Recent asthma exacerbations predict future exacerbations in children with severe or difficult-to-treat asthma

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Background: Children with severe/difficult-to-treat asthma experience high morbidity including frequent severe exacerbations. More knowledge is required to identify predictors of these exacerbations to reduce their occurrence.
Objective: To investigate the risk of future severe exacerbations (FSEs) in children with severe/difficult-to-treat asthma and recent severe exacerbations (RSEs).
Methods: We analyzed the occurrence and association of RSE (defined as 1 or more corticosteroid bursts during the 3 months before each of 3 annual visits) and FSE (defined as 1 or more corticosteroid bursts 6 or 12 months later) in children age 6 to 11 years in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens 3-year observational study. Repeated measures logistic regression analysis assessed the risk of FSE adjusted for demographics and clinical variables.
Results: In a multivariable model, FSE at 6 months was most strongly predicted by RSE (odds ratio [OR], 3.08; 95% CI, 2.21-4.28) and having 3 to 4 allergic triggers (OR, 2.05; 95% CI, 1.31-3.20). Race (OR, 1.77; 95% CI, 1.25-2.51) and being very poorly controlled according to the impairment component of the National Heart, Lung, and Blood Institute guidelines (OR, 1.59; 95% CI, 1.14-2.23) also significantly predicted FSE.
Conclusion: Recent severe asthma exacerbations are an important independent predictor of FSE in children with severe/difficult-to-treat asthma and should be considered when establishing asthma management plans. (J Allergy Clin Immunol 2009;124:921-7.)

Key words: *Severe asthma, pediatric asthma, exacerbation, predictor of exacerbation, corticosteroid burst, long-term control*

Asthma is a major health problem that affects nearly 300 million people[1] or as many as an estimated 20% of children and 8% of adults worldwide.[2] In 2005, more than 9 million children in the United States under 18 years of age (13%) had ever been diagnosed with asthma, and about 6.5 million (8.9%) still had the disease.[3] Severe or difficult-to-treat asthma, broadly defined as asthma that is refractory to treatment and poorly controlled over time,[4] affects only 5% to 10% of the patient population, but it accounts for a disproportionate share of health care costs and morbidity associated with the disease.[5-9]

Studies have documented the high cost of asthma-related medication and health care use (HCU) in children and how these costs relate to morbidity and symptom control.[8,10-12] As with adults, annual per capita health care costs for children increase significantly with severity; the annual cost for severe asthma is $1840 compared with $390 and $682 for mild and moderate asthma, respectively.[10] Among children with severe or difficult-to-treat asthma, rates of HCU are high despite use of multiple medications; of patients using 3 or more long-term controllers, 53% of children reported an oral corticosteroid burst and 25% had an emergency department visit within a 3-month period.[8]

The ability to identify patients at greatest risk for future severe exacerbation (FSE) is important for developing effective prevention strategies, reducing health care costs, and achieving the goals of asthma management.[13,14] A previous analysis of adult patient data from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, the largest prospective, 3-year, multicenter observational study of patients with severe or difficult-to-treat asthma,[8,15] showed that a recent severe exacerbation (RSE) or recent corticosteroid burst is a strong independent predictor of FSE in this patient population.[16] Given the burden of asthma in children and the lack of available data in this age group, particularly in children with severe asthma, we performed an additional analysis focusing on young patients, age 6 to 11 years, in the TENOR study. The objective was to evaluate RSE as a potential predictor of FSE after adjustments for asthma impairment domain of asthma control and other risk factors.

METHODS

Study design

The methods and baseline cohort characteristics of the TENOR study have been previously described.[8,15] Briefly, TENOR was a prospective, observational,

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Abbreviations used
ATAQ: Asthma Therapy Assessment Questionnaire
FSE: Future severe exacerbation
HCU: Health care use
NHLBI: National Heart, Lung, and Blood Institute
OR: Odds ratio
PACT: Pediatric Asthma Controller Trial
PAQLQ(S): Pediatric Asthma Quality of Life Questionnaire With Standardized Activities
RSE: Recent severe exacerbation
TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

3-year study (2001-2004) conducted in the United States in patients with severe difficult-to-treat asthma followed by asthma specialists. Patients were recruited from diverse geographic areas to represent typical patient care settings, including managed care organizations, community physicians/practices, and academic centers. No experimental intervention was involved; patients continued to receive asthma medications and treatments as recommended by their allergists or pulmonologists. At baseline, 4756 patients were enrolled at 283 study sites, of whom 637 (13.4%) were children age 6 to 11 years.

