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Original article

Rate of drug-resistant *Streptococcus pneumoniae* in children with invasive pneumococcal disease: a decade review

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Background: *Streptococcus pneumoniae* is a common causative organism of pneumonia, bacteremia and meningitis in children. Rate of drug-resistant *Streptococcus pneumoniae* (DRSP) is an important information to guide appropriate empirical antibiotics.
Objectives: This study aimed to describe rates of DRSP and clinical outcomes of patients with invasive pneumococcal disease (IPD).
Methods: A retrospective study was conducted among pediatric patients with IPD from 2008 -2017. DRSP was defined as National Committee for clinical laboratory standards guidelines 2013.
Results: From January 2008 to December 2017, 71 patients with diagnosis of IPD were identified. Median (interquartile range) age was 2 years (2 months - 15 years 2 months). Forty-seven patients (66.0%) had underlying diseases, the most was congenital heart diseases (15.0%). There were 25 patients with bacteremia with or without localized infection and 46 patients with pneumonia. Proportion of penicillin-resistant *S. pneumoniae* (PRSP) infection increased from 17.5% (95% CI 7.4 - 32.8) during 2008 - 2012 to 25.8% (95% CI 11.9 - 44.6) during 2013 - 2017 (*P* - value = 0.39). Third generation cephalosporins-resistant *S. pneumoniae* infection was stable during the two time periods, which was 5.0% (95% CI 1.0 - 16.9) during 2008 - 2012 and 3.2% (95% CI 0.1 - 16.7) during 2013 - 2017 (*P* - value = 0.71). The common empirical antibiotics treatment included third generation cephalosporins (79.0%), meropenem (8.0%), third generation cephalosporins plus vancomycin (4.0%) and others (9.0%). Only one patient died from bacteremia with sepsis directly related to IPD.
Conclusion: There is an increasing trend of PRSP over the past decade but not to the extent of third generation cephalosporins-resistant. Therefore, third generation cephalosporins stand as a good option for IPD empirical treatment.

Keywords: *Streptococcus pneumoniae* , pneumococcal disease.

Streptococcus pneumoniae is a common causative organism that can cause serious infection such as pneumonia, bacteremia, and meningitis in children.[1] Drug-resistant *Streptococcus pneumoniae* (DRSP) infection has been reported worldwide including in Thailand.[2 - 11] A study from the United States reported the rate of drug-resistant *S. pneumoniae* 19A isolates, 3.5% were penicillin-resistant *S. pneumoniae* (PRSP) in 2000, it has increased to 13.8% in 2008. However, the rate of third generation cephalosporins resistance did not change significantly during the 10-year study period.[12] Additionally, a study conducted in Asia in 2012 showed a persistently high prevalence of penicillin resistance with the rate of 0.7% and 57.5% in nonmeningeal isolations and meningeal isolations, respectively,[13] when compared to previous Asian Network for Surveillance of Resistant Pathogens (ANSORP) studies in Asian countries in 2004 (52.4% from both meningeal and non-meningeal isolations).[14] This increasing trend of drug-resistant

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S. pneumoniae in the USA and Asian countries was similar to Thailand. The National Antimicrobial Resistance Surveillance Center, with data from 85 hospitals in Thailand, reported the increase in prevalence of PRSP in blood culture specimens during the past decade from 37.8% (2008) to 39.1% (2019).[15] Not only in children, the rate of resistance in adult was also high. There is a relatively high prevalence of infections caused by penicillin and third generation cephalosporins-resistant *S. pneumoniae* in patients at King Chulalongkorn Memorial Hospital 2008 - 2009. There were 48.4% PRSP and third generation cephalosporins intermediate *S. pneumoniae* was 13.2%.[16]

S. pneumoniae infection remains a leading cause of morbidity and mortality especially in children with invasive pneumococcal disease (IPD).[5, 8] Effective antibiotics can reduce mortality in these patients. From 2001 to 2015, a few studies in Thailand reported variation in the rates of DRSP in different geographical area and size of hospital, which varied from 0 to 48.4%.[4, 17, 18] Therefore, an update on current situation of drug-resistant *S. pneumoniae* in a tertiary care hospital with many cases of IPD could be beneficial in making clinical decisions in certain situations. In this study, we aimed to describe the trend of penicillin and third generation cephalosporins-resistant *S. pneumoniae* and clinical outcomes in children with IPD at King Chulalongkorn Memorial Hospital in the past decade.

