

Original article

Predicting episodes of poor asthma control in treated patients with asthma

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Background: Asthma exacerbations are dangerous, expensive, and difficult to anticipate.

Objective: To characterize patients with asthma who had asthma episodes and exacerbations during 4 weeks of observation.

Methods: A total of 2032 volunteers with asthma (age, 3-64 years; 62% female subjects) were studied over two 2-week intervals after flu vaccine and placebo. Baseline data, including several asthma questionnaires, were analyzed for prediction of subsequent asthma events as recorded on diaries detailing peak flow, medication use, and health care use.

Results: During 28 days of diary collection, 43.2% of participants had at least 1 episode of poor asthma control. Most episodes were characterized by increased use of rescue medications or reductions in peak flow, but nearly 15% of participants had exacerbations characterized by use of systemic corticosteroids, unscheduled health care visits, or both. Episode frequency was highest in children <10 years of age. Additional risk factors were smoking, African American ethnicity, low lung function, and past history of severe asthma. The best predictors were symptom questionnaires, and a simple questionnaire concerning the preceding 2 weeks worked as well as more complex questionnaires or those reflecting longer periods. In regression analyses, questionnaire results, smoking, lung function, ethnicity, and asthma history all were associated with asthma episodes in people older than 10 years, whereas only asthma history was predictive in those <10 years.

Conclusion: Symptom questionnaires are predictive of subsequent asthma episodes in people older than age 10 years, but not in younger people.

Clinical implications: Simple assessments may be helpful in identifying patients most at risk for future asthma episodes. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma exacerbations, asthma symptom questionnaires, asthma control

Asthma is the most common chronic respiratory disorder among children and adults in the United States. Health care costs related to asthma are high and are largely related to care for asthma exacerbations.¹ Asthma exacerbations are potentially life-threatening events, accounting for about 5000 deaths annually in the United States.¹ The risk of asthma death may be independent of the underlying severity of disease, at least in children.² The focus of both US (National Institutes of Health) and international (Global Initiatives for Asthma; GINA) asthma treatment guidelines has been avoidance of serious exacerbations along with control of asthma symptoms.^{3,4} Despite guidelines, morbidity, mortality, and costs associated with asthma continue to rise. Early and reliable prediction of exacerbation and loss of asthma control would be an important advance, especially if applicable to patients treated in primary care settings.

In this report, we provide an analysis of data previously collected during the multicenter clinical trial Safety of Inactivated Influenza Vaccine in Adults and Children with Asthma (SIIVA).⁵ These data characterize a large group of children and adults with diagnosed asthma and no acute exacerbation who subsequently had loss of asthma control or exacerbations. The goal of the current study was to determine the factors that appear to be associated in the short term with the occurrence of these asthma episodes to facilitate the development of improved approaches to predicting them.

METHODS

Subjects and design

Over the period from September 15 to November 30, 2000, a total of 2032 patients with asthma were recruited by 19 centers of the American Lung Association Asthma Clinical Research Centers to evaluate the safety of influenza vaccine with respect to asthma

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*Participating centers listed in Appendix B.

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Abbreviations used

AS-2:	Two-week Asthma Symptom score
AS-52:	Fifty-two-week Asthma Symptom score
ASUI:	Asthma Symptom Utility Index
BMI:	Body mass index
EPAC:	Episode of poor asthma control
GINA:	Global Initiative for Asthma
GINAMED:	Global Initiative for Asthma medication group
ICS:	Inhaled corticosteroid
IRA:	Increased Risk Assessment
OCS:	Oral corticosteroid
RR:	Relative risk

exacerbations. The study was a randomized, double-masked, cross-over trial of influenza vaccine and placebo administration (vaccine followed by placebo or placebo followed by vaccine) separated by 2 to 4 weeks (mean, 22 days). Patients were eligible if they were age 3 to 64 years, had physician-diagnosed asthma, had been receiving prescribed medication for asthma within the previous 12 months, and had no acute asthma exacerbation, defined as the absence of unscheduled physician or emergency department visits, hospitalizations, or increased doses of systemic steroids during the 2 weeks before enrollment. Exclusion criteria were allergy to egg or thimerosal, inability to perform peak flow maneuvers adequately (if older than 5 years), lack of a telephone, history of Guillain-Barré syndrome, influenza vaccine within the previous 6 months, a febrile illness (temperature $\geq 38^{\circ}\text{C}$) within 24 hours of enrollment, or any condition that, in the opinion of the investigator, might put a patient at risk or interfere with his/her participation in the study. All centers had approval by their Institutional Review Boards, and all subjects (or their parents/guardians) gave written informed consent.

