Tobacco Smoking as a Risk Factor for Increased Antibiotic Prescription

Michael B. Steinberg, MD, MPH,[1,2,3] Ayse Akincigil, PhD,[4,5] Eun Jung Kim, PharmD,[6] Rory Shallis, MD,[1] Cristine D. Delnevo, PhD, MPH[2,3]

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Introduction: Antibiotic resistance is rapidly spreading, affecting millions of people and costing billions of dollars. Potential factors affecting antibiotic prescription, such as tobacco use, could dramatically influence this public health crisis. The study determined the magnitude of impact that tobacco use has on antibiotic prescribing patterns.

Methods: Pooled data were analyzed in 2015 from the 2006–2010 National Ambulatory Medical Care Survey, a cross-sectional survey describing use of ambulatory medical services in the U.S. via healthcare provider–patient encounters. Patients aged >18 years with documented tobacco use status diagnosed with an infection were included (i.e., all encounters in the analysis included an infectious diagnosis of interest). The analytic sample included 8,307 visits, representing 294 million visits nationally.

Results: Half (49.9%) of encounters that included any infection had an antibiotic prescribed. Adjusted odds of receiving antibiotics among current tobacco users was 1.20 (95% CI=1.02, 1.42), and even higher for encounters of respiratory infections (AOR=1.31, 95% CI=1.05, 1.62). Antibiotic prescription rates were lower among patients aged >65 years, those with comorbid asthma or cancer, non-whites, and those covered by Medicaid and higher for primary care physicians.

Conclusions: Despite lack of evidence-based rationale, among a national sample of patients with an infectious diagnosis, tobacco users had 20%–30% higher odds of receiving antibiotics than non-tobacco users. This is the first U.S. study to quantify the magnitude of this unsubstantiated practice. Prescribers should understand that tobacco use could be associated with higher antibiotic prescription, which may subsequently increase antimicrobial resistance in the community.
(Am J Prev Med 2016;50(6):692–698)

Introduction

Tobacco use remains the leading cause of preventable death, not only causing chronic diseases such as heart disease, cancer, stroke, and emphysema, but also contributing to acute illnesses, such as infections.[1] Infectious diseases not only result in significant morbidity and mortality but also are increasingly important public health issues, as bacterial antibiotic resistance spreads rapidly. Each year in the U.S., at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.[2] Drug-resistant infections cost approximately $20 billion each year in healthcare costs,[2] and experts in the field, such as the Director of the National Institute of Allergy and Infectious Disease, have recently called for a multifaceted solution to this problem.[3]

The 2014 Surgeon General's Report on Tobacco concluded that cigarette smoking compromises the immune system and, as such, is associated with increased risk for respiratory infections, including pneumococcal pneumonia, influenza, and the common cold.[1,4] Tobacco smoke impacts many aspects of pulmonary physiology[5] and interferes with immune cell function at multiple levels,[6–8] leading to higher rates of respiratory and other

From the [1]Rutgers Robert Wood Johnson Medical School, Division of General Internal Medicine, New Brunswick, New Jersey; [2]Rutgers School of Public Health, Department of Health Education and Behavioral Science, New Brunswick, New Jersey; [3]Rutgers Cancer Institute of New Jersey, Population Science Section, New Brunswick, New Jersey; [4]Rutgers School of Social Work, New Brunswick, New Jersey; [5]Rutgers Institute for Health, Health Care Policy and Aging Research, New Brunswick, New Jersey; and [6]Rutgers Ernest Mario School of Pharmacy, Piscataway, New Jersey

Address correspondence to: Michael B. Steinberg, MD, MPH, Rutgers Robert Wood Johnson Medical School, Division of General Internal Medicine, 125 Paterson Street, Suite 2300, New Brunswick NJ 08903. E-mail: michael.steinberg@rutgers.edu.

0749-3797/$36.00
http://dx.doi.org/10.1016/j.amepre.2015.11.009

infections. Considering the increased risk of infectious diseases, it is reasonable to expect that smokers overall might receive more antibiotics to treat these infections,[9] despite the fact that, for example, the benefit of antibiotics for smokers with bronchitis appears to be the same or less than that for non-smokers.[10]

Owing to the overuse of antibiotics in general, many bacterial infections are becoming resistant to various commonly prescribed antibiotics.[11] Although there has been a collective effort to reduce the antibiotic prescribing rate in the last decade, the prescribing rate in the U.S. remains among the highest in the world.[12] If smokers disproportionately receive more antibiotics than non-smokers, then smoking may be thought of as a risk factor for the development of antibiotic resistance in the population. This antibiotic resistance in the smoking population could subsequently spread to the non-smoking population as well. The goal of this study is to describe rates of prescription of antibiotics in a national sample, characterizing differences between smokers and non-smokers, with the hypothesis that smokers receive more antibiotic prescriptions.

