Frequency and Clinical Course of Invasive Pneumococcal Disease Caused by Penicillin-Resistant and Penicillin-Sensitive *Streptococcus pneumoniae* in Thai Children

Natawan Siripongpreeda MD*,
Weerawan Hattasingh MD**, Patcharin Amornvipas MD**,
Boonchuay Eampokalap MSc*, Supachat Sakoolgnam MD***,
Chitsanu Pancharoen MD**, Usa Thisyakorn MD**

** Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand*
***** Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand***
****** Paholponpayuhasena Hospital, Kanchanaburi, Thailand***

Objective: *This study assessed clinical differences between invasive pneumococcal disease (IPD) caused by penicillin-resistant and penicillin-sensitive Streptococcus pneumoniae.*
Material and Method: *Patients with IPD confirmed during January 1996-December 2007 at three hospitals were included. Clinical characteristics and outcomes were compared between patients infected with penicillin-resistant Streptococcus pneumoniae (PRSP) and penicillin-sensitive Streptococcus pneumoniae (PSSP).*
Results: *Sixty-nine patients with IPD were identified during the study period, 20 (29%) of whom were infected with PRSP and 49 (71%) with PSSP. Sex, mean age, underlying diseases and seasonal variation did not differ statistically between the two groups. No significant differences were identified in clinical course as measured by time until defervescence, duration of hospitalization and clinical outcome. Minimum inhibitory concentrations (MIC) for other antibiotics were determined; 20% and 10% of PRSP isolates were nonsusceptible to cephalosporins and meropenem, respectively, but all isolates were sensitive to vancomycin.*
Conclusion: *There were no significant differences identified in the clinical epidemiology of IPD cases caused by PRSP and PSSP.*

Keywords*: Invasive pneumococcal disease (IPD), Penicillin-sensitive Streptococcus pneumoniae (PSSP), Penicillin-resistant Streptococcus pneumoniae (PRSP)*

J Med Assoc Thai 2010; 93 (Suppl. 5): S1-S5
Full text. e-Journal: *http://www.mat.or.th/journal*

Invasive pneumococcal disease (IPD) is a leading cause of morbidity and mortality among young children throughout the world. High rates of *Streptococcus pneumoniae* nasopharyngeal colonization have been demonstrated among young children[1-3]. Nasopharyngeal colonization typically precedes respiratory tract diseases caused by *Streptococcus pneumoniae*, including pneumonia and acute otitis media, as well as invasive infections, most commonly bacteremia with or without focal complications. In developing countries, common underlying conditions of children with serious pneumococcal infections include HIV infection and malnutrition, while the majority of cases in developed countries occur among previously healthy infants and toddlers[4-6].

In Thailand, estimates of total IPD incidence are limited. One study estimated the incidence of hospitalized cases of pneumococcal bacteremia among children aged < 5 years to be 10.6 to 28.9 per 100,000 population. IPD has emerged as a significant public health problem due to the rapidly increasing prevalence of drug-resistant *Streptococcus*

Correspondence to:
Siripongpreeda N, Bamrasnaradura Infectious Diseases Institute, Nonthaburi 11000, Thailand.
Phone: 0-2591-7380
E-mail: natawan_sir@yahoo.com

pneumoniae (DRSP)[1,7].

The objective of this study was to assess potential clinical differences between IPD caused by penicillin-resistant and penicillin-sensitive *Streptococcus pneumoniae*.

Material and Method

This retrospective study was performed at three hospitals: 1) King Chulalongkorn Memorial hospital, a 1,500-bed university hospital in Bangkok, 2) Bamrasnaradura Infectious Diseases Institute, a 400-bed institute in Nonthaburi province and 3) Paholponpayuhasena hospital, a 440-bed provincial hospital in Kanchanaburi province.

Demographic, clinical, and treatment information on IPD cases was abstracted from medical records using a standardized case report form. Data collected included age, sex, specimen type, clinical presentation, month of disease onset, underlying diseases, outcome and laboratory results. A case of IPD was defined as illness in a patient < 18 years of age with *Streptococcus pneumoniae* isolated from a normally sterile body site during January 1997 through December 2007. Normally sterile body fluid sites included blood, cerebrospinal fluid, pleural fluid, and ascitic fluid.