Before randomization, all patients completed a detailed questionnaire that included demographic characteristics, height and weight, medical insurance, smoking, current and past asthma symptoms, asthma history (hospitalization, unscheduled health care visits, systemic corticosteroid use during the previous 12 months), and current asthma medications, including rescue medication use for the preceding 2 weeks. Peak flow was measured in all participants at baseline and preceding each injection. FEV₁ and forced vital capacity were measured at baseline in a subgroup of patients. For 14 days after each injection, patients recorded symptoms thought to be associated with the injection and completed a detailed daily asthma diary, recording asthma symptoms, use of asthma medications including corticosteroids, unscheduled contact with health care providers (telephone or visit) for asthma, and absence from school or work because of asthma. They also recorded morning peak expiratory flow rates (Mini-Wright peak flow meters; Ferraris Respiratory, Louisville, Colo) at least 6 hours after any inhalation of bronchodilator rescue medication. Questionnaires and daily diary cards were permitted to be filled out by parents for participants unable to complete them independently.

We defined an episode of poor asthma control (EPAC) as any 1 or more of the following: (1) peak flow decrease, a decrease of at least 30% in the peak expiratory flow rate from the second highest morning peak expiratory flow rate measured during the study (the personal best); (2) increased rescue medication, an increase in the daily use of bronchodilator rescue medication (eg, albuterol) above the average use reported in the 2 weeks before randomization (increase of 4 or more puffs from a metered dose inhaler, or 2 or more uses of nebulized albuterol, for the relief of symptoms); (3) new/increased oral corticosteroids (OCSs), additional or new OCSs in the treatment regimen; or (4) unscheduled healthcare, the unscheduled use of health

care for the treatment of asthma, including a visit to the emergency department, a hospitalization, or a visit or a telephone call to a health care provider. We further defined an exacerbation to be the subset of EPACs characterized either by new or increased OCSs or by an unscheduled healthcare encounter for asthma.

We compared baseline demographics, symptoms, and lung function with EPAC and exacerbation rates over the subsequent two 2-week periods. Because exacerbation rates after placebo and influenza vaccine were similar,⁵ we pooled the data after both injections. Twenty-five percent of the diary periods were consecutive, 65% were separated by 1 week or less, and 87% of the periods were separated by 2 weeks or less.

Severity scores were derived from baseline data concerning past asthma history and current medication use. We developed an Increased Risk Assessment (IRA) Questionnaire that dichotomized participants on the basis of past asthma history and was considered positive if a participant had ever been intubated for asthma, had been hospitalized 2 or more times for asthma, had received 3 or more courses of OCS for asthma in the past year, or had 2 or more unscheduled health contacts for asthma in the past year. Medication use was assessed according to approximate GINA medication classifications,⁴ a 4-point scale of ascending severity, which we refer to as GINAMED.

Asthma questionnaires administered at enrollment were the Asthma Symptom Utility Index (ASUI)⁶ and 2 shorter questionnaires evaluating symptoms over the previous year (AS-52) and the previous 2 weeks (AS-2; questionnaires are detailed in [Appendix A](#)). The ASUI is a validated scale with 10 questions concerning the previous 2 weeks that assess the frequency and severity of asthma symptoms (cough, wheeze, dyspnea, and nighttime waking) and medication side effects. The ASUI was scored using a sophisticated scheme based on multiattribute utility assessment methods as described previously.⁶ The AS-2 was derived from a subset of the ASUI using 4 questions concerning symptom frequency over the period of the preceding 2 weeks. The AS-52 was derived from 5 questions concerning symptom frequency (nighttime waking, cough or wheeze with exercise, cough or wheeze without exercise, rescue medication use, and work or school limitation for asthma) over the period of the preceding 52 weeks. For both the AS-2 and the AS-52, each symptom was evaluated on a 1 to 4 scale, with higher numbers indicating greater symptom frequencies. The AS-2 and the AS-52 for each patient were the average of the responses to the questions. Average scores were then grouped arithmetically: 1.00 to 1.75, 1.75 to 2.50, 2.50 to 3.25, and 3.25 to 4.00.

