

Potential predictors of relapse after treatment of asthma exacerbations in children

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ARTICLE INFO

Article history:

Received for publication December 4, 2013.

Received in revised form January 4, 2014.

Accepted for publication January 29, 2014.

ABSTRACT

Background: Knowledge of factors that affect relapse will allow close monitoring of patients at risk, resulting in a decreased rate of readmission to the emergency department.

Objective: To determine risk factors associated with relapse within 7 days after treatment of asthma exacerbations in children.

Methods: This was a multicenter, prospective study of children with asthma attacks. Patients between the ages of 6 months and 17 years who met the criteria between June 2009 and September 2012 were considered.

Results: The study included 1177 patients (775 males [65.8%]) with a mean (SD) age of 70.72 (48.24) months. Of them, 199 (16.9%) had a relapse within 1 week after being discharged from the hospital. Factors independently associated with relapse identified by a logistic regression model for the 1,177 study visits were having taken a short-acting inhaled β_2 -agonist within 6 hours before admission (odds ratio [OR], 2.43; 95% confidence interval [CI], 1.728–3.426; $P = .001$), presence of retraction on physical examination (OR, 1.76; 95% CI, 1.123–2.774; $P = .01$), no prescription for high-dose inhaled steroids on release (OR, 2.02; 95% CI, 1.370–3.002; $P < .001$), and not being given a written instructional plan (OR, 1.55; 95% CI, 1.080–2.226; $P = .02$).

Conclusion: Whereas having taken short-acting β_2 -agonists within 6 hours before admission and the presence of retractions on physical examination increased the risk of relapse after treatment of the acute attack, being given high-dose inhaled steroids and a written instructional plan when being sent home reduced the risk.

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Introduction

Asthma is the most common chronic disease in childhood; its prevalence is estimated to be 5% to 10%.^{1–3} Asthma attacks account for 6% of the cases admitted to the pediatric emergency department.^{4–6} A few studies have tried to determine the revisit rate and risk factors associated with this in the short-term follow-up of patients after asthma attacks. Risk factors identified have included age younger than 2 years, persistent asthma, frequent admission to the hospital with asthma attacks in the previous year, and lower asthma quality-of-life scores.^{7–10} Knowledge of the factors that affect relapse will allow close monitoring of patients at risk, resulting in a decreased rate of readmission to the emergency department. Decreased emergency department readmissions will provide better quality of life, less absenteeism from school for children,

less absenteeism from work for parents, and a decrease in the costs of treatment.

The objective of our study was to identify variables associated with the relapse of asthma symptoms within 7 days after an initial treatment for an asthma exacerbation. We sought to identify unique factors and also to assess whether factors identified in previous studies were significant.

Methods

Study Design

Patients diagnosed as having asthma attacks who were admitted to the pediatric emergency departments and the pediatric allergy and asthma departments at 3 teaching and research hospitals (Gazi University Faculty of Medicine, Gülhane Military Medical Academy, and the Medical School, Diskapi Education and Research Hospital) from June 2009 to September 2012 and who met the study criteria were entered into the study.

The patients who were included were between the ages of 6 months and 17 years, had been diagnosed previously as having

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Disclosure: Authors have nothing to disclose.

asthma by a physician, or had a history of at least 3 wheezing attacks that necessitated treatment with short-acting β_2 -agonists, and patients with mild or moderate asthma attacks at admission.

Patients younger than 6 months or younger than 2 years in the season of the respiratory syncytial virus infection, severe attack at admission, chronic lung disease (cystic fibrosis or bronchopulmonary dysplasia), or cardiac disease (congenital heart disease) comorbid with diagnosed asthma and/or wheezing attacks; those with a history of premature birth; those with a birth weight of less than 2,500 g; those who underwent asthma attack treatment at the emergency department within 7 days before admission; patients in whom treatment with β_2 -agonists and/or corticosteroids was contraindicated; and those who had severe or life-threatening asthma attacks were excluded from the study. In addition, patients whose symptoms continued because they did not take the given treatment were excluded.

