

Invasive Cefotaxime-nonsusceptible *Streptococcus pneumoniae* Infection in Children in Northern Thailand

Virat Sirisanthana, M.D.*

Piyada Chatborirak, M.D.**

Vilai Baosung, M.Sc. (Pharmaco.)***

Banyong Khantawa, M.Sc. (Med. Microbio.)***

Abstract

Invasive infection caused by *Streptococcus pneumoniae* (*S. pneumoniae*) is among the leading causes of illness and death in children. The problem is compounded by the rapid increase in the prevalence of strains of *S. pneumoniae* which are resistant to penicillin and cephalosporins. We conducted a prospective study of invasive *S. pneumoniae* infection in children during a 3-year period (1997-1999) at Chiang Mai University Hospital in northern Thailand. There were 51 episodes of invasive *S. pneumoniae* infection diagnosed from 50 patients. The types of infection were pneumonia (25 episodes), bacteremia (17), meningitis (6), soft tissue infection/sepsis (2) and endocarditis (1). Using agar dilution and/or Epsilometric test (E-test), nonsusceptibility to penicillin was detected in 25 of 51 (49.0%) strains isolated. Nonsusceptibility to cefotaxime was found in 20 of the 51 (39.2%) strains. All penicillin-susceptible strains were susceptible to cefotaxime. Twenty strains (80.0%) of penicillin-nonsusceptible strains were nonsusceptible to cefotaxime. There was no difference in age, sex, type of infection, previous beta-lactam antimicrobial therapy and underlying diseases between the 31 cases with cefotaxime-susceptible and the 20 cases with cefotaxime-nonsusceptible organism. All 45 cases with non-meningeal infection were treated with a beta-lactam antibiotic. The types of beta-lactams given were comparable in both groups. Eight patients died. All were infected with cefotaxime-susceptible organism. The rest of the patients had favorable response to the treatment. Of the six patients with meningitis, four were infected with cefotaxime-nonsusceptible organism. Three of these four patients were successfully treated with 300 mg/kg/day of cefotaxime together with 60 mg/kg/day of vancomycin. We conclude that cases with meningitis caused by cefotaxime-nonsusceptible *S. pneumoniae* should be treated with cefotaxime plus vancomycin, whereas cases with non-meningeal infection responds to treatment with a beta-lactam antibiotic alone. (*J Infect Dis Antimicrob Agents* 2001;18:8-14.)

INTRODUCTION

Invasive infection caused by *Streptococcus pneumoniae* (*S. pneumoniae*) is among the leading

causes of illness and death of young children and children with underlying immunocompromised conditions. In the early 1980's, *S. pneumoniae* was

* Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200,

** Lampang Hospital, Ministry of Public Health of Thailand, Lampang 52000.

*** Central Laboratory, Chiang Mai University Hospital, Chiang Mai 50200, Thailand.

Received for publication: July 6, 2000.

Reprint request: Virat Sirisanthana, M.D., Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

Keywords: Drug-resistant *Streptococcus pneumoniae*, DRSP, penicillin-nonsusceptible *S. pneumoniae*, cefotaxime-nonsusceptible *S. pneumoniae*, pneumococcal infection

uniformly susceptible to penicillin, allowing physicians to treat infected patients with penicillin without performing an antibiotic susceptibility testing. Since then, strains of *S. pneumoniae* that are resistant to penicillin and other beta-lactam antibiotics have been reported and spread rapidly in many parts of the world. From 1994 to 1997, the proportion of penicillin-nonsusceptible *S. pneumoniae* (PNSSP) was reported to be between 33 and 58 percent in Thailand.¹⁻⁴ Although there had been case reports of infection caused by *S. pneumoniae* that was not susceptible to cefotaxime prior to 1997, the prevalence of cefotaxime-nonsusceptible *S. pneumoniae* (CNSSP) was not known. This prevalence has an important implication for the management of invasive *S. pneumoniae* infection. In the area with high prevalence of CNSSP, it is recommended that cefotaxime plus vancomycin is given as an initial treatment regimen in children with bacterial meningitis possibly caused by the organism.⁵ In patients with non-meningeal infection, the choice of treatment is less clear. Because of the high achievable blood level of the drug, these patients may still respond to treatment with beta-lactam antibiotics alone. This was supported by reports that showed a lack of clinical outcome with *in vitro* susceptibility test results for patients treated with penicillin.^{1,6-9}

We conducted a prospective study of invasive *S. pneumoniae* infection in children during a 3-year period to determine the frequency of CNSSP infection and the response to treatment in patients infected with this organism.

