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Original Article

Intranasal corticosteroids reduced acute rhinosinusitis in children with allergic rhinitis: A nested case—control study

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KEYWORDS
Allergic rhinitis;
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Second-generation antihistamines;
Nested case—control study

Abstract *Background:* Children with allergic rhinitis (AR) have substantially more acute rhinosinusitis than children without AR. We evaluated whether intranasal corticosteroids (INCS), second-generation antihistamines (SGH), and/or intranasal antihistamines (INH) for AR affect acute rhinosinusitis in children with AR aged 2—18 years.
Methods: By using the National Health Research Institutes Database 2005 of Taiwan, a cohort of patients with AR aged 2—18 years treated with AR medications between 2002 and 2018 was made, within which a nested case—control study was performed. Risk settings for acute rhinosinusitis cases matched controls for age, sex, and comorbidities. Current users of INCS, INH, and/or SGH were compared with remote and recent users of any AR medications and current users of INCS with and without SGH were compared with current users of SGH.
Results: Current users of SGH and/or INCS had a higher risk of acute rhinosinusitis than remote users of AR drugs, and current users of SGH had a higher risk of acute rhinosinusitis than recent users; however, no difference in the risk of acute rhinosinusitis was found between current users of INCS and recent users of AR drugs. Current users of INCS with and without SGH had a lower risk of acute rhinosinusitis than current users of SGH alone.
Conclusions: Treatment of INCS with and without SGH diminished the risk of acute rhinosinusitis compared with treatment using SGH alone. Adequate INCS treatment for patients with AR is important to reduce the incidence of acute rhinosinusitis.

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Introduction

Allergic rhinitis (AR) is a common disease that affects approximately 30% of children in Taiwan.[1,2] Upper airway diseases such as rhinosinusitis and otitis media are highly associated with AR.[3] Children with AR experience substantially more acute rhinosinusitis than children without AR.[4]

Viral cold is believed to be the main contributor to the pathogenesis of acute sinusitis. Upper respiratory tract infections (URTIs) lead to osteomeatal obstruction with a significant impairment in sinus ventilation and mucociliary clearance.[5] Levels of intercellular adhesion molecule-1 (ICAM-1) are higher in epithelial cells in patients with grass pollen-induced AR than in healthy controls exposed to pollens.[6] The upregulation of the expression of ICAM-1, a major rhinovirus receptor, may increase tissue susceptibility to rhinovirus infection.[7] AR is involved in impaired paranasal sinus function. Individuals with AR demonstrated more severe paranasal sinus obstruction in CT than non-AR individuals during viral colds.[8] Therefore, URTIs and allergic inflammation are significant risk factors for acute rhinosinusitis.

A previous study revealed that antibiotic therapy alone cannot resolve acute rhinosinusitis symptoms in children with AR.[9] The use of antihistamines as standard treatment in patients and acute rhinosinusitis having AR has improved the control of some sinusitis symptoms.[10] Another study found that antihistamines are closely associated with acute rhinosinusitis.[11] In patients with AR, treatment with intranasal corticosteroids (INCS) and/or secondary generation antihistamines (SGHs) for asthma may reduce the incidence of acute exacerbation of asthma.[12] Meta-analysis studies have demonstrated that INCS provides a small therapeutic advantage in resolving or improving acute rhinosinusitis symptoms.[13,14]

However, no studies have determined whether the treatment of AR with INCS, SGHs, and/or intranasal antihistamines (INHs) could prevent the risk of acute rhinosinusitis in children with AR. This study aimed to investigate whether the treatment of AR with INCS, SGH, and/or INH could reduce the incidence of acute rhinosinusitis in children with AR of different ages. Therefore, we assessed the association between AR drugs and the risk of acute rhinosinusitis in children with AR in a nested case—control study using data from the Taiwan National Health Insurance Research Database (NHIRD) database.

Methods

Data resources

The data analyzed in this study were retrospectively derived from a subset of the NHIRD known as the Longitudinal Health Insurance Database 2005 (LHID2005) that was administered by Taiwan's National Health Research Institutes. The NHIRD contains details of beneficiaries registered in Taiwan's National Health Insurance program launched in 1995. Up to 99.8% of the population of Taiwan is included in this program. Data included in the LHID2005 are claims data from 2 million randomly selected patients in the 2005 registry for the NHIRD, which in turn contains all the claims data collected from January 01, 2000, to December 31, 2018.

