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Original article

Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma

Background: Characterization of uncontrolled asthma burden in a natural treatment setting can influence treatment recommendations and clinical practice. The objective was to characterize and compare the economic burden of severe or difficult-to-treat asthma in uncontrolled and controlled patients.
Methods: Baseline patient data (age ≥ 13 years; $n = 3916$) were obtained from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study. Disease control was assessed using two approaches: (i) applying criteria for control based on the Gaining Optimal Asthma ControL study, and (ii) using the Asthma Therapy Assessment Questionnaire (ATAQ) to identify the number of asthma control problems. Assessments were performed at baseline, and at months 12 and 24. Monetary values were assigned to productivity loss and medical resource use. Direct and indirect costs were aggregated over 24 months and compared using Student's *t*-test for continuous measures and chi-squared for categorical variables.
Results: Throughout the study, most patients had uncontrolled asthma (83% uncontrolled; 16% inconsistent control; 1.3% controlled). Controlled patients experienced fewer work or school absences and less healthcare resource use than uncontrolled patients at all study time points. Using the multilevel ATAQ control score, asthma costs increased directly with the number of asthma control problems. Costs for uncontrolled patients were more than double those of controlled patients throughout the study ($14 212 *vs* $6452; adjusted to 2002 dollars; $P < 0.0001$).
Conclusions: This study demonstrated that few severe or difficult-to-treat asthma patients achieved control over a 2-year period and the economic consequence of uncontrolled disease is substantial.

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Achieving disease control is a universal therapeutic goal for patients with chronic disease. In asthma, the concept of disease control as the principal outcome measure only recently has been the focus of management strategies, clinical trials and evidence-based consensus guidelines (1, 2). Unlike hypertension or hypercholesterolemia where an easily measured biomarker defines the treatment target, control of asthma is multidimensional and includes objective and patient-reported measures.

The concept of disease control is distinct and separate from disease severity, although some of the same measures are included in definitions of both concepts. Patients and clinicians routinely underestimate both severity and control (3). Additionally, physician-rated severity is poorly correlated with patient-reported asthma symptoms (4). Although control of asthma remains the central focus of therapy, many patients fail to achieve partial or full control with available therapies (5–7).

Previous studies have evaluated the impact and effectiveness of asthma treatment on disease control (8, 9). A recent study of asthma patients, the Gaining Optimal Asthma ControL (GOAL) study, assessed the impact of achieving and maintaining a target level of disease control using a guideline-defined, composite measure of control (10). The upward stepwise treatment regimen applied in the GOAL study facilitated the achievement of control for a majority of the patients, but it was not reflective of treatment approaches used in usual care settings, and some 30% of patients treated in the stepwise manner remained uncontrolled at the end of the study period.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is a naturalistic observational study of asthma patients with no specified treatment interventions, thus providing an opportunity to examine the extent and economic impact of disease control in a long-term cohort of individuals with severe or difficult-to-treat asthma (11).

The objectives of this study were to characterize the extent to which patients with severe or difficult-to-treat asthma were uncontrolled using specific criteria and then

to evaluate the economic consequences of asthma stratified by control status over a 24-month period.

Methods

Study design

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens is a multicenter prospective, observational study of severe or difficult-to-treat asthma patients in the USA. Detailed study characteristics for TENOR have been described previously (11). Briefly, the study subjects were recruited, and followed for 3 years (2001–2004). Subjects were from diverse geographical areas and healthcare settings. Patients continued to receive usual asthma treatment as indicated by their asthma specialist. The study design and protocol were approved by a central institutional review board, and, when necessary, by the institutional review board at each site.

Assessment of asthma severity

Asthma severity in TENOR was determined based on the physician's subjective clinical opinion. In addition, physicians reported whether their patient's asthma was considered difficult-to-treat based on specified parameters (i.e. complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations and/or unresponsive to therapy).

Assessment of asthma control

Two measures of asthma control were employed. The first used an approximation of the composite control endpoint developed by the GOAL investigators (10). This endpoint included measures of daytime symptoms, peak expiratory flow (PEF), nighttime awakening, and exacerbations [including emergency department (ED) visits, hospitalizations, and steroid use]. Although TENOR was an observational study, rather than a clinical trial, and measures of control were assessed less frequently than in the GOAL study, we developed proxies for the same set of control categories.

