Original Article

Asthma Exacerbation Rates in Adults Are Unchanged Over a 5-Year Period Despite High-Intensity Therapy

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What is already known about this topic? Prior asthma exacerbations increase the short-term risk of subsequent asthma exacerbations.

What does this article add to our knowledge? For patients on high-intensity pharmacologic treatment, the risk of exacerbations does not change over time, and prior exacerbations increase the risk of subsequent asthma exacerbations over a several-year period, in spite of therapy.

How does this study impact current management guidelines? New therapeutic options are needed for patients who experience asthma exacerbations in spite of high-intensity pharmacologic treatment.

BACKGROUND: Few data exist regarding the natural history of asthma exacerbations over time.
OBJECTIVE: To evaluate the frequency and risk factors of asthma exacerbation occurrence over a 5-year period in a large cohort of adult patients with persistent asthma.
METHODS: Health insurance claims from the Truven Health MarketScan database were analyzed for 2543 patients who had full medical and drug claims for years 2006 to 2011, did not have co-occurring chronic obstructive pulmonary disease in the index year (2006), and were treated with high-dose inhaled corticosteroids and long-acting β2-agonists for at least 120 days ("high intensity" therapy) in the index year. A retrospective analysis was conducted to assess the pattern of severe exacerbations (encounter with health care system and steroid burst) over time and their associations with the other measures of health status.
RESULTS: Despite the use of high-intensity asthma therapy, there was only a small decrease in total asthma exacerbations over time, but no significant time trend for asthma hospitalizations. An exacerbation in the prior year increased the risk for exacerbations almost 8-fold, (odds ratio 7.8 [95% CI, 7.1-8.6]). A 50% increase in exacerbation risk (odds ratio 1.5 [95% CI, 1.4-1.6]) was associated with continued high-intensity treatment for the duration of the study. Patients with encounters of chronic obstructive pulmonary disease after the index year were at 60% increased risk of an exacerbation.
CONCLUSIONS: This study showed that exacerbation rates for patients with asthma in a real-world setting remained relatively constant over time, and continuous high treatment intensity was not associated with a substantially lower risk of exacerbations. **(J Allergy Clin Immunol Pract 2014;2:570-4)**

Key words: *Asthma; Exacerbations; Natural history; Inhaled corticosteroids; Long-acting β-agonists*

Asthma affects 18.8 million people in the United States[1] and imposes a substantial humanistic and economic burden on patients and society. Asthma exacerbations have particularly important adverse effects on the quality of life of people with asthma, and exacerbations account for the largest proportion of the nondrug direct costs of asthma care.[2] Risk factors for asthma exacerbations, such as prior exacerbations[3,4] and asthma severity,[4] have been defined but generally over no more than a 1-year period of follow-up. Few data exist regarding the year-to-year occurrence of asthma exacerbations and risk factors for their occurrence over longer time periods. The purpose of this study was to evaluate the natural history and risk factors of asthma exacerbation that occur over a 5-year period in a large cohort of patients with persistent asthma on high-intensity (HI) asthma treatment. Asthma severity in this study was based on treatment intensity, as suggested by current national asthma guidelines for patients on controller therapy.[5]

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Abbreviations used
COPD- Chronic obstructive pulmonary disease
ED- Emergency department
HI- High-intensity asthma treatment
CD-9- International Classification of Diseases, Ninth Revision
ICS- Inhaled corticosteroid
LABA- Long-acting β-agonist
OR- Odds ratio

METHODS

Data source

This study used the Truven Health MarketScan Commercial Claims and Encounters research database (Ann Arbor, Mich), composed of health insurance claims from more than 200 large employers and more than 100 health plans across the United States that provide private health care coverage. The database covers more than 78 million patients from the working population, age 65 years old and younger, and their dependents. This database reflects the real world of treatment patterns by using patient encounters with the health care system from all providers of care, including inpatient, outpatient, emergency department (ED), office visit, and pharmacies at the patient level. This database is fully Health Insurance Portability and Accountability Act compliant.

