Relationship Between Asthma Medication and Antibiotic Use*

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Study objectives: Increasing morbidity due to asthma and antimicrobial resistance among human pathogens are both major public-health concerns. Numerous studies describe the overuse of antibiotics in general populations and underuse of anti-inflammatory medications by asthmatic patients. However, little is known about the relationship between asthma medication and antibiotic use in asthmatics. Specifically, we tested the hypothesis that higher use of bronchodilator and anti-inflammatory medication by asthmatics, as a marker of problematic asthma, is associated with greater antibiotic use. We also test the hypothesis that physicians who are low prescribers of anti-inflammatory medications are high prescribers of antibiotics.

Design: We conducted a retrospective cohort study evaluating asthma medication and antibiotic use by children and adults with asthma and the prescribing of these medications by primary-care physicians.

Setting/patients: Subjects were continuously enrolled asthma patients aged 6 to 55 years receiving care in an urban, group-model, health maintenance organization.

Interventions: None.

Measurement and results: Main outcome measures were (1) antibiotic use by asthmatics stratified by low, moderate, and high bronchodilator use; (2) antibiotic use by asthmatics stratified by no, intermittent, and long-term anti-inflammatory use; and (3) correlation between physician-level anti-inflammatory agent to bronchodilator ratio (AIF:BD) and their rate of antibiotic prescribing. We found that (1) high bronchodilator users received 1.72 antibiotics per person-year (95% confidence interval [CI], 1.62 to 1.83), whereas low bronchodilator users received 1.23 antibiotics per person-year (95% CI, 1.19 to 1.27; p < 0.0001); (2) long-term users of anti-inflammatory agents received 1.85 antibiotics per person-year (95% CI, 1.76 to 1.95), whereas those not receiving an anti-inflammatory agent received 0.95 antibiotics per person-year (95% CI, 0.90 to 1.00; p < 0.0001); and (3) despite variations in physician AIF:BDs and antibiotic prescribing, respectively, these measures were not correlated.

Conclusions: Antibiotic use and asthma medication use are positively associated in a cohort of asthma patients. Greater effort is needed to define the appropriate role of antibiotics in asthma management. (CHEST 2001; 120:1485–1492)

Key words: antibiotics; asthma; physician profiling

Abbreviations: AIF:BD = anti-inflammatory agent to bronchodilator ratio; CI = confidence interval; HMO = health maintenance organization

Asthma is the most common chronic disease of childhood and a major cause of work loss among adults. Antibiotics are among the most commonly prescribed medications by office-based physicians. The ubiquitous use of antibiotics contributes to the growth of antimicrobial resistance in human pathogens. Evidence is accumulating of the contribution of suboptimal prescribing patterns to these growing public-health challenges. The use and overuse of antibiotics exert a selective pressure for the emergence of resistant bacteria. Conversely, the underuse of anti-inflammatory medications by asthmatics,
through nonprescription and nonadherence, contributes to preventable morbidity.1–6

The overuse of antibiotics and underuse of anti-inflammatory medications may be related. Respiratory tract infections are a common trigger of asthma exacerbations, especially in persons with poorly controlled asthma. Symptoms of asthma may be severe because of either the severity of the underlying disease or insufficiency of treatment relative to the severity of the patient’s asthma. Such individuals may seek medical intervention for these exacerbations, whatever the mechanism contributing to their symptoms, and thereby may be more likely to receive antibiotics.

Symptoms associated with poor control of chronic asthma overlap with symptoms for which physicians often prescribe antibiotics, such as chronic productive cough or bronchial congestion,7 which is another mechanism that may increase the frequency with which patients with problematic asthma control are prescribed antimicrobial therapy. Appropriate prescribing of antibiotics for respiratory tract infections and of anti-inflammatory agents for asthma symptoms depends on both the judgment and skill of the physician. Variation in physician prescribing practices is likely to be greater in areas of relative clinical uncertainty. It is therefore plausible that key attributes, such as adherence to guidelines or evidence-based decision making, mediate how physicians manage these common clinical problems and that performance in these domains, reflected in their prescribing patterns, may be correlated.

