EVALUATION OF SUSCEPTIBILITY STATUS OF INVASIVE PNEUMOCOCCAL ISOLATES TO VARIOUS ANTIBIOTICS AND RISK FACTORS ASSOCIATED WITH INVASIVE PENICILLIN-NONSUSCEPTIBLE PNEUMOCOCCAL INFECTION: BANGKOK 1997-1998

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Abstract. The antibiotic susceptibility pattern of *Streptococcus pneumoniae* isolated from specimens of invasive infections was examined at Siriraj Hospital, a tertiary care center in Bangkok, during December 1996 April 1998. The percentage of *S. pneumoniae* isolates intermediate and resistant to various antibiotics were: penicillin, 25% and 21%; amoxicillin-clavulanate, 24% and 0%; cefuroxime, 6% and 36%; cefotaxime, 6% and 1.4%; ceftibuten, 5% and 42%; imipenem 22% and 0%; co-trimoxazole, 6% and 41%; chloramphenicol, 2% and 26%; erythromycin, 12% and 16%; azithromycin, 0% and 30%; and roxithromycin 0% and 33%. Most of the penicillin-nonsusceptible *S. pneumoniae* (PNSP) were also nonsusceptible to other antibiotics except cefotaxime, and imipenem. The isolates from respiratory specimens have a higher rate of resistance to all antimicrobial agents with a significant rise in MIC_{50} of beta-lactam antibiotics. There was no difference in the outcome of infections caused by penicillin-susceptible and -nonsuscetible *S. pneumoniae*. The only identifiable risk factor associated with PNSP infection was prior use of antibiotic within 3 weeks.

INTRODUCTION

Streptococcus pneumoniae has been a major pathogen causing various common infections in children and adults. For decades, penicillin had been perfectly effective for the treatment of pneumococcal infections and its use has resulted in a remarkable decline in mortality caused by these infections. In 1967 resistance to penicillin was first reported in Australia (Hansman and Bullen, 1967). Not too long afterwards reports from many countries *eg* Spain, Israel, Eastern Europe and South Africa also revealed the occurrence of penicillin resistance (Jacobs and Appelbaum,1995). It was not until early 1990 that resistance to penicillin and other antimicrobial agents became a problem as the incidence of resistance from clinical isolates remarkedly increased over time (Butler *et al*, 1996; Turett *et al*, 1999; Aswapokee *et al*, 1998). Resistance is now spreading worldwide. In 1997, percentages of penicillin-nonsusceptible *S. pneumoniae* (PNSP) isolates were 24-68% in North America (Doern *et al*, 1998) and 4-80% in Asian countries (Song *et al*, 1999). The prevalence of resistance to other antimicrobial agents is higher among penicillin-nonsusceptible strains (Doern *et al*, 1998; Barry *et al*, 1994) making antibiotic selection difficult.

Infections caused by drug-resistant *S. pneumoniae* (DRSP) may not result in clinical impact if the level of the empirical antibiotic at the infection sites exceeds the minimal bactericidal concentration (MBC). Clinical failure of therapy mostly occurs when antibiotic penetration to infection sites is limited, such as in meningitis. Knowledge of antimicrobial susceptibility will help determine the guidelines for empirical antibiotic regimens. It is important to evaluate the resistance rate of *S. pneumoniae* in individual hospitals because the resistance rate varies even in the same geographic area and the rate from a surveillance center may not represent the rate for other hospitals (CDC,1999).

We conducted this study to evaluate the susceptibility status of pneumococcal isolates from invasive infections to 13 different antibiotics available in our hospital in 1997-1998 and to characterize risk factors associated with invasive infections caused by PNSP in our patient population.

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We also evaluated the outcome of infections caused by penicillin-susceptible and -nonsusceptible pneumococci (PSSP and PRSP).

MATERIAL AND METHODS

All the clinical isolates of *S. pneumoniae* in our hospital were collected from December 1996 to April 1998. These isolates were from pediatric and adult patients with invasive infections caused by *S. pneumoniae*. Redundant isolates from the same episode of infections were discarded.

Antimicrobial susceptibility test

All the isolates were screened for penicillin susceptibility by using 1 μg oxacillin disc diffusion method according to the performance standards from the National Committee for Clinical Laboratory Standards (NCCLS). Isolates with a clear zone of ≥ 20 mm were considered sensitive to penicillin.

