

Original Article

Disease Burden and Long-Term Risk of Persistent Very Poorly Controlled Asthma: TENOR II

Tmirah Haselkorn, PhD^a, Stanley J. Szefer, MD^{b,c}, Bradley E. Chipps, MD^d, Eugene R. Bleeker, MD^e, Michelle S. Harkins, MD^f, Brandee Paknis, PharmD^g, Farid Kianifard, PhD^g, Benjamin Ortiz, MD^g, and Robert S. Zeiger, MD, PhD^h *Los Altos, Sacramento, San Diego, and Pasadena, Calif; Aurora, Colo; Tucson, Ariz; Albuquerque, NM; and East Hanover, NJ*

What is already known about this topic? The Epidemiology and Natural history of Asthma: Outcomes and Treatment Regimens I demonstrated that patients with severe/difficult-to-treat asthma have a substantial disease burden and unmet medical need. More than a decade later, The Epidemiology and Natural history of Asthma: Outcomes and Treatment Regimens II provides a longitudinal assessment of these patients receiving standard of care.

What does this article add to our knowledge? Nearly 50% of patients had persistent very poorly controlled asthma. Risk factors predictive of persistent very poorly controlled asthma were black versus white race/ethnicity, allergic trigger count (4 vs 0), systemic corticosteroid use, and reduced percent predicted postbronchodilator FEV₁.

How does this study impact current management guidelines? Despite standard of care, persistent very poorly controlled asthma remains a severe disease characterized by excess comorbidities, numerous allergic triggers, poor lung function, and high health care utilization, emphasizing need for more intensive management, including assessment and improvement of modifiable risk factors.

BACKGROUND: Severe/difficult-to-treat disease occurs in 5% to 10% of patients with asthma, but accounts for more than 50% of related economic costs. Understanding factors associated with persistent very poorly controlled (VPC) asthma may improve outcomes.

OBJECTIVE: To characterize persistent VPC asthma after more than 10 years of standard of care.

METHODS: The Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) II (N = 341) was a multicenter, observational study of patients with severe/

^aEpiMetrix, Inc, Los Altos, Calif

^bThe Breathing Institute, Children's Hospital Colorado, Aurora, Colo

^cDepartment of Pediatrics, Section of Pediatric Pulmonary and Sleep Medicine, University of Colorado School of Medicine, Aurora, Colo

^dCapital Allergy and Respiratory Disease Center, Sacramento, Calif

^eDepartment of Medicine, Division of Pharmacogenomics, Center for Applied Genetics and Genomics Medicine, University of Arizona Health Sciences, Tucson, Ariz

^fDivision of Pulmonary, Critical Care and Sleep Medicine, University of New Mexico, Albuquerque, NM

^gNovartis Pharmaceuticals Corporation, East Hanover, NJ

^hDepartments of Allergy and Research and Evaluation, Kaiser Permanente Southern California, San Diego and Pasadena, Calif

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Corresponding author: Tmirah Haselkorn, PhD, EpiMetrix, Inc, 858 Riverside Dr, Los Altos, CA 94024. E-mail: tmirah@epimetrixinc.com.

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*Abbreviations used**ARQOL- Asthma-related quality of life**ATS- American Thoracic Society**COPD- Chronic obstructive pulmonary disease**FENO- Fractional exhaled nitric oxide**ICS- Inhaled corticosteroid**LABA- Long-acting β_2 -agonist**OR- Odds ratio**TENOR- The Epidemiology and Natural history of Asthma:
Outcomes and Treatment Regimens**VPC- Very poorly controlled*

difficult-to-treat asthma with a single, cross-sectional visit more than 10 years after TENOR I. Persistent VPC asthma was defined as VPC asthma at TENOR I and TENOR II enrollment; without VPC asthma was defined as well- or not well-controlled asthma at either or both visits. Multivariable logistic regression assessed long-term predictors of persistent VPC asthma using TENOR I baseline variables.

RESULTS: Of 327 patients, nearly half (48.0%, $n = 157$) had persistent VPC asthma. Comorbidities and asthma triggers were more frequent in patients with persistent VPC asthma than in patients without VPC asthma. Total geometric mean IgE was higher in patients with persistent VPC asthma (89.3 IU/mL vs 55.7 IU/mL); there was no difference in eosinophil levels. Lung function was lower in patients with persistent VPC asthma (mean % predicted pre- and postbronchodilator FEV₁, 63.0% vs 82.8% and 69.6% vs 87.2%, respectively). Exacerbations in the previous year were more likely in patients with persistent VPC asthma (29.7% vs 9.0%, respectively). Predictors of persistent VPC asthma were black versus white race/ethnicity, allergic trigger count (4 vs 0), systemic corticosteroid use, and postbronchodilator FEV₁ (per 10% decrease).

CONCLUSIONS: The burden of persistent VPC asthma is high in severe/difficult-to-treat disease; management of modifiable risk factors, maximization of lung function, and trigger avoidance may improve outcomes. © 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; Severe; Difficult-to-treat asthma; Very poorly controlled asthma; Prevalence; Risk factors; Long-term outcomes; Observational study; The Epidemiology and Natural history of asthma; Outcomes and treatment Regimens (TENOR)

INTRODUCTION

Asthma is a chronic illness associated with substantial morbidity and mortality; 24 million persons had asthma in the United States in 2014, including 17.7 million adults and 6.3 million children.^{1,2} The prevalence of asthma is increasing,^{1,2} and most patients with asthma can be effectively treated with nonbiologic medications, though a subpopulation of patients with severe or difficult-to-treat asthma exists.³ Severe or difficult-to-treat asthma occurs in 5% to 10% of patients with asthma,⁴⁻⁷ but accounts for more than 50% of the total health care costs of treating this illness^{4-6,8} due to high rates of health care utilization. The projected economic and health

burden costs of uncontrolled asthma in the United States continue to grow.^{9,10} Impairment at work or school and reduced productivity due to days lost from work or school contribute to the total health care costs associated with this condition.¹¹⁻¹⁷

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimen (TENOR) I study was a multicenter, observational study of 4756 patients with severe or difficult-to-treat asthma conducted between 2001 and 2004 and is the largest study to date to examine the natural history of the disease.¹⁸ Data from TENOR I showed that patients with severe or difficult-to-treat asthma experience a high disease burden and increased risk of future exacerbations despite long-term use of multiple controller medications.¹⁹ Patients with consistently very poorly controlled (VPC) asthma over a 2-year period had more than a 3-fold increased risk of a future asthma exacerbation compared with patients whose asthma control improved.^{14,20,21}

The possible reasons for lack of asthma control in severe or difficult-to-treat refractory disease include underuse of long-term control medications,²² increased rate of exacerbations,²³ overuse of quick relievers, poor treatment adherence,⁵ treatment resistance to corticosteroids,²⁴ presence of comorbidities (such as diabetes, chronic obstructive pulmonary disease [COPD], sleep apnea, and insomnia),²⁵ and/or presence of airborne triggers.

A follow-up study, TENOR II,²² was conducted between 2013 and 2014, more than 10 years after enrollment in TENOR I. The objective of TENOR II was to determine long-term outcomes and natural history of patients with severe or difficult-to-treat asthma by characterizing disease burden, including asthma-related health outcomes. This analysis examined characteristics and risk factors for persistent VPC asthma more than a decade after TENOR I. We hypothesized that those who remained VPC would be at increased risk for asthma exacerbations. We also sought to evaluate associated features that might contribute to this increased risk for exacerbations.