Methods

The National Ambulatory Medical Care Survey (NAMCS) is an annual survey conducted by CDC describing the provision and use of ambulatory medical care services in the U.S. The current study analyzes repeated cross-sectional survey data pooled from NAMCS for 2006–2010. The unit of observation for NAMCS is the healthcare provider–patient encounter, and healthcare providers complete a data collection form describing outpatient encounters. Practices were surveyed over a 1-week study period. Survey items include patient demographic information, reason for visit, continuity of care, provider's diagnosis for the visit, tobacco use, and prescribed medications. NAMCS includes data from non-federally employed office-based physicians who are primarily engaged in direct patient care. The sample is a multilevel probability sample of visits, and survey procedures generate nationally representative estimates of the annual physician–patient encounters. Details on survey methodology and the survey instruments and data are available publicly.[13] The study was determined exempt by the Rutgers University IRB.

Study Sample

The population of interest was patients aged >18 years, diagnosed with an infection for which antibiotics may be clinically indicated, and who have tobacco use status documented. Physicians can record up to three presenting symptoms and are instructed to list the following: *Patient's complaint(s), symptom(s), or other reason (s) for this visit—Use patient's own words*. CDC then used their own classification scheme for presenting symptoms during data processing.[14] The survey instrument also allows the physician to record up to three diagnoses. Physicians were instructed to *as specifically as possible, list diagnoses related to this visit including chronic conditions*. Diagnoses were classified according to ICD-9.[15] The definition of patients with an infection for which antibiotics may be clinically indicated include ICD-9 diagnosis codes representing: acute nasopharyngitis, sinusitis, upper respiratory infection, bronchitis, pneumonia, cellulitis/skin infection, abscess, pyelonephritis, cystitis, urinary tract infections, otitis, osteomyelitis, intestinal infections, and other bacterial diseases. These represent common infectious diagnoses treated in the outpatient setting. Respiratory infections were classified to include sinusitis, upper respiratory infection, bronchitis, and pneumonia for analyses. It is not the case that antibiotics are indicated in all of these encounters, but there is a potential that they could be indicated, and thus they were included. Diagnoses that had clear viral etiologies were excluded as antibiotics would not be indicated.

A total of 20,575 visits with an infection for which antibiotics may be clinically indicated were identified. Of those, 12,275 were aged ≥18 years. Patient's tobacco use was included in the survey instrument as "current," "not current," and "unknown." Visits were excluded if the tobacco use information was missing or marked unknown (3,968 visits representing 32% of adult encounters with an infection). Therefore, the final analytic sample included 8,307 visits, representing an estimated number of 294 million visits nationally between 2006 and 2010.

Measures

Medications in the data were coded in terms of their generic components and therapeutic classes using Lexicon Plus, a comprehensive database of all prescription and some nonprescription drug products available in the U.S. drug market. Using the classifications, visits in which the provider mentioned a prescription of antibiotics for infectious disease were identified. These medication classes included antibacterials such as penicillins, cephalosporins, macrolides, quinolones, sulfonamides, tetracyclines, carbapenems, aminoglycosides, urinary tract antibiotics, lincosamides, and glycylcycline. These agents were under the category of anti-infectives from Lexicon Plus, and commonly prescribed antibiotics were chosen based on the disease states of interest. Amebicide, anti-helminth, antifungal, anti-malarial, anti-tuberculosis, and antiviral medications were excluded, as they were not the antibiotics of interest and are less likely associated with tobacco use.

The survey instrument included demographic characteristics. The three-level race category (white, black, and other, including Hispanic) was the one that was reported consistently by CDC from 2006 to 2010, and thus used. Expected source of payment is also collapsed into three groups: private insurance, Medicaid, and other. The physician was inquired about the existing chronic conditions with a question worded *regardless of the diagnoses written, does the patient now have … (mark all that apply)*. The covariates included four indicators for chronic conditions: asthma, cancer, chronic obstructive pulmonary disease, and diabetes.

Statistical Analysis

Data were analyzed in 2015. The univariate statistics of the covariates are presented describing the populations of interest. Next, antibiotic rates for subpopulations defined by covariates are presented. Chi-square tests were conducted to test whether there is a significant difference between the frequencies of antibiotic use by covariates, including smoking status. All calculations were

weighted, producing nationally representative estimates, unless stated as sample sizes (Stata, version 13.1). Survey methods were used to correct for the effect of multilevel sampling design on the calculation of SEs. The regression model included all variables presented in Table 2—tobacco status, gender, race, age, source of payment, primary care physician or not, and presence of comorbid conditions—and reports all the estimated coefficients and their 95% CIs.