This study used data from 2002 to 2016 to ensure that each patient's medical history was traceable for at least 2 years. Information from the NHIRD includes the registry of beneficiaries, clinical records detailed in ambulatory care claims, hospitalizations, diagnostic codes, and prescription records. The information from the NHIRD employs a scrambled clinical record in ambulatory care claims, hospitalization of patients, diagnostic codes (which follow the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes), and prescription drugs.

This study was endorsed by the Institutional Review Board of Chia-Yi Christian Hospital in Taiwan (Institutional Review Board No. CYCHIRB: 2020134).

Study population

This study assembled a cohort of patients with AR to undertake a nested case—control study. Patients diagnosed with AR (ICD-9-CM: 477.X) more than twice within a 90 days between 2002 and 2016 and had had to take AR medications were enrolled in the cohort. AR medications comprise an INCS, INH, and/or SGH. INCS include beclometasone (ATC code R01AD01), budesonide (ATC code R01AD05), betamethasone (ATC code R01AD06), fluticasone (ATC code R01AD08), mometasone (ATC code R01AD09), triamcinolone (ATC code R01AD11), and fluticasone furoate (ATC code R01AD12). INHs include levocabastine (ATC code R01AC02), and azelastine (ATC code R01AC03). SGH includes cetirizine (ATC code R06AE07), levocetirizine (ATC code R06AE09), ebastine (ATC code R06AX22), fexofenadine (ATC code R06AX26), mequitazine (ATC code R06AD07), and desloratadine (ATC code R06AX27).

Patients diagnosed with AR from January 01, 2000, to December 31, 2001, were excluded from this study. However, all patients with incomplete claims data or those aged <2 years or >18 years were excluded.

The primary outcome of interest in this study was the occurrence of acute rhinosinusitis after 90 days to 2 years of a confirmed diagnosis of AR in children of different ages. The study included patients with acute rhinosinusitis (ICD-9-CM: 461. x) who were in an outpatient setting and had concurrent oral antibiotic prescriptions. Antibiotics given orally included amoxicillin (ATC code J01CA04), ampicillin and sulbactam (ATC code J01CR01), amoxicillin and clavulanate (ATC code J01CR02), cephalexin (ATC code J01DB01), cefaclor (ATC code J01DC04), cefuroxime (ATC code J01DC02), cefixime (ATC

code J01DD08), ceftibuten (ATC code J01DD14), sulfamethoxazole and trimethoprim (ATC code J01EE01), ciprofloxacin (ATC code J01MA02), levofloxacin (ATC code J01MA12), erythromycin (ATC code J01FA01), clarithromycin (ATC code J01FA09), and azithromycin (ATC code J01FA10). Among patients who met the AR criteria, we identified all those with acute rhinosinusitis between the entry date (defined as the AR date + 90 days) and the last date of follow-up (defined as the AR date +2 years); these patients were defined as having acute rhinosinusitis. Controls were selected from patients who did not have acute rhinosinusitis between the time of AR diagnosis and the end of follow-up. Each case was matched to four controls based on patients' AR date (±180 days). The date of acute rhinosinusitis (for cases) or the equivalent date of follow-up without acute rhinosinusitis (for controls) was referred to as the "study reference date" (Fig. 1).

Exposures and covariates

The primary exposure of interest was AR treatment before the study index date, including INCS, INH, and SGH. Patients were current users if the duration of the INS, SGH, and INH prescription time closest to and before the study index date overlapped with the study index date. Remote users were those who had their drug supply terminated over 30 days before the study index date. These patients were considered unlikely to take the prescription drugs INS, SGH and INH as of the study index date. Recent users were individuals whose AR medication prescriptions were terminated between 1 and 30 days before the study index date. The flow chart is shown in Fig. 1. Patients whose acute rhinosinusitis occurred on the prescribed date were excluded. These patients were categorized separately for some reasons. The effects of INS, SGH, and INH on the nasal mucosa may persist for a short time after the last dose. Because of dosage requirements or incomplete compliance, some recent users may have taken the medication after the nominal cessation of distribution. Therefore, we use a separate category to avoid misclassification as a result of considering these patients as current or remote users.[15]

Comorbidities

Comorbidities most frequently associated with AR, including asthma (ICD-9-CM: 493.x), atopic dermatitis (AD; ICD-9-CM: 691.8), chronic rhinitis (ICD-9-CM: 472.0), and gastroesophageal reflux disease (GERD; ICD-9-CM: 530.81) were investigated. The baseline comorbidities were determined for each patient throughout the study period.