MATERIALS AND METHODS

Subjects

The study was conducted at Chiang Mai University Hospital, Chiang Mai, Thailand between January 1, 1997 and December 31, 1999. Children whose blood and/or cerebrospinal fluid (CSF) and/or pleural fluid cultures grew *S. pneumoniae*, were followed prospectively. Children were enrolled as soon as clinical isolates were identified as *S. pneumoniae*, generally within 24-36 hours of admission. The attending medical staff made decision regarding antimicrobial therapy although they were encouraged not to alter therapy if the clinical response was satisfactory.

All patients with non-meningeal infection

received a beta-lactam agent alone or as part of the initial antimicrobial regimen. The daily parenteral dosage of beta-lactam agents used were 100,000 units/kg of penicillin G sodium (PGS) (400,000 units/kg in case of endocarditis); or 100 mg/kg of ampicillin, cloxacillin, cefotaxime, or cefazidime. One patient was given 40 mg/kg of amoxicillin orally.

All patients with meningitis were treated with 200-300 mg/kg/day of cefotaxime, together with 40-60 mg/kg/day of vancomycin regardless of the susceptibility of the organism to cefotaxime.

The sites of infection were classified according to the followings (1) pneumonia: signs of respiratory infection with compatible radiographic changes and isolation of *S. pneumoniae* from blood and/or pleural fluid; (2) bacteremia: febrile illness without focus of infection and isolation of *S. pneumoniae* from blood; (3) meningitis: abnormal CSF profile compatible with meningitis and isolation of *S. pneumoniae* from blood and/or CSF; (4) soft tissue abscess/sepsis: isolation of *S. pneumoniae* from pus and blood; (5) endocarditis: vegetation detected by echocardiography and isolation of *S. pneumoniae* from blood.

Antimicrobial susceptibility testing

The Kirby-Bauer disk diffusion method was performed as described by the National Committee for Clinical Laboratory Standards (NCCLS).¹⁰ The antimicrobial disks used contained 30 µg of vancomycin or 1 µg of oxacillin (BBL, Becton Dickinson and Company, Lockesville, Maryland, USA). Minimal inhibitory concentration (MIC) of penicillin and cefotaxime for all isolates were determined by the E-test (Epsilometric test, AB Biodisk, Solna, Sweden)¹¹ at the time of original isolation. Additionally, MIC's of isolates obtained from patients who were diagnosed in 1999 were determined by the agar dilution method. Susceptibility to penicillin was defined as: susceptible if MIC ≤ 0.06 µg/mL, intermediate nonsusceptible if MIC is 0.1-1 µg/mL, and resistant nonsusceptible if MIC ≥ 2 µg/mL. Susceptibility to cefotaxime was defined as: susceptible if MIC ≤ 0.5 µg/mL, intermediate nonsusceptible if MIC is 1 µg/mL, and resistant nonsusceptible if MIC ≥ 2 µg/mL.¹² When both E-test and agar dilution method were done on the same isolate, the MIC values reported were those obtained from agar dilution testing. When only the E-test was used, MIC values between the conventional log₂ concentrations

was rounded to the next higher MIC value as recommended in the manufacturer's package insert.

Statistics

Differences between continuous variables were evaluated with Student's t-test and those between proportions with the chi-square or Fisher's exact test as appropriate. All p-value reported were for two-tailed tests. The analysis was done using Epi Info version 6 program (Center for Disease Control & Prevention, USA).