Results

Among encounters that included an infectious disease diagnosis or reasons for visit (Table 1), 18.9% of encounters involved patients who currently use tobacco, with the majority being female (66.6%); white (85.2%); having private insurance (60%); and with the patients' primary care physician (62.2%). Within this population (encounters for infectious disease), characteristics of tobacco users were somewhat different from those who do not use tobacco, with more men (42% vs 32%); more comorbid chronic obstructive pulmonary disease (22% vs 13%); and more insured by Medicaid (15% vs 7%). Substantially significant differences were similar to the subgroup of encounters for respiratory infections.

Table 2 presents adjusted odds of receiving antibiotics based on covariates. Overall, half (49.9%) of encounters that included any infection had an antibiotic prescribed. After adjusting for factors associated with antibiotic prescription, the main result is that the odds of receiving antibiotics were 20% higher among current tobacco users. The odds were even larger (1.31) in the subpopulation of encounters with respiratory infections. Antibiotic prescription rates varied by some clinical factors: The elderly (compared with those aged <65 years) and those with comorbid asthma or cancer were less likely to receive an antibiotic prescription. Rates also varied by factors that may serve as a proxy for socioeconomic characteristics: Those with minority status (compared with whites) and those insured by Medicaid (compared with private insurance) were less likely to be prescribed antibiotics. Primary care physicians were more likely to prescribe antibiotics than other physicians.

Discussion

Despite the lack of evidence that tobacco users should receive more antibiotics, in a national sample representing nearly 300 million patient encounters between 2006 and 2010, tobacco users seen with an infection had approximately 20%–30% higher odds (95% CI=1.02, 1.42 and 1.05, 1.62, respectively) of receiving antibiotics than non-tobacco users with an infection, after controlling for covariates and comorbidities. People might respond, "of course smokers receive more antibiotics; they should because they get more infections." To answer this question, the current study starts with a national sample of encounters with infectious diagnoses. Thus, everyone in the sample has an infection, and among those, smokers still receive more antibiotics. This is the first study in the U.S. to quantify the magnitude of this unsupported practice. These findings have important implications regarding the public health impact that high rates of antibiotic use could have on antibiotic resistance. Despite a lack of evidence-based rationale, for example in bronchitis,[10] this practice continues.

According to CDC, the prevention of antimicrobial-resistant infections includes appropriate use of antimicrobial agents, thus reducing populations of resistant micro-organisms in humans, animals, and the environment. Many prior studies have demonstrated that resistance to antibacterial drugs is correlated with community prescribing of that drug.[16–20] The dynamics between prescribing and resistance can be very complicated.[21] Generally, resistance rates are low after a new antimicrobial drug is introduced, and then resistance appears and increases steadily until it reaches a steady-state level. The rate of increase in resistance depends on the drug, how much is used, the bacteria, and the nature of the community.[21] Regardless, most agree that controlling overuse of antibiotic prescribing is a cornerstone of preventing resistance.

These findings are consistent with prior studies from Europe demonstrating higher rates of antibiotic use among smokers (60%) than non-smokers (53%) with respiratory conditions, with an OR of 1.44 for smokers receiving antibiotics.[9] In addition, smokers not only received more antibiotics but tended to receive more broad-spectrum antibiotics as their cigarette consumption increased.[22] This higher usage of antibiotics among smokers may be one of the factors contributing to higher rates of resistant infections in these groups. Ex-smokers have been shown to have more than twice the odds (OR=2.3) of nasal carriage of *Staphylococcus aureus* than non-smokers.[23] Another small study demonstrated a higher recovery of resistant organisms in smokers compared with non-smokers.[24] Other factors related to smoke exposure itself may contribute to antibiotic resistance, as even exposure to maternal smoke has been shown to increase risk of methicillin-resistant *S. aureus* colonization in infants.[25] Therefore, tobacco use is not only a health risk for the individual smoker but may be a larger public health problem because smokers receive more antibiotics and thus may serve as a reservoir for antibiotic-resistant organisms, which could potentially spread to the population overall.

