Extremely High Prevalence of Nasopharyngeal Carriage of Penicillin-Resistant *Streptococcus pneumoniae* among Children in Kaohsiung, Taiwan

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Resistance (intermediate and high) to penicillin among *Streptococcus pneumoniae* strains is an emerging problem worldwide. From 1995 to 1997, isolates of *S. pneumoniae* not susceptible to penicillin were seen with increasing frequency from blood, cerebrospinal fluid, pleural fluid, and middle ear fluid from pediatric patients at the Veterans General Hospital-Kaohsiung. To determine the prevalence of carriage of these penicillin-nonsusceptible *S. pneumoniae* isolates, we obtained nasopharyngeal swab specimens from 2,905 children (ages, 2 months to 7 years) attending day-care centers or kindergartens or seen in our outpatient clinic. *S. pneumoniae* was isolated from 611 children, and 584 strains were available for analysis. The oxacillin disc test was used as a screening test to evaluate penicillin susceptibility. The MICs of 11 antibiotics (penicillin, cefaclor, cefuroxime, ceftriaxone, cefotaxime, imipenem, chloramphenicol, clarithromycin, rifampin, vancomycin, and teicoplanin) were determined by the E-test. Only 169 (29%) of the strains were susceptible to penicillin; 175 (30%) strains were intermediately resistant and 240 (41%) were highly resistant. The isolates also demonstrated high rates of resistance to other β-lactams (46% were resistant to cefaclor, 45% were resistant to cefuroxime, 45% were resistant to ceftriaxone, 31% were resistant to cefotaxime, and 46% were resistant to imipenem). The rate of resistance to macrolide antimicrobial agents was strikingly high; 95% of the isolates were not susceptible to clarithromycin. However, 97% were susceptible to rifampin and 100% were susceptible to the two glycopeptides (vancomycin and teicoplanin). While reports of penicillin-resistant *S. pneumoniae* increased worldwide through the 1980s, the high prevalence (71%) of resistance reported here is astonishing. Surveillance of nasopharyngeal swab specimen cultures may provide useful information on the prevalence of nonsusceptible strains causing invasive disease. Such information could be used to guide therapy of pneumococcal infections.
were determined. Using MIC as the “gold standard,” we showed that the oxacillin disc screening test has a sensitivity of 96.1% and a specificity of 94.9%. The antibacterial activities of 11 antimicrobial agents against 584 isolates of *S. pneumoniae* are indicated in Table 1. Table 2 illustrates the individual numbers and percentages of susceptibility of these agents stratified by PCN susceptibility.

**DISCUSSION**

We have detected an extraordinarily high prevalence of resistance to PCN among *S. pneumoniae* strains isolated from the nasopharyngeal cultures of children in Kaohsiung, Taiwan. Reports of antimicrobial-resistant *S. pneumoniae* have increased worldwide during the past two decades, but geographic and temporal patterns vary (3, 19, 21, 26, 30, 34, 40, 43, 44, 45, 50, 54, 57). The prevalence of highly resistant strains was higher (41% of all isolates and 58% of nonsusceptible strains) than those published in reports from other geographic areas (3, 16, 18, 28, 32, 54, 55). The use of high levels of PCN has been advocated against intermediately resistant strains causing otitis media, pneumonia, and bacteremia (51). Our surveillance study is a warning to pediatric clinicians in Taiwan that caution should be exercised when treating pneumococcal infections, since many strains (41%) are highly resistant to PCN; high doses of PCN may not be adequate as empirical therapy. MICs should be determined for all clinically significant isolates of *S. pneumoniae* to aid in the selection of appropriate antibiotics for therapy.

