Editorial

Pneumococcal resistance to penicillin and macrolides: implications for the treatment of respiratory infections

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The appearance of penicillin-resistant Streptococcus pneumoniae strains, resulting from chromosomal mutations and alterations in the antibiotic-binding proteins in the bacterial cell wall, has had wide repercussions for the clinical use of the drug. These strains, which were apparently restricted to South Africa in the 1970s, have spread throughout the world and have been increasingly gaining ground as agents of community-and hospital-acquired infections. With the greater goal of guiding a more efficacious treatment for pneumococcal meningitis, the international criteria for interpreting the minimum inhibitory concentration (MIC) of penicillin G for pneumococcus have been reviewed. Pneumococci are currently classified as presenting sensitivity (MIC < 0.06 g/mL), intermediate resistance (MIC between 0.12 and 1.0 g/mL) or strong resistance (MIC > 2.0 g/mL). The prevalence of pneumococcal samples falling into these two last categories (penicillin resistant strains) varies country by country and region by region. In recent years, such strains were responsible for 40% to 60% of the cases of pneumococcal infection in France, Spain, Mexico, Chile and Israel. In a study conducted in Latin America from 1993 to 1999, sensitivity tests were performed using samples isolated in 20 hospitals in 12 Brazilian cities.[1] The authors found 20.7% of the Brazilian samples to be penicillin resistant, 1.6% of those presenting strong resistance. The prevalences were lower in Brazil than in any of the other Latin American countries that participated in this study. Unfortunately, the proportion of penicillin-resistant samples isolated has been progressively increasing, and these pneumococcal strains frequently present resistance to antimicrobials of other classes or even multidrug resistance.

For decades, erythromycin, an antibiotic of the macrolide class, has been prescribed for the treatment of patients with upper and lower respiratory tract infections. During that time, it has been a secondary treatment for patients with pneumococcal pneumonia who cannot be given penicillin. The pharmaceutical availability of new macrolides (clarithromycin and others) and azalides (azithromycin), together with their longer half-lives, simpler posology and better tolerance in comparison to erythromycin, has brought a marked increase in the clinical use of antibiotics of these classes. It is possible that knowledge of the lower sensitivity of pneumococcus to penicillins has also contributed to encouraging clinicians and pediatricians to widen their use of macrolides and azalides. As is the case for most of the antimicrobials, their frequent use has resulted in the selection of resistant microorganisms. Pneumococcal resistance to erythromycin, which includes clarithromycin and azithromycin, has increased rapidly and significantly in various regions of the world. A greater number of resistant strains have been isolated in children than in adults, and such resistance has been correlated with previous use of macrolides.[2] A study carried out by Zettler et al. in five hospitals in the city of Porto Alegre and published in this issue of the Brazilian Journal of Pulmonology[3] revealed that 5.2% of the pneumococcal strains isolated were resistant to erythromycin, a value similar to the 4.3% found among samples isolated in three Brazilian states from 1990 to 1999.[4] The two mechanisms of resistance found were alteration in the bacterial ribosome, with a decrease in the affinity for antimicrobials (MSLB phenotype), and alteration in the active efflux, in order to remove drugs from the cytoplasm of the microorganism (M phenotype). Whereas resistance to erythromycin, clarithromycin and azithromycin is typically low in the strains presenting the latter mechanism, resistance to these, as well as to clindamycin and to streptogramins, is high among the pneumococci presenting the MSLB phenotype, thereby precluding their use in the treatment of the infected patients.

The decrease in antimicrobial sensitivity of pneumococci, which are still the principal agents of pneumonia in nonhospitalized adults, has led to a review of antibiotic therapy, both in infections of known etiology as well as in the empirical treatment of community-acquired pneumonia. Regarding penicillins and cephalosporins, evaluations of the

clinical impact of pneumococcal resistance have brought contradictory results in cases of pneumonia, some authors showing an increase in patient mortality and others finding no such correlation. For infections with pneumococci presenting a high level of resistance to beta-lactams, antimicrobials of other classes with antipneumococcal properties, such as quinolones, and, eventually, vancomycin, should be used. However, there is some confusion regarding the microbiological criteria for interpretation of the bacterial susceptibility test since, in high doses, penicillin G, amoxicillin, ceftriaxone, cefotaxime and other more active beta-lactams reach tissue levels for a sufficient length of time to control respiratory infections caused by samples with intermediate resistance to penicillin. Amoxylin, in particular, has been investigated in the treatment of patients infected with these pneumococci and has been found to present favorable pharmacodynamic properties and clinical efficacy, especially when used in daily doses of 4 g in adults.[5]

Pneumococcal resistance to macrolides and azithromycin also limited the use of these antibiotics in respiratory infections. Numerous cases of treatment failure with macrolides, confirmed by persistently positive cultures, were correlated with an MIC for erythromycin of 4 g/mL. In infections caused by these bacteria, other classes of antimicrobials are used, as previously mentioned regarding penicillin-resistant pneumococci. However, considering the small percentage of bacterial samples that are resistant to macrolides and azalides in Brazil, these drugs are still useful alternatives in the empirical monotherapy of mild cases of community-acquired pneumonia. In severe cases requiring hospitalization, the efficacy of the combination of third-generation cephalosporins and macrolides has been evidenced by a more favorable prognosis for pneumonia patients treated with this combination. It should be borne in mind that telithromycin, a ketolide antibiotic derived from clarithromycin, is effective against most of the macrolide-resistant pneumococci.

Judicious use of antimicrobials, at the community or hospital level, will contribute to maintaining the less dramatic pneumococcal resistance in Brazil, thereby making it possible to continue using beta-lactam antibiotics and macrolides in pneumococcus-related respiratory infections.

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REFERENCES

1. DiFabio JL, Castañeda E, Agudelo CI, De La Hoz F, Hortal M, Camou T, et al. Evolution of Streptococcus pneumoniae serotypes and penicillin susceptibility in Latin-America, Sireva-Vigía Group, 1993 to 1999. Pediatr Infect Dis J. 2001; 20(10):959-67.
2. Mason OE Jr, Wald ER, Bradley JS, Barson WJ, Kaplan SL; The United States Pediatric Multicenter Pneumococcal Surveillance Study Group. Macrolide resistance among middle ear isolates of Streptococcus pneumoniae observed at eight United States pediatric center: prevalence of M and MLSB phenotypes. Pediatr Infect Dis J. 2003;22(7):623-7.
3. Zettler FR, Zettler EW, Schmitt VM, Jahns MT, Dias CAG, Fritscher CC. Estudo fenotípico e genotípico da resistência aos macrolídeos do Streptococcus pneumoniae em amostras clínicas de hospitais de Porto Alegre - RS. J Bras Pneumol. 2005;31(4)312-7.
4. Mendonça-Souza CR, Carvalho MG, Barros RR, Dias CA, Sampaio JL, Castro AC, et al. Ocurrence and characteristics of erythromycin-resistant Streptococcus pneumoniae strains isolated in there major Brasilian states. Microb Drug Resist. 2004;10(4):313-20.
5. Craig WA. Overview of newer antimicrobial formulations for overcoming pneumococcal resistance. Am J Med. 2004;117(Suppl 3A):16S-22S.