

Original Article

Comorbidities in Difficult-to-Control Asthma

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What is already known about this topic? Comorbidities are associated with difficult-to-control asthma, but the prevalence and nature of comorbidities in patients with difficult-to-control asthma are unknown. Also, it is unclear which patients are most at risk of comorbidities.

What does this study add to our knowledge? This Dutch pharmacy database study shows that the majority of patients with difficult-to-control asthma have at least 2 comorbidities, and that asthmatic women of older age, former smokers, and prednisone-dependent asthmatics are at greatest risk of comorbidities.

How does this study impact current management guidelines? Patients with difficult-to-control asthma, in particular older women, former smokers, and prednisone-dependent patients, should be thoroughly screened, monitored, and, if necessary, treated for comorbidities.

BACKGROUND: Difficult-to-control asthma is associated with significant medical and financial burden. Comorbidities are known to contribute to uncontrolled asthma. Better insight into the prevalence, nature, and risk factors of comorbidities may optimize treatment strategies in patients with difficult-to-control asthma and decrease disease burden.

OBJECTIVES: The objectives of this study were to assess the prevalence, number, and type of comorbidities in difficult-to-control asthma compared with not-difficult-to-control asthma, and to investigate whether specific patient characteristics are associated with particular comorbidities.

METHODS: A total of 5,002 adult patients with a prescription for high-dose (>1,000 µg) fluticasone or oral corticosteroids, extracted from 65 Dutch pharmacy databases, were sent questionnaires about patient characteristics. Of the 2,312 patients who returned the questionnaires, 914 were diagnosed with difficult-to-control asthma. Diagnoses of comorbidities (gastroesophageal reflux, nasal polyps, cardiovascular disease, anxiety/depression, obesity, and diabetes) were based on treatment

prescriptions or questionnaires. Associations were assessed using multivariable logistic regression analyses.

RESULTS: A total of 92% of patients with difficult-to-control asthma had ≥1 comorbidity. Patients with difficult-to-control asthma had more comorbidities (mean ± SD comorbidities 2.22 ± 1.27 vs 1.69 ± 1.32; $P < .01$), and a significantly higher prevalence of each comorbidity, compared with patients with not-difficult-to-control asthma, except for diabetes and nasal polyposis. Comorbidities were associated with specific patient characteristics, including older age, female gender, smoking history, and chronic prednisone use.

CONCLUSIONS: Almost all patients with difficult-to-control asthma have comorbidities, in particular asthmatic women of older age, former smokers, and asthmatics who are prednisone dependent. Recognition of these typical characteristics can help physicians in the diagnostic workup, so that adequate preventive measures can be taken. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Asthma; Difficult-to-control asthma; Comorbidity; Prevalence; Uncontrolled asthma

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Difficult-to-control asthma is defined as uncontrolled asthma despite treatment with high-dose inhaled corticosteroids (ICS) or chronic systemic corticosteroids, and is characterized by everyday asthma symptoms, frequent exacerbations, and/or hospitalizations.^{1,2} A substantial proportion of the adult asthma population suffers from difficult-to-control asthma,³ which is problematic because uncontrolled disease leads to significant medical and financial burden.⁴⁻⁸

Many factors are known to be associated with uncontrolled asthma including poor adherence to treatment, inadequate inhalation technique, socioeconomic and psychological factors, environmental exposures, and smoking.⁹⁻¹¹ Also comorbidities such as gastroesophageal reflux,^{12,13} obesity,¹⁴⁻¹⁶ and psychiatric disorders^{17,18} have been shown to be associated with

Abbreviations used

ACO- Asthma COPD overlap

ATS- American Thoracic Society

COPD- Chronic obstructive pulmonary disease

ERS- European Respiratory Society

ICS- Inhaled corticosteroids

LABA- Long-acting β_2 -agonist

OCS- Oral corticosteroids

PY- Pack years

difficult-to-control asthma, and managing these comorbidities may improve asthma control.^{11,19} Better insight into the prevalence and nature of comorbidities, and early identification of patients at risk may help to optimize diagnostic, preventive, and management strategies for patients with difficult-to-control asthma. However, only few studies have investigated the prevalence of comorbidities in these patients,^{11,19,20} and none of these studies have explored risk factors or patient characteristics associated with these comorbidities.

In the present study, we hypothesized first that patients with uncontrolled asthma have a higher number of comorbidities than those with controlled asthma, second, that not all comorbidities are associated with uncontrolled asthma, and third, that specific patient characteristics are associated with comorbidities that have impact on asthma control. To test these hypotheses we used questionnaires and prescription data from 1,571 patients with controlled and uncontrolled asthma despite high-dose ICS and bronchodilator treatment.

