ORIGINAL RESEARCH

Antibiotic Use in Children Who Have Asthma: Results of Retrospective Database Analysis

LEILA E. STALLWORTH, MD; DONNA M. FICK, PhD, RN; DENNIS R. OWNBY, MD; and JENNIFER L. WALLER, PhD

ABSTRACT

OBJECTIVE: Inappropriate antibiotic use is a well-recognized public health problem because of its association with the emergence of resistant bacteria. It also is a source of unnecessary health care costs and of potentially severe adverse drug reactions. Although there are no evidence-based indications for the use of antibiotics in the treatment of asthma in the absence of comorbid bacterial conditions, physicians might feel more pressure to prescribe them to children with this common chronic disease. The objectives of this study were to (a) determine if antimicrobial prescription utilization rates are higher for pediatric patients with asthma than a matched comparison group and (b) identify common variables (gender and age) that might explain higher antibiotic utilization rates in children.

METHODS: Using administrative claims data, we conducted a retrospective cohort study of children with asthma (age range 5 to 18 years) who were members of a large health plan from January 1, 2000, to December 31, 2002, in the southeastern United States. A comparison group was created that was matched according to age, sex, regional codes, and insurance product line. *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes were used to identify asthmatic patients (493.xx), as well as to link antibiotic prescriptions to diagnosis codes from claims for medical office visits.

RESULTS: Asthmatics consistently received significantly more services, including a mean of 1.74 (SD 1.82) antibiotics per patient per year (PPPY) compared with a mean of 0.96 (SD 1.32) antibiotics PPPY for nonasthmatics ($t = 25.71$, $P < 0.001$). Asthmatics received antibiotics more often for all diagnoses. The more frequent receipt of antibiotics was true for conditions related to the respiratory tract (e.g., upper respiratory infection and bronchitis) as well as for conditions unrelated to the respiratory tract (e.g., urinary tract infection and acne). A diagnosis of asthma significantly increased the likelihood of a prescribed antibiotic by 26% to 86%.

CONCLUSION: This study demonstrated that pediatric asthmatic patients received significantly more antibiotic prescriptions than nonasthmatics for conditions caused by bacteria as well as for conditions more likely to be viral in origin. In this era of concern about the widespread use of antibiotics and consequent antimicrobial resistance, further research needs to be conducted concerning the appropriateness of antibiotics in the treatment of asthma. Studies on the appropriate use of antibiotics in asthma could help reduce the overall use of antibiotics in children.

KEYWORDS: Children, Asthma, Antibiotics

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Inappropriate antibiotic use is a well-recognized public health problem because of its association with the emergence of resistant bacteria.[1-4] It also is a source of unnecessary health care costs and of potentially severe adverse drug reactions.[5-6] The Centers for Disease Control and Prevention (CDC) and other national organizations such as the American Academy of Family Physicians and the American Academy of Pediatrics actively promote judicious use of antibiotics in populations such as children who have a historically high rate of antibiotic use.[7-10] In addition, previous studies have attempted to determine the patterns of behavior that influence the misuse of antibiotics by physicians.[11]

The latest data from the National Ambulatory Medical Care Survey (NAMCS) did find decreasing trends in both the population- and visit-based antimicrobial prescription rates overall, and for respiratory tract infections for children and adolescents seen by office-based physicians. However, antibiotics were still prescribed inappropriately for diagnoses most likely due to viral infection such as colds, upper respiratory tract infection (URI), and bronchitis.[12] Other studies in children and adults have noted similar misuse of antibiotics.[13-15]

A diagnosis of asthma may further complicate the physician's decision to use or not use antibiotics for respiratory tract infections.[16-18] Although there are no evidence-based indications for the use of antibiotics in the treatment of asthma in the absence of comorbid bacterial conditions, physicians might feel more pressure to prescribe them to children with this common chronic disease. However, the National Asthma Education and Prevention Program Expert Panel Report, "Guidelines for the Diagnosis and Management of Asthma, Update on Selected Topics 2000," states, "Antibiotics are not recommended for the treatment of acute asthma exacerbations except as needed for comorbid conditions—e.g., for those patients with fever and purulent sputum, evidence of pneumonia, or suspected bacterial sinusitis." In addition, patients with asthma might present to the physician more often with respiratory complaints.