METHODS

Study design and population

TENOR II consisted of a cross-sectional, single study visit for patients with severe or difficult-to-treat asthma who had been originally enrolled in the 3-year prospective, multicenter, observational TENOR I study ($N = 4756$).¹⁸ The original study was conducted from 2001 to 2004.²² All TENOR I sites were invited to participate in TENOR II. Of the 283 sites that originally participated in TENOR I, 59 sites (with 1230 TENOR I patients) enrolled patients in TENOR II. The single follow-up visit was conducted between December 17, 2013, and December 19, 2014. TENOR II patients at participating sites ($n = 341$) were generally representative of the broader TENOR I study cohort enrolled across all of the originally participating sites, as shown in a subsequent analysis.²²

The TENOR II study protocol was approved by an institutional review board for each center. All participants gave their written informed consent to participate.

Data collection

Data collected in TENOR II included demographic and clinical information, comorbid conditions (by study coordinator interview), self-reported asthma triggers, current and prior asthma-related medication use, self-reported health care utilization, and use of concomitant medications.^{13,14,18,22} It should be noted that only the biologic omalizumab was Food and Drug Administration–approved during the study period.

Spirometry. Spirometry was performed using the American Thoracic Society (ATS)/European Respiratory Society guidelines.²⁶ Predicted values and *z* scores were derived from the Global Lung Function Initiative reference equations to normalize race, ethnicity, and sex data.²⁷ Maximum reversibility was determined according to ATS/European Respiratory Society standardization and computed as $100 \times (\text{postbronchodilator FEV}_1 \text{ minus prebronchodilator FEV}_1) / (\text{prebronchodilator FEV}_1)$.²⁶

Fractional exhaled nitric oxide (FENO) was measured using a calibrated device (NIOX MINO, Aerocrine AB, Solna, Sweden) at sites where this device was available. Measurements were performed according to ATS/European Respiratory Society guidelines,²⁸ with a mean value recorded after at least 2 measurements were taken.

Asthma control. The impairment domain of the National Heart, Lung, and Blood Institute asthma guidelines²⁹ was used to classify patients' asthma as VPC, not well controlled, or controlled, as previously described by Haselkorn et al.¹⁴ Assessment categories included symptoms, nighttime awakenings, interference with normal activity, short-acting β_2 -agonist use for symptom control, and lung function via measurement of FEV₁ or peak flow.¹⁴ Patients were defined as having persistent VPC asthma if they had VPC asthma at both the TENOR I and TENOR II enrollment visits. Patients were defined as without VPC asthma if they had controlled or not well-controlled asthma at either TENOR I enrollment, TENOR II enrollment, or both study visits. Patients with missing level of asthma control at TENOR I or TENOR II enrollment were excluded from the analysis (*n* = 14).

Because the TENOR database does not contain all requisite components (ie, reduction in lung growth or treatment-related adverse effects) to sufficiently map to the risk domain of the guidelines, this analysis focused solely on the impairment domain to ascertain asthma control.

Asthma exacerbations. Number of asthma exacerbations was obtained from self-reported health care utilization in the 3 and 12 months before the TENOR II study visit. An exacerbation was defined as any asthma-related overnight hospitalization, emergency department visit, or oral corticosteroid treatment. A severe asthma exacerbation was defined according to ATS criteria as an emergency room visit or hospitalization because of asthma that required systemic corticosteroids.^{3,30}

Laboratory assessments

Laboratory tests included total serum IgE, eosinophils, basophils, and specific IgE levels using blood samples collected at the study visit. These assays were performed using ImmunoCAP (Phadia, Uppsala, Sweden), radioallergosorbent test, and/or HYCOR methodologies at a Novartis or a designated central reference laboratory.

Asthma-related quality of life. Asthma-related quality of life (ARQOL) was measured using the validated Mini Asthma Quality of Life Questionnaire, which assesses 4 domains: symptoms, activity limitation, emotional function, and environmental stimuli. Asthma Quality of Life Questionnaire scores range from 1 to 7, with higher scores indicating better ARQOL.³¹ The estimated difference of 0.5 units has been defined as a criterion for the minimum clinically meaningful change at the individual level.³²

Statistical analyses

Demographic and clinical characteristics of patients with persistent VPC asthma and without VPC asthma were summarized using

means or geometric means, where appropriate, for continuous variables and proportions for categorical variables. Comorbidities with a frequency of greater than or equal to 5% were considered to be increased and were summarized for both groups. Analyses were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement,³³ where descriptive statistical analyses only were reported for demographic and clinical characteristics (item 14(a) of Strengthening the Reporting of Observational Studies in Epidemiology statement), and inferential statistical analyses for outcome variables were limited to reporting CIs for the differences between the 2 groups (eg, for percent predicted pre- and postbronchodilator FEV₁).

Odds ratios (ORs) and 95% CIs were used to assess long-term predictors of persistent VPC asthma in a multivariable logistic regression model³⁴ fitted with TENOR I baseline variables as predictors. The selection of variables for the model was based on expert recommendation during development of the protocol and statistical analysis plan. Some predictors were specified *a priori*, whereas others were added to the initial model after evaluation of the results, thus allowing model refinement. TENOR I baseline predictors were smoking status, race/ethnicity, self-reported allergic trigger count (eg, pollen, dust, animals, or mold/dampness), self-reported nonallergic trigger count (eg, emotional stress or cold/sinus infection), aspirin asthma trigger, corticosteroid course in the past 3 months, percent predicted postbronchodilator FEV₁ (per 10% decrease), obesity (body mass index, ≥ 30 kg/m²), duration of asthma (per 5 years), age (per 5 years), sex, emergency room visit/overnight hospitalization in the past 3 months, total IgE level, combined inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) use, and short-acting β_2 -agonist use.

RESULTS

Baseline demographic and clinical characteristics

A total of 157 patients (48.0%) of the 327 patients with available level of asthma control at both TENOR I and TENOR II were classified as having persistent VPC asthma and 170 (52.0%) without VPC asthma. Compared with patients without VPC asthma, those with persistent VPC asthma were more likely to be older (59.7 years vs 55.9 years), obese (50.3% vs 42.4%), black race/ethnicity (17.2% vs 5.3%), previously intubated (18.2% vs 7.6%), and a prior smoker (31.2% vs 17.1%) (Table I). Most patients in TENOR II were under the care of an allergist/immunologist. Geometric mean for total IgE was 89.3 IU/mL (95% CI, 68.9-115.8) in patients with persistent VPC asthma versus 55.7 IU/mL (95% CI, 38.8-80.0) in patients without VPC asthma.

Comorbidities

Prevalence of comorbidities was greater in patients with persistent VPC asthma than in patients without VPC asthma. The 5 most common were gastroesophageal reflux disease (52.2% vs 41.2%), high blood pressure (46.5% vs 38.2%), upper respiratory tract infection (35.0% vs 27.6%), food allergy (35.7% vs 27.6%), and insomnia (31.2% vs 19.4%) (Table II).