FEV₁ and peak flow were reported as a percent of the predicted normal values⁷ and were divided into 2 groups separated at 65% of predicted for each parameter.

Statistical methods

The primary analyses involved all EPACs and exacerbations, however defined, and secondary analyses examined each of the 4 possible EPAC components separately. Bivariate analyses compared EPAC and exacerbation rates across groups on the basis of baseline variables, questionnaire results, and lung function. The mean EPAC and exacerbation rates with 95% CIs and the relative risks (RRs) for each grouping of the explanatory variable were calculated. On the basis of results of bivariate analyses, logistic regression models were constructed for various subgroups, and checks for linearity and interaction were performed. All data analyses were performed with SAS software, version 8.01 (SAS Institute, Cary, NC).

RESULTS

Of 2032 patients initially enrolled and assigned to vaccine administration, 2009 (98.9%) received both

TABLE I. Participant baseline characteristics
(total N = 1949)

Characteristic	No.	Percent
Age (y)		
<10	353	18.1
10-19	380	19.5
20-29	187	9.6
30-39	272	14.0
40-49	341	17.5
50-59	251	12.9
>59	115	5.9
Ethnicity		
White	1266	65.0
African American	479	24.6
Hispanic	120	6.2
Other	75	3.9
Smoking		
Never	1524	78.2
Former	330	16.9
Current	93	4.8
Sex		
Male	740	38.0
Female	1207	61.9
Weight		
Underweight (BMI < 18.5)	13	0.7
Normal (BMI 18.5-25)	887	45.5
Overweight (BMI 25-30)	372	19.1
Obese (BMI > 30)	643	33.0
Health insurance		
Private	515	26.4
Health maintenance organization/ managed care	914	46.9
Medicaid/Medical Assistance	253	13.0
Medicare	75	3.9
Other	176	9.0
None	289	14.8
Current ICS		
No	700	35.9
Yes	1229	63.1
Education (age 18 y and older)		
Some postgraduate	282	14.5
College graduate	314	16.1
Some college	358	18.4
High school/equivalent	191	9.9
Grade 12 or less	303	15.6
Age < 18 or missing	500	25.7

injections, 1952 (96.1%) received both injections and completed 14-day diaries after each postinjection period, and 1949 also completed baseline questionnaires. The group with complete diary data (28 days) and baseline questionnaires was included in our current analysis, combining postvaccine and postplacebo data. Peak flow was measured at the time of each injection in 1821 (93.3%) and FEV₁ was measured in 990 participants.

Baseline characteristics of participants are shown in Table I. They were predominantly female, and nearly a quarter was African American. All age groups up to 59 years were well represented, as were various levels of education. There were few self-identified current smokers.

TABLE II. Episode frequencies

Episode type	Frequency (CI)*
Increased β -agonist	24.3 (22.4-26.2)
Drop in peak flow	24.0 (22.1-25.9)
New/increased OCS	9.9 (8.6-11.3)
Unscheduled health care	9.9 (8.6-11.2)
EPAC (see text)	43.3 (41.0-45.4)
Exacerbation (see text)	14.5 (12.9-16.0)

*Episode frequency rate in percentages with 95% CIs.

Approximate quartiles of body mass index (BMI) are shown, and these varied substantially. Most participants were taking inhaled corticosteroids (ICSs), although of the number reported, only 86% were taking ICSs daily.

Over the 28 days, 43.2% of the participants had an EPAC as defined. EPAC characteristics, which are not mutually exclusive, are shown in Table II. The predominant EPAC types were decreases in peak flow and increased use of rescue medication, with distinctly lower frequency of exacerbations, 14.5%, characterized by use of OCS or unscheduled health care. Nearly 10% of participants had unscheduled health care for asthma, and another 4.6% used systemic steroids in the absence of unscheduled health care.