The minimum inhibitory concentration (MIC) of penicillin was determined by standard agar dilution technique using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood with the inoculum size of 10^4 cfu/ml incubated overnight in 5% CO_2 at 35ºC. The MIC was defined as the lowest concentration that yielded no visible growth.

The MIC of other 12 antibiotics listed in Table 1 was determined by using the E-test method. The MIC interpretative standards for various antibiotics in this study were defined according to the 1997 NCCLS breakpoint (National Committee for Clinical Laboratory Standards, 1997). Because the MIC break points for cefprozil and cefpirome were not available by 1997 NCCLS guidelines, the interpretation of MIC for these two antibiotics was not performed. *S. pneumoniae* ATCC49619 was used as the control organism throughout this study.

Identification of risk factors and determination of outcomes

Medical records of the patients were reviewed for potential risk factors such as age, presence of children household members, nutritional status, underlying illness, previous illness, previous use of antibiotics within 3 weeks, and location of residence. The outcomes of the infection episodes were also reviewed.

Statistical analysis

The susceptibility of each antibiotic was described in percentages of sensitivity and 50th percentile (MIC_{50}) and 90th percentile (MIC_{90}). The MIC_{50} and MIC_{90} of the isolates from respiratory specimens (*eg* bronchoalveolar lavage, sputum) in patients with respiratory tract infections were com-

Table 1
Breakpoints for MIC interpretation according to 1997 NCCLS guidelines.

Antibiotics	μg/ml	S	I	R
1.Penicillin	0.002-32	≤0.06	0.1-1	≤2
2.Amoxicillin+Clavulanic acid	0.016-256	≤0.5	1	≤2
3.Cefuroxime	0.016-256	≤0.5	1	≤2
4.Cefprozil	0.016-256	-	-	-
5.Cefotaxime	0.002-32	≤0.5	1	≤2
6.Ceftibuten	0.016-256	≤8	16	≤32
7.Cefpirome	0.016-256	-	-	-
8.Imipenem	0.002-32	≤0.12	0.25-0.5	≤1
9.Co-trimoxazole	0.002-32	≤0.5/9.5	1/19-2/38	≤4/76
10.Chloramphenicol	0.016-256	≤4	-	≤8
11.Erythromycin	0.016-256	≤0.5	1-2	≤4
12.Azithromycin	0.016-256	≤0.5	1	≤2
13.Roxithromycin	0.016-256	≤0.25	0.5	≤1

NCCLS = National Committee for Clinical Laboratory Standards; S = susceptible, I = intermediate, R = resistant

pared with those of the isolates from sterile body fluid and pus, using Student's *t*-test. The risk factors for infections caused by PNSP were analyzed by univariate (chi-square and Student's *t*-test) and multivariate analyses (multiple logistic regression). The p-values were two-tailed.

RESULTS

During the period of 17 months, there were 71 isolates of *S. pneumoniae* collected and available for study. These specimens were from 21 children and 50 adults. Of these, 68 were from hospitalized patients. Ten isolates were also used in a previous study (Aswapokee *et al*, 1998). The source of specimens from which these isolates were grown are shown in Table 2. All the patients whose specimens were sputum or bronchial wash had pneumonia.

Table 2
Source of specimens.

Source	No. (%)
Sputum	24 (34)
Bronchial wash	6 (8)
CSF	3 (4)
Blood	29 (41)
Pus and other body fluid	9 (13)
Total	71 (100)

Susceptibility of *S. pneumoniae* to various antibiotics

The result of the oxacillin disc screening test was perfectly concordant with the MIC interpretation. As shown in Table 3, the rate of penicillin-nonsusceptibility in this study was 46.5% (25.4% of intermediate and 21.1% resistance). Amoxicillin-clavulanate had less MIC_{50}, MIC_{90} and nonsusceptibility rate (24.3%) than penicillin and the other two second generation cephalosporins, cefuroxime and cefprozil. Among the oral cephalosporins, cefuroxime had the lowest MIC_{50} and MIC_{90} followed by cefprozil and ceftibuten; however, nonsusceptibility rates were quite similar. Cefotaxime had a lower MIC_{50} but similar MIC_{90} to cefpirome. Among all the antibiotics tested, cefotaxime had the lowest rate of nonsusceptibility (7.1%), with only 1.4% resistance. If the MIC breakpoint of cefpirome settled at the same level as cefotaxime, the rate of cefpirome susceptibility would be the same as cefotaxime. Imipenem had the lowest MIC_{50} and MIC_{90} among all the antibiotics tested. However, eleven isolates (22.4%) had MIC just right above the breakpoint for susceptibilities and, therefore, were determined as intermediate although the actual MIC were lower than the range classified for intermediate. Only 53% of the isolates were susceptible to co-trimoxazole. Susceptibility rates to macrolides and chloramphenicol were around 70% and most of the nonsusceptible isolates had MIC in the resistant range.