RESULTS

During the 3-year period, there were 51 *S. pneumoniae* isolates cultured from 50 children. Twenty-five isolates (49.0%) were nonsusceptible to penicillin and twenty (39.2%) were nonsusceptible to cefotaxime. The prevalence of PNSSP and CNSSP was 57.9, 50.0, 40.0 and 47.4, 33.3, 35.0 percent in 1997, 1998 and 1999 respectively (Table 1). There were more intermediate nonsusceptible isolates than resistant nonsusceptible isolates. The MIC of cefotaxime in the 9 resistant CNSSP isolates ranged from 2.0-6.0 µg/mL. All strains of *S. pneumoniae* that were susceptible to penicillin were also susceptible to cefotaxime. Twenty of the twenty-five strains (80.0%) of penicillin-nonsusceptible strains were also nonsusceptible to cefotaxime.

For the 8 PNSSP isolates obtained in 1999, the MIC's of penicillin determined by the E-test were consistently within two-fold dilution of those determined by the agar dilution tests. This was also true for the 7 CNSSP isolates obtained in 1999 with regards to the MIC's of cefotaxime. With the Kirby-Bauer disk diffusion test, all penicillin susceptible isolates (as determined by E-test) produced zones of 20 mm or greater with the oxacillin disk, whereas

zones produced by all PNSSP isolates were of 19 mm or less. All 37 isolates that were tested with vancomycin disks were susceptible to the drug. These included all 25 strains of PNSSP and all 20 strains of CNSSP.

There were 51 episodes of invasive *S. pneumoniae* infection, 31 by cefotaxime-susceptible *S. pneumoniae* (CSSP) and 20 by CNSSP (Table 2). One HIV-infected girl had two episodes of pneumococcal pneumonia when she was 17 and 19 months of age. Both were caused by CNSSP. Patients' age ranged from 1 to 168 months (mean 43 months, median 24 months). Forty percent were boys. The types of infection were pneumonia (25 episodes), bacteremia (17), meningitis (6), soft tissue infection/sepsis (2), and endocarditis (1). Forty-two episodes (82.4%) were in patients with underlying diseases. Of the 5 patients with congenital heart disease, one had congenital rubella syndrome and one had Down syndrome. All 5 thalassemic patients had had splenectomy. All children who had malignancy were receiving chemotherapy. Two of them had neutropenia (neutrophil count < 500/mm³). Patients with nephrotic syndrome, systemic lupus erythematosus and diabetes mellitus were receiving corticosteroid therapy. There were no difference in age, sex, type of infection, previous beta-lactam antimicrobial therapy and underlying diseases between the two groups.

Clinical response of patients with non-meningeal infection

All children with non-meningeal infection were treated initially with a beta-lactam antimicrobial agent. The types of beta-lactams given in the first 72 hours of admission were comparable in CSSP and CNSSP groups (Table 3). Three children in the CSSP group also received aminoglycoside as part of

Table 1. Penicillin and cefotaxime susceptibility of *S. pneumoniae*.

Studied period	No. of isolates	Penicillin-nonsusceptible <i>S. pneumoniae</i>				Cefotaxime-nonsusceptible <i>S. pneumoniae</i>			
		Intermediate no. (%)	Resistant no. (%)	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)	Intermediate no. (%)	Resistant no. (%)	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)
1997	19	8 (42.1)	3 (15.8)	0.25	3.20	3 (15.8)	6 (31.6)	0.50	4.00
1998	12	6 (50.0)	0 (0)	0.14	1.00	2 (16.7)	2 (16.7)	0.16	2.80
1999	20	5 (25.0)	3 (15.0)	0.01	2.00	6 (30.0)	1 (5.0)	0.02	1.00

the initial regimen. The aminoglycosides were discontinued after the causative organism was identified. In a child with CNSSP bacteremia and pneumonia,

vancomycin was used to replace imipenem when a history of allergy to beta-lactam was obtained. Repeated blood cultures obtained before the adminis-

Table 2. Clinical characteristics in children with cefotaxime-susceptible and cefotaxime-nonsusceptible *S. pneumoniae* infection.

