ICER were not calculated. This is further supported by the Cost-Benefit Analysis plot (Figure 2) which shows that as Willingness to Pay per QALYs increases, marginal net monetary benefit consistently decreases for intermittent therapy while stays constant for daily therapy. This signals that at no price is intermittent therapy worth paying for based on health utilities. The Cost-Effectiveness plot (Figure 3) also underscores this conclusion as the intermittent therapy has a negative gain in QALYs for a higher price compared to daily therapy.

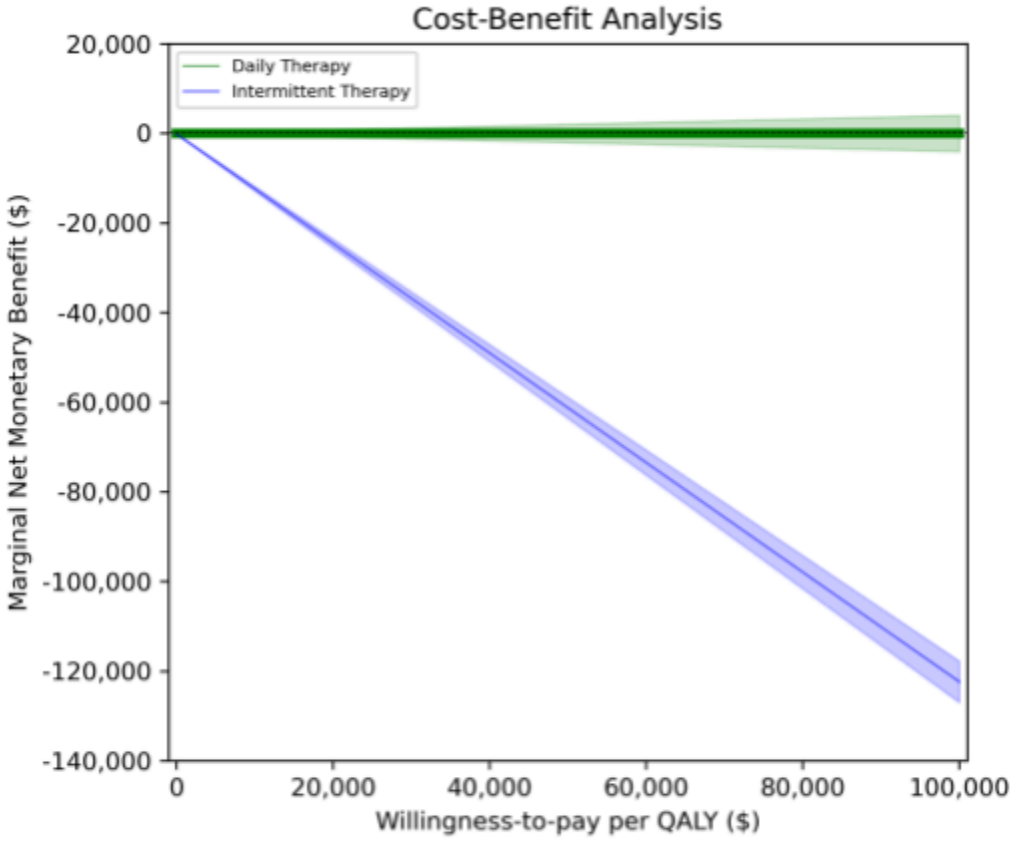

Figure 2: Baseline Cost-Benefit Analysis Plot

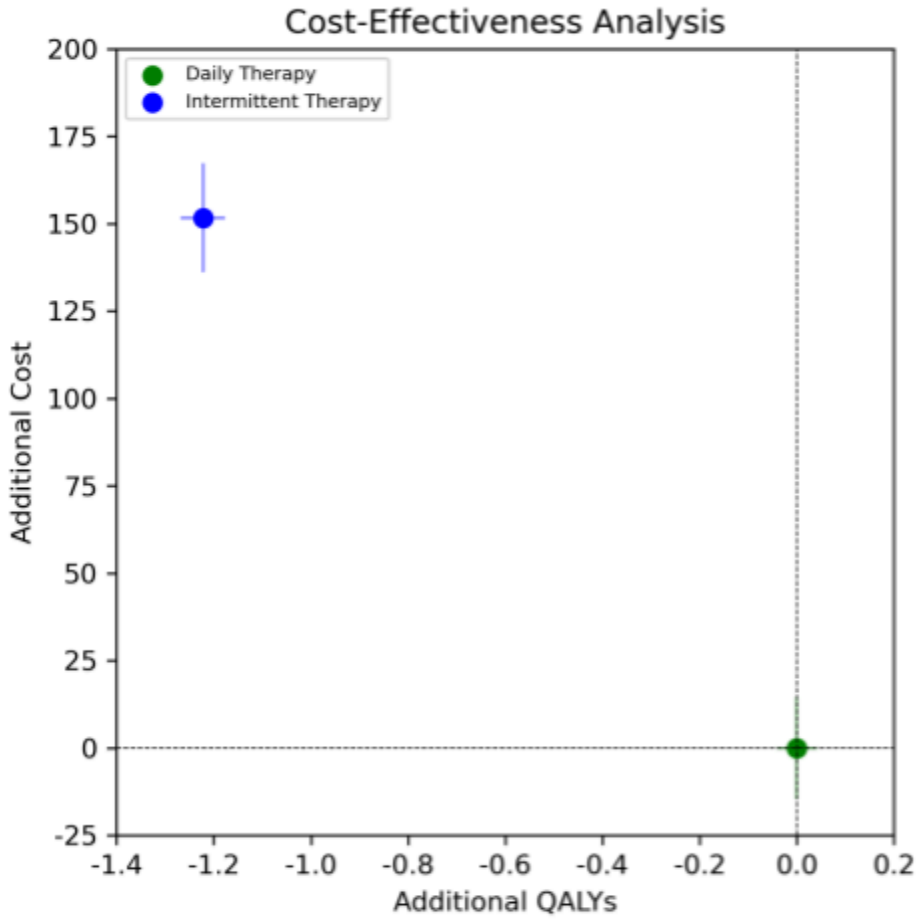

Figure 3: Baseline Cost Effectiveness Analysis Plot

Sensitivity Analysis

In the original study, 10,000 cohorts with an unspecified sample size were used to analyze parameter uncertainty and to demonstrate the sensitivity of the conclusions to the key model parameters and/or assumptions.In our analyses, we only used 1000 cohorts due to computational limitations. Additionally, we used a sample size of 259, in line with the original sample size from the literature search used to calculate transition probabilities and health costs and utilities. Parameter distributions used were taken from the original study (Table 5).

Table 5. Parameter Distributions used in the Probabilistic Sensitivity Analysis

Probability distribution	**Distribution parameters**	**Distribution parameters**
Beta distribution	**Alpha**	**Beta**

Probability from no symptoms to no symptoms		
Daily ICS	106.106	7.607
Intermittent ICS	226.582	37.545
Probability from no symptoms to asthma exacerbation		