Table 3
Susceptibility pattern to 13 antibiotics.

Antibiotics	N	Range	%S (N)	%I (N)	%R (N)	MIC_{50}	MIC_{90}
Penicillin	71	0.006 - 4	53.5 (38)	25.4 (18)	21.1 (15)	0.064	2
Amoxicillin + Clavulanic acid	70	0.016 - 1.5	75.7 (53)	24.3 (17)	-	0.023	1
Cefuroxime	70	0.016 - 256	58.6 (41)	5.7 (4)	35.7 (25)	0.064	3
Cefprozil	49	0.016 - 16				0.250	6
Cefotaxime	70	0.004 - 32	92.9 (65)	5.7 (4)	1.4 (1)	0.023	0.5
Ceftibuten	59	1.0 - 256	52.5 (31)	5.1 (3)	42.4 (25)	6	256
Cefpirome	70	0.016 - 12				0.032	0.5
Imipenem	49	0.002 - 0.19	77.6 (38)	22.4 (11)	-	0.008	0.19
Co-trimoxazole	49	0.094 - 32	53.1 (26)	6.1 (3)	40.8 (20)	0.5	12
Chloramphenicol	49	1.0 - 16.0	71.4 (35)	2.0 (1)	26.5 (13)	2	16
Erythromycin	49	0.016 - 256	71.4 (35)	12.2 (6)	16.3 (8)	0.064	256
Azithromycin	43	0.064 - 256	69.8 (30)	-	30.2 (13)	0.380	256
Roxithromycin	52	0.047 - 256	67.3 (35)	-	32.7 (17)	0.125	256

Table 4
Antimicrobial susceptibility of *S. pneumoniae* isolates to 12 antimicrobial agents, according to penicillin susceptibility category.

Antibiotics	Penicillin susceptible N=38			Non-susceptible N=33		
	%S (N)	MIC_{50}	MIC_{90}	%S (N)	MIC_{50}	MIC_{90}
Amoxicillin + Clavulanic acid	97.4 (37/38)	0.016	0.023	50 (16/32)	0.625	1.35
Cefuroxime	97.4 (37/38)	0.023	0.07	12.5 (4/32)	1.75	4
Cefprozil		0.125	0.263		3	8
Cefotaxime	100 (38/38)	0.012	0.025	84.4 (27/32)	0.38	0.75
Ceftibuten	90.9 (30/33)	3	17.6	3.8 (1/26)	256	256
Cefpirome		0.016	0.033		0.38	0.75
Imipenem	100 (28/28)	0.007	0.012	47.6 (10/21)	0.125	0.19
Co-trimoxazole	85.7 (24/28)	0.19	1.2	9.5 (2/21)	4	28
Chloramphenicol	96.4 (27/28)	1.5	2.1	38.1 (8/21)	12	16
Erythromycin	96.4 (27/28)	0.055	0.097	38.1 (8/21)	1.5	256
Azithromycin	95.8 (23/24)	0.315	0.5	36.8 (7/19)	4	256
Roxithromycin	93.1 (27/29)	0.125	0.25	34.8 (8/23)	6	256

From Table 4, most penicillin-nonsusceptible isolates were also nonsusceptible to other antimicrobial agents. The concordance with penicillin-nonsuceptibility was notable in cefuroxime, cefprozil, ceftibuten and co-trimoxazole. Among the penicillin-nonsusceptible isolates, the lowest MIC_{50} and MIC_{90} belonged to imipenem, followed by cefotaxime and cefpirome. These three antimicrobial agents are useful for most PNSP. However, with the lower MIC breakpoint, only 47.6% of PNSP were defined susceptible to imipenem while 84% were defined as susceptible to cefotaxime.

Difference of susceptibility between respiratory and non-respiratory isolates

In comparing the antimicrobial susceptibility between the isolates from respiratory specimens and those from non-respiratory, including blood, CSF, pus and body fluid, the MIC_{50} of beta-lactam antibiotics were significantly higher among isolates from respiratory specimens. The difference in MIC_{50} or MIC_{90} was not significant in co-trimoxazole, chloramphenicol or macrolides (Table 5). Finally, isolates from non-respiratory specimens were always less resistant to all antibiotics than those from respiratory specimens.

