CHAPTER 5

DISCUSSION

Antimicrobial susceptibility data of *Streptococcus pneumoniae* in local area is very necessary because the selection of antibiotic therapy, especially, for empirical treatment should base on resistance pattern. Due to the limited number of pneumococcal isolates received from each province, the prevalence of penicillin-nonsusceptible pneumococci in each province could not be determined. The percentage of penicillin-nonsusceptible in upper Southern area (69%) was higher than in lower Southern area (50.8%) despite of no statistical significance. The prevalence of penicillin-nonsusceptible pneumococci in Southern Thailand reported in this study (56.5%) was not different from that reported by Song and colleagues in ANSORP study (57.9%) in 1996-1997, where Bangkok, Thailand, was the only one target region in the study (Song, *et al*, 1999). However, it was slightly higher rate than that reported by Warachit *et al* (10^{th} International congress on infectious diseases, 2002) study (43%) at Hat Yai hospital located in the south of Thailand at the same time. Moreover, prevalence of penicillin-nonsusceptible pneumococci in Southern Thailand increased from 17.1% in 1993-1994 (Chup-uppakarn, 1998) to 56.5% in our study. Prevalence of penicillin-nonsusceptible in this study also was higher than that established in the United States (33.1-34.2%). On the other hand, the rate of penicillin-nonsusceptible isolates with MIC $\geq$ 2 μg/ml in this study was lower than that reported in the United States in the same period (7.6% VS 21.5-24.8%) (Doern, *et al*, 2001; Thornsberry, *et al*, 2002). Due to limited number of pneumococcal isolates, exclusion of outpatients and short period of data collection, penicillin-resistant pneumococci with MIC $\geq$ 4 μg/ml were not found in our study. However, it did not indicate that pneumococcal isolates with penicillin

MIC $\geq$ 4 μg/ml did not exist in this area. Importantly, because of the fact that prevalence of drug-nonsusceptible pneumococci increased rapidly in this region, it can be predicted that prevalence of drug-nonsusceptible pneumococci, particularly in high resistant level had the capacity to elevate in the future.

There were certain similarities between prevalence of imipenem-susceptible pneumococci in this study (71.7%) and the study performed in Bangkok in 1997 (71.9%) (Aswapokee, *et al*, 1998). The prevalence of imipenem-susceptible in Thailand was not changed, perhaps, because imipenem is the broad-spectrum antibiotic so it was reserved for serious infection such as hospital-acquired infections. Furthermore, this drug is not the first line antibiotic agent for treating drug-resistant pneumococcal infection.

Prevalence of cefotaxime-susceptible pneumococci in Southern Thailand was more than 95%. Therefore, non-pseudomonal third generation cephalosporin still be the effective antibiotic agent against penumococcal infection, particularly, meningitis. On the contrary, high prevalence of cefotaxime-susceptible pneumococci was found in this study might be due to an adoption of the newest NCCLS breakpoint (NCCLS, 2002) in which the cefotaxime breakpoint was separated into 2 classes: for meningitis and for non-meningitis. Present NCCLS breakpoint of cefotaxime for nonmeningeal infection is higher than that described in previous NCCLS guideline and consequently lowers the prevalence of cefotaxime-nonsusceptible pneumococci in our study. However, if we followed the previous NCCLS guideline, prevalence of cefotaxime-susceptible pneumococci was reduced to 72.8%. Similarly, if the MIC susceptible breakpoint of other antibiotics, for example, penicillin and imipenem also is separated based on the site of infection, the prevalence of penicillin- or imipenem-susceptible *S.pneumoniae* should be increased.

Levofloxacin has been available in Thailand for 5 years. Due to the high cost of this agent, the frequent use of levofloxacin to treat community-acquired pneumonia is limited to private hospital. This may result in 100% levofloxacin susceptibility in our study. However, the abundant use of other fluoroquinolones, such as norfloxacin, ofloxacin and ciprofloxacin to treat urinary tract infection or diarrhea in the community may result in an increasing of levofloxacin-resistant bacteria, including *S. pneumoniae* in the future.