Specific IgE and asthma triggers

Based on specific IgE values, the 3 most common allergen sensitizations in patients with persistent VPC asthma versus patients without VPC asthma were cat dander (51.0% vs 37.1%), dog dander (43.0% vs 35.1%), and *Dermatophagoides pteronyssinus* (dust mite) (36.0% vs 27.2%) (Figure 1).

TABLE I. Demographic and clinical characteristics according to VPC persistency in the TENOR II cohort

Characteristic	Persistent VPC asthma, n (%) (n = 157)	Without VPC asthma, n (%) (n = 170)
Age (y), mean $\pm$ SD	59.7 $\pm$ 14.0	55.9 $\pm$ 18.2
Age at diagnosis (y), mean $\pm$ SD	19.1 $\pm$ 17.4*	22.7 $\pm$ 18.2
Obese with BMI ≥ 30 kg/m ² , n (%)	79 (50.3)	72 (42.4)
BMI (kg/m ²), mean $\pm$ SD	31.3 $\pm$ 7.4	29.6 $\pm$ 6.8
Sex: female, n (%)	103 (65.6)	111 (65.3)
Race/ethnicity, n (%)		
White	115 (73.2)	148 (87.1)
Black	27 (17.2)	9 (5.3)
Other	15 (9.6)	13 (7.6)
Smoking status, n (%)		
Ever smoked (at least 1 per day for ≥ 6 mo)	48 (31.2)*	29 (17.1)
Current smoker	5 (10.4)	4 (13.8)
Years smoking, mean $\pm$ SD	15.4 $\pm$ 11.3†	11.6 $\pm$ 9.4‡
Cigarettes per day, mean $\pm$ SD	17.5 $\pm$ 13.5†	12.9 $\pm$ 9.0‡
Pack-years, mean $\pm$ SD	15.7 $\pm$ 17.5†	9.2 $\pm$ 10.6‡
Asthma specialist, n (%)	147 (93.6)	162 (95.3)
Pulmonologist	42 (28.6)	23 (14.2)
Allergist	105 (71.4)	139 (85.8)
Health care coverage, n (%)		
Commercial/PPO	49 (31.4)	71 (41.8)
HMO	28 (17.9)	28 (16.5)
Medicare/Medicaid	67 (42.9)	55 (32.4)
Other	12 (7.7)	16 (9.4)
History of intubation, n (%)	28 (18.2)*	13 (7.6)
Positive for any specific IgE, n (%)§	115 (75.2)	106 (70.2)
Total IgE (IU/mL), n	151	151
Geometric mean (95% CI)	89.3 (68.9-115.8)	55.7 (38.8- 80.0)
Spirometry at TENOR II, mean $\pm$ SD		
Prebronchodilator % predicted FEV ₁	63.0 $\pm$ 22.3	82.8 $\pm$ 16.0
Postbronchodilator % predicted FEV ₁	69.6 $\pm$ 21.8	87.2 $\pm$ 15.8
Maximum reversibility	12.6 $\pm$ 17.2	5.6 $\pm$ 8.2

BMI, Body mass index; HMO, health maintenance organization; PPO, preferred provider organization.

Estimates of percent predicted pre- and postbronchodilator FEV₁ were derived from the Global Lung Function Initiative reference equations.²¹

Persistent VPC asthma was defined as VPC at both TENOR I and TENOR II enrollment visits, whereas without VPC asthma was defined as controlled or not well controlled at either TENOR I enrollment, TENOR II enrollment, or both

*n = 154.

†n = 48.

‡n = 29.

§The threshold for a positive specific IgE reading was 0.35 kU/L.

Self-reported asthma triggers were highly prevalent in both persistent VPC asthma and without VPC asthma groups. However, the percentage of all triggers was higher in patients with persistent VPC asthma; the most common triggers were breathing dust (77.1% vs 71.8%), cold or sinus infection (77.1% vs 73.5%), exercise (73.9% vs 65.3%), pollen (74.5% vs 62.9%), change in the weather (71.3% vs 57.1%), and breathing cold air (70.1% vs 67.1%), respectively (Table III).

Lung function

Lung function was lower in the persistent VPC asthma group than in the without VPC asthma group, with little change seen over the course of the 10 years between TENOR I (prebronchodilator FEV₁: VPC: 64.2% of predicted; without VPC: 81.6%; postbronchodilator FEV₁: VPC: 70.3%; without

VPC: 86.0%) and TENOR II (prebronchodilator FEV₁: VPC: 63.0% of predicted; without VPC: 82.8%; postbronchodilator FEV₁: VPC: 69.6%; without VPC: 87.2%). In TENOR II, mean percent predicted pre- and postbronchodilator FEV₁ in the persistent VPC group versus the without VPC group was 63.0% $\pm$ 22.3% versus 82.8% $\pm$ 16.0%, and 69.6% $\pm$ 21.8% versus 87.2% $\pm$ 15.8%, respectively. The percentage of patients with percent predicted postbronchodilator FEV₁ greater than or equal to 90% was 17.1% and 45.5% in patients with persistent and without VPC asthma, respectively. Maximum reversibility was greater in the persistent VPC group versus the without VPC group (mean, 12.6% $\pm$ 17.2% vs 5.6% $\pm$ 8.2%, respectively). In the persistent VPC asthma group, 53.3% had a postbronchodilator FEV₁/forced vital capacity ratio less than 70%, whereas in the without VPC asthma group this was 32.9%.

TABLE II. Comorbidities with reported frequency $\geq 5\%$ by VPC persistency in the TENOR II cohort

Comorbidity	Persistent VPC asthma,* n (%) (n = 157)	No VPC asthma,† n (%) (n = 170)
Allergic reactions	46 (29.3)	44 (25.9)
Urticaria/hives	25 (15.9)	24 (14.1)
Rash	27 (17.2)	19 (11.2)
Anaphylaxis	15 (9.6)	11 (6.5)
Other	8 (5.1)	12 (7.1)
Autoimmune diseases	11 (7.0)	16 (9.4)
Rheumatoid arthritis	11 (7.0)	14 (8.2)
Diabetes	31 (19.7)	19 (11.2)
Obesity	40 (25.5)	29 (17.1)
Cardiovascular	86 (54.8)	72 (42.4)
High blood pressure	73 (46.5)	65 (38.2)
Other heart disease	22 (14.0)	14 (8.2)
Coronary artery disease	11 (7.0)	7 (4.1)
Congestive heart failure	8 (5.1)	0 (0.0)
Gastrointestinal/digestive	102 (65.0)	88 (51.8)
Gastroesophageal reflux disease	82 (52.2)	70 (41.2)
Inflammatory bowel disease	9 (5.7)	12 (7.1)
History of bariatric surgeries	8 (5.1)	1 (0.6)
Respiratory	135 (86.0)	122 (71.8)
Acute or chronic sinusitis	74 (47.1)	83 (48.8)
Upper respiratory tract infection	55 (35.0)	47 (27.6)
Nasal polyps	32 (20.4)	36 (21.2)
History of nasal polypectomies	30 (19.1)	30 (17.6)
Obstructive sleep apnea	37 (23.6)	22 (12.9)
Chronic obstructive pulmonary disease	34 (21.7)	8 (4.7)
Chronic bronchitis	29 (18.5)	11 (6.5)
Vocal cord dysfunction	11 (7.0)	6 (3.5)
Restrictive lung disease	10 (6.4)	3 (1.8)
Skin	15 (9.6)	9 (5.3)
Acute or chronic urticaria/angioedema	10 (6.4)	7 (4.1)
Other comorbidities	131 (83.4)	134 (78.8)
Increased/ease of bruisability	57 (36.3)	56 (32.9)
Food allergy	56 (35.7)	47 (27.6)
Cataracts	50 (31.8)	48 (28.2)
Insomnia	49 (31.2)	33 (19.4)
Aspirin sensitivity	33 (21.0)	31 (18.2)
Osteoporosis and osteoporotic fractures	31 (19.7)	23 (13.5)
History of malignancy, including lymphoma	14 (8.9)	17 (10.0)
Glaucoma	8 (5.1)	9 (5.3)
Other‡	38 (24.2)	46 (27.1)

Note: Number of patients with nonmissing data is the denominator for computation of percentages.