Risk factors of PNSP infection and outcomes

Of 71 patients whose clinical specimens were included in the antimicrobial susceptibility study, only 52 patients had medical records available. Lung infections including pneumonia, bronchiectasis, and empyema were associated with higher risk of PNSP ($p = 0.029$, Table 6). Of the potential risk factors evaluated, the only risk factor found associated with PNSP infections was prior use of antibiotics within 3 weeks (16% in PSSP *vs* 63% in PNSP, $p < 0.001$). The outcomes of infections caused by PSSP and PNSP were not different ($p = 0.09$, Table 7).

DISCUSSION

Although DRSP is prevalent worldwide, the resistance patterns to various antimicrobial agents are different (Doern *et al*, 1998; Song *et al*, 1999; Syrogiannopoulos *et al*, 1994). Our study revealed an alarming prevalence of resistance to various antimicrobial agents available. These isolates were from clinical specimens of invasive infections and are believed to confer less resistance than isolates from nasopharyngeal swab (Lehmann *et al*, 1997; Kellner *et al*, 1998; Jorgensen *et al*, 1990). The prevalence of beta-lactam resistance in this study was very close to that in North America (Doern *et al*, 1998) in the same period; however, the resistance to co-trimoxazole and chloramphenicol was much higher in our study. This may be due

Table 5
Susceptibility of isolates from respiratory and non-respiratory specimens[b].

Antibiotics	Specimen	N	Range	%S (N)	%I (N)	%R (N)	MIC_{50}	MIC_{90}
Penicillin	Non-respiratory	41	0.012 - 4	65.9 (27)	17.1 (7)	17.1 (7)	0.032[a]	2
	Respiratory	30	0.006 - 4	36.7 (11)	36.7 (11)	26.7 (8)	0.5[a]	2
	Total	71	0.006 - 4	53.5 (38)	25.4 (18)	21.5 (15)	0.064	2
Amoxicillin+	Non-respiratory	41	0.016 - 1.5	82.9 (34)	17.7 (7)	-	0.016[a]	0.75
Clavulanic acid	Respiratory	29	0.016 - 1.5	65.5 (19)	34.5 (10)	-	0.38[a]	1
	Total	70	0.016 - 1.5	75.7 (53)	24.3 (17)	-	0.023	1
Cefuroxime	Non-respiratory	41	0.016 - 3	68.3 (28)	4.9 (2)	26.8 (11)	0.023[a]	2[a]
	Respiratory	29	0.016 - 256	44.8 (13)	6.9 (2)	48.3 (14)	1.0[a]	4[a]
	Total	70	0.016 - 256	58.6 (41)	-	34.3 (24)	0.064	3
Cefprozil	Non-respiratory	26	0.016 - 16				0.19[a]	4.6
	Respiratory	23	0.016 - 8				1.0[a]	7.2
	Total	49	0.016 - 16				0.25	6
Cefotaxime	Non-respiratory	41	0.004 - 0.75	97.6 (40)	2.4 (1)	-	0.016[a]	0.464
	Respiratory	29	0.008 - 32	86.2 (25)	10.3 (3)	3.4 (1)	0.19[a]	0.75
	Total	70	0.004 - 32	92.9 (65)	5.7 (4)	1.4 (1)	0.023	0.5
Ceftibuten	Non-respiratory	32	1.5 - 256	68.8 (22)	-	31.3 (10)	3[a]	256
	Respiratory	27	1.0 - 256	33.1 (9)	11.1 (3)	55.6 (15)	24[a]	256
	Total	59	1.0 - 256	52.5 (31)	5.1 (3)	42.4 (25)	6	256
Cefpirome	Non-respiratory	41	0.016 - 0.75				0.023[a]	0.5
	Respiratory	29	0.016 - 12				0.19[a]	0.75
	Total	70	0.016 - 12				0.032	0.5
Imipenem	Non-respiratory	26	0.002 - 0.19	88.5 (23)	11.5 (3)	-	0.008[a]	0.19
	Respiratory	23	0.003 - 0.19	65.2 (15)	34.8 (8)	-	0.047[a]	0.19
	Total	49	0.002 - 0.19	77.6 (38)	22.4 (11)	-	0.008	0.19
Co-trimoxazole	Non-respiratory	26	0.094 - 32	61.5 (16)	-	38.5 (10)	0.25	15.2
	Respiratory	23	0.12 - 32	43.5 (10)	13.0 (3)	43.5 (10)	1.0	12
	Total	49	0.094 - 32	53.1 (26)	6.1 (3)	40.8 (20)	0.5	12
Chloramphenicol	Non-respiratory	26	1.0 - 16	76.9 (20)	3.8 (1)	19.2 (5)	1.75	16
	Respiratory	23	1.0 - 16	65.2 (15)	-	34.8 (8)	2	16
	Total	49	1.0 - 16	71.4 (35)	2.0 (1)	26.5 (13)	2	16
Erythromycin	Non-respiratory	29	0.016 - 256	80.8 (21)	7.7 (2)	11.5 (3)	0.064	256
	Respiratory	23	0.016 - 256	60.9 (14)	17.4 (4)	21.7 (5)	0.094	256
	Total	49	0.016 - 256	71.4 (35)	12.2 (6)	16.3 (8)	0.064	256
Azithromycin	Non-respiratory	26	0.064 - 256	80.8 (21)	-	19.2 (5)	0.38	256
	Respiratory	17	0.094 - 256	52.9 (9)	-	47.1 (8)	0.38	256
	Total	43	0.064 - 256	69.8 (30)	-	30.2 (13)	0.38	256
Roxithromycin	Non-respiratory	26	0.047 - 256	80.8 (21)	-	19.2 (5)	0.125	256
	Respiratory	26	0.047 - 256	53.8 (14)	-	46.2 (12)	0.187	256
	Total	52	0.047 - 256	67.3 (35)	-	32.7 (17)	0.125	256