Statistical analyses

As regards categorical variables, data were shown as frequencies (percentages), whereas for continuous variables, data were shown as standard deviations (SDs). Student's t-test was used to compare the AR and non-AR groups for continuous parametric data, whereas the categorical data of the two groups were compared using the chi-square test. The risk factors for acute rhinosinusitis were evaluated using conditional logistic regression with adjustments for potential risk factors (age, sex, asthma, AD, and GERD). All statistical analyses were conducted using SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA), and a two-tailed p-value of <0.05 indicated statistical significance.

Results

Demographic characteristics

This study enrolled a total of 172,065 individuals with AR aged 2–18 years. Patients with AR had a mean (SD) age of 7.93 (4.30) years at diagnosis, and 58.76% (101,100) were boys. The basic demographic characteristics of the AR groups with acute rhinosinusitis and non-acute rhinosinusitis are listed in Table 1. Among children with AR, acute rhinosinusitis cases were matched with four controls; therefore, 34,413 (20.00%) patients had acute rhinosinusitis, and 137,652 (80.00%) patients had non-acute rhinosinusitis. Thus, 35,487 (20.62%), 11,317 (6.58%), and 17,631 (10.25%) patients had asthma, AD, and chronic rhinitis. Three patients with AR were treated with only INH, which is a significantly low number to achieve a significant difference. Therefore, the "others" group encompassed patients with AR who were treated with only INH, INH plus INCS, INH plus SGH, and INH plus INCS plus SGH.

Increased risk of acute rhinosinusitis in patients with AR aged 7–18 years vs those aged 2–6 years

Table 2 reveals the risk factors of acute rhinosinusitis in patients with AR and specific risk factors for patients aged 2–6 and 7–18 years. The incidence of acute rhinosinusitis

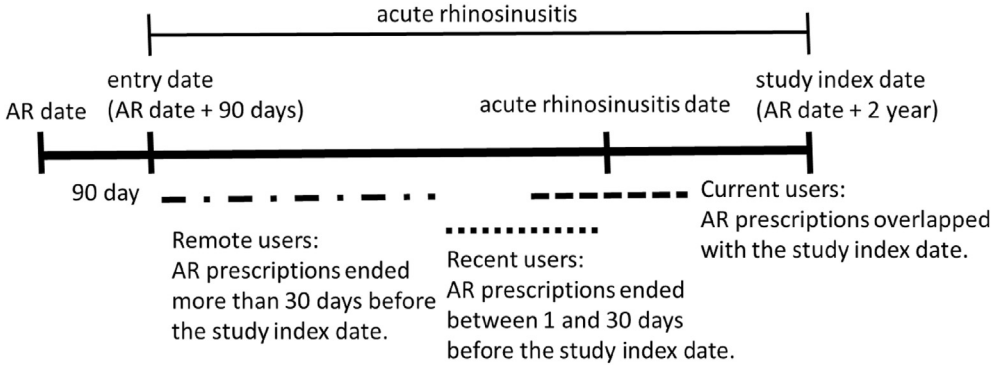

Figure 1. Flow chart of participant enrollment.

Table 1 Baseline characteristics between acute rhinosinusitis and non-acute rhinosinusitis among children with allergic rhinitis.

Characteristic, n (%)	Total	non-acute rhinosinusitis	acute rhinosinusitis	P value
	(N = 172,065)	(n = 137,652)	(n = 34,413)	
Age, mean (SD)	7.93 (4.30)	7.92 (4.29)	7.96 (4.30)	0.112
2–6	90,988 (52.88)	72,902 (52.96)	18,086 (52.56)	0.178
7–18	81,077 (47.12)	64,750 (47.04)	16,327 (47.44)	
Gender				
Female	70,965 (41.24)	56,772 (41.24)	14,193 (41.24)	>0.999
Male	101,100 (58.76)	80,880 (58.76)	20,220 (58.76)	
Comorbidities				
Asthma	35,487 (20.62)	28,392 (20.63)	7095 (20.62)	0.972
Atopic dermatitis	11,317 (6.58)	9412 (6.84)	1905 (5.54)	<0.001
Chronic rhinitis	17,631 (10.25)	13,878 (10.08)	3753 (10.91)	<0.001
Nasal polyps	623 (0.36)	505 (0.37)	118 (0.34)	0.508
GERD	329 (0.19)	274 (0.20)	55 (0.16)	0.136
Drug				
Remote	129,843 (75.46)	106,944 (77.69)	22,899 (66.54)	<0.001
Recent	26,286 (15.28)	20,050 (14.57)	6236 (18.12)	
Current				
SGH only	11,601 (6.74)	7454 (5.42)	4147 (12.05)	
INCS only	2542 (1.48)	1910 (1.39)	632 (1.84)	
SGH + INCS	1774 (1.03)	1281 (0.93)	493 (1.43)	
Others	19 (0.01)	13 (0.01)	6 (0.02)	

