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Emergence of Multiple-Antibiotic-Resistant *Streptococcus pneumoniae* in Hong Kong

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Two hundred four strains of *Streptococcus pneumoniae* isolated in Hong Kong from January 1993 to May 1995 were analyzed for their antibiotic susceptibilities and epidemiological patterns. The ages of the patients from whom the strains were isolated ranged from 1 month to 93 years (median, 53 years); the male-to-female ratio was 2.8, with a predominance of males in the pediatric group. Fifty-nine (28.9%) strains showed reduced penicillin susceptibility, including 40 (19.6%) with frank penicillin resistance (MIC > 1 μg/ml). Tetracycline resistance alone was found in 28.4% of strains. Isolates with reduced penicillin susceptibility were more common in children than adults (40 versus 23.9%; $P = 0.02$), and penicillin resistance rates were significantly higher in hospitalized patients than in outpatients (39.5 versus 12.5%; $P < 0.001$). Penicillin resistance was significantly associated with resistance to ceftriaxone, erythromycin, and tetracycline ($P < 0.01$) but not with ofloxacin or vancomycin ($P = 0.5$). Among eight different patterns of resistance to three or more antibiotics, the commonest one (14.2%) was multiple resistance to penicillin, chloramphenicol, ceftriaxone, erythromycin, and tetracycline. Emergence of multiple-antibiotic-resistant *S. pneumoniae* reflects recent changes in the pneumococcus itself and the general indiscriminate use of antibiotics in treatment of respiratory infections in Hong Kong.

Despite the prompt use of antibiotic treatment, the pneumococci persist as a significant cause of morbidity and mortality in humans (5, 7, 8, 30, 31). The number of pneumococcal strains found to be resistant to different antimicrobial drugs is increasing worldwide (2). In the Southeast Asian region, the recent report of a penicillin resistance rate of 70% in Korea was one of the highest reported to date (15, 17). In Hong Kong, earlier case reports have indicated the possible spread of penicillin-resistant pneumococci in the community (29). Prompted by an earlier pilot study (18), we embarked on a comprehensive survey to assess the extent of the problem. We describe here the results of our study on the antibiotic susceptibilities and epidemiology of the multiple-antibiotic-resistant pneumococci in Hong Kong.

MATERIALS AND METHODS

Bacterial strains. Strains of *Streptococcus pneumoniae* were collected from four public hospital and two outpatient clinic laboratories from January 1993 to May 1995. These laboratories were scattered over most urban districts of Hong Kong. Isolates were transported in screw-cap bottles with cooked-meat medium and subcultured on 5% horse blood agar plates with 5% CO_2 on arrival. Identification was performed by colonial morphology on blood agar, Gram stain, optochin susceptibility, bile solubility, and API 20S tests (bioMerieux, Marcy l'Etoile, France). After identity was confirmed, strains were lyophilized and stored at room temperature before further examination.

Antibiotic susceptibility tests. The broth microdilution method as described by the National Committee for Clinical Laboratory Standards (24) was used to test for susceptibilities to penicillin, azithromycin, ceftriaxone, chloramphenicol, erythromycin, vancomycin, ciprofloxacin, levofloxacin, ofloxacin, and pefloxacin. These antimicrobial agents were supplied as laboratory powders or tablets of known potency. Stock solutions were made according to the manufacturers' recommendations. The inoculum was prepared with pneumococcal suspensions with turbidity adjusted to that of a 0.5 MacFarland standard. Medium used was cation-supplemented Mueller-Hinton broth (Oxoid, Basingstoke, England) containing 5% lysed horse blood. All cultures were incubated for 18 h in 5% CO_2 at 37°C. The MIC was taken as the lowest concentration of antibiotics which prevents visible growth. Control strains of *S. pneumoniae* ATCC 49619 and *Staphylococcus aureus* ATCC 29213 were included in each batch of testing. The MICs for these control strains were within the acceptable range throughout the experiments. Criteria used for definition of breakpoint concentrations were according to published guidelines (25).

Statistical analysis. Tests for significant associations were performed using the chi-square or two-tailed Fisher exact test when appropriate. A P value of <0.05 was taken as statistically significant.

RESULTS

Of a total of 204 pneumococcal strains collected during the study period, 13 (6.4%), 157 (77%), 10 (4.9%), 17 (8.3%), and 7 (3.4%) were isolated from the upper respiratory tract, the lower respiratory tract, the blood or cerebrospinal fluid (CSF), the eye, and other sites, respectively. The relationship between the specimen source and the age and sex of patients is shown in Table 1. The age range of patients was 1 month to 93 years (median, 53 years; mean, 45.6 years). The overall male-to-female ratio was 2.8, with a predominance of males in the pediatric age group (<14 years; $P = 0.03$). No information on sex and age could be obtained for patients giving nine isolates from sputum ($n = 5$) and other sites ($n = 4$).

