Macrolide Prescriptions and Erythromycin Resistance of *Streptococcus pyogenes*

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This study shows a significant association between the number of macrolide prescriptions reimbursed by the Italian National Health Service and resistance of *Streptococcus pyogenes* to erythromycin in children from a region in northern Italy with high prevalence of erythromycin resistance. Recent prescription of a macrolide (especially azithromycin) is a predictor of erythromycin resistance, as well as a possible risk factor for resistance at a community level.

High prevalence of macrolide resistance in *Streptococcus pyogenes* has been recorded in several European countries [1]. A significant positive correlation between macrolide use and erythromycin resistance has been found in some studies using an ecological analysis; those studies correlated treatment with macrolides either with rates of erythromycin resistance of *S. pyogenes* in different areas (provinces, regions, or countries) or with a temporal trend of erythromycin resistance [1–5]. The main limitation of the available studies, which collect data only at the population level, is that the ecological bias does not allow for investigation of associations between individual exposure to macrolides and erythromycin resistance. For this reason, studies that collect data at the individual level are needed.

Erythromycin resistance in *S. pyogenes* is common in Emilia-Romagna, a region in northern Italy with 4 million inhabitants, where heavy exposure of the pediatric population to antibiotics (especially macrolide exposure in older children) has been observed [6, 7]. We aimed to investigate the association between previous prescription of macrolides and isolation of erythromycin-resistant *S. pyogenes* with throat swab specimen culture among the pediatric population of Emilia-Romagna.

Methods. The study population included consecutive children aged 0–14 years who had a throat swab specimen culture performed in 1 of the 9 laboratories in Emilia-Romagna during 2003 that was positive for *S. pyogenes*. Those laboratories, belonging to 7 of the 16 local health authorities of the region, participate in the Antimicrobial Resistance Surveillance System of Emilia-Romagna, which is based on electronic transmission of bacteriology data from regional laboratories with high volume of activity (performance of $\geqslant$500 blood cultures per year). For children with >1 positive culture during 2003, the first positive culture of the year was used. Data from laboratory databases were linked with an integrated database on patterns of care of the Emilia-Romagna resident population, including data on drug prescriptions received for outpatient therapy and reimbursed by the Italian National Health Service and data on admissions to public and accredited private hospitals. Thus, it was possible to obtain data on systemic antibiotic prescriptions (antibiotics from the J01 anatomic therapeutic chemical group [8]) and hospital admissions during the 12-month period before patients' throat swab specimens were collected.

The outcome of interest from this study was the resistance of *S. pyogenes* to erythromycin; those strains with erythromycin MICs of $\geqslant$1 μg/mL or erythromycin zone diameters of $\leqslant$15 mm (with a 15-μg disk) were defined as resistant [9]. Case patients were those with an erythromycin-resistant strain, according to this definition, and control subjects were those with a nonresistant strain.

Stata software, version 8.0 (Stata), was used for analysis. A significance level of .05 was used throughout. Categorical variables were compared using the χ^2 test. Multivariate analysis was performed with unconditional logistic regression using the likelihood ratio test; variables associated with P values of $\leqslant$.1 in the univariate analysis were included in the multivariate analysis.

Results. The study population included 1301 children who had $\geqslant$1 throat swab specimen culture that was positive for *S. pyogenes* in 2003. Seventy-six children were excluded, either because they did not reside in Emilia-Romagna or because their individual identification information from laboratory databases did not match information from the integrated database on patterns of care (48 children), or because the isolated strains were not tested for susceptibility to erythromycin (28 children). Analysis was performed with the remaining 1225 children. The prevalence of resistance to erythromycin was 25% (95% CI,

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22%–27%) among the whole population, and it was 21% among children who had not received a macrolide during the year before their throat swab specimen culture (818 [67%] of 1225 children). When azithromycin was prescribed during the month before culture, 2–3 months before culture, and 4–12 months before culture, the prevalence of erythromycin resistance was 67%, 44%, and 23%, respectively. When macrolides other than azithromycin were prescribed during the month before culture, 2–3 months before culture, and 4–12 months before culture, the prevalence of resistance was 41%, 38%, and 20%, respectively (figure 1).

One hundred ninety of 1225 children were treated with macrolides in the 3-month period before throat swab specimen collection (63 were treated with azithromycin; 86 with clarithromycin; 30 with rokitamycin; and 11 with other agents). Use of macrolides in the 3 months before throat swab specimen collection and geographical area (local health authority of the laboratory where throat swab specimen cultures were processed) were associated with erythromycin resistance in both univariate and bivariate analyses ($P < .001$). After adjusting for the local health authority of the laboratory, ORs of erythromycin resistance, compared with no use of macrolides during the 3 months before throat swab specimen collection, were 5.0 (95% CI, 2.9–8.6) for use of azithromycin and 2.2 (95% CI, 1.5–3.3) for use of other macrolides. The other variables considered (age, sex, hospital admission during the previous year, and prescription of antibiotics other than macrolides) were not associated with the outcome.

Discussion. Our results show that prevalence of resistance to erythromycin varied according to previous use of macrolides and time at which they were prescribed; prevalence of resistance was highest when macrolides were administered during the last month before the throat swab specimen was collected and if azithromycin was prescribed. Prevalence of resistance decreased with increasing lag between throat swab specimen collection and previous prescription of macrolides and returned to baseline (defined as the prevalence of resistance in children who did not receive macrolides during the year before culture) if prescriptions were given >3 months before throat swab specimen collection (figure 1). When prescriptions in the 3 months before throat swab specimen collection were considered, previous use of azithromycin and other macrolides was strongly associated with resistance of *S. pyogenes* to erythromycin, after adjusting for the local health authority of the laboratory.

