Implications of antimicrobial resistance in the empirical treatment of community-acquired respiratory tract infections: the case of macrolides

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Macrolide resistance among pneumococci is increasing worldwide and is associated with increasing macrolide use. Recent studies show that use of macrolides and azalides increases nasopharyngeal carriage of both macrolide-resistant and penicillin-resistant pneumococci. Carriage of a resistant pneumococcus may foster dissemination. The clinical relevance of in vitro resistance has been debated. However, recent data from a matched case–control study showed that 18 (24%) of 76 patients had breakthrough bacteraemia with an erythromycin-resistant pneumococcus while taking a macrolide, whereas none of the 136 matched controls with an erythromycin-susceptible pneumococcal bacteraemia was taking a macrolide (P = 0.0000001). Moreover, five (24%) of 21 patients bacteraemic with the low-level resistant M phenotype and none of the 40 matched controls were taking a macrolide (P = 0.00157). These data indicate that macrolide resistance due to both the efflux and the methylase mechanisms is clinically relevant. Furthermore, they favour guidelines for the empirical treatment of outpatients with community-acquired pneumonia that recommend high-dose oral amoxicillin and reserve coverage of atypical pathogens for selected high-risk populations.

Introduction

Macrolide antibiotics exhibit strong antibacterial activity against Streptococcus pneumoniae and have traditionally been used for the treatment of community-acquired pneumonia because of their spectrum of activity against the major pathogens. Historically, they were the best alternative to penicillin in cases of allergy or resistance to β-lactams. Additionally, they also have good antibiotic activity against the so-called atypical pathogens, and the newer macrolides have improved activity against Haemophilus influenzae. For these reasons, some current guidelines advocate their use alone for empirical treatment of community-acquired pneumonia in patients who do not require hospitalization.1,2

Macrolide resistance is particularly frequent in penicillin-resistant pneumococci and has been detected at a variable rate in different epidemiological settings, with a clear trend toward increasing resistance in many parts of the world, putting into question the efficacy of these agents in the treatment of pneumococcal pneumonia. In this article, we review selected aspects of pneumococcal resistance to macrolides, including the main mechanisms of resistance to these agents, the effect of macrolides on nasopharyngeal carriage of S. pneumoniae and, finally, the increasing evidence of in vivo failures in patients treated with macrolides for pneumonia due to macrolide-resistant pneumococci.

Macrolide antibiotics inhibit S. pneumoniae by binding to rRNA, thus inhibiting protein synthesis. However, some isolates of S. pneumoniae become resistant to macrolides by altering the target (rRNA) or acquiring an efflux pump.3,4 The most common target alteration is methylation of a specific adenine residue of rRNA by a methylase encoded by the erm gene. In pneumococci this gene is usually expressed constitutively and confers cross-resistance to lincosamides (clindamycin) and streptogramin B type antibiotics as well as macrolides. This phenotype is called MLSB resistance. This mechanism produces high-level resistance to macrolides, usually with MICs of erythromycin ≥ 128 mg/L. Rarely this gene is expressed inducibly; these isolates test resistant to erythromycin and susceptible to lincosamides and streptogramin B.

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The other common resistance mechanism is efflux. Strains with this actively transport erythromycin and other macrolides from the interior of the bacterial cell to the exterior. Hence, the macrolide antibiotic cannot reach its intracellular target. This requires an energy-dependent efflux pump that is encoded by the *mef* gene. Isolates with this mechanism are resistant to macrolides and remain susceptible to lincosamides and streptogramin B. This pattern of resistance is the M phenotype. Isolates with this resistance mechanism show a moderate level of resistance to macrolides with MICs of erythromycin in the range 1–64 mg/L.

Up to 3% of macrolide-resistant *S. pneumoniae* either obtained *in vitro* after serial passage in macrolide-containing media or found in clinical isolates that lack *mef* or *erm* genes, are being recognized. Studies of these strains have revealed that mutations of a variety of structures including domains V and II of 23S rRNA and proteins L22 and L4, which are part of the binding sites of macrolides, can be responsible for resistance. 5-7

**Impact of macrolides on nasopharyngeal carriage of *Streptococcus pneumoniae***

Pneumococcal nasopharyngeal carriage is important since it is related both to development of disease and to spread of the pathogen. Recent studies have shown an association between use of antibiotics and colonization by resistant pneumococci. In this context, it is of interest to examine the effect of the macrolide class of antimicrobials on nasopharyngeal carriage of *S. pneumoniae*. Antibiotic-resistant strains are more often carried by infants and children than by adults, the only current exception being the strains resistant to the quinolones, which are usually isolated from older adults, reflecting the infrequent exposure of children to this group of antimicrobials.

