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THE EFFECT OF CHANGES IN THE CONSUMPTION OF MACROLIDE ANTIBIOTICS ON ERYTHROMYCIN RESISTANCE IN GROUP A STREPTOCOCCI IN FINLAND

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ABSTRACT

Background In the early 1990s there was an increase in erythromycin resistance among group A streptococci in Finland. In response, policies regarding outpatient antibiotic therapy were changed, and nationwide recommendations were issued that called for reductions in the use of macrolide antibiotics for respiratory and skin infections in outpatients. We studied the effect of this policy on the pattern of erythromycin resistance throughout Finland.

Methods From 1991 through 1996, a total of 39,247 group A streptococcal isolates from throat swabs (82 percent of the isolates) and pus samples (18 percent) and 290 isolates from blood cultures were studied in regional microbiology laboratories. The susceptibility of the isolates to erythromycin was tested by the disk-diffusion or the screening-plate method.

Results Consumption of macrolide antibiotics decreased from 2.40 defined daily doses per 1000 inhabitants per day in 1991 to 1.38 in 1992 ($P=0.007$) and remained near the lower level during the study period. The change in consumption was followed by a steady decrease in the frequency of erythromycin resistance among group A streptococcal isolates from throat swabs and pus samples, from 16.5 percent in 1992 to 8.6 percent in 1996 (odds ratio for 1996 as compared with 1992, 0.5; 95 percent confidence interval, 0.4 to 0.5).

Conclusions In Finland, after nationwide reductions in the use of macrolide antibiotics for outpatient therapy, there was a significant decline in the frequency of erythromycin resistance among group A streptococci isolated from throat swabs and pus samples. (N Engl J Med 1997;337:441-6.)

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DURING the past decade there has been a resurgence of severe forms of disease caused by group A streptococci (*Streptococcus pyogenes*) in various parts of the world.¹ In the management of group A streptococcal infections, an important question is the effectiveness of antimicrobial therapy. Fortunately, group A streptococci are still susceptible to penicillin, which has remained the drug of choice.² In Finland, however, a troubling increase in resistance to erythromycin, which is widely used to treat patients with allergies to penicillin, was noted in the early 1990s. The frequency of erythromycin resistance among isolates of group A streptococci from pharyngeal and pus samples increased from approximately 5 percent in 1988–1989 to 13 percent in 1990.³

During the 1980s, before the increase in resistance occurred, the consumption of erythromycin in Finland had nearly tripled.³ An analysis that included 92 percent of all health-authority areas in the country confirmed that the level of erythromycin use in an area correlated significantly with the level of erythromycin resistance among group A streptococci isolated in that area.⁴

After the nationwide increase in resistance to erythromycin among group A streptococci was recognized, it became clear that the only way to control this clinically important problem in Finland was to

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restrict the use of erythromycin and, because of cross-resistance, of other macrolide antibiotics.³ National guidelines were therefore issued that recommended reductions in the use of these agents in the treatment of respiratory and skin infections in outpatients.^{5,6} The problem of erythromycin resistance received wide publicity in Finland, and specialists in the field of infectious diseases and microbiology agreed on the need for changes in policies regarding outpatient antibiotic therapy. Finnish physicians were informed and educated about the use of alternative drugs, and a considerable reduction in the use of macrolide antibiotics by outpatients soon resulted.

We undertook this study to investigate whether the recommended reductions in the outpatient use of macrolide antibiotics would lead to decreased erythromycin resistance among group A streptococci.

METHODS

Use of Macrolide Antibiotics

Data on the use of macrolide antibiotics were obtained from *Finnish Statistics on Medicines 1995*, published by the National Agency for Medicines and the Social Insurance Institution.⁷ Consumption is expressed in terms of the number of defined daily doses per 1000 inhabitants per day.

Group A Streptococcal Isolates

A total of 39,247 isolates of group A streptococcus from throat swabs (82 percent of the isolates) and pus samples (18 percent) were studied from 1991 through 1996 in 26 regional microbiology laboratories of the Finnish Study Group for Antimicrobial Resistance network. In the analysis of regional differences, the participating laboratories were grouped, according to the origin of the isolates, into five geographic areas (see the Appendix). In a given year, only one isolate per patient was included in the study; the majority of the patients could be identified.