[a]$p < 0.05$ in comparison between respiratory and non-respiratory strains on the same antibiotics.
[b]All the respiratory specimens were from patients with respiratory tract infections.

to the selective pressure from the pattern of antimicrobial utility.

Data from our study, as well as that from the SENTRY multinational antimicrobial resistance surveillance program in North America (Doern *et al*, 1998), found that most of the PNSP strains were also nonsusceptible to other antimicrobial agents particularly oral cephalosporins, macrolides and cotrimoxazole. Conversely, some other studies did not find a strong correlation of nonsusceptibility between erythromycin and penicillin (Fenoll *et al*,

Table 6
Diagnoses of 52 patients with invasive infections caused by *S. pneumoniae* strains of known penicillin susceptibility status.

Diagnoses[a]	Penicillin susceptible (N=27)	Penicillin-nonsusceptible (N=25)			Total (N=52)
		I	R	Total	
Lung infections[b]	14[c]	14	7	21[b]	35[c]
Sepsis	13	2	1	3	18
Meningitis	3	-	-	-	3
Peritonitis	4	1	-	1	-
Others	2	-	-	-	-

[a]One patient may have more than one diagnosis.
[b]Lung infections included pneumonia, bronchiectasis, empyema.
[c]p=0.029 in univariate analysis of association between lung infections and penicillin-nonsusceptibility.

Table 7
Outcomes for invasive infections caused by penicilin-suscepible and non-susceptible *S. pneumoniae*.

Outcomes	Pen-susceptible N=27(%)	Pen-nonsusceptible N=25%(%)
Recovered	16 (59)[a]	21 (84)[a]
Dead from the infection	4 (15)	1 (4)
Dead from other causes	7 (26)	3 (12)

[a]p=0.09

1991; Geslin *et al*, 1992). This may be due to the different pattern of erythromycin use.

Of note was that MIC_{90} of penicillin and amoxicillin in this study were lower than those of second generation cephalosporins and ceftibuten. The highest MIC for penicillin in our study was 4 μg/ml, the level at which it can be overcome by higher dosage. Moreover, the time above MIC_{90} of the antibiotic level needed to cure infections caused by *S. pneumoniae* was only ≥ 40-50% of dosing interval (Craig and Andes, 1996). Therefore the treatment outcome was successful even with *in vitro* nonsusceptibility. This is particularly true for non-meningeal infections where most empirical beta-lactam treatment regimens yield exceedingly high serum levels. Treatment failure may be higher with oral antibiotics such as macrolides and cephalosporins where side effects limit higher dosage and bioavailability limits high serum level. Oral amoxicillin is the exception due to the wide safety margin and oral dosage which may increase to double without any significant problem. Considering these reasons, penicillin and amoxicillin, at high dose, remains the appropriate first-line empirical treatment for non-meningeal pneumococcal infections in our institution. In central nervous system infections, blood-brain barrier limits the desirable drug level in CSF. The antibiotics chosen must have good CSF penetration and low MIC. Ampicillin and chloramphenicol should no longer be used for empirical treatment of meningitis in our setting. Clavulanate is not helpful to reduce resistance because the mechanism of penicillin resistance is not caused by beta-lactamase. However, clavulanate is a weak beta-lactam antibiotic and may add on the efficacy to combined amoxicillin.

