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Real life data on incidence and risk factors of severe asthma exacerbations in children in primary care

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A B S T R A C T

Real-life data on the incidence rates (IR) and risk factors of severe asthma exacerbations in children are sparse. We aimed to assess IR and risk factors of severe asthma exacerbations in children in real life.

We conducted a population-based cohort study using a Dutch GP database containing complete medical records of >1 million patients. All records of children with physician-diagnosed asthma aged 5–18 years between 2000 and 2012 were examined for exacerbations, defined as either hospitalization, emergency department visit or need of systemic steroids for asthma. IR was expressed as number of exacerbations per person year (PY).

We identified 14,303 asthmatic children with 35,118 PY of follow-up and 732 exacerbations. The overall IR was 2.1/100PY (95% CI 1.9–2.2), 4.1/100PY (3.8–4.4) for children on asthma treatment. Re-exacerbation occurred in 2% (1.3–4.3) of patients within 1 month, in 25% (20.6–28.8) within 1 year. Predictors for (frequent) exacerbations were age, medication use and prior exacerbations (all $p < 0.001$).

The overall IR of severe asthma exacerbations was 4/100PY in children on asthma treatment, highest in spring and fall. 25% of the patients with an exacerbation will experience a next exacerbation within 1 year. More severe asthma is a predictor of subsequent and future exacerbations.

1. Introduction

Asthma continues to be a public health concern due to its high prevalence in industrialized countries [1,2]. Poor asthma control resulting from inadequate treatment or non-response to available treatments was associated with adverse long-term outcomes [3]. Asthma can usually be well controlled by treatment as described in asthma management guidelines [4]. A severe asthma exacerbation is defined as a hospitalization or emergency department (ED) visit because of worsening asthma, or need of systemic corticosteroids because of asthma [5]. Reported frequencies of severe asthma exacerbations in the literature vary by the definition of an exacerbation, patient population, the severity of asthma, degree of asthma control, and the data source and incidence rates (IR) are sparse [6]. Most data on IR of severe asthma exacerbation derive from adults in clinical trials. These showed IRs ranging between 0.24 and 0.92/PY [7–11] and in cross-sectional data, IRs that ranged between 0.23 and 0.41/PY [12,13]. As far as we know, only 4 studies investigated the rate of exacerbation in children, showing IR ranging from 0.04 to 0.64/PY. This broad range can be explained by differences in patient selection, sample size or study duration [7,14,15]. Asthma related hospitalization rates in asthmatic children ranged from 4 to 15% per year, depending on factors like age, sex, and asthma severity [12,16]. The CAMP study observed an exacerbation-requiring-hospitalization-rate of 2.5/100 PY in children from 5 to 12 years of age with mild-to-moderate asthma [17]. Surveys in real-life indicated that the true incidence of severe asthma exacerbations may be higher than in clinical trials [6]. Insight in the real life incidence of severe asthma exacerbations and characteristics of children with frequent exacerbations is important to optimize management in those who are prone to exacerbations. Hence, the purpose of the present study was to evaluate the incidence of severe asthma exacerbations and to identify characteristics of children with severe asthma exacerbations over a 12 year period in a large cohort of children with physician-diagnosed asthma.

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2. Methods

We conducted a retrospective population-based cohort study within the Integrated Primary Care Information (IPCI) database, a longitudinal observational dynamic database containing the complete electronic medical records of more than 450 general practitioners (GPs) throughout the Netherlands, the study population and the GPs participating in the study are representative for the Dutch population. In the Dutch health care system, people are registered with a single GP who has a crucial role as a gatekeeper for and receiver of information from secondary care [18]. Details of the database have been published elsewhere [19,20]. Briefly, the database contains the complete electronic medical records of approximately 1,500,000 patients, containing anonymous longitudinal data on demographics, symptoms and diagnosis in coded and free text, referrals, laboratory findings, discharge letters, and drug prescriptions. The system complies with European Union guidelines on the use of data for medical research and has been proven valid for pharmaco-epidemiological studies [20]. The scientific and ethical advisory board of the IPCI database approved the present study. (no 07/55 2011).

2.1. Asthma cohort

The dynamic source population (n = 176,516) comprised all children aged 5–18 years with a database history of at least 12 months. The study period was from the 1st of January 2000 until the 1st of January 2012.

