ORIGINAL ARTICLES

Prevalence of *Streptococcus pneumoniae* resistance to penicillin in two hospitals of Caxias do Sul*

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Streptococcus pneumoniae *resistance to penicillin was studied in two hospitals in Caxias do Sul, Rio Grande do Sul, Brazil, between May 1998 and November 2001. From the 176 strains of invasive* Streptococcus pneumoniae *that were identified, 2.28% (CI 0.62-5.74) presented intermediate resistance, and 3.42% (CI 1.26-7.31) presented high-level resistance. The conclusion was that in Caxias do Sul the use of penicillin was still justified as treatment of pneumococcal pneumonia, differently from other centers where penicillin was replaced by other antibiotics. These results confirm the statement of IDSA (Infectious Diseases Society of America) guideline for the management of community-acquired pneumonia in adults, that the choice of antimicrobial drug to treat pneumococcal pneumonia should be guided by local or regional prevalence of resistance to penicillin.* (**J Pneumol** 2003;29(1):15-20)

Key words – Penicillin resistance. *Streptococcus pneumoniae.* Pneumococcus. Epidemiology. Community-acquired pneumonia.

Abbreviations used in this paper
ISDA – Infections Disease Society of America
SBPT – Brazilian Society of Pneumology and Tisiology
NCCLS – National Committee for Clinical Laboratory Standards
MIC – Minimal inhibitory concentration
CDC – Centers for Disease Control and Prevention

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INTRODUCTION

An increase of *Streptococcus pneumoniae* resistance to penicillin has been described all over the world, leading to a concern about failure in the treatment of diseases caused by this germ. Doern et al. [(1)] assessed the prevalence of resistant strains in 34 medical centers in the United States, from November, 1997 to April, 1998 and found a rate of 29.5%, of which 17.4% were intermediate resistant and 12.1%, highly resistant. Three years earlier, these authors have already performed the same evaluation in 24 of these hospitals and, in 19 of them, resistance to penicillin increased from 2.9% to 39.2%. The authors also observed that the increased resistance to penicillin was related to an increased resistance to other betalactamic antibiotics. According to Spika et al. [(2)], from 1979 to 1987, only 0.02% of the *Streptococcus pneumoniae* samples cultivated in the United States were resistant to penicillin. However, in 1992, the ratio of resistance raised to 1.3%. In other countries, resistance to penicillin reported in 1990 showed variable results: 70% in Korea [(3)], 70% in China[(4)], 12% in Canada[(5)], 29% in Greece[(6)], 52% in Spain[(7)], being 16% of intermediate and 33% of high resistance, 2.5% in England[(8)]. In South American countries, such as Peru, a multicentric study performed by Shirazawa et al. [(9)] between 1993 and 1994 reported that from 61 isolated streptococcus, two (3.3%) were highly resistant to penicillin. In Chile, Castillo et al. [(10)] found in 1994 3.3% of high resistance and 23.6% of intermediate resistance. In Colombia, Leal and

Castañeda[11] reported 6% of high resistance and 11% of intermediate resistance in 1997. In 1999, the same authors [12] described 8.4% of high resistance and 24.3% of intermediate resistance.

The Brazilian Consensus of Pneumonia in Immunocompetent Adults, SBPT, 2001[13], reports that in Brazil, intermediate resistance to penicillin is between 20% and 25% and, in general, high resistance, below 5%, based on the works by Sessegolo et al. [14], Sader et al.[15], Brandileone et al.[16], Zettler et al. [17]. Sessegolo and colleagues analyzed 288 strains of *S. pneumoniae* and found 0.8% of resistance and 17.9% of intermediate resistance; in 1993, Brandileone and co-workers studied 360 samples of pneumococcus isolated from children with invasive infections in three Brazilian cities. Intermediate resistance to penicillin was detected in 20% of the samples and 1.4% of them presented high resistance to this antibiotic. Nonetheless, higher overall values, 6.1%, and intermediate values, 23.7%, antimicrobial resistance were found by Zettler et al., in 1999. These authors assessed the resistance to penicillin for five years and identified a crescent increase of this ratio, which in 1995 was 1.9% overall and 11.1% intermediate resistance. According to these findings and to the patterns of other places, the future expectation is of progressive increase of microbial resistance to penicillin.