Materials and methods

Study design

We conducted a retrospective study of patients aged 1 month to less than 18 years old who had IPD at King Chulalongkorn Memorial Hospital. Inclusion criteria were the patient: 1) was hospitalized during January 2008 to December 2017; 2) was diagnosed as IPD disease; and, 3) had a drug susceptibility testing resulting from clinical isolates of *S. pneumoniae* from microbiology laboratory department of the hospital. Patient identified from ICD-10 coding with invasive pneumococcal infection and microbiologic records which *S.pneumoniae* isolated cultured from all sites. The medical records of patients with IPD were retrospectively reviewed for demographic data, clinical diagnosis, drug susceptibility pattern of *S. pneumoniae*, treatment and clinical outcomes. Institutional Review Board approval was granted by the Faculty of Medicine, Chulalongkorn University.

Definitions

Invasive pneumococcal disease

Clinical syndromes of IPD in this study were categorized to two main categories including definite IPD and probable IPD.

Definite invasive pneumococcal disease (Definite IPD)

Definite IPD was defined as documented of clinical isolates from blood or sterile body fluid sites. Patients were diagnosed occult bacteremia or bacteremia with localized infection such as meningitis, pleural effusion, pericarditis, endocarditis and arthritis, and localized infection without documented bacteremia.

Probable invasive pneumococcal disease (Probable IPD)

Probable IPD was defined as documented isolates from tracheal aspiration fluid or sputum within 48 hours of diagnosis in patient who had pneumonia with respiratory failure or severe pneumonia.

Pneumonia with respiratory failure

Pneumonia with respiratory failure was defined as pneumonia with intubation or tracheostomy that need the utilization of ventilator.

Severe pneumonia

Severe pneumonia was defined when the needed positive airway pressure for respiratory support that included continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) and high flow nasal cannula (HFNC).

Laboratory methods for antibiotic susceptibility

Specimens collected from sterile sites and non-sterile sites were tested for penicillin and third generation cephalosporins susceptibility to obtain minimal inhibitory concentration (MIC) by E-tests method. Drug-resistant *S. pneumoniae* (DRSP) was defined by drug susceptibility criteria from the National Committee for Clinical Laboratory Standards Institute Guidelines 2013 as shown in Table 1.[19] Penicillin-resistant *S. pneumoniae* (PRSP) was defined as a clinical isolate with MIC above 2 μg/mL for non-cerebrospinal fluid specimen and above 0.06 μg/mL for cerebrospinal fluid specimen. Third generation cephalosporins-resistant *S. pneumoniae* was defined as a clinical isolate with MIC above 1 μg/mL for non-cerebrospinal fluid specimen and above 0.5 μg/mL for cerebrospinal fluid specimen.

Table 1. Clinical and laboratory standard institute for penicillin and third generation cephalosporins susceptibility testing of *Streptococcus pneumonia*. [19]

Drug and isolate location	Susceptibility (μg/mL)	Non-susceptibility (μg/mL)	
		Intermediate	Resistant
Penicillin (Oral)	≤ 0.06	0.12 - 0.1	≥ 2.0
Penicillin (intravenous)			
Nonmeningeal	≤ 2.0	4.0	≥ 8.0
Meningeal	≤ 0.06	None	≥ 0.12
Cefotaxime or ceftriaxone			
Nonmeningeal	≤ 1.0	2.0	≥ 4.0
Meningeal	≤ 0.5	1.0	≥ 2.0

Statistical analysis

The baseline characteristics (gender, age, underlying disease), clinical diagnosis, empirical treatment and clinical outcomes were analyzed and reported in the terms of percentage or mean. The rate of penicillin and third generation cephalosporins-resistant were expressed with percentage with 95% confidence interval (95%CI) and then compared between two periods (2008 - 2012 *vs.* 2013 - 2017) by Chi square test. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp. Armonk, NY). P – value < 0.05 was considered as statistical significance.

Results

From January 2008 to December 2017, there were 78 patients diagnosed with definite IPD or probable IPD; 7 patients were excluded from analysis due to no data on drug susceptibility testing. Therefore, 71 patients were recruited in this study, where 40 patients were from the period of 2008 to 2012 and 31 patients from the period 2013 to 2017.

