

Clinical Burden and Predictors of Asthma Exacerbations in Patients on Guideline-based Steps 4-6 Asthma Therapy in the TENOR Cohort

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What is already known about this topic? Patients with severe or difficult-to-treat asthma have high rates of asthma-related health care utilization and medication use. Asthma exacerbations are an important predictor of future exacerbations and have been investigated in the overall TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) cohort.

What does this article add to our knowledge? This study characterizes the clinical burden of disease and risk of asthma exacerbations in a subcohort of TENOR patients with more severe disease who were being treated with National Heart, Lung, and Blood Institute Steps 4/5/6 therapy.

How does this study impact current management guidelines? Patients with severe or difficult-to-treat asthma who are on Steps 4/5/6 therapy have substantial clinical burden and risk of exacerbations. Improved treatment strategies, therapies, and management of risk factors may improve asthma-related health outcomes in these patients.

BACKGROUND: Patients with severe or difficult-to-treat asthma on guideline-recommended Steps 4/5/6 therapy have not previously been described.

OBJECTIVE: To characterize patients with severe or difficult-to-treat asthma on Steps 4/5/6 therapy and assess predictors of future asthma exacerbations.

METHODS: Patients ages ≥ 12 years with baseline and month 12 medication data were assigned to Steps 4/5/6 care levels from the 2007 National Heart, Lung, and Blood Institute guidelines.

Demographic, atopic, and clinical characteristics at baseline and month 12 were assessed by using descriptive statistics. Asthma-related quality of life was assessed by using the Mini Asthma Quality of Life Questionnaire, and work and activity impairment was assessed by the Work Productivity and Activity Impairment Questionnaire-Asthma. Odds ratios (OR) and 95% CI for asthma exacerbation risk at month 12 were generated by using multivariable logistic regression.

RESULTS: A total of 1186 patients were included. More than two-thirds of the patients (67.4%) were on ≥ 3 long-term controllers, and 55.1% were considered difficult to treat due to frequent exacerbations. Patients reported low asthma-related quality of life scores and considerable impairment in overall work and daily activity (21.4% and 32.1%, respectively). After adjustment for covariates, exacerbation history (hospitalization, OR 6.27 [95% CI, 3.61-10.88]; emergency department visit, OR 3.84 [95% CI, 2.50-5.91]; corticosteroid burst, OR 2.89 [95% CI, 2.18-3.82]) and very poorly controlled asthma (OR 1.95 [95% CI, 1.41-2.71] vs not well controlled) were independently associated with risk of a future exacerbation (all $P < .001$).

CONCLUSION: Despite multiple long-term controller medications, patients with severe or difficult-to-treat asthma on Steps 4/5/6 therapy present with significant clinical burden and risk of future asthma exacerbations. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:193-200)

Key words: Severe or difficult-to-treat asthma; Uncontrolled asthma; Exacerbations; Asthma therapy; Asthma guidelines; Anti-asthmatic agents

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Abbreviations used

BMI-	Body mass index
COPD-	Chronic obstructive pulmonary disease
ED-	Emergency department
EPR-3-	Expert Panel Report 3
FVC-	Forced vital capacity
ICS-	Inhaled corticosteroid
LABA-	Long-acting β_2 -agonist
Mini-AQLQ-	Mini Asthma Quality-of-Life Questionnaire
NHLBI-	National Heart, Lung, and Blood Institute
NWC-	Not well controlled
OCS-	Oral corticosteroid
OR-	Odds ratio
QoL-	Quality of life
TENOR-	The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
VPC-	Very poorly controlled
WC-	Well controlled
WPAI-	Work Productivity and Activity Impairment Questionnaire

Asthma is associated with significant morbidity and places a substantial burden on patients and health care systems. In 2007, asthma was responsible for approximately 15 million physician visits, 2 million emergency department (ED) visits and almost 500,000 hospitalizations in the United States.¹ Despite combination therapy with inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA),² and other controller medications,³ asthma is often inadequately controlled. Severe asthma, as described by the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Severe Asthma Research Program, is characterized by persistent symptoms and high health care resource use, despite multiple concomitant treatments.⁴ The link between increasingly severe asthma and an increased risk of asthma-related death and hospitalizations has been reported.^{5,6}

The NHLBI Expert Panel Report 3 (EPR-3) guidelines⁷ provide guidance for diagnosis and management of asthma and focus on symptom control, current impairment, and future risk in adolescents and adults ages ≥ 12 years. Medications are increased as necessary and, if possible, decreased to achieve and maintain asthma control. In Step 1, short-acting β_2 -agonists are used as needed for patients with intermittent asthma, with increasing doses and/or numbers of long-term controller medication used in Steps 2-6 to achieve asthma control for patients with persistent asthma (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is the largest cohort of patients with severe or difficult-to-treat asthma.^{8,9} TENOR provides the opportunity to examine patients on standard-of-care asthma therapy, as recommended by the 2007 NHLBI EPR-3 guidelines,⁷ and assess their risk for future asthma exacerbations. The primary objective of the present analysis was to characterize patients with severe or difficult-to-treat asthma who were enrolled in TENOR and who were consistently receiving Steps 4/5/6 therapy. The secondary objective was to assess associations between clinical and demographic measures and risk for future exacerbations in this cohort.