The three study hospitals identified *Streptococcus pneumoniae* according to standard laboratory techniques from the Clinical and Laboratory Standards Institute (CLSI)[8]. Penicillin susceptibility was determined by disc diffusion using oxacillin discs or by minimum inhibitory concentration (MIC) using the E-test method. The E-test method was applied to determine the MIC of five antibiotics. These included penicillin, cefotaxime, ceftriaxone, meropenem, vancomycin. The MIC interpretative standards for all antibiotics in this study were defined according to the 2008 CLSI break points[8].

For isolates recovered from cerebrospinal fluid, MIC > 0.06 μg/ml defined PRSP and isolates with MIC ≤ 0.06 μg/ml were described as PSSP. For non-meningitis, isolates from non-meningeal specimens (blood, pleural fluid, ascitic fluid), nonsusceptible to penicillin was defined as MIC > 2.0 μg/ml while susceptible to penicillin was defined as MIC ≤ 2.0 μg/ml.

Statistical analysis

Chi-square test and Student's t-test were used for statistical comparisons of categorical and continuous variables, respectively.

Results

During January 1997 through December 2007, 109 cases of IPD were identified. Of these, medical records were available in 69 cases, 20 caused by PRSP and 49 caused by PSSP. The analysis were performed exclusively in these 69 cases. The highest proportion of IPD cases overall occurred in patients who were under 2 years of age (45%) followed by those over 5 years of age (40%) and 2-5 years of age (15%). The ratio of males to females, mean age and proportion with underlying diseases did not differ between IPD patients with PSSP and PRSP (Table 1). There appeared to be an increasing trend in the proportion of isolates that were PRSP from 2002-2007 as shown in Fig. 1. A higher number of IPD cases overall was seen in January and July in both groups as shown in Fig. 2.

The rank order for clinical diagnoses was the similar for PSSP and PRSP cases with bacteremia being the most common (Table 2). There were no statistically significant differences in the frequency of clinical diagnoses between PSSP and PRSP cases.

Table 1. Epidemiological characteristics of IPD cases caused by penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* (PSSP and PRSP)

	PSSP n = 49 (%)	PRSP n = 20 (%)
Male/female	34/15	8/12
Age		
Mean (years)	4.6 ± 4.2	4.6 ± 4.3
≤ 2 years	22 (45%)	9 (45%)
2-5 years	7 (15%)	4 (20%)
> 5 years	20 (40%)	7 (35%)
Underlying diseases		
HIV	5 (10%)	6 (30%)
Hepatobiliary diseases	2 (4%)	1 (5%)
Nephrotic syndrome	1 (2%)	1 (5%)
Heart diseases	5 (10%)	0 (0%)
Chronic lung discase	1 (2%)	0 (0%)
Hematological malignancy	4 (8%)	0 (0%)
Meningomyelocele	0 (0%)	1 (5%)
Brain tumor	2 (4%)	1 (5%)
Others*	6 (12%)	1 (5%)
None	20 (40%)	6 (30%)
Unknown	3 (6%)**	3 (15%)**

*Others included head injury, post cerebral shunt, post tonsillectomy, asthma, burn, DiGeorge syndrome and hyper IgE.

**No data available from patients' records.

Most (62%) patients had white blood cell counts above 10,000 cells/mm^3. The mean (± standard deviation) white blood cell counts among PSSP- and PRSP-infected patients were 18,336 (± 13,644 cells/mm^3) and 18,281 (± 9,363 cells/mm^3) (p = 0.989).