Inclusion and exclusion criteria

Children were included in the TENOR study if they were diagnosed with severe asthma or with mild/moderate asthma considered difficult-to-treat by the study site asthma specialist, had received health care from their current provider for ≥1 year, could read and understand English, and satisfied at least 1 of the following conditions of high medication or HCU:

- ≥2 oral corticosteroid bursts during the past 12 months
- ≥2 unscheduled clinic or hospital visits for asthma care during the past 12 months
- current requirement for chronic, daily high doses of inhaled corticosteroids as defined by the National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education and Prevention Program refractory asthma guidelines for children[17]or ≥5 mg oral prednisone
- current use of 3 or more medications to control asthma

Patients were excluded from the study if they had a primary diagnosis of cystic fibrosis, severe cardiovascular disease (New York Heart Association class II or higher), cancer (not including nonmelanoma skin cancer or cancer in remission for ≥5 years), severe psychiatric disorder (not including anxiety or depression), or significant systemic disease (<2-3 years of life expectancy).

Data collection

Data were collected at semiannual visits. Demographic and clinical data were collected by study coordinator interview and evaluation. In addition, patients completed a self-administered questionnaire. For children younger than 12 years of age, the parent or guardian was present to help answer interview questions and complete the questionnaires. At study entry and at each 6-month visit during the 3-year follow-up, patients reported asthma-related HCU during the previous 3 months. Patients brought their medications, including long-term controllers and quick-relief medications, to the coordinator interview to record current use. Histories of allergic rhinitis and atopic dermatitis, as well as asthma trigger information, were self-reported.

Asthma control

Asthma control was assessed by using the NHLBI guidelines impairment domain.[18] The impairment metrics (symptoms, nighttime awakenings, interference with normal activity, short-acting β_2-agonist use, and lung function) were obtained from data collected in the TENOR study at baseline and annual visits. Information regarding symptoms, nighttime awakenings, and interference with normal activity was obtained from the Pediatric Asthma Quality of Life Questionnaire With Standardized Activities (PAQLQ[S]).[19] The PAQLQ(S), a validated questionnaire developed for patients with asthma age 7 to 17 years, was administered and yielded data on the basis of recall of the previous 1-week period. Although the age range of subjects for whom the instrument was developed does not include 6-year-olds, who are included in the present analysis, the individual items evaluated provided the requisite data for mapping the responses accurately to the guidelines. Detailed information describing the data collected with the PAQLQ(S) and their correspondence to the NHLBI guideline criteria has been reported previously.[20] The use of short-acting β_2-agonists for symptom control was captured as part of medication use data, and lung function—prebronchodilator FEV_1—was assessed by spirometry. Medication use and spirometry were measured on the date of assessment. At each time point, patients were grouped by their asthma impairment status into 1 of 3 cohorts defined by the impairment domain of the NHLBI guidelines:[18] very poorly controlled, not well controlled, and well controlled.

Predictors and outcome measures

An RSE was defined as 1 or more corticosteroid bursts within the 3 months before baseline, month 12, and month 24 of the study period. For consistency with a previously reported analysis of adult patients,[16] a similar set of additional candidate predictor variables was considered: age at baseline, duration of asthma at baseline, sex, race/ethnicity (white/nonwhite), body mass index for age-assessed obesity, number of allergic triggers (animals, dust, mold, pollen), and number of nonallergic triggers (emotional stress, sinus infection). Four additional candidate variables (passive smoking exposure, number of long-term controllers used at baseline, the NHLBI guidelines control impairment domain, and median income within zip code) were added for the current pediatric analysis.

As the key outcome, FSE was defined as 1 or more corticosteroid bursts reported 6 months and 12 months after an RSE.

