Invasive Pneumococcal Disease in Phramongkutklao Hospital 2004-2008: Clinical Data, Serotype Distribution and Antimicrobial Resistance Patterns

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Objective: *To describe the clinical course, serotype distribution and antimicrobial resistance patterns of invasive pneumococcal disease (IPD) cases in a public hospital.*
Material and Method: *Retrospective review of IPD cases occurring from January 2004 through December 2008 was performed. Antibiotic susceptibility testing and serotyping were performed for available isolates.*
Results: *Fifty one IPD cases occurred during the study period, of which 47 had medical records available for review. The majority of cases occurred among children under 5 years of age (23.4%) and adults over 60 years of age (36.1%). Underlying diseases were identified in 72.3% of patients. Fifty-three percent of cases were associated with pneumonia, while 17% had meningitis, and 15% had isolated bacteremia. Serotype could be determined for 15 (31.9%) isolates, and 6B was most common. Based on current antibiotic susceptibility breakpoints for meningitis, 4 of the 7 available isolates from meningitis cases were penicillin resistant and one had reduced susceptibility to cefotaxime. Among non-meningitis isolates, 96.7% were penicillin susceptible and 3.3% had intermediate susceptibility to penicillin. Overall case fatality proportion was 19%.*
Conclusion: *At this tertiary care hospital in Bangkok, IPD has disproportionately affected young children and the elderly. High rates of penicillin resistance among meningitis cases, the most severe form of IPD, underscore the need of appropriate treatment strategies and vaccine usage.*

Keywords: *Invasive pneumococcal disease, antibiotic susceptibility, serotype*

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Streptococcus pneumoniae is an important bacterial pathogen in children and adults. It colonizes the nasopharynx, particularly in young children, with the prevalence of colonization gradually declining with age. Nasopharyngeal colonization with *S. pneumoniae* typically precedes disease states such as sinusitis, otitis media, pneumonia, and invasive pneumococcal disease (IPD), including bacteremia and meningitis[1]. Globally, the incidence of IPD is high in children under two years old and in adults over 65 years old with underlying disease[2,3].

The incidence of IPD in Thailand has been estimated to be around 10.6-28.9/100,000 persons/year[4]. Because of the high disease burden, high mortality rate and adverse consequences of increasing drug resistant *Streptococcus pneumoniae* (DRSP)[5], IPD has become an important public health problem in Thailand. Understanding local antibiotic susceptibility patterns of pneumococcus is important for guiding empirical treatment. Additionally, knowledge of pneumococcal serotype distributions is necessary to estimate potential impact of vaccination. The objective of this study was to describe the clinical course, antimicrobial susceptibilities, and serotype distribution

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of IPD cases in a tertiary public care center.

Material and Method

A retrospective study was conducted at the Phramongkutklao hospital, a tertiary care center of 1,200 bed facilities including 200 beds for pediatrics patients. Most of patients were in middle to low socioeconomic levels. Medical record reviews were conducted for patients with IPD confirmed from January 2004 through December 2008. Pediatrics patient defined as age less than 18 year old. All IPD cases were confirmed by at least one positive culture of *Streptococcus pneumoniae* from a normally sterile site, such as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid or joint fluid. *Streptococcus pneumoniae* identification and antibiotic susceptibility testing were performed using standard methods, according to guidelines of the Clinical and Laboratory Standards Institute (CLSI)[6]. Briefly, penicillin susceptibility was determined by disc diffusion using an oxacillin disc. The MIC for penicillin and cefotaxime was determined by E-test. The MIC interpretative standards were defined according to the 2008 CLSI breakpoints, which depend on the site of infection (meningitis or non-meningitis) and the route of antibiotic therapy. All isolates were serotyped at the national reference laboratory, National Institute of Health, Department of Medical Science, Nonthaburi. Serotyping was based on capsular swelling (*i.e.*, Quellung reaction) observed microscopically after treating isolates with antisera prepared by Statens Serum Institute(Copenhagen, Denmark). Clinical, demographic and laboratory data were analyzed using Microsoft Excel or SPSS.

Results

Fifty one IPD cases occurred between January 2004 and December 2008. Four cases were excluded because medical records were not available for review. All of the patients had pneumococcal isolates available from blood cultures. Three patients also had positive cerebrospinal fluid cultures and one had a positive pleural fluid culture. The cases were distributed throughout the year without clear evidence of seasonal pattern.

