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Rhinitis in adult-onset asthma – subtypes, long-term treatment and outcomes

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Abstract

Background

Rhinitis has been associated with poor outcomes of asthma, but long-term treatment and role of different rhinitis subtypes remain unknown. The aim of this study was to assess the prevalence and long-term treatment of various rhinitis subtypes, and their role in outcomes of adult-onset asthma.

Methods

Patients diagnosed with adult-onset asthma (n = 203) were followed for 12-years as part of Seinäjoki Adult Asthma Study. Rhinitis was assessed by questionnaire and intranasal corticosteroid dispensing records and allergy evaluated by specific IgE-testing. Data on hospitalizations were based on medical records.

Results

Of the patients with adult-onset asthma, 150 (74%) had rhinitis. Of those, 45% had allergic rhinitis, 50% non-allergic rhinitis and 5% mixed rhinitis, and 55% had perennial symptoms. During the 12-year follow-up, patients with rhinitis dispensed median (IQR) 48 (0-245) and those with perennial rhinitis 90 (11–330) doses per year of intranasal corticosteroids, respectively. Compared to group with asthma alone, patients with concomitant rhinitis had more often been admitted to hospital due to respiratory reasons (31% vs 13%, p = 0.011). In multivariate logistic regression analyses, rhinitis (OR = 4.9 (95% CI = 1.05–22.9), p = 0.043) and perennial rhinitis (OR = 7.2, 1.4–36.4, p = 0.017) were associated with unplanned respiratory-related hospitalizations. Of allergy subtypes, non-allergic rhinitis (OR 5.6, 1.1–28.2, p = 0.035) and mixed rhinitis (OR 14.1, 1.4-146.6, p = 0.026) were associated with unplanned respiratory-related hospitalizations.

Conclusions

In patients with adult-onset asthma, rhinitis is common and undertreated. Rhinitis, perennial rhinitis, non-allergic rhinitis and mixed rhinitis were all associated with unplanned respiratory-related hospitalizations. Assessment and treatment of rhinitis in patients with asthma should be focused.

Introduction

Asthma and rhinitis often co-exist, allergic rhinitis often precedes asthma and is a risk factor for the development of asthma[1]. Prevalence of allergic rhinitis among adult asthmatics varies substantially between studies but typically prevalences between 50-100% are reported[2-4]. Among patients with rhinitis, 10-40% have asthma. Allergic multimorbidity is an often used term to describe coexistence of asthma, rhinitis and atopic dermatitis, even though non-allergic mechanisms may exist or even predominate in some disease manifestations (e.g. non-allergic asthma/non-allergic rhinitis). One-airway-one-disease / unified airways concepts have been developed since it was observed that T2 inflammation

was similar in the nose and bronchi of asthmatic patients. Genetic studies have also revealed shared heritability to asthma, chronic rhinosinusitis with and without nasal polyps and allergic phenotypes[32], explained in part by T2 inflammation. However, unified airways concept has been regarded as over-simplification[1]. Rhinitis, after excluding acute infectious rhinitis, can be divided into allergic rhinitis, non-allergic rhinitis and mixed rhinitis presenting at least two rhinitis phenotypes[5,6]. Allergic rhinitis is caused by IgE-mediated reaction to inhaled allergens, while non-allergic rhinitis is a heterogenous group of different nasal conditions[6,7]. In addition, they can also coexist. Allergic rhinitis often starts in childhood and symptoms exacerbate seasonally, and are often associated with eye symptoms. Non-allergic rhinitis starts typically later, eye symptoms are uncommon, and symptoms are triggered by non-allergenic exposures such as irritants, medications, hormonal imbalance and neuronal dysfunction. In many previous studies allergic and non-allergic rhinitis have not been studied as separate entities (all rhinitis are referred to as allergic rhinitis) or rhinitis has been defined by self-report[8,9].

Conflicting results have been previously reported on asthma outcomes when comparing patients with asthma alone to patients with asthma and comorbid allergic rhinitis. Comorbid allergic rhinitis has been associated with more asthma-related hospitalizations and GP visits[8] but also to less severe asthma and less doctor visits and work/school absenteeism compared to asthma alone[9].

The aim of the present study was to evaluate the prevalence of rhinitis and its subtypes among patients with adult-onset asthma and to evaluate long-term treatment of rhinitis. Moreover, we aimed to elucidate the role of rhinitis and its subtypes in the outcomes of asthma in a well-characterized population of patients with adult-onset asthma.