The main limitation of this study is its design, which did not allow for the determination of any causal relationship between macrolide use and erythromycin resistance of *S. pyogenes,* even if the observed association was strong. Further studies (possibly with a longitudinal design) should be performed to fulfill this objective.

Another important limitation is the method of defining the control group (children with throat swab specimen cultures positive for *S. pyogenes* that was not resistant to erythromycin). When compared with the population of children from whom the case patients originated, this control group has less probability of including subjects who had had a past throat swab specimen culture positive for *S. pyogenes* and who had been successfully treated with antibiotics, and it has a greater probability of including subjects who relapsed after treatment. This selection bias tends to increase the ORs of association between previous use of antibiotics and resistance of *S. pyogenes* to erythromycin, especially for agents that are less likely to constitute an effective treatment (antibiotics to which erythromycin-resistant strains are resistant or less sensitive). For this reason, the observed ORs of association between previous use of macrolides and resistance of *S. pyogenes* to erythromycin are higher than ORs that probably would have been observed in the absence of the bias and are not suitable for measuring the individual risk for colonization or infection with erythromycin-resistant *S. pyogenes* [10]. On the other hand, results from this study are useful for predicting the probability of *S. pyogenes* resistance to erythromycin in subjects with group A strepto-

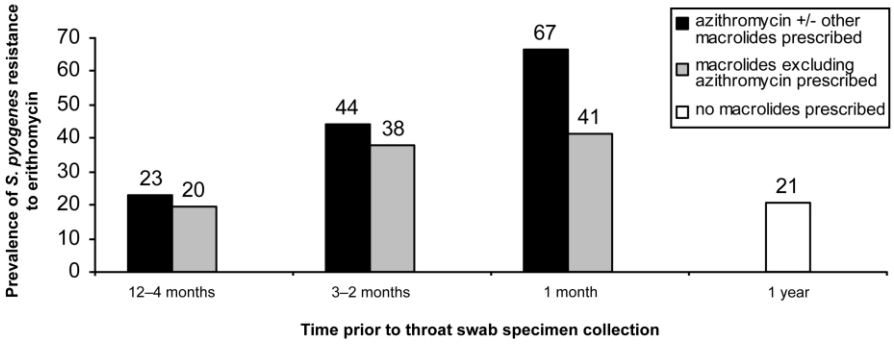

Figure 1. The prevalence of *Streptococcus pyogenes* resistance to erithromycin among the study population. Macrolide prescriptions referring to the year before throat swab specimens were collected were considered. When a subject received several macrolide prescriptions, only those prescribed during the time period closest to throat swab specimen collection were included in the study.

coccal pharyngitis, according to their history of macrolide use and date of prescription [10]. Moreover, the observed ORs could represent a measure of the community-level effect of macrolide prescription; the use of these agents has an indirect effect at the population level by reducing the transmission of erythromycin-susceptible *S. pyogenes* and promoting the transmission of erythromycin-resistant strains [10]. Although prevalence of erythromycin resistance tends to decrease with the increase of the lag from macrolide prescription, in the long term, macrolide use could influence the baseline risk of colonization or infection due to erythromycin-resistant *S. pyogenes,* leading to an increased burden of macrolide resistance among the whole population.

Another limitation of the study is the lack of information about prescriptions that were not reimbursed by the Italian National Health Service; in our study population, that can be a relevant proportion of all prescriptions, because ~40% of the children included did not have reimbursed systemic antibiotic prescriptions during the time period close to throat swab specimen collection. Accordingly, some children who were not recorded as having reimbursed macrolide prescriptions could actually have received these agents. Because of this, the impact of misclassification should be an increase in the absolute risk of having a throat swab specimen culture positive for erythromycin-resistant *S. pyogenes* in children who did not receive reimbursed prescriptions for macrolides and, consequently, a reduction of the relative risk for children who received reimbursed prescriptions of macrolides.

In the present study, the risk of erythromycin resistance associated with previous use of azithromycin was greater than the risk associated with use of other macrolides. A possible explanation for this finding is the long half-life of azithromycin, which, allowing for prolonged time of sub-MIC concentrations, could select resistance to erythromycin more efficiently than other macrolides. These findings are consistent with those from a previous study that positively correlated administration of macrolides taken once or twice daily (but not of those taken 3 or 4 times daily) and erythromycin resistance of *S. pyogenes* [4]. Similarly, a recent study investigating factors associated with antimicrobial resistance in invasive pneumococcal infections showed a greater probability of erythromycin resistance in patients previously treated with azithromycin than in those treated with clarithromycin [11]. In the same study, previous treatment (during the 3-month period before infection) with azithromycin and clarithromycin, but not with erythromycin, was associated with erythromycin resistance [11]. In our study, we found an association between recent administration of azithromycin or macrolides other than azithromycin and erythromycin resistance in *S. pyogenes.* It is important to note that patients in our population who were treated with macrolides other than azithromycin usually received clarithromycin or roxitamycin, which are both taken twice daily, while erythromycin was rarely prescribed.

For invasive pneumococcal infections, history of recent antibiotic treatment (with a 3-month cutoff) has been proposed as a possible criterion for choosing the appropriate therapy [11]. In the same way, it might be reasonable to recommend avoiding prescribing macrolides for patients with *S. pyogenes* infections who have been treated recently (in the 3 months prior to infection) with long-acting macrolides, because of the increased risk of being infected by an erythromycin-resistant strain. According to the results of this study, a stringent drug policy for the reduction of prescriptions for macrolides should be instituted in the Emilia-Romagna region to contain and possibly reduce the burden of erythromycin resistance of *S. pyogenes.*

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