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Modeling Asthma Exacerbations Through Lung Function in Children

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Abstract

Background—Formal economic evaluation using a model-based approach is playing an increasingly important role in healthcare decision making.

Objective—To develop a model using an objective measure of lung function, prebronchodilator forced expiratory volume in 1 second as a percent of predicted (FEV₁% predicted), as the primary independent factor to predict the frequency of adverse events related to exacerbation of asthma on a population level.

Methods—We developed a Markov simulation model of childhood asthma using data from the Childhood Asthma Management Program (CAMP). The primary outcomes were the result of asthma exacerbations defined as: hospitalizations, emergency department (ED) visits, and the need for oral corticosteroid therapy. Predicted monthly frequencies for each acute event were based on negative binomial regression equations estimated from the placebo arm of CAMP with covariates of age, prebronchodilator FEV₁% predicted, time in study, prior hospitalizations, and prior nocturnal awakenings.

Results—Simulated versus observed mean number of acute events were similar within the placebo and treatment groups. While the trial demonstrated treatment effects of 48% reduction in hospitalizations, 46% reduction in ED visits, and 44% reduction in the need for oral corticosteroid therapy at 48 months; the model simulated similar reductions of 49% in hospitalizations, 41% in ED visits, and 46% in the need for oral corticosteroid therapy.

Conclusion—Our findings suggest that longitudinal intervention effects may be modeled through FEV₁% predicted to estimate hospitalizations, ED visits, and need for oral corticosteroid therapy in childhood asthma for planning and evaluation purposes.

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Keywords

asthma; pediatric patients; lung function; FEV percent predicted; hospitalizations; emergency department visits; model

INTRODUCTION

Asthma is the most common chronic disease in children.¹ It affects up to 300 million people of all ages in the world and 24.6 million people in the United States, including 9.6% of children.¹ More than half of asthmatics in the United States reported having an asthma attack in the year 2008.² In 2007, 1.75 million emergency department visits, 456,000 hospitalizations, and 3,445 deaths were attributed to asthma.³ The total incremental cost of asthma. Including incremental direct cost and productivity costs) in the United States was estimated to be US\$56 billion in 2007.⁴ This amount represents direct medical costs, such as hospitalizations and pharmaceuticals (\$50 billion), and indirect medical costs (\$6 billion), such as time cost of work and school days lost and productivity due to death.⁴

Formal economic evaluation is playing an increasingly important role in health-care decision making. The importance of formal economic analysis in asthma care is partly a reflection of the burden of the disease in terms of resource costs. Most of the economic evaluations of asthma therapies to date are piggybacked on to randomized clinical trials, many of which have relatively small sample sizes and short time horizons.⁵ Model-based cost-effectiveness analyses use multiple sources of data but rely on assumptions that allow for data integration. Thus, model-based analyses have the benefit of being able to examine long time horizons. Furthermore, model-based analyses can allow predictions without waiting years for costly clinical trials to be completed.

In our prior development of the Asthma Policy Model⁶⁻⁸ we assembled data from a range of observational studies to estimate the functional relationships between prebronchodilator forced expiratory volume in 1 second as a percent of predicted (FEV₁% predicted) – a valid and reliable marker of the degree of airflow obstruction^{9, 10} and disease outcomes such as emergency department (ED) visits. We then used these relationships to predict the effect of a therapy on the decrease in ED visits by using estimates of the percent increase in prebronchodilator FEV₁% predicted associated with therapy. Using surrogate markers of disease to predict disease outcomes associated with alternative interventions is an approach commonly used within a decision-analytic framework.¹¹⁻¹³ While a model-based approach has several advantages over trial-based studies, it demands a careful assessment of the extent to which the underlying assumptions are valid. The Asthma Policy Model has been used to assess several interventions in adults.^{6, 14, 15}

The objective of this study was to conduct analyses of the Childhood Asthma Management Program (CAMP) trial data¹⁶ in conjunction with simulation modeling to determine whether changes in prebronchodilator FEV₁% predicted with inhaled corticosteroids (ICS) can predict changes in hospitalizations, ED visits, and need for oral corticosteroid therapy.

METHODS

Overview

Using TreeAgePro 2011 (TreeAge Software Inc.; Williamstown, MA), we developed a Markov model¹⁷ employing microsimulation to estimate the cumulative number of acute events (ED visits, hospitalizations, or need for oral corticosteroid therapy) for asthmatic children undergoing placebo or ICS treatment over the course of 48 months. Four-month

frequencies for ED visits, hospitalizations, and need for oral corticosteroid therapy were derived from regression analyses, based upon our candidate predictors, using data from the placebo arm of CAMP. Validation of the model was accomplished by comparisons of model-outputs to actual trial outcomes in the placebo and treatment arms of CAMP.