Baseline characteristics are shown in Table 2. Among the 71 patients with invasive pneumococcal disease, 44 patients were male (62.0%). The median of age was 2 years 4 months (ranged from 2 months to 15 years 2 months). Forty-seven patients (66.0%) had underlying disease; the most common were congenital heart diseases (15.0%), neurological diseases (11.0%), malignancy (11.0%) and, chronic liver diseases (10.0%). There were only 17 patients who had information regarding immunization history prior to illness, only 1 patient had documents receiving IPD vaccines prior to the illness. This patient had 2 doses of PCV13 at age 1 year 3 months but developed illness at age 1 year 6 months.

Table 2. Demographic data with baseline characteristics and clinical diagnosis of patient with invasive pneumococcal disease (IPD).

Characteristics	Total (n = 71) (%)
Male/Female	44/27 (62/38.0)
Age, median (IQR) years	2 (0.2 - 15.2 years)
Underlying disease (%)	66.0
Congenital heart disease	15.0
Neurological disease	11.0
Malignancy	11.0
Chronic liver disease	10.0
Multiple anomaly	7.0
Immune deficiency and connective tissue diseases	4.0
Metabolic disease	4.0
Gastrointestinal and urinary system diseases	3.0
Asthma	1.0
Clinical diagnosis	
Definite invasive pneumococcal disease	25 (35.0)
Occult bacteremia	6
Bacteremia with localized infection	19
Pneumonia/pleural effusion	11
Meningitis	4
Endocarditis/pericardial effusion	2
Orbital infection/otitis media	2
Probable invasive pneumococcal disease	46 (65.0)
Pneumonia with respiratory failure	35
Severe pneumonia	11b

Among the 71 patients, 25 patients (35.0%) were diagnosed definite IPD and 46 patients (65.0%) as probable IPD (Table 2). Among the definite IPD, the most common diagnosis was bacteremia with pneumonia (11 patients), occult bacteremia (6 patients), and bacterial meningitis (4 patients). Among the probable IPD, there were 35 patients with pneumonia with respiratory failure and 11 patients with severe pneumonia. Among the 2 patients who had serotype data, they were serotype 9A and 6B.

Rate of drug-resistant Streptococcus pneumoniae

Among the 71 patients, the proportion of penicillin-resistant *S. pneumoniae* (PRSP) increased from 17.5% (95% CI 7.4 – 32.8) during 2008 - 2012 to 25.8% (95% CI 11.9 – 44.6) during 2013 – 2017 (*P* - value = 0.39). While resistance to third generation cephalosporins remained relatively constant from 5.0% (95% CI 1 - 16.9) during 2008 – 2012 to 3.2% (95% CI 0.1 - 16.7) during 2013 - 2017 (*P* – value = 0.71).

Among the 25 patients with definite IPD, the proportion of penicillin-resistant was 13.3% (95% CI 1.7 - 40.5) during 2008 – 2012 and 20.0% (95% CI 2.5 - 55.6) during 2013 – 2017 (*P* - value = 0.66). While the third generation cephalosporins-resistant was increased from 6.7% during 2008 - 2012 (95% CI 0.2 – 31.9) to 10.0% (95% CI 0.3 – 44.5) during 2013 – 2017 (*P* - value = 0.76).

Treatment

The most common empirical antibiotics given during the first 48 hours were third generation cephalosporins (79.0%), meropenem (8.0%), third generation cephalosporins plus vancomycin (4.0%) and others (9.0%). Among the four cases of bacterial meningitis, three of them were given third generation cephalosporins plus vancomycin as empirical treatment and one of them was given only third generation cephalosporins. All of them were resistant to penicillin, and one patient with third generation cephalosporin resistance; however, this patient was prescribed cefotaxime plus vancomycin as empirical treatment. From four bacterial meningitis patients, the first patient was a 6-year old girl with infected ventriculoperitoneal shunt. Cerebrospinal fluid culture showed penicillin-resistant *S. pneumoniae* with susceptible to third generation cephalosporins. She was treated with high dose ceftriaxone for 26 days plus removal of ventriculoperitoneal shunt and temporary replace with external ventricular drainage. The second patient was a 4-year old, a previously healthy boy. He had a fever and developed alteration of consciousness 3 days prior to his presence at the hospital. He was given empirical treatment with cefotaxime plus vancomycin. Cerebrospinal fluid culture and hemoculture were penicillin-resistant *S. pneumoniae* but susceptible to third generation cephalosporins. After the drug susceptibility reported, vancomycin was taken off and only cefotaxime was prescribed as targeted therapy for 15 days. The third patient was a 17-day female newborn with obstructive hydrocephalus and myelomeningocele. She was placed with ventriculoperitoneal shunt and had a repair of ruptured myelomeningocele then cerebrospinal fluid was sent for culture after operation. She was empirical treated with cefotaxime and vancomycin. Cerebrospinal fluid culture showed penicillin-resistant *S. pneumoniae* but sensitive to third generation cephalosporins and vancomycin. After the drug susceptibility reported, cefotaxime was used for targeted therapy and vancomycin was used because of post-operation for 14 days. The fourth patient was an 8-month male infant with tricuspid atresia, atrial and ventricular septal defect. He was admitted due to viral pneumonia and developed bacterial meningitis at day 4 of hospitalization. He was empirical treated with cefotaxime plus vancomycin. Cerebrospinal fluid culture and hemoculture was penicillin and third generation cephalosporins-resistant *S. pneumoniae* but susceptible to vancomycin and meropenem. After drug susceptible was reported, cefotaxime plus vancomycin were continued for treatment for another 14 days.

