

Despite the large number of children with a reported penicillin allergy, our survey suggests that the general pediatric community perceives that most of these allergies are misdiagnosed. Our study also reveals that, although all surveyed pediatricians understand the importance of addressing this public health issue, approximately one-quarter of surveyed pediatricians would currently feel comfortable conducting low-risk oral amoxicillin challenges in their clinics. Thus, this finding highlights the need for further efforts in (1) establishing a protocol to safely distinguish low-risk children from high-risk children (to begin oral challenges for low-risk patients in clinics), (2) developing educational materials to increase public awareness about the importance of delabeling misdiagnosed penicillin allergies, and (3) exploring ways to address potential testing barriers. Because there is still a potential risk of a severe anaphylactic reaction during an oral challenge, it will be especially important to address the main barriers (lack of time and lack of adequate staff) to ensure patient safety. In the end, although partnering with pediatricians to delabel misdiagnosed penicillin allergies is a step in the right direction, it is only part of the solution—this should be paired with standardized approaches to prevent mislabeling in the first place.

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Urban-rural differences in health care utilization and prescription filling for childhood asthma



Despite lower asthma prevalence in rural compared with urban children,^{1,2} studies suggest that rural children have higher asthma morbidity and uncontrolled asthma.^{2–4} Investigation into potential differences in management and health care utilization after asthma diagnosis would help provide a better understanding of these results. Potential barriers to health care access in rural areas may contribute to poor management of asthma and help explain uncontrolled disease in these areas.

We investigated urban-rural differences in health care utilization among children with asthma. Specifically, we investigated differences in physician visits and hospitalizations for asthma and asthma medication prescription filling in the year after diagnosis and during a 10-year follow-up period. This was a population-based retrospective cohort study of 66,589 children born between January 1, 1995, and December 31, 2014, who had an asthma diagnosis during this time. Data for the study were obtained from Saskatchewan Ministry of Health administrative databases, which cover approximately 99% of the population of Saskatchewan, Canada. Four databases were linked: (1) the Person Registry System, (2) the physician visits, (3) the hospital services, and (4) the outpatient prescription drug databases. Identification of asthma diagnosis was based on *International Classification of Diseases, Ninth Revision* (code 493) and *International Classification of Diseases, Tenth Revision* (code J45.x) codes. We excluded 15,021 First Nations children because no information on medication use was available, leaving 51,568 participants. Of these children, 18,086 had 10 years of follow-up

after diagnosis. The study was approved by the University of Saskatchewan Research Ethics Board.

Asthma health care utilization information and prescription filling were obtained for each year of follow-up after the index date (date of first asthma diagnosis). Physician visits for asthma required a diagnostic code of 493 listed on the claim. For asthma hospitalizations, the diagnostic code (J45.x) had to be the primary reason for admission. For asthma prescriptions, we considered filling of a prescription for inhaled corticosteroids (ICSs; yes vs no) or inhaled short-acting β -agonists (SABAs; yes vs no) in the first year after the index date and each year during the 10-year follow-up period. The number of SABA prescriptions filled during a 12-month period was categorized as less than 4 and 4 or more prescription fillings.⁵

The independent variable for this study was location of residence at the index date based on the Census Metropolitan Area⁶ and categorized as large urban (population >40,000), medium urban (population of 15,000–40,000), small urban (population of 3500–14,999), and rural (population <3500). Other covariates included were sex, age at index date, cohort group, and history of allergic condition.

We used multiple logistic regression to evaluate the associations between location of residence and health care encounters in the first year after the index date with large urban as the reference group. To determine trends in health care utilization during the 10-year follow-up period, the average annual percentage change (AAPC) was calculated by location of residence using Joinpoint trend analysis.

Most of the study population lived in a large urban area (51%) compared with medium urban (14.6%), small urban (6.9%), and rural (27.5%) areas. The sex distribution was similar across location of residence ($P = .28$).