Methods

Study population

Seinäjoki Adult Asthma Study (SAAS) is a 12-year follow-up study, where 256 patients were diagnosed with new-onset adult asthma between 6 October 1999 and 17 April 2002. Asthma diagnosis was made by a respiratory specialist based on lung function measurements and typical symptoms of asthma. Asthma diagnosis requirements, inclusion and exclusion criteria have been previously reported[10].The exclusion criteria were a previous diagnosis of asthma at age <15 years and inability or unwillingness to sign the informed consent. Patients were not excluded due to smoking history, comorbidities or another lung disease. Patients were recruited from the diagnostic visit and after diagnosis the patients were treated in primary care, occupational healthcare, private healthcare or in specialized healthcare according to principles of Finnish Asthma Programme[11]. The mean follow-up time was 12.2 years (range 10.8-13.9 years), after which 203 patients (79%) returned to a follow-up visit (between 10 December 2012 and 31 October 2013). A written informed consent was obtained to a study protocol approved by the Ethics committee of Tampere University Hospital, Tampere, Finland (R12122).

Assessment of allergen-specific IgE

At 12-year follow-up visit, allergen-specific IgE testing was performed by using ImmunoCAP ISAC multiplex microarray (Thermo Fisher Scientific, Uppsala, Sweden), which includes 112 allergen components from 48 different allergen sources[12]. The assay measures IgE levels between 0.3 and 100 ISAC standardized unit (ISU) and values of ≥0.3 ISU indicate sensitization[13].At the time of asthma diagnosis, RAST and skin prick test were performed for part of patients.

Definitions of rhinitis and allergy

Rhinitis was defined as answering YES to either of questions: Do you have continuously runny nose or nasal congestion OR do you have allergic rhinitis or allergic rhinoconjunctivitis. Alternatively, rhinitis was defined by >700 doses of nasal corticosteroid purchases during 12-year follow-up (corresponds to >58 doses annually).

Rhinitis was defined as **allergic** if specific IgE was ≥0.30 towards any aeroallergen determined by specific IgE antibody panel or RAST AND/OR at least one positive response (≥ 3 mm) in skin prick test towards common aeroallergens AND/OR if presence of allergic rhinitis was mentioned in patient's medical history.

Rhinitis was defined as **non-allergic** if specific IgE was always <0.30 towards any aeroallergen determined by specific IgE antibody panel or RAST and no positive response (<3 mm) towards common aeroallergens was found in skin prick test.

Rhinitis was defined as **mixed** (allergic and non-allergic) if specific IgE was ≥0.30 towards pollen determined by specific IgE antibody panel or RAST AND/OR at least one positive response (≥ 3 mm) in skin prick test towards pollen only, but nasal steroid purchases were not seasonal (e.g. sensitization found only to birch but nasal steroid purchases repeatedly outside allergic season).

Perennial nasal symptoms were defined by YES to "Do you have continuously runny nose or nasal congestion?" OR "Do you have allergic rhinitis or allergic eye inflammation?" and "Yes, symptoms are prevalent year-round"

Seasonal (only) nasal symptoms were defined as follows: YES to "Do you have allergic rhinitis or allergic eye inflammation?" and to "Yes, symptoms are prevalent only certain time of year" and NO to "Do you have continuously runny nose or nasal congestion?"

Nasal symptoms only in certain situations were defined as YES to"Do you have allergic rhinitis or allergic eye inflammation?" and to "Yes, symptoms are prevalent during certain situations, e.g. near animals" and NO to "Do you have continuously runny nose or nasal congestion?"

Chronic rhinosinusitis (CRS) was defined as follows: YES to "Do you have continuously runny nose or nasal congestion" and facial pain or pressure was mentioned at least once in the patient records, or nasal polyps mentioned at least once in the patient records or functional endoscopic sinus surgery (FESS) mentioned at least once in the patient records.

CRS with nasal polyps (CRSwNP) was defined as nasal polyps mentioned at least once in the patient records during follow-up.

CRS without nasal polyps (CRSsNP) was defined as YES to “Do you have continuously runny nose or nasal congestion” AND one of the following mentioned in the patient records: facial pain, pressure or FESS but nasal polyps not mentioned.

Medication, hospitalizations, asthma control, lung function and inflammatory parameters

Information ondispensed nasal steroids, oral and intranasal antihistamines, inhaled corticosteroids, oral steroids and antibiotics was obtained from Finnish Social Insurance Institution. More detailed information is included in the Online Supplement. Hospitalizations and visits to healthcare were collected from medical records. Daily user of nasal corticosteroids was defined as annual nasal corticosteroid purchases of at least 584 doses (according to and assumption of 80% medication adherence and a daily dose of 2 sprays of nasal steroids (one per nostril) ie. 0.8 x 365 d x 2 sprays). Asthma control test (ACT) was filled at the follow-up visit. Asthma control was based on GINA 2010 report[34]. Further information is available on the Online Supplement.

Statistical analyses

Continuous data is expressed as mean (SD) or median and interquartile range. Comparisons between two groups were done by t-test, Mann-Whitney test or χ^2–test. Multivariable binary logistic regression analysis was performed to evaluate if rhinitis was associated with hospitalization for unplanned respiratory reason. Independent variables were sex, age, BMI, smoked pack years and COPD.In model 2, rhinitis was replaced by perennial rhinitis/non-perennial rhinitis/no rhinitis, in model 3 by CRS/rhinitis without CRS, in model 4 by perennial symptoms/non-perennial symptoms/CRS and in model 5 by allergic/non-allergic/mixed/no rhinitis. The final models 1-5 contained no strong multicollinearity with r≥0.7. Statistical analyses were performed using IBM SPSS Statistics software, version 29 (IBM SPSS, Armonk, NY). A *p*-value < 0.05 was regarded as statistically significant.