Patients enrolled into the study and their parents were questioned. Patient demographic features, patient histories, asthma histories, the nature of previous asthma attacks, the controller medication they were using, the attack medications they used immediately before presenting to the emergency department, physical examination signs, and treatment administered at the emergency department and when being sent home were recorded in a previously prepared survey form. The severity of the attack and the decision on hospitalization of patients who were admitted to the hospital with an asthma attack were determined according to the Global Initiative for Asthma (GINA)¹¹ guidelines. Patients who were treated and sent home were advised to return in cases of increased, or not reduced, symptoms despite taking the treatments.

The families of patients were contacted by the researchers (E.T., O.A.G., and M.A.) 7 days after the patients were discharged from the hospital. Information regarding the continuity of symptoms, such as cough, wheezing, and shortness of breath, drug use, and revisits to a physician, were ascertained from these interviews and the survey completed.

Definitions

Asthma attack is defined as an episode of progressive increase in shortness of breath, cough, wheezing, or chest tightness or some combination of these symptoms.¹¹ *Severe asthma attack* is defined as a potentially life-threatening attack that requires close supervision. *Relapse* is worsening of symptoms (eg, cough, wheezing, shortness of breath, and chest tightness) or revisiting a physician because of no decrease in the symptoms despite treatment after the patient was treated for the asthma attack and discharged from hospital. The *severity of the asthma attack* in the patients who presented with an asthma attack was categorized as mild, moderate, severe, or life-threatening, according to GINA. Choice of *treatment* according to the severity of the attack was also determined according to GINA.¹¹

Patients newly diagnosed or those already diagnosed as having asthma and who did not use a controller medication regularly, taking into consideration their complaints in the last 3 months, had the *severity of asthma* categorized as intermittent, mild-persistent, moderate-persistent, and severe-persistent, according to GINA.¹¹ *Asthma control* was categorized in patients taking a controller medication regularly, taking into consideration their symptoms in the last 3 months, as asthma controlled, partially controlled, or uncontrolled, according to GINA.¹¹ *Controller medication* refers to the long-term use of inhaled corticosteroids, leukotriene receptor antagonists, long-acting β_2 -agonists, and the use of one or more of these medications to control asthma-related symptoms. *High-dose inhaled steroid treatment* is the use of more than 1,000 $\mu\text{g}/\text{d}$ of nebulized budesonide.¹¹ Short-acting β_2 -agonists and high-dose inhaled steroids were prescribed in mild asthma attacks.

Short-acting β_2 -agonist, high-dose inhaled steroids, and systemic steroids were prescribed in moderate asthma attacks.¹¹

Predictor Variables

Potential risk factors that could be associated with relapse were evaluated statistically. These included demographic data (age, sex, exposure to cigarettes, and having used breast milk for <6 months), history of asthma (being under regular follow-up by an allergy specialist, severity of asthma, level of control, preventive treatment taken, time of the last attack, number of attacks in the previous year, number of attacks requiring systemic steroids, and number of attacks requiring hospitalization), information about the attack (being given short-acting β_2 -agonists within 6 hours before admission and severity of the attack at admission), signs on physical examination (retractions and oxygen saturation), treatment given at the hospital, drugs prescribed when discharged from the hospital, and whether an instructional plan was provided.

The research protocol was approved by the Ethics Committee of Gazi University Faculty of Medicine (No. 5295; date, 6.15.2009). All participants (parents and children >12 years old) provided written informed consent.

Statistical Analysis

Statistical analyses were performed using the SPSS software (version 15; SPSS Inc, Chicago, Illinois). Categorical variables were compared using a χ^2 test, and quantitative variables were compared using the Mann-Whitney test. A 2-sided $P < .05$ was considered to indicate statistical significance. A logistic regression model was constructed. In the model, multivariate analysis was used, including statistically significant variables from the univariate analyses and/or important parameters (eg, no prescription of high-dose inhaled steroids and no provision of a written care plan) to identify factors that affect relapse after being treated.

