Invasive Pneumococcal Infection in Urban Thai Children: A 10-Year Review†

Supichaya Netsawang MD*, Warunee Punpanich MD, PhD*,
Vipa Treeratweeraphong BSc, MSc**, Tawee Chotpitayasunondh MD*

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**Department of Pediatrics, Queen Sirikit National Institute of Child Health College of Medicine, Rangsit University, Bangkok, Thailand*
***Department of Pathology, Queen Sirikit National Institute of Child Health College of Medicine, Rangsit University, Bangkok, Thailand*

Objective: *To determine the disease frequency, demographic characteristics, clinical manifestations, laboratory findings and drug susceptibility patterns of childhood invasive pneumococcal infections in a hospital setting in Thailand.*
Material and Method: *A retrospective review was conducted of invasive pneumococcal infections among children aged <18 years from January 1, 1998 - December 31, 2007 at the Queen Sirikit National Institute of Child Health (QSNICH). Medical records of case-patients were reviewed to collect information on demographics, clinical manifestations, laboratory findings, and drug susceptibility patterns of infecting isolates.*
Results : *Among the 745,983 children receiving care at QSNICH during the study period, culture-proven invasive pneumococcal infections were identified in 126 patients for an estimated incidence of 17 cases per 100,000 patients. Patient diagnoses included bacteremia (59.4%), meningitis (29.3%), and pneumonia (11.3%). Of the 31 pneumococcal meningitis cases, 54.8% were caused by penicillin-nonsusceptible S. pneumoniae (PNSSP), while 25.3% of 75 non-meningitis cases were PNSSP (records not available for the remaining 20 cases). Of 126 PNSSP, 8.2% were resistant to cefotaxime and 12.3% were resistant to ceftriaxone. All of the isolates were susceptible to vancomycin. The case fatality rate was 12.3%; 23.1% of fatal cases were associated with HIV infection. Outcomes did not differ significantly between patients infected with penicillin-susceptible and non-susceptible pneumococcal strains.*
Conclusion: *The results of this hospital-based study indicate that the incidence of invasive pneumococcal infection in QSNICH remains relatively low, but the case fatality rate is high, especially among those with HIV infection.*

Keywords: *Invasive pneumococcal infection, Children*

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Streptococcus pneumoniae is a significant cause of morbidity and mortality among children and adults[1] and is the leading cause of meningitis, pneumonia, bacteremia, otitis media, sinusitis, and suppurative infection of other sterile body sites. The high prevalence of penicillin-resistant *Streptococcus pneumoniae* in Asia, as recently reported from the Asian Network for Surveillance of Resistant Pathogens Study, is alarming[2,3]. Decreased susceptibility of *S. pneumoniae* to multiple antimicrobial agents is increasing rapidly worldwide[4-8]. However, there are limited data regarding the disease burden, fatality rate, and long-term outcome in Thai children.

This study aimed to describe the disease frequency, demographic distribution, clinical manifestations, laboratory findings, and drug susceptibility patterns of childhood invasive pneumococcal infections in a large children's hospital in Thailand over a 10 year period.

Correspondence to:
Netsawang S, Division of Infectious Disease, Department of Pediatric, Queen Sirikit National Institute of Child Health, 420/8 Rajavithi Rd, Rajathevi, Bangkok 10400, Thailand.
Phone: 0-2354-8333 ext. 2414, Fax: 0-2354-9344
E-mail: ni_ngs@hotmail.com, nsupichaya@gmail.com

Material and Method

Patients

A hospital-based retrospective study was conducted of childhood invasive pneumococcal

infections diagnosed from January 1, 1998 to December 31, 2007 at the Queen Sirikit National Institute of Child Health, a large public children hospital in Bangkok, Thailand, which provides both primary and tertiary care. The study included all children aged 0-18 years from whom *S. pneumoniae* were isolated from a normally sterile body site.

Data collection

Patients were identified from microbiological records. Those from whom *S. pneumoniae* were isolated from a normally sterile site with available medical records were eligible for data collection and analysis. Information on patient demographics, clinical manifestations and outcomes, laboratory findings, and drug susceptibility patterns of the *S. pneumoniae* were abstracted and descriptively analyzed.