Table III shows EPAC and exacerbation frequencies (events) analyzed in relation to baseline characteristics. Children < 10 years old had significantly higher event rates than other age groups, which did not differ greatly. African Americans had higher event rates than participants of other ethnicities. People with greater educational attainment were less likely to have events, but differences were not significant. Current smokers had relatively high event rates. Medicaid recipients were more likely to have events than participants with other, or no, health insurance. Participants with a past history of serious acute episodes, measured by the IRA instrument, were more likely to have events than those without such a history. Participants on more intensive therapy were more likely to have events as indicated by the GINAMED index. Participants with baseline peak flows of <65% predicted normal were more likely to have events, as were participants with FEV₁ < 65% predicted normal. Sex and obesity per se (defined as BMI > 30 for adults and BMI > 95th percentile for children) were not significantly associated with event rates; however, individuals in the lowest and highest BMI quartiles did have significantly more events than those in the middle quartiles (risk ratio, 1.26; $P < .001$).

Positive responses to symptom questionnaires predicted events in a relatively quantitative manner; the RR for both EPACs and exacerbations increased more or less linearly with the presence and intensity of symptoms (Table IV). Results obtained with the different questionnaires were closely correlated with each other, and performed similarly in multivariate analyses. We will present data from such analyses using the AS-2 because it performed as well as the others, it was the shortest, and its focus on the preceding 2 weeks seemed most relevant

TABLE III. Participant baseline characteristics and episode frequencies

Variable	N	EPACs		Exacerbations	
		Frequency (CI)*	RR	Frequency (CI)*	RR
Age (y)					
≥10	1592	40.0 (37.6-42.4)	1.00	12.8 (11.2-14.5)	1.00
<10	357	57.7 (52.6-62.9)	1.44	21.8 (17.5-26.2)	1.70
Ethnicity					
Other	1461	38.8 (36.3-41.3)	1.00	12.4 (10.7-14.1)	1.00
African American	479	56.6 (52.1-61.0)	1.46	20.7 (17.0-24.3)	1.67
Smoking					
Not	1854	42.3 (40.1-44.6)	1.00	14.3 (12.8-15.9)	1.00
Current	93	62.4 (52.3-72.4)	1.48	17.2 (9.4-25.0)	1.20
GINAMED					
1	526	35.9 (31.8-40.0)	1.00	7.8 (5.5-10.1)	1.00
2	892	43.3 (40.0-46.5)	1.21	16.0 (13.6-18.4)	2.05
3	350	46.3 (41.0-51.5)	1.29	16.0 (12.1-19.9)	2.05
4	181	58.6 (51.3-65.8)	1.63	23.2 (17.0-29.4)	2.97
IRA					
Negative	1131	37.0 (34.1-39.8)	1.00	9.9 (8.2-11.6)	1.00
Positive	818	52.0 (48.5-55.4)	1.41	20.8 (18.0-23.6)	2.10
Peak flow (% predicted)					
≥65%	1657	41.8 (39.4-44.1)	1.00	14.0 (12.3-15.7)	1.00
<65%	153	59.5 (51.6-67.3)	1.42	17.6 (11.5-23.8)	1.26
FEV ₁ (% predicted)					
≥65%	853	38.6 (35.3-41.8)	1.00	12.3 (10.1-14.5)	1.00
<65%	131	56.5 (47.9-65.1)	1.46	20.6 (13.6-27.6)	1.67
Health insurance					
All other	1696	40.9 (38.6-43.3)	1.00	13.5 (11.9-15.1)	1.00
Medicaid/Medical Assistance	253	58.9 (52.8-65.0)	1.44	20.9 (15.9-26.0)	1.55
Education					
Some postgraduate	282	25.2 (20.1-30.3)	1.00	11.0 (7.3-14.7)	1.00
College graduate	314	35.7 (30.3-41.0)	1.42	10.2 (6.8-13.6)	0.93
Some college	358	42.7 (37.6-47.9)	1.69	12.0 (8.6-15.4)	1.09
High school graduate	192	50.5 (43.4-57.7)	2.00	14.6 (9.5-19.6)	1.33
Grade 12 or less	303	45.5 (39.9-51.2)	1.81	14.5 (10.5-18.5)	1.32
BMI quartiles					
<19.86	479	49.9 (45.4-54.4)	1.00	17.3 (13.9-20.7)	1.00
19.87-24.94	478	38.5 (34.1-42.9)	0.77	14.6 (11.5-17.8)	0.84
24.95-30.42	479	38.0 (33.6-42.4)	0.76	10.0 (7.3-12.7)	0.58
≥30.43	479	46.6 (42.1-51.0)	0.93	16.1 (12.8-19.4)	0.93
Weight groups					
Norm (BMI 18.5-25)	887	44.5 (41.3-47.8)	1.00	16.3 (13.9-18.8)	1.00
Underweight (BMI < 18.5)	13	15.4 (NA)	0.35	NA	NA
Overweight (BMI 25-30)	372	34.7 (29.8-39.5)	0.78	8.3 (5.5-11.2)	0.51
Obese (BMI > 30)	643	47.0 (43.1-47.8)	1.06	15.9 (13.0-18.7)	0.98
Sex					
Male	740	43.4 (39.8-47.0)	1.00	13.6 (11.2-16.1)	1.00
Female	1207	43.1 (40.3-45.9)	0.99	14.9 (12.9-16.9)	1.10
ICS use					
No	700	38.6 (35.0-42.2)	1.00	10.6 (8.3-12.9)	1.00
Yes	1229	45.9 (43.1-48.7)	1.19	16.8 (14.7-18.9)	1.58