We defined asthma control as (i) no or hardly any daytime symptoms using three items from the Juniper Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (12) (shortness of breath as a result of asthma, chest tightness/heaviness, and wheezing in the chest), (ii) no nighttime symptoms using one item from the MiniAQLQ (difficulty getting a good night's sleep as a result of asthma), (iii) PEF ≥ 80% of predicted at the time of assessment, (iv) no use of systemic corticosteroids, and (v) no ED visits or hospitalizations in the past 3 months. Complete asthma control was assigned if patients met all five criteria at the study visit. Otherwise, patients were classified as uncontrolled. Table 1 shows the GOAL criteria and our approximation using TENOR data.

A second and independent measure of control was used and involved the previously validated Adult Asthma Therapy Assessment Questionnaire (ATAQ). The ATAQ is a brief self-administered instrument, validated as a simple clinical index for assessing patient-perceived control of asthma. The ATAQ asks patients to assess whether or not they have had problems due to asthma in the past 4 weeks. The instrument was administered to TENOR patients semi-annually (13, 14). The ATAQ generates a control score ranging from zero to four asthma-related barriers, with zero representing no asthma control problems.

Resource use in TENOR

Data on asthma-related healthcare utilization were collected semi-annually by study coordinator interview; ED visits, overnight hospitalizations, and unscheduled office visits/contacts with physician during the previous 3 months are reported. Asthma-related medications were also collected semi-annually and categorized into seven therapeutic groups: inhaled corticosteroids, oral/systemic corticosteroids, short-acting beta-agonists, long-acting beta-agonists, methylxanthines, cromoglycates, and leukotriene modifiers.

Work and school absence was assessed annually using the asthma-specific adaptation of the Work Productivity and Activity Index – Allergy specific (WPAI-AS) instrument (15) in which

Table 1. Definition of controlled asthma and relationship to GOAL criteria of Bateman et al. (10)

	TENOR			
Bateman criteria*	Proxy measurements	Controlled asthma requirement	Collection frequency	Recall period
Daytime symptoms	Shortness of breath due to asthma	'None of the time' or 'Hardly any of the time' for all measurements	Annual	2 weeks
	Chest tightness/heaviness		Annual	2 weeks
	Wheezing in chest		Annual	2 weeks
Morning PEF	Prebronch PEF	≥80% predicted†	Annual	NA
Night-time awakening	Difficulty getting good night's sleep due to asthma	'None of the time'	Annual	2 weeks
Exacerbations	Emergency visits for asthma	No occurrences of any exacerbations	Semi-annual	3 months
	Hospitalizations for asthma		Semi-annual	3 months
	Steroid bursts		Semi-annual	3 months
	Systemic corticosteroids		Semi-annual	NA

GOAL, Gaining Optimal Asthma ControL; TENOR, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens; PEF, peak expiratory flow.
*Bateman et al. (10) defined weekly controlled asthma as the achievement of all criteria for the assessment week. Controlled asthma was achieved if the patient reported seven controlled weeks (out of eight consecutive assessment weeks) and did not violate exacerbations criteria for each day of each week.
†Percent predicted PEF was calculated based on the European Community for Steel and Coal standards (35) for patients aged ≥ 18 years and on the Polgar standards (36) for patients aged 13 to 17.

'asthma' was substituted for all the occurrences of the term 'allergies.' The WPAI-Asthma has been validated in severe or difficult-to-treat asthma to measure asthma-related work and/or classroom productivity impairment (16).

Unit cost estimation

Monetary values for work and school absence were estimated by applying gender-specific dollar amounts for a lost day of work (17). Missed school days for children were valued as the lost work of a parent caring for the child and calculated using a gender-blended pay rate. All monetary values associated with productivity loss were adjusted to 2002 dollars (18).

Average transaction prices with respect to resource use costs were derived from a large administrative claims database (PharMetrics Integrated Outcomes Database, 2002) containing patient-level reimbursement claims for more than 22 million managed care patients in the US over a 4-year period.