Table 2 summarizes the susceptibilities of the 204 pneumococcal isolates to 11 antibiotics. While 59 (28.9%) isolates showed reduced susceptibility to penicillin, the penicillin MIC at which 50% of the strains tested were inhibited (MIC_{50}) and MIC_{90} were the same as those of ceftriaxone. Notably, 40 (19.6%) strains displayed frank penicillin resistance (MIC > 1 μg/ml). Tetracycline resistance, being found in 78.9% of strains tested, was the highest rate in this study. On the other hand, chloramphenicol resistance was also common, with 37.7% of isolates showing reduced susceptibility. Among the four quinolones tested, MIC_{50}s and MIC_{90}s of levofloxacin and ciprofloxacin were onefold lower than those of ofloxacin. All but one isolate were susceptible to ofloxacin. This strain with reduced ofloxacin susceptibility (MIC = 16 μg/ml) also required similarly increased MICs of ciprofloxacin (MIC = 8 μg/ml),

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TABLE 1. Distribution of patient sex and age and specimen types of pneumococcal isolates in Hong Kong (1993 to 1995)

Site	No. of patients							
	Male	Female	With age (yr) of:					Total (%)
			<2	2–14	15–65	>65	Unknown	
Upper respiratory tract								
Ear	3	1	0	3	1	0	0	4 (2.0)
Nose	3	4	0	5	2	0	0	7 (3.4)
Throat	1	1	1	0	1	0	0	2 (1.0)
Lower respiratory tract								
Endotracheal aspirate	0	2	2	0	0	0	0	2 (1.0)
Pleural fluid	1	0	0	0	0	1	0	1 (0.5)
Sputum	115	34	4	11	67	67	5	154 (75.5)
Blood and CSF	9	1	1	2	3	4	0	10 (4.9)
Eye	10	7	14	1	0	2	0	17 (8.3)
Others	2	1	1	0	1	1	4	7 (3.4)
Total (%)	144 (73.8)	51 (26.2)	23 (11.3)	22 (10.8)	75 (36.8)	75 (36.8)	9 (4.4)	204 (100)

levofloxacin (MIC = 8 μg/ml), and pefloxacin (MIC = 16 μg/ml). No vancomycin-resistant strain was found.

Distribution of various antibiotic resistance patterns for the 204 pneumococcal strains is shown in Table 3. While 24 (11.8%) remained fully susceptible to the antibiotics tested, 58 (28.4%) were tetracycline resistant. In addition, 18 (8.8%) and 19 (9.4%) strains were resistant to three and four of the antibiotics tested, respectively. Most alarmingly, 29 (14.2%) strains showed multiple resistance to all five antibiotics, the commonest resistance pattern following that of tetracycline resistance. In total, 66 (32.4%) strains tested were resistant to three or more antibiotics.

The distribution of high-level penicillin resistance at various body sites is shown in Table 4. A total of 40 (19.6%) isolates showed high-level penicillin resistance; all isolates recovered from the nose were fully penicillin susceptible, while those from endotracheal aspirates were all penicillin resistant, the difference being statistically significant ($P = 0.03$, two-tailed Fisher exact test). Of 13 strains from the upper respiratory tract, 2 (15.4%) were penicillin resistant compared with 32 of 157 strains isolated from lower respiratory tract (20.4%; $P = 0.3$). Of particular interest, was 1 of 10 (10%) blood or CSF isolates showed penicillin resistance.

Relationships between penicillin resistance, age, and hospitalization status are shown in Table 5. Pneumococci with reduced penicillin susceptibility were more likely to be found in children than adults (40 versus 23.9%; $P = 0.02$). Moreover, hospitalized patients had penicillin resistance rates significantly higher than those of outpatients (39.5 versus 12.5%; $P < 0.001$). The association of penicillin resistance with resistance to seven other antibiotics is shown in Table 6. Statistically significant associations with penicillin resistance were found for four antibiotics—ceftriaxone, chloramphenicol, erythromycin, and tetracycline ($P < 0.001$)—but not for ofloxacin or vancomycin.

