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Increased Use of Second-Generation Macrolide Antibiotics for Children in Nine Health Plans in the United States

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ABSTRACT. *Background.* Widespread use of broad-spectrum antibiotics contributes to increasing rates of bacterial resistance to antibiotics. Second-generation macrolides have become popular for use among children because of their broad spectrum and favorable dosing and side-effect profiles, although experts do not generally recommend them for use as initial treatment of infections among younger children.

Objective. To assess trends in second-generation macrolide use from 1996 to 2000 among children treated as outpatients in 9 US health plans, including associated diagnoses and use as initial treatment.

Methods. We sampled claims data for 25 000 children, 3 months to <18 years of age, who were enrolled between September 1, 1995, and August 31, 2000, in each of 9 US health plans. Medications dispensed were linked with ambulatory visit claims to assign diagnoses. Dispensings without another antibiotic dispensing recorded in the previous 42 days were analyzed as initial treatment of a new illness episode. We analyzed trends in prescribing overall, for initial therapy, and, within specific diagnoses, for differences among health plans.

Results. From 1995–1996 to 1999–2000, although overall antibiotic use decreased from 1.15 to 0.91 dispensings per person-year, second-generation macrolide use increased from 0.022 to 0.063 dispensings per person-year. Use as a proportion of all antibiotic dispensings increased from 1.9% to 6.9%, and use as initial therapy increased from 1.4% to 6%. For children <6 years of age, second-generation macrolide use as initial therapy increased from 0.9% to 5.0% for otitis media and from 5.2% to 24.0% for pneumonia. There was a wide range of prescribing rates among health plans during the last year of the study, from 0.006 to 0.135 dispensings per person-year.

Conclusions. Despite recent trends toward decreased antibiotic use among children, the use of second-generation macrolides among children has increased dramatically, even among younger children, for whom use for initial treatment of illness is not recommended. Large differences in prescribing rates exist among health plans. Continued efforts to promote the use of narrower-spectrum agents when appropriate are needed. *Pediatrics* 2004;114:1206–1211; antibiotics, macrolides, respiratory infection, managed care.

The overuse of antibiotics for treatment of respiratory tract infections among children is a well-recognized problem.^{1,2} At the level of the prescriber, perceived pressures to prescribe antibiotics include time pressures, the desire for children to return to school and child care more quickly, and parental pressure.^{3–6} National campaigns have been undertaken to promote the judicious use of antibiotics, as part of a strategy to address increasing bacterial resistance.² The Centers for Disease Control and Prevention, in partnership with national physicians' groups, disseminated principles of judicious antibiotic use in 1998.⁷ Two recent studies in large populations^{8,9} showed marked decreases in antibiotic prescribing for children in the late 1990s. However, rates of bacterial resistance continued to increase during the same period, with notable increases in *Streptococcus pneumoniae* strains resistant to penicillin,¹⁰ macrolides,¹¹ and multiple antibiotics.^{10,12} Overuse of macrolide agents in particular has been responsible for substantial bacterial resistance in other countries.^{13,14}

Second-generation macrolides, including azithromycin and clarithromycin, have the advantages of a broad antibacterial spectrum, a less-frequent dosing regimen, and a lower incidence of gastrointestinal side effects, compared with erythromycin. The use of these agents among children may be indicated when their broader coverage is needed or when allergy prohibits the use of other antibiotics. However, clinicians and parents may use them in other situations because of ease of administration or greater perceived effectiveness. Some health plans have placed restrictions on their use, both to contain costs and to promote prescribing of narrower-spectrum agents.

Two previous studies^{9,11} identified increases in the use of second-generation macrolides during the late 1990s. One of those studies,⁹ undertaken by the HMO Research Network Center for Education and

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Research on Therapeutics, linked health plan claims data for outpatient pharmacy dispensing to assigned diagnoses, making it possible to describe prescribing patterns in detail. Here we analyze the data more extensively, to describe trends in second-generation macrolide dispensing for specific respiratory tract infections (such as otitis media) among children in different age groups and to assess rates of use as initial treatment in situations where these antibiotics are not recommended. We also report variations in use among participating health plans and the range of formulary restrictions among plans that may affect prescribing.

METHODS

Data Collection

We analyzed automated claims data from 9 US health plans, varying with respect to location, size, and delivery system models, between September 1, 1995, and August 31, 2000. Sampling and data management methods are described in detail elsewhere.⁹ Briefly, from each of these 9 health plans, we randomly selected 25 000 children, 3 months to <18 years of age, who were enrolled with pharmacy benefits for a minimum of 90 days during any study year. Because antibiotic use follows a seasonal pattern, rates for each year were calculated from September 1 to August 31 of the following year (eg, the 1996 rate was calculated from September 1, 1995, to August 31, 1996). For each individual, claims for all outpatient encounters, excluding emergency department visits, and all antimicrobial agents dispensed were analyzed. Pharmacy claims were generated at health plan-based or retail pharmacies; therefore, they represent actual dispensings of medications, rather than medications prescribed. Medications administered to hospital inpatients were not included.