*Defined as VPC at both TENOR I and TENOR II enrollment visits.

†Defined as controlled or not well controlled at either TENOR I enrollment, TENOR II enrollment, or both.

‡Conditions not individually listed in this part of the table.

Asthma exacerbations in the 3 months and 12 months before the TENOR II study visit

The frequencies of asthma exacerbations in the 3 and 12 months before the TENOR II study visit by VPC persistency were comparable (Figure 2, A and B). In the 12 months before the study visit, 91 patients (58%) in the persistent VPC asthma group and 67 patients (39%) in the without VPC asthma group reported exacerbations. Patients with persistent VPC asthma were more than 3 times as likely to report an ATS severe exacerbation as patients without VPC asthma (29.7% vs 9.0%, respectively) (Figure 2, B). In addition, emergency room visits or

overnight hospitalizations were more common in patients with persistent VPC. In the year before enrolling in TENOR II, 95.6% of patients with persistent VPC asthma and 97.0% without VPC asthma reported receiving an oral corticosteroid course.

Biomarkers

Analyses of biomarkers by VPC persistency showed that mean levels of eosinophils ($209 \pm 151/\mu\text{L}$ in the persistent VPC group vs $189 \pm 138/\mu\text{L}$ in the without VPC asthma group), basophils ($55 \pm 59/\mu\text{L}$ vs $50 \pm 51/\mu\text{L}$), and FENO

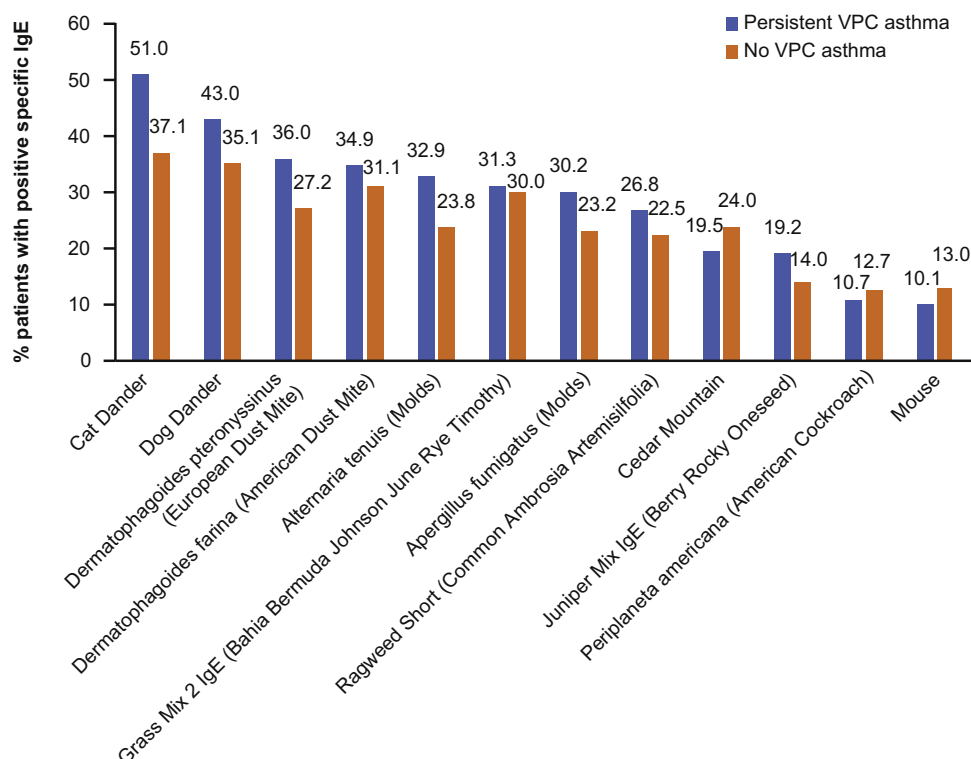


FIGURE 1. Specific IgE for allergens by VPC persistency in the TENOR II cohort.

TABLE III. Self-reported asthma triggers in the TENOR II cohort

Variable	Persistent VPC asthma,* n (%) (n = 157)	No VPC asthma,† n (%) (n = 170)
Cold or sinus infection (not flu)	121 (77.1)	125 (73.5)
Breathing dust	121 (77.1)	122 (71.8)
Pollen	117 (74.5)	107 (62.9)
Exercise	116 (73.9)	111 (65.3)
Change in the weather	112 (71.3)	97 (57.1)
Breathing cold air	110 (70.1)	114 (67.1)
Other people's cigarette smoke	99 (63.1)	101 (59.4)
Moldy, musty, or damp spaces	96 (61.1)	91 (53.5)
Air pollution	89 (56.7)	78 (45.9)
Emotional stress	84 (53.5)	65 (38.2)
Being near animals	83 (52.9)	81 (47.6)
Nontobacco smoke	75 (47.8)	74 (43.5)
Other indoor irritants	59 (37.6)	44 (25.9)
Taking aspirin	23 (14.6)	22 (12.6)
Personal cigarette smoking	11 (7.0)	1 (0.6)
Substance use (marijuana, cocaine, etc)	2 (1.3)	4 (2.4)

*Defined as VPC at both TENOR I and TENOR II enrollment visits.

†Defined as controlled or not well controlled at either TENOR I enrollment, TENOR II enrollment, or both.

(30.6 ± 33.8 ppb vs 26.7 ± 23.0 ppb) were similar between the 2 groups. Approximately 60% of patients in each group had FENO less than 25 ppb. When FENO and eosinophil levels were considered together, 10.7% with persistent VPC asthma and 13.6% without VPC asthma had both elevated eosinophils ($\geq 300/\mu\text{L}$) and elevated FENO (≥ 25 ppb).