More detailed clinical data were available for 34 patients infected with PSSP and 15 patients infected with PRSP (Table 3). The main antimicrobial agents used to treat both PSSP and PRSP cases were 3rd generation cephalosporins, penicillin, vancomycin and carbapenems. 3rd generation cephalosporins were the most common antimicrobial agents used to treat patients in both groups. Twenty percent of PRSP isolates were also nonsusceptible to 3rd generation cephalosporins (10% intermediate susceptibility and 10% resistant), and 10% were nonsusceptible to meropenems (all with intermediate susceptibility). All isolates were sensitive to vancomycin. PSSP- and PRSP- infected patients did not differ significantly in days to defervescence, days of hospitalization and frequency of death. Three of four deaths occurred in patients with underlying diseases (two patients with HIV infection and one with nephrotic syndrome). All fatal cases had been treated with cefotaxime and/or vancomycin. Three patients died related to complications of sepsis, one of whom died 1 hour after admission, and two others that died 3 and 6 days after admission. The fourth fatal case occurred in a patient who developed acute respiratory distress syndrome and died 16 days after admission.

Table 2. Comparison of clinical features between patients with invasive pneumococal disease caused by penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* (PSSP and PRSP).

	PSSP n = 49 (%)	PRSP n = 20 (%)	p-value
Bacteremia	29 (59%)	8 (40%)	0.061
Meningitis	8 (16%)	7 (35%)	0.088
Pneumonia	10 (20%)	5 (25%)	0.751
Peritonitis	1 (2%)	0 (0%)	
Unknown	1 (2%)**	-	

******No data from a patient's record.

Discussion

One quarter of IPD patients in this study were infected with PRSP, which was an increasing problem during 1997-2007 in Thailand and worldwide[1,9]. Higher numbers of IPD cases were seen in January and July. This could be from that January is a cooler month and July is a usually a rainy month of the year. during rainy and cooler months as reported by others[9]. Children aged less than 2 years represented the most common age group identified with IPD in our study, which was similar to findings from studies in western countries[11-13]. Although immunocompromised patients and patients with other underlying diseases (*e.g.*, heart, lung, or renal diseases, cirrhosis, diabetes) are known to be at increased risk for pneumococcal disease, we found no evidence that they are at higher risk of being infected with PRSP[11,14,15]. Clinical syndromes associated with IPD in our study were similar for PSSP- and PRSP-infected patients and included bacteremia, meningitis, and pneumonia. These findings were similar to those seen by others[12,14].

Table 3. Treatment and clinical outcomes of patients with invasive pneumococcal disease caused by penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* (PSSP and PRSP).

	PSSP n = 34 (%)	PRSP n = 15 (%)	p-value
Treatment			0.062
Penicillins	14 (41%)	2 (13%)	
3rd generation Cephalosporins	15 (44%)	11 (73%)	
Carbapenems	3 (9%)	0 (%)	
Vancomycin	2 (6%)	2 (13%)	
Clinical outcome			
Days to defervescence (mean ± SD)	4.55 ± 8.09	3.06 ± 5.39	0.526
Days of hospitalization (mean ± SD)	24.00 ± 26.83	14.87 ± 9.16	0.106
Death	2 (6%)	2 (13%)	0.442
Recovered	32 (94%)	13 (87%)	

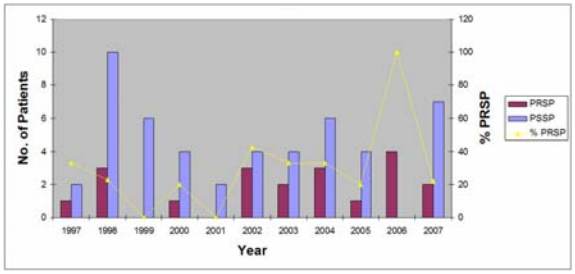

Fig. 1 Yearly distribution of invasive pneumococcal disease cases caused by penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* (PSSP and PRSP)

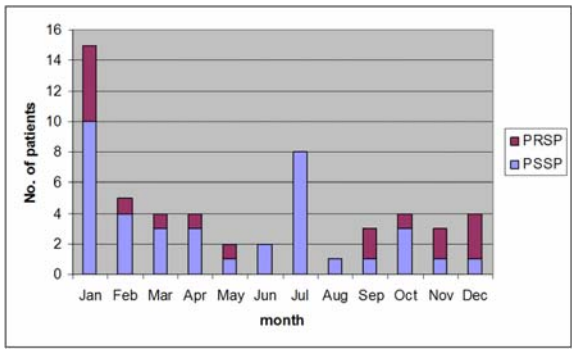

Fig. 2 Monthly distribution of invasive pneumococcal disease cases caused by penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* (PSSP and PRSP)

We found the most common empirical antimicrobial therapy in both groups was 3rd generation cephalosporins. This may reflect increased concerns for and awareness of increases in DRSP in Thailand and may have contributed to the similar clinical outcomes among PSSP- and PRSP-infected patients. The high prevalence of DRSP in Thailand is alarming and underscores the importance of appropriate use of antimicrobial agents[1,16].