METHODS**Study design and participants**

TENOR was a multicenter, prospective, noninterventional, observational cohort study conducted over 3 years (2001-2004) with 4756 patients ages ≥ 6 years and with severe or difficult-to-treat asthma. Allergists and pulmonologists enrolled patients from 283 US sites, including managed care organizations, community physicians, group practices, and academic centers. Patients from diverse racial or ethnic backgrounds and geographic areas were represented. Asthma was considered difficult to treat based on prespecified parameters that included the following: the need for multiple asthma medications, frequent exacerbations, severe exacerbations, unable to avoid triggers, and complex medication regimen (multiple reasons were allowed). Additional inclusion criteria are shown in the Online Repository (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Patients with mild or moderate asthma were eligible if their asthma was considered difficult-to-treat and they met the additional inclusion criteria.⁸ The TENOR study was approved by a central institutional review board and by institutional review boards at each site when necessary.

Data collection

Demographics, medical history, and clinical data were collected by study coordinator interview and evaluation at baseline, semiannual, and annual clinic visits. At baseline and each 6-month visit, the patients brought their medications to the study coordinator interview to record current use, including long-term controller use and quick-relief medications. Patients also reported asthma-related health care use during the previous 3 months at study entry and semiannually. Medication adherence was measured by using a proxy question from the Asthma Therapy Assessment Questionnaire¹⁰ (see Appendix E1 in this article's Online Repository at www.jaci-inpractice.org).

Patients completed validated questionnaires at baseline and annual clinic visits. These included the Juniper Mini-Asthma Quality of Life Questionnaire¹¹⁻¹³ and an adapted section of the allergy-specific Work Productivity and Activity Impairment instrument,¹⁴ which has been validated as a measure of productivity loss and impairment in severe or difficult-to-treat asthma (Work Productivity and Activity Impairment Questionnaire-Asthma).¹⁵ Self-reported health care utilization in the previous 3 months was collected at baseline and semiannually. Spirometry was measured at baseline and annually according to American Thoracic Society guidelines.¹⁶ The patients were asked whether they had ever had a skin test for allergies, with results recorded as positive, negative, or never tested. Total serum IgE levels were measured at baseline by using approved, commercially available assays.

Analytic cohort

Adolescents and adults (ages ≥ 12 years) with no missing medication and exacerbation data at baseline and month 12 were included. Patients with a history of chronic obstructive pulmonary disease were excluded.

Assigning patients to Steps 4/5/6 therapy

By using medication data from baseline and month-12 visits, the patients were assigned to the NHLBI EPR-3 Steps⁷

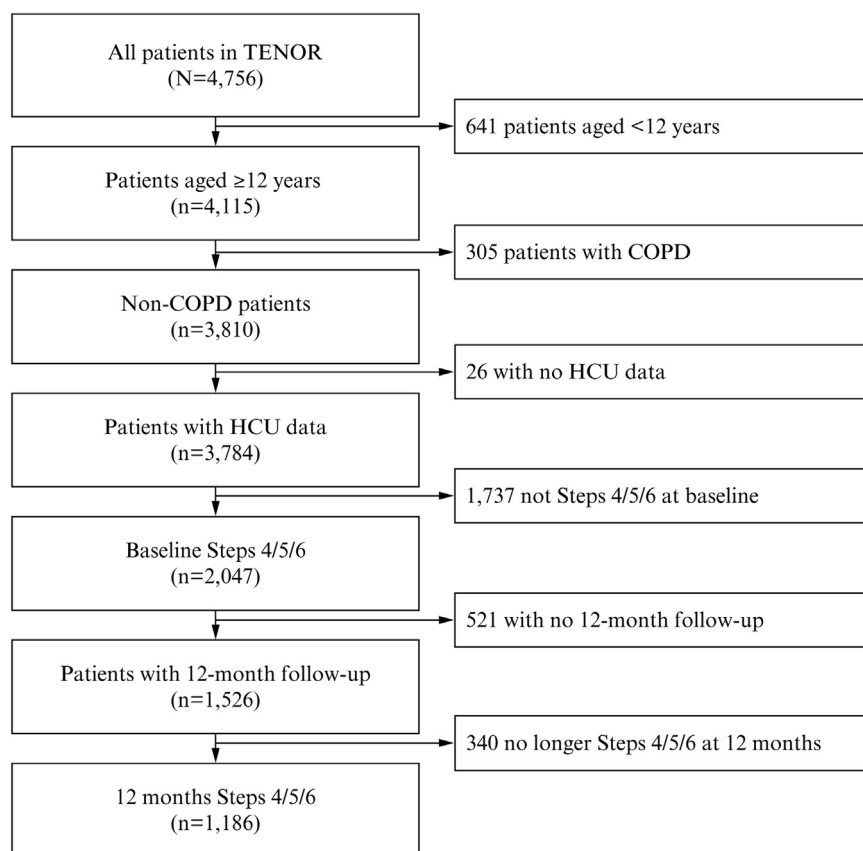


FIGURE 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram for subcohort taking Steps 4/5/6 therapy. *COPD*, Chronic obstructive pulmonary disease.