CAMP Trial

Details of the design and methods of CAMP have been previously published.¹⁶ Briefly, CAMP is a multicenter, randomized, double-blinded clinical trial designed primarily to compare the long-term safety and effectiveness of budesonide, nedocromil, and placebo (as needed albuterol). CAMP enrolled 1,041 subjects from ages 5 to 12 years with mild to moderate persistent asthma. Entry criteria included asthma symptoms and/or medication use for six months or more in the previous year. The institutional review board at each of the eight participating institutions approved the study and parents or guardians of the subjects gave informed consent.¹⁶

The subject (or their parents or guardians) completed diary cards each day, recording night awakenings due to asthma, morning and evening peak flows as measured by a peak-flow meter (Assess, HealthScan Products, Cedar Grove, N.J.), use of study medication, use of albuterol for symptoms and to prevent exercise-induced bronchospasm, use of prednisone, absences from school due to asthma, visits to a physician's office or hospital because of asthma, and severity of symptoms. Data were also collected by interview of parents/guardians by the research coordinator regarding demographics, history of asthma symptoms and severity, treatment of asthma, allergy history, characteristics of the home environment, and relevant family history. Follow-up visits occurred two and four months after randomization and at four-month intervals thereafter.

Pre-bronchodilator spirometry was performed at least three times per year; it was performed at randomization, 2 months following randomization, and then every 4 months throughout the 4 years of the study. Spirometry was performed at least four hours after the last use of a short-acting bronchodilator and 24 hours after the last use of a long-acting bronchodilator.¹⁶ Spirometry testing met or exceeded the American Thoracic Society (ATS) standards. Equations used to predict the average value of lung function measures for age, sex, and height were race-corrected according to Coultas and coworkers¹⁸ for Hispanics, and according to Knudson and coworkers¹⁹ for all other ethnic groups. Children's height (measured by Harpenden stadiometer) and weight were recorded at every visit. The maximum number of follow-up visits available for any child was 12 visits, and the average was 11.1 visits [SD: 2.3].

Analytic Approach

Three separate multivariate negative binomial regression analyses were conducted with hospitalization, ED visit, and need for oral corticosteroid therapy as the dependent variables and prebronchodilator FEV₁% predicted as the primary independent variable of interest (Table 2). The analyses were conducted on forty-eight months of data from 417 children within the placebo arm of CAMP with inclusion criteria of at least one completed spirometry during follow-up visits. We paired the prebronchodilator FEV₁% value recorded at a given visit with outcomes reported over a subsequent four-month period. An additional Poisson regression analysis was conducted to predict the number of nocturnal awakenings in the four-week period as a function of prebronchodilator FEV₁% predicted, age, study time, and hospitalization in the past year. In the Markov model, this equation provided the estimate of nocturnal awakenings for the negative binomial regression equations which were used to predict the number of ED visits, hospitalizations, and exacerbations which required oral corticosteroid therapy. (Note that the results of this Poisson regression are not presented

in our results, as they are not germane to our outcomes. However, any reader seeking details concerning this regression may obtain these results by contacting the corresponding author). All regression analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC, 2007).

Description of the Model

A Markov model was developed to predict the frequency of asthma-related events (ED visits, hospitalizations, and need for oral corticosteroid therapy) among asthmatic children over a course of forty-eight months using the equations predetermined by our regression analyses. Markov models are a particular type of decision tree that models events as a series of repeated cycles of fixed time length; in our case the likelihood for an asthma exacerbation to occur over a period of one month. The model was estimated using a microsimulation process. This method allows the investigator to recognize both individual and population level variability by simulating a cohort of individual cohort members, one member at a time.²⁰

The basic structure of the model is shown in Figure 1. Upon entry into the model, each simulated child (cohort member) is assigned an initial age, initial prebronchodilator FEV₁% predicted value, and history of hospitalizations within the past year each drawn from distributions derived from the CAMP placebo arm (Table 1). Simulated children were also initially assigned a number of nocturnal awakenings in the past four weeks based upon the equation derived from the Poisson regression analysis.

Each month, each simulated child faced a risk of experiencing the need for oral corticosteroid therapy, an ED visit, and/or a hospitalization. These risks were derived from the four-month predicted frequencies estimated from our regression equations. We converted the four-month frequencies to one-month frequencies to fit with the model's fixed cycle length of a month. The number of events during the month was estimated using negative binomial regression equations to generate the monthly frequency of each event (i.e., hospitalization, ED visit, or need for oral corticosteroid therapy). When the result of the equation was a value ≥ 1 , that value was accepted as the number of events that month. When a value of less than 1 was produced, that value was treated as the probability that one event had occurred, and provided the parameter for a binomial function to determine if the child had experienced that event or not. This process recurred for each month while the model tracked the cumulative frequency of hospitalizations, ED visits, and need for oral corticosteroid therapy in four-month intervals for each simulated children.