Medication costs were based on US average wholesale prices minus 15% to approximate actual acquisition costs (19, 20). Cost computations for medications used average recommended daily dose by medication (standard dose per day) and were adjusted to 2002 dollars (18).

Statistical methods

Analyses were limited to patients aged ≥ 13 years at baseline. For inclusion, patients had to have valid nonmissing data for each criterion associated with the definition of asthma control at the assessment period of interest.

Demographic and clinical characteristics, along with the burden of uncontrolled asthma (productivity loss, healthcare utilization, medication use) and associated costs were summarized by the dichotomous measure of asthma control status and by ATAQ score. These assessment-specific analyses were performed cross-sectionally to characterize patients with respect to their control status. A subgroup analysis of the uncontrolled asthma group was planned to compare those on guideline-recommended therapy with those not on guideline-recommended therapy.

Additional analyses were performed to assess patterns of asthma control over time. Patients who were controlled at all three assessments were compared with patients who were uncontrolled at all three assessments with respect to productivity loss, healthcare utilization, and medication use.

Statistical significance between groups was assessed through the Student's *t*-test for continuous variables and chi-squared test for categorical variables. The *P*-values comparing geometric means of immunoglobulin E (IgE) were based on *t*-tests of log values. In situations where cell sample sizes were < 30, nonparametric Wilcoxon methods were used to compare groups due to the potential skewness of the data. For analyses in which some data are missing, sample sizes were provided for test statistics. Confidence intervals based on 1000 bootstrap samples were calculated around all mean costs. All analyses were performed using the SAS Version 8 for Windows (SAS Institute, Cary, NC, USA).

Results

Study population

Of the 4756 TENOR patients, 3916 were aged ≥ 13 years and included in the current analysis. Table 2 summarizes select demographic and clinical variables by control status at baseline. Only 216 patients met the criteria for complete disease control using the GOAL criteria. Patients with controlled asthma had significantly lower body mass index, less asthma control problems on the ATAQ, higher forced expiratory flow (FEV_1) and higher IgE levels. No significant differences were observed by race/ethnicity, age, smoking history, number of long-term controller medications, and usage of several other medications (e.g. cromolyn and nedocromil, long-acting beta-agonists, and methylxanthines). Of interest is the discordance of classification of asthma control between the clinically oriented GOAL criteria and the patient reported ATAQ score. Fully 32% of patients classified as uncontrolled using the GOAL criteria report zero or one asthma-related barrier.

Table 2. Demographic and clinical variables at baseline assessment

	Controlled ($n = 216$)	Uncontrolled ($n = 3700$)	*P*-value*
Age (years) at baseline, mean (SD)	43.4 (18.2)	44.8 (17.9)	0.2894
Weight (kg), mean (SD)	76.7 (18.2)	82.2 (22.9)	0.0005
BMI (kg/m^2), mean (SD)	27.7 (6.0)	29.9 (7.9)	<0.0001
IgE, geometric mean (95% CI)	131.4 (106.8–161.5)	94.1 (8.01–99.4)	0.0045†
Gender, *n* (%)			
Female	125 (57.9)	2521 (68.2)	0.0016
Male	91 (42.1)	1176 (31.8)	
Race/ethnicity, *n* (%)			
White	176 (81.5)	2872 (77.6)	0.1599
Black	20 (9.3)	493 (13.3)	
Hispanic	9 (4.2)	219 (5.9)	
Asian or pacific islander		58 (1.6)	
Other/unknown	5 (2.3)	58 (1.6)	
Physician-assessed severity, *n* (%)			
Mild	10 (4.7)	100 (2.7)	<0.0001
Moderate	139 (64.7)	1671 (45.3)	
Severe	66 (30.7)	1920 (52.0)	
Smoking history‡, *n* (%)			
Never smoked	116 (64.4)	2072 (63.6)	0.0929
Past smoker	62 (34.4)	1040 (31.9)	
Currently smoke	2 (1.1)	144 (4.4)	
FEV_1 percent predicted, mean (SD)	92 (20.7)	79.5 (23.0)	<0.0001
ATAQ index score: 0–4 barriers, *n* (%)			
No barriers	101 (48.3)	489 (13.7)	<0.0001
1 barrier	56 (26.8)	674 (18.8)	
2 barriers	49 (23.4)	1184 (33.1)	
3+ barriers	3 (1.4)	1234 (34.5)	

BMI, body mass index; IgE, immunoglobulin E, FEV_1, forced expiratory volume; ATAQ, Asthma Therapy Assessment Questionnaire.