Compared with children living in large urban areas, children living in rural areas were less likely to visit a physician or

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Table 1
Prevalence and Adjusted Associations Between Location of Dwelling and Asthma Health Care Utilization and Medication Use in the 12 Months After Asthma Diagnosis (N = 51,481)^a

Variable	Large urban	Medium urban	Small urban	Rural
Visited any physician for asthma				
Patients, %	52.4	46.0	50.3	47.1
OR (95% CI)	1.00 [Reference]	0.76 (0.72–0.80) ^b	0.91 (0.85–0.98) ^c	0.80 (0.77–0.84) ^b
Visited any asthma specialist				
Patients, %	32.0	17.9	17.4	19.8
OR (95% CI)	1.00 [Reference]	0.44 (0.42–0.47) ^b	0.43 (0.39–0.47) ^b	0.51 (0.49–0.54) ^b
Asthma as a primary reason for a hospitalization				
Patients, %	5.0	5.9	4.1	4.6
OR (95% CI)	1.00 [Reference]	1.16 (1.04–1.30) ^c	0.78 (0.66–0.94) ^c	0.89 (0.81–0.98) ^c
Prescription for ICSs				
Patients, %	62.2	62.2	59.3	59.7
OR (95% CI)	1.00 [Reference]	1.02 (0.96–1.07)	0.89 (0.83–0.95) ^c	0.93 (0.89–0.97) ^c
Filled prescription for inhaled SABA				
Patients, %	57.3	57.7	59.1	56.4
OR (95% CI)	1.00 [Reference]	1.03 (0.98–1.09)	1.08 (1.01–1.16) ^c	0.99 (0.95–1.03)
Filled ≥4 inhaled SABA prescriptions				
Patients, %	4.2	6.4	6.0	5.6
OR (95% CI)	1.00 [Reference]	1.55 (1.39–1.74) ^b	1.46 (1.26–1.70) ^b	1.38 (1.25–1.51) ^b

Abbreviations: CI, confidence interval; ICSs, inhaled corticosteroids; OR, odds ratio; SABA, short-acting β -agonist.

^aModels adjusted for sex, age at index date, cohort group, and allergic status. A total of 87 of the 51,568 patients had missing information for location of residence at the index date.

^b $P < .001$.

^c $P < .05$.

asthma specialist or to be hospitalized for asthma care, whereas children in medium urban areas were more likely to be hospitalized ($P < .001$; Table 1). However, children living in rural settings were less likely to fill a prescription for ICSs and more likely to fill 4 or more SABA prescriptions compared with children in a large urban center ($P < .05$). There was a decreasing trend in asthma health care utilization and filling of asthma prescriptions during the 10-year follow-up period with a higher percentage decrease in children in large urban areas compared with rural areas (eFig 1): physician visit for asthma (AAPC = -20.8 vs -19.9 ; $P < .05$), asthma hospitalization (AAPC = -32.2 vs -31.5 ; $P < .05$), filled ICS prescription (AAPC = -20.1 vs -19.5 ; $P < .05$), and filled SABA prescription (AAPC = -19.7 vs -19.3 ; $P < .05$).

Our results indicate that rural children with asthma are less likely to visit a physician, visit a specialist, or fill an ICS prescription but were more likely to fill 4 or more SABA prescriptions in the year after diagnosis. The overall lower decrease in health care utilization in children in rural areas compared with large urban areas could be attributable to better management of asthma in children in large urban areas or more exposure to triggers in rural environments that exacerbate asthma in children in rural areas, resulting in continued health care use during the follow-up period.

If we use frequency of SABA prescriptions filled per year as an indicator of poor asthma control,^{7,8} children in rural areas were more likely to have uncontrolled asthma. This finding is especially likely given the lower likelihood of filling a prescription for ICSs. In addition, children in rural areas were less likely to visit a physician or to be hospitalized compared with children in large urban areas. Reasons for this are unknown, but access to health care services for children with asthma could be a barrier in rural areas. Rural areas have fewer physicians and specialists as well as longer travel times to treatment facilities.⁹ These factors could affect the decision to present a child to a health care center for continuous care, thus making children with asthma in rural areas a population at high risk for uncontrolled asthma. Furthermore, children in medium compared with large urban areas have increased odds of hospitalization. Reasons for the nonlinear relationships are unclear and warrant future investigation.

One limitation of this study is that it was difficult to determine whether the lower health care utilization of children living in rural areas was due to accessibility or a reflection of overuse of health care resources among children living close to health care services. Administrative databases cannot provide information regarding reasons for use of health care resources. In addition, we did not have information on environmental exposures and socioeconomic status, which might have influenced the degree of health care utilization independent of location of residence.