Patients under five years of age and those over 60 years of age accounted for 59.5% of the cases. Thirty-four (72.3%) cases had one or more underlying disease. In children age less than 18 years the underlying diseases were nephrotic syndrome (3.6%), congenital malformation (3.6%), systemic lupus erythematosus (3.6%), Down syndrome (1.8%), hematologic malignancy (1.8%), and autoimmune hemolytic anemia (1.8). Among adults the underlying diseases were diabetes mellitus (14.6%), hypertension (9.1%), chronic liver disease (9.1%), malignancy (7.3%), chronic kidney disease (7.3%), coronary artery disease (7.3%), hematologic malignancy (5.5%), HIV infection (5.5%), obstructive lung disease (5.5%), cerebrovascular disease (3.6%), dyslipidemia (3.6), systemic lupus erythematosus (1.8%), asplenia (1.8%), primary immune deficiency (1.8) and valvular heart disease (1.8%). Isolated pneumococcal bacteremia was found in 7 (15%) cases; 4 cases were children age less than 18 years, and 3 cases were adults over 65 years old. The most common diagnosis among IPD case-patients was pneumonia (53.1%) (Table 1).

Table 1. Characteristics of 47 cases of invasive pneumococcal disease-Phramongkutklao Hospital, 2004-2008

	n (%)
Years of the episode	
2004-2006	22 (46.8)
2007-2008	25 (53.2)
Sex	
male	33 (70.2)
female	14 (29.8)
Age group	
< 2 years	4 (8.5)
2-5 years	7 (14.9)
6-18 years	3 (6.4)
19-40 years	9 (19.2)
41-60 years	7 (14.9)
> 60 years	17 (36.1)
Underlying disease	
absence	13 (27.7)
presence	34 (72.3)
Final diagnosis	
Pneumonia with bacteremia	25 (53.1)
Meningitis with bacteremia	8 (17)
Isolated bacteremia	7 (15)
Diarrhea with bacteremia	2 (4.3)
Cellulitis with bacteremia	2 (4.3)
Septic arthritis with bacteremia	1 (2.1)
Acute bronchitis with bacteremia	1 (2.1)
Acute otitis media with bacteremia	1 (2.1)

Serotyping

Serotyping was attempted on all isolates from blood cultures; 15 (31.9%) were typeable and 32 (68.1%) were non-typeable. The most common serotype found

Table 2. Serotypes of invasive pneumococcal isolates by age groups

	Number of isolates of each serotype (%)								
Age	4	5	6B	9V	14	15	19F	23A	Non-typeable
0-18 years	-	-	3(6.4)	-	2(4.3)	1(2.1)	1(2.1)	1(2.1)	6(12.8)
> 18 years	1(2.1)	1(2.1)	2(4.2)	1(2.1)	1(2.1)	-	1(2.1)	-	26(55.3)
Total	1(2.1)	1(2.1)	5(10.6)	1(2.1)	3(6.4)	1(2.1)	2(4.2)	1(2.1)	32(68.1)

Table 3. Penicillin and cefotaxime susceptibilities for 30 isolates from patients without meningitis.

Antibiotic	Susceptible	Intermediate susceptibility	Resistant
Penicillin			
- Oral penicillin	14 (46.7%)	14 (46.7%)	2 (6.6%)
- Parenteral penicillin	29 (96.7%)	1 (3.3%)	-
Cefotaxime	29 (96.7%)	1 (3.3%)	-

*CLSI 2008 criteria in non-meningitis pneumococcal isolates. Oral penicillin: susceptible, intermediate susceptibility and resistant defined as MIC $\leq$ 0.06, 0.12-1, $\geq$ 2 mcg/ml. For parenteral penicillin: susceptible, intermediate susceptible and resistant defined as MIC $\leq$ 2, 4, $\geq$ 8 mcg/ml. For cefotaxime: susceptible, intermediate susceptible and resistant defined as MIC $\leq$ 1, 2, $\geq$ 4 mcg/ml

in both children and adults was serotype 6B (10.8%), followed by serotype 14 (6.4%) and serotype 19F (4.2%) (Table 2).

Twelve (80%) of the 15 serotyped isolates were serotypes included in heptavalent pneumococcal conjugate vaccine (PCV7), and 13 (87.7%) were serotypes included in 23-valent polysaccharide pneumococcal vaccine (PPV23). Three isolates (20%) belonged to serotypes not included in either vaccine.