Statistical analyses

Categorical data and continuous data are reported by using percentages or means and SDs, respectively. The Pearson χ^2 test for categorical data and the 2-sample *t* test for continuous data are used to describe the differences between patients with RSE and those without RSE. Both proportions and means are reported as a function of nonmissing data. Missing data were uncommon and occurred typically in less than 1% of study patients, except for spirometry (13.7%) and responses to the Asthma Therapy Assessment Questionnaire (ATAQ; 25.4%). Assessments with missing covariate data were excluded from the final models if any of the significant covariates were missing. Exacerbation outcomes for the preceding 3 months were measured in 6-month intervals. These repeated dichotomous outcomes were analyzed by using a repeated measures logistic regression with generalized estimating equations. All patients with data for at least 1 follow-up outcome contributed to the regression models.

To arrive at a final model, backward selection was used starting with the prespecified set of candidate variables. An entry criterion of $P < .05$ was used for statistical significance during this process.

Two models were considered for this analysis. Model I (Fig 1) used the first 3 annual visits to define the candidate predictor variables and the 2 subsequent semiannual follow-ups to define the outcome variable. Patients with complete 3-year data could contribute as many as 6 assessments to the model. Backward selection proceeded as described until a list of significant predictor variables was achieved. Model II (Fig 2) started with this list of candidate variables but only considered FSE in the 3 months before the subsequent semiannual visit as the outcome. Thus, each patient could only contribute a maximum of 3 assessments to the model, and the interpretation could be more tightly focused on near-term events. Additional backward selection was then conducted, resulting in a reduced set of predictors, which was used to compute the predicted probabilities of FSE.

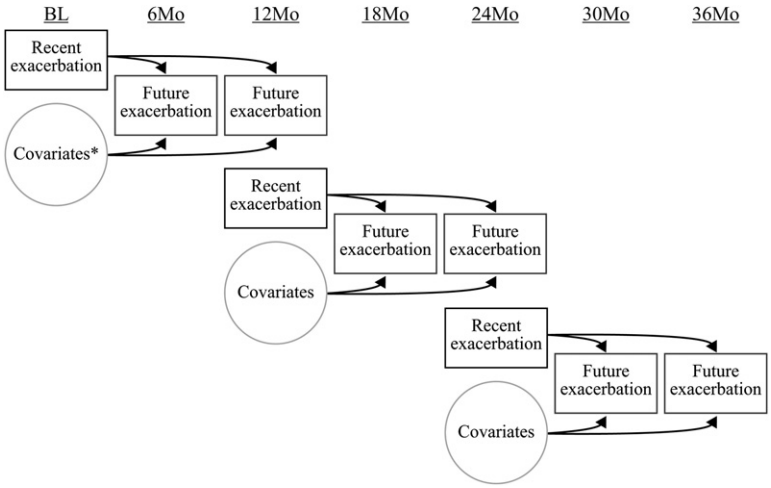

FIG 1. Model I diagram. *Many covariates were collected annually and not semiannually, requiring that the covariates be defined only at baseline *(BL)*, 12 months, and 24 months.

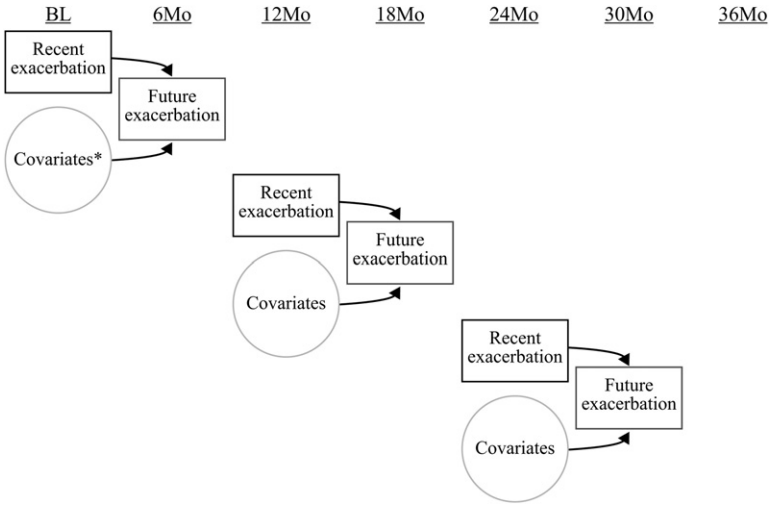

FIG 2. Model II diagram. *Many covariates were collected annually and not semiannually, requiring that the covariates be defined only at baseline *(BL)*, 12 months, and 24 months.