Study design and population

This study was a retrospective cohort analysis. Study subjects were identified by a claim for a primary asthma diagnosis (International Classification of Diseases, Ninth Revision [ICD-9] 493.x) during the index year (2006). To be included in this study, at index, patients needed to be at least 18 years of age, have at least 120 days filled of high-dose inhaled corticosteroid (ICS) and long-acting β-agonist (LABA) medication (defined as HI asthma treatment), not have a diagnosis of chronic obstructive pulmonary disease (COPD), and be continuously enrolled with both medical and drug coverage for the entire study period from 2006 to 2011 or to death. Drug usage (ie, filling at least 1 prescription for any medication, not necessarily asthma related) during each calendar year (2006-2011 or death) also was required to confirm the use of the patient's drug coverage. As defined in the Healthcare Effectiveness Data and Information Set (HEDIS) measures,[6] COPD was defined by using the following ICD-9 diagnosis codes: 491.2x, 492.x, 493.2x, 496, 506.4, 518.1, and 518.2. High-dose ICS thresholds were defined by using the National Institutes of Health Severe Asthma Research Program[7] definitions (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The daily dose calculation was based on the method by Lafeuille et al.[8] Due to the nature of claims databases, drug information is based on prescriptions filled, not prescriptions used or prescribed.

Exacerbations

Exacerbations were defined as an oral corticosteroid prescription within 7 days of a hospitalization, emergency department (ED) visit, outpatient encounter or physician office visit with a diagnosis of asthma (primary ICD-9 code of 493 or secondary ICD-9 code of 493 with other respiratory primary diagnosis). The proportion of patients and the rate (exacerbations/subject per year) of total exacerbations as well as those exacerbations that led to a hospitalization, were calculated for years 2007 to 2011.

Analysis

Regression models were used to assess whether there was a time trend for exacerbations. The regressions also were used to assess the association between exacerbations over time and previous exacerbations, HI asthma treatment over the entire follow-up period (in addition to the index year), COPD status, age, and sex over the 5-year period of the study (2007-2011). Previous exacerbations were modeled as a time-varying covariate; all other covariates were modeled as constant over time: HI asthma treatment (at least 120 days filled of high-dose ICS and LABA medication per year) was assessed over the entire 5-year period, age was set at index, and patients were considered positive for COPD if they had a diagnosis code at any time during the study because the onset of COPD may be several years before diagnosis. Some potential exacerbation risk factors were not available in the data set, such as lung function, smoking status, race, and socioeconomic status. In all the models, 2 different outcomes were assessed: any exacerbation and asthma hospitalization. Regression analysis was conducted by using generalized estimating equations to account for clustering within patients over time. An autoregressive correlation matrix with robust errors using a binomial logit-link structure was used for all generalized estimating equation models, except for analyses of exacerbation rates, which used a Poisson log-link structure. To assess whether these relationships were the same for patients who were continuously treated with HI asthma treatment, all analyses were repeated after restricting the population to those who were treated with HI asthma treatment for at least 120 days per year in all 5 years.

An analysis also was conducted to assess the impact over time of frequent exacerbator status in year 1. Frequent exacerbator status was modeled as 0, 1, and 2 or more exacerbations, either any exacerbation or exacerbations that required a hospitalization or an ED visit. Frequent exacerbator status was evaluated alone and, when adjusting for time, HI asthma treatment, age, and sex. The generalized estimating equation regressions for the frequent exacerbator analyses used the same framework as the other regressions, except that these regressions analyzed the years 2008 to 2011 because 2007 was used to assess exacerbator status. Regression analyses were conducted with Stata IC version 12.1 (2011) (College Station, Texas), and data management was conducted by using SAS version 9.1.3 (SAS Institute Inc, Cary NC).

RESULTS

Baseline characteristics and medications received

Baseline demographics and patient characteristics are displayed in Table I. This study identified 2543 patients with asthma who received HI asthma treatment without a diagnosis of COPD during the index year. The average age of the patients was 48 years, and 63% were women. At index, 97% of the patients were on ICS plus LABA combination therapy, and the remaining 3% were on separate ICS and LABA products. During the index year of 2006, 41% of patients had an asthma exacerbation, with 2% of patients having an asthma exacerbation that resulted in a hospitalization. Between 2007 and 2011, there was a marked reduction in the percentage of patients who received each type of most asthma maintenance medications, including ICS, LABA, leukotriene modifiers, and theophylline (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). However, 725 patients (28.5%) received HI treatment for the entire study period.

