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Cost-utility of use of sputum eosinophil counts to guide management in children with asthma

Jefferson Antonio Buendía, MD, MSc, PhD^a  and Hernan Lucio Talamoni, MD^b

^aDepartment of Pharmacology and Toxicology, School of Medicine, Research Group in Pharmacology and Toxicology (INFARTO), Universidad de Antioquia, Medellín, Colombia; ^bDepartamento de Clínica Pediátrica, Sección de Neumonología Pediátrica, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

ABSTRACT

Background: Tailoring asthma interventions based on sputum eosinophils are beneficial in reducing the frequency of asthma exacerbations. The routine use of sputum eosinophils in asthma in children is not uniformly adopted. The main barriers to policymakers adopting new technologies are always doubts about their cost-utility in scenarios with scarce health resources. This study aimed to evaluate the cost-utility of sputum eosinophil counts to guide management in children with asthma, from a societal perspective.

Methods: A Markov simulation with three mutually exclusive nonabsorbent states was used. The intervention evaluated was adjustment of asthma therapy based on sputum eosinophils to adjusting therapy based on clinical symptoms with or without spirometry/peak flow in children between 4 and 18 years of age (EO). The group comparison was adjusting therapy based on clinical symptoms with or without spirometry/peak flow (SC). The analysis was carried out from a societal perspective. The analytic horizon was 12 months

Results: The model showed that EO was associated with lower cost than SC (US \$1375 vs US \$1454 average annual cost per patient), and higher QALYs (0.95 vs 0.92 average per patient); showing dominance. The probability that EO provides a more cost-effective use of resources compared with standard therapy exceeds 99% for all willingness to pay thresholds

Conclusion: EO was cost-effective for infants with asthma to guide asthma management in Children. Our study provides evidence that should be used by decision-makers to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

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Health economics; public health; healthcare

Introduction

Asthma is the most commonly found pulmonary chronic disease in children. A large proportion of patients have inadequate control of their asthma; only 2.4% of patients have complete control of their asthma (1). The international and local clinical guidelines recommend periodic assessment and the early management of airway inflammation (2,3). However, despite inhaled corticosteroids being the mainstay of treatment, the principal limitation of current guidelines is that few direct measures of inflammation are used in routine clinical practices. Eosinophil counts in hypertonic saline-induced sputum from asthma patients are related to those found in bronchial washes (4). Increases in sputum eosinophils were correlated with decreases in airway function, including decreases in

morning PEF and FEV1 (5). Current assessment tools such as clinical control and lung function do not correlate with underlying inflammation (6).

Tailoring asthma interventions based on sputum eosinophils is beneficial in reducing the frequency of asthma exacerbations (OR 0.36, 95% CI 0.21–0.62) (7). Induced sputum is a noninvasive, easy method to obtain sputum. In children, the principal limitation was the reduced quantity of the sputum sample. However, recently, new techniques have been developed to use small sputum sample processing with feasible and reliable (8). A recent study of 33 asthmatic children demonstrated that this procedure was well tolerated, and all sputum samples obtained were sufficient (9).

The routine use of sputum eosinophils in asthma in children is not uniformly adopted. The main