These observations lead to the primary hypotheses for the proposed study: (1) asthmatics with evidence of problematic control, measured by asthma medication use, will receive more antibiotics than those with better control; (2) increased use of anti-inflammatory medications relative to bronchodilators will be associated with decreased use of antibiotics; and (3) physicians who prescribe less anti-inflammatory medication will tend to prescribe more antibiotics to asthmatics.

Materials and Methods

We conducted a retrospective cohort study of the population with asthma (age range, 6 to 55 years) who were receiving care at one of 14 practices of a group-model health maintenance organization (HMO) from January 1, 1996, through December 31, 1997. Asthmatic patients were identified if they had either (1) a hospitalization or an emergency department visit with a primary diagnosis of asthma (International Classification of Diseases code 493), or (2) an outpatient visit with asthma as the primary diagnosis or insufficiency of treatment relative to the severity of the patient’s asthma. Such individuals may seek medical intervention for these exacerbations, whatever the mechanism contributing to their symptoms, and thereby may be more likely to receive antibiotics. Only those medications dispensed at HMO on-site pharmacies are included in our analysis. Approximately 90% of members have prepaid drug coverage available for a nominal co-payment at health-center pharmacies. The patient-level analysis evaluated all bronchodilators, anti-inflammatory agents, and antibiotics prescribed to the asthma cohort; the physician-level analysis evaluated only the subset of these medications prescribed to cohort members by staff-level primary-care physicians. Anti-inflammatory medications included nebulized and inhaled cromolyn, nedocromil, and inhaled steroids. Salmeterol, the leukotriene modifiers, and ipratropium were not included in our analysis because initial analysis showed that they were used infrequently during the study period.

Canister equivalents for nebulized bronchodilators and inhaled and nebulized anti-inflammatory medications were created on the basis of expected duration of supply with typical dosages. This method corrects for differences in days of medication supplied by various anti-inflammatory preparations at standard dosages and for the use of bronchodilators administered by a metered-dose inhaler vs a nebulizer. We defined one canister equivalent of a bronchodilator as one canister of albuterol and considered 2.5 mg of nebulized albuterol equivalent to two puffs of the metered-dose inhaler. Oral bronchodilators were dispensed infrequently; hence, one dispensing of an oral formulation was treated as one canister equivalent regardless of the quantity dispensed.

For anti-inflammatory medication, we estimated the defined daily dose as the median number of daily puffs recommended by the 1997 National Heart, Lung, and Blood Institute guidelines for a person with mild persistent asthma. The expected days supplied was obtained by dividing the number of puffs per canister by the defined daily dose. The canister equivalent for each inhaled anti-inflammatory preparation was then determined by forming a ratio of the expected days supply to the beclomethasone 42-μg/puff preparation. For example:

\[
\text{beclomethasone } 42 \mu g = (120 \text{ puffs per canister})/(2 \text{ puffs per day}) = 60 \text{ days}
\]

\[
\text{beclomethasone } 42 \mu g = (200 \text{ puffs per canister})/(8 \text{ puffs per day}) = 25 \text{ days}
\]

We assigned one canister equivalent to all asthma medications comprising <1% of the total number of medications dispensed in its respective drug class (ie, for bronchodilators, pirbuterol comprised <1% of the total dispensed). Further details of the canister-equivalents conversion method are available on request.

We stratified subjects by bronchodilator use: (1) low users: zero to five canister equivalents per person-year; (2) moderate users: more than five to eight canister equivalents per person-year; and (3) high users: more than eight canister equivalents per person-year. We also stratified subjects by anti-inflammatory medication use: (1) none; (2) intermittent: zero to five canister equivalents per person-year; and (3) long-term: more than five canister equivalents per person-year.

We compared the mean number of antibiotic prescriptions per person-year among the three bronchodilator strata and the three anti-inflammatory strata. We also conducted these analyses for both the pediatric (6 to 16 years old) and adult (17 to 55 years old) asthma populations. Secondary analyses explored potential gender differences in the use of asthma medications and antibiotics. Antibiotics were identified through the American Hospital Formulary System codes for antibiotics in ambulatory use. Specific antibiotics that had only nonrespiratory indications were excluded from analysis (ie, metronidazole, nitrofurantoin, and minocycline).