In summary, we found that location of residence can be an important determinant in the ongoing management of childhood asthma. Rural populations represent a gap in health care service that should be addressed. This gap could be addressed through recruitment and retention of physicians in rural communities and/or telehealth services.

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Supplementary Data

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Can tiotropium add-on therapy safely improve clinical outcomes in children and adolescents with persistent asthma?



Tiotropium, a long-acting form of anticholinergic bronchodilator, has been indicated for the treatment of chronic obstructive pulmonary disease for more than 10 years, followed by its more recent approval for use in patients with asthma. In 2014, tiotropium administered through an inhaler (Respimat Soft Mist inhaler, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was indicated as the first long-acting muscarinic antagonist approved for asthma maintenance therapy. A systematic review and meta-analysis by Sobieraj et al¹ reported an association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled persistent asthma, but patients younger than 12 years were not included in the study because tiotropium was only approved for adults and adolescents when the study was designed. Since that time, tiotropium has also been found to be well tolerated and efficacious in school-age (6–11 years old) children with persistent asthma, and the indication for the tiotropium inhaler as an add-on maintenance therapy has been updated in the current guidelines for patients older than 6 years with symptomatic asthma. Recently, Murphy and Chipps² found in a systematic review that once-daily tiotropium is efficacious and safe in adolescents and children with asthma aged 1 to 17 years. We conducted a meta-analysis of randomized clinical trials (RCTs) to provide the therapy with stronger evidence and help practitioners gain a deeper understanding of the role of tiotropium in children and adolescents with uncontrolled, symptomatic asthma.

We identified eligible studies through a comprehensive literature search of PubMed, MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials databases. The last search was performed on September 27, 2019. We performed this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance.³

A total of 7 published RCTs were enrolled for analysis.^{4–10} In general, tiotropium add-on therapy indicated a marked improvement in pulmonary function compared with placebo. A significant increase in peak forced expiratory volume in 1 second (FEV₁) (0–3 hours) change from baseline was found in patients receiving tiotropium than those receiving placebo (mean difference, 110 mL; 95% confidence interval [CI], 80–140 mL; $I^2 = 9\%$; $P < .001$; $n = 2158$) (Fig. 1). Subgroup analysis of treatment duration found a significantly greater benefit of tiotropium after longer therapy (24-week

vs relatively short therapy (12 week or 4 week) (160 vs 90 vs 90 mL). A significant increase was also found in the change from baseline in trough FEV₁ (mean difference, 50 mL; 95% CI, 0–100 mL; statistical heterogeneity [I^2] = 50%; $P = .03$; $n = 2167$). Benefits in trough FEV₁ were also more pronounced with longer treatment duration, especially in the 24-week subgroup (mean difference, 110 mL; 95% CI, 50–170 mL; $P < .001$), whereas no significant increase occurred in the 4-week subgroup ($P = .67$). A similar result was found in the change from baseline in peak forced vital capacity (0–3 hours) (mean difference, 40 mL; 95% CI, 0–70 mL; $I^2 = 24\%$; $P = .03$; $n = 2158$). No statistical significance was found in change of trough forced vital capacity ($P = .34$).

Assessment of asthma control mainly consisted of a 7-question Asthma Control Questionnaire (ACQ) score, the patient-reported version ACQ-7 in 4 trials^{4–7} or the interviewer-administered version (ACQ-IA) in 2 trials (among them 1 study did not report the requisite data).^{8,9} In brief, the overall analysis found no significant benefit of tiotropium over placebo in ACQ-7 or ACQ-IA score ($P = .26$; $n = 1888$). Benefit of tiotropium was observed only in the patients with moderate asthma (mean difference, -0.14 ; 95% CI, -0.22 to -0.07 ; $I^2 = 0\%$; $P < .001$) but not severe asthma (mean difference, 0.06 ; 95% CI, -0.03 to 0.15 ; $I^2 = 0\%$; $P = .22$). However, the minimal clinically important difference of a 0.5-point reduction was still not achieved. There was no significant benefit of tiotropium in decreasing the number of puffs of 24-hour rescue medication use ($I^2 = 3\%$; $P = .34$).