Abbreviation: AR, allergic rhinitis; AD, atopic dermatitis; GERD, Gastroesophageal reflux disease; SGH, Secondary generation antihistamine; INCS, Intranasal corticosteroid; INH, Intranasal antihistamine. 'Others' group included INH only or INH + SGH or INH + INCS or INH + SGH + INCS.

in patients with AR was higher in the older (aged 7–18 years) group than in the preschool (aged 2–6 years) group (adj. odds ratio [OR]: 1.29, 95% confidence interval [CI] 1.16–1.42).

The risk of acute rhinosinusitis is lower in patients with AR having AD but higher in patients with AR having chronic rhinitis

The risk of acute rhinosinusitis was lower in patients with AR having AD than in those without AD (adj. OR 0.78, 95% CI 0.74–0.82). The risk of acute rhinosinusitis was higher in patients with AR having chronic rhinitis than in those without chronic rhinitis (adj. OR 1.08, 95% CI 1.04–1.12). No significant difference in other comorbidities (asthma, nasal polyps, and GERD) of AR was noted (Table 2).

The risk was higher not only between recent and current AR drug users and remote AR drug users, but also between current AR drug users and recent AR drug users

To determine whether the use of INCS, SGH, and/or INH can treat AR associated with acute rhinosinusitis in patients with AR, we assumed that the use of AR drugs more than 30 days before the diagnosis date of acute rhinosinusitis indicated remote use, the use of AR drugs in 1 and 30 days before the diagnosis date of acute rhinosinusitis indicated recent use, and overlapped with the diagnosis date of acute rhinosinusitis indicated current use. When recent and current users of AR drugs were compared with remote users, the risk of acute rhinosinusitis increased 1-47- and 2.33-fold (95% CI 1.42–1.52 and 2.25–2.42). When current users of AR drugs were compared with recent users, the risk of acute rhinosinusitis was enhanced 1.59-fold (95% CI 1.52–1.66).

Current users of SGH and INCS had a higher risk of acute rhinosinusitis than remote users of AR drugs, and current users of SGH had a higher risk of acute rhinosinusitis than recent users of AR drugs; however, the risk for acute rhinosinusitis was not different between current users of INCS and recent users of AR drugs regardless of the age groups

When current users of any AR drugs were compared with remote users, the risk of acute rhinosinusitis was enhanced 2.62-fold (95% CI 2.52–2.73) in current users of SGH; 1.55-fold (95% CI 1.42–1.70) in current users of INCS; 1.81-fold (95% CI 1.63–2.02) in current users of SGH with INCS (Table 2). Compared with recent users, the odds ratio of acute rhinosinusitis was increased in current users of SGH and SGH with INCS. (adj. OR 1.78, 95% CI 1.70–1.87; 1.24, 95% CI 1.11–1.38), but not in current users of INCS (adj. OR 1.06, 95% CI 0.96–1.16) (Table 2).

Similar results were observed in different age groups. Compared with remote users of AR drugs, the risks of acute rhinosinusitis in recent and current users of AR drugs were 1.44- and 2.00-fold ($p < 0.001$) among patients aged 2–6 years; 1.50- and 2.80-fold ($p < 0.001$) among those aged

Table 2 Risk of acute rhinosinusitis with the use of AR drugs, comparing remote with recent use of allergic rhinitis drugs in children with allergic rhinitis.

