Changing Use of Antibiotics in Community-Based Outpatient Practice, 1991–1999

Michael A. Steinman, MD; Ralph Gonzales, MD, MSPH; Jeffrey A. Linder, MD, MPH; and C. Seth Landefeld, MD

Background: Judicious use of antibiotics can slow the spread of antimicrobial resistance. However, overall patterns of antibiotic use among ambulatory patients are not well understood.

Objective: To study patterns of outpatient antibiotic use in the United States, focusing on broad-spectrum antibiotics.


Setting: The National Ambulatory Medical Care Survey, a nationally representative sample of community-based outpatient visits.

Patients: Patients visiting community-based outpatient clinics.

Measurements: Rates of overall antibiotic use and use of broad-spectrum antibiotics (azithromycin and clarithromycin, quinolones, amoxicillin–clavulanate, and second- and third-generation cephalosporins). All comparisons were made between the first study period (1991–1992) and the final study period (1998–1999).

Results: Between 1991–1992 and 1998–1999, antibiotics were used less frequently to treat acute respiratory tract infections, such as the common cold and pharyngitis. However, use of broad-spectrum agents increased from 24% to 48% of antibiotic prescriptions in adults (P < 0.001) and from 23% to 40% in children (P < 0.001). Use of broad-spectrum antibiotics increased across many conditions, increasing two- to threefold as a percentage of total antibiotic use for a variety of diagnoses in both adults and children. By 1998–1999, 22% of adult and 14% of pediatric prescriptions for broad-spectrum antibiotics were for the common cold, unspecified upper respiratory tract infections, and acute bronchitis, conditions that are primarily viral.

Conclusions: Antibiotic use in ambulatory patients is decreasing in the United States. However, physicians are increasingly turning to expensive, broad-spectrum agents, even when there is little clinical rationale for their use.

METHODS

National Ambulatory Medical Care Survey

We used the National Ambulatory Medical Care Survey (NAMCS) to collect data on outpatient antibiotic use. We collapsed 6 survey years into three study periods (1991–1992, 1994–1995, and 1998–1999), combining data from consecutive years to add power to our analyses. The NAMCS is an annual sample of outpatient visits to office-based community physicians who are principally engaged in patient care. Patient care encounters in emergency departments or hospital-based clinics and visits outside the office (for example, house calls or nursing home visits) were not recorded. Visits were sampled by using a multistage clustered probability sample design based on geographic location, provider specialty, and visits within individual physician practices. When patient weights are used, these data can be extrapolated to the approximately 650 million community-based outpatient visits that occur in the United States each year (15). Participation in the survey ranged from 63% to 73% of invited practices, with different physicians and patients being surveyed each year (15, 16).

The NAMCS collected information on up to five (1991–1994) or six (1995–1999) medications prescribed for each patient at the conclusion of his or her visit, including both new and ongoing prescriptions. The NAMCS also collected data on up to three physician diagnoses related to the visit, including new diagnoses and ongoing medical conditions. All data, including demographic char-
Changing Use of Antibiotics

Context
Indiscriminate use of antibiotics promotes the development of antibiotic-resistant strains of bacteria.

Contribution
This survey of patient visits to community-based clinics shows that antibiotic use for ambulatory infections, especially upper respiratory tract infections, decreased from 1991–1992 to 1998–1999. However, the use of broad-spectrum antibiotics rose over this period.

Implications
Efforts to encourage rational use of antibiotics should focus on which antibiotic to use as well as whether or not to use antibiotics.

—The Editors

certainties, were recorded by the physician or by office staff completing the visit encounter form.

Design and Classification
We were interested in the use of oral and intramuscular antibiotics, but the NAMCS does not provide information on the route of drug administration. We therefore excluded patient visits to dermatologists and ophthalmologists because these specialists frequently prescribe topical antibiotics, which we could not distinguish from systemic forms of the same drugs. Visits to these specialists made up approximately 10% of patient encounters in each study period. Among the remaining sample, 60 252 visits were recorded in 1991–1992, 62 169 visits were recorded in 1994–1995, and 37 467 visits were recorded in 1998–1999. The smaller sample size in the last study period reflects a smaller number of visits surveyed by the NAMCS in those years.