Bacteriology

S. pneumoniae isolates were identified according to standard laboratory procedures. Penicillin susceptibilities were determined by a gradient plate technique[9]. The susceptibility standards were defined according to the National Committee for Clinical Laboratory Standards breakpoints[10]. Susceptibility interpretations used the Clinical and Laboratory Standards Institute (CLSI) 2008 guidelines. For meningitis isolates (isolates from CSF), the minimum inhibitory concentration (MIC) values of ≤ 0.06 μg/mL were penicillin-susceptible and MIC values of ≥ 0.12 μg/mL were penicillin-resistant. For non-meningitis isolates (isolates from sterile sites other than CSF), MIC values of ≤ 2 μg/mL were penicillin-susceptible, an MIC of 4 μg/mL was penicillin-intermediate, and MIC values of ≥ 8 μg/mL were penicillin-resistant[11]. *S. pneumoniae* serotyping was not performed during the study period.

Statistical analysis

SPSS statistical software[12] was used for analysis of this study. Descriptive statistics were used to summarize patients and isolate characteristics. Chi-square and Fischer exact tests were used to assess differences in clinical characteristics between patients infected with penicillin-susceptible *S. pneumoniae* (PSSP) strains and penicillin-nonsusceptible *S. pneumoniae* (PNSSP) strains. P-values < 0.05 were considered statistically significant.

Results

Among the 745,983 children receiving outpatient or inpatient care at the Queen Sirikit National Institute of Child Health during January 1, 1998 through the December 31, 2007, 126 patients with culture-proven invasive pneumococcal infections were identified for an estimated incidence of 17 per 100,000 patients. However, only 106 (84.1%) medical records were available for analysis.

Patients' age distribution is shown in Fig. 1. The proportion of patients under ≤ 24 and ≤ 60 months of age were 65.1% and 84.9%, respectively. Median age was 1.04 years (range 26 days-13.00 years). Pneumococcal infections were more common in the cooler season, *i.e,* from October to March (63.6%) (Fig 2). The male to female ratio was 2:1.

The majority of the patients (52.8%) had no documented underlying disease. The most common underlying disease was HIV infection (34%), followed by acute lymphoblastic leukemia (8%), neonatal hepatitis (8%), beta-thalassemia with previous splenectomy (8%), and cerebral palsy (8%) (Table 1).

Of the 106 isolates with MIC values available, 70 (66%) were PSSP and 36 (34%) were PNSSP. Common diagnoses were bacteremia (59.4%), meningitis (29.3%), and pneumonia (11.3%). Among 12 patients with pneumonia, common radiographic findings included patchy infiltration (6), interstitial infiltration (3), and lobar infiltration (3).

The median (range) white blood cell count (WBC) was 22,700 (3,100-42,800); 35.8% of patients had a WBC within the normal range (5,000-15,000 cell/mm^3). Of the 101 patients presented with fever. The median

Table 1. Underlying diseases of patients with invasive pneumococcal infections

Underlying diseases	Number (%)
HIV	17 (34)
Acute lymphoblastic leukemia	4 (8)
Neonatal hepatitis	4 (8)
Beta-thalassemia s/p splenectomy	4 (8)
Cerebral palsy	4 (8)
Congenital heart disease	3 (6)
Biliary atresia s/p Kasai operation	3 (6)
Complex heart disease	2 (4)
Nephrotic syndrome	2 (4)
Preterm, BPD, ROP, GER	2 (4)
CSF fistula	1 (2)
Down syndrome	1 (2)
Imperforated anus s/p colostomy	1 (2)
Neuroblastoma	1 (2)
Hirschsprung disease	1 (2)
Total	50 (100)