Medication use in the 6 months before the study visit

Combined ICS/LABA use in patients with persistent VPC asthma versus those without VPC asthma was 75.2% versus 65.6%, respectively, use of systemic corticosteroids was 21.7% versus 12.3%, respectively, and use of long-acting anticholinergic/muscarinic antagonists was 15.3% versus 6.7%, respectively (Table IV). Use of leukotriene modifiers and

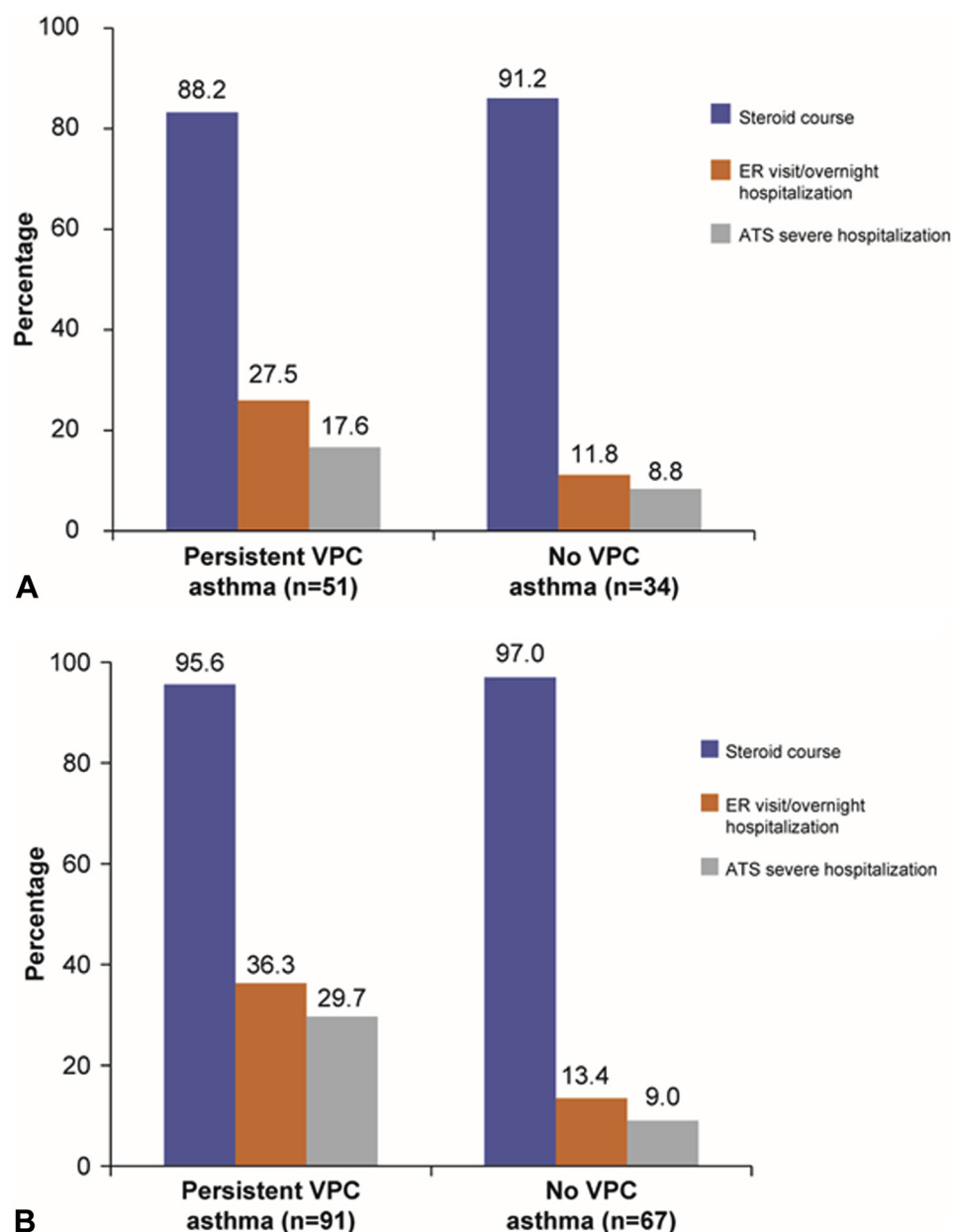


FIGURE 2. Asthma exacerbation events reported by patients with persistent VPC asthma and without VPC asthma in the previous (A) 3 months and (B) 12 months. Severe asthma exacerbation was defined according to the ATS³ as emergency room visit or hospitalization because of asthma or exacerbation requiring systemic corticosteroids.²³ Persistent VPC asthma was defined as VPC at both TENOR I and TENOR II enrollment visits. ER, Emergency room. *Note:* Recall bias may affect the reliability of 12-month data as indicated by its similarity to 3-month data.

methylxanthines was also higher in the persistent VPC group. The proportion of patients receiving omalizumab was similar between the 2 groups (12.7% vs 11.7%, respectively); no other biologics were taken by patients in this study, because none were Food and Drug Administration–approved for use at the time of this noninterventional trial.

Asthma-related quality of life

Mean Asthma Quality of Life Questionnaire scores were lower in the persistent VPC group than in the without VPC group for

all domains (Figure 3). All differences in scores between the 2 groups were clinically meaningful (>0.5), with the largest differences observed for the emotional (1.6) and the activity domains (1.5).

Multivariable analysis of predictors of persistent VPC asthma

Figure 4 presents the long-term predictors of persistent VPC asthma in the multivariable logistic regression model. In decreasing order of magnitude for the OR, the variables with

TABLE IV. Medication use in 6 mo before study visit according to VPC persistency in the TENOR II cohort

Medication	Persistent VPC asthma,* n (%) (n = 157)	Without VPC asthma,† n (%) (n = 163)
SABA	147 (93.6)	133 (81.6)
ICSs	140 (89.2)	129 (79.1)
Low dose‡	18 (13.7)	33 (27.0)
High dose‡	57 (43.5)	39 (32.0)
Combined ICS and LABA	118 (75.2)	107 (65.6)
Leukotriene modifiers	75 (47.8)	54 (33.1)
LAMA	24 (15.3)	11 (6.7)
Methylxanthines	18 (11.5)	9 (5.5)
Intranasal steroids	42 (26.8)	65 (39.9)
Intranasal nonsteroid medications	19 (12.1)	21 (12.9)
Systemic corticosteroids	34 (21.7)	20 (12.3)
Omalizumab§	20 (12.7)	19 (11.7)
Oral nonседating antihistamines	53 (33.8)	66 (40.5)
Anticholinergics (short- or long-acting)	19 (12.1)	15 (9.2)
H ₂ -antagonists	3 (1.9)	1 (0.6)
PPIs	16 (10.2)	14 (8.6)

LAMA, Long-acting anticholinergic/muscarinic antagonist; NHLBI, National Heart, Lung, and Blood Institute; PPI, proton pump inhibitor; SABA, short-acting β_2 -agonist.

Number of patients with nonmissing medication data is the denominator for computation of percentages.

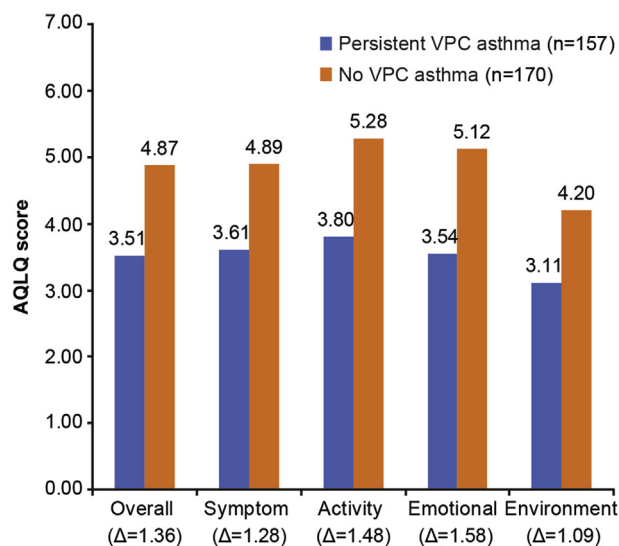
Counts of ICS and LABA include medications reported in the Combined ICS and LABA row. The combined group includes the following medications: budesonide/formoterol (Symbicort), mometasone/formoterol (Dulera), and fluticasone/salmeterol (Advair).