In conclusion, we found no differences in clinical manifestations or outcomes between patients infected with PRSP compared to those infected with PSSP. The empiric antibiotic treatment strategies employed similarly in both groups may have been an important factor in the comparable outcomes and should remain in place.

References

1. Siripongpreeda N, Hattasingh, W, Thisyakorn U. Community acquired *Streptococcus pneumonia* infection in Thailand. Asian Biomed 2009; 3: 117-20.
2. Levine S, Dejsirilert S, Sangsuk L, Chantra S, Feikin DR, Dowell SF, et al. Serotypes and antimicrobial resistance of *streptococcus pneumoniae* in Thailand 2002-2004. Pediatr Infect Dis J 2006; 25: 176-8.
3. Madhi SA, Pelton SI. Epidemiology, diagnosis, and treatment of serious pneumococcal infections in children. In: Siber GR, Klugman KP, Makela PH, editors. Pneumococcal vaccines: the impact of conjugate vaccine. Washington, DC: ASM Press; 2008: 95-116.
4. Greenwood B. The epidemiology of pneumococcal infection in children in the developing world. Philos Trans R Soc Lond B Biol Sci 1999; 354: 777-85.
5. Madhi SA, Petersen K, Madhi A, Wasas A, Klugman KP. Impact of human immunodeficiency virus type 1 on the disease spectrum of *Streptococcus pneumoniae* in South African children. Pediatr Infect Dis J 2000; 19: 1141-7.
6. Molyneux E, Riordan FA, Walsh A. Acute bacterial meningitis in children presenting to the Royal Liverpool Children's Hospital, Liverpool, UK and the Queen Elizabeth Central Hospital in Blantyre, Malawi: a world of difference. Ann Trop Paediatr 2006; 26: 29-37.
7. Baggett HC, Peruski LF, Olson SJ, Thamthitiwat S, Rhodes J, Dejsirilert S, et al. Incidence of pneumococcal bacteremia requiring hospitalization in rural Thailand. Presented at the 6th International Symposium on Pneumococci and Pneumococcal Diseases; June 8-12, 2008; Reykjavik, Iceland.
8. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 18th Information supplement. CLSI Publication No. M100-S18. Wayne, PA: CLSI; 2008.
9. Song JH, Lee NY, Ichiyama S, Yoshida R, Hirakata Y, Fu W, 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.
10. Ho PL, Chiu SS, Cheung CH, Lee R, Tsai TF, Lau YL. Invasive pneumococcal disease burden in Hong Kong children. Pediatr Infect Dis J 2006; 25: 454-5.
11. Scheifele D, Halperin S, Pelletier L, Talbot J. Invasive pneumococcal infections in Canadian children, 1991-1998: implications for new vaccination strategies. Canadian Paediatric Society/Laboratory