Antibiotic susceptibility

All of 47 IPD isolates were screened with oxacillin disc diffusion, 19 of them were penicillin susceptibility defined by inhibition zone equal or greater than 20 millimeters. MIC measurements were available for 36 0f 47 IPD isolates; 11 isolates could not be grown for MIC measurement. Of these, 7 (20%) isolates from meningitis patients were available for antibiotic susceptibility. Using the new criteria, 4 (57%) were penicillin susceptible *Streptococcus pneumoniae* (PSSP) and 3 (43%) were penicillin resistant *Streptococcus pneumoniae* (PRSP). One PRSP isolate had intermediate (*i.e.*, reduced) susceptibility to cefotaxime. Penicillin nonsusceptibility was higher among isolates from children age 0-18 years than those from adults. All PSSP isolate were susceptible to cefotaxime. Four out of six patients had no underlying diseases.

Penicillin and cefotaxime susceptibilities for the 30 non-meningitis isolates are shown in Table 3.

Treatment and clinical outcome

Nine of 47 IPD patients died (case fatality proportion = 19%); 3 of 14 (20%) paediatric cases and 6 of 33 (18.2%) in adult cases. Of the deaths, 2 (66.7%) children and 1 (17%) adult did not have underlying disease.

Of the three pneumococcal meningitis patients infected with PSSP, two were treated with a third generation cephalosporin and one with penicillin; all recovered without sequelae. All three meningitis patients infected with PRSP died. Two of these patients were children under 5 years old who presented with meningitis and were treated with third generation cephalosporin plus vancomycin; the isolate from one child had intermediate susceptibility to cefotaxime. Another death occurred in a 78 year old patient who was treated with a third generation cephalosporin.

Among 30 non-meningitis patients with antibiotic susceptibility data available, 4 (13.3%) died,

all of whom were infected with PSSP. Of the four fatal cases, 3 were treated with parenteral third generation cephalosporins and the fourth was treated with carbapenem. All four of these fatal cases occurred in patients over 60 years old, and all had underlying diseases. Of the remaining 26 non-meningitis patients who recovered, 21 (80.7%) were treated with third generation cephalosporin. One patient in this group was infected with *S. pneumoniae* that had only intermediate susceptibility to cefotaxime.

Discussion

Our study found IPD cases spread out year round. In contrast to previous study in Thailand that mentioned higher prevalence in cooler months (November to April)[12]. Several respiratory viruses commonly circulate in this period of the year in temperate climates[6-8]; therefore IPD may be a co-incident event or secondary bacterial infection on top of a primary viral illness. However, like many studies[4,5], surveillance data in our hospital showed that less than 5% of patients with pneumonia had bacteremia[13]. Certain factors influenced risks of IPD including age younger than 5 years and over 60 years, which were the major population groups in the study.

S. pneumoniae can cause invasive disease with high morbidity and mortality in all age groups. The case fatality proportion in previous studies ranged from 2 to 20 % and was as high as 26.1-28.8% in those with underlying diseases[9-12]. When compared with our study, overall fatality was similar except in the patient who had underlying disease that this study had higher fatality proportion than other reports. We found that most fatal cases occurred in patients with underlying medical conditions, many of which are diseases that can affect neutrophil function including opsonisation, chemotaxis and intracellular killing[17,18]. For instance, we found diabetes mellitus or cirrhosis was common (34%) among the fatal cases. However, young age could be a factor influencing mortality even when appropriate and adequate dosages of antimicrobial agents are administered. Vaccinating children with pneumococcal conjugate vaccines, as recommended by the World Health Organization[21], is the best way to prevent diseases caused by *S. pneumoniae*. In our study, none of the participants recieved the vaccine.

Among the isolates that were able to be serotyped, the proportion with serotypes included in PCV7 was similar to that reported previously in Thailand[14,15]. Of the 15 serotyped isolates, three were serotypes not included in PCV7 (serotypes 5, 15 and 23A). Only one of these serotypes are included in the newer 13-valent pneumococcal vaccine (PCV13).

Three of the six isolates tested from meningitis patients had reduced sensitivity to penicillin. The prevalence of oral penicillin nonsusceptibility, including PRSP, among isolates in this study was similar to that of isolates from National Antimicrobial Resistance Surveillance Center Thailand (NARST), which received data from 28-31 provincial hospitals and reported relatively stable prevalence (48-52%) during 2000-2007[20]. Unfortunately, 2 of 36 isolates were also nonsusceptible to cefotaxime. This is an alarming finding, because all invasive pneumococcal isolates in previous reports from Thailand were sensitive to cefotaxime[14,15].