Erythromycin is one of macrolide agents that the American Thoracic Society (2001) recommended for empirical treatment of community-acquired pneumonia in outpatients or inpatients who had no risk factors for drug-resistant pneumococci. Similar to penicillin, prevalence of erythromycin non-susceptible pneumococci was nearly 50% (1.1% intermediately susceptible, 42.4% resistant). The percentage of erythromycin resistance in this study was higher than that reported in ANSORP study (32.5%) and in the United States, 26.8% (0.2% intermediately susceptible, 26.6% resistant) (Thornsberry, *et al*, 2002). Moreover, we found that 4 pneumococcal isolates from patients with pneumonia had remarkably high erythromycin MIC of > 256 µg/ml. The high prevalence of erythromycin- and penicillin-nonsusceptible pneumococci mentioned above may result from inappropriate use of these antibiotic classes for upper respiratory tract infection in the community. Furthermore, there is a different antibiotic distribution route between Thailand and the United States. In Thailand, antibiotic can be obtained from community pharmacy without prescription, leading to widespread use of antibiotic in community.

The prevalence of multidrug-resistant pneumococci in this study (22.8%) was similar to the prevalence in the United Sates (22.4%) (Doern, *et al*, 2001). Erythromycin- and penicillin-resistance was commonly found in multidrug-resistant strains. However, we did not test other antibiotic classes that have activity against *S. pneumoniae*, such as tetracycline, chloramphenicol, and co-trimoxazole. If we did other antibiotics testing, the

prevalence of multidrug-resistant in our study was possibly higher than in the United States.

In our study, prevalence of penicillin-nonsusceptible strains was significantly higher in advance age group. Since most elderly patients have underlying diseases, they were more likely to expose to antibiotics, including, penicillins class. Type of clinical specimens were the one variable that had significant associated with penicillin-nonsusceptible pneumococci. Penicillin-nonsusceptible pneumococci were isolated from sputum more than from other site of infection. Due to a greater density of organism colonized in the nasopharynx, the more number of pneumococci exposed to antibiotic. Thus, drug selection of resistant pneumococci was easily occurred.

Many studies suggested that the selective pressure was generated by antimicrobial use in commonplace, particularly, injudicious antibiotic therapy in viral respiratory tract infection in community, inappropriate antibiotic regimen including dose, duration, class of antibiotic given and route of administration. Another important factor for the selection of resistant organism was an inappropriate antibiotic use in animal. Therefore, closed relationship of pattern of antibiotic use with levels of resistance in community is very important in order to prevent selection of resistance.

Risk factor of drug resistant pneumococcal infection was also studied. In Thailand, the major risk factor associated with penicillin-nonsusceptible pneumococci infection was prior use of antibiotic (Chokephaibulkit, *et al*, 2000; Dejthevaporn, *et al*, 2000). In contrast, our study showed that patient who had co-morbidity was considered as risk for infection with penicillin-nonsusceptible strains (OR=3.6; 95%CI, 1.1-11.7) and with erythromycin-nonsusceptible strains (OR=4.0; 95% CI, 1.2-13.1) by multiple logistic regression. Moreover, patient age also was the influence on drug-resistant pneumococcal infection among adults. Even though antibiotic use in previous 6 months

was statistically significant associated with the risk of drug-resistant pneumococcal infection in our study, its correlation was powerless due to retrospective reviewing.

The difference of clinical characteristics and outcome between infection caused by drug-susceptible and drug-resistant pneumococci was demonstrated in many studies. Tan *et al* (1998) and another study by Silverstein and colleagues (1999) compared the clinical characteristics in children with pneumococcal pneumocnia caused by isolates that either susceptible or nonsusceptible to penicillin and ceftriaxone. They found that clinical characteristics (such as peripheral white blood cell count, chest radiographic finding and respiratory distress status) of inpatients who infected with penicillin-susceptible versus those with isolate of penicillin-nonsusceptible showed no difference between two groups. Our study did not compare clinical characteristics of patients with drug-susceptible and –nonsusceptible pneumococci. However, severity of illness on admission between patients with penicillin-susceptible and –nonsusceptible isolates was compared. We found that severity of illness (SAPS II score) at presentation among adult patients with penicillin-nonsusceptible pneumococcal infection was significantly higher than among those patients with drug-susceptible pneumococci. Because of age is one parameter to calculate severity of illness score and most elderly patients were infected with penicillin-nonsusceptible strains, higher score of severity of illness was found in patients who were infected with pneumococci nonsusceptible to penicillin. Furthermore, clinical outcome of patient who infected with drug non-susceptible pneumococci also was studied. Choi and Lee (1998) and Kaplan and colleagues (2001) reviewed the medical records of pediatric patients to determine outcome of antibiotic therapy. Choi and Lee report was similar to our results that there was no significant difference in favorable response rate between episodes due to penicillin- or ceftriaxone-susceptible strains, whether the episodes were treated with penicillin or cefotaxime. Moreover, their study showed 4 children with ceftriaxone-resistant (MIC$\geq$2 μg/ml) had a favorable response to cefotaxime. Kaplan *et al* concluded that 165 of 166 children infected by ceftriaxone-nonsusceptible (MIC$\geq$1 μg/ml) isolates who received β-lactam therapy had