Model Calibration

To assess the validity of our model and the accuracy of predicting asthma-related outcomes from prebronchodilator FEV₁%, we simulated a cohort of 100,000 children twice---once for the placebo and once for the treatment---using a first-order Monte Carlo method. We used the results for these simulations to calibrate the models by comparing the predicted outcomes to the actual for the placebo and untreated arms.

RESULTS

Figure 2 shows the cumulative number of acute events observed in the placebo arm of CAMP and predicted by the simulation model for each four-month follow-up interval. In the placebo arm of the model, we found that at 48 months the event rates were similar between the actual and predicted.

The placebo model differed substantially in the prediction of outcomes from the treatment group indicating that the influence of prebronchodilator FEV₁% on the three outcomes of interest is not homogeneous. Therefore, we introduced adjustment factors reflecting

difference in the influence of prebronchodilator FEV₁% on each outcome. The adjustment factors may represent subjective or biologic factors that influence utilization of asthma providers, ED, or hospital. After testing a number of different options we found that the best adjustment to prebronchodilator FEV₁% was 1.17 (hospitalizations), 1.78 (ED visits) and 1.43 (rescue therapies). These adjustments indicate that treatment to improve prebronchodilator FEV₁% has a synergistic influence on these outcomes beyond that which is gained by improving prebronchodilator FEV₁% compared to placebo.

In Figure 3, we present the comparison of the outcomes predicted for the treatment arm compared to actual outcomes. After calibration, the treatment arm did not fit quite as closely as the placebo arm, however the differences are extremely small---less than 0.2 cumulative ED visits/person over four years, and 0.02 cumulative hospitalizations/person over 48 months. Overall, model predictions showed a 48% reduction in hospitalizations with ICS therapy compared with placebo, whereas trial data demonstrated a 49% reduction in hospitalizations. The model predicted a 41% reduction in ED visits while the trial data showed a 46% reduction in ED visits. Finally the model predicted a 46% reduction in oral corticosteroid therapy, while the trial data demonstrated a 44% reduction in oral corticosteroid therapies.

DISCUSSION

Our results suggest that prebronchodilator FEV₁% predicted predicts changes in hospitalizations, ED visits, and need for oral corticosteroid therapy. Based on a combination of the relationships between prebronchodilator FEV₁% predicted and the asthma-related events in the placebo arm and the percent change in prebronchodilator FEV₁% predicted from ICS therapy, prebronchodilator FEV₁% predicted was able to predict changes in hospitalizations, ED visits, and oral corticosteroid therapy while on ICS treatment. The use of objective measures of disease with established relationships with disease outcomes is appealing for conducting policy analyses of alternative interventions. Using an established linkage between an objective surrogate disease measure and an outcome of interest provides a useful framework for evaluating intervention effects that are not biased by patient self-report or health-care utilization patterns. In the case of interventions for children with asthma, prebronchodilator FEV₁% predicted provides an appealing measure, and several studies have shown significant relationships between prebronchodilator FEV₁% predicted and asthma-related outcomes.^{7, 21} However, because the degree to which therapy-induced changes in asthma outcomes are mediated through prebronchodilator FEV₁% predicted has not been studied, its utility as a surrogate marker remains in doubt. To address this question, we adopted a simulation modeling approach in conjunction with a long-term pediatric asthma trial to determine whether ICS-mediated changes in prebronchodilator FEV₁% predicted can adequately predict changes in hospitalizations, ED visits, or need for oral corticosteroid therapy.

Some readers might be concerned that in our modeling we did not find that the influence of ICS treatment on ED visits, hospitalizations, and oral corticosteroid treatment was homogeneous across all three outcomes. However, it is not clear why one would expect that (for example) a 20% reduction in hospitalization following initiation of treatment would also result in a 20% reduction in ED visits (or steroid treatments). Indeed, we would argue that a homogeneous relationship would indicate a lack of face validity in the model. The demand for health services has been demonstrated to be multifactorial and includes biological, demographic and socio-economic factors.²² Those factors mediating influences between FEV₁ and the consumption of emergency medical services, hospitalization, and steroid therapy would be different. In the absence of empirical evidence to the contrary, it would be unreasonable to assume that the interactions between the mediating factors and FEV₁ with

are uniform. Our finding that an objective measure of lung function is a good predictor of the effect of ICS therapy on the probability of being hospitalized is clinically reasonable. Many of the clinical features of asthma are the direct result of airway obstruction, and improvements in prebronchodilator FEV₁% predicted are paralleled by improvements in other clinical asthma outcomes.²³⁻²⁸ Our finding that lung function does less well at predicting ED visits and oral corticosteroid therapy in the uncalibrated model is consistent with the fact that the decision to visit the ED or use additional therapy depends on many objective and subjective factors and the decision is generally made by the caregiver and their perception of the child's health.²⁹ Our calibrated model helps account for these subjective factors.