Previous antimicrobial use is a strong risk factor for nasopharyngeal carriage of erythromycin-resistant pneumococci. It is clear that aminopenicillins promote the carriage of penicillin-resistant *S. pneumoniae*. However, because of cross-resistance and reduced activity against penicillin-resistant pneumococci, the selection pressure exerted by macrolides may be even higher. Arason et al.8 found that the odds of erythromycin being associated with the carriage of penicillin-resistant pneumococci was twice that of β-lactams. Similarly, a study from Slovakia9 showed that erythromycin selected twice as many strains of penicillin-resistant *S. pneumoniae* as penicillin (OR = 7.9 versus 3.9).

In healthy children attending day-care centres in Rome, those with exposure to macrolides in the previous month had a higher risk of being colonized by macrolide-resistant strains as well as by strains resistant to both penicillin and erythromycin.10 Leach et al.11 administered one dose of azithromycin to children with trachoma and monitored them for *S. pneumoniae* nasopharyngeal carriage. Before treatment, 68% were colonized, but only 1% had azithromycin-resistant *S. pneumoniae*. Two to 3 weeks later, the total colonization rate had decreased to 29%, but 16% were colonized by azithromycin-resistant strains. Two months later, 78% were colonized with pneumococci and 27% had azithromycin-resistant strains. Only 6 months after drug administration were the pneumococcal colonization rate and the prevalence of azithromycin-resistant organisms similar to the initial ones.

Similarly, Dagan et al.12 found a marked increase in nasopharyngeal carriage of macrolide-resistant pneumococci after only one dose of azithromycin. In another study, Morita et al.13 evaluated the efficacy of azithromycin as a short course regimen for eradication of nasopharyngeal colonization by Group A streptococci (GAS) and *S. pneumoniae*. Children carrying GAS were treated with daily azithromycin for 5 days, and post-treatment nasopharyngeal swabs were obtained. Azithromycin was effective for eradication of nasopharyngeal GAS, although it selected for macrolide-resistant strains of pneumococci. Nasopharyngeal colonization rates for pneumococci decreased from 46% to 12% by day 17 and were 20% by day 32. However, the prevalence of erythromycin-resistant pneumococcal isolates increased from 2% to 4% by day 17 and to 8% (P = 0.04) by day 32. The proportion of *S. pneumoniae* isolates resistant to erythromycin increased from 4% to 35% on day 17 and to 41% on day 32.

Azithromycin has a much smaller effect on azithromycin-susceptible *S. pneumoniae* than amoxicillin therapy has on penicillin-susceptible strains. Ghaffar et al.14 have observed a decrease in carriage of pneumococci from 51% to 28% following azithromycin therapy. Azithromycin cleared two-thirds of strains susceptible to azithromycin but none of the strains that were resistant to azithromycin. This suggests that the concentration of azithromycin in nasopharyngeal secretions is low, which might enhance the selection and dissemination of resistant pneumococci. As compared with co-amoxiclav, patients treated with azithromycin were more likely to remain carriers of *S. pneumoniae*, although in only one-third of these patients was this pathogen susceptible to azithromycin. In another study,15 the same authors found that azalide therapy cleared 69% of azithromycin-susceptible *S. pneumoniae* and 29% of azithromycin-resistant strains, whereas co-amoxiclav eradicated all penicillin-susceptible and -intermediate *S. pneumoniae* and 73% of penicillin-resistant strains. These results suggest that a patient who is carrying pneumococcus and has recently received an antibiotic course with a β-lactam is less likely to carry a resistant strain than a patient who has received a macrolide.

