Macrolide resistance in *Streptococcus pneumoniae*: Fallacy or fact?

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Streptococcus pneumoniae, a Gram-positive coccus, has been with humankind for centuries. Worldwide, it continues to rank as a significant cause of respiratory illness, hospitalization and death in young children, the elderly and people with chronic medical conditions. It is responsible for several types of infections including meningitis, pneumonia, otitis media, sinusitis and bacteremia. *S pneumoniae* ranks first among identified microbial causes of adult community-acquired pneumonia (CAP) that requires hospital admission, accounting for 30% to 50% of such cases (1). It is estimated to be responsible for 500,000 annual cases of CAP in the United States (2-5). Pneumococcal disease is also estimated to account for 3000 cases of meningitis, 50,000 cases of bacteremia and seven million cases of otitis media each year in the United States (6). Fatality rates for bacteremic pneumonia due to *S pneumoniae* range from 5% to 30% and have changed little over time (7-11). In nonindustrialized countries, pneumococcal pneumonia results in the deaths of more than one million children each year, half of whom are younger than one year of age (12). The incidence of invasive pneumococcal disease in Canada has not been as well elucidated. In 1996, the Sentinel Health Unit Surveillance System, an active population-based surveillance network in nine health units in eight provinces, was established to identify laboratory-confirmed invasive disease, and it revealed an overall incidence of 15.1 cases of invasive pneumococcal disease per 100,000 population (13). The age-specific incidence was greatest in children younger than five years of age and in people older than 65 years of age (55.3 and 46.4 cases per 100,000 population, respectively). Population-based surveillance for invasive pneumococcal disease in a single metropolitan centre revealed an incidence of 14.4 cases per 100,000 population in 1995, 16.1 cases per 100,000 population in 1996 and 11.8 cases per 100,000 population in 1997 (14).

Historically, *S pneumoniae* was uniformly susceptible to penicillin, which allowed penicillin G or ampicillin to be the mainstay of therapy for pneumococcal infections (15,16). Worldwide, however, resistance to penicillins, cephalosporins and nonbeta-lactam antibiotics, including the macrolides, has been increasing steadily over the past two decades and escalated at an alarming rate in the latter part of the 1990s (16-19). Depending on the surveillance methods that are used, 30% to 45% of pneumococci in the United States have an intermediate or high-grade resistance to penicillin (20-22). Some areas of the world report rates of penicillin resistance for pneumococci as high as 60% to 70% (23,24). Unfortunately, penicillin-resistant *S pneumoniae* are often resistant to nonbeta-lactam antibiotics, including macrolides, tetracyclines, chloramphenicol and trimethoprim/sulfamethoxazole (19,20). Multidrug-resistant (MDR) strains of *S pneumoniae* (defined as resistance to three or more classes of antibiotics) are endemic in many countries (25-27). In the United States, data from the Active Bacterial Core Surveillance program of the Center for Disease Control and Prevention (CDC) identified an increase in MDR *S pneumoniae* from 9% to 14% between 1995 and 1998 (21). Other studies have identified rates of MDR pneumococcus of up to 25% (16). Although the majority of MDR isolates of *S pneumoniae* are susceptible to the newer fluoroquinolones (levofloxacin, moxifloxacin and gatifloxacin), recent evidence suggests that in both Canada and the United States there has been an increase in pneumococcal isolates with reduced fluoroquinolone susceptibility (28,29).

With the increasing worldwide frequency of MDR *S pneumoniae*, and especially the parallel increases in macrolide and penicillin resistance, concerns have been raised with respect to the treatment guidelines for CAP, which have advocated macrolides as first-line therapy.

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Questions arise as to whether the in vitro susceptibility results of macrolides against *S pneumoniae* are relevant with respect to clinical efficacy and outcomes, and whether macrolides should continue to be the initial treatment of choice for CAP. Given this background, it was considered timely to review the mechanisms, epidemiology and clinical outcome evidence related to macrolide resistance in *S pneumoniae*.