We divided the remaining sample into patient visits that did and did not involve an antibiotic. Antimicrobial medications used by outpatients almost exclusively in topical or intravenous form, such as polymyxins and aminoglycosides, were not counted as antibiotics. We also did not count antimycobacterial medications as antibiotics because they are infrequently used for typical bacterial infections. Antibiotic use, according to these criteria, was recorded in 8208 sampled visits in 1991–1992, 7944 visits in 1994–1995, and 4200 visits in 1998–1999. However, the use of broad-spectrum antibiotics rose over this period.

For the purposes of this study, we defined broad-spectrum agents as azithromycin and clarithromycin, quinolones, amoxicillin–clavulanate, and second- and third-generation cephalosporins (17). Many of the broad-spectrum agents we studied were introduced more recently than narrow-spectrum agents that made up at least 2% of total antibiotic prescriptions in any study period received U.S. Food and Drug Administration approval before 1979. Among broad-spectrum agents that made up at least 2% of total antibiotic prescriptions, Food and Drug Administration approval was granted between 1979 and 1984 for amoxicillin–clavulanate, cefaclor, and cefuroxime; in 1987 for ciprofloxacin; in 1991 for azithromycin, cefprozil, and clarithromycin; and in 1996 for levofloxacin (Bergman E. Personal communication). Publically available data from the Tufts Center for the Study of Drug Development’s approved products database).

Patients were considered to have a common infectious condition if the corresponding International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code appeared as the first, second, or third diagnosis for that visit (18). Diagnoses included nasopharyngitis (the common cold) or upper respiratory tract infection not otherwise specified (ICD-9-CM codes 460, 465); acute or chronic sinusitis (ICD-9-CM codes 461, 473); pharyngitis and streptococcal sore throat (ICD-9-CM codes 462, 34.0); suppurative or nonsuppurative otitis media (ICD-9-CM codes 381.0–381.4, 382); acute or acute-on-chronic bronchitis and bronchiolitis (ICD-9-CM codes 466, 490, 491.21); acute tonsillitis, laryngitis, and tracheitis (ICD-9-CM codes 463–464); bacterial or unspecified pneumonia (ICD-9-CM codes 481–483, 485–486); urinary tract infection or acute or unspecified cystitis (ICD-9-CM codes 599.0, 595.0, 595.9); cellulitis, carbuncle, or furuncle (ICD-9-CM codes 680–682); prostatitis or pelvic inflammatory disease (ICD-9-CM codes 601, 614); and sexually transmitted diseases, including syphilis, gonococcal infections, and other venereal infections (ICD-9-CM codes 90–99, 647.0–647.2). In each study period, 11% to 13% of patients who were prescribed antibiotics received a diagnosis of more than one of these infectious conditions. To prevent confusion over which disease was treated by the listed antibiotics, we excluded these patients from the diagnosis-specific analyses. Among adults with a single diagnosis of an infectious disease, there were 1657 visits for the common cold and unspecified upper respiratory tract infections, 2652 visits for sinusitis, 963 visits for pharyngitis, 908 visits for otitis media, 1674 visits for acute bronchitis, and 1636 visits for urinary tract infection over the entire study period. Among children, there were 1976 visits for the common cold and unspecified upper respiratory tract infections, 651 visits for sinusitis, 1120 visits for pharyngitis, 3107 visits for otitis media, and 625 visits for acute bronchitis.

Statistical Analysis
We analyzed overall antibiotic use for a given patient at the level of the patient visit. Individual prescriptions were analyzed at the level of the antibiotic prescription. For example, a patient visit involving amoxicillin and cipro-
floxacin would be counted twice, once for each medication. We did not account for clustering of more than one antibiotic in a single visit because only 3% to 4% of visits at which an antibiotic was prescribed in each period involved more than one antibiotic.