	Cefotaxime-susceptible no. (%)	Cefotaxime-nonsusceptible no. (%)	p value
Number (M:F)	31 (15:16)	20 (9:11)	
Age, month (mean \pm SD)	52.26 \pm 47.21	29.65 \pm 35.94	0.205
Type of infection			
Pneumonia	13	12	
Bacteremia	14	3	
Meningitis	2	4	
Soft tissue infection/sepsis	2	-	
Endocarditis	-	1	
Beta-lactam use in previous 4 weeks	19 (66)	11 (55)	0.877
Underlying disease	24 (77)	18 (90)	0.454
HIV infection	11	7	
Thalassemia	5*	-	
Malignancy	3	1	
Nephrotic syndrome	2	-	
Congenital heart disease	2	3	
Liver cirrhosis	1	4	
Prematurity	1	-	
Diabetes mellitus	-	1	
Systemic lupus erythematosus	-	1	
Frontal meningocele	-	1	

Note : * One episode was in a thalassemic patient who was infected with HIV.

Table 3. Clinical responses of children with non-meningeal infection caused by cefotaxime-susceptible and cefotaxime-nonsusceptible *S. pneumoniae*.

	Cefotaxime-susceptible (n=29)	Cefotaxime-nonsusceptible (n=16)	p value
Initial beta-lactam therapy			
Penicillin G sodium	10	6	0.902
Cefotaxime	10	5	0.912
Ampicillin	4	4	0.427
Amoxicillin	3	1	0.542
Ceftazidime	1	-	1.000
Imipenem	-	1	0.356
Amoxicillin	1	-	1.000
Outcome			
Death	8	0	0.037
Response to therapy	21	16	0.037

tration of vancomycin were negative. Vancomycin was added to the regimen of PGS in a child with CNSSP endocarditis on the second day of therapy. Vancomycin was continued for 3 weeks, and PGS was given for 6 weeks. The patient responded well to the treatment. Eight patients died. All of them were infected with CSSP. All patients died within 72 hours after starting antimicrobial therapy. Six died within 48 hours and four within 24 hours after antimicrobial therapy was started. Seven of the 8 patients who died were found to have underlying diseases, including acquired immunodeficiency syndrome (3 patients), beta-thalassemia (post-splenectomy) (2), prematurity (1) and malnutrition (1). The rest of the patients had favorable response to the treatment. Sixteen (76.2%) of the children infected with CSSP and 13 (81.3%) of those infected with CNSSP became afebrile within 72 hours of therapy with resolving of signs and symptoms of the infection. In 5 (23.8%) of the children infected with CSSP and 3 (18.7%) of those infected with CNSSP, the fever last longer than 72 hours. By then the cultures were negative for *S. pneumoniae* and the signs and symptoms of the infection were resolving. The reasons for the delay of defervescence in these patients were inadequate drainage of the abscess or pleural fluid (3 patients), superimposed *Salmonella* infection (2), neutropenia (1), HIV myocarditis (1), and drug fever (1).

Clinical response of patients with meningitis

The clinical features of the 6 patients with meningitis were shown in Table 4. The first 4 cases were infected with CNSSP isolates. Case no. 1 was seen in 1997. She was treated with 100 mg/kg/day of cefotaxime for the first three days. The dose was increased to 200 mg/kg/day on the 4th day. On the 6th day, the dosage of cefotaxime was increased to 300 mg/kg/day and vancomycin in the dosage of 60 mg/kg/day was added. The CSF culture obtained on the 5th day still grew *S. pneumoniae*. By the 8th day of admission, the CSF culture was sterile and signs of meningitis subsided. The patient died on the 10th day of therapy due to the underlying disease. Since the latter part of 1997 when it was realized that CNSSP existed in Thailand, all cases of suspected pneumococcal meningitis were empirically treated with a combination of cefotaxime and vancomycin. Two of the four cases of CNSSP meningitis and one of CSSP meningitis died.