Daily ICS	396.254	42029.30
Intermittent ICS	395.869	38038.08
Probability from sub-optimal control, no exacerbation to no symptoms		
Daily ICS	44.313	5.645
Intermittent ICS	72.383	16.213
Probability from sub-optimal control, no exacerbation to asthma exacerbation		
Daily ICS	393.584	24205.42
Intermittent ICS	390.777	16599.53
Probability from asthma exacerbation to no symptoms		
Daily ICS	297.745	869.882
Intermittent ICS	357.895	3050.629
Probability from asthma exacerbation to asthma exacerbation		
Daily ICS	395.148	32261.70

Intermittent ICS	392.942	21933.33
Utilities		
No symptoms state	3.411	0.038
Sub-optimal control, no exacerbation state	117.295	49.081
Asthma exacerbation state	289.725	763.820
Gamma distribution	**Alpha**	**Lambda**
Cost of no symptoms state	44.444	21.063
Cost of sub-optimal control, no exacerbation state	44.444	1.353
Cost of weekly use of daily ICS	25.60	64.0
Lognormal distribution	**Mean for ln(x)**	**SD for ln(x)**
Cost of asthma exacerbation	5.477	1.006

In line with the baseline model, and the original study, sensitivity analysis shows that daily therapy tends to be associated with lower costs (Figure 4). The 95% confidence intervals for cost per patient treated with daily and intermittent therapy were US$1,196.67 to 1,924.06 and US$644.76 to 1,117.79, respectively. Likewise, the 95% confidence intervals for utilities were 0.8632- 0.9669, and 0.8494–0.9652, for daily and intermittent therapy respectively. Given that the confidence intervals for the utilities between daily and intermittent therapy with ICS overlap, differences could be due to imprecision of their estimates - something which was also addressed in the original paper.