DISCUSSION

Increasing rates of antibiotic resistance of *S. pneumoniae* have been reported in a number of countries. The antibiotic resistance rate (88.3%) in Hong Kong, which we documented in this study, is one of the highest reported to date (9, 16, 21). The problem of penicillin-resistant pneumococci in Hong Kong has gradually emerged during the past few years. In 1983, no isolate was found to be penicillin resistant (MIC range: 0.0037 to 0.06 μg/ml) (22). Strains showing intermediate resistance to penicillin (MIC range: 0.125 to 0.1 μg/ml) were first reported in 1993 (18). Our present study now documents rates of 9.3% for intermediate resistance and 19.6% for high-level resistance. A significant proportion of these strains with high-

TABLE 2. Antibiotic susceptibilities of 204 strains of pneumococci in Hong Kong, 1993 to 1995[a]

Antibiotic	MIC (μg/ml)			R (μg/ml)	No. (%) resistant	IR (μg/ml)	No. (%) intermediately resistant	S (μg/ml)	No. (%) susceptible
	Range	50%	90%						
Azithromycin	<0.016–>128	0.12	>128	>1	72 (35.3)	1	15 (7.4)	<1	117 (57.4)
Ceftriaxone	<0.008–2	0.03	2	>1	22 (10.8)	1	22 (10.8)	<1	160 (78.4)
Chloramphenicol	<0.25–32	2	16	>4	77 (37.7)	NA	NA	<8	127 (62.3)
Ciprofloxacin	<0.06–8	0.5	1	NA	NA	NA	NA	NA	NA
Erythromycin	<0.008–>32	0.06	>32	>2	50 (24.5)	1–2	30 (14.7)	<1	124 (60.8)
Levofloxacin	<0.06–8	0.5	1	NA	NA	NA	NA	NA	NA
Ofloxacin	<0.06–16	1	2	>4	1 (0.5)	4	0 (0)	<4	203 (99.5)
Pefloxacin	<0.25–16	4	8	NA	NA	NA	NA	NA	NA
Penicillin	<0.008–4	0.03	2	>1	40 (19.6)	0.1–1	19 (9.3)	<0.12	145 (71.1)
Tetracycline	<0.06–64	16	32	>4	161 (78.9)	4	15 (7.4)	<4	28 (13.7)
Vancomycin	<0.03–0.5	0.25	0.25	NA	0 (0)	NA	0 (0)	<2	204 (100)

[a] Abbreviations: 50%, MIC_{50}; 90%, MIC_{90}; R, resistance breakpoint; IR, intermediate-resistance breakpoint; S, susceptibility breakpoint; NA, interpretative standards not available.

TABLE 3. Distribution of antibiotic resistant patterns of 204 pneumococcal strains isolated in Hong Kong, 1993 to 1995

Resistance pattern[a]	No. (%) of strains with pattern
None	24 (11.8)
T	58 (28.4)
C	1 (0.5)
ET	29 (14.2)
CT	22 (10.8)
PT	2 (1.0)
CE	1 (0.5)
OT	1 (0.5)
CET	9 (4.4)
PET	8 (3.9)
PCT	1 (0.5)
PCCrT	8 (3.9)
PCrET	5 (2.5)
PCET	4 (2.0)
PECCr	2 (1.0)
PECCrT	29 (14.2)
Total	204 (100)

[a] P, penicillin; C, chloramphenicol; Cr, ceftriaxone; E, erythromycin or azithromycin; T, tetracycline; O, ofloxacin.

level resistance was found among pediatric and hospitalized patients. In the United States and most other areas, the percentage of frankly penicillin-resistant (MICs > 1 μg/ml) strains is much less than that of relative penicillin resistance (2). In a recent study in Korea (17), penicillin-resistant pneumococcal infections occurred more often in patients with hospitalization, aged <15 years, on antimicrobial therapy, and whose infection was nosocomially acquired.

Of special concern is the occurrence of pneumococci resistant to ceftriaxone, a broad-spectrum cephalosporin which is frequently used in septicemic and emergency conditions as a lifesaving agent. In 1983, there were no pneumococci for which the ceftriaxone MIC was >0.25 μg/ml. However, of 40 pneumococcal isolates with high-level penicillin resistance which we tested, for 22 the ceftriaxone MIC was 2 μg/ml. The clinical consequences should be marked because it is in these penicillin-resistant strains that we see the most cross-resistance, particularly to broad-spectrum cephalosporins.

The rapid emergence of penicillin-resistant pneumococci also resistant to other antimicrobial agents presents a new clinical challenge. Of 59 penicillin-resistant strains tested, 42 (74.6%) were also resistant to ceftriaxone. This will severely compromise effective treatment for invasive pneumococcal infections. Resistance to at least three of the antibiotics tested now was found in 32.4% of our isolates. This alarming figure probably reflects inate changes in the pneumococcus organism itself on the one hand and the antibiotic selection pressure from general indiscretion in prescribing antibiotics in the treatment of common respiratory tract infections on the other (13, 23). In South Africa, 21.5% of 93 strains with intermediate penicillin resistance also required cefotaxime MICs of at least 0.5 μg/ml (10). A recent study in Dallas (11) observed that while none of 258 strains required a cefotaxime MIC >0.5 μg/ml between 1981 and 1983, 4.5% of 112 strains isolated from 1991 to 1992 required such high MIC. Although optimal therapy for penicillin-resistant pneumococcal meningitis has yet to be defined, extended-spectrum cephalosporins have been recommended for most cases. However, treatment failures with broad-spectrum cephalosporins in meningitis caused by penicillin-resistant pneumococci have been reported in Spain and the United States (1, 3, 4, 6, 19, 28).