RESULTS

Baseline demographics and RSE

Of the 637 children age 6 to 11 years in the TENOR database, 68 did not have any follow-up data, and 6 others did not have follow-up visits during which HCU data were recorded, leaving data from 563 children available for analysis. Children excluded from the analysis were not appreciably different from those included in terms of age, physician-assessed asthma severity, and number of asthma control problems, but they were more likely to be girls (44.4% vs 31.3%; $P = .025$) and black (35.1% vs 23.4%; $P < .001$).

Approximately half of all children in the analysis had experienced RSE within 3 months before study enrollment (Table I). Compared with children without RSE, those with RSE had a slightly longer mean duration of asthma ($P = .011$) and also had poorer lung function than the non-RSE cohort, as assessed by prebronchodilator percent predicted FEV_1 ($P = .012$).

Asthma impairment and RSE

At baseline, compared with children without RSE, those who had RSE were more likely to have very poorly controlled asthma as measured by the NHLBI guidelines impairment domain (70.5% vs 54.3%; $P = .001$) and to have reported 2 or more asthma control problems by the ATAQ (86.0% vs 65.3%; $P < .001$; Table I).

Predictors of future exacerbations

When analyzed in a multivariable model that included 6-month and 12-month events, children with a recent exacerbation had a 2-fold greater risk of FSE (odds ratio [OR], 1.99; 95% CI, 1.51-2.61; Table II). Reporting 3 or more allergic triggers (OR, 2.01; $P < .001$), having at least 1 nonallergic trigger (OR, 1.52; $P = .019$), and being nonwhite (OR, 1.76; $P < .001$) were also strong independent predictors of FSE for children. In addition, having very poorly controlled asthma as measured by the NHLBI guidelines

TABLE I. Baseline patient demographics and clinical characteristics: stratification by RSE

Characteristic	No RSE	With RSE	*P* value
Total no. of children	282	281	
Age, n (%)			
6-8 y	91 (32.3)	111 (39.5)	.074
9-11 y	191 (67.7)	170 (60.5)	
Sex, n (%)			
Female	87 (30.9)	89 (31.7)	.83
Male	195 (69.1)	192 (68.3)	
Race/ethnicity, n (%)			
Nonwhite*	96 (34.0)	117 (41.6)	.063
White	186 (66.0)	164 (58.4)	
BMI for age obesity, n (%)			
Not obese	235 (83.3)	220 (78.6)	.15
Obese	47 (16.7)	60 (21.4)	
Median income in zip code, mean ± SD	$52,012 ± $19,263	$50,752 ± $19,894	.45
Duration of asthma (y), mean ± SD	5.8 ± 2.7	6.4 ± 2.4	.011
Long-term controllers, n (%)			
0-1	28 (9.9)	24 (8.5)	.15
2	98 (34.8)	79 (28.1)	
3+	156 (55.3)	178 (63.3)	
At least 1 smoker at home, n (%)			
No	206 (73.6)	212 (76.3)	.46
Yes	74 (26.4)	66 (23.7)	
Allergic triggers,† n (%)			
0	40 (14.3)	36 (12.9)	.66
1-2	128 (45.7)	121 (43.4)	
3-4	112 (40.0)	122 (43.7)	
Nonallergic triggers,‡ n (%)			
0	37 (13.2)	25 (9.0)	.11
1-2	243 (86.8)	254 (91.0)	
NHLBI guidelines control impairment domain, n (%)			
Well controlled	13 (5.3)	8 (3.3)	.001
Not well controlled	98 (40.3)	63 (26.1)	
Very poorly controlled	132 (54.3)	170 (70.5)	
No. of asthma control problems (ATAQ index score), n (%)			
0 problems	27 (12.7)	8 (3.9)	<.001
1 problem	47 (22.1)	21 (10.1)	
≥2 problems	139 (65.3)	178 (86.0)	
Prebronchodilator percent predicted FEV_1, mean ± SD	90.1 ± 18.5	85.7 ± 20.4	.012

BMI, Body mass index; *GL,* Guidelines.