*Episode frequency rate in percentages with 95% CIs.

to clinical practice. Similarly, results of measurements of peak flow and FEV₁ were closely correlated, and we used the former in multiple regressions because peak flow is more conveniently obtained in clinical practice.

In multiple regression analyses including all participants, age was an important covariate. This was because children ≤10 years old behaved differently from the

remainder of participants, and were therefore analyzed separately. In participants age >10 years, several factors predicted the likelihood of events independently of questionnaire results. These were ethnicity, lung function (peak flow), GINAMED score, smoking status, and past history of severe exacerbations (IRA; Table V). In young children, who had the highest event rates, the only

TABLE IV. Questionnaire scores and episode frequencies

Questionnaire/score	N	EPACs		Exacerbations	
		Frequency (CI)*	RR	Frequency (CI)*	RR
ASUI (in order of more symptoms)					
>0.982	398	29.4 (24.9-33.9)	1.00	9.5 (6.6-12.4)	1.00
0.883-0.982	564	38.5 (34.4-42.5)	1.31	12.8 (10.0-15.5)	1.35
0.755-0.882	482	47.9 (43.4-52.4)	1.63	16.8 (13.5-20.2)	1.77
<0.755	480	55.4 (51.0-59.9)	1.88	18.1 (14.7-21.6)	1.91
AS-52 (in order of more symptoms)					
1.00-1.74	472	32.4 (28.2-36.7)	1.00	11.4 (8.6-14.3)	1.00
1.75-2.49	905	42.5 (39.3-45.8)	1.31	14.0 (11.8-16.3)	1.23
2.50-3.24	373	51.7 (46.6-56.8)	1.60	16.4 (12.6-20.1)	1.44
3.25-4.00	128	61.7 (53.2-70.3)	1.90	22.7 (15.3-30.0)	1.99
AS-2 (in order of more symptoms)					
1.00-1.74	973	35.1 (32.1-38.2)	1.00	11.3 (9.3-13.3)	1.00
1.75-2.24	607	48.9 (44.9-52.9)	1.39	18.1 (15.0-21.2)	1.60
2.25-3.24	252	51.6 (45.4-57.8)	1.47	14.7 (10.3-19.1)	1.30
3.25-4.00	106	66.0 (56.9-75.2)	1.88	22.6 (14.5-30.7)	2.00

*Episode frequency rate in percentages with 95% CIs.

TABLE V. Logistic regression for predicting episodes: multiple logistic regression (participants ≥ 10 years old)

Variable	EPACs		Exacerbations	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Ethnicity other than African American	0.537 (0.414-0.696)	<.0001	0.559 (0.399-0.783)	.007
GINAMED group	1.335 (1.055-1.690)	.0163	1.312 (0.950-1.813)	.0992
Peak flow <65%	1.688 (1.167-2.441)	.0055	1.206 (0.754-1.930)	.4352
Insurance other than Medicaid	0.711 (0.500-1.011)	.0573	0.907 (0.586-1.403)	.6607
BMI quartile	0.996 (0.893-1.111)	.9449	0.975 (0.835-1.138)	.7443
Current smoker	1.785 (1.119-2.847)	.0149	1.017 (0.563-1.837)	.9545
IRA	1.297 (1.032-1.632)	.0261	1.911 (1.382-2.642)	<.0001
AS-2 group	1.615 (1.373-1.898)	<.0001	1.231 (0.994-1.525)	.0566

significant correlate of EPAC rates was IRA, although both IRA and the GINAMED classification were statistically significant when using exacerbations as the outcome. Questionnaire results did not predict events in young children (Table VI). We also looked at the individual components of the AS-2 questionnaire, and discovered that questions regarding wheeze and nighttime waking were marginally more discriminating than the others (not shown).