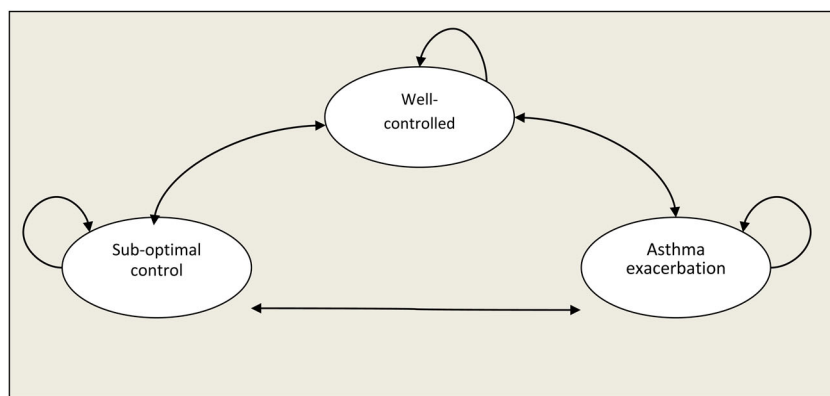


Figure 1. Markov model. Well controlled: Health state only needed daily inhaled corticosteroids and one scheduled medical visit every year. Sub-optimal control: Health state needed salbutamol via pMDI two puffs every 6 h during all the cycle length of 1 week and one unscheduled medical visit every two months. Asthma exacerbation: Health state needed salbutamol via pMDI two puffs every 20 min for the first hour, two puffs every hour for the next 2 h, two puffs every 2 h for the next 6 h, 2 puffs every 4 h for the next 48 h and finally 2 puffs every 6 h for the remainder of the week. Additionally, we assumed that patients in this health state needed prednisolone 1 mg/kg/day for five days.

barriers to policymakers adopting new technologies are always doubts about their efficiency in scenarios with scarce health resources. To our knowledge, no previous article has been published evaluating the cost-effectiveness of this procedure in pediatric asthma. In this paper, we aimed to evaluate the cost-utility of sputum eosinophil counts to guide management of asthma in children from a societal perspective.

Methods

Economic model

A Markov simulation model was used (as is recommended for economic modeling of chronic diseases (10)) with three mutually exclusive nonabsorbent states, and using previously published data (Figure 1). The intervention evaluated in this simulation was adjustment of asthma therapy based on sputum eosinophils to adjusting therapy based on clinical symptoms with or without spirometry/peak flow (EO) in children between 4 and 18 years of age. The group comparison was adjusting therapy based on clinical symptoms with or without spirometry/peak flow without use of sputum eosinophils or other biomarker. For this model, and according to the natural history, three health states were defined: “well controlled,” “suboptimal, control,” and “asthma exacerbation” with a cycle length of 1 week. All patients entering the simulation in the health state “were controlled,” and then, according to the probabilities obtained from the literature, they move to the other states previously declared. The analysis was carried out from a societal perspective (including direct and indirect costs). The

analytic horizon was 12 months. Given the short time horizon, no type of discount to costs or results was applied. The study protocol was reviewed and approved by the Institutional Review Board of University of Antioquia (No 18/2015).

Transition probabilities and utilities

To estimate the transition probabilities between health states and utility values of health and relative risk of reduction of exacerbations using adjustment of asthma therapy based on sputum eosinophils (Table 1), we performed a systematic review of systematic reviews or RCTs published or observational studies up to January 2020. In order to identify potentially relevant studies, we searched computerized databases (MEDLINE, CENTRAL, LILACS, and CINAHL) using the following search strategy: (asthma OR wheeze) and (sputum AND eosinophil) limited to clinical trials, meta-analysis, systematic review and child (birth-18 years). No language restrictions were applied. To be included in the model, studies had to be RCTs of a parallel-group or cross-over design or systematic reviews or economic evaluations or observational studies that included children between 4 and 18 years of age. Others observational studies obtained during the review of references cited in published literature were also included. To include data in the model, participants in the studies needed to comparing the adjustment of asthma medications based on EO versus adjustment of asthma medications based on clinical symptoms; and report at least one of the following outcomes: percentage of hospitalizations, admission in pediatric intensive unit. We excluded studies with

Table 1. Model inputs.

Model input	Base case value	Distribution
Transition probabilities		
W to S	0.09	β (SD: 0.03)
W to A	0.004	β (SD: 0.002)
S to W	0.81	β (SD: 0.03)
S to A	0.00	β (SD: 0.003)
A to W	0.27	β (SD: 0.04)
A to S	0.05	β (SD: 0.04)
Utility		
Well-controlled	0.99	β (SD: 0.01)
Sub-optimal control	0.70	β (SD: 0.07)
Asthma exacerbation	0.31	β (SD: 0.07)
EO effectiveness		
Relative risk of reduction of exacerbations	0.57	LogN(SD: 0.20)

W, well-controlled, S, sub-optimal control, A, asthma exacerbation.