*Statistical significance between groups was assessed through the Student's t-test for continuous variables and through the chi-square test for categorical variables.

†The *P*-value comparing geometric means of IgE were based on t-tests of log values.

‡Smoking history was tabulated for patients aged ≥ 18 years.

Patterns of control over time

Patients with uncontrolled asthma comprised almost 95% of the population at baseline. Of the patients uncontrolled at baseline, 93% remained uncontrolled at the 12-month follow-up assessment, and among these patients, 95% subsequently remained uncontrolled at the 24-month follow-up assessment. Hence, approximately 83% of all patients had uncontrolled asthma at all assessments during the first 24 months, compared with 1.3% of patients who had controlled asthma at all assessment periods. Approximately 16% of patients did not have consistent control status over the first 24 months of follow-up.

Outcomes and cost

Work and school absence, health service use, and medication use comprised the aggregate cost variable. Table 3 summarizes asthma-related costs by asthma control status at baseline, 12- and 24-month assessments. At all assessments, the annual mean number of work days lost, school days lost, and physician visits were significantly higher for patients with uncontrolled asthma. This difference is reflected in the individual cost of each component, as well as in the mean total costs. At baseline, the annual mean total cost for controlled asthma patients was \$2422 (95% CI: \$2310–\$2544), compared with \$5964 (95% CI: \$5655–\$6315) for uncontrolled asthma patients. At both follow-up assessments, the annual mean total cost for patients with uncontrolled asthma was almost double that for patients with controlled asthma. Results were statistically significant at all assessments ($P < 0.0001$). Additionally, mean costs were lower in the 24-month assessment when compared with the baseline and 12-month assessments. Lower rates of work and school days missed in the 24-month assessment are partly to explain for this finding.

In the sub-group analysis of patient's receiving guideline-appropriate therapy, data suggest that approximately 30% of the uncontrolled patients at the 12-month and 24-month follow-up assessments were receiving maximum guideline-recommended therapy (maximum dose single-unit combination therapy). Total mean cost for this subset of patients was \$6022 (95% CI: \$5313–\$6844) and \$4901 (95% CI: \$4388–\$5465) at the 12- and 24-month follow-up assessment, respectively, which was significantly higher than the mean costs of the overall uncontrolled population at both 12- and 24-month follow-up assessments. This finding can be explained by the higher rate of medical and work/school resources in the guideline-appropriate therapy sub-group.

To assess the cumulative potential economic burden of long-term uncontrolled asthma over the 24-month study period, those patients who displayed consistent control status at baseline, and 12- and 24-month follow-up were compared with patients with uncontrolled asthma at the same time points. The total mean cost for patients with controlled asthma over the 24-month study period was \$6452 (95% CI: \$5937–\$6970), while the total mean cost for patients with uncontrolled asthma over the 24-month study period was \$14 212 (95% CI: \$13 404–\$15 059), $P < 0.0001$; results not displayed in Table 3).

The ATAQ index score was used as an independent measure to assess burden and associated costs. Figure 1 represents the annual mean cost associated with work days lost, school days lost, physician visits, hospital nights, and ED visits. At all assessments, the healthcare utilization (physician visits, hospital nights, and ED visits) rates increased as the number of control problems increased.

Discussion

Past research has shown that asthma treatment costs in the USA are high, and indirect costs are a significant proportion of total costs (21–32). None of these studies, however, have assessed the asthma treatment costs stratified by disease control. This study is the first to evaluate costs of uncontrolled asthma based on a unique approach to defining asthma control, and is the first study to highlight the significant economic burden of uncontrolled asthma in a naturalistic study of severe or difficult-to-treat patients.