The objectives of this study were to (a) determine if antimicrobial prescription utilization rates are higher for pediatric patients with asthma than a matched comparison group and (b) identify common variables (gender and age) that might explain higher antibiotic utilization rates within specific diagnostic categories between children.

Methods

We conducted a retrospective cohort study in the southeastern United States of children with asthma (age range 5 to 18 years)

who were enrolled in a large health plan, including indemnity, preferred provider organization (PPO), and health maintenance organization (HMO) lines of service, from January 1, 2000, to December 31, 2002. To be included, all patients had to be continuously enrolled for at least 2 years and have pharmacy benefit coverage. Total enrollment in the health insurance plan is measured according to the number of members enrolled as of December 31 of each year. The HMO/point-of-service (POS) line of business had 579,567 enrolled in 2000, 659,314 enrolled in 2001, and 735,502 enrolled in 2002. The PPO line of business had 447,446 enrolled in 2000, 554,775 enrolled in 2001, and 740,717 enrolled in 2002. Continuous enrollment is defined as being enrolled in the health plan for at least 24 months without gaps in coverage.

Asthmatic patients were identified if they had 1 of the following: (a) 1 hospitalization or 1 visit to the emergency department with an asthma code (Common Procedural Terminology [CPT] 493.xx); (b) 2 or more outpatient visits with a 493.xx code; (c) 2 or more pharmacy claims for the following medications: inhaled fluticasone/salmeterol (Advair), inhaled triamcinolone (Azmacort), inhaled fluticasone (Flovent), inhaled budesonide (Pulmicort Turbohaler), inhaled budesonide (Pulmicort Respules), inhaled betahethasone (Vanceril), inhaled albuterol, nebulized albuterol, oral albuterol, inhaled pirbuterol (Maxair), inhaled formoterol (Foradil), inhaled salmeterol (Serevent), oral zafirlukast (Accolate), oral montelukast (Singulair), inhaled cromolyn, inhaled nedocromil, oral theophylline; or (d) 1 or more pharmacy claims for oral prednisolone *and* 1 of the above-listed medications. Patients could be identified by more than 1 criterion. Antibiotic use was identified by selecting National Drug Code (NDC) codes for antibiotics listed in oral forms in *The Harriet Lane Handbook*.[19] Any antibiotic with only nonrespiratory indications was excluded from analysis (i.e., metronidazole and nitrofurantoin).

To control for the effects that age, sex, geographical region, or insurance product line may have had on prescribing rates of antibiotics in children with asthma, a comparison group was created matched according to age, sex, regional codes, and insurance product line (indemnity, PPO, or HMO). Regional codes indicate specific "local market" areas. Each region code represents a specific geographic area of the state of Georgia. Each member's region code is based on his or her place of residence. Product line provides an indication of the member's benefit structure. The *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes[20] (ICD-9-CM) for the 5 respiratory tract infections studied were (1) otitis media, 381.0, 381.4, 382.0, 382.4, and 382.9; (2) pharyngitis, 034.0, 462, and 463; (3) sinusitis, 461 and 473; (4) bronchitis, 466.0 and 490; and (5) URI, 465, and common cold, 460. These are the same codes identified in the NAMCS data. A second category, including pneumonia (480-486), urinary tract infection (UTI; 595.0, 595.9, and 599.0), chlamydial cervicitis (099.53), gonococcal cervicitis (098.15), and acne (706.1), was also included in the analysis as an attempt to link antibiotic use with other diagnoses for which antibiotics are appropriate.

Visit codes were considered to be linked to an antibiotic fill if the medical visit was in the range of 5 days prior to or 1 day after an antibiotic fill. If more than 1 diagnosis was recorded for an encounter, we assigned a primary diagnosis, giving priority to a potential bacterial source. (For example, if URI and otitis media were coded, the latter was designated "primary.") All follow-up and medical visits not in the range of 5 days prior or 1 day after an antibiotic fill were excluded from analysis.