**Carriage of *S. pneumoniae***

Has been correlated with the emergence of clinical disease (28, 31, 39, 48). Thus, the characteristics of carriage isolates could serve as an indicator of the prevalence of resistance strains in the community (12, 18, 46, 60). A prevalence of 53% of PCN-nonsusceptible *S. pneumoniae* among children in a rural Kentucky community has been reported, with 33% of the strains being highly resistant (16). The rate of carriage of PCN-nonsusceptible *S. pneumoniae* was reported to range from 0 to 92.9% in eastern and central Europe (1). We confirmed that the prevalence of PCN-nonsusceptible *S. pneumoniae* among nasopharyngeal swab cultures (71%) was correlated with the clinical isolates (70%) in pediatric patients. Our findings of the widespread prevalence of PCN-resistant *S. pneumoniae* strains in the community documents the value of monitoring nasopharyngeal carriage of *S. pneumoniae*, since in the present study the day-care centers and kindergartens were located in different areas of Kaohsiung.

The MICs at which 50% of isolates are inhibited (MIC$_{50}$)
and MIC\textsubscript{90} of other \beta-lactams showed that for the isolates tested there was a trend toward decreased susceptibility which paralleled the PCN susceptibility, as was the case in previous reports (41, 47). Interestingly, a similar trend was not demonstrated for non-\beta-lactams. Although PCN resistance could be a marker for cephalosporin resistance, the degree of cross-resistance between cefalosporin and PCN among \textit{S. pneumoniae} is under debate (33). For individual strains the MICs of cephalosporins may vary widely. If susceptibility to individual drugs is stratified according to PCN susceptibility (Table 2), the data show that PCN-susceptible strains may be nonsusceptible to cephalosporins and vice versa. There is a report demonstrating that intermediate PCN resistance in \textit{S. pneumoniae} is associated with an impaired bacteriologic and clinical responses of acute otitis media to cefaclor and cefuroxime (14). The failure of cefotaxime or ceftriaxone in the treatment of pneumococcal meningitis has been reported previously (7, 8, 10, 20, 22, 55).

The rate of resistance to clarithromycin. Although clarithromycin is a macrolide, is polyresistant in 50% (37, 43). In the present survey, the nasopharyngeal isolates among children demonstrated a strikingly high incidence of resistance to clarithromycin. Although clarithromycin is a macrolide, the susceptibility of \textit{S. pneumoniae} to that drug was no better than that to erythromycin. The macrolide resistance was thought to have evolved in response to different antibiotic pressures in the community. For example, in Spain, one of the areas with a high prevalence of PCN-nonsusceptible \textit{S. pneumoniae}, the incidence of erythromycin resistance is low and is probably due to the infrequent use of erythromycin in Spain. However, in Taiwan, macrolides are often prescribed by physicians as first-line antibiotics and are readily available without prescription at drugstores.

Resistance to chloramphenicol in \textit{S. pneumoniae} was not common in most parts of the world (13, 37, 53, 58). However, our study showed that only 52.4% of nasopharyngeal isolates were susceptible to chloramphenicol and that the MIC\textsubscript{90} for the isolates was as high as 24 \mu g/ml. In the past, chloramphenicol has been suggested as an alternative for the treatment of meningitis caused by PCN-resistant \textit{S. pneumoniae} (23, 25). Such a recommendation should not be encouraged in Taiwan or in other geographic areas with a relatively high prevalence of strains with chloramphenicol resistance.

Resistance to antibiotics of at least three different groups has been defined as multiple drug resistance (3). A high rate of resistance (between 50 and 70\%) was documented in Spain, South Africa, Hungary, Korea, and Pakistan (17, 37, 40, 43). Our study demonstrated that 31\% of nasopharyngeal isolates were multiply resistant to multiple antibiotics (penicillin, clarithromycin, and chloramphenicol). Although the rate of multiple drug resistance was not particularly high compared with that in other countries, 98\% of our isolates were resistant to more than one of the antimicrobial agents tested. This means that physicians in Taiwan have a limited choice of drugs that can be used against \textit{S. pneumoniae}. It is difficult to explain such a high incidence of resistance; the injudicious and frequent use of antibiotics has been proposed as a risk factor in other areas (40). We are conducting a study to investigate the risk factors for antibiotic resistance in Taiwan. The availability of over-the-counter antibiotics may be an important risk factor.