(Figure E1). The definition of “consistently” being on Steps 4/5/6 therapy was based on medication data collection at these 2 point-in-time annual assessments. Because the focus of this analysis was on patients who were at Step 4 or higher at baseline and remained so at month 12, it included patients on medium- to high-dose ICS and a LABA, as defined in NHLBI EPR-3 guidelines.⁷ Step 4 in the NHLBI EPR-3 guidelines⁷ suggests an alternative medication combination of medium-dose ICS plus either a leukotriene receptor antagonist, theophylline, or zileuton; 27 patients who were categorized into this alternative Step 4 were excluded because the small number precluded meaningful analyses.

The patients who received high-dose ICS without other concomitant therapies or oral corticosteroids (OCS) (defined as any OCS use) were included in the analytic cohort and assigned as Step 5 or 6. Guidelines include high-dose ICS plus an LABA as Step 5 and high-dose ICS plus a LABA plus OCS as Step 6 but do not address patients on high-dose ICS or OCS without an LABA or other concomitant therapy. Because Steps 5 and 6 are the only steps to include high-dose ICS and OCS, respectively, any patient who received these medications was included under Steps 5/6.

Assessment of asthma control

Patients were categorized into groups based on baseline asthma control (very poorly controlled [VPC], not well controlled, and well controlled), according to the impairment

domain of the NHLBI EPR-3 guidelines⁷ determined by using a number of variables.¹⁷ These included symptoms, nighttime awakenings, and interference with normal activity, which were captured by using the Pediatric Asthma Quality of Life Questionnaire¹⁸ and the Mini-Asthma Quality of Life Questionnaire.¹¹⁻¹³ Although the age range of the analytic cohort did not correspond precisely to the age group for which these 2 instruments were developed, the individual items collected provided the requisite data for mapping questionnaire responses accurately to the asthma guidelines.¹⁷ Short-acting β_2 -agonists use for symptom control and lung function (FEV₁ or peak flow) also were used to assess the level of asthma control.

Asthma exacerbations

Asthma exacerbations were assessed at month 12 by using health care utilization data and defined as hospitalizations, ED visits, or corticosteroid bursts in the previous 3 months. Exacerbations were further defined hierarchically in descending order of severity: hospitalization, ED visit, corticosteroid burst, and no exacerbation. For patients with multiple exacerbations, only the most severe event was included.

Statistical analysis

Baseline demographics, atopic characteristics, and clinical characteristics, including long-term controller medication use,

TABLE 1. Patient characteristics of Steps 4/5/6 cohort

Characteristic	Patients categorized as Steps 4/5/6 (n = 1186)
Age (y), mean $\pm$ SD	44.1 $\pm$ 17.3
Sex, no. (%)	
Men	393 (33.1)
Women	793 (66.9)
Race, no. (%)	
White	924 (77.9)
Nonwhite	262 (22.1)
BMI, no. (%)	
>30 kg/m ²	493 (41.6)
≤ 30 kg/m ²	691 (58.4)
Health care provider, no. (%)	
Private	858 (72.3)
Nonprivate	328 (27.7)
Treatment setting, no. (%)	
Allergist	856 (74.0)
Pulmonologist	301 (26.0)
IgE, IU/mL	
Geometric mean (95% CI)	99.7 (90.7-109.6)
Median (range)	110.0 (1-14,114)
History of allergic rhinitis, no. (%)	
Yes	888 (74.9)
No	68 (5.7)
Uncertain	230 (19.4)
Skin test result, no. (%)	
No, I have never been tested	131 (11.1)
Yes, negative	57 (4.8)
Yes, positive	996 (84.1)
Duration of asthma, (y), mean $\pm$ SD	23.0 $\pm$ 15.8
Spirometry, mean (SD)	
Percent predicted FEV ₁ *	71.5 $\pm$ 21.7
Percent predicted FVC*	80.9 $\pm$ 19.1
Percent predicted FEV ₁ -FVC ratio*	88.0 $\pm$ 14.2
Reversibility	8.3 $\pm$ 13.9
Asthma control category, no. (%)†	
WC	8 (0.7)
NWC	257 (24.0)
VPC	807 (75.3)
ICS + other long-term controller medication, no. (%)	
ICS monotherapy‡	22 (1.9)
ICS + 1 controller§	365 (30.8)
ICS + 2 controllers	647 (54.6)
ICS + 3 controllers	152 (12.8)
ICS + OCS, any combination	274 (23.1)
Exacerbation hierarchy, no. (%)	
None	528 (44.5)
Corticosteroid burst	480 (40.5)
ED visit	113 (9.5)
Hospitalization	65 (5.5)

BMI, Body mass index; FVC, forced vital capacity; NWC, not well controlled; WC, well controlled.

*Prebronchodilator race-adjusted value.

†Defined according to the NHLBI EPR-3 guidelines on asthma control.⁷

‡These patients were included in Step 5 because they were on high-dose ICS; although the guidelines do not include a step for high-dose ICS without a LABA, high-dose ICS is not part of any step before Step 5.