Pneumococcal macrolide resistance is expressed usually as one of two phenotypes: the MLS_B phenotype, with a ribosomal methylase (encoded by the *ermB* gene), and the M phenotype, with a macrolide efflux pump alteration (encoded by the *mefE* gene) (30). With the MLS_B phenotype, the binding affinity of all macrolides for the 23s rRNA (domain 5) is reduced, which leads to cross-resistance between macrolides, lincosamides and streptogramin B. The MLS_B phenotype is associated with very high macrolide resistance (minimal inhibitory concentration [MIC] is greater than 64 mg/L) and resistance to clindamycin. With the M phenotype, the efflux pump alteration results in efflux of the macrolides from the cell, conferring resistance to all the 14- and 15-membered macrolides. Pneumococci that contain the *mefE* gene have MICs to erythromycin and other 14- and 15-membered macrolides that range between 1 mg/L and 32 mg/L.

These resistance phenotypes have been reported as independent events, but the dual presence of both the MLS_B and M phenotype has been identified recently in several strains of *S pneumoniae* from South Korea (31). Additionally, two new mechanisms of macrolide resistance, described previously only in laboratory isolates, have been described recently in clinical strains of *S pneumoniae*. Macrolide-resistant strains from both North America and Europe, with neither the *ermB* or *mefE* genes, were found to contain mutations in genes for either 23S rRNA or ribosomal proteins (32).

The breakpoints for macrolide resistance that are recommended by the National Committee for Clinical Laboratory Standards are 1 mg/L or higher for erythromycin and clarithromycin, and 2 mg/L or higher for azithromycin (33,34). Erythromycin-resistant strains are predictably cross-resistant to clarithromycin and azithromycin, and are usually resistant to penicillin and other antibiotics.

Although pneumococcal macrolide resistance has increased worldwide, prevalence rates vary highly from country to country. Macrolide resistance rates range from 15% to 49% in France, Belgium, Spain, Italy, Uruguay, Greece, Hungary and Korea (35,36), but macrolide resistance is rare (less than 3%) in South Africa and Israel, despite high levels of penicillin resistance (greater than 20%) in those countries (37,38). In Taiwan, rates of macrolide resistance to clinical isolates of *S pneumoniae* were found to be 90% (24). In the United States, macrolide resistance has increased significantly within the past decade. In a Centers for Disease Control and Prevention (CDC) survey conducted between 1979 and 1986, only 0.3% of more than 5000 isolates of pneumococci were resistant to macrolides (39). In another CDC survey conducted between 1993 to 1999, macrolide resistance increased from 10.6% in 1995 to 20.4% in 1999 (40). This is consistent with another American study that reported a 22% to 23% resistance to erythromycin, clarithromycin or azithromycin in 1998 (20). Rates of penicillin nonsusceptibility for the macrolide-resistant strains in the CDC study were 81% and 85% for the M and MLS_B phenotypes, respectively. In Canada, the prevalence of macrolide-resistant pneumococci was found to be relatively low at 8% in 1998 and 1999 (41); however, a surveillance survey for the year 2000 (Prospective Resistant Organism Tracking for the Ketolide Telithromycin) found a rate of macrolide resistance in Canada of 16% (www.protekt.org). Globally, the predominant phenotype for macrolide-resistant pneumococci varies considerably. In the United States and Canada efflux mechanisms (*mef A*) account for the majority (60% to 80%) of macrolide resistance. In contrast, in some locales in Europe, notably Spain (42) and Italy (35), the *ermB* gene makes up more than 80% of macrolide-resistant strains.

Previous antibiotic use is the dominant risk factor associated with antimicrobial-resistant pneumococci. Selection pressure from previous macrolide use is considered to be the main risk factor for macrolide resistance (40,43-48). Additional risk factors for macrolide-resistant *S pneumoniae* include age younger than five years, nosocomial acquisition and penicillin resistance (43).

Macrolides are important therapeutic agents and are recommended as first-line agents for CAP in numerous guidelines. With the trend of increased macrolide use and increasing macrolide resistance, the question that needs to be addressed is whether these in vitro results correlate with a negative impact on clinical efficacy. There has been significant controversy concerning this question, and arguments can be made for and against the relevance of in vitro macrolide resistance. Some authors have suggested that current treatment guidelines that recommend macrolides for CAP need to be re-evaluated (40), while other authors consider macrolide resistance to be a myth and of little clinical relevance (49).