We used an algorithm described previously¹⁵ to assign a primary diagnosis for each visit if >1 was recorded, giving priority to any diagnosis of a bacterial infection and using a hierarchy of bacterial diagnoses if >1 was present. Final diagnosis categories, with codes from the *International Classification of Diseases, Ninth Revision*,¹⁶ included acute otitis media (codes 382 and 384.0–384.2), otitis media with effusion (codes 381.0–381.4), pharyngitis (codes 034.0, 034.1, 041.0462, and 463), bronchitis (codes 466 and 490), sinusitis (codes 461 and 473), pneumonia (codes 481–483, 484.8, 485–487, 033.0, and 033.9) cold/upper respiratory tract infection (codes 460, 464 [excluding code 464.3], 465, 487 [excluding 487.0], and 786.2), bacterial-other (signifying a non-respiratory tract bacterial infection), and other (including well-child care and nonspecific viral diagnoses). Each antibiotic dispensing was linked to the most recent visit during the 3 days before the dispensing. Dispensings that could not be linked to a visit (which might include refills of previously prescribed medications or medications prescribed during a telephone encounter) were included in rates of antibiotics dispensed but were excluded from calculations of prescriptions attributed to specific conditions.

An initial dispensing for a new episode of bacterial infection was defined as the dispensing of an antibiotic for children who had received no other antibiotic dispensing in the preceding 42 days. We divided antibiotics into 8 categories for reporting, ie, first-generation penicillins (ampicillin, amoxicillin, penicillin, and dicloxacillin), second-generation penicillins (amoxicillin/clavulanate), first-generation macrolides (erythromycin and erythromycin/sulfisoxazole), second-generation macrolides (azithromycin and clarithromycin), cephalosporins, trimethoprim/sulfamethoxazole, tetracyclines, and others.

To describe restrictions on second-generation macrolide use, we queried the study investigator at each health plan about any relevant formulary policies during the period 1995–2000. Investigators from all 9 plans responded, using a variety of health plan contacts to collect this information. For each drug, we categorized the policies in effect during the final study year as no restrictions or provider education only, increased burden for prescribers (such as a requirement for prior authorization or prescribing restricted to infectious disease physicians only), or increased copayment for families.

Analyses

Rates of dispensing in each health plan are reported as events per person-year. Trends in dispensing of second-generation macrolides and differences among health plans were analyzed by using Poisson regression and χ^2 analysis for comparison of proportions. For selected diagnoses, dispensings of second-generation macrolides as initial treatment were also analyzed as a percentage of all initial antibiotic dispensings, with differences being analyzed with the χ^2 test. We also analyzed dispensings for children in the age groups of 3 months to <3 years, 3 to <6 years, 6 to <12 years, and 12 to <18 years, because indications for use as initial treatment vary with age and illness category. All analyses were conducted with SAS statistical software, version 8 (SAS Institute, Cary, NC). The study was approved by institutional review boards at each of the 9 participating sites.

RESULTS

Demographic features of the 9 health plans are described in detail elsewhere.⁹ The health plans varied in size from 240 000 to 3.1 million enrollees, represented each major region of the country, and included both staff/group model and network/independent practice association models. Racial/ethnic minority membership ranged from 6% to 38%. Because included children were enrolled for varying periods, the number of person-years (number of persons multiplied by the length of time observed) of observation varied among the health plans, from 55 000 to 73 000 person-years.

The rate of dispensing of all antibiotics to children in the plans decreased during the 5-year study period, from 1.15 to 0.91 dispensings per person-year.⁹ The overall prescribing rate of “non-first-line” antibiotics, defined as second-generation macrolides, second-generation penicillins, cephalosporins, and quinolones, increased from 0.22 dispensings per person-year (19.2% of all dispensings) to 0.24 dispensings per person-year (26.4% of all dispensings) ($P < .001$). The rate of second-generation macrolide dispensing increased from 0.022 dispensings per person-year (1.9% of all dispensings) to 0.063 dispensings per person-year (6.9% of all dispensings) ($P < .001$), with azithromycin representing 75% of second-generation macrolide dispensings in 2000. When we limited our analysis to children <6 years of age, the rate of dispensing of second-generation macrolides showed a similar increase, from 0.034 dispensings per person-year (1.8% of all dispensings) to 0.116 dispensings per person-year (8.0% of all dispensings) ($P < .001$). First-generation macrolide dispensing as a percentage of all dispensings decreased from 10.4% to 6.2%, and first-generation penicillin dispensing remained relatively stable, decreasing from 51% to 50% of all dispensings.