	Adj. OR (95%CI)	P value	Adj. OR (95%CI)	P value	Adj. OR (95%CI)	P value	Adj. OR (95%CI)	P value
Age								
2–6	Ref.		Ref.		Ref.		Ref.	
7–18	1.29 (1.16,1.42)	<0.001	1.29 (1.16,1.42)	<0.001	1.29 (1.17,1.43)	<0.001	1.29 (1.17,1.43)	<0.001
Comorbidities								
Asthma	0.99 (0.96,1.02)	0.350	0.99 (0.96,1.02)	0.350	0.99 (0.96,1.02)	0.440	0.99 (0.96,1.02)	0.440
Atopic dermatitis	0.78 (0.74,0.82)	<0.001	0.78 (0.74,0.82)	<0.001	0.78 (0.74,0.82)	<0.001	0.78 (0.74,0.82)	<0.001
Chronic rhinitis	1.08 (1.04,1.12)	<0.001	1.08 (1.04,1.12)	<0.001	1.08 (1.04,1.12)	<0.001	1.08 (1.04,1.12)	<0.001
Nasal polyps	0.90 (0.74,1.10)	0.316	0.90 (0.74,1.10)	0.316	0.90 (0.73,1.10)	0.289	0.90 (0.73,1.10)	0.289
GERD	0.80 (0.59,1.07)	0.126	0.80 (0.59,1.07)	0.126	0.80 (0.59,1.06)	0.125	0.80 (0.59,1.06)	0.125
Drug								
Remote	Ref.		0.68 (0.66,0.70)	<0.001	Ref.		0.68 (0.66,0.70)	<0.001
Recent	1.47 (1.42,1.52)	<0.001	Ref.		1.47 (1.42,1.52)	<0.001	Ref.	
Current	2.33 (2.25,2.42)	<0.001	1.59 (1.52,1.66)	<0.001				
SGH only					2.62 (2.52,2.73)	<0.001	1.78 (1.70,1.87)	<0.001
INCS only					1.55 (1.42,1.70)	<0.001	1.06 (0.96,1.16)	0.254
SGH + INCS					1.82 (1.63,2.02)	<0.001	1.24 (1.11,1.38)	<0.001
Others					2.22 (0.84,5.83)	0.107	1.51 (0.57,3.99)	0.404

Adjusted by age, gender and comorbidities.
Abbreviation: AR, allergic rhinitis; AD, atopic dermatitis; GERD, Gastroesophageal reflux disease; SGH, Secondary generation antihistamine; INCS, Intranasal corticosteroid; INH, Intranasal antihistamine; 'Others' group included INH only or INH + SGH or INH + INCS or INH + SGH + INCS.

7–18 years, respectively (Table 3). Current users of SGH and INCS had a higher risk of acute rhinosinusitis than remote users of AR drugs in each age group (adj. OR 2.21 and 1.45, $p < 0.001$, among aged 2–6 years; adj. OR 3.23 and 1.65, $p < 0.001$, among those aged 7–18 years), and current users of SGH had a higher risk for acute rhinosinusitis than recent users of AR drugs in each age group (adj. OR 1.54, $p < 0.001$, among those aged 2–6 years; adj. OR 2.16, $p < 0.001$, among those aged 7–18 years) (Table 3). However, no difference in the risks of acute rhinosinusitis was found between current users of INCS and recent users of AR drugs in each age group.

Table 3 Risk of acute rhinosinusitis with the use of allergic rhinitis drugs, comparing remote with recent use of allergic rhinitis drugs in different age groups of children with allergic rhinitis.

	Adj. OR (95%CI)	P value	Adj. OR (95%CI)	P value	Adj. OR (95%CI)	P value	Adj. OR (95%CI)	P value
Age 2–6								
Drug								
Remote	Ref.		0.70 (0.67,0.73)	<0.001	Ref.		0.70 (0.67,0.73)	<0.001
Recent	1.44 (1.38,1.50)	<0.001	Ref.		1.44 (1.38,1.50)	<0.001	Ref.	
Current	2.00 (1.90,2.10)	<0.001	1.39 (1.31,1.48)	<0.001				
SGH only					2.21 (2.09,2.34)	<0.001	1.54 (1.44,1.64)	<0.001
INCS only					1.45 (1.29,1.64)	<0.001	1.01 (0.89,1.15)	0.867
SGH + INCS					1.53 (1.32,1.78)	<0.001	1.07 (0.92,1.24)	0.405
Others					2.70 (0.79,9.22)	0.114	1.88 (0.55,6.42)	0.316
Age 7–18								
Drug								
Remote	Ref.		0.67 (0.64,0.70)	<0.001	Ref.		0.67 (0.64,0.70)	<0.001
Recent	1.50 (1.43,1.57)	<0.001	Ref.		1.50 (1.43,1.57)	<0.001	Ref.	
Current	2.80 (2.65,2.95)	<0.001	1.87 (1.75,2.00)	<0.001				
SGH only					3.23 (3.04,3.44)	<0.001	2.16 (2.01,2.32)	<0.001
INCS only					1.65 (1.43,1.90)	<0.001	1.10 (0.95,1.27)	0.193
SGH + INCS					2.14 (1.84,2.49)	<0.001	1.43 (1.23,1.67)	<0.001
Others					1.59 (0.32,7.98)	0.571	1.07 (0.21,5.34)	0.939

Adjusted by gender and comorbidities.
Abbreviation: AR, allergic rhinitis; AD, atopic dermatitis; GERD, Gastroesophageal reflux disease; SGH, Secondary generation antihistamine; INCS, Intranasal corticosteroid; INH, Intranasal antihistamine; 'Others' group included INH only or INH + SGH or INH + INCS or INH + SGH + INCS.