§Possible controllers are LABA, leukotriene modifiers, or other (cromolyn, nedocromil, and theophylline).

||Defined as any OCS use, including short courses of corticosteroids (OCS bursts).

were summarized by using percentages for categorical variables, and mean (SD) for continuous variables. Odds ratios (OR) and 95% CI for asthma exacerbations at month 12 were generated by using stepwise multivariable logistic regression. The candidate predictor variables included in the model were prespecified based on prior analyses (Table E1 in this article's Online Repository at www.jaci-inpractice.org).¹⁹

RESULTS

Patient characteristics

A total of 1186 adolescent and adult patients were consistently receiving Steps 4/5/6 therapy and were included in the analytic cohort (Figure 1). Baseline demographic, atopic, and clinical characteristics of the cohort are shown in Table 1. The mean (SD) age of the patients was 44.1 $\pm$ 17.3 years, with the majority being women (66.9%) and white (77.9%). Most (72.3%) had private insurance and fewer than half (41.6%) were considered obese (body mass index > 30 kg/m²). The geometric mean IgE (99.7 IU/mL [95% CI, 90.7-109.6 IU/mL]) was elevated compared with normal mean levels,²⁰ and the majority of the patients (74.0%) received care at an allergist site. Approximately three-fourths of the patients (74.9%) reported a history of allergic rhinitis and, of those who had a skin test for allergies (n = 1053), 94.6% reported to have a positive skin test to at least 1 aeroallergen.

The mean (SD) duration of asthma was 23.0 $\pm$ 15.8 years, and baseline prebronchodilator FEV₁ was 71.5% $\pm$ 21.7% predicted (Table 1). More than three-fourths (75.3%) had VPC asthma and fewer than 1% were considered to have well-controlled asthma. More than half of the patients in the Steps 4/5/6 cohort were receiving ICS with 2 additional long-term controllers (54.6%), and 12.8% were receiving ICS with 3 additional long-term controllers; thus, 67.4% were receiving ≥ 3 long-term controllers (including ICS as 1 controller). Nearly a fourth (23.1%) were receiving ICS and concomitant OCS (defined as any OCS use, including short corticosteroid bursts). A small proportion of patients were receiving high-dose ICS monotherapy (1.9%). At month 12, the pattern of long-term controller use remained relatively unchanged, with more than half (54.8%) still requiring ICS with 2 further controllers (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) and 65.5% received ≥ 3 long-term controllers. More than 90% of the patients self-reported using their prescribed controller agents daily. Most patients (97.5%) were considered difficult-to-treat at baseline. The reasons for physician-evaluated treatment difficulty are shown in Figure 2, with the most common being the need for multiple drugs (92.6%). More than half (55.1%) were considered difficult-to-treat due to frequent exacerbations.

Mini-Asthma Quality of Life Questionnaire scores (a measure of the functional impairments most troublesome to patients with asthma) at baseline ranged from 1 to 7, with a higher score indicating better asthma-related quality of life. For patients consistently on Steps 4/5/6 therapy, the scores were 4.3 to 5.1 across all domains, with the lowest score in the exposure domain (4.3 $\pm$ 1.7). As measured by the Work Productivity and Activity Impairment Questionnaire-Asthma, the patients reported considerable impairment in overall work and daily activity due to asthma symptoms (21.4% and 32.1%, respectively) (Table II). Differences in patient features by medical

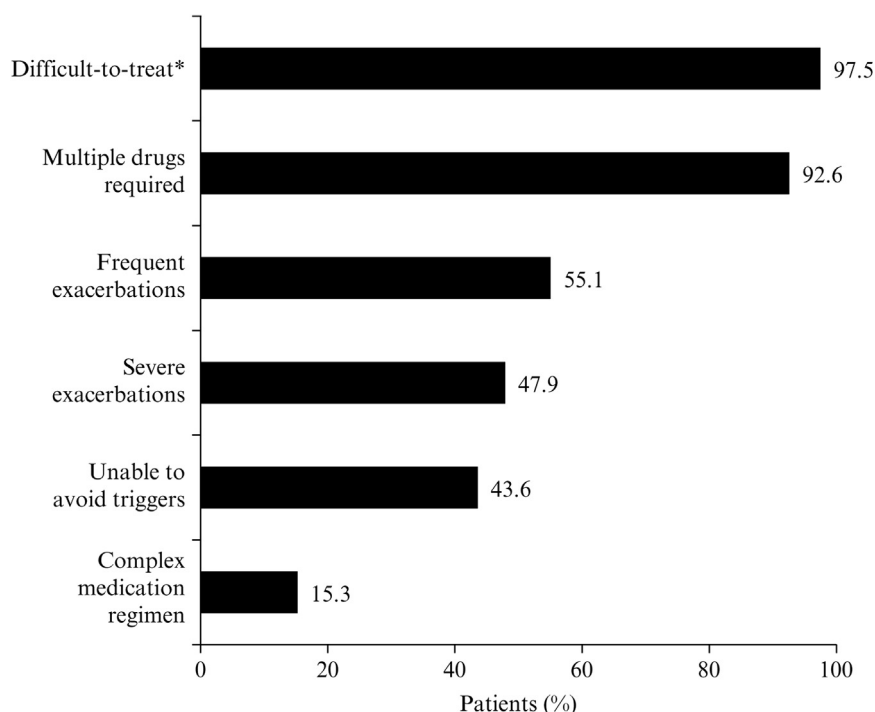


FIGURE 2. Physician's evaluation of patients with difficult-to-treat asthma for patients on Steps 4/5/6 therapy (≥ 12 years old).

insurance coverage (see Table E3 in this article's Online Repository at www.jaci-inpractice.org) were adjusted in the multivariable analyses.