Our study had some limitations; it was not population based and therefore unable to calculate the incidence. It was a retrospective study without controls, therefore unable to assess risk factors for disease. Many (68.1%) of the isolates could not be serotyped, limiting the strength of our conclusions about serotype distribution. Some (24%) of isolates were not performed MIC measurement due to inappropriate subculture technique.

In conclusion, we describe the serotypes, antimicrobial susceptibilities, and outcomes of IPD cases occurring at a large tertiary care hospital in Bangkok during 2004-2008. Based clinical diagnosis, pneumonia was the most common disease associated with IPD. The prevalence of penicillin nonsusceptibility was similar to that described in previous reports, but cefotaxime nonsusceptibility was a new finding. Based on a limited number of serotyped isolates, PCV7 and PPV23 cover a high proportion of invasive serotypes. Ongoing surveillance is important to monitor IPD trends, including changes in serotype distribution and antimicrobial susceptibilities. These data are important to guide clinical management and policy decisions about vaccine implementation.

References

1. Konradsen HB, Kaltoft MS. Invasive pneumococcal infections in Denmark from 1995 to 1999: epidemiology, serotypes, and resistance. Clin Diagn Lab Immunol 2002; 9: 358-65.
2. Fedson DS, Scott JA. The burden of pneumococcal disease among adults in developed and developing countries: what is and is not known. Vaccine 1999; 17(Suppl 1): S11-8.
3. Klein JO. The epidemiology of pneumococcal dis-

ease in infants and children. Rev Infect Dis 1981; 3: 246-53.
4. Baggett HC, Peruski LF, Olsen SJ, Thamthitiwat S, Rhodes J, Dejsirilert S, et al. Incidence of pneumococcal bacteremia requiring hospitalization in rural Thailand. Clin Infect Dis 2009; 48(Suppl 2): S65-74.
5. Siripongpreeda N, Hattasingh W, Thisyakorn U. Community acquired *Streptococcus pneumoniae* infection in Thailand. Asian Biomed 2009; 3: 117-20.
6. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; eighteenth edition information supplement. CLSI document M100-S18. Wayne, PA: CLSI; 2008.
7. Ampofo K, Bender J, Sheng X, Korgenski K, Daly J, Pavia AT, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008; 122: 229-37.
8. Madhi SA, Klugman KP. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med 2004; 10: 811-3.
9. Olson LC, Lexomboon U, Sithisarn P, Noyes HE. The etiology of respiratory tract infections in a tropical country. Am J Epidemiol 1973; 97: 34-43.
10. Leelarasamee A, Dhiraputra C, Hunnangkul S. Severe pneumococcal infection at a Thai hospital. Int J Infect Dis 1999; 3: 147-52.
11. Pancharoen C, Chongthaleong A, Reinprayoon S, Thisyakorn U. Invasive pneumococcal infection and drug-resistant *Streptococcus pneumoniae* in Thai children. J Med Assoc Thai 2001; 84: 1246-50.
12. Sirinavin S, Vorachit M, Thakkinstian A, Hongsanguensri S, Wittayawongsruji P. Pediatric invasive pneumococcal disease in a teaching hospital in Bangkok. Int J Infect Dis 2003; 7: 183-9.
13. Sangthawan P, Chantaratchada S, Chanthadisai N, Wattanathum A. Prevalence and clinical significance of community-acquired penicillin-resistant pneumococcal pneumonia in Thailand. Respirology 2003; 8: 208-12.
14. Chen YY, Yao SM, Chou CY, Chang YC, Shen PW, Huang CT, et al. Surveillance of invasive *Streptococcus pneumoniae* in Taiwan, 2002-2003. J Med Microbiol 2006; 55(Pt 8): 1109-14.
15. 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.
16. Chokephaibulkit K, Srifuengfung S, Mingbanjerdsuk J, Tosasuk K, Vanprapar N, Chearskul S, et al. Evaluation of susceptibility status of invasive pneumococcal isolates to various antibiotics and risk factors associated with invasive penicillin-nonsusceptible pneumococcal infection: Bangkok 1997-1998. Southeast Asian J Trop Med Public Health 2000; 31: 498-505.
17. Bigham M, Patrick DM, Bryce E, Champagne S, Shaw C, Wu W, et al. Epidemiology, antibiotic susceptibility, and serotype distribution of *Streptococcus pneumoniae* associated with invasive pneumococcal disease in British Columbia - A call to strengthen public health pneumococcal immunization programs. Can J Infect Dis 2003; 14: 261-6.
18. Jareo PW, Preheim LC, Lister PD, Gentry MJ. The effect of ethanol ingestion on killing of *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Staphylococcus epidermidis* by rat neutrophils. Alcohol Alcohol 1995; 30: 311-8.
19. Watt JP, O'Brien KL, Benin AL, McCoy SI, Donaldson CM, Reid R, et al. Risk factors for invasive pneumococcal disease among Navajo adults. Am J Epidemiol 2007; 166: 1080-7.
20. Konno M, Baba S, Mikawa H, Hara K, Matsumoto F, Kaga K, et al. Study of nasopharyngeal bacterial flora. Variations in nasopharyngeal bacterial flora in schoolchildren and adults when administered antimicrobial agents. J Infect Chemother 2007; 13: 235-54.
21. National Antimicrobial Resistance surveillance Center, Thailand (NARST). 2000-2007 prevalence of penicillin-resistant Streptococcus pneumoniae [database on the Internet]. 2008 [cited 2009 Nov 12]. Available from: http://www.narst.dmsc.go.th.