All plans showed increases in the rates of second-generation macrolide dispensing during this period (Fig 1). Dispensing rates among health plans varied between 0.006 and 0.135 dispensings per person-year ($P < .001$) in 2000. During the study period, several plans instituted formulary restrictions for one or both antibiotics, whereas none discontinued restrictions on either antibiotic. Four plans had no restrictions on use, with dispensing rates in 2000 varying between 0.023 and 0.082 dispensings per person-year. Three plans had higher patient copayments for azithromycin, with rates ranging from 0.042 to 0.135

Fig 1. Second-generation macrolide dispensing rates for children in each of 9 health plans (thin lines) and combined (thick line), in 1996–2000.

dispensings per person-year, and 2 plans restricted physician prescribing for azithromycin, with rates of 0.005 and 0.057 dispensings per person-year. The plan with the lowest dispensing rate was also the only plan that reported a requirement for prior authorization for both azithromycin and clarithromycin use. The small number of health plans precluded statistical analysis of the association between formulary restrictions and prescribing rates.

In each year, between 66% and 69% of all antibiotic

dispensings were administered for initial treatment of an illness episode. During the 5-year period, use of second-generation macrolides as initial treatment increased from 1.4% to 6.0% of all initial antibiotic dispensings ($P < .001$). Similarly, of all second-generation macrolide dispensings, the proportion that was used as initial treatment increased from 48% to 60% ($P < .001$).

Figure 2 presents the use of second-generation macrolides as initial treatment according to diagno-

Fig 2. Second-generation macrolide use as a percentage of all initial dispensings for 5 illness categories, according to age group, in 1996 and 2000. URI indicates upper respiratory tract infection.

sis in 1996 and 2000, according to age group. For children 3 months to <6 years of age, use for initial treatment of otitis media increased from 0.9% to 5.0% and use for treatment of pneumonia increased from 5.2% to 24.0%. The proportion of use for initial treatment of pneumonia for children 3 months to <6 years of age in 2000 ranged from 0% to 34% among health plans. ($P < .001$).

DISCUSSION

This study of children from 9 large health plans across the United States provides details of the dramatic increase in second-generation macrolide use in the late 1990s. It uses pharmacy and visit claims data to link dispensings with diagnoses and to identify drugs administered as initial therapy. These data show not only an overall increase in the use of second-generation macrolides but also an increase in the use as initial therapy. The rate of use as initial treatment was high for diagnoses for which guidelines and expert opinion do not recommend these agents,¹⁷⁻²⁰ specifically for pneumonia among younger children. These observed patterns during a time of overall reductions in antibiotic use are concerning, because limiting use of broad-spectrum antibiotics to children who need them is highly desirable, to provide more-targeted therapy and to avoid contributing to bacterial antibiotic resistance.

The striking increase in the use of second-generation macrolide antibiotics for children contrasts with the overall downward trend in antibiotic use during the late 1990s. Our findings are consistent with findings for a national sample during this time period. We found a 241% increase in dispensing of second-generation macrolides for children <6 years of age from 1996 to 2000, whereas investigators using data from the National Ambulatory Medical Care Survey found a 320% increase in macrolide use among children <5 years of age from 1993 to 1999, with azithromycin comprising the majority of prescriptions in this class.¹¹ The magnitude of increase in our sample might have been even greater in a population without health plan restrictions on use.

Our data agree with recent findings for adults,²¹ showing increased use of nonrecommended antibiotics for treatment of pharyngitis, as well as frequent use of broad-spectrum agents for treatment of respiratory tract infections.²² Use of second-generation macrolides accounted for the vast majority of the increase in non-first-line antibiotic prescribing in our sample from 1996 to 2000. The proportions of both second-generation macrolides (6.9%) and non-first-line antibiotics in general (26.4%) that were prescribed for our sample of children in 2000 were considerably less, however, than those for a national sample of adults between 1997 and 1999 (21% and 54%, respectively).²² The decrease in first-generation macrolide prescribing from 10.4% to 6.2% suggests that better-tolerated but more costly second-generation macrolides might have partially replaced this class during the period of the study. Some contribution might also have resulted from a decrease in the use of trimethoprim-sulfamethoxazole,⁹ which was frequently used for penicillin-allergic patients before

increases in bacterial resistance during this period. First-generation penicillins remained the most frequently dispensed antibiotics in our sample, accounting for approximately one-half of all dispensings.