Each year from 1992 through 1996, a total of 20 to 22 laboratories (3 to 5 from each area) participated in the study on a voluntary basis; the exception was the year 1993, when data on resistance were obtained from 15 laboratories (2 to 4 from each area). In 1991, data on resistance were not systematically collected, and data for that year were obtained only from the Kuopio laboratory. The variation from year to year in the number of isolates studied was caused by variations in the number of laboratories taking part in the study and possibly also by epidemiologic variation in the number of group A streptococcal infections. In 1994, most streptococci studied were isolated from June through December, a fact that explains the lower number of isolates studied during that year.

Nationwide collection of group A streptococcal isolates from patients with bacteremic infections has been carried out in Finland since 1988.⁸ During 1992 through 1996, a total of 290 group A streptococci from blood cultures (53 to 66 isolates per year) were collected by clinical microbiology laboratories and sent to the Department of Bacteriology of the National Public Health Institute in Helsinki. Isolates were identified as described previously.^{3,4}

Detection of Erythromycin Resistance

The susceptibility of the isolates to erythromycin was tested in the study laboratories by the disk-diffusion method and the screening-plate method, as previously described.^{4,9} The reliability of these methods was ensured by histogram analyses of the disk-

test results and by comparing the results obtained with these methods with those obtained with the minimal-inhibitory-concentration plate-dilution method.^{4,9} As part of an epidemiologic survey of the TIM1 serotype of group A streptococcal isolates in Finland conducted at the same time as this study,⁸ group A streptococcal isolates were sent to either the Antimicrobial Research Laboratory of the National Public Health Institute, Turku, or the Department of Bacteriology of the National Public Health Institute, Helsinki, by 21 regional laboratories from June through December 1994 and by 14 regional laboratories during 1995; at these central laboratories, the susceptibility of the isolates to erythromycin was confirmed with the screening-plate method.⁹

The susceptibility to erythromycin of all isolates from blood cultures during the study period was reevaluated in the Department of Bacteriology of the National Public Health Institute by the screening-plate method.⁹ With all the methods used, the definition of erythromycin resistance coincided with a minimal inhibitory concentration of ≥ 1 μg per milliliter, a breakpoint recommended by the National Committee for Clinical Laboratory Standards.¹⁰

Statistical Analysis

The proportions of group A streptococcal isolates that were erythromycin-resistant in different years were compared in a logistic-regression model.¹¹ This method tests the significance of the overall differences among the proportions of resistant isolates in all the years by entering the year as a categorical explanatory variable in the model. Odds ratios and 95 percent confidence intervals were calculated for the differences among the years and to demonstrate any trend. The reference year in the calculations of the odds ratio was 1992, except in the analysis of data from the Kuopio laboratory. Since data from 1990³ through 1996 were available from that laboratory, the reference year in the odds-ratio calculations was 1990. The Mann-Whitney U test was used to analyze the differences in consumption of macrolide antibiotics among the years. P values below 0.05 were interpreted as indicating statistical significance. The logistic-regression analysis was performed with the SAS statistical package.¹²

RESULTS

Consumption of Macrolide Antibiotics

At the end of the 1970s, outpatient consumption of macrolide antibiotics in Finland was 1 defined daily dose per 1000 inhabitants per day (Fig. 1). In the 1980s consumption increased sharply, so that more than 2 defined daily doses per 1000 inhabitants per day were sold each year from 1985 through 1991. In 1988, consumption reached almost 3 defined daily doses (Fig. 1).

The recommendations to reduce the use of macrolides were issued at the end of 1991 and the beginning of 1992. Total use of macrolide antibiotics in outpatient therapy decreased from 2.40 defined daily doses per 1000 inhabitants per day in 1991 to 1.38 in 1992 ($P=0.007$). Since then, consumption has remained at a level of 1.28 to 1.74 defined daily doses per 1000 inhabitants per day (Fig. 1).

Until 1990, erythromycin was the only macrolide drug available in Finland (Fig. 1). In 1991 it accounted for 86 percent of the total consumption of macrolide by outpatients; by 1995 its share had decreased to 33 percent. In 1995, roxithromycin accounted for 41 percent of the total macrolide con-

sumption in the country, azithromycin for 24 percent, and clarithromycin for 2 percent. The emerging use of the new macrolides caused an increase in the total consumption of macrolides by outpatients in 1995 (Fig. 1).