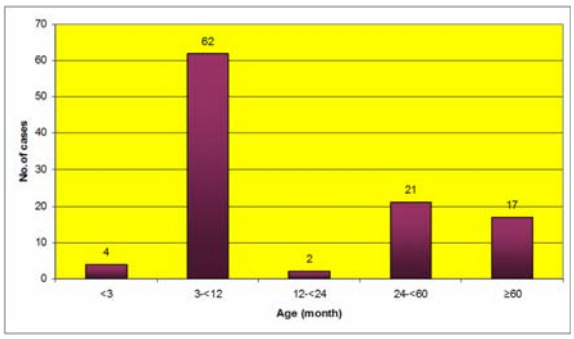

Fig. 1 Age distribution of patients with invasive pneumococcal infections

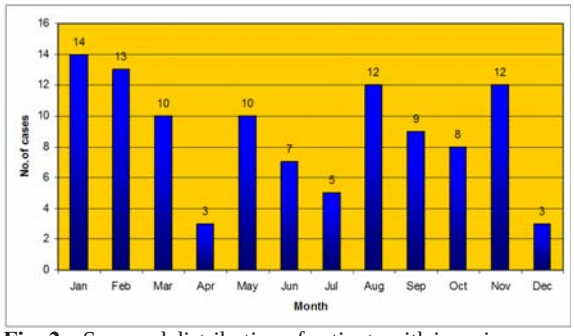

Fig. 2 Seasonal distribution of patients with invasive pneumococcal infections

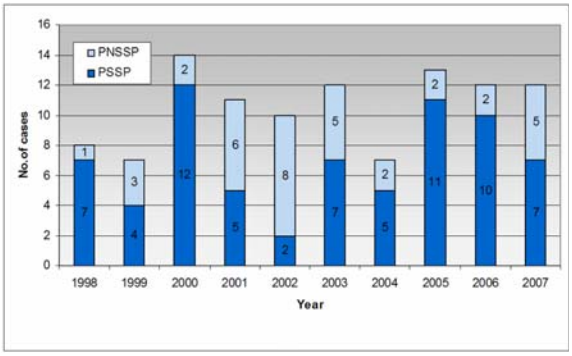

Fig 3. Yearly distribution of invasive pneumococcal disease cases by penicillin susceptibility. (PNSSP = penicillin non-susceptible *S.pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae).* Susceptibility interpretations used the Clinical and Laboratory Standards Institute (CLSI) 2008 guidelines.

time to defervescence after appropriate treatment was 2 days. Thirteen patients died (case fatality rate = 12.3%); three of the patients who died had HIV infection, two had congenital heart disease, and two had neonatal hepatitis. The case fatality rate among patients with pneumococcal meningitis was 5.9% and bacteremia was 8.3%. Long-term and neurologic sequelae were evaluated in 93.5% of cases with meningitis. Among those who were evaluated, one had hearing deficit, and nine had neurodevelopmental impairment.

Among the non-meningitis cases, those caused by PSSP did not differ from PNSSP cases in terms of demographic characteristics, clinical manifestations, outcomes, and contributing history of illness. However, among meningitis cases, PNSSP-infected patients were younger than those infected with PSSP (mean age 1.13 vs. 3.69 years, p = 0.032), were more likely to have had a seizure (100% vs. 29%, p = 0.005), and were less likely to present with headache (0% vs. 29%, p = 0.018) (Table 2).

The minimum inhibitory concentration (MIC) of penicillin for pneumococcal isolates from meningitis cases ranged from 0.006-1.5 µg/mL and for isolates from non-meningitis cases from 0.002-4 µg/mL. Increasing trend of antimicrobial resistance among *S. pneumoniae* was evident from our study. The proportion of cases caused by PNSSP was 12.5% in 1998, varied in subsequence years, and was 41.7% in 2007 (Fig. 3). Of 126 PNSSP, 8.2% were resistant to cefotaxime and 12.3% were resistant to ceftriaxone. All of the isolates remained susceptible to vancomycin.

Discussion

S. pneumoniae is an important cause of respiratory tract infection in children. Its clinical and public health significance have been well documented worldwide. As a common inhabitant of upper respiratory epithelium, *S. pneumoniae* must escape local host defenses to cause invasive disease. According to our study, a higher proportion (63.6%) of invasive pneumococcal infections occurred during the cooler months in Thailand, which is consistent with existing literature suggesting that impaired local defenses from viral upper respiratory tract infections may play a major role in the pathogenicity of disease[13,14].

The incidence of pneumococcal infection is generally high in neonates, infants, and young children[15], low in teenagers and young adults, and then increases again in the elderly (65 years of age up)[16-19]. In this study, 74% of the invasive pneumococcal infections occurred in patients are younger than 3 years of age. Cases were more common in males than females with a ratio of 2:1, which is similar to other studies[20,21]. The emergence of pneumococcal resistance to penicillin and other