*Nonwhite racial/ethnic groups include black, Hispanic, Asian/Pacific iIslander, American Indian/Alaskan Native, and patients who indicated their race/ethnicity as "other."

†Allergic triggers were pollen, dust, pets, and mold.

‡Nonallergic triggers were cold/sinus infection and emotional stress.

impairment domain (OR, 1.40; $P = .010$) and duration of asthma (OR, 1.06; $P = .021$) also significantly increased the risk of FSE in children. Age, sex, obesity, income, number of long-term controllers, and passive smoking were not significant predictors of FSE.

When analyzed in a multivariable model including only 6-month events, children with a recent exacerbation had more than a 3-fold greater risk of FSE (OR, 3.08; 95% CI, 2.21-4.28; Table II). Reporting 3 or more allergic triggers (OR, 2.05; $P = .002$), having very poorly controlled asthma by the impairment domain (OR, 1.59; $P = .007$), and being nonwhite (OR, 1.77; $P < .001$) were again strong independent predictors of FSE for children. Duration of asthma and nonallergic triggers were no longer significant predictors of FSE.

Predicted probabilities of a future exacerbation

Using the 6-month model to examine predicted probabilities of FSE, we found that white children with no RSE, well controlled asthma by the impairment domain, and no allergic triggers had a low (8.7%) risk of FSE, whereas nonwhite children with an RSE, very poorly controlled asthma by the impairment domain, and 3 to 4 allergic triggers had a high (63.4%) risk of FSE (Fig 3). The lowest probability of FSE for a child with an RSE and 3 to 4 allergic triggers was 37.7% (white, well controlled asthma by the impairment domain).

DISCUSSION

This study demonstrates a strong association between recent and future severe exacerbations in a large cohort of children with severe or difficult-to-treat asthma. This association persisted and remained strong (ORs ranged from 1.99 to 3.08) after adjusting for demographic and clinical variables, asthma control by the impairment domain, and allergic and nonallergic triggers, demonstrating that regardless of these other factors, RSE is the main driver of FSE in children with severe or difficult-to-treat asthma. In the adjusted regression models, asthma control as measured by the NHLBI guidelines impairment domain was an independent

TABLE II. Predictors of future exacerbations in children age 6 to 11 years: model results

	Model I*			Model II†		
	Stepwise model where future exacerbations include 6-mo and 12-mo time frame			Additional stepwise reduction of model B including only 6-mo events		
Predictors‡	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Recent exacerbation	1.99	(1.51-2.61)	<.001	3.08	(2.21-4.28)	<.001
Nonwhite vs white	1.76	(1.34-2.32)	<.001	1.77	(1.25-2.51)	.001
Allergic triggers§						
1-2 allergic triggers	1.39	(0.99-1.95)	.059	1.26	(0.82-1.93)	.29
3-4 allergic triggers	2.01	(1.40-2.89)	<.001	2.05	(1.31-3.20)	.002
NHLBI guidelines control impairment domain ||						
VPC vs NWC	1.40	(1.08-1.80)	.010	1.59	(1.14-2.23)	.007
WC vs NWC	0.89	(0.45-1.75)	.73	0.85	(0.37-1.92)	.69
Duration of asthma (per year)	1.06	(1.01-1.12)	.021	—	—	—
Nonallergic triggers,¶ 1-2 vs 0	1.52	(1.07-2.16)	.019	—	—	—

NWC, Not well controlled; *VPC,* very poorly controlled; *WC,* well controlled.

*The event of interest (future severe exacerbation) was observed at 469 assessments in 255 patients.

†The event of interest (future severe exacerbation) was observed at 250 assessments in 186 patients.