อาการทางคลินิกชนิดซีโรทัยป์และการดื้อยาปฏิชีวนะของผู้ป่วยโรคติดเชื้อนิวโมคอคคัสชนิดรุนแรงในโรงพยาบาลพระมงกุฎเกล้าระหว่างปี พ.ศ. 2547 ถึง พ.ศ. 2551

เดชวิจิตร์ สุวรรณภักดี, ฤดีวิไล สามโกเศศ, สยมพร ศิรินาวิน, อังกูร เกิดพานิช, ศรีลักขณ์ สิมะเสถียร, สุดาลักษณ์ ธัญญาหาร, สุรางค์ เดชศิริเลิศ , วีระชัย วัฒนวีรเดช

วัตถุประสงค์: *เพื่อศึกษาอาการทางคลินิกชนิดซีโรทัยป์ และรูปแบบการดื้อยาปฏิชีวนะของผู้ป่วยโรคติดเชื้อนิวโมคอคคัสชนิดรุนแรง*

วัสดุและวิธีการ: *ศึกษาเชิงพรรณนาจากการทบทวนข้อมูลเวชระเบียนย้อนหลังในผู้ป่วยโรคติดเชื้อนิวโมคอคคัสชนิดรุนแรงของโรงพยาบาลพระมงกุฎเกล้าระหว่างเดือนมกราคม พ.ศ. 2547 ถึง เดือนธันวาคม พ.ศ. 2551 โดยเชื้อจะได้รับการทดสอบความไวต่อยาปฏิชีวนะและตรวจแยกชนิดของซีโรทัยป์*

ผลการศึกษา: *จากผู้ป่วย 50 ราย พบข้อมูลในเวชระเบียน 47 ราย ผู้ป่วยส่วนใหญ่อายุน้อยกว่า 5 ปี และมากกว่า 60 ปี คิดเป็นร้อยละ 23.4 และ 36.1 ตามลำดับ พบร้อยละ 72.3 ของผู้ป่วยมีโรคประจำตัวลักษณะอาการทางคลินิกที่สำคัญ ได้แก่ปอดอักเสบ ร้อยละ 53 เยื่อหุ้มสมองอักเสบ ร้อยละ 17 และ ร้อยละ 15 พบเฉพาะการติดเชื้อในกระแสเลือดเท่านั้นจากตัวอย่างเชื้อทั้งหมดสามารถแยกชนิดได้จำนวน 16 ตัวอย่าง โดยซีโรทัยป์ 6B พบมากที่สุดในผู้ป่วยเยื่อหุ้มสมองอักเสบ พบการดื้อต่อยาเพนนิซิลิน ร้อยละ 50 ส่วนในผู้ป่วยที่ไม่ใช่เยื่อหุ้มสมองอักเสบ พบว่าร้อยละ 96.7 และ 3.3 ไว และกึ่งดื้อต่อยาเพนนิซิลินตามลำดับ โดยอัตราการตายเฉลี่ยคิดเป็น ร้อยละ 19*

สรุป: *กึ่งหนึ่งของผู้ป่วยโรคติดเชื้อนิวโมคอคคัสชนิดรุนแรงดื้อต่อยาเพนนิซิลิน และพบการเพิ่มขึ้นของการดื้อต่อยา cefotaxime*