Clinical outcomes

In this study, the clinical outcomes between patients with pneumonia and bacteremia are shown in Table 3. Among the 46 patients with pneumonia, there were 29 patients (63.0%) were admitted to intensive care unit (ICU), 35 patients (76.0%) were on ventilator, 7 patients (15.0%) had clinical hypotension, 2 patients (4.0%) died within 30 days after admission and 10 patients (22.0%) were PRSP infection. Among 25 patients with bacteremia, there were 5 patients (20.0%) admitted to intensive care unit (ICU), 4 patients (16.0%) were on ventilator, 2 patients (8.0%) had clinical hypotension, 1 patient (4.0%) died within 30 days after diagnosis and 5 patients (20.0%) were PRSP infected.

Table 3. Clinical outcomes of patients with invasive pneumococcal disease (IPD) stratified by diagnosis.

Diagnosis	Clinical outcomes				
	ICU admission	Ventilator Using	Hypotension	30-day mortality	Penicillin- resistant *S. pneumoniae* infection
IPD (n = 71) (%)	34 (48.0)	39 (55.0)	9 (13.0)	3 (4.0)	15 (21.0)
Pneumonia (n = 46) (%)	29 (63.0)	35 (76.0)	7 (15.0)	2 (4.0)	10 (22.0)
Bacteremia (n = 25) (%)	5 (20.0)	4 (16.0)	2 (8.0)	1 (4.0)	5 (20.0)

The overall 30-day mortality rate was 4.2% (95% CI 1.0 - 11.9). Three patients died with one case directly related to IPD with penicillin-susceptible *S. pneumoniae* (PSSP). From the three patients, the first patient was a 5-month old boy with congenital cyanotic heart disease with normal spleen presented with septic shock. Initial investigation showed total white blood count 7,630 cells/mm^3 with 21.0% neutrophils and hemoculture reported within 24 hours resulted in PSSP. He was prescribed ceftriaxone, which was later switched to meropenem; however, with overwhelming sepsis, he died within the day. The second case was a 4-year old girl with cirrhosis. She was diagnosed pneumonia with respiratory failure and septic shock. She was intubated then resuscitated with normal saline and inotropic drugs. Complete blood count showed white blood cells 10,940 cell/mm^3 with 88.0% neutrophils. Tracheal culture indicated PSSP with no blood culture growth. Empiric antibiotic was meropenem. She developed ventilator-associated pneumonia on day 8 after admission from pan drug-resistant *Acinetobacter baumannii*, and died on day 13 after admission. The third case was an 8-year-old girl with lymphoblastic leukemia and central nervous system relapse. She had low grade fever, developed status epilepticus and was intubated at the emergency department. She was diagnosed with pneumonia and central nervous system relapse leukemia at day 1 of admission. Initial investigation showed white blood cells 7,060 cells/mm^3 with no blast cell in peripheral blood smear. However, tracheal culture showed PSSP, and no blood culture growth. Prescribed antibiotics were ceftazidime and amikacin that was used until she died on day 9 of admission from central nervous system relapse and respiratory failure.

Discussion

In this study, the result showed that PRSP infection had an increasing trend during the past decade. The proportion of PRSP infection rate among patients with definite and probable IPD increased from 17.5% between 2008 and 2012 to 25.8% between 2013 and 2017. This trend is similar to those reported by the National Antimicrobial Resistance Surveillance Center of Thailand[15], where the prevalence of PRSP in blood culture specimens during past decade increased from 37.8% in 2008 to 39.1% in 2019. The rate of PRSP in this study was less than National Antimicrobial Resistance Surveillance Center of Thailand, this may be due to from data from only one university hospital and small sample size may not represent the overall population. Third generation cephalosporins-resistant *S. pneumoniae* infection was stable during the two time periods, which was 5.0% and 3.2% resistant. Therefore, third generation cephalosporins stand as a good option for IPD empirical treatment.