Results

Prevalence of rhinitis and its subtypes

Of the patients with adult-onset asthma, 150 (73.9%) fulfilled the definition of rhinitis. Of those with rhinitis, 94.7% had rhinitis based on self-report and 5.3% (n=8) had substantially (>700 doses) dispensed nasal steroids but reported not having rhinitis and were included in the group of rhinitis. Of the patients with rhinitis, half were sensitized to at least one aeroallergen. The prevalence of allergic rhinitis was 33.5% and non-allergic rhinitis was 36.9% in the whole population with adult-onset asthma. Seven patients with allergic rhinitis had repeatedly dispensed nasal steroid also outside allergy season and therefore were considered to have mixed rhinitis (Figure 1). Most of patients with allergic rhinitis (72.9%) were polysensitized and median (IQR) for sensitized aeroallergens was 3 (1-6). For sensitivity analysis,

we assessed degree of agreement between self-report and specific IgE-testing related to allergic rhinitis and found disagreement in 56 (38.4%) patients. Most of these patients (53/56) had reported allergic rhinitis or allergic rhinoconjunctivitis but specific IgE-positivity for any allergen was not found.

Overall, 54.6% of those with rhinitis reported having perennial nasal symptoms (40.4% prevalence in whole adult-onset asthma population). Prevalence of perennial symptoms was 55.9% in allergic, 50.7% in non-allergic, and 85.7% in mixed rhinitis group (p=0.197). The prevalence of chronic rhinosinusitis in adult-onset asthma was 13.8% (n=28); 8.4% with nasal polyps and 5.4% without nasal polyps. Among those with allergic, non-allergic and mixed rhinitis, the proportions of CRS were 13.2%, 22.7% and 28.6% (Table E1), respectively.

Treatment of rhinitis

Of patients with adult-onset asthma and comorbid rhinitis, 28.7% had no dispensing of nasal steroids during the 12-year follow-up whereas 10.7% were daily users (Figure 2A). Median dose dispensed was 48 (0-245) doses of nasal steroids per year, corresponding to less than one month of daily use (one spray per nostril per day) (Figure 2A).

Among patients reporting perennial nasal symptoms, median number of nasal steroid doses dispensed during 12-year follow-up was 90 (11-330) per year and proportion of daily users of nasal steroids was 13.4% (Figure 2B). In those with seasonal symptoms, 39.4% had no dispensing of nasal steroids (Figure 2C). Among patients with chronic rhinosinusitis, proportion of daily users was 25% (Figure 2D). In patients with allergic, non-allergic and mixed rhinitis, median (IQR) annual doses of dispensed nasal steroids during the 12-year follow-up were 37 (0-228), 59 (0-259) and 205 (113-272)(p>0.05), respectively. One patient with mixed rhinitis had omalizumab treatment, and three patients (two with allergic rhinitis and one with mixed rhinitis) had allergen immunotherapy during the follow-up.

Of those with rhinitis, 34.7% had no dispensing of oral antihistamines during 12-year follow-up, median dose dispensed was 5 (0-30) tablets per year (Figure 2E). Dispensing was closely similar in those with perennial symptoms (Figure 2F). Median (IQR) annually dispensed oral antihistamines in patients with allergic, non-allergic and mixed rhinitis were 10 (2-75), 0 (0-12) and 28 (8-56) doses per year (25-75 percentiles 2-75) during the entire follow-up period. During 12-year follow-up there was no dispensing of intranasal antihistamines. In total, 17.1% of those with rhinitis had no dispensing of either oral antihistamines or intranasal corticosteroids.

Outcomes of asthma in patients with and without rhinitis

To evaluate how rhinitis affects asthma outcomes, we compared patients with asthma with and without comorbid rhinitis (Table 1). Patients with comorbid rhinitis were less often current smokers and had fewer pack years smoked compared to those without, but other demographics were similar. Patients with comorbid rhinitis had been prescribed more ICS, had dispensed more SABA, had more often been admitted to hospital due to respiratory reasons (31% vs 13%, p=0.011) and had overall more asthma-

related visits to healthcare during 12-year follow-up (16 vs 13, p=0.044) (Table 1) compared to those without. In addition, blood eosinophil level was higher at diagnosis among those with comorbid rhinitis compared to those without (0.30 vs 0.20, p=0.05). Results on patient characteristics, medications and asthma outcomes according to rhinitis subtypes are shown in eTable 1.

Table 1. Demographics, asthma-related parameters and outcomes at 12-year follow-up visit in patients with and without comorbid rhinitis.