Table 2. Characteristics of 106 children with invasive pneumococcal infections

Basic-Demographic Data	Meningitis (n = 31)			Non-meningitis (n = 75)		
	PSSP (n = 14)	PNSSP (n = 17)	p-value	PSSP (n = 56)	PNSSP (n = 19)	p-value
Mean age in year (SD)	3.69 (3.89)	1.13 (1.36)	0.032	2.04 (2.17)	2.71 (3.35)	0.314
Gender (M:F)	10:4	10:7	0.465	39:17	10:9	0.178
Mean length of stay in day (SD)	21.07 (10.36)	22.71 (17.69)	0.763	14.29 (16.79)	11.32 (10.06)	0.470
Clinical manifestations						
Acute febrile illness	12 (85.7)	17 (100)	0.353	50 (89.3)	17 (89.5)	0.936
Lethargy	10 (71.4)	15 (88.2)	0.317	44 (78.6)	14 (73.7)	0.354
Poor feeding	9 (64.3)	14 (82.4)	0.297	41 (73.2)	13 (68.4)	0.358
Seizure	4 (28.6)	17 (100)	0.005	6 (10.7)	2 (10.5)	0.157
Dyspnea	1 (7.1)	1 (5.9)	0.999	16 (28.6)	8 (42.1)	0.102
Respiratory failure	0	1 (5.9)	0.356	3 (5.4)	2 (10.5)	0.655
Shock	0	2 (11.8)	0.185	3 (5.4)	1 (5.3)	0.317
Cyanosis	0	1 (5.9)	0.356	6 (10.7)	3 (15.8)	0.317
Diarrhea	0	0	-	2 (3.6)	4 (21.1)	0.414
Vomiting	1 (7.1)	0	0.263	1 (1.8)	1 (5.3)	0.999
Headache	4 (28.6)	0	0.018	0	0	-
Highest mean temperature (SD) (°C)	39.82 (1.09)	39.76 (1.30)	0.898	39.81 (1.27)	39.97 (1.11)	0.615
Lowest mean temperature (SD) (°C)	36.09 (0.18)	36.12 (0.45)	0.806	36.0 (0.09)	36.13 (0.28)	0.110
Outcome			0.415			0.841
Death	0	1 (5.9)		9 (16.1)	3 (15.8)	
Alive	14 (100)	15 (88.2)		46 (82.1)	16 (84.2)	
Discharged by request	0	1 (5.9)		1 (1.8)	0	
Neurodevelopmental outcomes			0.650			0.745
Normal	13 (92.9)	15 (88.2)		2 (3.6)	1 (5.3)	
Cannot be evaluated	1 (7.1)	1 (5.9)		54 (96.4)	18 (94.7)	
Profound	0	1 (5.9)		0	0	
Long-term sequelae						
Meningitis	2 (14.3)	2 (11.8)	0.999	0	0	-
Cerebral palsy	1 (7.1)	3 (17.6)	0.317	0	0	-
Hydrocephalus	0	3 (17.6)	0.098	0	0	-
Epilepsy	0	3 (17.6)	0.098	0	0	-
Delayed development	0	3 (17.6)	0.098	0	0	-
History of:						
Prior hospitalization	0	0	-	10 (17.9)	3 (15.8)	0.052
Hospital-acquired infection	0	0	-	2 (3.6)	0	0.404
Prior antibiotic use within 3 month	0	0	-	8 (14.3)	3 (15.8)	0.132
Prior beta-lactam antibiotic use	0	0	-	5 (8.9)	1 (5.3)	0.102
Mean Defervescence in day (SD)	3.93 (2.52)	3.65 (2.59)	0.282	2.27 (2.09)	2.42 (1.74)	0.775

* Number in table represent number of patients (%) unless indicated otherwise

antimicrobial agents has become a problem throughout the world. Penicillin-nonsusceptibility was documented in 70% and 65.3% of *S. pneumoniae* isolates causing invasive disease in children in the southern and northern parts of Taiwan, respectively, during 1998-1999[1,22]. In this study, we found the overall rate

penicillin- nonsusceptibility of 54.8% among meningitis isolates. This rate was close to the rate reported in Korea (79.7%), the country with the highest prevalence of PNSSP in Asia[2,23].

We found that HIV infection was the most common underlying disease (34%) among patients with invasive pneumococcal infections, followed by acute lymphoblastic leukemia (8%), neonatal hepatitis (8%), beta-thalassemia with previous splenectomy (8%), and cerebral palsy (8%). This finding supports previous reports illustrating that certain underlying conditions including asplenia, sickle cell disease, HIV/AIDS, agammaglobulinemia, hematologic malignancy, and complement deficiencies are associated with increased in both the frequency and severity of pneumococcal infections[24,25].

We found a case fatality rate of 12.3% with the highest rates among HIV-infected patients (23.1%). Additionally, long-term sequelae were common; hearing deficit and neurodevelopmental impairment were found in 3.2% and 29% of cases, respectively. Similarly, multi-center, hospital-based surveillance for invasive pneumococcal disease in India demonstrated the devastating impact of invasive pneumococcal infections[26], with a case-fatality rate of 21.3% (meningitis: 34%, pneumonia: 19%, septicemia: 21%).