To make our point estimates nationally representative, we used patient weights, which weight each visit’s contribution in inverse proportion to the likelihood of that visit being sampled from all community-based visits (15, 19). Patient weight can be interpreted as the number of visits in the population that the sampled visit represents. To adjust for the effects of survey design on standard errors, we clustered our analyses at the level of the physician. This accounts for correlation among outcomes sampled from the same physician and increases the standard errors to account for weighting and clustering within physicians. Identifiers of the true primary sampling unit (county or county equivalent) were not available to the public at the time this study was performed and therefore could not be used in our analyses. As a result, the calculated variances and point estimates in our analyses may differ slightly from those in analyses that incorporate both the primary and secondary sampling units.

We conducted all analyses using the design-based F test, comparing the first study period (1991–1992) with the final study period (1998–1999). This test is based on the Pearson chi-square statistic for two-way tables but uses the second-order Rao and Scott correction to adjust for effects of the survey design.

All analyses were performed by using Intercooled Stata, version 6.0 (Stata Corp., College Station, Texas). P values less than 0.05 were considered statistically significant. The Committee on Human Research of the University of California, San Francisco, approved the study.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Overall Antibiotic Use

The annual number of outpatient visits ranged from 599 million in 1991 to 746 million in 1998. Between 1991–1992 and 1998–1999, the proportion of visits that involved an antibiotic prescription decreased from 13% to 10% among adults (P < 0.001) and from 33% to 22% among children (P < 0.001). As a result, the total number of antibiotic prescriptions per year changed from 230 million prescriptions in 1991–1992 to 190 million prescriptions in 1998–1999.

These changes partially reflect a decrease in visits for common infectious conditions, which declined from 19% to 16% of total outpatient visits (P < 0.001). In addition, fewer common infectious conditions were treated with an antibiotic (Figures 1 and 2). Among adults, the frequency of antibiotic prescribing decreased from 1991–1992 to 1998–1999 for the common cold and unspecified upper respiratory tract infections (56% vs. 43% of patient visits; P = 0.011), pharyngitis (78% vs. 64% of patient visits; P = 0.02), and acute bronchitis (76% vs. 59% of patient visits; P < 0.001). Among children, the frequency of antibiotic prescribing decreased for the common cold and unspecified upper respiratory tract infections (41% vs. 21% of patient visits; P < 0.001) and pharyngitis (73% vs. 54%; P = 0.002) and trended toward a decrease for otitis media (78% vs. 72%; P = 0.08) and acute bronchitis (78% vs. 68%; P = 0.091). However, despite decreases in the frequency of antibiotic treatment of these conditions, nonpneumonic acute respiratory tract infections (the common cold and nonspecific upper respiratory tract infections, pharyngitis, otitis media, sinusitis, acute bronchitis, laryngitis, acute tonsillitis, and tracheitis) accounted for 47% to 56% of adult and 75% to 80% of pediatric antibiotic prescriptions in each study period.

Broad-Spectrum Antibiotic Use

Over the decade, use of broad-spectrum agents doubled among adults, from 24% to 48% of antibiotic prescriptions (P < 0.001). Azithromycin and clarithromycin increased from 2% to 13% of adult prescriptions (P < 0.001), quinolones increased from 8% to 16% (P < 0.001), amoxicillin–clavulanate increased from 4% to 6% (P < 0.001), and second- and third-generation cephalosporins remained stable at 11% to 12% (P > 0.2). Among children, broad-spectrum antibiotic use increased from 23% to 40% of antibiotic prescriptions (P < 0.001), azithromycin and clarithromycin increased from less than 1% to 13% (P < 0.001), amoxicillin–clavulanate increased from 6% to 11% (P < 0.001), and second- and third-generation cephalosporins remained stable at 16% to 15% (P > 0.2). Quinolones, which are usually contraindicated in children because of potential cartilage toxicity, made up 1% or less of pediatric prescriptions.