Resistance to Erythromycin

Susceptibility to erythromycin was tested in a total of 39,247 group A streptococcal isolates from throat-swab and pus samples. On a national level, no decrease from the earlier level in the frequency of erythromycin resistance was observed during 1992, when the frequency was 16.5 percent, and 1993, when it was 19.0 percent (Fig. 2). However, a nationwide decline began in 1994, when the rate of resistance decreased to 15.6 percent, followed by an additional decrease to 10.0 percent in 1995 and to 8.6 percent in 1996 (Fig. 2). In the statistical analysis, calculations of the odds ratio indicated that a significant trend toward lower levels of resistance started after 1993 in Finland (Table 1). The odds ratios also indicated that the ratio of resistant isolates to susceptible isolates in the whole country was 2.4 times as high in 1993 as in 1996 and 2.0 times as high in 1992 as in 1996 (Table 1).

When the data were analyzed according to geographic area (southern, western, eastern, central, and northern Finland), some variation in the patterns of resistance was found among the five areas (Fig. 3). However, the decrease in the frequency of resistance during the study period was statistically significant in all areas (Table 1). The most unusual pattern was in northern Finland, where a strong increase in the frequency of resistance occurred during 1994, after which resistance started to decline significantly (Fig. 3 and Table 1).

A separate analysis was performed on data from two laboratories, in Kuopio and Tampere, both in central Finland. Among the isolates from both laboratories there was a statistically significant decrease in the frequency of resistance during the study period (Fig. 4). In Kuopio, a significant decrease had already occurred in 1992.

When the available data on isolates from throat swabs and those from pus samples were analyzed separately, a significant decrease was apparent for both types of isolates, nationally and also in all geographic areas, except for isolates from pus samples in western Finland (data not shown).

A trend similar to that seen for throat-swab and pus samples was also evident in the 290 isolates from blood cultures that were studied; 8.8 percent of the group A streptococcal isolates were resistant to erythromycin in 1992, as were 16.7 percent in 1993; the corresponding figures for subsequent years were 6.7 percent in 1994, 5.7 percent in 1995, and 4.5 percent in 1996. The decrease was not statistically significant, however.

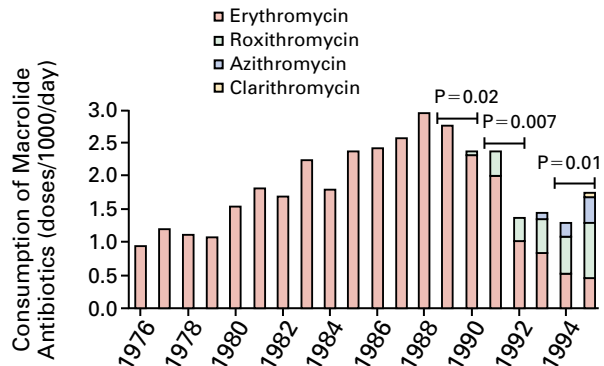


Figure 1. Total Consumption of Macrolide Antibiotics by Outpatients in Finland from 1976 through 1995. Consumption is expressed in terms of defined daily doses per 1000 inhabitants per day.

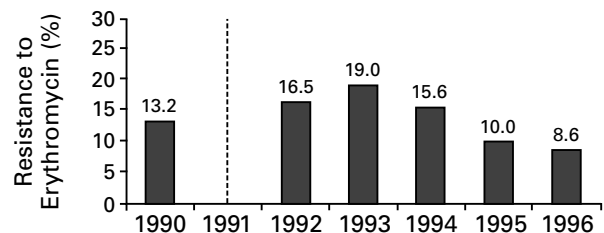


Figure 2. Frequency of Resistance to Erythromycin among Group A Streptococcal Isolates from Throat-Swab and Pus Samples in Finland in 1990 and in 1992 through 1996. The data from 1990,³ obtained from six regional microbiology laboratories, are shown here for comparison; the dashed line indicates that the 1990 data were not included in the statistical analyses reported in the text.

DISCUSSION

In Finland, there was a steady and statistically significant decline in erythromycin resistance among group A streptococcal isolates from throat-swab and pus samples after a reduction in the use of macrolide antibiotics in outpatient therapy. We believe that the reduced selection pressure of macrolides on group A streptococci is the chief explanation for the decrease, although temporal relations between the reduction in macrolide consumption and the decrease in resistance to erythromycin do not prove causality. However, the concept of a causal connection between the change in patterns of use and the change in the frequency of resistance is supported by the fact that restrictions on the use of a single class of antimicrobial agents — the macrolides — was followed by a decrease in resistance to those agents; no other type of antibiotic resistance was linked to macrolide resistance.¹³

More data are gradually accumulating on the positive association between the use of antimicrobial

TABLE 1. ERYTHROMYCIN RESISTANCE AMONG GROUP A STREPTOCOCCAL ISOLATES FROM THROAT-SWAB AND PUS SAMPLES IN 1992 THROUGH 1996 IN FINLAND AS A WHOLE AND IN FIVE GEOGRAPHIC AREAS.