Centre for Disease Control Immunization Monitoring Program, Active (IMPACT). Clin Infect Dis 2000; 31: 58-64.
12. Kaplan SL, Mason EO Jr, Wald E, Tan TQ, Schutze GE, Bradley JS, et al. Six year multicenter surveillance of invasive pneumococcal infections in children. Pediatr Infect Dis J 2002; 21: 141-7.
13. Dagan R, Engelhard D, Piccard E, Englehard D. Epidemiology of invasive childhood pneumococcal infections in Israel. The Israeli Pediatric Bacteremia and Meningitis Group. JAMA 1992; 268: 3328-32.
14. Choi EH, Lee HJ. Clinical outcome of invasive infections by penicillin-resistant *Streptococcus pneumoniae* in Korean children. Clin Infect Dis 1998; 26: 1346-54.
15. Watanabe H, Sato S, Kawakami K, Watanabe K, Oishi K, Rikitomi N, et al. A comparative clinical study of pneumonia by penicillin-resistant and -sensitive *Streptococcus pneumoniae* in a community hospital. Respirology 2000; 5: 59-64.
16. Phongsamart W, Srifeungfung S, Dejsirilert S, Chatsuwan T, Nunthapisud P, Treerauthaweeraphong V, et al. Serotype distribution and antimicrobial susceptibility of *S. pneumoniae* causing invasive disease in Thai children younger than 5 years old, 2000-2005. Vaccine 2007; 25: 1275-80.

การศึกษาความแตกต่างของปัจจัยทางคลินิกของโรค invasive pneumococcal ระหว่างเชื้อ Streptococcus pneumoniae ที่ดื้อและตอบสนองต่อยา penicillin ในประเทศไทย

ณฐวรรณ ศิริพงศ์ปรีดา, วีรวรรณ หัตถสิงห์, พัชรินทร์ อมรวิภาส, บุญช่วย เอี่ยมโภคลาภ, ศุภฉัตร สกุลงาม, ชิษณุ พันธุ์เจริญ, อุษา ทิสยากร

วัตถุประสงค์: *เพื่อเปรียบเทียบความแตกต่างทางคลินิกของโรค invasive pneumococcal disease (IPD) ที่เกิดจากการติดเชื้อ Streptococcus pneumoniae ที่ดื้อยา penicillin และกลุ่มที่ไวต่อยา penicillin ในผู้ป่วยเด็ก*

วัสดุและวิธีการ: *เก็บข้อมูลจากเวชระเบียนผู้ป่วยเด็กอายุน้อยกว่า 18 ปีที่เป็นโรค invasive pneumococcal disease และมารับการรักษาที่โรงพยาบาล 3 แห่ง คือ 1) โรงพยาบาลจุฬาลงกรณ์ กรุงเทพมหานคร 2) สถาบันบำราศนราดูร จังหวัดนนทบุรี 3) โรงพยาบาลพหลพลพยุหเสนา จังหวัดกาญจนบุรี ในระหว่างเดือน มกราคม พ.ศ. 2539-ธันวาคม พ.ศ. 2550 และนำมาศึกษาเปรียบเทียบอาการทางคลินิก ผลการตรวจทางห้องปฏิบัติการ และผลการรักษาระหว่างกลุ่มที่ติดเชื้อ Streptococcus pneumoniae ที่ดื้อยา penicillin และกลุ่มที่ไวต่อยา penicillin*

ผลการศึกษา: *จำนวนผู้ป่วยที่เป็นโรค IPD ที่นำมาศึกษาทั้งสิ้นมี 69 คน โดย 20 คน (28.98%) เป็นกลุ่มที่ติดเชื้อ Streptococcus pneumoniae ที่ดื้อยา penicillin 49 คน (71.02%) ไวต่อยา penicillin พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางคลินิกในเรื่อง เพศ อายุเฉลี่ย โรคประจำตัว ฤดูกาลที่เกิดโรคใน 2 กลุ่มการศึกษา อีกทั้งประสิทธิภาพในการรักษาทางคลินิก ซึ่งประเมินจากจำนวนวันที่ไข้ลงหลังรักษา ระยะเวลาที่รับไว้ใน โรงพยาบาล และผลการรักษาก็ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่าง 2 กลุ่ม ได้ทำ MIC ของยาปฏิชีวนะต่อเชื้อ Streptococcus pneumoniae พบว่าในกลุ่มที่ดื้อต่อยา penicillin จะดื้อต่อยา cephalosporin ร้อยละ 20 ดื้อต่อยา meropenem ร้อยละ 10 และไม่พบการดื้อต่อ vancomycin*

สรุป: *ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในเรื่องลักษณะทางคลินิกของโรค IPD ที่เกิดจากการติดเชื้อ Streptococcus pneumoniae ที่ดื้อและไวต่อยา penicillin*