Use of broad-spectrum agents increased across a range of adult and pediatric age groups. Among adults, use of broad-spectrum agents approximately doubled in all age groups, from 21% to 43% of antibiotic prescriptions in those 18 to 39 years of age, from 25% to 52% in those 40 to 59 years of age, and from 28% to 49% in those 60 years of age and older (P < 0.001 for each age group). Among children, broad-spectrum antibiotic use increased from 26% to 40% of antibiotic prescriptions in those younger than 1 year of age, from 25% to 44% in those 1 to 5 years of age, and from 19% to 36% in those 6 to 17 years of age (P < 0.01 for each age group).

Use of broad-spectrum antibiotics also increased across a wide range of infections (Figures 1 and 2). Among adults, use of these agents (as a percentage of total antibiotic use) increased approximately two- to threefold for all diagnoses shown in Figure 1 (for pharyngitis, P = 0.002; for all other conditions, P < 0.001). Among children, use
of broad-spectrum antibiotics increased for each diagnosis shown in Figure 2 (for common cold and unspecified upper respiratory tract infections (URTIs) \( P = 0.011 \)), for pharyngitis \( P = 0.02 \), and for acute bronchitis \( P < 0.001 \). Among adults receiving an antibiotic, broad-spectrum agents made up an increased proportion of antibiotic prescriptions for each condition shown (for pharyngitis, \( P = 0.002 \); for all other conditions, \( P < 0.001 \)). (Results are shown at the level of the patient visit: Broad spectrum indicates visits involving at least one broad-spectrum antibiotic; narrow spectrum indicates visits involving only narrow-spectrum agents.) The mean number of visits occurring annually during the study period is shown for each condition. UTI = urinary tract infection.

Overall use of antibiotics decreased in adult visits for the common cold and unspecified upper respiratory tract infections (URTIs) \( ( P = 0.011 ) \), for pharyngitis \( ( P = 0.02 ) \), and for acute bronchitis \( ( P < 0.001 ) \). Among adults receiving an antibiotic, broad-spectrum agents made up an increased proportion of antibiotic prescriptions for each condition shown (for pharyngitis, \( P = 0.002 \); for all other conditions, \( P < 0.001 \)). (Results are shown at the level of the patient visit: Broad spectrum indicates visits involving at least one broad-spectrum antibiotic; narrow spectrum indicates visits involving only narrow-spectrum agents.) The mean number of visits occurring annually during the study period is shown for each condition. UTI = urinary tract infection.

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spectrum antibiotic use were almost identical in urban versus rural settings in 1991–1992 (23% vs. 24% of prescriptions) but diverged substantially by the end of the decade (47% vs. 38% of prescriptions).

DISCUSSION

Antibiotics are among medicine’s most powerful tools. However, their popularity is their Achilles’ heel. The more frequently antibiotics are used, the more they promote the bacterial resistance that undercuts their effectiveness (9). As a result, physicians can be tempted to use newer and broader-spectrum agents, thereby fueling the expanding cycle of resistance (2, 14, 20).

Our study shows some encouraging signs. Overall, community-based outpatient physicians prescribed substantially fewer antibiotics over the course of the 1990s, particularly among children. Moreover, antibiotics are being used less often for illnesses for which they have limited utility, such as upper respiratory tract infections and acute bronchitis. This may reflect the success of many recent educational interventions to discourage unnecessary antibiotic use.

However, there is also reason for concern. When community-based physicians decide to use an antibiotic, they increasingly turn to broad-spectrum agents, such as azithromycin and clarithromycin, quinolones, and amoxicillin–clavulanate, and have maintained steady use of second- and third-generation cephalosporins. By 1998–1999, these broad-spectrum agents made up 5 of the 10 most commonly prescribed antibiotics in community-based outpatient practice. For many nonpneumonic acute respiratory tract infections, broad-spectrum antibiotics provide little clinical advantage over narrow-spectrum agents or no antibiotic therapy at all (21–29). However, these are the conditions for which broad-spectrum agents are most often used.