There are several limitations to our study. Our analysis is based only on one clinical trial and has not been validated in other studies. It is true that the robustness of a model should be demonstrated by external validation using data other than that used to create the model. However, we were unable to identify other clinical trials in which lung function was measured in children over age 4 years. We invite other investigators with such data who are interested in assisting in the validation of this model to contact the corresponding author. In our analysis of the CAMP trial data, we found and adjusted for a significant time variable – indicating that the trial outcomes were improving with time. However, there is published evidence that the covariates we identified in the clinical trial population can be extrapolated to general population samples; including prebronchodilator FEV₁% predicted,^{7, 30} prior hospitalization,³¹⁻³³ nocturnal awakenings³⁴ and in particular among pediatric cohorts, time (age) is an important factor on the morbidity associated with asthma.³⁵ Finally, it must be recognized that our model is designed to support clinical and health policy decision makers operating at the population level, not at the level of the individual patient. As such, while our model will be useful to individual clinicians and patients seeking to understand the probability of adverse events, we cannot say with certainty what occurrences will occur for individual patients.

The effects of asthma interventions may be modeled through prebronchodilator FEV₁% predicted to predict hospitalizations in childhood asthma for planning and evaluation purposes. The implication of our findings is that a policy analysis that relies only on an objective measure of lung function to predict asthma-related outcomes is possible. In summary, intervention effects may be modeled through prebronchodilator FEV₁% predicted to predict hospitalizations in childhood asthma over time for planning and evaluation purposes.

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Abbreviations

(ATS)	American Thoracic Society
(CAMP)	Childhood Asthma Management Program
(ED)	Emergency Department

(FEV1)	Forced Expiratory Volume in 1 second
(ICS)	Inhaled corticosteroid

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Key Messages

- Lung function can be used to predict hospitalizations, ED visits, and need for oral corticosteroid therapy in pediatric patients.
- Lung function is a good predictor of the effect of therapy with inhaled corticosteroids on the probability of being hospitalized or experiencing an ED visit.

Figure 1. Schematic of the Simulation Model. Each simulated child is assigned values for age and key clinical variables which, in turn, determine the monthly probabilities of events.

Figure 2.
Cumulative Mean Number of Acute Events per Subject Predicted by the Simulation Model Compared With CAMP Outcomes: Placebo Group.

Figure 3.
Cumulative Mean Number of Acute Events per Subject Predicted by the Simulation Model Compared With CAMP Outcomes: ICS Treatment Group.

Table 1

Starting Characteristics among Children in the CAMP Placebo Group

Variable	Value N?
Age at Randomization	8.9 (mean) 2.2 (standard deviation)
Prebronchodilator FEV ₁ % predicted	93.7 (mean) 13.4 (standard deviation)
One hospitalization within 12 months *	21.4%

* Children with 2 hospitalizations during the 12 months prior to study enrollment were excluded from CAMP.

Table 2

Negative Binomial Regression Equations of Four-month Outcomes from CAMP Placebo Group

Independent Variable	Dependent Variable					
	Hospitalization		ED visit		Oral corticosteroid Therapy	
	Beta	SE	Beta	SE	Beta	SE
Intercept	0.8140	1.0336	-1.0327	0.6004	1.4859	0.2703
Age at study entry	-0.1258	0.0619	-0.0589	0.0341	-0.0916	0.0154
FEV ₁ % predicted	-0.0321	0.0091	-0.0068	0.0049	-0.0149	0.0023
Nocturnal awakenings	0.0947	0.0571	0.0891	0.0389	0.1065	0.0180
Hospitalized once in months [*]	12 0.6311	0.4605	0.9076	.2737	0.4800	0.1382
Hospitalized twice or more in 12 months [*]	0.7309	0.9003	1.0766	.5685	0.2579	0.3182
Trial time (months)	-0.0420	0.0104	-0.0198	0.0052	-0.0134	0.0023

^{*} Reference is no hospitalizations in 12 months.