Arguments against the relevance of in vitro macrolide resistance are based on the pharmacokinetics and pharmacodynamics of the drugs in vivo. MIC breakpoints for macrolides, which are established for serum levels, greatly underestimate the concentration of the drug that is achieved at the site of pulmonary infection (49). The high degree of tissue penetration and accumulation of the macrolide in the infected tissue contrast with the antimicrobial levels that are achieved in serum, and provide grounds for the argument that the current National Committee for Clinical Laboratory Standards breakpoints for macrolides are not appropriate (49). For classic macrolide antibiotics such as erythromycin and clarithromycin, optimal activity is dependent on the time that the drug concentration is above the MIC of the organism, with a goal to exceed the MIC for at least 40% of the dosing interval. For azithromycin, optimal activity is depend-

ent on maximizing the 24-h, area-under-the-curve concentration per MIC. Both clarithromycin and azithromycin have demonstrated that they achieve their respective pharmacokinetic and pharmacodynamic parameters with respect to serum, epithelial lining fluid concentrations or intraphagocytic concentrations for MDR *S pneumoniae* (50). It is also thought that the avid uptake of macrolides by white blood cells at the site of infection contributes to additional extracellular release of the agents as well as exposure of organisms to high intracellular concentrations (49). An additional argument against the relevance of in vitro macrolide resistance is the paucity of studies suggesting that current macrolide resistance trends are translating into clinical failures (49). Clinical trials that have used macrolides such as erythromycin, clarithromycin and azithromycin as comparators have demonstrated equivalent high levels of activity against *S pneumoniae* infections of the upper and lower respiratory tree.

There are several arguments in favour of the clinical relevance of in vitro macrolide resistance that come from both laboratory and clinical data. Some in vitro data suggest that macrolides do not provide optimal coverage of penicillin-resistant pneumococci because macrolide resistance at relatively high MICs is more common among such strains (40). The increasing prevalence of higher MICs (21,40) for macrolide-resistant pneumococci with the M phenotype (MIC_{50} of 8 mg/L) and the increasing global prevalence of the more highly resistant MLS_B phenotype (24-27) are significant cause for concern, even taking the most optimal pharmacokinetic and pharmacodynamic parameters into account (51). The recent description of the concomitant presence of both target site alteration and efflux mechanisms of macrolide resistance, and the description of two new mechanisms of resistance (32) raise concern about the propensity for macrolide resistance development in pneumococci. The increases in high-level macrolide resistance have occurred at the same time as the dramatic increases in macrolide consumption in industrialized countries (40,43-48). In the United States, there was a 320% increase in macrolide use among children younger than five years of age between 1993 and 1999 (40). In Canada, there was a 30% increase in macrolide use between 1995 and 1998 (41). It has been proposed that the new, longer-acting macrolides (clarithromycin, azithromycin, spiramycin and roxithromycin) may be the most significant factor associated with the increases in macrolide resistance that have been observed (52). In a study of macrolide resistance as part of the Alexander Project, a linear increase in macrolide resistance occurred when plotted against new, long-acting macrolide use (correlation of 0.89), but not with short-acting macrolides (52). From a clinical perspective, there have been an increasing number of case series of patients with breakthrough pneumococcal bacteremia and clinical failures of patients with documented pneumococcal pneumonia while being treated with newer macrolides (43,53-57). Some authors contend that these identified clinical failures represent only the tip of the iceberg and are not truly representative of what may be found with detailed prospective studies (58). There is a dearth of prospective studies that investigate specifically the clinical activity of newer macrolide drugs against infections with pneumococcal isolates having varying degrees of resistance, especially bacteremic illness and pneumonia rather than otitis media and sinusitis, which have high spontaneous cure rates (51). Based on recent findings in the United States (40), the CDC has suggested that recent clinical treatment guidelines that advocate macrolides as first-line treatment of CAP need re-evaluation.

The debate will continue with respect to the clinical relevance of macrolide resistance in pneumococci until carefully conducted prospective studies determine the level at which in vitro resistance to macrolides translates into clinical failure. However, there is increasing evidence from case series that well documented failures have occurred in both bacteremic and pneumonic infections with macrolide resistant pneumococci, usually, but not always, with high-level macrolide in vitro resistance. Not to be forgotten in the debate is the need to continue to strive for reductions in inappropriate use, not only of macrolides, but of other antimicrobial agents, especially in light of the studies that identify antimicrobial use as the dominant factor associated with antimicrobial-resistant pneumococci.

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