participants with comorbidities/characteristics such as eosinophilic bronchitis, asthma-related underlying lung disease such as bronchiectasis and chronic obstructive pulmonary disease as well as diagnostic categories such as “cough variant asthma” and “wheezy bronchitis.” The searches yielded 561 citations and a total of 8 studies were examined in full (7,9,11–16). After reviewing these 12 studies the information regarding the effectiveness was extracted from a recent Cochrane systematic review with meta-analysis (7). Utilities and transition probabilities of pediatric patients with mild-moderate asthma treated with inhaled corticosteroids as maintenance therapy of the model were extracted from a local previous study that evaluates the cost-utility of inhaled steroids in pediatric asthma within national guidelines for pediatric asthma (3,17) (Table 1). The number of QALYs in each health state was calculated as the utility value, mentioned before, multiplied by length of time spent in that state; which is proportional to the number of people who reach this state in the model after applying the transition probabilities in the decision tree

Cost analysis

We included cost of children aged 4–18 admitted in tertiary centers in Rionegro, Colombia, due to asthma, according to the national clinical guidelines of asthma in children from January 2018 to December 2018 and reported by us in a previous paper (18). Our country has been characterized by having very limited price variation in the last 10 years, especially in health services between different clinics and over time (19). Moreover, the proportions of each of the costs have remained relatively constant with few variations in their composition in the last ten years (19). The municipality of Rionegro has a total population of 101,046 inhabitants and has two tertiary referral

hospitals (20). All costs and use of resources were collected directly from medical invoices and electronic medical records. The direct costs considered in the analysis include medical consultation at the emergency room, specialist referrals, chest physiotherapy, diagnosis support (laboratory, electrocardiogram, x-ray, etc.), medication (oxygen, nebulization, antibiotics, corticosteroids, bronchodilators, etc.), medical devices, hotel services in the intensive care unit, and hotel services in the general medical ward (Table 2).

Sensitivity analyses

To explore parameter uncertainty of the model inputs, a probabilistic sensitivity analysis was conducted by randomly sampling from each of the parameter distributions (beta distribution in the case of relative risk and utilities, Dirichlet distribution for multinomial data in the case of transition probabilities, and gamma distribution in the case of costs). The expected costs and expected QALYs for each treatment strategy were calculated using that combination of parameter values in the model. This process was replicated one thousand times (i.e. second-order Monte Carlo simulation) for each treatment option, resulting in the expected cost-utility. Decision uncertainty is represented in the cost-effectiveness acceptability frontiers, which plot the probable cost-effectiveness over a range of willingness-to-pay threshold values. Net monetary benefit was calculated by multiplying effect by societal willingness to pay and subtracting cost, with willingness to pay set at a 3 three times the Colombian annual GDP per capita ratio (US\$20,000 per QALY) (21). We estimated the expected value of perfect information (EVPI). The EVPI is the maximum value that the health care system would be willing to pay for additional evidence to inform the reimbursement decision in the future. The population expected value of perfect information (PEVPI) was calculated to inform the expected cost of uncertainty (expected opportunity loss surrounding the decision) (22). Microsoft Excel[®] was used in all analyses.

Results

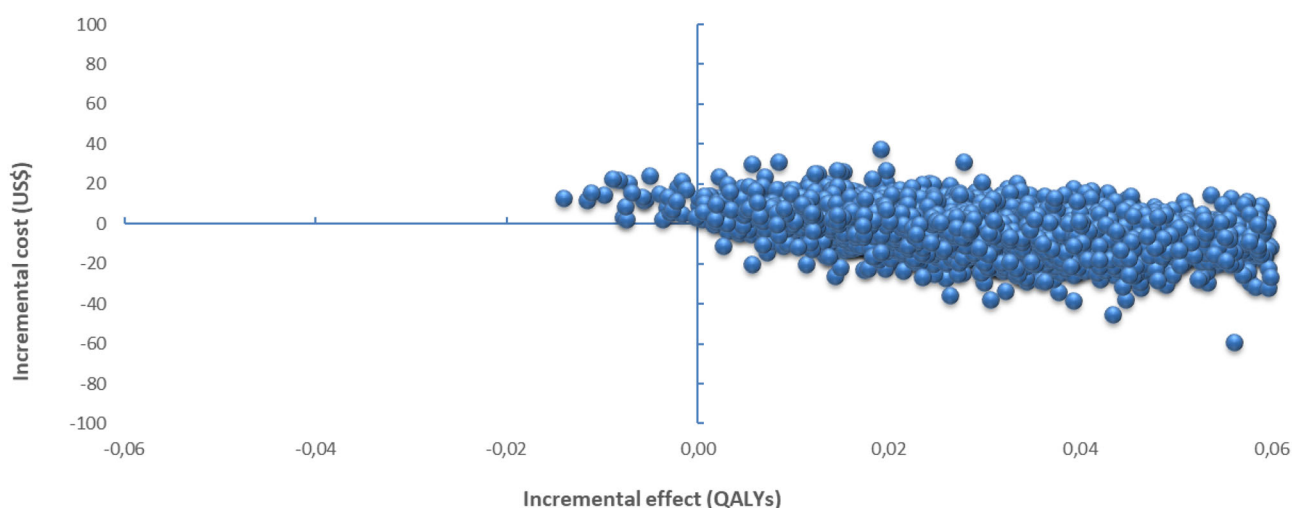
The model showed that EO was associated with a lower total cost than SC (US \$1,375 vs US \$1,454 average annual cost per patient) and higher QALYs (0.95 vs 0.92 average per patient); showing dominance. This position of dominance negates the need to calculate an incremental cost-effectiveness ratio (Table 3).