Variable	No rhinitis n=53	Rhinitis n=150	P value
Age of asthma onset, years	47.5 (13.8)	45.1 (13.8)	0.603
BMI	28.4 (25.7-30.9)	27.9 (24.4-31.6)	0.775
Female sex, n (%)	25 (47.2%)	93 (62%)	0.075
Smoking status, n (%)			**0.041**
Never smoker	25 (47.2%)	71 (47.3%)	
Ex	15 (28.3%)	62 (41.3%)	
Current	13 (24.5%)	17 (11.3%)	
Pack years	19.5 (10-33.5)	15 (3.8-26)	**0.043**
Co-existing COPD, n (%)	14 (26.4%)	20 (13.5%)	0.053
Daily ICS user, n (%)	39 (73.6%)	116 (77.3%)	0.577
ICS dispensed (average daily dose during 12 yrs as µg budesonide equivalents)	453 (223-730)	591 (314-833)	0.071
ICS prescribed (average daily dose during 12 yrs as µg budesonide equivalents)	767 (591-892)	830 (620-1031)	**0.031**
Asthma control test score	22 (21-24)	22 (19-24)	0.092
Uncontrolled asthma (GINA definition 2010), n (%)	11 (20.8%)	49 (32.7%)	0.117
Prednisolone dispensed (mg during 12 yrs)	600 (0-1975)	820 (0-2400)	0.172
SABA puffs per week during 12 yrs	1.0 (0.4-2.4)	2.1 (0.8-4.1)	**0.010**
Antibiotic courses dispensed during 12 yrs	7 (4-12)	8 (4-14)	0.827
Pre-BD FEV_1 (% predicted)	86 (74-94)	87 (76-97)	0.986
Post FEV_1/FVC ratio	0.74 (0.66-0.79)	0.76 (0.70-0.81)	0.089
Hospitalized during 12 yrs, n (%)			
Any respiratory-related	7 (13.2%)	47 (31.3%)	**0.011**
Unplanned respiratory-related	2 (3.8%)	21 (14%)	**0.046**
Any asthma-related	4 (7.5%)	38 (25.3%)	**0.005**
Unplanned asthma-related	1 (1.9%)	15 (10%)	0.075
Hospital days in 12 yrs, mean (SD)			

Any respiratory-related	0.75 (2.27)	4.16 (10.95)	**0.007**
Unplanned respiratory-related	0.19 (0.96)	1.99 (7.65)	**0.040**
Any asthma-related	0.55 (2.14)	3.09 (8.62)	**0.006**
Unplanned asthma-related	0.09 (0.69)	1.18 (5.89)	0.058
Healthcare visits during 12 years			
All asthma-related	13 (8-18)	16 (9-24)	**0.044**
Unplanned visits	3 (0-9)	3 (1-9)	0.393
Asthma control visits	6 (3-9)	6 (3-11)	0.094
Total IgE at diagnosis (kU/L)	79 (24-160)	84 (40-199)	0.460
Total IgE (kU/L)	61 (29-155)	59 (24-165)	0.936
Blood eosinophils at diagnosis (*10^9/L)	0.20 (0.15-0.30)	0.30 (0.16-0.50)	**0.050**
Blood eosinophils (*10^9/L)	0.16 (0.11-0.25)	0.17 (0.09-0.28)	0.749
FeNO (ppb)	12 (5-18)	11 (5-19)	0.811
Blood neutrophils (*10^9/L)	3.5 (2.8-4.6)	3.8 (3-4.8)	0.161

Shown are n (%), mean (SD) or median (25th-75th percentile). FeNO=Fractional exhaled nitric oxide, IgE=Immunoglobulin E, BD=bronchodilator, FEV_1=Forced expiratory volume in one second, FVC=Forced vital capacity, ICS=inhaled corticosteroid, COPD=chronic obstructive pulmonary disease, SABA=short-acting β_2 agonist. P values ≤0.05 are shown bolded.

Association between rhinitis and unplanned respiratory-related hospitalization

We carried out multivariable binary logistic regression analysis to evaluate if rhinitis and its subtypes are associated with unplanned respiratory-related hospitalizations. In adjusted analyses, rhinitis was associated with unplanned respiratory-related hospitalizations (Table 2, model 1). In adjusted analyses with rhinitis subtypes, perennial rhinitis, chronic rhinosinusitis, non-allergic rhinitis and mixed rhinitis were most strongly associated with unplanned respiratory-related hospitalizations (Table 2, models 2,3,5). If perennial symptoms and CRS were included in the same model (Table 2, model 4), perennial symptoms were still associated with unplanned respiratory-related hospitalizations, while CRS lost significance. In any of the models, non-perennial rhinitis or allergic rhinitis were not associated with unplanned respiratory-related hospitalizations (Table 2).

Table 2. Association between rhinitis, CRS and rhinitis subtypes with unplanned respiratory-related hospitalizations.