Statistical Analyses

All variables reflect rates or means per patient per year (PPPY) due to the fact that subjects had varying lengths of time for which claims data were available in the 3-year period. Each rate or mean PPPY was determined using a weighted average of each subject's data over 3 years. Rates and sums were determined for each year and the corresponding number of months the subject contributed data to a particular year. The weights were the inverse of the number of months per year per subject. Thus, the weighted average of each rate or mean across the 3 years was calculated using the total number of months with available data as the denominator for each subject. Descriptive statistics were calculated on all variables. To examine univariate differences between asthmatics and nonasthmatics in demographics (sex, marital status of home, and line of business), utilization (inpatient, outpatient, and office and emergency room visits), paid costs (total, facility, provider, and prescription), number of inappropriately prescribed antibiotics, number of appropriately prescribed antibiotics, and any prescribed antibiotic overall and by diagnosis, chi-square tests or *t* tests were used.

Logistic regression was used to examine age, sex, asthma status, the interaction between age and asthma status, and the interaction between sex and asthma status on each of the diagnoses of interest for which an antibiotic was prescribed. Data were analyzed using SAS statistical software (SAS version 8.2), and statistical significance was assessed using an alpha level of 0.05.

Results

The cohort included 5,856 asthmatics and 5,195 nonasthmatics. Of the 5,856 asthmatics, 748 (12.8%) had at least 1 inpatient or emergency room visit with an ICD-9-CM code for asthma, 2,415 (41.2%) had 2 or more outpatient visits with an ICD-9-CM code for asthma, 5,061 (85.7%) had 2 or more pharmacy claims for the specified asthma medications, and 435 (7.4%) had 1 or more pharmacy claims for oral prednisolone and 1 of the specified asthma medications. Patients could have more than 1 indication category for asthma (e.g., 1 inpatient visit with an ICD-9-CM code for asthma and a pharmacy claim

for 2 or more of the specified medications); thus the percentages of patients with individual criteria exceed 100%.

The gender distribution was similar for both populations (asthmatics 41.6 % female and nonasthmatics: 42.2% female). Age distribution was also similar between the 2 groups (Table 1). Table 2 lists the 4 inclusion criteria and how many patients within the study cohort fell into each category. The inclusion criteria were not mutually exclusive, and there were patients who were retained by more than 1 inclusion criterion.

Table 3 reports the average use of selected health care services. Asthmatics consistently received significantly more services, including a mean of 1.74 (SD 1.82) antibiotics PPPY compared with a mean of 0.96 (SD 1.32) antibiotics PPPY for nonasthmatics (t = 25.71, P <0.001). Specifically, female asthmatics were prescribed a mean of 1.88 (SD 1.88) antibiotics and male asthmatics were prescribed a mean of 1.63 (SD 1.78) antibiotics, while control females were prescribed 0.97 (SD 1.26) antibiotics and control males were prescribed 0.96 (SD 1.36) (analysis of variance [ANOVA] F (normal distribution function [ndf]=1, desirable degrees of freedom [ddf]=11,050) for interaction between asthma and sex = 13.94, P <0.001) Asthmatic females had significantly higher mean numbers of antibiotics prescribed than all other groups (Tukey-Kramer adjusted P <0.001 for each pair-wise comparison) and asthmatic males had significantly higher mean numbers of antibiotics prescribed than control females (Tukey-Kramer adjusted P <0.001) and control males (Tukey-Kramer adjusted P <0.001). Control male and female patients did not have significantly different mean numbers of antibiotics prescribed (Tukey-Kramer adjusted P = 0.988).

Primary diagnoses related to the prescription of antimicrobial agents are presented in Table 4. The upper half of the table shows that for all diagnoses of interest in this study, other than chlamydia, individuals with asthma were significantly more likely to fill a prescription for an antibiotic than were those individuals without asthma. The last line of the table shows that individuals with asthma were also more likely to fill a prescription for an antibiotic for the all diagnoses other than those specifically included in the study. The lower half of Table 4 shows that individuals with asthma were more likely to have an episode of health care with a diagnosis of URI, bronchitis, sinusitis, and pneumonia and not fill a prescription for an antibiotic.