Within this population a cohort of children with asthma was identified. Asthma cases were retrieved by an automated search on both International Classification of Primary Care asthma codes [21] (ICPC code, R96) and free text that was relevant to asthma. Asthma was defined as "definite" if diagnosed by a pediatrician. "Probable asthma" was defined as asthma diagnosed by the GP with at least 2 additional records/prescriptions of asthma medications in the 1 year following the initial diagnosis of asthma. A patient was labeled to have "possible asthma" in case of only 1 asthma record or inconsistency between records. Children were classified as not having asthma if the identified symptoms were not related to asthma or if the symptoms could be ascribed to other respiratory conditions (e.g. pneumonia, cystic fibrosis). If at any time during the follow-up asthma was diagnosed, the child was considered asthmatic from date of first diagnosis until the end of follow-up.

As this automated search resulted in a high number of potential asthma cases (n = 63,618), we used machine learning to facilitate the validation, as described in detail elsewhere [22]. Follow-up started on the latest of the following dates: start of study period, date on which the required 1 year of follow-up was obtained, the 5th birthday, or date of asthma diagnosis (for prevalent asthma cases, who had diagnosis before start of study period asthma diagnosis was not used as criterion) All patients were followed from study entry until the earliest of the following dates: end of the study period, transferring out of GP practice or age 18 years.

2.2. Severe asthma exacerbations

Severe asthma exacerbations were defined as any of the following; hospitalization, emergency department (ED) visit, or prescription of systemic corticosteroids for at least 3 days, all because of asthma. In case there were less than 7 days between two exacerbations, these were considered as one single exacerbation.

All potential exacerbations were identified in the electronic medical records and validated by a medical doctor (ME). To identify patients with ED visit or hospitalization for reasons of asthma, the medical file was searched for asthma-specific disease codes in combination with information on hospitalization, hospital referral and discharge letters. Use of systemic corticosteroids was retrieved from prescriptions via an automated search on the corresponding ATC codes. The indication of use was searched for in a window of 7 days before and 7 days after the prescription date.

2.3. Covariates

Covariates included age at study start, gender, age at time of exacerbation, eczema (ICPC code S87), allergic rhinitis (ICPC code R97), conjunctivitis (ICPC code F71), number of respiratory infections, number of prescriptions for any asthma medication, number of prescriptions for inhaled corticosteroids (ICS), eosinophil count (,<150 cells/uL, 150–300 cells/uL, ≥300 cells/uL and eosinophil count unknown) number of specialist visits for asthma and number of prior severe asthma exacerbations. Comorbidity was assessed by searching for the respective ICPC disease codes in the patient's file. Baseline covariates were retrieved in the 365 days prior to cohort entry.

2.4. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD). We used *t*-test, χ^2 test or Mann-Whitney test to compare baseline characteristics of children with and without exacerbations.

Three different regression techniques were used: (1) Poisson regression for count outcomes (=count of exacerbation), (2) Logistic regression for the binomial outcome (comparison of episodes with <2 exacerbations to episodes with ≥2 exacerbations) and (3) Cox regression for time to first exacerbation. The techniques are discussed in more detail below.

2.5. Rates of exacerbations

For each child the person time (in years, PY) of follow-up was stratified by calendar year, calendar month, gender and age (on January 1st of each year). Because of the dynamic nature of the population we used PY rather than persons. The incidence rate (IR) of exacerbations was calculated by dividing the number of exacerbations by the person time.

To assess seasonal effects monthly IRs were compared. Then to further assess interaction of seasonal rates with age, we compared monthly IRs in primary school (<13 years) and high school children (≥13 years of age) using Poisson regression.

IR for re-exacerbation was assessed in the following time-windows: 0–30, 0–90, 0–180 and 0–365 days after exacerbation, and in subsequent 90 day time-windows: 0–90, 90–180, 180–270 and 270–365 days. Cumulative incidences for re-exacerbation were calculated by multiplying the IR with the time duration.

2.6. Risk factors for exacerbations

Risk factors for exacerbations were estimated using Poisson regression. For the analysis of the total cohort, follow-up of each child was divided in episodes by year of age, the first episode started at the date of asthma diagnosis, or study entry whichever came last. For analysis of episodes after a previous exacerbation, follow up started was at the first exacerbation or at study entry (for prevalent cases), whichever was last. Subsequent episodes started at each birthday. Covariates were retrieved during the 365 days prior to the start of each episode and could change over time for the different episodes. The analysis incorporated the potential effect of age, gender and interaction between age and gender. Age was introduced as a quadratic term as the relation between age and