Current users of SGH with INCS had an increased risk for acute rhinosinusitis (adj. OR 1.43, 95% CI 1.23—1.67) among patients aged 7—18 years, but no difference in the risk for acute rhinosinusitis (adj. OR 1.07, 95% CI 0.92—1.24) was found among patients aged 2—6 years who were recent users of AR drugs (Table 3).

Current users of INCS and SGH with INCS had lower risk of acute rhinosinusitis than current users of SGH regardless of the age groups

Current users of INCS and INCS with SGH had reduced risk of acute rhinosinusitis compared with current users of SGH (adj. OR 0.60, 95% CI 0.54—0.66; adj. OR 0.68, 95% CI 0.61—0.76) among all age groups (aged 2—6 years, adj. OR 0.67, 95% CI 0.59—0.76; adj. OR 0.70, 95% CI 0.60—0.81; aged 7—18 years, adj. OR 0.53, 95% CI 0.45—0.61; adj. OR 0.66, 95% CI 0.57—0.78) (Table 4). However, no significant difference was found between current users of "others group" and current users of SGH regardless of the age groups (Table 4).

Discussion

In this nested case—control study, we investigated AR medications (INCS, SGH, and/or INH) that influence the incidence rate of acute rhinosinusitis by comparing remote, recent, and current users of AR drugs. Current users of SGH and/or INCS had a higher risk of acute rhinosinusitis than remote users of AR drugs, and current users of SGH had a higher risk of acute rhinosinusitis than recent users of AR drugs; however, no difference in the risk of acute rhinosinusitis was found between current users of INCS regardless of the age groups. However, when compared with recent users of AR drugs, current users of INCS in each age group and INCS with SGH in patients aged 2—6 years were not found to have significant difference in risks of acute rhinosinusitis. Current users of INCS with and without SGH were associated with a lower risk of acute rhinosinusitis than current users of SGH regardless of the age group.

This study found that acute rhinosinusitis was more likely to occur in patients with AR aged 7—18 years than in those aged 2—6 years. A previous study revealed that older children had more frequent acute rhinosinusitis among children with perennial and seasonal AR, especially those aged >6.5 years.[16] Another small-size study demonstrated that children aged >6 years with acute rhinosinusitis and AR had nasal peak expiratory flow rate values significantly lower than those of children without AR; however, this was not seen in patients aged <6 years.[17] Inflammation of nasal mucosa due to AR could lead to sinus ostia obstruction, particularly in children with AR aged >6 years. Patients with AR showed a more severe paranasal sinus dysfunction during URTI than patients without AR[8]; however, acute rhinosinusitis after URTI occurs at a lower frequency than acute otitis media (AOM).[18] Younger children are more vulnerable to AOM following URTI. Differences in the anatomy of the upper respiratory tract in children of different ages may contribute to this difference.

In a nationwide cross-sectional study, AD in children was associated with a higher probability of otitis media, urinary tract infection, and sinusitis but not pneumonia.[19] A systematic review and meta-analysis also revealed that AD is related to a rise in extracutaneous infections.[20] Interleukin (IL)-4 and IL-13 suppress the production of antimicrobial peptides, leaving the body vulnerable to *Staphylococcus aureus* colonization.[21] IL-13 also slows down the ciliary beat frequency of airway epithelial cells ex vivo, which leads to reduced mucociliary transport and facilitates microbial adhesion and mucosal invasion.[22] A study showed that the increased carriage rate of *S. aureus* was found in perennial AR, and nasal carriage of *S. aureus* may worsen perennial AR.[23] Type 2 inflammation results in a dysfunctional skin barrier, reduced antimicrobial peptides expression, and increased bacterial colonization, which may be associated with extracutaneous infections in patients with AD.[20] Topical anti-inflammatory treatment alone alleviates allergic skin inflammation in AD and decreases cutaneous colonization by *S. aureus*.[24] The overall risk of infection was not elevated by dupilumab treatment. The rate of serious or severe infections and non-herpetic skin infections was lower with the use of dupilumab. Dupilumab decreases the use of systemic anti-infective medication. The use of concomitant topical steroids with dupilumab results in a lower rate of skin infections than monotherapy with dupilumab.[25] Since the study population had AR, most of the patients with or without AD had type 2 inflammation. However, local or systemic steroids and immune modulation drugs may be used in patients with AD. Local or

Table 4 Risk of acute rhinosinusitis with the current use of allergic rhinitis drugs compared with the current use of second-generation antihistamines in children with allergic rhinitis.