Table 2. Cost used in base case and sensitivity analyses.

Model input	Base case value	SA range for one-way sensitivity analyses	Distribution
Intervention cost			
EO per patient day	9.14	5.15–13.20	γ (SD:4.09)
Hospitalization cost			
Daily cost in pediatric ward	95.05	80.23–102.01	γ (SD:8.53)
Hospital length of stay (days)	5.50	4.00–8.00	γ (SD:1.04)
PICU related cost			
Daily cost in PICU	406.52	430.26–350.43	γ (SD:18.89)
PICU length of stay (days)	10.9	7.75–15.05	γ (SD:3.26)
Emergency visit prior hospitalization cost			
Daily cost of emergency ward	64.30	51.19–71.46	γ (SD:19.27)
Direct medical cost per patient-day			
Specialist referrals	10.67	10.31–11.01	γ (SD:1.72)
Chest physiotherapy	5.15	4.90–5.39	γ (SD:1.23)
Chest radiography	2.84	2.70–2.98	γ (SD:0.73)
Others diagnostic imaging	0.01	0.0–0.022	γ (SD:0.08)
Complete blood cell counts	1.12	1.05–1.17	γ (SD:0.28)
Other laboratory tests	4.40	4.23–4.47	γ (SD:0.37)
Oxygen	1.37	1.28–1.45	γ (SD:0.41)
Nebulization	16.23	1.28–1.45	γ (SD:4.52)
LEV	1.10	1.07–1.13	γ (SD:0.16)
Antibiotics systemics	1.21	1.11–1.30	γ (SD:0.49)
Systemic of inhaled corticosteroids	0.08	0.0–0.90	γ (SD:4.18)
Bronchodilators	0.04	0.03–0.04	γ (SD:0.02)
Other drugs	0.65	0.60–0.68	γ (SD:0.04)
Medical devices	10.24	9.71–10.76	γ (SD:2.66)
Indirect cost patient-day	17.24	16.38–18.07	γ (SD:4.30)

Table 3. Cost-effectiveness of EO vs SC group.

Strategy	Cost	difference	QUALYs	difference	C/E	Marg C/E
EO used in asthma management	1,375.84		0.95		1446.15	
Standard asthma management	1,454.79	–78.94	0.92	0.28	1575.26	Dominated

**Figure 2.** Cost-effectiveness plane.

Sensitivity analyses

One-way sensitivity analysis showed that the probability of hospitalization has the highest impact on the outcome, but EO was the dominant strategy in all analyzed probability ranges. The results of PSA are graphically represented in the cost-effectiveness plane (Figure 2). 61.97% of simulations were graphed in quadrant 2 (lower cost, high QALYs), and 38.03% in quadrant 1 (high cost, high QALYs). The 95% CI for

the cost per patient treated with EO and with SC were US\$1,374 to 1,377 and US\$1,453 to 1,456 respectively. The 95% CI for QALYs per patient was 0.94 to 0.95 and 0.92 to 0.93 respectively. The net monetary benefits of EO was higher than those of SC (US\$19,001 vs US\$18,442). The expected net benefit with perfect information was US\$19,001 and the expected value of perfect information was US\$0.2901. The cost-effectiveness acceptability curve shows that the probability

that EO provides a more cost-effective use of resources compared with standard therapy exceeds 99% for all willingness-to-pay thresholds. The population expected value of perfect information (PEVPI) for the threshold of US\$20,000 was US\$3,719,778.