We explored the impact of increased anti-inflammatory use on the relationship between bronchodilator and antibiotic use. We restricted this analysis to high bronchodilator users (more than...
eight canister equivalents per person-year) for whom anti-inflammatory medication is both indicated and beneficial.

To explore the relationship between the prescribing of asthma medications and antibiotics by physicians, we calculated the anti-inflammatory agent to bronchodilator ratio (AIF:BD) for each staff primary-care physician treating at least 25 asthma patients during the study period. The automated pharmacy data link each dispensing to the prescribing physician by a unique physician identifier. Only medications prescribed by these physicians were included in this physician-level analysis. The AIF:BD is a proposed measure of appropriate prescribing of asthma medications.9 Calculation of the AIF:BD was based on the canister-equivalent methodology. Physician prescribing of antibiotics was expressed as the number of antibiotics dispensed divided by the number of unique asthmatics treated. Within the physician cohort, the AIF:BD was correlated with the rates of antibiotic prescribing.

**Anti-inflammatory Use**

Subjects received a mean of 3.4 prescriptions for anti-inflammatory preparations per person-year. Most subjects (65.4%) received an anti-inflammatory prescription (Table 2). Adults were more likely than children to be long-term users of anti-inflammatory medications (27.7% vs 16.1%, respectively). Most patients with moderate (89.3%) and high (91.3%) bronchodilator use also received an anti-inflammatory prescription; 61.4% of high bronchodilator users were receiving an anti-inflammatory medication on a long-term basis. These percentages were comparable for adults and children.

**Antibiotic Use**

Seventy-five percent of subjects were prescribed an antibiotic during the study period. Subjects received an average of 1.3 antibiotic prescriptions per person-year (range, 1 to 31 prescriptions). This excludes 4.3% of dispensed antibiotics prescribed for strictly nonrespiratory indications. The most commonly prescribed antibiotic classes are presented in Table 3.

We detected significant gender differences in the receipt of antibiotics, bronchodilators, and anti-inflammatory medications. Antibiotics were prescribed more frequently for girls than for boys (1.20/person-year vs 1.04/person-year, p < 0.0007). Antibiotics were also prescribed more frequently for women than for men (1.60/person-year vs 1.15/person-year, p < 0.0001). However, men received more intensive asthma pharmacotherapy than did women. Men received more anti-inflammatory prescriptions (4.48/person-year vs 3.72/person-year, p < 0.0001) and more bronchodilators (6.51/person-year vs 4.43/person-year, p < 0.0001) than did women. Boys tended to receive more anti-inflammatory medications than did girls, but the difference was not statistically significant (2.47/person-year vs 2.03/person-year, p > 0.09). Boys and girls did not differ with regard to bronchodilator use.

Antibiotic use significantly increased with higher use of anti-inflammatory and bronchodilator medication. High bronchodilator users received 40% more antibiotics per person-year than did low bronchodilator users, 1.72/person-year (95% confidence

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**Table 1—Bronchodilator Use in Asthmatics**

<table>
<thead>
<tr>
<th>Level of Use</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Low, 0–5 canister equivalents/yr</td>
<td>5,494 (75.2)</td>
</tr>
<tr>
<td>Moderate, &gt; 5–8 canister equivalents/yr</td>
<td>605 (8.3)</td>
</tr>
<tr>
<td>High, &gt; 8 canister equivalents/yr</td>
<td>1,211 (16.6)</td>
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</tbody>
</table>

**Table 2—Anti-inflammatory Use in Asthmatics**

<table>
<thead>
<tr>
<th>Level of Use</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2,530 (34.6)</td>
</tr>
<tr>
<td>Intermittent, 0–4 canister equivalents/yr</td>
<td>3,045 (41.7)</td>
</tr>
<tr>
<td>Long-term, &gt; 4 canister equivalents/yr</td>
<td>1,735 (23.7)</td>
</tr>
</tbody>
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interval [CI], 1.62 to 1.83) vs 1.23/person-year (95% CI, 1.19 to 1.27) \(p < 0.0001;\) Fig 1]. Long-term anti-inflammatory users received 95% more antibiotics per person-year than did those who did not use anti-inflammatory medications: 1.85/person-year (95% CI, 1.76 to 1.95) vs 0.95/person-year (95% CI, 0.90 to 1.00) \(p < 0.0001;\) Fig 2]. These relationships were essentially unchanged when we restricted the analysis to pediatric or adult subgroups (data not shown).