Severity rating, a standard with practitioners, will undoubtedly remain an important indicator of asthma control; however, the quest for asthma control will drive clinical decision making. As guideline recommendations increasingly reflect the need to manage asthma symptoms, evaluation of more complex, composite measures of disease control will become important.

The GOAL study confirmed that a significant proportion of asthma patients do not achieve the target control level even with high-dose combination therapy (10). Our findings demonstrate that achieving asthma control has a significant impact on patient outcomes and costs. At every assessment, the total mean costs for uncontrolled patients was consistently higher by about twofold the costs for the controlled group. Furthermore, a sub-analysis of the uncontrolled population draws attention to the significant unmet need in patients who remain uncontrolled despite receiving high-dose combination therapy.

In this study, although medication dose was not calculated, unit costs were comparable, indicating that those who had not achieved control might benefit from more aggressive treatment. Individualized therapy could offset the need for crisis management (ED visits) and hospitalizations, thus resulting in improved patient outcomes and lower costs. It is likely that frequency of office visits may increase to allow for appropriate adjustment of medication regimens; however, beneficial cost offset would still be expected.

Table 3. Annual burden and cost* at baseline, and 12- and 24-month follow-up by asthma control status

	Baseline			Month 12			Month 24		
					Uncontrolled			Uncontrolled	
	Controlled ($n = 216$)	Uncontrolled ($n = 3700$)	*P*-value†	Controlled ($n = 251$)	ALL‡ ($n = 2545$)	Max ICS + LABA§¶** ($n = 676$)	Controlled ($n = 215$)	All‡ ($n = 2063$)	Max ICS + LABA§¶** ($n = 619$)
Work days lost††									
n	176	3168		213	2232	603	177	1843	571
Mean (SD)	0.3 (3.9)	12.0 (48.2)	0.0013	1.3 (13.2)	8.3 (34.2)	13.4 (46.4)	0.4 (4.0)	7.1 (28.4)	9.3 (34.8)
Subcost	$37.00	$1730.80		$188.70	$1221.90	$2069.40	$52.20	$1031.10	$1237.10
95% CI subcost¶¶	$(0–121)	$(1495–2011)		$(7–456)	$(1017–1468)	$(1521–2771)	$(0–145)	$(849–1247)	$(954–1859)
School days lost									
n	28	382		30	210	53	30	133	31
Mean (SD)	1.4 (7.4)	13.6 (39.9)	0.0436	0.0 (0.0)	9.3 (34.3)	16.9 (50.3)	0.0 (0.0)	9.1 (33.3)	5.0 (17.3)
Subcost	$240.10	$2340.70		$0.00	$1595.30	$2917.50	$0.00	$1575.40	$867.50
95% CI subcost	$(0–747)	$(1747–3079)		NA	$(872–2438)	$(826–5020)	NA	$(714–2666)	$(66–1984)
Physician visits									
n	216	3695		251	2543	676	215	2061	619
Mean (SD)	3.8 (3.7)	10.0 (9.8)	<0.0001	2.7 (2.9)	6.5 (7.2)	8.2 (8.1)	2.4 (2.6)	5.6 (6.3)	6.9 (6.9)
Subcost	$296.60	$771.70		$212.70	$505.20	$634.80	$185.70	$435.90	$530.50
95% CI subcost	$(261–335)	$(749–795)		$(187–241)	$(484–526)	$(575–670)	$(159–212)	$(415–458)	$(478–567)
Hospital nights									
n	216	3695		251	2543	676	215	2061	619
Mean (SD)	0.0 (0.0)	1.3 (6.8)	0.0072	0.0 (0.0)	0.7 (4.5)	0.9 (4.3)	0.0 (0.0)	0.5 (3.3)	0.8 (3.7)
Subcost	$0.00	$921.20		$0.00	$524.10	$659.30	$0.00	$385.40	$610.70
95% CI subcost	NA	$(770–1103)		NA	$(406–655)	$(446–915)	NA	$(291–491)	$(404–839)
ED visits									
n	216	3695		251	2543	676	215	2061	619
Mean (SD)	0.0 (0.0)	1.1 (3.3)	<0.0001	0.0 (0.0)	0.6 (1.8)	0.7 (2.0)	0.0 (0.0)	0.5 (1.7)	0.6 (2.0)
Subcost	$0.00	$320.10		$0.00	$164.80	$213.30	$0.00	$140.50	$168.80
95% CI subcost	NA	$(289–351)		NA	$(146–186)	$(169–260)	NA	$(119–163)	$(129–221)
Mean Drug Cost‡‡	$2077.30	$2158.30	0.0372	$2034.20	$2122.00	$2397.00	$1960.50	$2070.40	$2343.40
95% CI cost	$(2016–2137)	$(2139–2175)		$(1972–2097)	$(2098–2144)	$(2347–2415)	$(1888–2024)	$(2040–2096)	$(2285–2357)
Mean total cost§§	$2422.20	$5963.60	<0.0001	$2410.20	$4530.00	$6022.40	$2194.40	$4046.30	$4901.40
95% CI cost	$(2310–2544)	$(5655–6315)		$(2229–2649)	$(4272–4827)	$(5313–6844)	$(2097–2292)	$(3810–4326)	$(4388–5465)