In addition to examining overall infections, respiratory infections were also assessed for several reasons. The

Table 1. Characteristics of Patient Encounters Involving Infections and Variations of Characteristics by Smoking Status, NAMCS 2006–2010

	Encounters identifying an infection for which antibiotics may be indicated, % (n=8,307)			Encounters identifying an infection related to the respiratory system, % (n=4,975)		
		Tobacco use			Tobacco use	
Characteristic	**All**	**No**	**Yes**	**All**	**No**	**Yes**
Tobacco use status						
No	81.1	100	—	79.8	100	—
Yes	18.9	—	100	20.2	—	100
Gender[a,b]						
Male	33.4	31.6	41.7	34.2	32.5	40.9
Female	66.6	68.4	58.7	65.8	67.5	59.1
Race						
White	85.2	85.6	83.6	86.1	86.4	84.6
Black	10.2	9.8	12.0	9.5	9.21	11.0
Other[c]	4.6	4.6	4.4	4.4	4.4	4.4
Age (years)[a,b]						
18–24	8.8	9.0	8.0	7.9	7.9	8.3
25–44	33.0	31.7	38.6	33.1	32.2	36.6
45–64	34.2	32.6	41.0	36.0	34.4	42.3
≥65	24.0	26.7	12.4	23.0	25.5	13.1
Source of payment[a,b]						
Private/other	60.0	60.5	57.7	61.7	62.6	57.9
Medicaid	8.4	6.9	15.2	8.2	6.7	14.2
Self-pay	31.6	32.6	27.1	30.1	30.7	27.9
Primary care physician[a]						
No	37.8	38.7	33.7	32.3	32.8	30.6
Yes	62.2	61.3	66.3	67.7	67.2	69.4
Comorbid conditions						
Asthma						
No	80.6	80.3	81.8	73.1	72.3	76.4
Yes	19.4	19.7	18.2	26.9	27.7	23.6
Cancer[a]						
No	96.3	96.0	97.7	97.5	97.3	98.4
Yes	3.7	4.0	2.3	2.5	2.7	1.6
COPD[a,b]						
No	85.4	87.2	78.0	79.1	81.4	70.2
Yes	14.6	12.8	22.0	20.9	18.6	29.8

(continued on next page)

Table 1. Characteristics of Patient Encounters Involving Infections and Variations of Characteristics by Smoking Status, NAMCS 2006–2010 *(continued)*

	Encounters identifying an infection for which antibiotics may be indicated, % (n=8,307)			Encounters identifying an infection related to the respiratory system, % (n=4,975)		
		Tobacco use			Tobacco use	
Characteristic	**All**	**No**	**Yes**	**All**	**No**	**Yes**
Diabetes[a]						
No	89.1	88.6	91.1	90.1	89.6	92.1
Yes	10.9	11.3	8.9	9.9	10.4	7.9

[a]Significant difference by tobacco use status among encounters with any infection.
[b]Significant difference by tobacco use status among encounters with respiratory infections.
[c]Includes white Hispanic, black Hispanic, and other race/multiple race non-Hispanic.
NAMCS, National Ambulatory Medical Care Survey; COPD, chronic obstructive pulmonary disease.

most common infectious diagnoses for which antibiotics are prescribed are respiratory tract infections.[26,27] A recent review of U.S. Department of Veterans Affairs data demonstrate persistently high rates of antibiotic prescription from 2005 to 2012 for acute respiratory infections,[28] but this review did not evaluate smoking status. Additionally, tobacco smoke has particular effects on respiratory physiology that increase susceptibility to respiratory infections. Cigarette smoke impairs mucociliary clearance, enhances bacterial adherence, disrupts respiratory epithelium,[5] decreases the effective inflammatory response of phagocytes, can produce lower immunoglobulin G levels, and reduces T- and B-cell responses to antigens.[29] Smokers have higher rates of carriage of pneumococci[30] and higher rates of invasive pneumococcal disease.[5] Various substances in tobacco smoke (e.g., nicotine, nicotine-derived nitrosamine ketone) can influence dysfunction of numerous immune cell types, including macrophages,[6] basophils,[7] and mast cells.[8] For these reasons, respiratory infections were of particular interest, and did in fact show a slightly higher AOR of antibiotic usage (1.31) compared with infections overall (1.20) in the findings.

Primary care physician encounters were more likely to result in prescription of antibiotics than non–primary care physician encounters. This result may be a function of the relationship or expectations between patients and their primary care physicians. Regardless of the reasons, it is clear that interventions to reduce the number of antibiotic prescriptions in the healthcare system should prioritize primary care. In addition, patients with private insurance received antibiotics at higher rates, possibly owing to better access to medications. Whites received antibiotics at higher rates than other race/ethnicities. This is an important covariate, possibly related to socioeconomic factors, that warrants further study.