Erythromycin resistance increased dramatically from 0% in 1983 to 42.4% in 1993 and 39.2% by this study. The corresponding figures for tetracycline were 52, 72.7, and 78.9%. Strains displaying chloramphenicol resistance also increased

TABLE 4. Distribution of penicillin susceptibility of pneumococci according to site of isolation in Hong Kong, 1993 to 1995

Source of specimen	No. of strains			
	Penicillin susceptible	Intermediately resistant	Penicillin resistant	Total (%)
Upper respiratory tract				
Ear	3		1	4 (2.0)
Nose	7			7 (3.4)
Throat	1		1	2 (1.0)
Lower respiratory tract				
Endotracheal aspirate			2	2 (1.0)
Pleural fluid		1		1 (0.5)
Sputum	111	13	30	154 (75.5)
Blood and CSF	7	2	1	10 (4.9)
Eye	15	1	1	17 (8.3)
Others[a]	1	2	4	7 (3.4)
Total (%)	145 (71.1)	19 (9.3)	40 (19.6)	204 (100)

[a] $P < 0.01$ by two-tailed Fisher exact test.

TABLE 5. Distribution of penicillin susceptibility of pneumococci according to patient age and hospitalization status (Hong Kong, 1993 to 1995)

Penicillin susceptibility[a]	No. (%) of patients			
	By age[b]		With hospitalization[c]	
	Children (<14 yr)	Adult (>14 yr)	Yes	No
S	27 (60.0)	114 (76.0)	75 (60.5)	70 (87.5)
IR	5 (11.1)	13 (8.7)	14 (11.3)	5 (6.3)
R	13 (28.9)	23 (15.3)	35 (28.2)	5 (6.3)
Total	45	150	124	80

[a] S, susceptible; IR, intermediately resistant; R, resistant.
[b] $P < 0.05$ for age distribution between susceptible and resistant strains by Yates corrected chi-square test.
[c] $P < 0.001$ for hospitalization status in susceptible and resistant strains by Yates corrected chi-square test.

TABLE 6. Association of penicillin resistance with resistance to other antibiotics in pneumococci in Hong Kong, 1993 to 1995

Antibiotic	No. (%) of isolates resistant[a] to indicated antibiotic	
	Penicillin susceptible (MIC < 0.12 μg/ml) (n = 145)	Penicillin resistant[b] (MIC > 0.06 μg/ml) (n = 59)
Tetracycline	119 (82.1)	57 (96.6)[c]
Erythromycin	35 (24.1)	45 (76.3)[c]
Chloramphenicol	33 (22.8)	44 (74.6)[c]
Ceftriaxone	0 (0)	44 (74.6)[c]
Ofloxacin	1 (0.7)	0 (0)
Vancomycin	0 (0)	0 (0)

[a] According to National Committee for Clinical Laboratory Standards breakpoints for definition of resistance.
[b] Includes intermediately resistant and resistant strains.
[c] $P < 0.001$ by chi-square test.

significantly, from 10 to 37.7%. Although erythromycin was suggested as an alternative oral therapy for problematic pneumococcal infections (19), our results do not support this recommendation.

We tested four quinolones to explore the potential of this group of antibiotics. The MICs of quinolones parallel each other, with pefloxacin less active and ciprofloxacin more active than ofloxacin for our strains, and corresponded with results of other workers (14, 20). While a good response to ciprofloxacin has been reported (27), treatment failures have also been observed (26). More clinical trials would need to be conducted to establish the potential therapeutic role in these infections. Our results also confirmed previous reports (12) that levofloxacin displayed in vitro activity for pneumococci similar to that of ciprofloxacin.

Emergence of multiple-antibiotic-resistant pneumococci means that newer antibiotics will have to be developed to combat these infections or that vaccination may be given in a much broader scale, provided that coverage be given for the resistant serotypes. Serological typing of our isolates would help to elucidate this latter point and establish whether this will be feasible. Moreover, control of proper use of antibiotics is now called for to decrease the selection pressure for these organisms. With the rapidity of modern travel, it is now mandatory to monitor possible spread of these multiple-antibiotic-resistant pneumococci.

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