*Persistent VPC defined as VPC at both TENOR I and TENOR II enrollment visits.

†Defined as controlled or not well controlled at either TENOR I enrollment, TENOR II enrollment, or both.

‡Low and high dose defined according to the estimated comparative daily dosages for ICS reported in NHLBI Expert Panel Report 3 (EPR 3) Summary Report 2007: Guidelines for the Diagnosis and Management of Asthma.¹⁶ Highest category of dosing over all ICS medications per patient is reported. The number of patients taking ICS medication with complete dose information is the denominator for computation of low-dose/high-dose percentages.

§Only the biologic omalizumab was Food and Drug Administration–approved use in this indication during the study period.

**FIGURE 3.** Mean Mini-AQLQ scores by VPC persistency in the TENOR II cohort. Clinically meaningful difference greater than or equal to 0.5. AQLQ, Asthma Quality of Life Questionnaire.

P values less than .05 were black versus white race/ethnicity (adjusted OR, 4.7; 95% CI, 1.8-12.4; *P* = .002), self-reported allergic trigger count (eg, pollen, dust, animals, or mold/dampness) 4 versus 0 (adjusted OR, 4.0; 95% CI, 1.0-15.9; *P* = .046), systemic corticosteroid course in past 3 months (adjusted OR, 2.3; 95% CI, 1.2-4.3; *P* = .008), and percent

predicted postbronchodilator FEV₁ per 10% decrease (adjusted OR, 1.6; 95% CI, 1.3-1.9; *P* < .001).

DISCUSSION

TENOR II provides a unique opportunity to evaluate the longitudinal natural history of disease in patients with severe or difficult-to-treat asthma after more than 10 years of standard of care treatment. Persistent VPC asthma was observed in approximately half the patients despite the likely guideline use of controller therapy from an asthma specialist. These patients experienced day and nighttime symptoms, reduced normal activities, and required short-acting β_2 -agonists for symptom control. Patients with persistent VPC asthma also exhibited a greater disease burden than patients without VPC asthma, including more comorbidities and asthma triggers, lower lung function, and higher rates of asthma exacerbations; patients with persistent VPC asthma also had higher total IgE levels. As expected, patients with persistent VPC asthma had lower and clinically meaningful differences on all measures of functional impairment for ARQOL compared with patients without VPC asthma.

Lung function values remained consistently low in the overall TENOR I/II cohort over the course of the more than 10 years. It is possible that the minimal change over time may be due to airway damage being done in the early stages of the disease, and subsequently, exacerbations may not have the same impact. When comparing patients in TENOR II with persistent VPC and without VPC asthma, lung function, as determined by FEV₁, and FEV₁/forced vital capacity, was considerably lower in patients with persistent VPC asthma

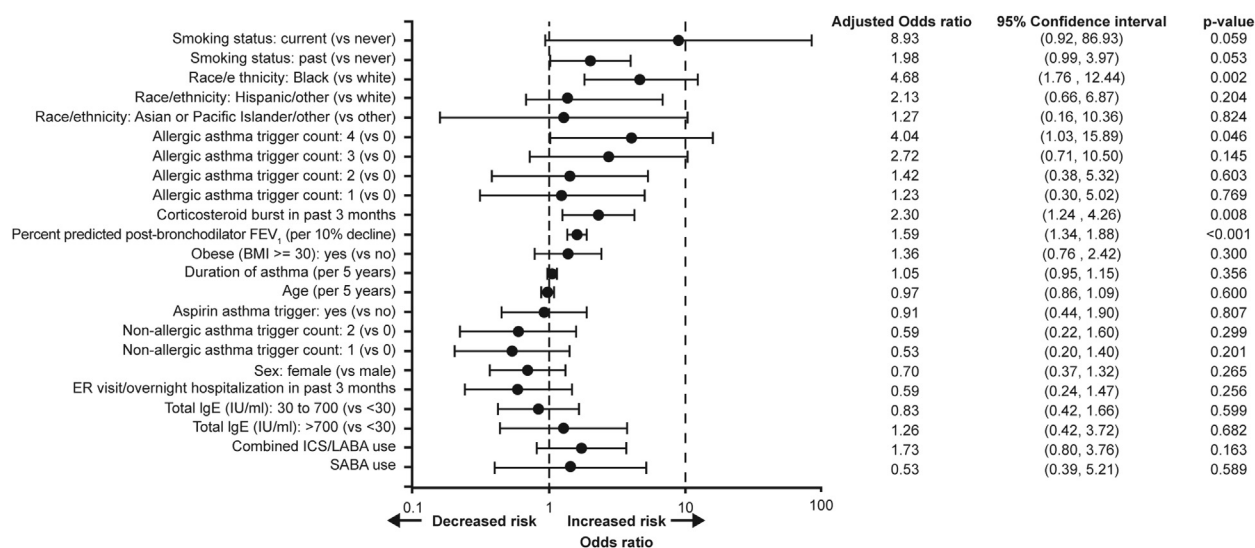


FIGURE 4. TENOR I baseline predictors of persistent VPC asthma in TENOR II in multivariable logistic regression model. The figure shows TENOR I baseline predictors of persistent VPC asthma analyzed in the multivariable logistic regression model. The multivariable model excluded patients with missing VPC asthma data at TENOR II or missing any predictors at TENOR I ($n = 289$ used in the model). Asthma triggers were self-reported and were categorized as allergic (pollen, dust, animals, or mold/dampness) or nonallergic (emotional stress or cold/sinus infection). *BMI*, Body mass index; *ER*, emergency room; *SABA*, short-acting β_2 -agonist.

than in those without VPC asthma. Greater maximum reversibility was also observed among patients with persistent VPC asthma, suggesting severe airflow obstruction. Indeed, high reversibility has been shown to be a physiologic indicator of reduced lung function and is more often associated with elevated T_H2 levels in moderate to severe asthma.^{35,36} Bronchial reversibility is also significantly correlated with worse asthma control³⁷ and is a distinguishing factor for difficult-to-control asthma in children and adolescents.³⁸

Longitudinal lung function trajectories in those with severe asthma can be used as potential indicators of reduced lung function and early decline; these trajectories may identify a subset of patients who have worse prognosis, such as those with structural changes linked to irreversible airway obstruction. This is a common phenotype seen in asthma-COPD overlap^{39,40} and likely to be present in some of the patients in this study. Indeed, COPD was self-reported in 22% of patients in the VPC asthma group, but in only 5% of patients without VPC asthma. This pattern of altered lung function trajectories also occurs in children.^{41,42} The consistently low lung function between TENOR I and TENOR II during the more than 10-year study period possibly signifies that current pharmacological therapy may have minimal benefit for improving airflow limitation in the long-term. Alternatively, it is possible that the lack of decline in lung function may reflect the beneficial effects of ICS use on loss of lung function. Although evidence is inconsistent, some studies have shown that prolonged ICS treatment may maximally benefit lung function in patients with asthma,^{43,44} particularly in subjects with high IgE,⁴⁴ adult males with less than 5 pack-years of smoking,⁴⁵ and when introduced early when symptoms are mild.⁴⁶ It must also be considered that the stability in lung function observed in TENOR II patients with severe or difficult-to-treat asthma may be due to the inherently lower lung function at TENOR I that did not substantially worsen in the more than 10 years before TENOR II.