Because they are largely protected by patent and exclusivity laws that prevent generic competition, broad-spectrum antibiotics have substantial direct costs. In 1999, the average wholesale price of the five most common broad-spectrum drugs exceeded $50 for a typical 7-day adult course. In contrast, the price of the five most common narrow-spectrum drugs (all of which had generic competition) averaged less than $5 per 7-day course (30).

Increasing use of broad-spectrum antibiotics also has important implications for bacterial resistance. In addition to their broad-spectrum activity, quinolones, amoxicillin–clavulanate, and second- and third-generation cephalospo-
rins are widely used for empirical treatment of severe or complicated infections and for directed treatment of otherwise resistant organisms (31–34). The expanding use of these agents, which by the late 1990s made up more than one third of all adult antibiotic prescriptions, can promote escalating antimicrobial resistance within both individuals and communities (35–37). As a result, the medical profession risks losing some of its most potent therapies for patients with the greatest need (38).

Several clinical factors may help explain the increasing use of broad-spectrum antibiotics. Community-based physicians are prescribing fewer antibiotics overall, perhaps selecting sicker patients for treatment. At the same time, the number of elderly persons is growing rapidly, creating a cohort of patients who are more susceptible to invasive infections and antibiotic-resistant pathogens (35, 36, 39, 40). In recent years, some treatment guidelines have endorsed broad-spectrum antibiotics for the treatment of outpatient conditions, such as community-acquired pneumonia and urinary tract infections (41, 42).

However, these reasons fail to fully account for the increasing use of broad-spectrum agents. By the end of our observation period, broad-spectrum antibiotics made up half of all antibiotic prescriptions for adults and 40% of prescriptions for children. Our findings suggest that only a minority of patients receiving these drugs were likely to have a resistant or complicated infection that mandated their use. These drugs were used almost as frequently in young, generally low-risk adults as in older patients. Moreover, they were often prescribed in situations for which they provide little antimicrobial benefit over older antibiotics. For example, azithromycin and clarithromycin were commonly used for pediatric otitis media despite having no established therapeutic superiority to amoxicillin for uncomplicated acute infections and limited utility in the treatment of complicated infections (43–45).

Broad-spectrum antibiotics are also being extensively used for conditions that often require no antibiotic treatment at all. Diseases with predominantly viral causes (the common cold, unspecified upper respiratory tract infections, and acute bronchitis) accounted for 22% of adult and 14% of pediatric prescriptions for broad-spectrum antibiotics. An additional one third of adult and two thirds of pediatric broad-spectrum prescriptions were for other nonpneumonic acute respiratory tract infections, for which the effectiveness of antibiotic treatment has been debated. Finally, the widening regional and geographic variation in antibiotic choice, which is inconsistent with known patterns of microbial resistance, suggests that prescribing decisions may be largely driven by forces other than microbiological characteristics of disease (1, 2, 40, 46).

Numerous other factors may influence prescribing behavior (20, 47). Once the decision to prescribe has been made, physicians and patients may believe that “newer is better” (48). They may also be attracted by the easy dosing schedules and the low rates of short-term side effects believed to be associated with some new agents (49). Physicians may not fully understand the bacteriologic characteristics of common infections and local resistance patterns and thus may be excessively skeptical about the likelihood and consequences of treatment failure (50, 51). Moreover, antibiotics may often be seen as a way to meet patient needs.
expectations and terminate an office visit (52). Although motivated by perceived clinical benefits, physicians also face strong personal, economic, and legal incentives to reduce repeated visits, improve patient satisfaction, and maximize physician efficiency (20, 52, 53).

Pharmaceutical marketing to both physicians and patients can substantially influence attitudes, beliefs, and behaviors toward prescribing (54–61). Such marketing promotes the use of patented, and thus lucrative, medications. Over the study period, five of the six most prescribed antibiotics that gained at least 1% market share did so in the absence of generic competition. In contrast, every medication that lost at least 1% market share had generic competition before or during the decade. This includes cefaclor, whose use gradually decreased from 8% to 1% of prescriptions after being challenged by generic competition in the mid-1990s.