TABLE I. Patient characteristics

All patients, no. (%)	2543 (100)
Age (y), mean ± SD	47.9 ± 8.6
Age group, no. (%)	
18-34 y	200 (8)
35-44 y	591 (23)
45-54 y	1077 (42)
55-64 y	675 (27)
Sex, no. (%)	
Men	941 (37)
Women	1602 (63)
Region, no. (%)	
Northeast	336 (13)
North central	750 (29)
South	810 (32)
West	641 (25)
Full-time employment, no. (%)	1887 (74)
COPD during study period, no. (%)*	757 (30)
Died during study period, no. (%)*	24 (1)

*Study period, 2007-2011.

Exacerbations over time

In 2007, 28% of patients had an exacerbation(s), whereas in 2011, 25% had an exacerbation(s) (Table II). The odds of an exacerbation showed a small, but statistically significant, reduction over time (odds ratio [OR] 0.96 [95% CI, 0.94-0.99]). Between 2007 and 2011, hospitalization rates varied between 1% and 2%, and there was no statistically significant time trend (Table II). In 2007, the exacerbation rate was 0.70 exacerbations/subject per year, whereas, in 2011, the exacerbation rate was 0.63 (Table II); the difference over time was not statistically significant.

HI asthma treatment subgroup

Among patients who had HI asthma treatment for all 5 years of follow-up, the percentage of patients with an exacerbation varied between 29% and 31% during follow-up (Table II). In 2007, the exacerbation rate for this subgroup was 0.67 exacerbations/subject per year and increased to 0.77 by 2011 (Table II), but the difference over time was not statistically significant. During that same time period, 1% to 2% of these patients experienced a hospitalization due to asthma; again, there was no significant trend over time.

Factors that influenced the risk of future exacerbations

The risk of having any exacerbation throughout the follow-up period increased almost 10-fold if the patient had an exacerbation in the previous year (OR 9.67 [95% CI, 8.79-10.68]). After adjusting for HI asthma treatment, age, sex, and COPD status, an exacerbation in the previous year increased the risk of any exacerbation almost 8-fold (OR 7.80 [95% CI, 7.07-8.61]) (Table III). Among patients who had no exacerbations in the previous year, 20% had an exacerbation in the subsequent year (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Receiving a COPD diagnosis code at any point during the study was associated with a 60% increased odds of exacerbation (OR 1.59 [95% CI, 1.44-1.75]) after adjusting for the previously mentioned risk factors. Receiving HI asthma treatment for the entire duration of the study was associated with a 50% increase in odds of exacerbation (OR 1.49 [95% CI, 1.36-1.63]) (Table III).

TABLE II. Percentage and rate of patients with exacerbations

	Year				
	1	2	3	4	5
Patients with exacerbations					
All patients					
No. patients	2543	2537	2532	2528	2525
% Exacerbations (hospitalizations)*	1	2	2	2	2
% Exacerbations†	28	28	26	25	25
HI treatment‡					
No. patients	725	725	725	725	725
% Exacerbations (hospitalizations)	1	2	1	2	1
% Exacerbations	29	30	30	31	30
Exacerbation rate (exacerbations/patient/y)					
All patients					
No. patients	2543	2537	2532	2528	2525
Exacerbations (hospitalizations)	0.02	0.02	0.02	0.02	0.02
Exacerbations	0.70	0.69	0.69	0.66	0.63
HI treatment					
No. patients	725	725	725	725	725
Exacerbations (hospitalizations)	0.01	0.02	0.02	0.02	0.02
Exacerbations	0.67	0.75	0.75	0.75	0.77

*Exacerbations (hospitalizations) are defined as needing an oral corticosteroid prescription within 7 days of a hospitalization, with a diagnosis of asthma (primary ICD-9 493 or secondary ICD-9 of 493 with other respiratory primary diagnosis).
†Exacerbations are defined as needing an oral corticosteroid prescription within 7 days of a hospitalization, ED visit, or outpatient encounter or physician office visit, with a diagnosis of asthma (primary ICD-9 493 or secondary ICD-9 of 493 with other respiratory primary diagnosis).
‡Each year for the entire study period, ≥120 days filled of high-dose ICS and LABA medication.