GEOGRAPHIC AREA AND YEAR	NO. OF LABORATORIES	TOTAL NO. OF ISOLATES	NO. OF RESISTANT ISOLATES	ODDS RATIO (95% CI)*	P VALUE†
Finland					<0.001
1992	21	10,262	1697	1.0	
1993	15	5,034	956	1.2 (1.1–1.3)	
1994	22	4,794	750	0.9 (0.9–1.0)	
1995	20	11,193	1120	0.6 (0.5–0.6)	
1996	22	7,734	666	0.5 (0.4–0.5)	
Southern Finland					<0.001
1992	5	2,439	330	1.0	
1993	4	1,586	275	1.3 (1.1–1.6)	
1994	5	670	61	0.6 (0.5–0.9)	
1995	5	4,658	242	0.4 (0.3–0.4)	
1996	5	2,822	266	0.7 (0.6–0.8)	
Western Finland					<0.001
1992	3	1,947	307	1.0	
1993	3	625	102	1.0 (0.8–1.3)	
1994	4	876	143	1.0 (0.8–1.3)	
1995	3	1,070	123	0.7 (0.6–0.9)	
1996	5	667	59	0.5 (0.4–0.7)	
Eastern Finland					<0.001
1992	4	1,565	427	1.0	
1993	3	1,327	324	0.9 (0.7–1.0)	
1994	4	916	134	0.5 (0.4–0.6)	
1995	3	1,413	155	0.3 (0.3–0.4)	
1996	3	1,360	143	0.3 (0.3–0.4)	
Central Finland					<0.001
1992	4	2,019	350	1.0	
1993	3	1,095	200	1.1 (0.9–1.3)	
1994	4	1,193	118	0.5 (0.4–0.7)	
1995	4	1,324	76	0.3 (0.2–0.4)	
1996	4	2,440	179	0.4 (0.3–0.5)	
Northern Finland					<0.001
1992	5	2,292	283	1.0	
1993	2	401	55	1.1 (0.8–1.5)	
1994	5	1,139	294	2.5 (2.1–3.0)	
1995	5	2,728	524	1.7 (1.4–2.0)	
1996	5	445	19	0.3 (0.2–0.5)	

*In calculations of the odds ratios for resistance, 1992 served as the reference year. CI denotes confidence interval.

†P values were calculated according to the logistic-regression model (see the Methods section). P values below 0.05 indicate that a statistically significant decrease in resistance occurred during the study period.

agents and the frequency of antimicrobial resistance in the community.^{4,14–17} Concurrent follow-up of both the consumption of antimicrobial agents and bacterial drug resistance over several years has not been reported for outpatients, however. For example, in Japan, where the frequency of erythromycin resistance among group A streptococci increased during the 1970s to approximately 80 percent¹⁸ after a rapid increase in the use of macrolides,¹⁴ no follow-up data on the relation between the use of macrolides and resistance to these drugs have been published, although decreasing rates of resistance have been reported.^{19,20} At a hospital in Asahikawa, Japan, an analysis of data on 670 group A streptococcal isolates collected during the 10-year period

from 1981 through 1990 (an average of 67 isolates per year) showed a decrease in resistance from 22 percent to almost zero²⁰; 2 percent of resistant isolates were among 205 pharyngeal isolates collected in Tokyo and at the U.S. Air Force Base at Yokota in 1990 and 1991.¹⁹ Our data confirm that the level of antimicrobial resistance in the community can be reduced by decreasing the use of antibiotics. The same temporal relation between a decrease in the use of an antibiotic agent and a decrease in the frequency of resistance to the same agent has previously been demonstrated in hospital settings.^{21–23}

The recommendation that the use of macrolide antibiotics in Finland be reduced was surprisingly effective; consumption of macrolides by outpatients

was nearly halved within one year (Fig. 1). This decline in use indicates that informing physicians about the current frequency of antimicrobial resistance among community-acquired pathogens and educating them about the use of antibiotic agents in outpatient therapy are important in the battle against antibiotic-resistant bacteria. In this case, the physicians were reached mainly through the *Finnish Medical Journal* and lectures at national and local meetings for general practitioners.