Cefotaxime, cefpirome and imipenem had the lowest MIC_{90} and most PNSP is still susceptible to cefotaxime, cefpirome (if considered of similar breakpoint to cefotaxime), and imipenem, although with somewhat higher MIC_{90} than PSSP. These three agents have good CSF penetration and are therefore very useful for treatment of pneumococcal infections, particularly for infections in the central nervous system. In our study, the rate of cefotaxime resistance was very low (1.4%). Because of the lower breakpoints, the imipenem sus-

ceptibility rate was determined as lower than that of cefotaxime. Although this determination may not currently confer clinical significance as the highest MIC of imipenem was just above the susceptible breakpoint, where serum level of therapeutic dose is well above, it should be a warning signal of further development of more resistance of this salvage antibiotic.

The MIC_{50} of beta-lactam antibiotics for isolates from respiratory specimens were significantly higher than for those from blood or sterile body fluid. The difference in MIC level for isolates from different sites was not seen in macrolides, cotrimoxazole or chloramphenicol, although there was a trend of less susceptibility among the respiratory isolates. Moreover, isolates from patients with lung infections also had a higher chance of penicillin-nonsusceptibility than those from other infections. This is probably the result of selective pressure from frequent use of beta-lactam antibiotics for treatment of respiratory tract infections. A study has shown that after 3-4 days of beta-lactam antibiotic treatment, resistant strains persisted in nasopharynx and newly resistant colonized strains were acquired. This effect was also demonstrated with azithromycin (Dagan *et al*, 1998). This implied the potential higher failure rate of beta-lactam therapy for pneumococcal respiratory tract infections, particularly for antibiotics with higher MIC level such as second generation cephalosporins and ceftibuten.

In our study all macrolides (erythromycin, azithromycin and roxithromycin) were quite similar in rate of susceptibility. However, erythromycin had the lowest MIC_{50}. Macrolides were not effective for PNSP.

Infections caused by PNSP are no more serious than those caused by PSSP. In fact, studies in animals have shown that resistant strains were not able to establish infection unless the animals are immunocompromised (Smith and Abbot,1994; Azoulay-Dupuis *et al*, 1992). Evidence that the resistant strains are less invasive than susceptible strains has been seen in many studies (Lehmann *et al*, 1997; Kellner *et al*, 1998; Jorgensen *et al*, 1990) and therefore these strains cause less invasive infections (Winston *et al*, 1999). Our study also found less resistance among isolates from blood, CSF and body fluid. Moreover mortality of infections caused by drug resistant strains were not associated with increased mortality (Winston *et al*, 1999; Kaplan *et al*, 1998; Borek *et al*, 1997; Tan *et al*, 1998; Bradley *et al*, 1998). The outcomes of infections caused by PNSP and PSSP in our study were also indifferent.

The only identifiable risk factor associated with PNSP infection is prior use of antibiotics within 3 weeks. This result concurred with many other studies (Arnold *et al*, 1996; Clavo-Sanchez *et al*, 1997; Tan *et al*, 1993) and raised the issue of the importance of judicious use of antimicrobial therapy. Vaccination may be the final answer to this problem.

In conclusion, we evaluated the antimicrobial susceptibility status of invasive pneumococci isolates in our hospital and found penicillin-nonsusceptible rate of 47% susceptibility to cefotaxime, cefpirome and imipenem was still high. The MIC_{50} and MIC_{90} of imipenem were the lowest. PNSP were also nonsusceptible to other antimicrobial agents; however, most remain susceptible to cefotaxime, cefpirome and imipenem. Clinical isolates from respiratory specimens were more resistant than those from nonrespiratory sites. Our data suggested that, due to high prevalence of PNSP, macrolides, second generation cephalosporins (cefuroxime, cefprozil), ceftibuten, chloramphenicol, and cotrimoxazole are not appropriate for empirical treatment of pneumococcal infections in our hospital. The outcomes of infections caused by PNSP and PSSP were not different and the only identifiable risk factor associated with infection caused by PNSP was prior use of antimicrobial agents within 3 weeks. Judicious use of antimicrobial agents may be helpful to stop the spread of DRSP.

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