DISCUSSION

In our study of patients with asthma recruited for a relatively short-term trial of influenza vaccine, we found factors suggestive of an increased risk of subsequent episodes of poor asthma control and exacerbation. We studied a large group of physician-diagnosed patients with asthma with wider ranges of age, demographics, and disease severity than are usually reported. Although we excluded individuals with current or recent exacerbations, and individuals under active therapy for an exacerbation, the rate of asthma episodes among our participants was

high,⁸⁻¹² amounting to 43% over the two 14-day periods of observation. Although this high rate is likely related to our liberal definition of an EPAC, 14.6% of participants experienced more serious exacerbations involving OCSs and/or unscheduled visits to health care providers in this relatively short follow-up period. We did study participants over the fall and winter months, which may also have contributed to somewhat increased rates of asthma episodes. Nevertheless, the rates of such episodes in this study were higher than those cited in other trials, probably because previous trials compared asthma drugs in adults only, featured more stringent entry criteria, and, in particular, used run-in periods to assure stability. Accordingly, our study group probably resembled the real world, and if this is the case, one might conclude that asthma control in the real world is suboptimal, as has been previously suggested.^{13,14}

Others have shown that symptom questionnaires can be predictive of health care use in asthma.¹⁵ In our study, increasing levels of symptoms revealed by 3 questionnaires related strongly to the probability of both a subsequent EPAC and an exacerbation (Table IV). The ASUI, which assessed the presence and severity of symptoms in the

TABLE VI. Logistic regression for predicting episodes: multiple logistic regression (participants < 10 years old)

Variable	EPACs		Exacerbations	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Ethnicity other than African American	1.069 (0.563-2.029)	.8375	1.688 (0.790-3.606)	.1766
GINAMED group	3.328 (0.914-12.121)	.0682	2.902 (1.112-7.576)	.0296
Peak flow <65%	0.883 (0.147-5.310)	.8918	0.402 (0.040-4.020)	.4379
Insurance other than Medicaid	0.654 (0.313-1.365)	.2582	0.744 (0.337-1.646)	.4660
BMI quartile	0.836 (0.570-1.227)	.3604	1.134 (0.729-1.766)	.5772
Current smoker	—	—	—	—
IRA	1.743 (1.036-2.934)	.0364	2.186 (1.176-4.062)	.0134
AS-2 group	1.224 (0.776-1.930)	.3849	1.334 (0.815-2.184)	.2524

previous 2 weeks, was the only previously validated questionnaire used. The AS-2 assessed the presence, but not the severity, of symptoms in the previous 2 weeks and represents a subset of the ASUI questions. Finally, the AS-52 assessed symptoms over the previous year. The risk ratios derived from the 3 questionnaires were essentially the same, and results were closely correlated because they basically asked the same questions. The AS-2 results are used in logistic regressions because the AS-2 was the simplest test and accordingly more relevant to clinical practice.

In adults, the strongest predictor of EPACs was questionnaire results, but other factors were also important (Table V). Being African American was an independent risk factor for both EPACs and exacerbations, even after potential confounders related to socioeconomic status such as educational attainment and the presence of health insurance were considered. This is not unprecedented,^{16,17} although the cause is unclear and controversial. EPACs were more common in adults with characteristics associated with severe asthma, such as a past history of severe events (IRA), high levels of medication use (GINAMED), and low levels of pulmonary function. These findings seem rational, and have been observed in other studies.¹⁷⁻¹⁹ Smokers were more likely to have events than nonsmokers, which has also been observed previously.²⁰ There is evidence that patients with asthma who smoke may respond less well to steroids than those who do not.^{21,22} It should be noted that although the multiple regression of Table V for EPACs was highly significant, it explained only about 12.7% of the variation in exacerbation frequency, and the area under the receiver-operator curve derived from it was 0.69, lower than that generally regarded as indicative of a reliable clinical test (0.80).