Independent predictors of exacerbations at month 12

Multivariable logistic regression analyses were conducted to assess factors independently associated with 1 or more asthma exacerbations in the 3 months before the 1-year visit in patients on Steps 4/5/6 therapy (Figure 3). An asthma exacerbation at baseline was the strongest predictor of a future exacerbation at month 12 ($P < .001$), with risk increasing with increasing severity of exacerbation. A hospitalization at baseline was associated with a more than 6-fold increase in the risk of an asthma exacerbation at month 12 (OR 6.27 [95% CI, 3.61-10.88]), followed by an ED visit (OR 3.84 [95% CI, 2.50-5.91]), and a corticosteroid burst (OR 2.89 [95% CI, 2.18-3.82]), all $P < .001$. The patients with VPC asthma were approximately twice as likely to experience an exacerbation at month 12 versus patients who were not well controlled (OR 1.95 [95% CI, 1.41-2.71]; $P < .001$). Concomitant LABA use was associated with a reduced risk of exacerbation at month 12 (OR 0.51 [95% CI, 0.30-0.87]; $P = .014$). Neither Step level (6 vs 5 vs 4) nor dose (high vs medium) was significantly predictive of outcome after adjustment for the variable in the model (data not presented).

DISCUSSION

TENOR was a large, 3-year multicenter observational study of patients with severe or difficult-to-treat asthma. Previous analyses of TENOR have evaluated the characteristics and asthma-related health outcomes of patients with severe or

TABLE II. Baseline quality of life scores (Mini-AQLQ) and work productivity and activity impairment (WPAI-Asthma) in patients taking Steps 4/5/6 therapy

Categories	Patients categorized as Steps 4/5/6 (n = 1186)
QoL score, mean (SD)*	
Overall QoL†	4.7 ± 1.4
Symptoms domain	4.6 ± 1.5
Activities domain	5.1 ± 1.5
Emotional domain	4.6 ± 1.8
Exposure domain	4.3 ± 1.7
WPAI-Asthma, (%), mean (SD)‡	
Overall work impairment	21.4 ± 27.2
Activity impairment	32.1 ± 29.1

QoL, Quality of Life; Mini-AQLQ, Mini-Asthma Quality of Life Questionnaire; WPAI-Asthma, an adapted section of the allergy-specific Work Productivity and Activity Impairment Instrument, validated in patients with severe or difficult-to-treat asthma.

*QoL was measured by using the Juniper Mini-AQLQ;¹¹⁻¹³ each domain is scored from 1 to 7, with 1 representing the greatest possible impairment (worse QoL) and 7 the least possible impairment (better QoL).

†Overall QoL is expressed as a score out of a total 7.

‡Data are presented as impairment percentages, with higher numbers indicating greater impairment (less productivity).^{15,27}

difficult-to-treat asthma, however, the subcohort of TENOR patients on guideline-recommended Steps 4/5/6 therapy had not been examined. The present analysis, to our knowledge, is the first to characterize adolescent and adult patients with severe or difficult-to-treat asthma consistently treated with NHLBI-guideline Steps 4/5/6 therapy and to identify

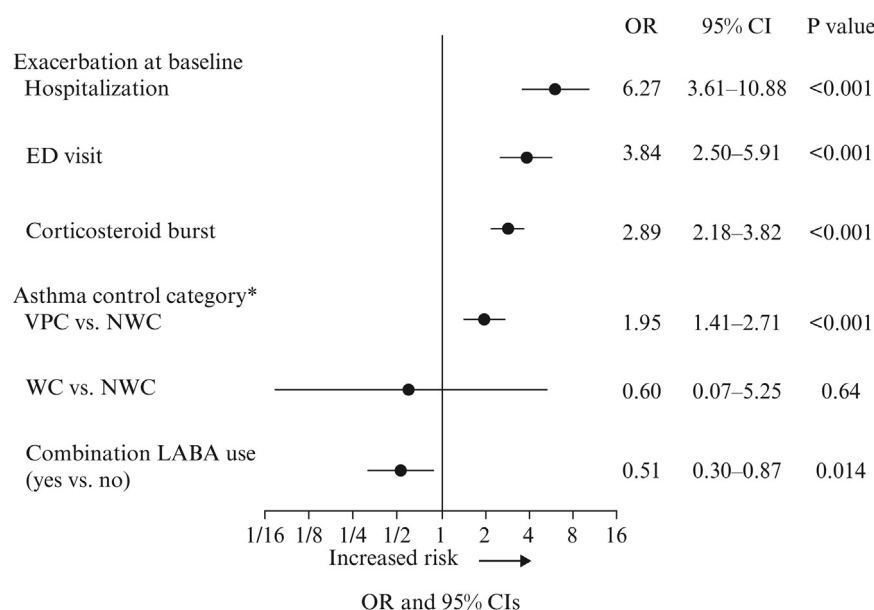


FIGURE 3. Clinical predictors of asthma exacerbation at month 12. ORs and 95% CIs that assessed risk of asthma exacerbations at month 12 were generated by using stepwise multivariable logistic regression. Candidate predictor variables included in the model were prespecified based on prior analyses (Table E1).¹⁹ COPD, Chronic obstructive pulmonary disease; NWC, not well controlled; WC, well controlled.

predictors of future asthma exacerbations in such patients in a real-world setting.