Asthma exacerbations, which are also common manifestations of poor control, are likely to contribute to the continued and rapid decline in lung function in persistent VPC asthma,²³ as well as increased morbidity and mortality.^{47,48} Indeed, the high rate of exacerbations in patients with VPC asthma has been linked to accelerated loss of lung function, as well as declining health and increased asthma-related mortality.⁴⁹ Exacerbations have been linked to structural changes and remodeling of the lung that develops over time in patients with persistent VPC asthma.^{47,50} The higher frequency of exacerbations in patients with persistent VPC asthma compared with those without VPC asthma has implications for patient care, such as increased health care utilization and loss of productivity.⁵¹

Consistent with other studies, data from TENOR II indicated that comorbid conditions were common in patients with persistent VPC asthma. Comorbidities are common in patients with difficult-to-control asthma and can be associated with specific patient characteristics, such as older age, female sex, smoking history, and chronic prednisone use.⁵² In a separate study, more than 50% of patients with persistent VPC asthma reported gastroesophageal reflux disease as a comorbidity, which is associated with poor asthma control.²⁵ Higher frequencies of diabetes, COPD, obstructive sleep apnea, and insomnia were also observed in the persistent VPC asthma group, while the presence of nasal polyps was similar between groups.²⁵ The greater frequency of comorbidities in patients with persistent VPC asthma suggests the possibility of increased exposure to polypharmacy, resulting in a higher risk of adverse effects due to use of multiple medications and potential drug interactions.

This analysis did not identify a link between specific biomarkers, including eosinophils and FENO, and persistent VPC asthma. This could be due to differential oral corticosteroid use and higher ICS dose in the VPC group, which may suppress biomarker levels. Indeed, about 22% of patients with persistent VPC asthma were using oral corticosteroids in the 6 months

before the TENOR II visit compared with about 12% of patients without VPC asthma.

On the basis of self-reported medication use, 25% of patients with persistent VPC asthma were not using ICS/LABA and only about 12% of patients in each group were using biologic therapy (omalizumab). A recent study indicated that omalizumab use for asthma has remained “steadily low” since 2003, and that a large group of individuals who may benefit from omalizumab are not receiving it.⁵³ The reasons for this are unclear, but do not appear to be explained by demographic data. Previous data from TENOR II also indicated poor medication adherence in the cohort.²² Taken together, these data suggest undertreatment of these patients, and highlight the need for increased implementation of step-up therapy, such as more targeted treatments, and improved medication adherence strategies that assess short- and long-term medication utilization. It may also reflect reduction in ICS dose to minimize the risk of adverse effects or, alternatively, discontinuation of medications that were felt to be ineffective or high cost. Assessing adherence and optimizing this if poor, possibly via use of electronic medication monitoring systems adapted for those with severe asthma, as well as alternative treatment strategies in this at-risk population, may reduce burden and improve long-term outcomes, including maximization of lung function.

Multivariable logistic regression analysis identified several factors that were predictive of persistent VPC asthma after more than 10 years. Black race versus white race was the strongest predictor, with a nearly 5-fold increase in odds. The next predictor was multiple self-reported allergic triggers, which was associated with a 4-fold increase in odds with an allergic trigger count of 4 versus 0. Oral corticosteroid use in the previous 3 months and, to a lesser extent, lung function based on the percent predicted postbronchodilator FEV₁ level per 10% decrease at baseline were also predictive. Other studies confirm that black patients with asthma are at a particularly high risk for persistent VPC asthma, although the specific role of socioeconomic factors, as well as genetics and pharmacogenetics, is yet to be clearly elucidated.⁵⁴⁻⁵⁶

More intensive management of modifiable factors and maximization of lung function, as well as avoidance of asthma triggers, are therefore strongly recommended. In addition, an increased understanding of the pharmacogenetics of asthma, as well as pertinent social determinants of health closely linked with refractory disease, may help clinicians identify patients at greatest risk of future exacerbations and allow closer monitoring of these patients with appropriate and timely early intervention. Attention to the risk component of asthma, including follow-up of asthma progression through assessment of lung trajectories, along with frequency of asthma exacerbations, could be used to identify patients with severe asthma at risk for irreversible changes in lung function.⁵⁷

Limitations of TENOR II included the use of self-reported data and a single study visit, which may lead to recall bias, including the assessment of comorbidities and health care utilization. Caution is needed when projecting the reasons why biologic therapy (omalizumab) was not used. It is possible that some of these patients may have been on a biologic and failed, or may have discontinued a standard therapy because of perceived lack of efficacy and not started on a biologic because of cost. Finally, selection bias and reduced generalizability are limitations inherent in the study size, but sensitivity analyses demonstrated

the representativeness of TENOR II to the TENOR I cohort.²⁰ This representativeness of the TENOR II cohort to those enrolled in the large-scale TENOR I study is one of the strengths of this study.

CONCLUSIONS

Despite treatment with ICS/LABA and long-acting anticholinergic/muscarinic antagonist, nearly 50% of patients with severe or difficult-to-treat asthma had persistent VPC asthma after more than 10 years of follow-up. These patients had greater disease burden than patients without VPC asthma, including greater comorbidities, more asthma triggers, lower lung function, higher rates of asthma exacerbations, and lower ARQOL; these patients also had higher total IgE levels. Medication usage suggested undertreatment of asthma. Although the associations identified do not imply causality, results from the multivariable analysis suggest that the asthma burden may be reduced by targeting modifiable risk factors, reducing exposure to triggers, and improving adherence in high-risk groups. Strategies to improve access and adherence to medications are paramount and highlight the need for increased implementation of step-up therapy after improved medication adherence is determined, for example with the use of novel Food and Drug Administration–approved treatment options, such as targeted biologics⁵⁸ and bronchial thermoplasty.³

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REFERENCES

- Centers for Disease Control and Prevention. Fast statistics; 2017. Available from: <https://www.cdc.gov/asthma/default.htm>. Accessed March 23, 2020.
- Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. *MMWR Morb Mortal Wkly Rep* 2011; 60:547–52.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
- Heck S, Nguyen J, Le DD, Bals R, Dinh QT. Pharmacological therapy of bronchial asthma: the role of biologics. *Int Arch Allergy Immunol* 2015;168: 241–52.
- Slejko JF, Ghushchyan VH, Sucher B, Globe DR, Lin SL, Globe G, et al. Asthma control in the United States, 2008–2010: indicators of poor asthma control. *J Allergy Clin Immunol* 2014;133:1579–87.
- Pakhale S, Mulpuru S, Boyd M. Optimal management of severe/refractory asthma. *Clin Med Insights Circ Respir Pulm Med* 2011;5:37–47.
- Carr TF, Kraft M. Management of severe asthma before referral to the severe asthma specialist. *J Allergy Clin Immunol Pract* 2017;5:877–86.
- Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018;6:545–554.e4.
- Yaghoubi M, Adibi A, Safari A, Fitzgerald JM, Sadatsafavi M, Canadian Respiratory Research Network. The projected economic and health burden of uncontrolled asthma in the United States. *Am J Respir Crit Care Med* 2019;200: 1102–12.
- Nurmagambetov TA, Krishnan JA. What will uncontrolled asthma cost in the United States? *Am J Respir Crit Care Med* 2019;200:1077–8.
- Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. *Natl Health Stat Report* 2011;1–14.
- Chen H, Blanc PD, Hayden ML, Bleecker ER, Chawla A, Lee JH. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health* 2008;11:231–9.

13. Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012;130:332-342.e10.
14. Haselkorn T, Fish JE, Zeiger RS, Szeffler SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009;124:895-902.e1-902.e4.
15. Szeffler SJ, Zeiger RS, Haselkorn T, Mink DR, Kamath TV, Fish JE, et al. Economic burden of impairment in children with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2011;107:110-119.e1.
16. Zeiger RS, Hay JW, Contreras R, Chen W, Quinn VP, Seal B, et al. Asthma costs and utilization in a managed care organization. *J Allergy Clin Immunol* 2008;121:885-892.e5.
17. Fitzpatrick AM, Moore WC. Severe asthma phenotypes — how should they guide evaluation and treatment? *J Allergy Clin Immunol Pract* 2017;5:901-8.
18. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al. Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2004;92:32-9.
19. Calhoun WJ, Haselkorn T, Mink DR, Miller DP, Dorenbaum A, Zeiger RS. Clinical burden and predictors of asthma exacerbations in patients on guideline-based steps 4-6 asthma therapy in the TENOR cohort. *J Allergy Clin Immunol Pract* 2014;2:193-200.
20. Covar RA, Szeffler SJ, Zeiger RS, Sorkness CA, Moss M, Mauger DT, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol* 2008;122:741-747.e4.
21. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107:61-7.
22. Chipps BE, Haselkorn T, Paknis B, Ortiz B, Bleecker ER, Kianifard F, et al. More than a decade follow-up in patients with severe or difficult-to-treat asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II. *J Allergy Clin Immunol* 2018;141:1590-1597.e9.
23. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;179:19-24.
24. Green BJ, Wiriyaichairom S, Grainge C, Rogers GB, Kehagia V, Lau L, et al. Potentially pathogenic airway bacteria and neutrophilic inflammation in treatment resistant severe asthma. *PLoS One* 2014;9:e100645.
25. Bardin PG, Rangaswamy J, Yo SW. Managing comorbid conditions in severe asthma. *Med J Aust* 2018;209:S11-7.
26. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
27. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324-43.
28. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912-30.
29. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
30. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
31. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14:32-8.
32. Wilson SR, Rand CS, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Asthma outcomes: quality of life. *J Allergy Clin Immunol* 2012;129:S88-123.
33. Vandembroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007;147:W163-94.
34. Tolles J, Meurer WJ. Logistic regression: relating patient characteristics to outcomes. *JAMA* 2016;316:533-4.
35. Busse WW, Holgate ST, Wenzel SW, Klekotka P, Chon Y, Feng J, et al. Biomarker profiles in asthma with high vs low airway reversibility and poor disease control. *Chest* 2015;148:1489-96.
36. Wei J, Ma L, Wang J, Xu Q, Chen M, Jiang M, et al. Airway reversibility in asthma and phenotypes of Th2-biomarkers, lung function and disease control. *Allergy Asthma Clin Immunol* 2018;14:89.
37. Heffler E, Crimi C, Campisi R, Sichili S, Nicolosi G, Porto M, et al. Bronchodilator response as a marker of poor asthma control. *Respir Med* 2016;112:45-50.
38. Pongracic JA, Krouse RZ, Babineau DC, Zoratti EM, Cohen RT, Wood RA, et al. Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents. *J Allergy Clin Immunol* 2016;138:1030-41.
39. Cosio BG, Soriano JB, Lopez-Campos JL, Calle-Rubio M, Soler-Cataluna JJ, de-Torres JP, et al. Defining the asthma-COPD overlap syndrome in a COPD cohort. *Chest* 2016;149:45-52.
40. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015;70:683-91.
41. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842-52.
42. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535-44.
43. Lange P, Scharling H, Ulrik CS, Vestbo J. Inhaled corticosteroids and decline of lung function in community residents with asthma. *Thorax* 2006;61:100-4.
44. de Marco R, Marcon A, Jarvis D, Accordini S, Bugiani M, Cazzoletti L, et al. Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE. *J Allergy Clin Immunol* 2007;119:611-7.
45. Dijkstra A, Vonk JM, Jongepier H, Koppelman GH, Schouten JP, ten Hacken NH, et al. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. *Thorax* 2006;61:105-10.
46. Shimoda T, Obase Y, Kishikawa R, Iwanaga T. Impact of inhaled corticosteroid treatment on 15-year longitudinal respiratory function changes in adult patients with bronchial asthma. *Int Arch Allergy Immunol* 2013;162:323-9.
47. Calhoun WJ, Haselkorn T, Miller DP, Omachi TA. Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2015;136:1125-1127.e4.
48. O'Byrne PM, Pedersen S, Schatz M, Thoren A, Ekholm E, Carlsson LG, et al. The poorly explored impact of uncontrolled asthma. *Chest* 2013;143:511-23.
49. Chapman KR, Bergeron C, Bhutani M, Bourbeau J, Grossman RF, Hernandez P, et al. Do we know the minimal clinically important difference (MCID) for COPD exacerbations? *COPD* 2013;10:243-9.
50. Bai TR. Evidence for airway remodeling in chronic asthma. *Curr Opin Allergy Clin Immunol* 2010;10:82-6.
51. Sullivan PW, Ghushchyan VH, Campbell JD, Globe G, Bender B, Magid DJ. Measuring the cost of poor asthma control and exacerbations. *J Asthma* 2017;54:24-31.
52. Hekking PP, Amelink M, Wener RR, Bouvy ML, Bel EH. Comorbidities in difficult-to-control asthma. *J Allergy Clin Immunol Pract* 2018;6:108-13.
53. Jeffery MM, Shah ND, Karaca-Mandic P, Ross JS, Rank MA. Trends in omalizumab utilization for asthma: evidence of suboptimal patient selection. *J Allergy Clin Immunol Pract* 2018;6:1568-77.
54. Kitsantas P, Kornides ML, Cantiello J, Wu H. Chronic physical health conditions among children of different racial/ethnic backgrounds. *Public Health* 2013;127:546-53.
55. Pearlman DN, Zierler S, Meersman S, Kim HK, Viner-Brown SI, Caron C. Race disparities in childhood asthma: does where you live matter? *J Natl Med Assoc* 2006;98:239-47.
56. Smith LA, Hatcher-Ross JL, Wertheimer R, Kahn RS. Rethinking race/ethnicity, income, and childhood asthma: racial/ethnic disparities concentrated among the very poor. *Public Health Rep* 2005;120:109-16.
57. Szeffler SJ. Asthma across the lifespan: time for a paradigm shift. *J Allergy Clin Immunol* 2018;142:773-80.
58. Katial RK, Bensch GW, Busse WW, Chipps BE, Denson JL, Gerber AN, et al. Changing paradigms in the treatment of severe asthma: the role of biologic therapies. *J Allergy Clin Immunol Pract* 2017;5:S1-14.