The PRSP infection rate of definite IPD isolates in this study during the latter 5 years between 2013 - 2017 was 20.0%. These results were higher than a previous study in Chiang Mai (17.4%, 1993 - 2003).[17] and a multicenter study in Bangkok (10.3%, 2009 - 2012).[7] This could indicate that penicillin may not be the appropriate empirical antibiotic for IPD due to increasing trend of its resistance in the past decade. However, it can be utilized as the target antibiotic if drug susceptibility test showed PSSP.

The proportion of third generation cephalosporins-resistant *S. pneumoniae* infection has been fairly constant remaining less than 5.0% occurrence overtime among patients with definite IPD and probable IPD, from 5.0% (95%CI 1 - 16.9) in the former 5 years (2008 - 2012) to 3.2% (95% CI 0.1 - 16.7) in the latter 5 years (2013 - 2017). The results showed fewer resistance to third generation cephalosporins when compared to penicillin. The mechanisms of resistance to penicillin and cephalosporin are different pathway. Thus, it is reasonable to utilize third generation cephalosporins as empirical antibiotics.

The most common empirical antibiotics in the first 48 hours after diagnosis was third generation cephalosporins, which was selected 79.0% of the times. Our results showed that it was reasonable to use third generation cephalosporins as empirical treatment due to low rate of third generation cephalosporins-resistant *S. pneumoniae* infection. The second most common empirical antibiotic was meropenem with 8.0% (6 patients) of its usage. One of them had PRSP infection and none of them had third generation cephalosporins-resistant *S. pneumoniae*. They were prescribed with meropenem continuously after drug susceptibility had been reported. This could be an inappropriate usage according to drug susceptibility that showed a possibility of de-escalation to third generation cephalosporins. However, all of them had underlying disease and severe clinical manifestation, clinician may consider antibiotics choices from underlying disease and clinical severity.

All cases of meningitis in this study were PRSP infection; one of them was third generation cephalosporins-resistant and all was vancomycin-susceptible. This result still showed DRSP meningitis that supported the clinical practice guideline of acute meningoencephalitis from Pediatric Infectious Disease Society of Thailand [20], where recommended empirical antibiotics was third generation cephalosporins and consider to add vancomycin in the case which Gram-positive diplococci in cerebrospinal fluid, latex agglutination with *S. pneumoniae* or risk for DRSP infection. In this study, all but one was prescribed third generation cephalosporin plus vancomycin due to severe clinical manifestation or underlying diseases that risk for DRSP infection.

Among the 71 patients with invasive pneumococcal disease, their median age was 2 years, and 31.0% are less than 5 years old, and two-third had underlying diseases. These group of children are recommended to receive a conjugate pneumococcal vaccine; however, the vaccine has not been included in expand program of immunization in Thailand.

Two-third of patients with pneumonia used ventilator support or required intensive care unit admission. This is subject to selection bias due to the inclusion criteria of this study that we included only children who documented a *S. pneumoniae* infection from respiratory tract specimen collected during 48 hours of admission. Therefore, it biased towards patient who had respiratory failure on admission. There was no difference in rate of PRSP among children who presented with bacteremia or pneumonia group.

It should be noted that this study was retrospective chart review. Therefore, we did not have complete information on history of immunization with pneumococcal vaccines among these children. However, during 2008 - 2017, the vaccination coverage of vaccine in public hospital is quite low. We also did not have information of *S. pneumoniae* serotype performed systematically. Even though the data is from single university hospital, it is aligned with the finding from The National Antimicrobial Resistance Surveillance Center, with data from 85 hospitals in Thailand. A multi-center study with various sites throughout Thailand with clinical management and treatment outcomes is underway to improve generalizability of our findings.

Conclusion

There is an increasing trend in the rate of penicillin-resistant *Streptococcus pneumoniae* infection in children with invasive pneumococcal disease. Third generation cephalosporins are reasonable empiric antibiotics for children with suspected IPD as the rate of resistance to third generation cephalosporins has been fairly constant at less than 5.0% overtime.

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Conflict of interest

The authors, hereby, declare no conflict of interest.

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