In our study, 97\% of the isolates were susceptible to rifampin. All isolates were susceptible to vancomycin and teicoplanin as in the previous study (2). Rifampin should not be used alone because of the rapid emergence of resistance (24). It has been shown that the combination of vancomycin and rifampin was effective in sterilizing the cerebrospinal fluid of patients with meningitis caused by PCN-nonsusceptible \textit{S. pneumoniae} (52), regardless of whether dexamethasone was administered. We agree with the recommendation of the use of the combination of these two drugs.

\textit{S. pneumoniae} can no longer be considered a pathogen with uniform susceptibility to PCN, cephalosporins, and macrolide antimicrobial agents in Taiwan. The relative frequencies of intermediate and high-level resistance among \textit{S. pneumoniae}

\begin{table}[h]
\centering
\caption{Susceptibilities to drugs stratified by PCN susceptibility}
\label{tab:drug susceptibility}
\begin{tabular}{lcccccccccc}
\hline
\textbf{Status}\textsuperscript{a} & \multicolumn{3}{c}{\textbf{PCN susceptibility}} & \multicolumn{6}{c}{\textbf{No. (%) of isolates}} \\
\cmidrule{4-11}
 & \textbf{Cefaclor} & \textbf{Cefuroxime} & \textbf{Ceftriaxone} & \textbf{Cefotaxime} & \textbf{Imipenem} & \textbf{Chloramphenicol} & \textbf{Clarithromycin} & \textbf{Rifampin} & \textbf{Vancomycin} & \textbf{Teicoplanin} \\
\hline
\textbf{Susceptible} & \textbf{(n = 169)} & & & & & & & & & \\
\textbf{S} & 1 (1) & 111 (66) & 111 (66) & 143 (85) & 111 (66) & 91 (54) & 27 (16) & 167 (99) & 169 (100) & 169 (100) \\
\textbf{I} & 162 (96) & 6 (3) & 49 (29) & 17 (10) & 56 (33) & 30 (18) & 33 (20) & & & \\
\textbf{R} & & & 9 (5) & 9 (5) & 2 (1) & 48 (28) & & & & \\
\hline
\textbf{Intermediately resistant} & \textbf{(n = 175)} & & & & & & & & & \\
\textbf{S} & 102 (58) & 103 (59) & 104 (61) & 102 (58) & 94 (54) & 3 (2) & 172 (98) & 175 (100) & 175 (100) & \\
\textbf{I} & 78 (45) & 97 (55) & 65 (37) & 62 (35) & 70 (40) & 36 (20) & 33 (19) & & & \\
\textbf{R} & 73 (42) & 7 (4) & 6 (4) & 3 (2) & 45 (26) & & & & & \\
\hline
\textbf{Highly resistant} & \textbf{(n = 240)} & & & & & & & & & \\
\textbf{S} & 100 (42) & 145 (60) & 151 (63) & 104 (43) & 121 (50) & 5 (2) & 230 (96) & 240 (100) & 240 (100) & \\
\textbf{I} & 19 (8) & 121 (50) & 41 (17) & 31 (13) & 7 (3) & 87 (35) & 185 (77) & 9 (3.6) & \\
\textbf{R} & 240 (100) & & & & & & & & & \\
\hline
\end{tabular}
\textsuperscript{a} S, sensitive; I, intermediate; R, resistant.
\end{table}
have important therapeutic implications for the selection of antimicrobial agents to be used for initial empirical treatment of infections frequently caused by *Streptococcus pneumoniae*, e.g., pneumonia and meningitis, particularly in critically ill patients. The Centers for Disease Control and Prevention has recommended that clinicians base their decisions about empirical antibiotic therapy for presumptive pneumococcal infections on local prevalence data (9). Prospective studies of the treatment of invasive infections due to PCN-resistant *Streptococcus pneumoniae* are urgently needed.

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**REFERENCES**