Our analysis shows that, despite multiple long-term controller use, patients with severe or difficult-to-treat asthma while on Steps 4/5/6 therapy continue to have a substantial clinical burden and are at increased risk of future exacerbations. Few patients on Steps 4/5/6 therapy had well-controlled asthma (<1%) despite management by a specialist and use of multiple long-term controller medications; more than 65% of patients were receiving ≥ 3 long-term controllers at baseline and at 1 year. The majority of patients had an allergic component to their asthma, including elevated IgE levels and a high prevalence of self-reported allergic rhinitis and skin test positivity. Patients on Step 4/5/6 therapy had poor asthma-related quality of life as demonstrated by scores across a number of domains. The degree of work and daily activity impairment was also significant.

When identifying predictors of future exacerbations in patients on Steps 4/5/6 therapy, baseline exacerbation history was the strongest independent predictor of a future exacerbation at month 12. The risk of exacerbation increased with increasing severity of exacerbation at baseline. Patients who consistently required Steps 4/5/6 therapy were more than 6 times more likely to have a future exacerbation at month 12 if they had been hospitalized at baseline and nearly 3 times more likely to have a future exacerbation at month 12 if they had received a course of corticosteroids at baseline. Although previous studies have reported the association between increased risk of future asthma exacerbation and history of recent asthma exacerbations,^{19,21} to our knowledge, the relationship between increasing future exacerbation risk with increasing severity of previous exacerbations, assessed by using a direct hierarchical approach, has not been reported. VPC asthma also was independently associated with an almost 2-fold increase in risk for

future exacerbation at month 12 in patients on Steps 4/5/6 therapy compared with patients classed as having not well controlled asthma.

We observed that neither Step level nor dose was significantly predictive of outcome. This finding may suggest that patients on Steps 4/5/6 therapy are similar in terms of exacerbation risk, and, potentially, the need for recommended anti-IgE therapy. However, it must be noted that, in nonrandomized comparisons, it is difficult to fully adjust for pretreatment severity, so the absence of an effect may reflect unmeasured confounding rather than the ineffectiveness of the treatments.

Although the majority of patients benefit from combination therapy with a LABA, some still experience exacerbations and remain poorly controlled. In this analysis of observational data, adding a LABA to other controller medications appeared to protect against future exacerbations. Several other studies have noted a protective effect of LABAs when used with ICS.^{22,23} A 2010 systematic review²⁴ reported on the protective effect and safety of combination ICS and LABA therapy in 48 randomized, controlled trials (15,155 participants, including 1155 children and 14,000 adults and adolescents with asthma). In adults and adolescents with suboptimal control on low-dose ICS, adding an LABA reduced the risk of exacerbations (which required systemic corticosteroids) and improved lung function, asthma symptoms, and the use of rescue medication compared with high-dose ICS alone. In children, however, there remains a concern regarding the safety of combination ICS and LABA therapy, given an observed trend of increased risk of exacerbations,²⁴ and results of some studies suggest that use of LABAs, even in combination with an ICS, is associated with poorer asthma outcomes and asthma deaths.²⁵ Large-scale placebo-controlled safety studies of add-on LABAs to ICS are currently being conducted, as recommended by the US Food

and Drug Administration to resolve uncertainty regarding LABA safety.

There were several limitations to this analysis. Findings from the TENOR cohort are representative of specialist care in the United States approximately 10 years ago, with the majority of patients from allergist sites, and may not be applicable to patients with asthma in the general population or in primary care practices. Furthermore, the enrolled population may bias observations because the study specifically enrolled patients with severe or difficult-to-treat asthma, many of whom may have poorly controlled asthma. In addition, some patients included in the Steps 4/5/6 analytic cohort were not being treated in accordance with NHLBI guidelines. For example, 1.9% of patients were receiving high-dose ICS monotherapy at baseline (1.8% at month 12); the NHLBI guidelines do not advocate treatment with high-dose ICS without an LABA at any of the steps. Thus, some patients may have had poor asthma control due to being treated with medication regimes that do not follow best practice, rather than their disease being refractory to treatment. The assessment of patient adherence to controller medication was based on a proxy question from the Asthma Therapy Assessment Questionnaire instrument. Self-reported patient adherence to medications was more than 90% in this study. However, self-reported adherence overestimates actual adherence compared with direct electronic monitoring of medication use.²⁶ Poor medication adherence would likely increase the risk of a future exacerbation and lead to an underestimation of the beneficial effects of currently available treatment. The definition of “consistently” being on Steps 4/5/6 therapy was based on only 2 point-in-time annual assessments and likely overstates the proportion of patients who were consistently on Steps 4/5/6 treatment throughout the full year. Finally, it should be noted that the most recent (2007) version of the guidelines was used to retrospectively analyze patients in Step 4/5/6 who received treatment that was most likely based on a previous iteration of the guidelines. Notably, Xolair (omalizumab; Genentech, Inc, South San Francisco, Calif) was not US Food and Drug Administration approved for use during the period of data collection for this analysis, and allergen immunotherapy was not collected in TENOR. It is difficult to ascertain the impact on our results should these medications have been available and/or collected in this study.