Results

During the study period, 1,476 patients with an asthma attack were admitted to the pediatric emergency departments or pediatric allergy asthma departments. In total, 1,177 patients who met the study criteria and who could be contacted for follow-up were included (Fig 1). Of the patients, 775 (65.8%) were male, with a mean (SD) age of 70.72 (48.24) months. Of the patients, 827 (70%)

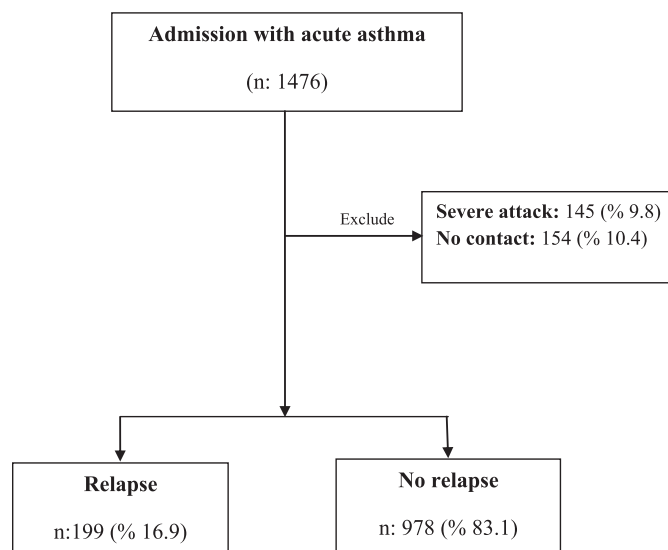


Figure 1. Flow diagram of children with acute asthma included in the study.

had already been diagnosed as having asthma before admission, 571 (69%) of these were under regular control at one of the pediatric allergy and asthma departments, and 511 (61.7%) were taking controller medications. On closer examination, of the patients undergoing treatment, 18% had controlled asthma, 71% had partial controlled asthma, and 11% had uncontrolled asthma. Of the 1,177 patients, 666 (56.6%) did not take a controller medication or were newly diagnosed as having asthma. Of these patients, 57.6% had intermittent asthma, 26.2% had mild-persistent asthma, 15% moderate-persistent asthma, and 1.2% had severe-persistent asthma. Regarding severity of the attack, in 784 patients (53.1%), severity was mild; in 549 (37.1%), moderate; in 137 (9.3%), severe; and in 8 (0.5%), life-threatening. Of the patients, 199 (16.9%) had a relapse within 1 week after being treated and sent home. Of them, 136 (68.3%) had a relapse within the first 3 days, and 16 (8%) of them were rehospitalized. The characteristics of the study visits are given in Tables 1 and 2. The factors found to be related to relapse in the univariate analyses were age younger than 5 years ($P = .04$), having taken short-acting β_2 -agonists within 6 hours before admission ($P < .001$), having retractions at admission ($P = .001$), not being given a written instructional plan when being released ($P = .003$), not being prescribed high-dose inhaled steroids when being released ($P = .02$), having experienced more than 2 attacks in the previous year ($P = .04$), and having been admitted for more than 2 hours at the emergency department ($P = .03$). Factors independently associated with relapse identified by the logistic regression model for the 1,177 study visits were having taken short-acting β_2 -agonists within 6 hours before admission, retraction on physical examination, not being prescribed high-dose inhaled steroids on being released, and not being provided with a written instructional plan (Table 3). There was no statistically significant association between relapse and sex, cigarette exposure, having used breast milk for less than 6 months, severity of asthma, level of control, having undergone preventive treatment, having experienced an attack that required systemic steroids or hospital admission in the previous year, severity of the attack at presentation, or oxygen saturation being 93% or less ($P > .05$; Tables 1 and 2).

Discussion

In the current study, we found an early relapse rate of 16.9% after discharge from the emergency department after an asthma attack, and 4 independent risk factors were identified related to relapse. Within these risk factors, taking a short-acting β_2 -agonist within 6 hours before admission and retraction on physical examination were associated with an increased risk of relapse. Furthermore, prescription of high-dose steroids when being sent home and being given a written instructional plan decreased the risk of relapse.

In previous studies, it was reported that the rate of revisiting a physician because of symptoms was between 4.1% and 31%.^{7,10,12,13} Emerman et al¹² gave systemic steroids to more than 75% of the patients in their study, and in their 2-week follow-up, they found the rate of revisits to be 10%. In the study by Ducharme et al,¹³ a few patients were given systemic steroids when sent home. They reported that the rate of revisit was 31% at the end of a 2-week follow-up. In the current study, systemic steroids were given to more than one-third of patients, and the relapse rate was 16.9% at the 1-week follow-up. We believe the differences in these rates are due to the differences in treatment approach and period of follow-up.