*Burden and associated costs were calculated per year for each measure.

†Significance was assessed by the Student's *t*-test. For situations where cell sizes were ≤ 30, nonparametric Wilcoxon methods were employed.

‡$P < 0.001$ for each subcost category and mean total cost, compared with controlled patients at respective assessment timepoint.

§Patients who were receiving maximum dose inhaled corticosteroid and long-acting beta-agonist combination therapy.

¶$P < 0.05$ for each subcost category and mean total cost compared with controlled patients at respective assessment timepoint.

**Maximum dose of inhaled corticosteroid and long-acting beta-agonist combination therapy.

††Work days lost were calculated for patients aged ≥19 years; school days lost were restricted to patients who were aged ≤ 18 years.

‡‡Drug costs included inhaled corticosteroids, oral/systemic corticosteroids, short- and long-acting beta-agonists, methylxanthines, cromolyns, and leukotriene modifiers.

§§Mean total cost includes variables relating to productivity loss, healthcare utilization, and medication use.

¶¶Confidence intervals are based on 1000 bootstrap samples.

ED, emergency department; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists.

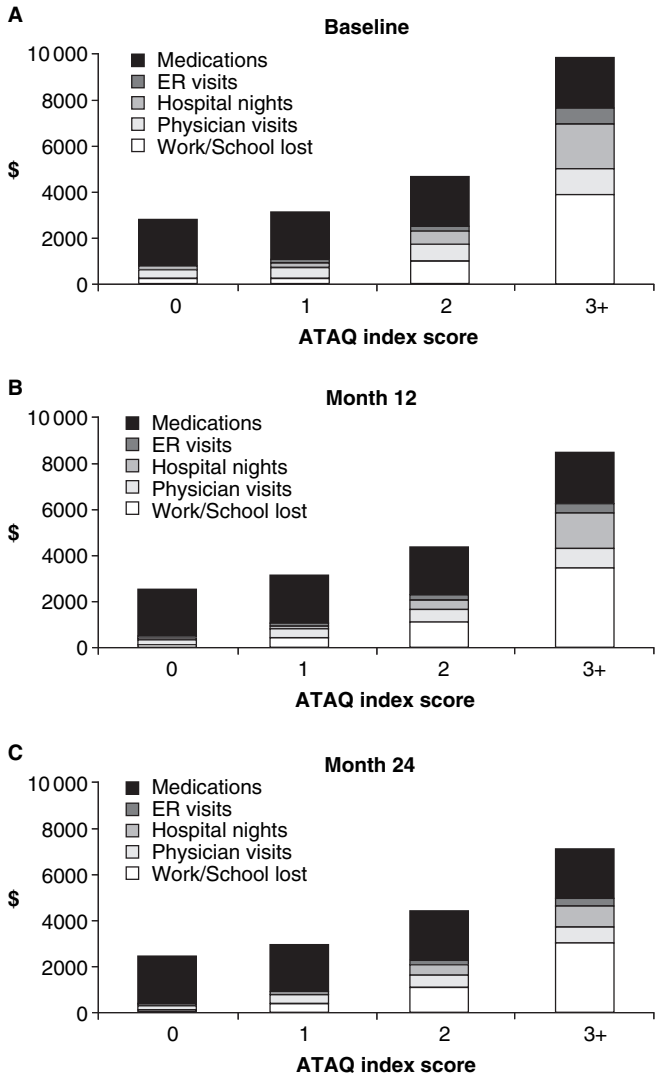

Figure 1. Annual costs associated with burden by ATAQ score at baseline, and 12- and 24-month follow-up. At all assessment periods, significant differences ($P \leq 0.0001$) were observed between ATAQ groups for individual burden costs and total burden cost.

In addition to evaluating the burden of disease by control as defined by a dichotomous measure, we also looked at the number of asthma control problems as measured by the ATAQ. The alternate view of control based on a categorical measure derived from the ATAQ provided a validation approach for testing the composite control measure. An increase in control problems was associated with negative patient outcomes. In most instances, the occurrence of an event doubled or tripled between each control problem category. However, for those with ≥3 problems the burden of asthma increased from twofold to >20-fold when compared with those with no problems in terms of number of work days lost (results not displayed in Fig. 1). Total costs of care increased as the number of asthma control problems increased. Patients with ≥3 control problems had expenditures that were two to 3.5 times greater than patients with fewer control problems. These findings further underscore the impact of control on patient outcomes and the cost of managing this disease.