We hypothesized that increasing the use of anti-inflammatory medication relative to use of bronchodilators would be associated with decreased use of antibiotics. We restricted the analysis to subjects who were dispensed more than eight bronchodilators per person-year. Similar to the entire cohort, long-term anti-inflammatory users were significantly more likely to receive antibiotics than were subjects using anti-inflammatory medications intermittently or not at all (1.93 antibiotics/person-year vs 1.62/person-year and 1.35/person-year, \(p < 0.0001\)). We also calculated the AIF:BD for each subject \((n = 1,045)\) dispensed at least four canisters per person-year of each medication class. We correlated this patient-level AIF:BD to the number of antibiotics received per year. Patient-level AIF:BD was positively correlated \((r = 0.078; p < 0.01)\) to antibiotic use.

### Physician Prescribing of Asthma Medications and Antibiotics

We limited our analysis to staff-level primary-care physicians because they provided ongoing management for chronic asthma. There were 265 staff primary-care physicians, of whom 197 treated at least 25 asthma patients during the study period. These 197 physicians treated a mean of 57 asthma patients and prescribed 44.1% of the bronchodilators, 33.2% of the anti-inflammatory medications, and 36.3% of the antibiotics received by patients with asthma. Sixty-two percent of primary-care physicians were internists; 38% were pediatricians. Internists prescribed more antibiotics per asthma patient than pediatricians (0.69/treated-patient vs 0.58/treated-patient, respectively; \(p < 0.003\)). Internists had lower AIF:BD than pediatricians, but this did not reach statistical significance (0.58 vs 0.68, \(p > 0.10\)).

Two percent of anti-inflammatory prescriptions, 1% of bronchodilator prescriptions, and 5% of antibiotic prescriptions were missing prescribing physician identification. When the analysis was restricted to antibiotics missing prescribing physician identification, the overall relationship among bronchodilator, anti-inflammatory medication, and antibiotic use, respectively, was unchanged.

There was variability both in physician AIF:BD and the number of antibiotics prescribed per patient treated. The mean physician AIF:BD was 0.61 (interquartile range, 0.42 to 0.77). These physicians prescribed a mean of 0.65 antibiotics per treated asthma patient (interquartile range, 0.48 to 0.79). There was no correlation between these physician-prescribing measures \((r = -0.01; p < 0.87)\). Re-

### Table 3—Antibiotics Prescribed to Asthma Population, 1996–1997

<table>
<thead>
<tr>
<th>Drug Names</th>
<th>No. of Prescriptions (%</th>
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<tbody>
<tr>
<td>Amoxicillin</td>
<td>5,984 (31.8)</td>
</tr>
<tr>
<td>Erythromycin preparations*</td>
<td>2,976 (15.7)</td>
</tr>
<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>2,633 (13.9)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>2,137 (11.3)</td>
</tr>
<tr>
<td>Doxycycline/tetracycline</td>
<td>1,199 (6.3)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1,175 (6.2)</td>
</tr>
<tr>
<td>Azithromycin/clarithromycin</td>
<td>881 (4.7)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>750 (4.0)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>573 (3.0)</td>
</tr>
<tr>
<td>Other</td>
<td>451 (2.4)</td>
</tr>
</tbody>
</table>

*Includes 189 erythromycin ethylsuccinate prescriptions.

\[\text{Figure 1. Antibiotic use stratified by level of bronchodilator use; PY = person-year.}\]
stricting this analysis to internists and pediatricians, respectively, yielded similar results. There was also no correlation between the overall number of bronchodilators prescribed by physicians and their rate of antibiotic prescribing ($r = 0.039; p < 0.58$) or between the overall number of anti-inflammatory medications prescribed by physicians and their rate of antibiotic prescribing ($r = -0.004; p < 0.89$).