DISCUSSION

Thailand and other Asian countries are facing increasing prevalence of drug-resistant *S. pneumoniae*.¹⁻⁴ The prevalence of PNSSP in this study (40-58%) increased from a similar study in the same hospital in 1994-1996 (33%).¹ Although cases of meningitis caused by *S. pneumoniae* which was not susceptible to cefotaxime or ceftriaxone had been reported prior to 1997, the prevalence of CNSSP in Thailand was not known. Studies in 1997 showed that the prevalence of PNSSP and CNSSP isolates in Thailand were high, ranging from 56-59 percent and 18-42 percent respectively.²⁻⁴ Our study supports the study by Jorgensen et al which demonstrated that oxacillin disk could be reliably used to predict the susceptibility of *S. pneumoniae* to penicillin.¹³ It also supports the recommendation by NCCLS that isolates susceptible to penicillin are considered to be also susceptible to cefotaxime (but not vice versa).¹⁰ Since disks impregnated with cefotaxime or other cephalosporins are usually unstable and/or commercially unavailable, oxacillin disks can be used in Kirby-Bauer test to predict the susceptibility of *S. pneumoniae* to cefotaxime.

The types of invasive diseases due to *S. pneumoniae* in our study are similar to those in other studies.⁷⁻⁸ Invasive *S. pneumoniae* infection is common in immunocompromised persons, so the finding that the majority of our patients had underlying diseases is not unusual. Although some studies showed that patients infected with beta-lactam non-susceptible *S. pneumoniae* were more likely to be younger, to have underlying immunocompromised conditions, or to have prior treatment with beta-lactam agents^{7-8,14}, our study did not show these associations. These findings were supported by studies by Kronenberger et al and Tan et al.^{6,15} Before 1992, a third generation cephalosporin is generally adequate therapy for meningitis due to PNSSP.¹⁶ When cases of meningitis caused by *S. pneumoniae* that was not susceptible to third generation cephalosporins were reported, choosing an optimal therapeutic regimen became more problematic. In 1997, the American Academy of Pediatrics recommended that cefotaxime/ceftriaxone plus vancomycin is given as an initial regimen in children with bacterial meningitis possibly caused by *S. pneumoniae*.⁵ The result of our study supports this recommendation. One of our cases of meningitis (case no. 1) failed to respond to

cefotaxime therapy given alone. The signs of meningitis subsided and CSF became sterile when the dose of cefotaxime was increased and vancomycin was added to the treatment regimen. Presumably the initial failure was related to the inability to achieve adequate bactericidal activity in the CSF relative to the increased *in vitro* MIC.

With the presence of CNSSP in the community, the treatment of endocarditis caused by *S. pneumoniae* also became a problem. Failure of monotherapy with cefazolin or cefotaxime in CNSSP endocarditis has been reported.¹⁷ The only case of endocarditis in our study was caused by CNSSP. The patient responded well to the treatment with PGS plus vancomycin for 3 weeks followed by PGS alone for another 3 weeks.

Except for meningitis and endocarditis, our study suggests that infection with CNSSP could be

adequately treated with penicillin or cephalosporin alone (Table 4). This was in spite of the fact that the majority of our patients had underlying immunocompromised conditions. In fact, the case fatality rate was higher in patients infected with CSSP than those with CNSSP. However, 4 of the 8 deaths in the group occurred within the first 24 hours of admission and thus could not be attributed to failure of the antimicrobial regimen. If these 4 patients were excluded from the statistical evaluation, the response to treatment in the two groups was not different from one another ($p = 0.143$). Results similar to our study had been reported in the literature.^{1,6-8} However, the American Academy of Pediatrics has recommended empiric treatment with cefotaxime/ceftriaxone and vancomycin for critically ill children who are immunocompromised.⁵ Further study is needed to reconcile this difference.

Table 4. Clinical characteristics and outcome of children with meningitis.