We demonstrated alarmingly high rates of penicillin non-susceptibility among this invasive pneumococcal isolates; 41.7% of *S. pneumoniae* had reduced penicillin susceptibility in 2007. This information is essential for clinicians in order to devise appropriate empiric antimicrobial treatment regimens for patients who are at high risk of invasive pneumococcal infection. Similar to other studies, we identified no significant differences between patients infected with penicillin susceptible and those infected with non- susceptible pneumococcal isolates in terms of underlying diseases and outcomes[27-30]. However, we found that the patients with PNSSP meningitis were younger, more likely to have seizures, and less likely to have headaches than meningitis patients infected with PSSP. It is possible that younger children were more likely than older children to have been exposed to antibiotics, which may have increased their chances of being infected with PNSSP. Previous work supports young age as a risk factor for infection with PNSSP[20,21,31-35]. However, the association we found between seizures and PNSSP infections in meningitis cases has not been described previously[27-30,35]. The association of PNSSP infection and headache infection may have been confounded by the association between PNSSP infection and young age, because younger patients often cannot describe having a headache.

In summary, we found a relatively low frequency of invasive pneumococcal infection in hospitalized children. However, we demonstrated a high case fatality rate among those with underlying disease. We did not find significant differences in outcomes between patients infected with penicillin-susceptible and non-susceptible *S. pneumoniae*. Our study has further highlighted the value of hospital-based data for monitoring trends in invasive pneumococcal disease as well as potential risk factors. Continued regional surveillance for pneumococcal disease burden and resistance patterns is essential.

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การติดเชื้อ Streptococcus pneumoniae แบบรุกรานในเด็กในเมือง: การศึกษาย้อนหลัง 10 ปี

สุพิชญา เนตรสว่าง, วารุณี พรรณพานิช, วิภา ตรีรัตน์วีรพงษ์, ทวี โชติพิทยสุนนท์

วัตถุประสงค์: *เพื่อศึกษาการติดเชื้อ Streptococcus pneumoniae แบบรุกราน ในแง่ของความชุก, ลักษณะอาการทางคลินิก, ผลการตรวจทางห้องปฏิบัติการ และ drug susceptibility patterns ในเด็กที่มารับการรักษา ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังเชิงพรรณนา โดยศึกษาจากเวชระเบียนผู้ป่วยที่ติดเชื้อ Streptococcus pneumoniae แบบรุกราน เกี่ยวกับข้อมูลทั่วไป, ลักษณะอาการทางคลินิก, ผลการตรวจทางห้องปฏิบัติการ และ drug susceptibility patterns*

ผลการศึกษา: *จำนวนผู้ป่วยเด็กทั้งผู้ป่วยในและผู้ป่วยนอกที่มารับการรักษาที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ในระยะเวลา 10 ปี มีทั้งหมด 745,983 ราย โดยที่ 126 ราย ที่มีผลการเพาะเชื้อ จากตัวอย่างสิ่งส่งตรวจที่เป็น sterile site พบเชื้อ Streptococcus pneumoniae คิดเป็น 17 รายต่อแสนคน พบกลุ่ม penicillin-nonsusceptible S. pneumoniae จากสิ่งส่งตรวจน้ำไขสันหลัง 54.8% และสิ่งส่งตรวจอื่น 25.3% ได้รับการวินิจฉัยเป็นการติดเชื้อในกระแสโลหิต 59.4%, เยื่อหุ้มสมองอักเสบ 29.3% และปอดอักเสบ 11.3% พบอัตราการตาย 12.3% โดยสัมพันธ์กับ HIV infection 23.1% และมีการดื้อต่อยาปฏิชีวนะในกลุ่ม cephalosporin คือ cefotaxime 8.2% และ ceftriaxone 12.3% แต่เชื้อยังมีความไวต่อ vancomycin ทั้งหมด*

สรุป: *แม้ว่าความชุกของการติดเชื้อแบบรุกรานของ S. pneumoniae ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินีจะไม่สูงมาก แต่พบว่ามีอัตราการตายที่สูงโดยเฉพาะในกลุ่มที่ติดเชื้อเอชไอวี พบเชื้อดื้อยาเพิ่มขึ้นอย่างรวดเร็วในหลายประเทศทั่วโลกจากการศึกษานี้ ไม่พบความแตกต่างในแง่ลักษณะผลลัพธ์ของการรักษาระหว่าง กลุ่มที่ติดเชื้อดื้อยาและไม่ดื้อยาอย่างมีนัยสำคัญ*