	Univariate	Multivariate OR (95% CI), p[a]
Model 1		
Rhinitis	4.2 (0.9-18.3), 0.06	4.9 (1.05-22.9), 0.043
Model 2		
Perennial symptoms	5.1 (1.1-23.3), 0.037	7.2 (1.4-36.4), 0.017
Non-perennial symptoms	2.9 (0.6-14.4), 0.201	3.1 (0.6-16.5), 0.186
Model 3		
CRS	4.3 (0.7-24.8), 0.107	6.5 (1.01-42.0), 0.049
Rhinitis without CRS	4.1 (0.9-18.6), 0.064	4.7 (0.99-22.1), 0.052
Model 4		
Perennial symptoms		7.1 (1.3-37.0), 0.021
Non-perennial symptoms		3.1 (0.6-16.5), 0.186
CRS		1.07 (0.3-3.9), 0.919
Model 5		
Allergic rhinitis	2.9 (0.6-14.7), 0.193	3.5 (0.6-19.2), 0.144
Non-allergic rhinitis	4.9 (1.04-22.7), 0.045	5.6 (1.1-28.2), 0.035
Mixed rhinitis	10.2 (1.2-88.8), 0.035	14.1 (1.4-146.6), 0.026

[a]Multivariate binary regression models were adjusted for sex, age, BMI, smoked pack-years and COPD.

Discussion

In this study we found that rhinitis is highly common among patients with adult-onset asthma (74%), most of those presenting with perennial symptoms. Allergic and non-allergic rhinitis were equally common. Long-term treatment of rhinitis was poor as based on 12-year dispensing records of nasal steroids and antihistamines. Patients with comorbid rhinitis had more often been admitted to hospital

due to respiratory reasons compared to patients without rhinitis. Of the subtypes, perennial rhinitis, non-allergic rhinitis and mixed rhinitis were associated with hospital admissions.

A close relation has been reported between asthma and rhinitis; rhinitis even in the absence of allergy increases risk of adult-onset asthma[14]. In a previous Italian study in patients with late-onset asthma, prevalence of rhinitis was 53%[15]. However, definition of late-onset (onset > 40 years) differed from our study (> 15 years). As allergic rhinitis is more common in asthma with earlier age of onset, this may partly explain the higher prevalence of rhinitis (74%) in our study. A questionnaire-based study reported 50% prevalence of allergic rhinitis in adult-onset asthma[16]; the lower proportion (37%) seen in our study may be due to our requirement of positive specific IgE testing. Allergic sensitization has often been reported in studies with adult-onset asthma ranging from 30 to 48%[17–19] but does not necessarily imply nasal symptoms. In our study, the prevalences of perennial rhinitis (40.4%) and seasonal rhinitis (20.2%) were consistent with a previous report in adult-onset asthma (39%, 22.6%, respectively)[20]. Prevalence of chronic rhinosinusitis was not reported in previous studies with adult-onset asthma, but 11–20% were reported to have nasal polyps[16,18,21]. In a recent study including patients with all asthma age of onset, 36% had chronic rhinosinusitis, and 19.5% nasal polyps[22]. This is somewhat higher than the prevalence of chronic rhinosinusitis or nasal polyps in our study (8.4%). The reason may be that CRS or nasal polyps were not consistently assessed in our study. They were retrospectively collected from medical records and may have remained underdiagnosed. The possible underdiagnosis may, however, well reflect the real-world situation[32,33].

Epidemiological data on non-allergic rhinitis is overall limited because of lack of uniform definition[23]. In a previous Asian study in younger adults with asthma and mean asthma onset at adult age, prevalence of non-allergic rhinitis was 24.7%[24]. In a study comparing patients with allergic and non-allergic rhinitis, non-allergic patients were reported to be older, predominantly female, more often with perennial symptoms and had a higher prevalence of asthma[25]. This supports the relatively high prevalence of non-allergic rhinitis (37%) found in our study population, as our patients were predominantly older females. To our best knowledge, this is the first study reporting prevalence of non-allergic rhinitis in adult-onset asthma.

Allergic rhinitis and its impact on asthma (ARIA) guideline recommends treatment of perennial allergic rhinitis with intranasal corticosteroids alone, while seasonal rhinitis may be treated with oral antihistamines or intranasal corticosteroids or both[26]. Treatment of non-allergic rhinitis depends on its phenotype and may consist of intranasal corticosteroids, intranasal antihistamines, ipratropium bromide or capsaicin[27]. We found overall a limited long-term use of intranasal corticosteroids in patients with adult-onset asthma and comorbid rhinitis; e.g. patients with perennial rhinitis had dispensed the median annual dose of 90 corresponding to only 45 days of daily use annually and 22.9% had no dispensings during 12 years. Use of oral antihistamines was even lower but may be partially explained by over the counter dispensing that we were not able to collect. In a previous study among patients with adult-onset asthma, 57% were shown to use nasal corticosteroids, but the proportion of rhinitis was not reported[17].