Table 5 gives the logistic regression results for each of the diagnoses for which an antibiotic was prescribed, examining age, sex, asthma status, the interaction between age and asthma status, and the interaction between sex and asthma status. For URI, pharyngitis, and otitis media, there were no statistically significant interactions. For each of these models the main effects of age, sex, and asthma status were statistically significant, indicating that those with a diagnosis for which an antibiotic was prescribed were more likely to be female, more likely to have asthma, and less likely to be in the 11-to-14 age group compared with the 5-to-10 age group. For bronchitis, sinusitis, and pneumonia, significant interactions were detected, and thus the main effects cannot be interpreted. For bronchitis and sinusitis, a significant interaction between sex and asthma status was found, with those having a diagnosis for which an antibiotic was prescribed being more likely to be female asthmatics. A significant interaction between age and asthma

TABLE 1 Baseline Characteristics of Asthmatics and Comparison Group*

Variable	Asthmatics N	Asthmatics %	Nonasthmatics N	Nonasthmatics %	*P* Value
Sex					0.565
Female	2,437	41.6	2,190	42.2	
Male	3,419	58.4	3,005	57.8	
Age group					0.642
5-10 years	2,204	37.6	2,000	38.5	
11-14 years	1,919	32.8	1,684	32.4	
15-18 years	1,733	29.6	1,511	29.1	

** There were 5,856 persons in the asthmatics group and 5,195 in the nonasthmatics group.*

TABLE 2 Patient Inclusion Criteria

Criteria Applied*	Number (%) of Patients Retained
1. Identification of patients with at least 1 inpatient or emergency room visit with an ICD-9 code for asthma	748 (12.8)
2. Identification of patients with 2 or more outpatient visits with an ICD-9 code for asthma	2,415 (41.2)
3. Identification of patients with 2 or more pharmacy claims for specific asthma medications	5,061 (85.7)
4. Identification of patients with 1 or more pharmacy claim for oral prednisolone *and* 1 of the specific asthma medications	435 (7.4)

** Patients can be retained by more than one criterion.*
ICD-9=International Classification of Diseases, Ninth Revision.

TABLE 3 Prescription and Medical Visit Utilization for Asthmatics and Nonasthmatics per Patient per Year*

Variable	Asthmatics N	Asthmatics %	Nonasthmatics N	Nonasthmatics %	*P* Value
Number of study years	2.85	0.30	2.92	0.23	<0.001
Number of medical visits	5.70	5.69	2.94	3.26	<0.001
Number of total pharmacy claims	9.14	8.89	3.50	5.38	<0.001
Number of antibiotic claims	1.74	1.82	0.96	1.32	<0.001
% of antibiotic claims	19.0		27.4		
Pharmacy claims per medical visit	1.60		1.19		
Antibiotic claims per medical visit	0.31		0.33		

** There were 5,856 persons in the asthmatics group and 5,195 in the nonasthmatics group.*

TABLE 4 Descriptive Statistics and Univariate Tests for Asthmatics and Nonasthmatics