The highest EPAC and exacerbation rates we observed were in children ≤10 years of age (Table III), in agreement with studies showing relatively high asthma hospitalization rates in young children.²³ However, in multiple regression analyses, the only significant baseline correlate with EPAC frequency was IRA (history of previous severe exacerbations as defined previously). Specifically, questionnaire results did not predict EPAC or exacerbation rates in our model, in contrast with our finding in older age groups, and therefore symptom questionnaires appear to be a much less useful tool for predicting events in young

children. It would seem either that communication with children regarding symptoms is much more difficult than with adults, or that EPACs relate much less well to past symptoms in this age group. The former seems more likely, and it is worth noting that the ASUI, the best-validated questionnaire, has not been previously used in children. Children may have poorer recall, and additional training in self-appraisal may be needed for questionnaires to be useful in this group. Our finding is not unprecedented. In a clinical trial involving low-income children, Sharek et al²⁴ found that parent-reported symptoms and diary data did not correlate well initially, but agreement improved throughout the trial. The absence of significance for other risk factors is easier to explain. Ethnicity was not important, perhaps because this was a volunteer population, and differences in medical insurance were considered. Failure of lung function measurements to predict events was also noted by Sharek et al.²⁴ The fact that medication levels (GINAMED) were not explanatory probably reflects the relatively short duration of the disease in children.

Our study does have several important limitations. First, the diary data were collected over 2 periods that were not consecutive in many participants, although most of the gaps were quite short and were determined before study entry (ie, the 2nd injection was scheduled at the time of the 1st injection). Second, our data represent a relatively short duration, and thus, additional study would be required to determine whether our conclusions apply over longer periods. Third, we do not have complete information to relate baseline treatment with conventional measures of asthma severity, so we are unable to ascertain what proportion of our participants was treated appropriately or undertreated, although our population may well represent typical patients with asthma in the community. Finally, in the youngest children, our data may have problems of poor recall, biased surrogate reporting, and increased attention. These problems are not unique to our study and have been discussed previously.^{24,25}

In summary, in a large, diverse group of patients with asthma, episodes of poor asthma control and asthma exacerbations were common (43.3% and 14.5%, respectively) within a 4-week period. Events were most common in younger (<10 years) patients, and we were unable to identify major significant risk factors other than IRA in these children. In older patients, several significant risk factors were identified but were not strong enough to

predict EPACs or exacerbations reliably in individual patients. We suggest that further investigation is needed to explore other factors or biomarkers that better predict future worsening of asthma status and to evaluate our findings over longer periods.

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APPENDIX A

Questionnaires

The AS-52 is the average of the numeric responses to the following 5 questions: (1) In the past year, did you awake from sleep because of cough or wheeze? (2) In the past year, did you cough or wheeze with exercise? (3) In the past year, did you cough or wheeze without exercise? (4) In the past year, did you require the use of an inhaled quick relief bronchodilator to relieve asthma symptoms (eg, cough, wheeze, chest tightness)? (5) In the past year, did you limit your work, school, or other daily activities because of asthma symptoms (eg, cough, wheeze, chest tightness)? Each question had the following possible responses: 1 (almost every day/night), 2 (at least 1 time per week but not daily), 3 (at least 1 time per month but not weekly), 4 (never).

The AS-2 is the average of the numeric responses to the following 4 questions: (1) How many days were you bothered by coughing during the past 2 weeks? (2) How many days were you bothered by wheezing during the past 2 weeks? (3) How many days were you bothered by shortness of breath during the past 2 weeks? (4) How many days were you awakened at night by your asthma during the past 2 weeks? Each question had the following possible responses: 1 (not at all), 2 (1-3 days), 3 (4-7 days), 4 (8-14 days). These questions represent a subset of the questions used for the ASUI.

The ASUI asks questions about both symptom frequency and symptom severity and has been described previously.⁶

APPENDIX B

Participating centers

The following persons participated in the study: Baylor College of Medicine, Houston, Tex: N. Hanania (principal investigator), P. Enright (coprincipal investigator), M. Sockrider (coprincipal investigator), A. Delgado (principal clinic coordinator for adults), R. McConnell (principal

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