**Discussion**

We have demonstrated that asthma patients dispensed more anti-inflammatory medication and bronchodilators have higher rates of antibiotic use. Specifically, asthmatics with higher levels of anti-inflammatory medication use received almost twice as many antibiotics as those asthmatics who did not receive an anti-inflammatory prescription. Similarly, subjects with more symptomatic asthma, as evidenced by high levels of bronchodilator use, received 40% more antibiotics than did subjects whose bronchodilator use was consistent with intermittent asthma. However, our hypothesis that increasing anti-inflammatory use relative to bronchodilator use would be associated with decreased antibiotic use proved incorrect. In fact the opposite relationship emerged: anti-inflammatory use remained positively associated with antibiotic use among high users of bronchodilators.

We found higher antibiotic and lower anti-inflammatory use among female subjects with asthma. These differences may reflect gender differences in asthma phenotype or management. Boys may experience more typical asthma symptoms, such as wheezing, than girls because of the smaller airway diameter relative to lung volume (dysanapsis) in boys.12-14 This difference may contribute to the higher prevalence and more aggressive treatment of asthma in boys. Girls with asthma, in contrast, may experience more night cough than boys.15 Predominance of cough relative to wheeze may contribute to the increased prescribing of antibiotics to female patients. Despite differences in asthma phenotype in male and female patients, female patients report greater asthma-related hardship. In a comparable population of HMO-enrolled asthmatics, the intensity of symptoms was greater in female than in male subjects of all ages and asthma quality-of-life scores were lower in female than in male subjects.15 It is a concern that women experience greater impairment from asthma than do men, yet they receive more treatment aimed at symptoms, antibiotics, and less treatment for the airway inflammation that underlies the disease.

Despite the central role of physician prescribing in these treatment patterns, we found no correlation between the AIF:BD for physicians and their rates of antibiotic prescribing. Nevertheless, we detected variability in the prescribing by physicians of both asthma medications and antibiotics. Despite restricting the analysis to primary-care staff physicians who treated an average of 57 asthma patients, there was over fourfold difference in the AIF:BD between physicians at the 95th percentile and those at the fifth percentile and over a threefold difference in antibiotic prescribing rate, respectively. We cannot quantify the relative contributions of physician skill, practice setting, patient case-mix, and chance to this observed variation.16,17 Although this variation is worrisome, the “optimal” AIF:BD or rate of antibiotic prescribing is not easily defined. Nevertheless, each measure reflects physicians’ adherence to pre-
scribing guidelines for asthma and infectious diseases, respectively. Although “guideline adherence” is a theoretical construct to explain physician-prescribing performance, these measures were not significantly correlated. Our inability to correlate these performance measures agrees with the findings of Palmer et al., who found no correlation between provider performance on several guideline-related quality measures.

The physicians in our analysis prescribed less than half of the bronchodilators, anti-inflammatory medications, and antibiotics received by this cohort. Physicians excluded from our analysis (ie, less experienced primary-care physicians, specialists, urgent-care providers) may have patterns of prescribing different from those of experienced primary-care physicians. Therefore, efforts to promote appropriate asthma management must include physicians that provide both ongoing and episodic care to patients with asthma.

The appropriate role for antibiotics in the treatment of asthma is not clearly defined. The 1997 National Heart, Lung, and Blood Institute asthma guidelines state that “antibiotics are not recommended for asthma treatment but may be necessary for comorbid conditions.” The guidelines reserve the use of antibiotics for patients with focal bacterial sinusitis, pneumonia, and fever associated with purulent “sputum.” Viral infections, however, are the predominant trigger of asthma exacerbations. Johnston et al. detected upper respiratory tract viruses in 80 to 85% of episodes of asthma exacerbations in school-age children. Studies in both hospital and ambulatory settings have found no benefit of antibiotic therapy in the management of acute asthma. Nevertheless, physicians commonly prescribe antibiotics to patients with acute asthma exacerbations. Kljakovic and McLeod reported, based on chart review, that approximately 25% of patients with acute asthma are treated with an antibiotic. A survey in Great Britain found that 43% of general practitioners and 69% of physicians “frequently prescribe antibiotics in the treatment of asthma”; only 6% of pediatricians responded similarly. The majority of these physicians responded that they sometimes prescribe antibiotics without steroids for acute asthma exacerbations and that they considered a history of colored sputum an indication for antibiotics. This finding was replicated in a recent survey of European physicians regarding their asthma management practices. The reliance on sputum color as an indication for antibiotic therapy also was promoted in a randomized study of asthma self-management based on peak expiratory flow. These patients were instructed to “promptly initiate antibiotic therapy” when they noted purulent sputum. However, recent guidelines on judicious antibiotic prescribing argue against using the character of sputum or nasopharyngeal secretions to predict bacterial infection.