The risk factor related to relapse after treatment of a patient given short-acting β_2 -agonists before admission has not been identified in previous studies. Because the hospitals in our study have allergy and asthma departments, all patients diagnosed as having asthma are given a written instructional plan on how to administer asthma attack treatments. They were advised to refer to

Table 1

Comparison of demographic characteristics and variables associated with relapse

Variable	Relapse (n = 199)	No relapse (n = 978)	P value
Demographic			
Age, mean (SD), mo	66.47 (50.68)	71.58 (47.70)	.05
<5 Years old	106 (53.3)	445 (45.5)	.04
Male	131 (65.8)	644 (65.8)	.10
History			
Regular follow-up by an allergist	53 (50.0)	268 (48.2)	.73
Persistent asthma	47 (45.6)	236 (41.8)	.48
Partly controlled or uncontrolled asthma	81 (81.8)	349 (81.4)	>.99
Controller medication use	98 (49.2)	415 (42.5)	.08
Inhaled steroids	88 (44.2)	360 (36.8)	.051
Leukotriene modifiers	33 (16.6)	147 (15.0)	.58
Long-acting inhaled β_2 -agonists	10 (5.1)	28 (3.0)	.18
Tobacco exposure	49 (24.6)	223 (22.8)	.58
Breastfeeding <6 months	32 (16.1)	198 (20.2)	.18
Previous 12 months			
Time of the last exacerbation, mean (SD), mo	5.74 (7.06)	6.67 (7.82)	.13
No. of exacerbations, mean (SD)	2.08 (1.49)	1.85 (1.36)	.04
No. of exacerbations requiring systemic steroids, mean (SD)	0.83 (1.02)	0.68 (0.89)	.08
No. of exacerbations requiring hospitalization, mean (SD)	0.34 (0.85)	0.23 (0.60)	.24

the emergency department in cases where there was no reduction in symptoms despite use of the treatment. Approximately three-quarters of our patients who were admitted to the pediatric emergency department were diagnosed as having asthma, and one-third of the patients came in after taking a short-acting β_2 -agonist at home. Patients who took short-acting β_2 -agonists at home before coming to the hospital had a relapse rate 2.43-fold higher than those who did not. It was considered that the short-acting β_2 -agonists taken by these patients before admission may have improved the physical examination and pulmonary function tests and caused misinterpretation of the severity of the attack. Thus, appropriate treatment was not given; this resulted in the higher rate of relapse. Consequently, patients who present with acute attacks should be questioned on any treatment they took before admission. Indeed, patients should be examined more carefully if they took a short-acting β_2 -agonist within 6 hours before admission.

According to the GINA guidelines,¹¹ use of accessory muscles is one parameter used to determine the severity of an attack; a

Table 2

Comparison of variables associated with relapse

Variable	Relapse (n = 199)	No relapse (n = 978)	P value
Duration of symptoms before admission, mean (SD), d	5.95 (7.25)	6.11 (6.55)	.11
Use of inhaled β_2 -agonists within 6 hours before admission	99 (49.7)	301 (30.8)	<.001
Moderate attack at admission	93 (46.7)	392 (40.1)	.08
ED management			
Pulse oximetry $\leq 93\%$ at admission	37 (18.6)	152 (15.6)	.28
Use of accessory respiratory muscles	42 (21.1)	117 (12.0)	.001
ED steroid course	85 (57.0)	404 (55.3)	.70
ED ipratropium bromide course, mean (SD), dose	0.52 (1.40)	0.48 (1.21)	.96
ED length of stay, mean (SD), h	1.96 (1.29)	1.72 (1.17)	.03
Follow-up after ED			
Systemic steroids was prescribed	71 (35.7)	373 (38.1)	.51
Being prescribed of high-dose inhaled steroids	128 (64.3)	709 (72.5)	.02
Being given a written instructional plan	48 (24.1)	342 (35.0)	.003

Abbreviation: ED, emergency department.