‡The stepwise model candidate predictors were age, duration of asthma, sex, white/nonwhite, obesity, number of long-term controllers, allergic triggers, nonallergic triggers, passive smoking, NHLBI 2007 guidelines of asthma control (impairment domain), and median income in zip code. Variables that are components of the NHLBI guidelines impairment domain (eg, ATAQ control problems, spirometry, and symptoms) were included only as components of the NHLBI definition.

§Patients with no triggers are the reference group. Allergic triggers include pollen, moldy/musty places, animals, and dust and are based on the question, "Symptoms of asthma are a result of…."

||Because NWC and WC are not meaningfully different, a single OR was computed for VPC vs all others and was used to calculate the predicted probabilities (OR, 1.62; 95% CI, 1.16-2.25; $P = .004$).

¶Nonallergic triggers include emotional stress and cold/sinus infection.

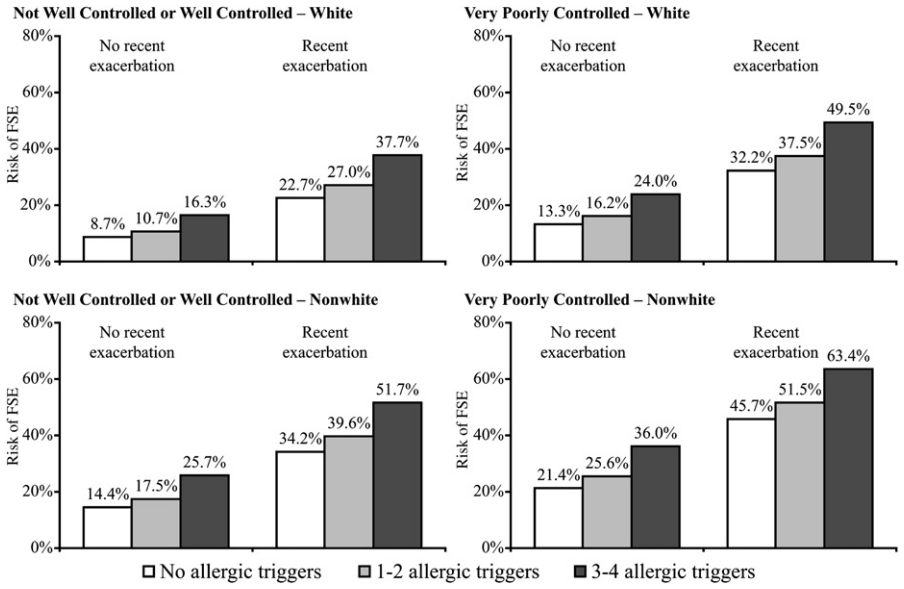

FIG 3. Predictors of future exacerbations.

predictor of FSE, whereas the number of long-term controllers were not found to be associated with FSE, which suggests that even maximally treated patients can be at high risk. Race/ethnicity, allergic triggers, and nonallergic triggers were also independent predictors of FSE.

The TENOR data set, derived from a multicenter, prospective study of the largest available pediatric cohort with severe or difficult-to-treat asthma, made it possible to investigate several potential prognostic factors for severe exacerbations. To our knowledge, this is the first study to evaluate RSE history and asthma control as 2 separate, independent risk factors for FSE in children with severe or difficult-to-treat asthma. RSE was the strongest predictor of FSE, which supports the recent NHLBI Expert Panel Report 3 thesis suggesting that recent exacerbation history is important in the overall clinical assessment of a patient.[18] This is especially true for children and adolescents with severe or difficult-to-treat asthma, who have more frequent and more severe exacerbations than adults.[21]

The most striking findings in these analyses are that children with RSE, compared with those without, are 3 times more likely

to have an exacerbation 6 months later even after adjustment for asthma control by impairment domain and other risk factors. Our findings are similar to those reported in the children with mild to moderate asthma participating in the Pediatric Asthma Controller Trial (PACT) study, in which only recent exacerbation history (exacerbations requiring prednisone in the previous year) was identified as a predictor for future exacerbations (OR, 2.1; $P <$ .001) despite administration of long-term controllers, including inhaled corticosteroids.[22] Moreover, in the PACT study, recent exacerbation history remained an independent predictor of subsequent exacerbations after adjusting for other variables, such as treatment.