METHODS**Patients**

Adults (≥ 18 years) with asthma and a prescription for high-intensity asthma treatment were selected from a Dutch pharmacy database. High-intensity treatment was defined as $\geq 1,000$ $\mu\text{g}/\text{d}$ fluticasone equivalent plus a long-acting β_2 -agonist (LABA), or 500-1,000 $\mu\text{g}/\text{d}$ fluticasone equivalent plus chronic oral corticosteroids (OCS) (≥ 6 months, ≥ 5 mg/d prednisone equivalent) plus LABA. Questionnaires were sent by regular mail to all patients (5,002), of which 2,312 (46.2%) were returned and analyzed. Questionnaires contained questions on demographics (gender, age, height, weight), asthma symptoms, airborne allergies (house dust mite, cat dander, dog dander, mixed grass pollens, mixed tree pollens, mixed fungi), smoking, childhood asthma, and treatment for nasal polyposis. Responses to these questions were used to identify patients with asthma. Asthma diagnosis was based on physician diagnosed "asthma" or "chronic obstructive pulmonary disease (COPD)" with no or limited smoking history (< 10 pack years [PY]). If smoking history was ≥ 10 PY, asthma diagnosis was based on a history of childhood asthma and/or presence of allergic symptoms and/or treatment for nasal polyposis (Figure 1).

Definition of difficult-to-control asthma and not-difficult-to-control asthma

A diagnosis of difficult-to-control asthma was based on the recent European Respiratory Society/American Thoracic Society (ERS/ATS) severe asthma guidelines, which distinguishes between severe asthma and difficult-to-control asthma.² Patients had to fulfill at least one of the following criteria: (1) Asthma Control Questionnaire ≥ 1.5 ,²¹ (2) > 2 exacerbations in the previous year for which a course of OCS was needed, (3) ≥ 1 hospitalization

because of asthma in the previous year, and/or (4) chronic treatment with OCS. Patients not fulfilling one of these criteria were labeled as having not-difficult-to-control asthma (Figure 1).

Assessment of comorbidities

The diagnosis of comorbidities was based on at least one prescription for medications for the following: (1) anxiety/depression; (2) cardiovascular disease; (3) diabetes; (4) gastroesophageal reflux. Obesity (5) was defined as body mass index ≥ 30 kg/m^2 and was calculated from self-reported weight. Data on height and nasal polyposis were retrieved from the questionnaires. A diagnosis of nasal polyposis was based on a self-reported doctor diagnosis or previous surgery for nasal polyps.

Analysis

Group characteristics were described as proportions, mean \pm standard deviation for normally distributed variables, or median (interquartile range) for non-normally distributed variables. Proportions of the total number of comorbidities and of each type of comorbidity were calculated and compared between patients with difficult-to-control and not-difficult-to-control asthma. Student *t*-tests, Mann-Whitney *U* tests, and χ^2 tests were used to compare patient characteristics, based on distribution of data, as appropriate. Multivariable logistic regression models were applied to investigate independent risk factors for the presence of particular types of comorbidities. The following patient characteristics were entered into the models: (1) age, (2) gender, (3) PY of smoked cigarettes, (4) childhood asthma, (5) allergic symptoms, (6) ICS dose, and (7) chronic use of OCS. Characteristics with *P* values of $< .05$ were considered significantly different between the groups or associated with comorbidities. All analyses were performed with SPSS 22.0 (IBM Corporation, Armonk, NY). The study was approved by the hospital medical ethics board (MEC W11-064; NTR no. 3546).

RESULTS

Of the 2,312 patients who returned the questionnaires, 1,571 (67.9%) had asthma and were on high-intensity treatment. Of these, 914 (58.2%) had difficult-to-control asthma and 657 (41.8%) not-difficult-to-control asthma (Figure 1). Patients with difficult-to-control asthma were older (65.0 ± 13.8 y vs 61.5 ± 15.5 y; $P < .01$) and had a more extensive smoking history (22.5 (9.6-39.0) PY vs 16.5 (6.4-31.0) PY; $P < .01$) as compared with patients with not-difficult-to-control asthma (Table 1).

Prevalence of comorbidities in difficult-to-control and controlled asthma

Patients with difficult-to-control asthma had more comorbidities than patients with not-difficult-to-control asthma (2.22 ± 1.27 vs 1.69 ± 1.32 ; $P < .01$). Figure 2 shows that the majority of patients with difficult-to-control asthma had at least one comorbidity (92.3%) that was lower (78.0%) in not-difficult-to-control asthma ($P < .01$). Diabetes was least prevalent in both groups (12.5% and 11.1%, respectively), followed by obesity (18.6% and 13.9%), nasal polyps (24.4% and 21.9%), and anxiety/depression (36.1% and 24.7%). More than half of the patients with difficult-to-control asthma had cardiovascular disease (63.8%) and gastroesophageal reflux (66.8%), whereas in patients with not-difficult-to-control asthma, these figures were 52.5% and 45.4%, respectively. All

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