Increasing macrolide use is associated with increasing macrolide resistance among *S. pneumoniae*. For example, Hyde et al.16 showed that macrolide use increased by 13% between the years 1993 and 1999 in the United States. Moreover, there was a 320% increase in macrolide use among children less than 5 years of age. The resistance of pneumo-
coccı to macrolıdes increased from 10.6% in 1995 to 20.4% in 1999. The greatest increase was in isolates with the M phenotype (from 7.5% to 16.5%). Furthermore, in more recent years the MICs for isolates with the M phenotype have been higher. The median MIC increased from 4 to 8 mg/L. The percentage of isolates with the MLSB phenotype remained stable at ∼3–4%.

In the United States, approximately one in five pneumococci are resistant to macrolide antibiotics.16 The prevalence of macrolide resistance in pneumococci is also increasing in Europe. Data for 1999 from the multinational Alexander Project show a mean prevalence of macrolide resistance in pneumococci of 17.2%, with rates from 7.8% in Germany to 35.2% in Spain.17 The highest rates of macrolide resistance among pneumococci have been found in East Asia, from 66% in Japan and 72% in China, to 81% in Taiwan.18,19

Clinical implications of macrolide resistance in the treatment of community-acquired respiratory tract infections

Despite the numerous reports of resistance, there is limited information on the clinical relevance of macrolide resistance. Also, some authors have debated the clinical relevance of macrolide-resistant pneumococci. For example, Amsden20,21 stated in a recent review that in vitro resistance is not a problem because macrolides and azalides achieve high intracellular concentrations. In 1967, Dixon22 reported the first case of a patient infected with a macrolide-resistant pneumococcus that failed to respond to macrolide therapy. Sanchez et al.23 reported two patients with pneumonia who failed to respond to erythromycin. Needle aspiration of the lung grew a macrolide-resistant pneumococcus. Both patients were treated with a β-lactam antibiotic and improved. Lonks & Medeiros24 reported on a young man, 32 years of age, who, while taking oral erythromycin for lobar pneumonia, presented to the hospital because he was getting worse. Blood cultures grew an erythromycin-resistant pneumococcus. Recently there have been reports of breakthrough bacteraemias in patients taking azalides as well as macrolides. Fogarty et al.25 reported that three patients who failed to respond to azithromycin had breakthrough bacteraemia. Kelley et al.26 reported the clinical failure of oral azithromycin in three patients and of oral clarithromycin in one patient. Five of the seven isolates had the M phenotype; one isolate was available for genotyping and contained the mef gene.25,26 These reports are, however, anecdotal and do not prove that the clinical failures were due to the antibiotic resistance. Breakthrough bacteraemias may have occurred because of non-compliance in taking the antibiotic or poor absorption.

Failure of macrolides in patients with bacteraemia caused by erythromycin-resistant pneumococci

Lonks et al.27,28 presented results of a matched case–control study at the Forty-first Annual ICAAC meeting in Chicago in December 2001. It was a collaborative study involving three hospitals in the United States and one in Spain. The issue of non-compliance or poor absorption was addressed by including matched controls. In that study, a case is a patient bacteraemic with an erythromycin-resistant pneumococcus and a control is a patient bacteraemic with an erythromycin-susceptible pneumococcus. The null hypothesis of the study was that the probability of a case taking a macrolide was equal to the probability of a control taking a macrolide. Hence, if poor absorption or non-compliance were the reason for breakthrough bacteraemias, then cases and controls would have had an equal probability of breakthrough bacteraemia.

Controls were matched to cases for age, gender, year of bacteraemia and geographical location. Site of infection, underlying medical illnesses, social history and other patient information were recorded in addition to concurrent consumption of a macrolide antibiotic at the time of bacteraemia. Data were analysed using a variable ratio matching Z-score. Initial statistical analysis included all patients. A separate analysis was carried out excluding patients with meningitis. The hospitals included were the Hospital Mutua de Terrassa, Terrassa, Spain (1989–2000), the Miriam Hospital in Providence, RI, USA (1987–1999), Rhode Island Hospital, Providence, RI, USA (1997) and Brigham and Women’s Hospital, Boston, MA, USA (1987–1999).