Increased incidence of sinus infection, a recognized asthma trigger, may have contributed to the higher antibiotic use by subjects who received more asthma medications. The lack of diagnostic data prevents us from assessing the contribution of recognized sinusitis to overall antibiotic use.

Several studies have associated Chlamydia pneumoniae infection with both acute and chronic asthma. Increased prescribing of antibiotics would be appropriate if chlamydial infection were a major determinant of asthma severity and its eradication resulted in improvement in symptoms. However, evidence to support this causal relationship is lacking.

Our analysis has several important limitations. The observed relationship between asthma medication and antibiotic use is cross-sectional and pertains to a population receiving care in a single group-model HMO and may not be generalizable to other asthma populations. We also made inferences about asthma control based on medication dispensing patterns. Prescription, receipt, and use of a medication are not strictly correlated; therefore, it is likely that we underestimate prescribing and overestimate use when considering dispensed medication. Our analysis is also limited by the absence of data about the diagnoses for which antibiotics were prescribed. Cross-sectional associations found in pharmacy data, in the absence of diagnostic data, preclude our drawing definitive conclusions regarding underlying disease severity or appropriateness of therapy.

Several factors may explain the observed relationship between asthma medication and antibiotic use. First, physicians’ thresholds for prescribing antibiotics may be lower for patients perceived to have more severe asthma. Second, patients with more severe asthma may get more bacterial infections than patients with milder asthma or be more likely to seek medical attention when infections occur. Third, sicker asthmatics may experience more severe disease exacerbations requiring medical intervention in the context of respiratory tract infections. Fourth, physicians may overuse antibiotics, consistent with findings for the general population, in treating respiratory tract infections in asthma patients. Specifically, physician threshold for antibiotic prescribing may be selectively lower for asthmatics assessed as having more severe disease. In this context, higher anti-inflammatory use may merely serve as a marker for asthma severity. Our data set does not permit conclusions regarding whether the increased antibiotic use observed among long-term anti-inflamma-
tory users was appropriate or beneficial. However, our data cannot exclude the possibility that higher use of inhaled anti-inflammatory medication by asthma patients may increase their predisposition to bacterial infections.

We excluded asthmatics < 6 years old from our analysis despite the higher reported use of antibiotics during early childhood. Differentiating asthma from recurrent infection-related wheezing in this age group is difficult, and dosages of asthma medication are less standardized. These factors make cohort definition and stratification by asthma medication use problematic. In addition, otitis media is the principal indication for antibiotic use in young children; less of the variability in antibiotic use, therefore, may be attributable to asthma control. However, the contribution of antibiotics and infections to the pathogenesis of early childhood asthma is vital to understanding the changing epidemiology of asthma.

Does the increased antibiotic use demonstrated among high users of anti-inflammatory medications reflect suboptimal asthma control and overuse of antibiotics? Recent evidence demonstrates that improved overall asthma control is associated with decreased antibiotic use. Adult asthmatics randomized to an intervention consisting of asthma education, optimization of drug therapy, and monthly follow-up visits had decreased utilization of urgent asthma services, reduced steroid use, improved asthma-quality-of-life scores, and a 33% reduction in antibiotic use. These findings suggest that utilization of physician services mediates the relationship between asthma control and antibiotic use.

Our findings are limited to physicians and patients within one group-model HMO in an urban academic environment. The variation in physician prescribing and the differences in antibiotic use may not be replicable in other care settings. However, this integrated medical group serves an HMO that is among national leaders in quality ratings and has active programs for asthma education and case management. Thus, we may be reporting the best-case scenario regarding prescribing variation and antibiotic use among asthmatics. Given the dramatic global increases in asthma prevalence and microbial antibiotic resistance, the potential public-health impact of increased antibiotic use among subgroups of asthmatics is substantial. Heightened attention is warranted to define the appropriate role of antibiotics in the management of asthma.

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