In conclusion, these real-world data highlight an unmet need, assessed by using several end points, in a large subcohort of patients with severe or difficult-to-treat asthma who were receiving NHLBI guideline-recommended Steps 4/5/6 therapy. Despite “consistent” use and reported good adherence to these medications, the majority of these patients had poorly controlled asthma, poor asthma-related quality of life, a high degree of work and activity impairment, and a high risk of future asthma exacerbation. For this subcohort of patients, their disease remains severe and refractory to current therapies, which highlights the need for new and improved treatments. Characterizing these patients and identifying predictors of asthma exacerbations may help physicians tailor individual asthma management needs and prevent future events.

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APPENDIX E1

Medication adherence was measured by using a proxy from the Asthma Therapy Assessment Questionnaire. The question is stated as follows: "What best describes how you take this medicine now?" Possible responses include the following: (1) "I take it every day," (2) "Some days I take it, but other days I don't," (3) "I used to take it, but now I don't," (4) "I only take it when I have symptoms," or (5) "I never took it".¹⁰

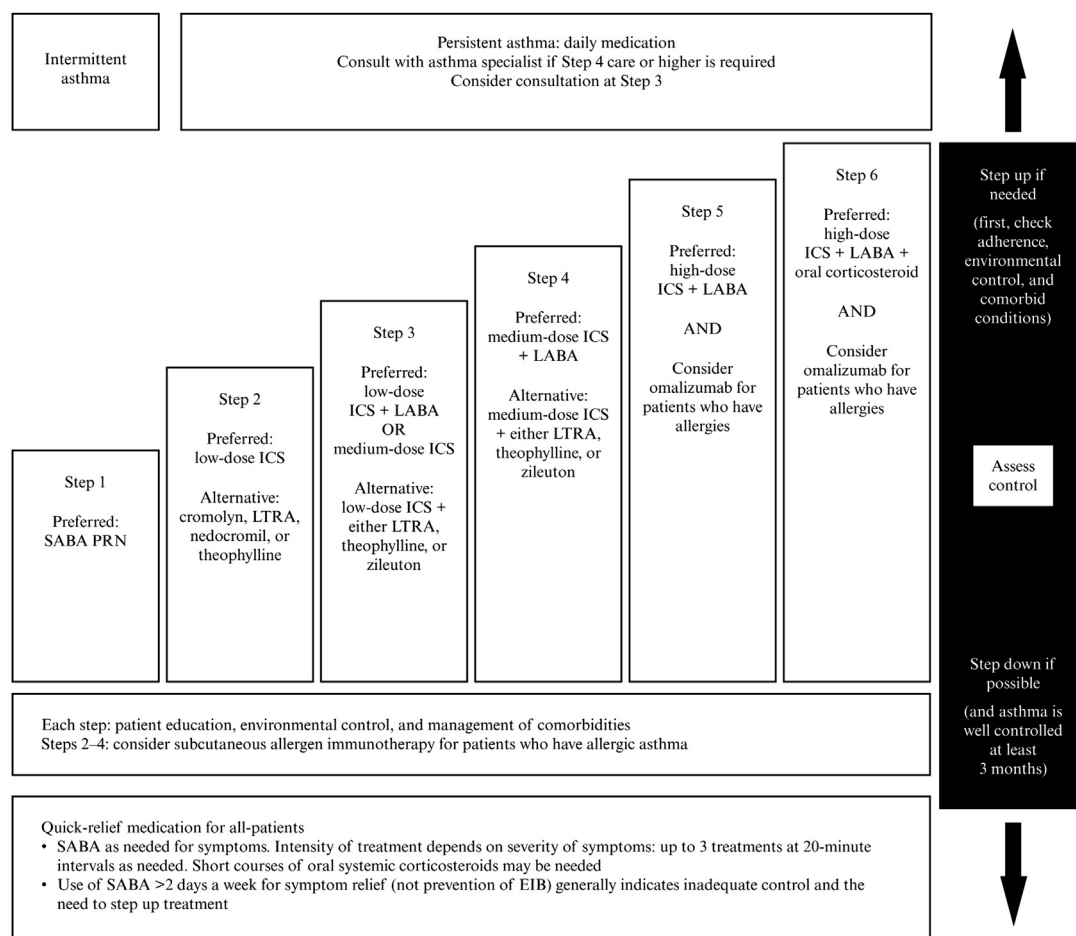


FIGURE E1. Stepwise approach for managing asthma in adults and adolescents (≥12 years of age). Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.⁷