Because the problem of resistance to erythromycin gained wide publicity in the country and the specialists in the fields of infectious diseases and microbiology agreed on the need for change in the use of antibiotics to treat outpatients, the recommendations regarding the use of macrolides were also accepted by the pharmaceutical companies. When the consumption of macrolide drugs decreased, however, the reduction was compensated for by an increase in the use of other antibiotics, since the total rate of use of antimicrobial agents remained unchanged.^{7,24}

The decrease in the consumption of macrolides was uniform throughout the country (data not shown). When the recommendations were issued, it was expected that the use of macrolide antibiotics would have to be maintained at a reduced level for several years before resistance would start to decline, since antibiotic-resistant organisms, like any other bacteria, may spread in favorable circumstances, even without the selection pressure exerted by antibiotics.²⁵ Fortunately, the rate of resistance started to decline markedly after two years of reduced consumption. The changes in the frequency of resistance during the study period were more or less uniform in the different geographic areas, except in northern Finland, where the rate peaked and decreased later than elsewhere (Fig. 3 and Table 1). Another, more local, temporal difference was observed in central Finland, where the overall frequency of resistance started to decrease after 1993; among the isolates from the Kuopio laboratory, however, a significant decrease had already occurred in 1992 (Fig. 3 and 4 and Table 1). The contribution of geographic or other local factors to these temporal patterns is difficult to assess and therefore remains unknown. In 1992 through 1996, there were no epidemics of severe group A streptococcal infections in Finland, a fact that explains the rather low annual number of isolates from blood cultures, among which the proportion of resistant organisms decreased nonsignificantly.

We hope that the frequency of erythromycin resistance among group A streptococcal isolates will continue to decline in Finland. However, we are concerned that there may be a gradual shift toward wider use of the newer macrolides, especially roxithromycin and azithromycin (Fig. 1). If this happens, it

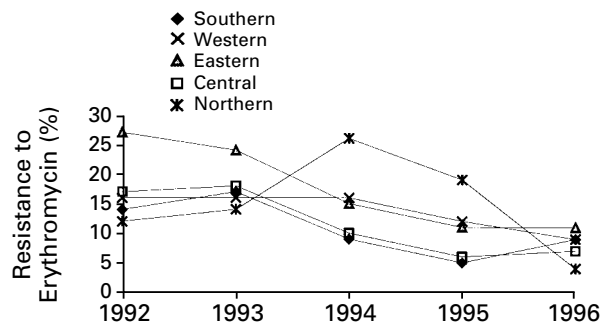


Figure 3. Frequency of Resistance to Erythromycin among Group A Streptococcal Isolates from Throat-Swab and Pus Samples According to Geographic Area, 1992 through 1996.

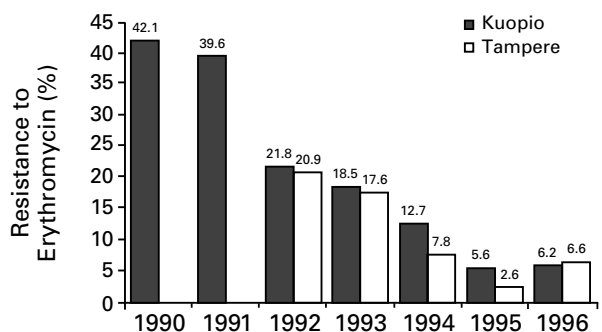


Figure 4. Frequency of Resistance to Erythromycin among 3022 Group A Streptococcal Isolates from Throat-Swab and Pus Samples (230 to 537 Isolates per Year) from the Kuopio Laboratory in 1990 through 1996 and among 2155 Isolates (153 to 814 per Year) from the Tampere Laboratory in 1992 through 1996.

The frequency of resistance decreased significantly ($P < 0.001$) during the study period in both Kuopio (odds ratio for 1996 as compared with 1990, 0.09; 95 percent confidence interval, 0.06 to 0.14) and Tampere (odds ratio for 1996 as compared with 1992, 0.3; 95 percent confidence interval, 0.2 to 0.4).

remains to be seen at what level of macrolide consumption erythromycin resistance in group A streptococci will begin to increase once again. Since there is cross-resistance among erythromycin, roxithromycin, clarithromycin, and azithromycin,¹³ the newer macrolides may well select for resistance.

In conclusion, our study documented that recommendations to decrease the use of erythromycin and other macrolides by outpatients were followed by a significant decrease in erythromycin resistance among group A streptococci in Finland. These results provide hope for the management of other problems of antimicrobial resistance in outpatient therapy as well.²⁵⁻²⁷ Thus, guidelines for the prescription of antibiotics for outpatient therapy should be regarded as an important tool in the management of problems of antimicrobial resistance in the community.

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APPENDIX

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