A previous study of patients with asthma and perennial rhinitis treated in primary care showed that proportion of days covered for nasal corticosteroids and antihistamine dispensing were 40% and 50%, respectively, but were only assessed for one year period. Study was based on electronic health records[28] and therefore the study population may be biased to those visiting healthcare more often. In another questionnaire-based study, 37% of responders with asthma and rhinitis were classified as under/untreated regarding rhinitis[29]. Over 70% of patients with asthma and under/untreated rhinitis had impaired quality of life due to rhinitis compared to 44% in those with treated rhinitis[29]. The reasons for undertreatment of rhinitis may be mild symptoms, rhinitis may have been considered as a trivial disease, adverse events, economic reasons, ineffective treatment, physician/pharmacist guidance for short-time use or doctors may concentrate more in treating the asthma symptoms with less attention to rhinitis[29,30]. Especially non-allergic rhinitis may be less responsive to intranasal corticosteroids, which might lead to non-adherence. Given that in a previous case-control study, treatment with either nasal corticosteroids or second-generation antihistamines was associated with a significant reduction in the risk of hospitalization for asthma in patients with asthma and allergic rhinitis[31], the undertreatment of allergic rhinitis seen in this study may have resulted in unnecessary respiratory-related hospitalizations. To our best knowledge, this study in real-life patients with asthma and comorbid rhinitis is the longest follow-up for treatment of rhinitis.

In our study, patients with concomitant rhinitis had more often been admitted to hospital due to respiratory reasons compared to patients with asthma alone (31% vs 13%). This was found to be driven by perennial rhinitis symptoms, as well as non-allergic and mixed rhinitis. In a previous study based on general practice database of 27 000 adults, rhinitis was associated with asthma-related hospitalizations and GP visits, and incurred higher asthma medication costs than did adults with asthma alone[8]. However, the prevalence of allergic rhinitis was low in the study (16.9%), suggesting that lot of allergic rhinitis was undiagnosed or not documented. Rhinitis has also been associated with uncontrolled asthma; prevalence of chronic rhinitis was 42% among controlled adult-onset asthma and 70% among uncontrolled adult-onset asthma[19]. Inconsistently, in an Italian study based on GP data, patients with asthma alone had more frequently moderate persistent or severe asthma and more doctor visits and work/school absenteeism compared to patients with asthma and comorbid allergic rhinitis[9]. However, patients with asthma alone were also older compared to those with comorbid rhinitis, and treatment status of allergic rhinitis was unknown. As chronic rhinosinusitis was likely underdiagnosed in our study, it is possible that part of perennial rhinitis represents actually chronic rhinosinusitis. To our best knowledge, association of the rhinitis subtype (perennial, non-allergic or mixed) to hospitalizations in patients with asthma or adult-onset asthma has not been previously documented.

It is well established that T2 inflammation is a common mechanism behind adult-onset asthma and especially in those with more severe disease[36–38]. T2 inflammation is clearly defined also in allergic rhinitis and CRSwNP[32, 35]. In non-allergic rhinitis the clinical evidence of T2 inflammation remains more debated but subtypes with eosinophil involvement have been identified[35]. In this study patients with asthma and comorbid rhinitis exhibited higher blood eosinophil levels at diagnosis before start of ICS

treatment compared to patients with asthma alone, suggesting higher T2 inflammation as a driver of the increased number of hospitalizations also in patients with comorbid disease.

Our study has several strengths. Unselected population with confirmed diagnosis of adult-onset asthma and long follow-up period with high amount of detailed clinical information, questionnaire-based information and dispensed medication are major strengths of this study. Allergen sensitization was defined by specific IgE measurements. As limitations of the study, we had no information on the severity or onset of rhinitis symptoms. Prevalence of mixed rhinitis was likely underestimated, as it could only be estimated by nasal steroid dispensing if patient had seasonal allergies. Chronic rhinosinusitis was not consistently assessed but was based on medical records. The sample size could have been higher to assess associations between rhinitis subtypes and hospitalizations. Antihistamines are also available over the counter in the pharmacy, so all use could not be collected in this study. The assumption was made that antihistamines were used to treat rhinitis, but are also used for urticaria that could be a comorbidity in our study.

Use of intranasal corticosteroids and antihistamines have been previously shown to significantly decrease asthma-related hospital admissions in patients with asthma and allergic rhinitis[31]. Comorbid patients with adult-onset asthma and rhinitis, especially those with perennial rhinitis symptoms should be better motivated to adhere to treatment of upper airways. Still, in patients with adult-onset asthma, non-allergic rhinitis and chronic rhinosinusitis are common, and may be less responsive to standard treatments which should be considered. The high prevalence of perennial rhinitis among adult-onset asthma and its association with increased risk of respiratory-related hospitalizations, combined with significant long-term undertreatment of upper airways suggests that assessment of symptoms of rhinitis and chronic rhinosinusitis, and their long-term treatment need further attention in the management of patients with adult-onset asthma.