a satisfied response to treatment. Only one child with severe combined immunodeficiency had cefprozil treatment failure. Similarly, our study found 2 patients with β-lactam failure: 1 child with penicillin and cefotaxime MIC=1 μg/ml received high dose of ampicillin and another child with cefotaxime MIC=0.75 μg/ml received cefotaxime 100 mg/kg/day. Our finding quite resembled to Friedland (1995) study that some patients with penicillin resistant strains failed to respond to penicillin or ampicillin therapy. In addition, we had one patient who resolved spontaneously without antibiotic therapy. Similar to other studies, we found no significant difference of clinical outcome and mortality between drug-susceptible and –resistant pneumococcal pneumonia among children.

Among adult patients, Pallares and colleagues (1995) studied the relationship between penicillin and ceftriaxone nonsusceptibility and mortality among patients with pneumonia. Our study was relevant with Pallares and other studies (Feikin, *et al*, 2000; Metlay, *et al*, 2000; Moroney, 2001). We found that patients with penicillin-resistant pneumococcal isolates had higher mortality rate than those with penicillin-susceptible strains, but after adjustment for potential variables, resistance to penicillin was not related to mortality. Furthermore, elderly patients who were infected with penicillin-susceptible isolates had significant lower rate of unfavorable response within 3 days than those with penicillin-nonsusceptible strains (P=0.023). But, drug-resistant pneumococci did not significantly correlate with a favorable response within 72 hours after adjustment of the severity of illness, underlying diseases and admission to ICU.

The issue regarding to the patients with penicillin-nonsusceptible pneumococcal pneumonia who had satisfied response to antibiotic therapy should be discussed. Because of those penicillin-nonsusceptible strains which were isolated from sputum might be the colonized organism in nasopharynx, those patients may be really infected with pneumococci susceptible to penicillin resulting in responding to antibiotic therapy. However, if pneumococci were isolated from blood, those pneumococci were real

organisms that caused pneumonia and microbiological susceptibility results could be reliable.

According to the clinical irrelevance of resistance in the therapy of pneumococcal pneumonia and bacteremia resulting from those patients with penicillin-nonsusceptible pneumococci responded to penicillin therapy in our study and many studies, the interpretation of the penicillin breakpoint also should be discussed. The penicillin MIC cutoff was classified into susceptible, intermediately susceptible and resistant based on concentrations in the CSF. But, antibiotic concentrations in the CSF are much lower than concentrations found in the serum and lung interstitial. Therefore, the penicillin serum concentrations achieved in blood and lung tissue are much higher than the MICs. This might be one reason that we found no difference between patient with penicillin-susceptible and -nonsusceptible strains (with MIC<4 μg/ml) in term of favorable response within 72 hours, final clinical outcome and death in many studies. The Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group (DRSPTWG), in year 2000 suggested alterations to the susceptibility categories when treating pneumonia. They recommended that penicillin susceptible pneumococci be defined as an MIC $\leq$ 1 μg/ml, intermediate susceptibility be defined as an MIC of 2 μg/ml, and resistance be defined as an MIC $\geq$ 4 μg/ml (File JR, 2002).

Due to limited number of patients with meningitis (10 cases) included in this study, it was difficult to determine the difference between infection caused by drug-susceptible and –nonsusceptible pneumococci. However, our result was similar to Fiore *et al* (2000) and Olivier *et al* (2000) studies that mortality, an ICU stay, death and clinical outcome were not significantly different among patients with susceptible- and nonsusceptible-pneumococcal meningitis. Since this study did not find cefotaxime-nonsusceptible pneumococci isolated from CSF and the number of subjects was too small (n=10), it was difficult to draw a conclusion whether vancomycin should be added to empirical therapy of meningitis. Meningitis episodes often follow bacteremia, therefore, we perhaps