On the other hand, increased antimicrobial penicillin resistance has been applied as a criterion for the use of alternative drugs for empirical treatment of diseases in which this germ is a likely etiologic agent. However, penicillin G or amoxilin are seen as betalactemic drugs of choice for the treatment of infections induced by penicillin sensitive or intermediate resistant *Streptococcus pneumoniae* strains, according to the guidelines of the *Infectious Diseases Society of America* for adult, immunocompetent patients with community-acquired pneumonia [18].

There are two strategies to treat communitarian pneumonia: one of them tries to identify the etiological agent and in the other, the diagnosis is based on probabilities resulting from epidemiological data, and clinical and laboratory findings [13,18]. The preference for the method depends on multiple factors involved with the local conditions where the patient is. To make the treatment easier to follow, a search has been carried out for a method that reduces the diagnostic effort and widens the spectrum of germs covered by the antibiotic, resulting in efficient treatment at reduced cost without causing damage to the patient [19]. In order to do so, studies are performed in large centers and the results are generalized.

The main purpose of the present study was to measure the prevalence of *Streptococcus pneumoniae* resistant to penicillin in two hospitals of Caxias do Sul, thus contributing to the epidemiological vigilance of this germ's resistance and with a therapeutic strategy to be applied to the treatment of community-acquired pneumonia.

MATERIAL AND METHODS

A transversal study was performed in two of the five hospitals of Caxias do Sul, a country town in the State of Rio Grande do Sul, Brazil, with approximately 350,000 inhabitants, from May, 1998 and November, 2001, to examine the prevalence of resistance of *Streptococcus pneumoniae* to penicillin. All exams were evaluated with the same technique by a single microbiologist. We analyzed several biological specimens (liquor, lung secretions and blood) collected from inpatients of the two hospitals in which *Streptococcus pneumoniae* grew. Patients with any infectious respiratory disease, of community or hospital origin, meningitis or eye infections, were included. In case of more than one sample in the same site and date from a single patient, only one sample was considered. Specimens were analyzed by the Gram technique only after the quality of the sample was examined by identification of neutrophils, macrophages and fagocitosis. In the analysis of slides stained by the Gram method, the visualization of lanceted, capsulated or not gram-positive diplococcus raised the suspicion of *Streptococcus pneumoniae* presence. To distinguish lung-originated from tracheobronchial secretions, slides stained by Gram's method were searched for more than 25 leukocytes per field, for alveolar macrophages, for absence of epithelial cells and presence or absence of cells in fagocitosis. Preparation of lung specimen for performance of staining by Gram's method and culture was made by separation of saliva pus grooms in a sterile Petri dish.

When *Streptococcus pneumoniae* was suspected, the biological specimens were sown in 5% sheep-blood agar and incubated at 35°C for 24 h at 5 to 10% CO_2. Alfa-hemolytic colonies were tested with a 6mm optokin disk in sheep-blood agar dish. Reading of halo diameter was performed after 24 h of incubation. A 0.5 standardization in the MacFarland scale was used. Isolates of *Streptococcus pneumoniae* were considered when inhibition halo diameter was equal or larger than 14mm. Rare strains of *Streptococcus pneumoniae* were described as resistant to optokin [20]. Therefore, the proof of bile solubility was included for identification of type and species. The strains were inoculated in a tube containing 10% deoxycolate solution for 60 min at 35°C. Readings were performed by clearing of the tube, thus indicating the positiveness of the test for *Streptococcus pneumoniae*.

The test of sensitivity was carried out by Muller Hinton agar medium supplemented with 5% of sheep blood. The sown was performed by means of direct suspension of the colonies in 5% to 10% CO_2 and the reading was done after 24 h of incubation. Susceptibility to penicillin was assessed by screening test, using a 1 μg oxalacin disk (according to NCCLS documents)[21-23]. Pneumococcus isolates with inhibition zones equal or higher than 20mm were considered sensitive to penicillin.