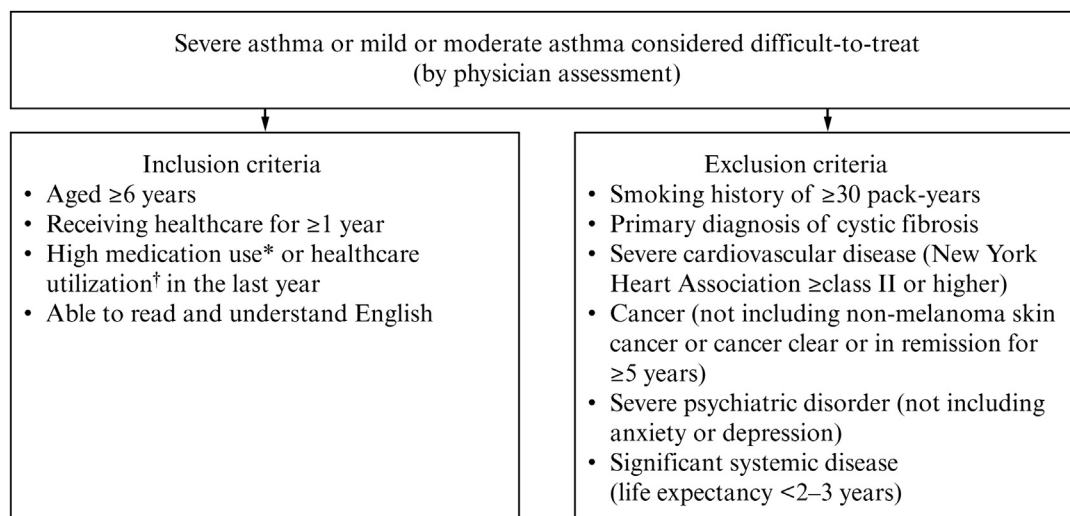


FIGURE E2. Patient inclusion and exclusion criteria for the TENOR study *Requiring ≥ 3 asthma controller medications, long-term daily high doses of inhaled corticosteroid, or use of ≥ 5 mg/day oral prednisone. †Two or more unscheduled asthma care visits or ≥ 2 oral corticosteroid courses.

TABLE E1. Candidate variables included in stepwise multivariable logistic regression

Demographic variables	Clinical variables	Atopic variables
Age	Baseline exacerbations	History of AD
Sex	Duration of asthma	History of AR
Race/ethnicity	Nonallergic asthma triggers	Allergic asthma triggers
BMI	Asthma control	IgE
Health care provider	Reversibility	
Treatment setting	Percent predicted FEV ₁ *	
	Percent predicted FVC*	
	FEV ₁ -FVC ratio*	
	No. of long-term controllers	
	Medication compliance	
	LABA use	

AD, Atopic dermatitis; AR, allergic rhinitis; BMI, body mass index; FVC, forced vital capacity.

*Prebronchodilator race-adjusted value.

TABLE E2. Distribution of long-term controller use at month 12 in patients taking Steps 4/5/6 therapy

Long-term controller medication	Patients categorized as Steps 4/5/6, no. (%) (n = 1186)
ICS monotherapy*	21 (1.8)
ICS + 1 controller†	388 (32.7)
ICS + 2 controllers	650 (54.8)
ICS + 3 controllers	127 (10.7)
ICS + OCS, any combination‡	230 (19.4)

*These patients were included in Step 5 because they were on high-dose ICS; although the guidelines do not include a step for high-dose ICS without LABAs, high-dose ICS is not part of any step before Step 5.

†Possible controllers are LABAs, leukotriene modifiers, or other (cromolyn, nedocromil, and theophylline).

‡Defined as any OCS use, including short courses of corticosteroids (OCS bursts).

TABLE E3. Patient characteristics of Steps 4/5/6 cohort by health care provider

Patient characteristics	Private health care provider (n = 858)	Nonprivate health care provider (n = 328)
Asthma control category, no. (%) [*]		
WC	7 (0.8)	1 (0.3)
NWC	210 (24.5)	47 (14.3)
VPC	565 (65.8)	242 (73.8)
ICS + other long-term controller medication, no. (%)		
ICS monotherapy [†]	17 (2.0)	5 (1.5)
ICS + 1 controller [‡]	256 (29.8)	109 (33.2)
ICS + 2 controllers	469 (54.7)	178 (54.3)
ICS + 3 controllers	116 (13.5)	36 (11.0)
ICS + OCS, any combination [§]	176 (20.5)	98 (29.9)
Exacerbation hierarchy at month 12, no. (%)		
None	520 (60.6)	194 (59.2)
Corticosteroid burst	274 (31.9)	80 (24.4)
ED visit	37 (4.3)	36 (11.0)
Hospitalization	27 (3.2)	18 (5.5)

NWC, Not well controlled; WC, well controlled.

^{*}Defined according to the NHLBI EPR-3 guidelines on asthma control.⁷

[†]These patients were included in Step 5 because they were on high-dose ICS; although the guidelines do not include a step for high-dose ICS without an LABA, high-dose ICS is not part of any step before Step 5.

[‡]Possible controllers are LABAs, leukotriene modifiers, or other (cromolyn, nedocromil, and theophylline).

[§]Defined as any OCS use, including short courses of corticosteroids (OCS bursts).

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