There were 1071 bacteraemias, of which 8.4% were resistant to erythromycin. At the Hospital Mutua de Terrassa, there were 316 bacteraemias; 15% were macrolide resistant. At the Miriam Hospital, there were 264 bacteraemias; 5.7% were macrolide resistant; Brigham and Women’s Hospital, 438 bacteraemias, 4.8% of which were macrolide resistant; Rhode Island Hospital, 53 bacteraemias, 15% of which were macrolide resistant. The highest rate of recovery of macrolide-resistant pneumococcus was from children between the ages of 0 and 17 years: 20% of the 69 isolates were macrolide resistant. The lowest prevalence of resistance was found among 233 pneumococci isolated from patients between the ages of 45 and 64 years, of which 0.4% were macrolide resistant. This was statistically significant compared with the two other adult age groups, 18–44 years and >64 years, in which there were 320 and 449 patients, respectively, with resistance rates of 9.1% and 10.2%, respectively. For the matched case–control study there were 57 cases that had two controls, and 30 cases had one matched control. Eight neonates were excluded from the matched case–control study, one neonate with an erythromycin-resistant, and seven with an erythromycin-susceptible, pneumococcus. Two cases were excluded because

Resistance and macrolide treatment of RTIs

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the medical record could not be located. Two patients with HIV, both taking prophylaxis once a week, were excluded; one with a macrolide-susceptible, and the other with a macrolide-resistant, pneumococcus. The date of the last dose taken of azithromycin was not documented for either patient.

In general, cases and controls were demographically similar. One difference was that blacks were less likely than whites to have an erythromycin-resistant pneumococcus (P = 0.015), perhaps because whites are more likely to receive outpatient medical care and get antibiotics.20 Cases were more likely to have meningitis (P = 0.006). The key finding was that 18 (23%) of the 76 cases and none of the 136 matched controls were taking a macrolide at the time of pneumococcal bacteraemia, excluding patients with meningitis (P = 0.000001). In a separate analysis of patients bacteraemic with an isolate that had the M phenotype, excluding patients with meningitis, five (24%) of the 21 cases and none of the 40 matched controls were taking a macrolide at the time of bacteraemia (P = 0.00157).

Of the patients who developed breakthrough bacteraemia, 12 adults and three children had pneumonia. Two adults had an empyema and one had meningitis in addition to pneumonia. One adult and three children had no identified site of infection.

Among patients with an erythromycin-resistant pneumococcal bacteraemia, those not taking a macrolide were older (mean age 55 versus 40 years, P = 0.04) and tended to have a higher mortality rate (18% versus 0%, P = 0.06) than those taking a macrolide.

Among the macrolides taken, those that had breakthrough bacteraemia with an MLSB phenotype pneumococcus were: erythromycin, three; azithromycin, five; clarithromycin, three; josamycin, two; for the M phenotype: erythromycin, three; azithromycin, one; clarithromycin, three (one patient received both erythromycin and azithromycin). The average duration of macrolide therapy was 3.9 days at the time of pneumococcal bacteraemia. The range was from 2 to >30 days. Doses of macrolide antibiotic taken were: erythromycin 1000 mg/day, three patients; 2000 mg/day, two patients; clarithromycin, 1000 mg/day, three patients; azithromycin, a child 120 mg/day, one; azithromycin, 500 mg one patient; unknown dose of macrolide for nine patients.

Isolates from patients who developed breakthrough bacteraemia were further analysed. From Spain, 10 of the 11 with the MLSB phenotype were available for genotyping and contained the erm gene. None contained the mef gene. In the United States, two isolates had the MLSB phenotype; one was available for testing and contained the erm gene. From the United States, six isolates had the M phenotype; three were available for genetic testing; all three contained the mef gene. Susceptibility to erythromycin was determined by the microdilution method. Those with the erm gene had an MIC of erythromycin of ≥128 mg/L, except for one isolate for which the MIC of erythromycin was 64 mg/L. The MICs of erythromycin were 4, 16 and 16 mg/L for the three isolates with the mef gene. One isolate required carbon dioxide for growth and testing (MIC of erythromycin 16 mg/L). The isolates were of various capsular polysaccharide types (6, 6A, 6B, 9N, 14, 15A, 19, 23F).

These data indicate that macrolide resistance due to both the efflux and the methylase mechanisms is clinically relevant. Furthermore, they favour guidelines for the empirical treatment of outpatients with community-acquired pneumonia that recommend high-dose oral penicillin or amoxicillin and reserve coverage of atypical pathogens for selected high-risk populations.

References