The shift away from reserving second-generation macrolides for second-line therapy is clearly evident in these data; second-generation macrolides were 4 times as likely to be selected for initial treatment of an infection in 2000 as in 1996. This was particularly true for younger children. For children 3 months to <6 years of age, there was a 5.5-fold increase in dispensing for otitis media; although the absolute percentage of second-generation macrolide use as initial treatment remained fairly low (5.0%), otitis media was the single diagnosis most responsible for the increase. Guidelines do not endorse second-generation macrolides as initial therapy for otitis except when type I allergy to other antibiotics dictates their use,^{18,23,24} and we have no reason to think that the prevalence of penicillin allergy increased during this period.

Perhaps more concerning is the increase in the use of broad-spectrum antibiotics as initial treatment for pneumonia among children between 3 months and 6 years of age and for bronchitis. Although the absolute number of dispensings attributable to these diagnoses was small, compared with overall use of these antibiotics, the percentage of time that a second-generation macrolide was chosen as initial treatment increased to 24% for pneumonia and 20% for bronchitis. Although atypical bacterial infections occur with some frequency in all age groups,²⁵ penicillins, not macrolides, are generally recommended as initial therapy for pneumonia among children up to 5 years of age.^{19,26,27} Bronchitis is generally recognized as a viral illness for which no antibiotics are needed.²⁰

Although our study provides no evidence for a direct link between increased second-generation macrolide use and bacterial resistance, the increase in rates of use reported here coincides with the observed increase in macrolide resistance among *S pneumoniae* isolates from 10.6% to 20.4% between 1995 and 1999.¹¹ In that study, the average minimal inhibitory concentration among resistant strains increased to the point at which treatment failure would be expected to occur with second-generation macrolides. Such a link between use and resistance was demonstrated for group A streptococci in other studies,¹³ and decreased use of macrolides was associated with decreased resistance in group A streptococci, within a short period, in other countries.¹⁴ It is not known whether the trend toward increased *S pneumoniae* resistance may also be reversible.

Our data support the conclusion that increased use of second-generation macrolides as initial therapy accounts for the majority of the overall increase in the use of this class of antibiotics. One explanation for this increase might be the well-publicized increase in *S pneumoniae* resistance to penicillin during this period,¹⁰ which might have led clinicians to increase the use of nonpenicillin agents as a group for initial treatment. However, resistance to macrolides

also increased during this period,¹¹ and macrolides may not be superior to high-dose penicillins for treatment of many non-penicillin-susceptible strains. A more likely explanation for the increase is the greater ease of administration of second-generation macrolides, which are generally given only once or twice per day, often for shorter courses, and are well tolerated. To reverse the increase in nonrecommended use of these agents, these advantages must be taken into consideration. The advantages of giving fewer doses of antibiotics may be achievable in other ways; short-course, narrow-spectrum antibiotic treatment for otitis media was shown to be effective in some studies,²⁸ and the practice of "watchful waiting" for otitis media in selected circumstances, completely eliminating the need to administer antibiotics, has been endorsed as an option by some experts and professional societies.^{23,29-32} Finally, the observed increase in second-generation macrolide use as initial therapy for pneumonia among younger children and for treatment of bronchitis suggests that renewed educational efforts directed toward parents and physicians may be needed.

The variation in dispensing rates among health plans was large, even among groups with similar formulary policies. We were unable to conduct a meaningful statistical analysis of the relationship between formulary policies and prescribing rates because of the small number of health plans in the study. However, the observation that the plan with the most restrictive prescribing policy had the lowest rates of second-generation macrolide dispensing highlights the need for additional research on how such restrictions influence antibiotic prescribing patterns. Increased copayments have been found to be effective in reducing the use of numerous medications among adults,^{33,34} but the effects of restrictions on prescribing trends for medications used to treat acute conditions among children have not been well described.

Our study population was large, geographically diverse, and selected at random from within 9 health plans; however, it might not be representative of the entire US population. The proportion of Medicaid-insured patients was low, and formulary policies might differ from those in other delivery systems. However, the large increase in second-generation macrolide use was also observed for a nationally representative sample during this period.¹¹ Because most health plans in our sample had some restrictions on the use of these agents, our results may represent an underestimate of the national increase in prescribing of these agents. In addition, prescriptions billed to other insurers, paid for out of pocket, or dispensed as samples were not included in this study. Finally, there was not enough detail regarding factors other than formulary restrictions that might have affected prescribing within each plan to permit a full analysis of the relationship between restrictions and prescribing. Studies with greater focus on these factors may be able to shed light on the effectiveness of such policies in promoting appropriate prescribing.

CONCLUSIONS

Second-generation macrolide use among children increased greatly during the late 1990s, in contrast to the nationwide decrease in antibiotic use. Use of these agents for initial therapy increased to an even greater extent than did overall use, as did use among younger children. These patterns conflict with current expert recommendations for judicious use of antimicrobial agents. Use of effective narrow-spectrum antibiotics for children should remain a priority, and dissemination of strategies to improve the ease of their use is needed.

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