The risk of having an asthma hospitalization increased 47-fold if the patient had been hospitalized for an exacerbation in the previous year (OR 47.03 [95% CI, 34.45-64.21]). After adjusting for age, sex, COPD status, and higher intensity asthma treatment, the association with previous hospitalization was reduced to almost 6-fold (OR 5.75 [95% CI, 2.87-11.50]) (Table IV). Receiving a COPD diagnosis code at any point after entry into the study was associated with a 6-fold increased risk of an asthma hospitalization after adjusting for the previously mentioned factors (OR 6.11 [95% CI, 4.08-9.14]). Receiving HI asthma treatment for the entire duration of the study was not associated with an increased risk of an asthma hospitalization (OR 1.20 [95% CI, 0.88-1.62]) (Table IV).

Frequent exacerbator analysis

When frequent exacerbations were defined as any type of exacerbation, patients who had 1 exacerbation in 2007 had a more than 2-fold (OR 2.26 [95% CI, 1.92-2.67]) increased risk of a subsequent exacerbation, and those who had 2 or more exacerbations had more than a 4-fold (OR 4.66 [95% CI, 3.97-5.49])

TABLE III. Factors that predict exacerbations: all exacerbation types

	OR (95% CI)*	*P* value
Exacerbation in previous year	7.80 (7.07-8.61)	<.01
COPD†	1.59 (1.44-1.75)	<.01
HI treatment‡	1.49 (1.36-1.63)	<.01
Women	1.18 (1.07-1.30)	<.01
Age	0.99 (0.99-1.00)	<.01

*All ORs are from a generalized estimating equation model when adjusting for COPD status, HI, sex, age, and exacerbation in the previous year.
†If the patient had a COPD encounter any time during the study period, then he or she was classified as having COPD.
‡Each year for the entire study period, ≥120 days filled of high-dose ICS and LABA medication.

TABLE IV. Factors that predict exacerbations: hospitalized exacerbations

	OR (95% CI)*	*P* value
Hospitalization in previous year	5.75 (2.87-11.50)	<.01
COPD†	6.11 (4.08-9.14)	<.01
HI treatment‡	1.20 (0.88-1.62)	.24
Women	1.86 (1.24-2.77)	<.01
Age	0.96 (0.95-0.98)	<.01

*All ORs are from a generalized estimating equation model when adjusting for COPD status, HI, sex, age, and exacerbation in the previous year.
†If the patient had a COPD encounter any time during the study period, then he or she was classified as having COPD.
‡Each year for the entire study period, ≥120 days filled of high-dose ICS and LABA medication.

increased risk of exacerbations each subsequent year compared with those who had no exacerbations in 2007. This relationship was not affected by adjusting for time, HI asthma treatment, sex, or age (data not shown). After adjusting for frequent exacerbator status in 2007, age, sex, COPD status, and HI, there was a small but statistically significant decrease in exacerbations each year (OR 0.96 [95% CI, 0.92-1.00]; $P = .04$).

When we restricted the definition of an exacerbation to only an exacerbation that led to a hospitalization or ED visit, the patients with 1 exacerbation in 2007 had an almost 6-fold increase in the likelihood of a subsequent exacerbation (OR 5.78 [95% CI, 3.37-9.92]), and those with 2 or more exacerbations had an almost 13-fold (OR 12.86 [95% CI, 8.55-19.35]) increased risk of a future exacerbation each year. This relationship also was not affected by adjusting for time, HI asthma treatment age and sex (data not shown). The relationship between time and an asthma hospitalization or an ED visit was no longer statistically significant after adjusting for frequent exacerbator status, HI, COPD, sex, and age (OR 0.96 [95% CI, 0.88-1.04]).