Variable	Asthmatics (N = 5,856)		Nonasthmatics (N = 5,195)		Odds Ratio (95% CI)
	No. of Individuals	%	No. of Individuals	%	
Antibiotic prescribed for diagnosis*					
URI	1,831	31.3	937	18.1	2.07 (1.89-2.26)
Bronchitis	1,701	29.1	574	11.1	3.30 (2.97-3.66)
Pharyngitis	2,976	50.8	2,062	36.7	1.57 (1.46-1.69)
Sinusitis	2,324	39.7	1,174	22.6	2.25 (2.07-2.45)
Otits media	1,575	26.9	1,006	19.4	1.53 (1.40-1.68)
UTI	336	5.7	192	3.7	1.59 (1.32-1.90)
Chlamydia	1	0.0	0	0.0	
Acne	495	8.5	352	6.8	1.27 (1.10-1.46)
Pneumonia	744	12.7	298	5.7	2.39 (2.08-2.75)
No antibiotic prescribed for diagnosis†	4,343	74.2	2,796	53.8	2.46 (2.27-2.67)
URI	1,820	41.9	943	33.7	1.42 (1.28-1.56)
Bronchitis	869	20.0	255	9.1	2.49 (2.15-2.89)
Pharyngitis	2,313	53.3	1,494	53.3	0.99 (0.90-1.09)
Sinusitis	1,024	23.6	465	16.6	1.55 (1.37-1.75)
Otitis media	710	16.4	483	17.3	0.94 (0.82-1.06)
UTI	266	6.1	152	5.4	1.13 (0.92-1.39)
Chlamydia	1	0.0	0	0.0	
Acne	444	10.2	304	10.9	0.93 (0.80-1.09)
Pneumonia	555	12.8	229	8.2	1.64 (1.40-1.93)
Antibiotic for other diagnosis‡	4,235	72.3	2,695	51.9	2.42 (2.24-2.62)

Note: An individual could potentially have multiple medical claims for the same diagnosis during the 3-year study time period. For each of these medical claims, an antibiotic may or may not have been prescribed.

* *The number of individuals with at least 1 medical claim for each diagnosis during the study time period for which an antibiotic was prescribed.*

† *The number of individuals with at least 1 medical claim for each diagnosis during the study time period for which an antibiotic was not prescribed.*

‡ *The number of individuals with at least 1 medical claim during the study time period for which an antibiotic was prescribed for a diagnosis other than one of the target diagnoses.*

CI = confidence interval; Rx = prescription; URI = upper respiratory infection; UTI = urinary tract infection.

was not detected for bronchitis or sinusitis, and thus the main effect for age can be examined. For both bronchitis and sinusitis, age was significant, and those in the 11-to-14 age group were less likely to have a diagnosis of bronchitis for which an antibiotic was prescribed than those in the 5-to-10 age group. For pneumonia, a significant interaction between age and asthma status was found, with those having a pneumonia diagnosis for which an antibiotic was prescribed being less likely to be asthmatics in the 11-to-14 age group.

Discussion

We have demonstrated that pediatric asthma patients receive antibiotics significantly more frequently than do pediatric patients who do not have asthma. This includes receiving antibiotics appropriately for conditions such as otitis media and sinusitis, which are more likely to be caused by bacteria, but also receiving antibiotics inappropriately for conditions more likely to be viral in origin, such as URI, bronchitis, and the common cold. Additionally, pediatric patients with asthma presented to the physician more often with these complaints. This suggests that patients with asthma perhaps suffer more respiratory infections or that their parents bring them to the physician more than nonasthmatics when they have respiratory complaints. Unfortunately, the data available for this study did not allow us to determine which of these 2 possible explanations was more probable.

We found higher antibiotic use among female subjects with asthma for all the respiratory tract diagnoses except for pneumonia (URI, bronchitis, pharyngitis, sinusitis, and otitis media). Previous studies have also noticed gender differences in asthma management.[21] It has been suggested that girls with asthma may experience less wheezing and more night-time cough than boys and, therefore, may be treated more often for secondary diagnoses rather than receiving aggressive management of their asthma.[22-24] Also, female patients report greater asthma-related hardship. They rate their intensity of symptoms higher than male subjects and report lower quality of life related to their asthma.[24] These perceptions may influence how often they present to the physician and how often the physician prescribes antibiotics. Previous studies have documented that female subjects receive fewer inhaled steroids than male subjects, thus resulting in less treatment for the airway inflammation that underlies the disease.[21] Of interest, middle-school-aged patients were often less likely to receive antibiotics than their older counterparts in our study.