Abbreviations

ACT=asthma control test

ARIA=Allergic rhinitis and its impact on asthma

COPD=chronic obstructive pulmonary disease

CRS=chronic rhinosinusitis

CRSwNP = chronic rhinosinusitis with nasal polyps

CRSsNP = chronic rhinosinusitis without nasal polyps

d=days

FeNO=fractional exhaled nitric oxide

GP=general practice

IgE=immunoglobulin E

ICS=inhaled corticosteroid

ISU=immuno solid-phase allergen chip (ISAC) standardized unit

IQR=interquartile range

RAST= radioallergosorbent test

SAAS=Seinäjoki Adult Asthma Study

SABA=short-acting β_2 agonist

T2=type 2

Declarations

Ethics approval and consent to participate

A written informed consent was obtained to a study protocol approved by the Ethics committee of Tampere University Hospital, Tampere, Finland (R12122).

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its Supplementary Information File. According to ethical permission and patient data-protection laws of Finland, single patient data cannot be made available.

Competing interests

PI is employed by GSK as medical advisor. HK reports personal fees for lectures and/or consultations from AstraZeneca, Boehringer-Ingelheim, COVIS Pharma, GSK, Orion Pharma and Sanofi. L.E.T. reports personal fee for lecture from Boehringer-Ingelheim and support for attending congress from Orion Pharma. STS reports consultancies for ALK-Abelló, AstraZeneca, Clario, GSK, Sanofi and OrionPharma and, grants from GSK and Sanofi. All are outside the submitted work. IV and ON reports no conflict of interest related to this study.

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Authors' contributions

P.I, L.E.T., H.K. and STS designed the study. P.I wrote the report with input from the other authors. P.I. performed the statistical analyses and O.N. contributed to laboratory analyses, respectively. I.V. assembled dispensed data. All authors contributed to interpretation of the data. All authors made critical revisions of the manuscript and approved the final version of the manuscript.