considered pneumococci which isolated from blood as potential organism that can cause meningitis. When we combined the isolates from sterile sites (blood; n=27 and CSF; n=10) and used NCCLS meningitis cefotaxime breakpoint to determine susceptibility, the prevalence of cefotaxime-susceptible and -intermediately susceptible strains were 81.5 and 18.5%, respectively. From this result, high dose of non-pseudomonal third generation cephalosporin, cefotaxime (300 mg/kg/day; maximum dose, 24 g/day) may be sufficient therapy for meningitis caused by cefotaxime-intermediately susceptible pneumococci. Accordingly, the minimal bacteriocidal concentrations (MBC) of cefotaxime for pneumococci was ranged from 1-4 μg/ml, and the high dose cefotaxime therapy was well tolerated (Viladrish, *et al*, 1996). Vancomycin may be added to empirical meningitis therapy if prevalence of cefotaxime-nonsusceptible *Streptococcus pneumoniae* was more than 5% (Friedland and Klugman, 1997). Moreover, some studies experimented to treat pneumococcal meningitis with levofloxacin because CSF levofloxacin concentration at 2 hours after dosing may be sufficient to treat CNS infection (1.99±0.67 μg/ml) in patients with spontaneous acute bacterial meningitis (Scotton, *et al*, 2001). However, levofloxacin showed slow bactericidal activity compared with ceftriaxone in the experimental pneumococcal meningitis therapy in rabbits model (Nau, *et al*, 1995). Thus, levofloxacin therapy for pneumococcal meningitis was not recommended at present time, and required randomized prospective clinical trial to prove its efficacy.

The optimal antimicrobial regimen for treatment of infections caused by pneumococcal isolates that are nonsusceptible to penicillin has been established in many studies (Jacobs, 1999; Klugman and Feldman, 1999; Chenoweth, *et al*, 2000; Harwell and Brown, 2000; Musher, 2000; File Jr., 2002). Pharmacokinetic and pharmacodynamic are the important factors that influence the consideration of antimicrobial use. Since β-lactam antibiotics possess time dependent bactericidal activity, the successful treatment outcome is observed when the free-drug concentration is above the MIC for at least 40%-50% of the dosing interval. A pharmacokinetic-

pharmacodynanic parameter target of time (T>MIC) which more than 40% is variability existed among the various parenteral β-lactam antibiotics regarding to their abilities for 85%-100% eradication of pneumococcal strains. Standard dose of penicillin or ampicillin achieves $T>MIC_{90}$ more than 40%. Similar to penicillin, cephalosporins such as cefotaxime, ceftriaxone and cefepime produce T>MIC exceeding than 40% (range from 87%-100%) against pneumococci (File Jr, TM, 2002). In contrary, one study showed that none of the cephalosporins achieved a substantial time above the geometric mean MIC during its dosing interval for fully penicillin-resistant pneumococci (Mason, *et al*, 2000). Although, there were a few case reports of β-lactam treatment failure addition to our study (Kaplan, *et al*, 2001), many studies recommended standard β-lactam antibiotics to be an appropriate drugs for intermediately susceptible pneumococcal isolates disease except meningitis. Most experts suggested non-pseudomonal third generation cephalosporins as the effective drug against susceptible pneumococcal meningits. However, we had 2 children infected with cefotaxime susceptible pneumococci (MIC, 0.064 and 0.5 μg/ml) who failed in cefotaxime treatment. This result was similar to Jacobs and colleagues (1996) study that successful treatment with cefotaxime did not correlate well with the NCCSL breakpoint for the susceptibility of pneumococci to penicillin and cefotaxime. Nevertheless, our study did not found the difference of clinical outcome and death between drug-susceptible and -nonsusceptible pneumococcal strains.

Some limitation of this study should be discussed. First, resistant pneumococcal isolate with penicillin MIC $\geq$ 4 μg/ml was not found; thus, we did not have clinical outcome of patients who were infected with those strains. Second, small sample size in this study result from losing of viable organism during transportation, and limitation to obtain complete medical records for retrospective review. Third, since our study design was retrospective review, we could not observe medical outcome during hospitalization leading to missing some clinical data. Fourth, we limited study in inpatients with pneumococcal infection, while pneumococcal infections from community were also

found in ambulatory patient. The last, we could not compare the difference of clinical characteristic of patients at presentation because of limited data based, such as chest radiographic findings and respiratory distress status.

Moreover, we suggested that large number of sample size and prospective study should be done in the future for strong results. Additionally, genetic study of DRSP should be the further work.