On the other hand, strains whose halo readings were equal or lower than 19mm were tested by the E test and microdilution in broth (penicillin quantitative methods). The strains tested for penicillin by the E test were considered sensitive when the MIC readings were equal or lower than 0.006 μg/l. In such cases, there is response to penicillin, regardless of the infected site. Non-sensitive strains were so categorized when MIC readings were equal or lower than 0.12 μg/l. MIC readings equal or higher than 0.12 and equal or lower than 1 μg/l were considered as low resistance level, i.e., intermediate resistance to penicillin. MIC readings equal or higher than 2.0 were considered as strains highly resistant to penicillin, i.e., which did not respond to penicillin when the infection site was the central nervous system. For the characterization of strains as resistant or intermediate by the E test method, the readings done with intermediate dilutions, such as 0.75 and 1.5, were rounded up.

Statistical analysis were made by the Epi-Info 6.04, with 95% confidence interval, considering random samples for a target population estimated to represent patients with diseases caused by *Streptococcus pneumoniae* in Caxias do Sul.

TABLE 1
Sites and sensitivity to penicillin where *Streptococcus pneumoniae* was identified

Site	Sensitivity	Number of samples	Percentage
Lung	Resistant	4	2.28 (CI 0.62-5.74)
	Intermediate	5	2.85 (CI 0.93-6.54)
	Sensitive	148	84.57 (CI 78.35-89.57)
Pleural fluid	Intermediate	1	0.57 (CI 0.00-3.14)
	Sensitive	9	5.14 (CI 2.37-9.53)
Blood culture	Sensitive	2	1.14 (CI 0.14-4.06)
Liquor	Sensitive	3	1.71 (CI 0.35-4.92)
Eye secretion	Intermediate	1	0.57 (CI 0.00-3.14)
	Sensitive	2	1.14 (CI 0.14-4.06)
Total		175	100

RESULTS

One hundred and seventy five samples were analyzed and four cases of *Streptococcus pneumoniae* resistance to penicillin were detected – 2.28% (CI 0.62-5.74) – and six other cases of intermediate resistance – 3.42% (CI 1.26 – 7.31). Table 1 shows the sites where samples were collected, the numbers, sample ratios and their confidence intervals.

The sample consisted of 38 females (36.5%) and 66 males (63.5%). The age varied from the newborn to 89 years of age. Mean age was 55 ± 23 years.

DISCUSSION

The results obtained in the present study described the epidemiological period of two of five hospitals in Caxias do Sul, in which *Streptococcus pneumoniae* showed low resistance to penicillin (2.28%). The hospitals where the study was carried out have different characteristics and may represent the town's population. One of the hospitals assists patients from the public health system, trauma patients, and patients from other health insurance programs, whereas the other one accepts other insurances and admits few trauma patients. Different places present distinct realities and, consequently, demand specific solutions for their problems. Infections caused by *Streptococcus pneumoniae* are a reason for worldwide concern. Bartlett et al. [18] mention a metanalysis of 122 studies published in English, from 1966 to 1995, in which *Streptococcus pneumoniae* was prevalent in 66% of community pneumonias and had a 66% ratio among lethal pneumonias, thus indicating that this germ is highly relevant among

the inducers of community pneumonias, being the main etiology of pneumonias in number of deaths. The importance of epidemiological vigilance of this germ must be emphasized, even because it causes other infections, such as otitis, sinusitis, bronchitis and meningitis. Nonetheless, resistance of the germ to penicillin has not shown the same regularity.