DISCUSSION

This study evaluated the impact of time, previous exacerbations, and continuous HI asthma treatment on asthma exacerbations and hospitalizations over a 5-year period in a population of 2543 privately insured US patients with intensely treated asthma without co-occurring COPD at baseline. In this population, the frequency of asthma exacerbation and asthma hospitalization did not vary substantially over time. Exacerbations in the previous year predicted exacerbations (any and those that required hospitalization) in the following year. In addition, for patients with 1 exacerbation in year 1 ("frequent exacerbators"), the increased risk of any exacerbation or an asthma hospitalization was sustained over at least the next 4 years, despite using HI asthma treatment; if the patient had 2 exacerbations at baseline, then the sustained risk was even greater. In this study, ongoing utilization of high-dose ICS and LABA was not associated with a decrease in exacerbations over time.

There have been a number of other studies that have evaluated the frequency and predictors of asthma exacerbations over a 1-year follow-up period. Most of these studies found that prior exacerbations were an important risk factor for future exacerbations[3,9,10] The current study extends those findings to show that this increased risk persists over a 4-year period for patients with an exacerbation in the first year, despite using HI asthma treatment. Although this study confirms that a prior exacerbation increases the risk of a subsequent exacerbation, it should be noted that approximately 20% of patients in our sample who did not have an exacerbation in a given year did have an exacerbation the following year. Therefore, although preventative measures are appropriately targeted at patients with a prior exacerbation, this will not eliminate at least 20% of exacerbations, because even patients on HI treatment who are not "frequent exacerbators" are at risk for subsequent asthma exacerbations.

In contrast to some studies,[9,11-13] our study showed that consistent high-dose asthma controller use was not associated with a reduction in exacerbations over time. In fact, persistent dispensing of high-dose asthma therapy was actually associated with a higher risk of exacerbations. This is probably because more intense therapy is a marker of asthma severity[5] in addition to an attempt to provide control. The persistence of the risk of asthma exacerbations over time in this group of patients suggests that there are unmet therapeutic needs for a subset of patients with asthma, at least regarding asthma exacerbations.

A subsequent diagnosis code of COPD also was shown to increase the risk of exacerbations over time, which is consistent with prior studies that showed an increased risk of uncontrolled asthma in patients with a coexistent diagnosis of COPD.[14] Whether this represents an issue with diagnosis (patients with COPD have been mislabeled as having asthma or patients with severe asthma are misdiagnosed as having COPD) or reflects the presence of the overlap syndrome, which is associated with worse outcomes than asthma alone,[15] cannot be determined from the current administrative data.

There are several limitations to this analysis. First, claims data are designed for billing, not for tracking disease status over time. Some potential exacerbation risk factors, such as lung function, smoking status, race, and socioeconomic status, were not available in the data set. Lung function would also have allowed us to more accurately assess the severity of asthma. In the absence of lung function data, Global Initiative For Asthma (GINA) guidelines step-4 therapy was chosen as a proxy. In general, patients who require high-dose ICS and LABA would be considered patients with a more severe condition, and we thus included patients who were dispensed more than a 4-month supply of such therapy in the index year (2006). However, we only had dispensing data, so we do not know what dosages the patients were prescribed or actually took; we only know what medications were filled. Nonetheless, studies have shown a link between electronic pharmacy records–based medication usage and patient outcomes.[16] Exacerbations may have been underestimated due to our requirement that

patients have an encounter with the health care system for asthma in addition to a prescription for a corticosteroid burst. We thought that this was necessary because there are many reasons that a patient could fill a prescription for corticosteroids that are not asthma related. This data source came from employer-based insurance data and was restricted to adults younger than 65 years old. Because these patients are either employed (or are a dependent of an employee), they are likely to be of higher socioeconomic status than the general asthma population in the United States and, therefore, slightly healthier overall and more likely to have better controlled asthma.[17-19] Thus, the generalizability of these results to a lower socioeconomic, uninsured, elderly, or pediatric population is limited.