	Adj. OR (95%CI)		
	All[&]	Age 2—6[#]	Age 7—18[#]
Drug			
Current			
SGH only	Ref.	Ref.	Ref.
INCS only	0.60 (0.54,0.66)***	0.67 (0.59,0.76)***	0.53 (0.45,0.61)***
SGH + INCS	0.68 (0.61,0.76)***	0.70 (0.59,0.81)***	0.67 (0.57,0.78)***
Others	0.83 (0.32,2.20)	1.18 (0.35,4.04)	0.51 (0.10,2.54)

Adjusted by age, gender and comorbidities[&], Adjusted by gender and comorbidities[#], <0.05*, <0.01**, <0.001***.
Abbreviation: AR, allergic rhinitis; SGH, Secondary generation antihistamine; INCS, Intranasal corticosteroid; INH, Intranasal antihistamine; 'Others' group included INH only or INH + SGH or INH + INCS or INH + SGH + INCS.

systemic steroids and immune modulation medications may lead to significant reductions in the type 2 axis. As a result, patients with AR having AD had a lower risk of acute rhinosinusitis than those not having AD.

In a large longitudinal study, antihistamines were approximately 1.53-fold more likely to be associated with sinusitis in patients with AR, regardless of prescription duration.[11] Another study revealed that the use of azelastine and sodium chloride spray is an effective therapy to prevent acute sinusitis in patients admitted to the ICU.[26] Antihistamines modify the carbohydrate—water composition of the mucus, leading to ciliary stasis.[27] The anticholinergic effect of first-generation antihistamines may reduce clearance by increasing the discharge viscosity and thickening mucus. The anticholinergic effect depresses the ciliary beat, which cannot function efficiently in the dry nasal mucosa.[28] These effects may be more harmful than beneficial for the treatment of rhinosinusitis. However, SGHs are highly selective on the H1 receptor (H1R) and do not have anticholinergic properties. Azelastine intranasal spray was found to significantly reduce the ciliary beat frequency.[28] Mast cells and basophils are not implicated in the pathophysiology of rhinovirus infection because histamine levels remain the same in rhinovirus or non-rhinovirus infection. SGHs should not be expected to be effective in treating rhinovirus colds.[29] The pathophysiology of rhinosinusitis is independent of histamine release by mast cells. SGHs are not effective for the prevention of rhinosinusitis.[30] However, antihistamines may be beneficial because of their anti-inflammatory effects. Antihistamines prevent the production of activator protein-1 and nuclear factor kappa B (NF-kB), leading to anti-inflammatory effects.[31] Although antihistamines have pros and cons, our study demonstrated that the current use of SGH was associated with a higher risk (2.62- and 1.55-fold) of acute rhinosinusitis compared with remote and recent uses of AR drugs.

The use of inhaled corticosteroid (ICS) has the potential to increase the risk of pneumonia in patients with chronic obstructive pulmonary disease (COPD).[32,33] However, an increased risk of COPD was predominantly reported for fluticasone, but not for budesonide.[34] ICS use was related to an increase in the incidence of pneumonia in patients with asthma, which may be because ICS users were older and had more comorbidities than ICS non-users.[35] However, several studies have demonstrated that pneumonia was not linked to ICS use.[36] A meta-analysis illustrated that ICS use in patients with asthma was associated with a reduced risk of pneumonia.[37] It has been supposed that ICS reduces respiratory tract inflammation and mucus production, contributing to a reduction in airway viscosity and abnormal mucociliary clearance, thereby decreasing bacterial infection. The ciliary beat frequency of airway epithelial cells is slowed down by IL-13 ex vivo, leading to reduced mucociliary transport and promoting microbial adhesion and invasion of the mucus; therefore, IL-13 may favor bacterial infection in patients with AR.[22] INCS has not altered mucociliary function in patients with AR.[38,39] In contrast to antihistamines, the current use of INCS were not significantly associated with the risk of acute rhinosinusitis compared with the recent use of AR drugs. In addition, current users of INCS with and without SGH had a reduced risk of acute rhinosinusitis compared with current users of SGH regardless of age groups. We hypothesized that INCS may reduce the inflammation of the sinuses and nasal cavity, thereby enhancing sinusoidal drainage and reducing the risk of acute rhinosinusitis. Stepwise treatment based on disease severity or symptom control level is a global strategy for AR management. The Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines showed more severe AR symptoms in patients with AR using INCS with and without SGH than in patients with AR using SGH alone. More severe or uncontrolled AR requires the use of INCS or more AR drugs.[40] Our study demonstrated that treatment with INCS with and without SGH resulted in a lower risk of acute rhinosinusitis than treatment with SGH alone. We suggest that treatment with INCS may be associated with a reduced risk of acute rhinosinusitis. This study revealed that current users of INCS with SGH aged 7—18 years had a significantly higher risk of acute rhinosinusitis than recent users of AR drugs, but not those aged 2—6 years. The probable reason is that INCS is more effective in patients aged 2—6 years than in those aged 7—18 years because of differences in the anatomy of the upper respiratory tract in children.