The exacerbation risk was assessed by number of patients with minimum 1 severe asthma exacerbation who required treatment with systemic corticosteroids for minimum 3 days. The pooled effect showed no difference between tiotropium and placebo in reducing exacerbation risk (relative risk [RR], 0.94; 95% CI, 0.52–1.69; $I^2 = 0\%$; $P = .83$).

As for safety, no meaningful differences were observed in the incidence of any adverse effects, serious adverse effects, or drug-related adverse effects between tiotropium and placebo ($P = .51$, .35, and .15, respectively). Most adverse effects were mild or moderate in intensity. Notably, tiotropium significantly decreased the risk of asthma (RR, 0.80; 95% CI, 0.67–0.95; $I^2 = 0\%$; $P = .01$) but substantially increased the incidence of headache (RR, 3.93; 95% CI, 1.20–12.90; $I^2 = 0\%$; $P = .02$).

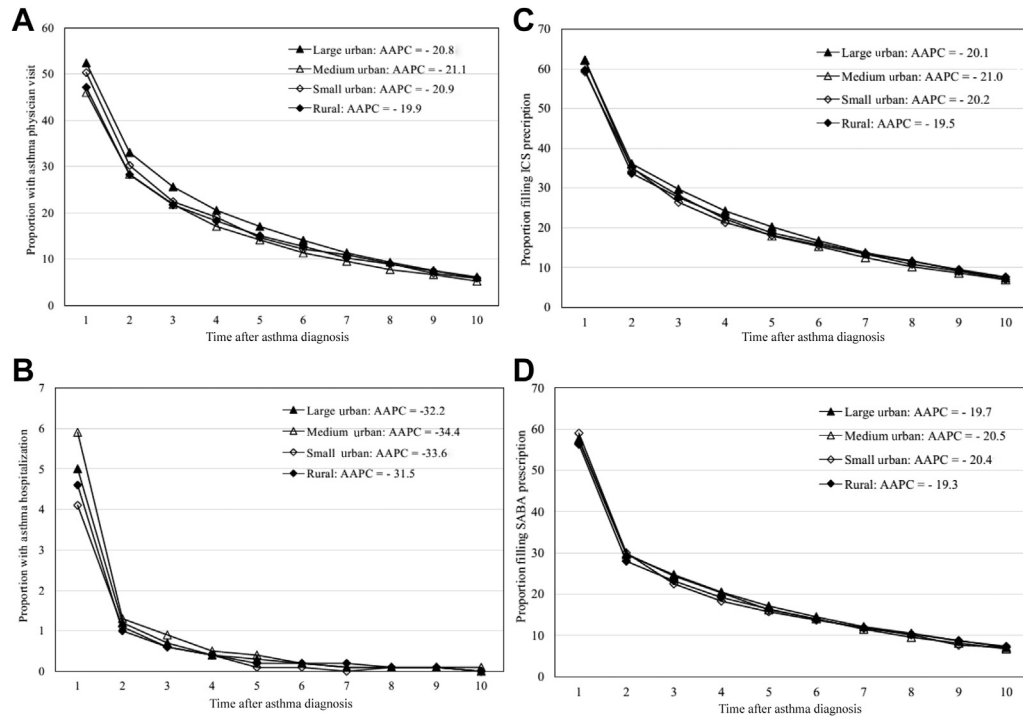
No meaningful advantages were observed in lung function, asthma control, or severe exacerbations of the 5- μ g dose than in the 2.5- μ g dose of tiotropium. No statistical significance was found among the 2 doses in peak FEV₁ (0–3 hours) change (mean difference, 30 mL; 95% CI, -10 to 60 ; $P = .13$; $n = 1335$) from 6 studies.^{4–9} No significant benefit of the 5- μ g tiotropium over the 2.5- μ g dose was found in the ACQ-7 or ACQ-IA score (mean difference, 0.03;

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Supplementary Data



eFigure 1. Trends in physician visits for (A) asthma, (B) hospitalizations for asthma, (C) inhaled corticosteroid (ICS) prescription fillings, and (D) inhaled short-acting β -agonist (SABA) prescription fillings during a 10-year follow-up period after asthma diagnosis among the study population. All findings are statistically significant at $P < .05$. AAPC, average annual percentage change.