In conclusion, this study confirms and expands upon the finding that prior exacerbations predict future exacerbations. This effect is pronounced for the following year but also persists for at least the 4 years that we were able to follow up the patients in this study. In addition, this study indicates that, for patients in a real-world setting, exacerbation rates remain relatively constant over a several-year period, and continuous HI asthma treatment is not associated with a substantially lower risk of exacerbations over time. For the frequent exacerbator asthma phenotype, new treatment options are needed.

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TABLE E1. Severe Asthma Research Program definitions of high-dose ICS

Medication	Total daily dose (mcg)
Aerobid, Forest Pharmaceuticals, Inc., St. Louis, Mo	2500
Alvesco, Sunovion Pharmaceuticals, Inc., Marlborough, Mass	640
Asmanex Twisthaler, Merck & Co., Inc., Whitehouse Station, N.J.	880
Flovent, GlaxoSmithKline Pharmaceuticals, Philadelphia, Pa	880
Flovent Diskus, GlaxoSmithKline Pharmaceuticals, Philadelphia, Pa	1000
Flovent HFA, GlaxoSmithKline Pharmaceuticals, Philadelphia, Pa	880
Pulmicort Flexhaler, AstraZeneca, London, United Kingdom	1440
Pulmicort Turbuhaler, AstraZeneca, London, United Kingdome	1600
Qvar, Teva Pharmaceuticals, Petah Tikva, Israel	640
Advair Diskus, GlaxoSmithKline Pharmaceuticals, Philadelphia, Pa	1000
Advair HFA, GlaxoSmithKline Pharmaceuticals, Philadelphia, Pa	920
Dulera, Merck & Co., Inc. Whitehouse Station, N.J.	800
Symbicort, AstraZeneca, London, United Kingdom	640

TABLE E2. Medication use over time

	Percentage of patients who had at least 1 fill of the medication				
Maintenance	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
All patients	100	100	100	100	100
ICS or combination	95	90	88	85	83
ICS HD or combination HD	85	73	67	62	58
LABA or combination	93	88	84	81	79
Leukotriene modifiers	59	56	53	50	48
Theophylline	6	5	5	4	4
Omalizumab	4	5	5	4	4

TABLE E3. Percentage of asthma exacerbations over time by first year of exacerbator status

	Year				
Exacerbations During 2007	**1**	**2**	**3**	**4**	**5**
0					
No. patients	1843	1839	1837	1833	1830
% Exacerbations (hospitalizations)*	0	1	1	1	1
% Exacerbations†	0	20	19	19	19
1					
No. patients	351	350	349	349	349
% Exacerbations (hospitalizations)	1	1	1	1	1
% Exacerbations	100	38	36	35	31
2 or more					
No. patients	349	348	346	346	346
% Exacerbations (hospitalizations)	9	6	4	6	4
% Exacerbations	100	58	54	47	51
0 (hospitalization or ED)‡					
No. patients	2427	2421	2418	2414	2411
% Exacerbations (hospitalizations)	0	1	1	1	1
% Exacerbations	24	26	25	24	24
1 (hospitalization or ED)					
No. patients	48	48	47	47	47
% Exacerbations (hospitalizations)	33	8	4	13	11
% Exacerbations	100	52	34	43	49
2 or more (hospitalization or ED)					
No. patients	68	68	67	67	67
% Exacerbations (hospitalizations)	26	13	10	10	9
% Exacerbations	100	63	66	61	55

*Exacerbations (hospitalizations) are defined as needing an oral corticosteroid prescription within 7 days of a hospitalization, with a diagnosis of asthma (primary ICD-9 493 or secondary ICD-9 of 493 with another respiratory primary diagnosis).
†Exacerbations are defined as needing an oral corticosteroid prescription within 7 days of a hospitalization, ED visit, or outpatient encounter, or physician office visit, with a diagnosis of asthma (primary ICD-9 493 or secondary ICD-9 of 493 with another respiratory primary diagnosis).
‡Exacerbations (hospitalization or ED) are defined as needing an oral corticosteroid prescription within 7 days of a hospitalization or an ED visit, with a diagnosis of asthma (primary ICD-9 493 or secondary ICD-9 of 493 with another respiratory primary diagnosis).