Discussion

Our findings suggest that EO achieves better outcomes at a lower cost compared to standard treatment in children with mild to moderate allergic asthma, particularly thanks to reductions in the probabilities of asthma exacerbation and sub-optimal control of the disease, with the consequent increase of patients being well controlled. The magnitude of annual cost savings for the health system (US\$78 per patient) is not negligible if we consider that there are around 11 million children aged under 12 in our country and that this disease affects 10–13% of children in Colombia. Our results constitute a new argument for including the EO in pediatric asthma clinical practice guidelines.

Previous economic evaluations found that the use of EO to guide treatment was more effective and less costly than management using symptoms and spirometry. D'Silva studied 39 adult patients, in Ontario Canada, and compared costs of guide treatment using EO compared to the use of symptoms and spirometry (CS). This study reveals that the cost of the EO method was lower than that of CS (\$2,265 vs \$3,369), and that this cost difference occurred due to the lower cost of hospital visits ($p=0.078$), inhaled short-acting bronchodilators ($p=0.067$) and inhaled corticosteroids ($p=0.064$) (23). Similar results were reported by Kennedy et al., in four Canadian centers, where EO testing had a lower cost per additional correct diagnosis in comparison to specific inhalation challenge (\$3,465 vs \$418), and a higher proportion of correct diagnosis compared to serial peak expiratory flow rate monitoring in occupational asthma (0.72 vs 0.52) (24). Although our study is the first in the pediatric population, it confirms previous findings in the adult population regarding the efficiency of this technique for making decisions in asthma management. One of the principal concerns in the pediatric population relates to safety and ease of sampling. Sputum induction is a relatively noninvasive and safe procedure in children. In a Childhood Asthma Management Program (CAMP) study, Covar et al. found that 90 out of 117 children provided an adequate sputum sample for analysis, all without any adverse event (13). Similar results were found by Lönnkvist and subsequently by Fleming (14,25). In addition, more up-

to-date techniques replace the filtration step of the gold standard technique by micro-centrifugation to reduce salivary and squamous cell contamination, allowing a sample of <100 mg to be used with a mean difference of 0.2% in eosinophil percentage between the two methods; facilitating times and analysis of samples in pediatric patients (8).

Clinical guidelines are inconclusive in terms of recommending EO as a routine method in the current clinical setting (2). However, international and local guidelines' recommendations only included randomized clinical trials in their bibliographic support and no economic evaluations. The complexity of transferring economic evaluations is not unknown, however this situation highlights the need to assess health technologies in clinical guidelines not only by evaluating effectiveness or safety, but also by reviewing economical topics to increase the level of recommendation in clinical guidelines and maximize the benefits for our populations. Our model was robust in changing the values of the model's utilities, probabilities, and costs using one-way and probabilistic sensibility analysis. EO was always the cost-effective strategy in all value ranges of utilities, probabilities, and costs. Furthermore, EO was always the cost-effective strategy in all evaluated ranges of thresholds with a low population EVPI.

Our study has some limitations. The cost data were collected retrospectively. Asthma treatment and costs, including hospital prices, did not markedly change. Furthermore, our country has had little price variation in the last 10 years, especially in the health service sector (19). Additionally, we use utilities extracted from the literature and not assessed directly from our population. The results of this study must be compared with studies that prospectively obtain cost data and directly estimate profits in the target population. As was mentioned previously, the reliability and robustness of the results were evaluated by sensitivity analyses and no changes were found in the conclusions of our evaluation.

In conclusion, EO was cost-effective for infants with moderate or severe asthma to guide asthma management in children. Our study provides evidence that should be used by decision-makers to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

Data availability statement

All data can be request to ciemto@udea.edu.co.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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ORCID

Jefferson Antonio Buendía  <http://orcid.org/0000-0003-2404-6612>

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