Limitations

Despite the study's strengths of a large, weighted, nationally representative sample, this study has some limitations. First, it is possible that factors occurring during the patient encounter were not coded for on the data coding sheet and could have influenced antibiotic prescription (e.g., severity of illness, patient request for antibiotics). Second, the data coding sheet was limited to eight medications. It is possible that the number of medications prescribed during an encounter exceeded eight, and thus an antibiotic was not recorded. This would be unlikely, as it would be expected that an antibiotic prescribed during an encounter for an acute infection would be considered a high priority to record, as opposed to a chronic, long-standing medication. Third, this analysis did not address the question of whether tobacco users had more infections but instead whether tobacco users with infections received more antibiotics than non-tobacco users with infections. Finally, one third of encounters with an infection diagnosis did not have tobacco use status identified by the provider and were therefore excluded, and tobacco use classification only included current and not current.

Conclusions

This study demonstrates that in a national sample of medical encounters where an infection is identified, tobacco use was an independent predictor for patients receiving an antibiotic, after controlling for covariates, and is the first to quantify the magnitude of this behavior. The clinical "custom" of prescribing antibiotics to smokers, although still commonly practiced, is done so without supporting evidence and has serious societal implications. Prescribers need to be aware of the risks of antibiotic resistance development and that tobacco use may be an independent factor for this public health challenge.

Table 2. Antibiotic Prescription Among Outpatient Encounters with Infection Diagnosis, NAMCS 2006–2010

	Encounters for any infection (n=8,307)		Encounters for respiratory infections (n=4,975)	
Characteristic	**Rates, %**	**AOR (95% CI)**	**Rates, %**	**AOR (95% CI)**
All	49.9		51.4	
Tobacco use status				
No	48.7	ref	49.8	ref
Yes	55.2	**1.20** (1.02, 1.42)	57.8	**1.31** (1.05, 1.62)
Gender				
Male	51.2	ref	52.9	ref
Female	48.9	0.92 (0.81, 1.05)	50.7	0.98 (0.84, 1.14)
Race				
White	51.1	ref	52.1	ref
Black	45.2	**0.81** (0.66, 0.99)	49.8	1.00 (0.75, 1.32)
Other	38.8	**0.56** (0.38, 0.82)	41.1	0.60 (0.39, 0.93)
Age (years)				
18–24	53.4	ref	51.7	ref
25–44	54.2	1.02 (0.80, 1.30)	56.4	1.16 (0.86, 1.56)
45–64	50.8	0.84 (0.67, 1.06)	52.7	0.97 (0.73, 1.29)
≥65	41.6	**0.59** (0.46, 0.77)	42.2	**0.67** (0.48, 0.92)
Source of payment				
Private/other	53.0	ref	54.9	ref
Medicaid	40.9	**0.61** (0.47, 0.79)	39.0	**0.54** (0.39, 0.77)
Self-pay	46.4	1.00 (0.85, 1.17)	47.8	0.99 (0.80, 1.23)
Primary care physician				
No	42.2	ref	43.7	ref
Yes	54.6	**1.64** (1.39, 1.94)	55.1	**1.50** (1.21, 1.88)
Comorbid conditions				
Asthma				
No	54.8	ref	60.3	ref
Yes	29.5	**0.35** (0.30, 0.42)	27.2	**0.26** (0.21, 0.33)
Cancer				
No	50.3	ref	51.7	ref
Yes	39.4	**0.73** (0.52, 1.04)	39.2	0.70 (0.42, 1.16)
COPD				
No	49.5	ref	50.9	ref
Yes	52.5	**1.24** (1.04, 1.47)	53.6	1.13 (0.93, 1.39)
Diabetes				
No	50.4	ref	51.7	ref
Yes	45.5	0.89 (0.71, 1.12)	49.2	0.97 (0.72, 1.29)

Note: Boldface indicates statistical significance ($p < 0.05$).
COPD, chronic obstructive pulmonary disease; NAMCS, National Ambulatory Medical Care Survey.

This study was partially funded through a pilot grant from the Rutgers Cancer Institute of New Jersey (P30CA072720).

Michael B. Steinberg: Consultant for Arena Pharmaceuticals ($500). No other financial disclosures were reported by the authors of this paper.

All of the listed authors made a substantial contribution to conception and design of the study, to data acquisition, or to data analysis and interpretation; wrote the article or revised the article for important intellectual content; and read and approved the final version of the submitted manuscript. M.B. Steinberg: design of study, statistical analysis and interpretation of data, drafting and revision of manuscript, supervision; A. Akincigil: design of study, statistical analysis and interpretation of data, drafting and revision of manuscript; E.J. Kim: design of study, analysis and interpretation of data, drafting and revision of manuscript, technical support; R. Shallis: interpretation of data, drafting and revision of manuscript, technical support; C.D. Delnevo: interpretation of data, drafting and revision of manuscript, technical support.

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