Limitations

Although the validity of using ICD-9-CM codes to identify diseases of interest has been shown, and several similar studies have used data such as ours, there are limitations of our study related to the use of coding data.[25-29] The first limitation is the high number of antibiotics dispensed that we could not link to a diagnosis. When we could not link an antibiotic to a diagnosis, we could not include the event in our analyses. However, more antibiotics were given to asthmatics than nonasthmatics, reflecting the patterns seen when antibiotics were associated with a diagnosis. Also, we do not know if any antibiotics were prescribed that were filled without a pharmacy claim being filed. We feel that few antibiotic prescriptions were filled without a payment claim, but we have no way to verify this opinion.

An additional limitation of our study was the use of matching for potential confounding variables that may have resulted in our control population's differing from the population of all children who do not have asthma. Additionally, our population only includes 1 group of children insured by a single company

TABLE 5 *Odds Ratios From Multivariable Logistic Regression of Age Groups, Sex, and Asthma on Diagnoses for Which an Antibiotic Was Received*

Diagnosis	Age 11-14 Years (Referent 5-10 Years)	Age 15-18 Years (Referent 5-10 Years)	Female Sex	Asthma	Age 11-14 Years + Asthma	Age 15-18 Years + Asthma	Female Sex + Asthma
URI	0.72† 0.67-0.77	1.01 0.94-1.08	1.08† 1.03-1.13	1.47† 1.40-1.54	1.07 0.99-1.14	1.00 0.94-1.07	1.01 0.97-1.06
Bronchitis	0.82† 0.76-0.89	0.95 0.88-1.03	0.95 0.90-1.00	1.96† 1.76-1.96	1.02 0.94-1.10	1.03 0.96-1.12	1.06* 1.01-1.11
Pharyngitis	0.61† 0.57-0.64	1.02 0.97-1.08	1.17† 1.12-1.21	1.28† 1.23-1.33	1.00 0.94-1.06	1.00 0.94-1.05	1.03 0.99-1.7
Sinusitis	0.91 0.85-0.97	0.99 0.93-1.05	1.10† 1.05-1.14	1.51† 1.45-1.58	0.99 0.93-1.06	1.00 0.94-1.06	1.05† 1.01-1.10
Otitis media	0.56† 0.52-0.60	1.00 0.93-1.07	1.07† 1.02-1.12	1.26† 1.20-1.32	1.00 0.93-1.08	1.02 0.96-1.10	0.99 0.94-1.04
Pneumonia	0.73† 0.65-0.82	1.05 0.95-1.16	1.02 0.95-1.09	1.49† 1.39-1.61	0.88† 0.79-0.98	0.98 0.88-1.08	0.96 0.90-1.03

** P value less than 0.05.*
† P value less than 0.01.
URI=upper respiratory infection.

in 1 state; thus, our results may not be generalizable across the country. Also, within our study group of patients we were not able to obtain demographic data on race, socioeconomic class, or urban versus suburban residence, all of which are known to affect asthma rates and care. However, we did attempt to minimize demographic differences between our patients and the control group by matching for insurance type and regional codes (regional divisions within the state assigned by the managed care organization). We also were not able to estimate the severity of asthma in each patient. It is possible that there are subgroups of asthmatics that are responsible for the majority of the increased use of antibiotics. Unfortunately, the limitations of the data source (administrative claims) did not allow us to meaningfully subdivide the study subjects further.

Conclusion

This research, using administrative medical and pharmacy claims, found that asthmatic children are significantly more likely to receive antibiotics than their nonasthmatic counterparts and that girls with asthma receive more antibiotics than boys. This conclusion adds weight to the concern about the widespread use of antibiotics and subsequent resistance. Our study did not address the indications for antibiotic use in children with asthma or the reasons that antibiotics are prescribed more often for patients with asthma. While we found a higher rate of use of antibiotics in children with asthma, we are not able to determine if these antibiotic pharmacy claims represent either appropriate or inappropriate use. Also left to future research is identification of the interventions that should be instituted to decrease inappropriate antibiotic use in pediatric asthmatic patients. Since asthma is so common, guidelines on the appropriate use of antibiotics in asthma may help reduce the overall use of antibiotics in children.

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