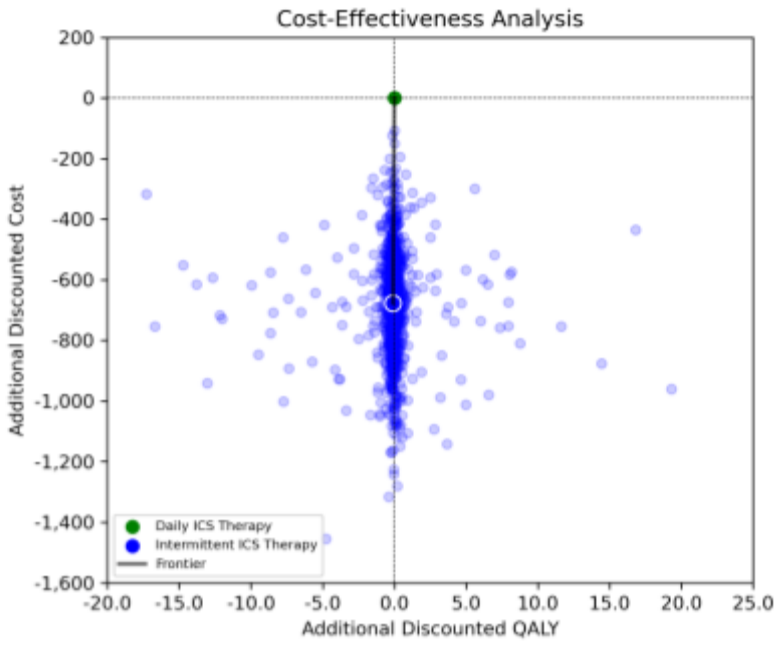

Figure 4: Cost-Effectiveness Analysis across Sensitivity Analysis Cohorts

Our sensitivity analysis showed that the willingness to pay threshold for daily therapy was $5,725.66 (Table 6). Conversely, the original study found that the willingness to pay threshold for daily therapy dominated across all monetary values. This is likely due to the significantly larger simulation size of the original study as our cohort was not even large enough to warrant a 95% confidence interval for the willingness to pay threshold.

Table 6. Sensitivity Analysis Cost-Utility Analysis of Daily Therapy vs. Intermittent Therapy with Inhaled Corticosteroids for Pediatric Patients with Recurrent Wheezing and Mild Persistent Asthma

Strategy	**Cost**	**Effect**	**Incremental Cost**	**Incremental Effect**	**ICER**
Intermittent ICS Therapy	$861 (645, 1,118)	0.9411 (0.8494, 0.9652)	–	–	–
Daily ICS Therapy	$1,537 (1,197, 1,924)	0.9435 (0.8632, 0.9669	$677 (321, 1,051)	0.002 (-0.0138, -0.0017)	$5,725.66 (nan, nan)

Conclusion

The escalating prevalence of asthma symptoms among children underscores the urgent need for effective interventions and healthcare strategies, especially in developing countries like Colombia. Inhaled corticosteroids (ICS) represent a cornerstone of asthma management, offering benefits in symptom control and reducing the risk of exacerbations.

The simulation model developed in this study aimed to assess the optimal ICS treatment strategy for pediatric asthma in Colombia, comparing daily versus intermittent therapy by replicating an existing study. Through comprehensive analyses, we found that daily therapy with ICS tends to be associated with lower costs and higher utilities compared to intermittent therapy, aligning with findings from the original study. Sensitivity analyses further supported these conclusions, highlighting the robustness of the findings despite limitations in sample size and computational constraints.

In interpreting these findings, it is important to acknowledge certain limitations inherent in the model. The assumptions made regarding treatment adherence variability, homogeneous patient populations, and constant transition probabilities may not fully capture the complexity of real-world clinical scenarios. Additionally, the use of a 1-year simulation period and the absence of discounting may limit the model's applicability to long-term health and economic evaluations.

Despite these limitations, the study provides valuable insights into the comparative effectiveness and cost-effectiveness of daily versus intermittent ICS therapy in pediatric asthma management, serving as a foundation for future research and policy decision-making in this critical healthcare domain.

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