Prebronchodilator FEV_1 differed significantly between children with RSE and those without RSE in the univariate analysis. The NHLBI guidelines control impairment domain definition, which incorporates this spirometry measure, was associated with FSE in the multivariable analyses. Our findings are consistent with studies in children with mild to moderate asthma, in which prebronchodilator percent FEV_1,[23] or a baseline peak flow or FEV_1 predicted <65%[24] was a significant risk factor for exacerbations. Our findings also support the approach of the guidelines that both impairment and risk, as measured by exacerbations, must be considered.

Allergic triggers and race/ethnicity were also independent predictors for FSE in this study. Evaluation of triggers and related phenotypic characteristics may be necessary to supplement the approach proposed by the guidelines. Exposure to inhaled allergens and indoor mold has been associated with increased exacerbations in young children with severe asthma.[25,26] More than 50% of a large (N = 937) sample of inner-city children with severe asthma had positive skin tests to multiple aeroallergens and higher exacerbation frequencies (83%) despite high-dose inhaled corticosteroid treatment compared with children with mild to moderate asthma (43%).[27] Approaches to prevent or alleviate allergen-induced asthma morbidity include immunotherapy, anti-IgE antibody therapy, and environmental interventions that reduce allergen exposure.[18,28,29]

Nonwhite (black or other) race/ethnicity was associated with a significantly increased risk of future exacerbations compared with white subjects (Model I: OR, 1.76, $P <$ .001; Model II: OR, 1.77, $P =$ .001; Table II). In adult TENOR patients, nonwhite race/ethnicity was similarly associated with a higher risk of FSE (OR, 1.59; $P =$ .008) and future corticosteroid burst (OR, 1.30; $P =$ .025; based on data from Miller et al[16]). Other studies evaluating the likelihood of exacerbations in black (African American) children[24,30,31] and adults[16,32] have shown similar results. Factors related to this association include suboptimal use of preventive services for asthma, poor adherence and access to care, ineffective asthma management, and a greater likelihood of steroid insensitivity.[30,31,33] A limitation of our study is that these potential confounding effects were not collected. Further investigations of factors associated with race/ethnicity and exacerbations may be warranted. Like allergic triggers, these factors may be helpful in supplementing the approach recommended by the guidelines.

There are several additional limitations of this analysis. Recall bias may have been introduced by the self-report of exacerbations from patients, and gaps in data collection prevented a full assessment of exacerbations over the past year as proposed by the guidelines. Nonetheless, limiting recall to 3 months was deemed necessary to maximize the quality of the patient-reported data. In addition, the risk of FSE found in this study is only directly generalizable to a severe or difficult-to-treat patient population and may be higher than in the general asthma population. However, as Robertson et al[34] reported, a substantial percentage of asthma mortality can be attributed to individuals who are not considered high-risk. Therefore, a comprehensive evaluation of risk factors and identification of new risk factors may also be important in the general asthma population. Differences between patients with complete data and those lost to follow-up also reduce the generalizability of our study, but the repeated-measures approach in which all available data are used for each patient reduces that bias.

In summary, RSE is the most powerful independent predictor of FSE in children with severe or difficult-to-treat asthma regardless of lung function or use of long-term controllers. As such, RSE should be considered during the clinical assessment of asthma and establishment of asthma management plans to prevent FSE. Whereas inhaled corticosteroid therapy in the PACT study[35] and multiple controller therapy in the TENOR cohort did not reduce the rate of FSE or improve asthma control, identification and more aggressive treatment of children who are at increased risk for FSE may help to reduce the rate of FSE and improve asthma control.

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Key messages

- **Recent severe exacerbations are a significant predictor of FSEs in children with severe or difficult-to-treat asthma, independent of asthma control, duration of asthma, use of long-term controllers, or the presence of allergic triggers.**
- **Race/ethnicity (black or other nonwhite), asthma impairment, and allergic triggers, but not use of long-term controllers, are independent predictors of severe exacerbation in children with severe asthma.**
- **Recent exacerbation history should be included as a component of pediatric asthma assessment and management plans.**

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