No.	Age	Cefotaxime MIC ($\mu\text{g/ml}$)	Underlying disease	Prior antimicrobial agent	Antimicrobial therapy (time started)	Outcome
1	2 yr	4	Biliary atresia, liver cirrhosis	Yes	Cef* (1 st day), Van** (6 th day)	Died on 10 th day***
2	11 mo	3	Frontal meningocele, leakage of CSF	Yes	Cef (1 st day), Van (3 rd day)	Cured
3	4 yr	2	HIV, thalassemia, splenectomy	Yes	Cef (1 st day), Van (1 st day)	Cured
4	8 mo	1	Liver cirrhosis (CMV hepatitis)	Yes	Cef (1 st day), Van (1 st day)	Died on 3 rd day
5	2 mo	0.05	Congenital rubella syndrome	No	Cef (1 st day), Van (1 st day)	Died on 3 rd day
6	8 yr	0.06	Thalassemia, splenectomy	No	Cef (1 st day), Van (1 st day)	Cured

Note : * Cef = cefotaxime, ** Van = vancomycin, *** died of underlying disease

References

- Sirisanthana V, Baosoung V. Invasive penicillin-resistant *Streptococcus pneumoniae* infection in children at Chiang Mai University Hospital. *Thai J Pediatr* 1997;36:107-18.
- Aswapokee N, Tiengrim S, Charoensook B, Dhiraputra C. Resistant pneumococci in a university hospital. *J Infect Dis Antimicrob Agents* 1998;15:111-4.
- Song JH, Lee NY, Ichiyama S, et al. Spread of drug-resistant *Streptococcus pneumoniae* in Asian countries: Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study. *Clin Infect Dis* 1999;28:1206-11.
- Sunakorn P, Kusum M, Nabhuket TR, et al. Antimicrobial resistance of *S. pneumoniae* and *H. influenzae* in Thailand from National surveillance in 1993, 1994, 1997. *Thai J Tuberc Chest Dis* 1999;20:169-77.
- Committee on Infectious Diseases: American Academy of Pediatrics. Therapy for children with invasive pneumococcal infections. *Pediatrics* 1997;99:289-99.
- Tan T, Mason E, Kaplan S. Penicillin-resistant systemic pneumococcal infections in children: a retrospective case-control study. *Pediatrics* 1993;92:761-7.
- Friedland I. Comparison of the response of antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. *Pediatr Infect Dis J* 1995;14:885-90.
- Choi ES, Lee HJ. Clinical outcome of invasive infections by penicillin-resistant *Streptococcus pneumoniae* in Korean children. *Clin Infect Dis* 1998;26:1346-54.
- Silverstein M, Bachur R, Harper M. Clinical implications of penicillin and ceftriaxone resistance among children with pneumococcal bacteremia. *Pediatr Infect Dis J* 1999;18:35-41.
- National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests; approved standard-seventh edition. NCCLS document M2-A7. NCCLS, Wayne, Pennsylvania, USA, 2000.
- Macias EA, Mason EO Jr, Ocera HY, LaRocco MT. Com-

- parison of E-test with standard broth microdilution for determining antibiotic susceptibilities of penicillin-resistant strains of *Streptococcus pneumoniae*. *J Clin Microbiol* 1994;32:430-2.
12. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard-fifth edition. NCCLS document M7-A5. NCCLS, Wayne, Pennsylvania, USA, 2000.
 13. Jorgensen JH, Swenson JM, Tenover FC, Ferado MJ, Hindler JA, Murray PR. Development of interpretive criteria and control limits for broth microdilution and disk diffusion antimicrobial susceptibility testing of *Streptococcus pneumoniae*. *J Clin Microbiol* 1994;32:2448-59.
 14. Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: a population-based study. *Clin Infect Dis* 1994;19:884-90.
 15. Kronenberger CB, Hoffmann RE, Lezotte DC, Marine WM. Invasive penicillin-resistant pneumococcal infections: a prevalence and historical cohort study. *Emerging Infectious Diseases* 1996;2:121-4.
 16. Tan T, Mason E, Kaplan S. Systemic infection due to a *Streptococcus pneumoniae* relatively resistant to penicillin in a children's hospital: clinical management and outcome. *Pediatrics* 1992;90:928-33.
 17. Panchareon C, Thisyakorn C, Lertsapchareon P, Likitnukul S, Thisyakorn U. Endocarditis caused by drug-resistant *Streptococcus pneumoniae* in a child. *Scand J Infect Dis* 1999;31:597-8.