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Figures

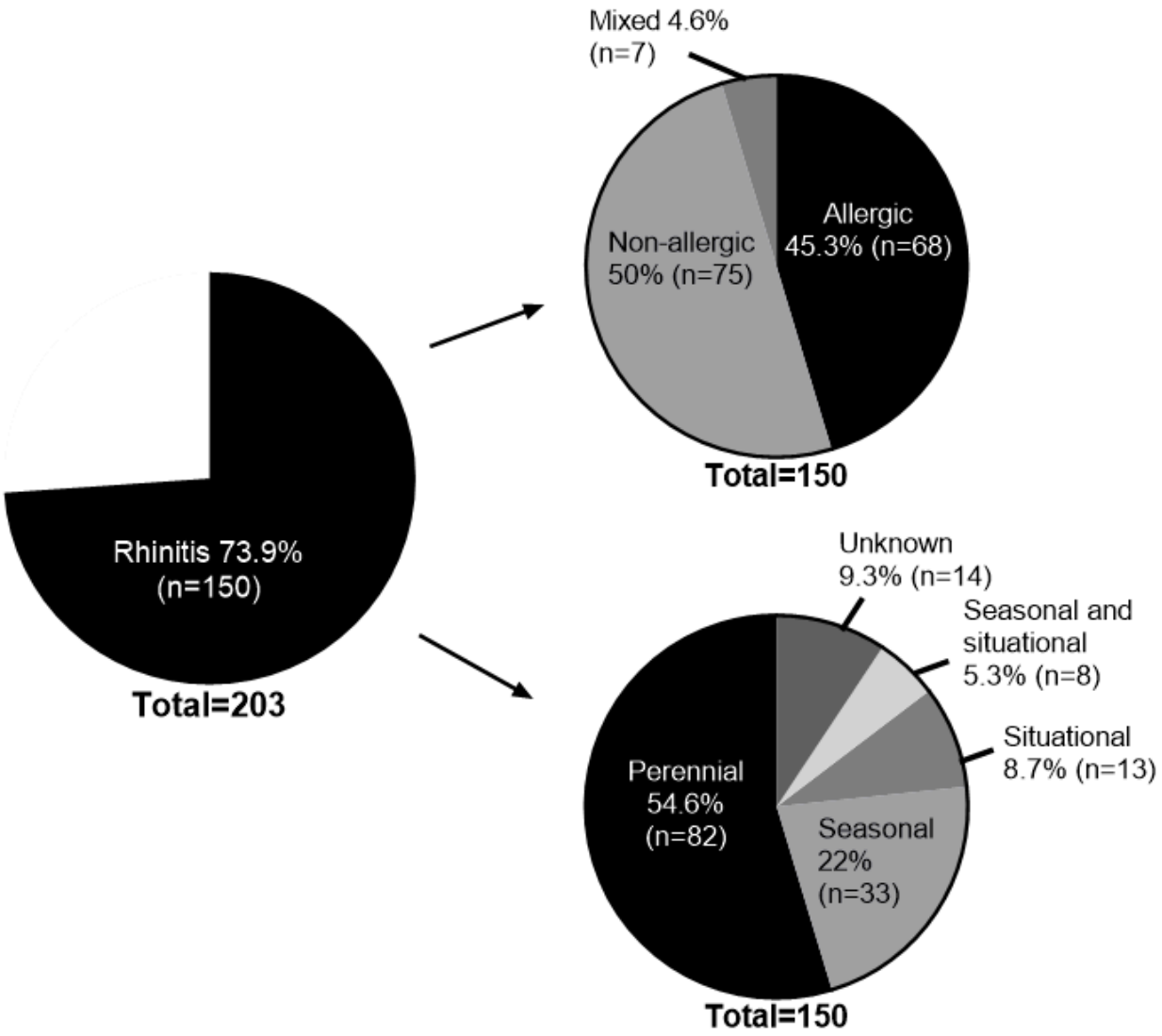

Figure 1

Prevalence of rhinitis and its subtypes among adult-onset asthma patients.

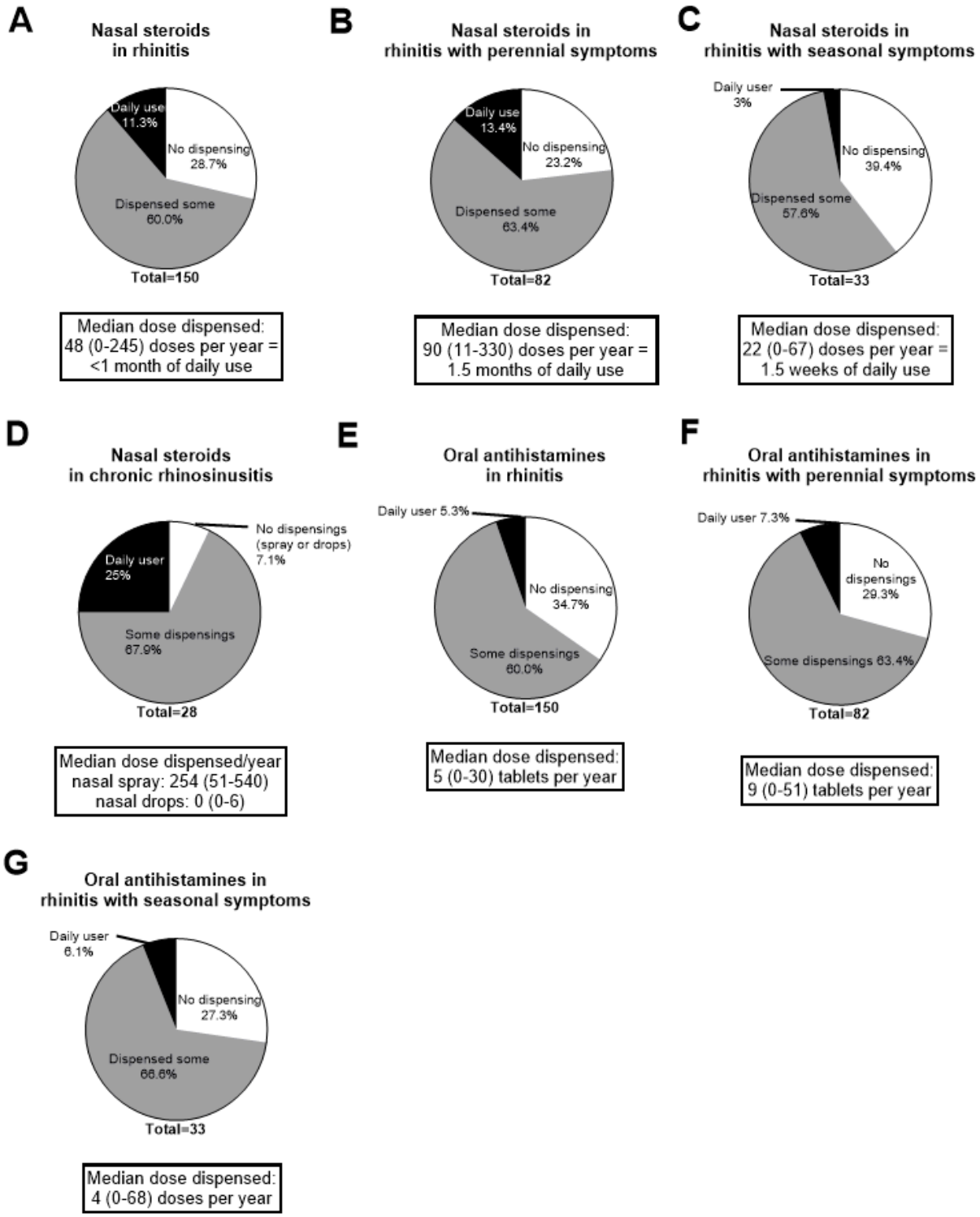

Figure 2

Dispensed nasal medication among patients with adult-onset asthma and comorbid rhinitis or chronic rhinosinusitis. A-D shows dispensed intranasal steroids and E-G oral antihistamines during 12-year follow-up.

Supplementary Files

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