Table 3

Multivariate analysis: potential predictors that affect relapse after treatment of asthma exacerbations^a

Variable	β	OR (95% CI)	P value
Use of short-acting β_2 -agonists within 6 hours before admission	0.88	2.43 (1.728–3.426)	<.001
Not being prescribed of high-dose inhaled steroids	0.70	2.02 (1.370–3.002)	<.001
Use of accessory respiratory muscles at admission	0.56	1.76 (1.123–2.774)	.01
Not being given a written instructional plan	0.43	1.55 (1.080–2.226)	.02

Abbreviations: CI, confidence interval; OR, odds ratio.

^aVariables in the logistic regression model are as follows: age younger than 5 years, number of exacerbations in the previous year, number of exacerbations requiring systemic steroids in the previous year, use of controller medications, use of short-acting β_2 -agonists within the 6 hours before admission, use of accessory respiratory muscles at admission, moderate attack at admission, not being prescribed of high-dose inhaled steroids, and not being given a written instructional plan.

patient who uses accessory muscles is having at least a moderate asthma attack, and any patient who has had a moderate attack should be hospitalized despite short-acting β_2 -agonist treatment if there is no improvement on physical examination at the emergency department. In our study, use of accessory respiratory muscles at admission increased the relapse rate by 1.76-fold. Thus, patients who are using accessory muscles at the time of an attack should be considered to be at risk of relapse when being sent home.

Addition of inhaled steroids to the treatment of patients who were admitted with an asthma attack to the emergency department reduced the rate of hospital admission.¹⁴ In the study by Fitzgerald et al,¹⁵ after the release of patients who presented with asthma attacks from the emergency department, half of them were given systemic steroids and the other half high-dose inhaled budesonide (2,400 μ g/d). They reported that high-dose budesonide was at least as effective as systemic steroids in preventing a relapse and in improving forced expiratory volume in 1 second, asthma symptoms, peak expiratory flow, and quality of life. In our study, patients who were given high-dose inhaled steroids because of their asthma attack also had a reduced relapse risk, by 2.02-fold. Indeed, we could explain this by bronchial inflammation being effectively suppressed by high-dose inhaled steroids. For this reason, addition of high-dose inhaled steroid treatment to the home treatment of patients with asthma attacks should decrease the relapse rate.

International guidelines recommend that patients who are admitted to the emergency department with an asthma attack should be educated about asthma and given a written instruction plan on how to use appropriate drugs once at home.¹¹ Lieu et al¹⁶ reported that providing a written instructional plan to asthma patients reduced both the rate of hospital admissions and visits to the emergency department. Similarly, Walsh-Kelly et al¹⁰ reported that the revisit rate of patients given a written instructional plan was much lower. Likewise, our study indicated that the relapse risk of patients given a written instructional plan was 1.55-fold lower. Consequently, providing a written instructional plan to patients who are admitted to the emergency department because of an asthma attack will reduce the rate of relapse.

Factors found by multivariate analyses to be related to relapse in previous studies were presence of persistent asthma, being younger than 2 years, low asthma quality-of-life scores, frequent visits to the emergency department because of asthma attacks in the previous year, and exposure to cigarettes.^{10,12} Although having frequent attacks in the previous year and being younger than 5 years were borderline risk factors in our univariate analyses, when we evaluated factors reported in previous studies using a logistic regression model, they were not statistically significant. We think

that the differences between these results are due to differing study methods and treatment approaches. However, several features differentiated our study from the other studies: patients were followed up for a period of 1 week and were administered treatments according to the GINA recommendations (only a third of the patients were prescribed systemic steroids).

Our study had several limitations. First, although the study was conducted at 3 hospitals, the hospitals are situated in the city center, so patients referred from rural areas were not included. In addition, 10.4% of the patients initially interviewed failed to contact us again. Thus, we cannot generalize the results of the study. Second, other environmental factors beyond upper respiratory tract infection and cigarette exposure that could affect relapse were not considered when evaluating the patients.

In conclusion, taking a short-acting β_2 -agonist within 6 hours before admission, the presence of retractions on physical examination, not being prescribed high-dose inhaled steroids, and not being given a written instructional plan on release were risk factors for relapse in short-term follow-up after discharge from the hospital after an asthma attack. Among these factors, taking short-acting β_2 -agonists within 6 hours before admission was considered the most important. Thus, in patients who are discharged from an emergency department after an asthma attack, those who took short-acting β_2 -agonists before admission should be followed up closely because of the possibility of relapse.

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