Our study can only raise, not answer, questions about the factors that influence prescribing behavior. Moreover, our results should be interpreted in light of our study’s limitations. Inaccurate survey completion, including failure to record antibiotics prescribed after the visit (for example, after chest radiography or throat culture results became available), may have led us to underestimate antibiotic use. We were also unable to distinguish initial visits from follow-up visits that may have occurred after a course of antibiotics was completed. Together, these factors may explain why patients with illnesses such as pneumonia and urinary tract infections received fewer antibiotics than would be expected. Data were collected on prescribed medications and therefore may not reflect which medications were actually taken. Finally, some patient diagnoses may have been inaccurately or imprecisely reported. This may include diagnosis shifting, in which physicians implicitly justify their choice of antibiotics by recording a modified diagnosis. However, because use of newer antibiotics increased across a wide variety of diagnoses, only extreme degrees of random misclassification would change our conclusions. Moreover, diagnosis shifting would probably underestimate the use of broad-spectrum antibiotics in clinically inappropriate settings.

Throughout the 1990s, many efforts were made to reduce the volume of unnecessary antibiotic prescribing. Physicians seem to have responded, but their increasing reliance on newer, largely broad-spectrum antibiotics may be breeding a new crisis in antibiotic resistance. Broad-spectrum agents have an important role in clinical care. However, their common use across many diagnoses, including predominately viral illnesses, suggests that they are often prescribed unnecessarily. Improving the quality, not just the quantity, of medication prescribing will require better diagnostic tests, clinical trials, and new types of education (62, 63). Yet this will not be enough. Patients, providers, and health care leaders must make a serious commitment to changing the dynamics of outpatient prescribing. If this is done, the care of individual patients and the health of the community at large can be substantially improved.

From San Francisco Veterans Affairs Medical Center and University of California, San Francisco, San Francisco, California; and Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts.

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Requests for Single Reprints: Michael A. Steinman, MD, Division of Geriatrics, Box 181-G, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121; e-mail, mstein@itsa.ucsf.edu.

Current author addresses and author contributions are available at www.annals.org.

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About a dozen beds away from me was numero 57—I think that was his number—a cirrhosis of the liver case. Everyone on the ward knew him by sight because he was sometimes the subject of a medical lecture. On two afternoons a week the tall, grave doctor would lecture in the ward to a party of students, and on more than one occasion old numero 57 was wheeled on a sort of trolley into the middle of the ward, where the doctor would roll back his nightshirt, dilate with his fingers a huge, flabby protuberance on the man’s belly—the diseased liver, I suppose—and explain solemnly that this was a disease attributable to alcoholism, commoner in the wine-drinking countries. As usual he neither spoke to his patient nor gave him a smile, a nod of any kind of recognition. While he talked, very grave and upright, he would roll the wasted body between his two hands, sometimes giving it a gentle roll to and fro, in just the attitude of a woman handling a rolling-pin. Not that numero 57 minded that kind of thing. Obviously he was an old hospital inmate, a regular exhibit at lectures, his liver long since marked down for a bottle in some pathological museum. Utterly uninterested in what was said about him, he would lie with his colourless eyes gazing at nothing, while the doctor showed him off like a piece of antique china.

George Orwell
“How the Poor Die”
Essays

Submitted by:
Stephen J. Williams, MD
Bologna, Italy

Submissions from readers are welcomed. If the quotation is published, the sender’s name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.—The Editor
Current Author Addresses: Drs. Steinman and Landefeld: Division of Geriatrics, Box 181-G, San Francisco Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121. Dr. Gonzales: Department of Medicine, Box 1211, University of California, San Francisco, San Francisco, CA 94143-1211. Dr. Linder: Division of General Medicine, Department of Medicine, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115.