The ARIA guidelines suggested to step-up or step-down the treatment depending on the disease severity or symptom control level. If there are decreased or no symptoms of AR, the use of AR medication will be reduced or discontinued. Current users of SGH and/or INCS may have more severe AR symptoms than remote users of AR drugs. A more serious or uncontrolled AR may increase the risk of acute rhinosinusitis. Therefore, compared with remote users, current users of SGH and/or INCS probably have a more serious or uncontrolled AR, which may increase the risk of acute rhinosinusitis. Recent users of AR drugs may have more severe AR symptoms than current users of AR drugs. Thus, current users of SGH had a higher risk of acute rhinosinusitis than recent users of AR drugs; however, our study demonstrated no difference in the risk of acute rhinosinusitis between current users of INCS and recent AR drug users. Thus, we suggest that treatment with INCS may reduce AR severity to decreases the risk of acute rhinosinusitis.

This study has notable strengths. First, this study analyzed a large sample of real-world patients and national prescription data and followed a nested case—control design. Second, the washout period was approximately 2 years (2000—2001). Patients diagnosed with AR in the first 2 years were not included in this study. To our knowledge, this study is the first to demonstrate the correlation of AR drugs with acute rhinosinusitis in pediatric patients with AR through a population-based and nested case—control design. Nevertheless, this association study contained some limitations. For example, the validation of AR and acute rhinosinusitis may be problematic because the study population was extracted from the NHIRD according to arbitrary coding by physicians, whereas the NHIRD lacks laboratory or imaging data to support the diagnosis of AR and acute rhinosinusitis. However, we attempted to improve the accuracy of the diagnosis of AR and cute rhinosinusitis by defining AR as having at least two outpatients with any AR medication in 90 days and acute rhinosinusitis as having concurrent oral antibiotic prescriptions. Furthermore, treatment decisions for AR were based on the severity of AR in clinical settings; however, verifying the

severity of AR using NHIRD data is not easy. Another potential limitation is that patients may have deviated from their prescribed medication regimen, resulting in misclassification of their exposure. In addition, the study data may have been affected by potential residual confounders, such as cases of respiratory viral infection, increasing the rate of acute rhinosinusitis. Finally, not enough patients with AR were treated with INH to achieve a significant difference.

A step-by-step therapy based on the visual analog scale is a global strategy for AR management. More severe or uncontrolled AR requires the use of INCS or more AR drugs.[40] The impaired sinus function is thought to be a pivotal factor in the development of acute rhinosinusitis. Nasal congestion caused by allergens may block sinus drainage and augment subsequent bacterial infection.[8] As a result, a more serious or uncontrolled AR may increase the risk of acute rhinosinusitis. Nevertheless, this study illustrated that treatment with INCS with and without SGH resulted in a diminished risk of acute rhinosinusitis than treatment with SGH alone. It was not found that combining oral H1 antihistamines with INCS was more effective than INCS alone.[40] INCS may diminish allergic inflammatory factors to enhance sinusoidal emptying and lower the risk of acute rhinosinusitis. We hypothesized that INCS may reduce the inflammation of the sinuses and nasal cavity, thus improving sinusoidal drainage and lowering the risk of acute rhinosinusitis. As such, adequate INCS treatment for patients with AR is important to reduce acute rhinosinusitis. Future randomized and prospective studies are crucial to confirm that INCS significantly reduces the risk of acute rhinosinusitis in patients with AR.

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