Previous research has shown that indirect costs, because of lost productivity, remain a sizeable portion of the total costs of treating asthma (23, 32). Our study shows that uncontrolled patients cost twice as much as controlled patients with severe or difficult-to-treat asthma. A recent study found that annual asthma-related direct and indirect cost per patient (1998 US dollars) was approximately $4900 with indirect costs (due to lost productivity) accounting for about 35% of the total costs (32). The same study also found that total annual asthma costs significantly increased with increase in levels of patients' self-reported asthma severity, ranging from $2646 for mild patients up to $12 813 for severe patients. However, total direct and indirect costs of the uncontrolled asthma population had not been demonstrated prior to our analyses. In this study, stratification by control revealed that indirect costs as measured by productivity loss accounted for a much larger proportion of the total costs. Given that an uncontrolled asthma population would have significantly less productivity, our findings suggest the importance of disease control and highlight the need for treatment regimens and disease management programs that emphasize prevention of exacerbation as a central asthma management strategy. As the treatment paradigm is shifting towards disease control, emphasis should be put on evaluating treatment options based on economic evidence, in addition to clinical evidence, to arrive at the best treatment approaches for patients (33).

There are limitations of this study that necessitate further discussion. Importantly, the limitations of undertaking a large, multi-year cohort study of asthma patients should be acknowledged. These include generalizability of subjects, methods of recruitment, retention of subjects, and issues related to measurement. Many of these issues are detailed in the paper by Dolan et al. (11) and apply to this secondary analysis of the data. Resource use data were not verified by matching patient responses with administrative claims or other independent sources of data. Data on medication consumption and persistence with therapy were not collected. We used unit cost data from a typical and reliable data source, but recognize that costs are healthcare system specific. Our cost estimates are not necessarily generalizable to other jurisdictions.

Finally, the 283 study sites that participated in TENOR were from diverse geographical areas and managed by more than 400 pulmonologists and allergists. The sites represented typical settings in which asthma patients receive care and were representative of specialist care in the US. While using data from a large naturalistic cohort study, some of our sub-group analyses involved small samples of patients. We suggest caution in interpreting these results.

We found that uncontrolled asthma patients incur significantly more healthcare costs than controlled patients. Despite maximum guideline-recommended therapy, patients continue to remain uncontrolled. Although achieving disease control is imperative to disease management for asthma patients, varying clinical interpretations of control can be expected (34). Application of a guideline-driven composite measure of control in asthma treatment management may provide an excellent opportunity to positively impact clinical and policy decision making.

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