The Centers for Disease Control and Prevention report that a study carried out in several places in the USA in 1997[24], with 3,237 samples of invasive *Streptococcus pneumoniae*, where rates of microbial resistance to penicillin were compared, showed an average value of 25% (11.4% of intermediate and 13.6% resistant) that varied regionally from 15.3% in Maryland to 38.3% in Tennessee. It also reports significant variations among hospitals of the same region, such as 22 hospitals in Connecticut, whose rates varied from 0.0% to 39.1%. When commenting about these CDC findings, Paterick and Pollack[25] also stated that the isolates resistant to penicillin are likely more resistant to cephalosporin, macrolide, sulfamethoxazole-trimethropim and tetracycline. Pallares et al.[26], who followed on 504 patients with severe pneumococcal pneumonia for a period of 10 years, concluded that mortality does not seem to be influenced by microbial resistance when the treatment consists of penicillin, ceftriaxone or cefotaxime, and that an increase of penicillin dosage, even in cases of resistant strains, would work to treat airway infections. Of these patients, 29% presented penicillin-resistant strains of *Streptococcus pneumoniae* and 6%, strains resistant to ceftriaxone or to cefotaxime. Apparently, mortality was significantly higher (38%) in patients with penicillin-resistant strains compared to patients who were assaulted by penicillin-sensitive strains (24%), p = 0.001. Nonetheless, when excessive mortality was controlled by other factors such as age, co-morbidities, heart failure and severe pneumonia, death risk was similar for both groups. Following-up with the analyses, the authors studied the relationship between mortality and the use of penicillin G or ampicillin and *in vitro* sensitivity tests. Among the patients who received penicillin G or ampicillin, mortality was similar (p = 0.51) between those with penicillin-resistant (n = 24, 23%) and those with penicillin-sensitive strains (n = 126, 19%). Patients who received ceftriaxone or cefotaxime presented 22% of mortality (n = 59) when strains were penicillin or cephalosporin-resistant and 25% with cephalosporin-sensitive strains (n = 127, p = 0.64). Other studies obtained similar conclusions [27-29]; however, Fine et al. [30] did not find the same results when resistance to penicillin was high or when the infection was meningitis [31].

Discovery of penicillin was one of the major medical advances of the 20th century, being indicated for the treatment of community pneumonia by *Streptococcus pneumoniae*. Nevertheless, in the beginning of the 21st century it has been losing its role in the treatment of pneumonias due to the crescent increase of antimicrobial resistance [18]. Moreover, the Brazilian Consensus on Pneumonia in Immunecompetent Adult Individuals SBPT, 2001[13], concluded that among penicillins, only clavulonic acid amoxicillin, alone or associated to macrolide is referred for the treatment of anaerobic germ-induced pneumonia, or also, of *Streptococcus pneumoniae* sensitive or intermediately resistant to penicillin. However, amoxicillin and crystalline penicillin are indicated as a more adequate treatment for penicillin sensitive strains [18]. The consensus on community pneumonias of ISDA [18] advises that pneumococcal pneumonias should not be treated solely with crystalline penicillin without the result of antimicrobial sensitivity test, since microbial resistance of *Streptococcus pneumoniae* penicillin in the USA is high. On the other hand, the consensus advised that the optimum choice of treatment for pneumococcal pneumonia must be guided by the regional prevalence of pneumococcus resistance to penicillin. Epidemiological results of antimicrobial resistance in large center hospitals tend to be generalized and are used as a reference for the treatment of pneumonias. However, these samples may not represent other centers, specially the smaller ones, where epidemiological vigilance is not observed. The temptation to use large spectrum drugs must be considered; although it represents some advantages, it fosters the appearance of microbial resistance [32]. Considering the cost difference between the new drugs and penicillin, and the high prevalence of community pneumonias induced by *Streptococcus pneumoniae*, between 20 and 60%[33], it is worth emphasizing the usefulness to promote epidemiological vigilance of *Streptococcus pneumoniae* microbrial resistance, since low prevalence of resistance to penicillin ceases to become a reason to use replacement drugs, thus providing a better cost-benefit relationship and postponing the onset of microbial resistance[34]. In Germany, Reinert et al.[35], performed a study with 844 samples of *Streptococcus pneumoniae*, obtained from 40 laboratories of clinical microbiology, and found a reduction of sensitivity to penicillin of 1.8%. In this country and in other places with low prevalence of resistance to penicillin, the purpose of the fight against microbial multiresistance is to maintain its levels, whereas with high resistance, the need is to identify new and effective drugs against a resistant germ.

CONCLUSION

The prevalence of *Streptococcus pneumoniae* resistance to penicillin in two hospitals of Caxias do Sul was 2.28% (CI 0.62-5.74). This finding alone does not support the proposal of penicillin replacement, used empirically

in the beginning of the treatment, by other drugs efficient against resistant germs, when the etiological agent is *Streptococcus pneumoniae*. The importance of local epidemiological vigilance of microbial resistance for therapeutic decisions must be emphasized, due to the different rates in different centers or regions.

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