Original Report

Severe Pneumococcal Infection at a Thai Hospital

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ABSTRACT

Objectives: To determine clinical manifestations, prognostic factors, and therapeutic outcomes of severe pneumococcal infection.

Methods: Hospitalized patients with specimens cultured positive for *Streptococcus pneumoniae* were identified retrospectively by reviewing hospital records from 1992 to May 1998 at Siriraj Hospital.

Results: Of 205 evaluable cases, 130 (63.4%) patients were male. Nineteen (9.3%) patients were less than 2 years old, 29 (14.1%) were between 2 and 13 years, 99 (48.3%) were between 14 and 60 years, and 58 (28.3%) were over 60 years of age. From 1992 to 1997, the average admission rate was highest (36.4%) between January and March (range = 20–45%). Average admission rates during other periods ranged from 20.0% to 23.1%. Pneumonia (50.7%) and acute exacerbation of chronic obstructive pulmonary disease or infected bronchiectasis or bronchopneumonia (21.0%) were the most frequent diagnoses, followed by meningitis (14.6%) and primary sepsis without localized lesion (8.3%). The mortality rate during the first 7 days of hospitalization was 28.8%, and thereafter, 11.7%. The odds ratios (95% CI) of old age, congestive heart failure, and alcoholism for death were 3.4 (1.4–8.2), 8.6 (0.97–76.1), and 8.0 (3.1–20.9), respectively. For pneumonitis only, mortality rates among alcoholic and nonalcoholic patients were 76.9% and 39.6%, respectively (P = 0.025).

Conclusions: Patients who were alcoholic, over 60 years of age, or had congestive heart failure were vulnerable to severe pneumococcal infection with significant mortality, in spite of proper selection of empirical antimicrobials. Diabetes mellitus and multiple myeloma also contributed to late mortality after 7 days of hospitalization.

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Streptococcus pneumoniae has long been a leading cause of community-acquired infection associated with significant morbidity and mortality. In developed countries, the incidence is estimated to be 50 to 200 cases per 100,000 population and pneumococcal bacteremia occurs more frequently among children under the age of 5 years and among the elderly.[1,2] The infection can occur in apparently healthy people, although more frequently it affects patients with diabetes mellitus, splenectomy,[3] advanced human immunodeficiency virus (HIV) infection, alcoholism, nephrotic syndrome, and immunosuppressive therapy. Until recent years pneumococci were uniformly susceptible to penicillin and cephalosporins; however, the widespread use of antimicrobials is claimed to account for numerous reports of emerging penicillin-resistant *S. pneumoniae* (PRP) from Thailand and elsewhere.[4–6] The authors assessed the current situation of severe pneumococcal infection in terms of clinical manifestation and therapeutic outcome at Siriraj Hospital, Bangkok, Thailand.

MATERIAL AND METHODS

Hospitalized patients with cultures positive for *S. pneumoniae* were identified retrospectively by reviewing hospital records from 1992 to May 1998 at Siriraj Hospital, a primary- and tertiary-care hospital with 2500 beds, located in Bangkok. Those with positive sputum cultures and without preceding symptoms or signs related to respiratory tract infection were excluded. Demographic data, association with study diseases, type of infection, empirical antimicrobials, and therapeutic outcomes were extracted from the charts. Susceptibility reports of pneumococci to penicillin, cefotaxime, ceftriaxone, amoxicillin, and erythromycin, from the microbiology laboratory, were collected, but in many cases, these were unavailable. The minimal inhibitory concentration (MIC) of penicillin-resistant strains to penicillin G and

cefotaxime with E-test strip (AB Biodisk, Solna, Sweden) also was obtained for some blood isolates.

Distribution of cases by admission period, age group, type of infection, and associated disease were analyzed; percentage susceptible results were shown according to type of specimen and antimicrobials. Mortality rates also were analyzed by age group, admission period, type of infection, and associated disease. Chi-square, two-sided test was used to indicate statistically significant differences in mortality rates among the groups.

RESULTS

Positive cultures for *S. pneumoniae* were found in 309 hospital records; however, data were not accessible for 46 cases. Another 58 cases were excluded because *S. pneumoniae* was isolated from sputa, without preceding clinical manifestations of respiratory tract infection. These patients were admitted for treatment of cerebrovascular disease, leukemia, or malignancy, and the causes of fever other than pneumococcal infection were apparent when hospital charts were retrospectively reviewed. The remaining 205 cases are the subjects of this report.

One hundred and thirty (63.4%) patients were male; 19 (9.3%) were younger than 2 years, 29 (14.1%) were 2 to 13 years, 99 (48.3%) were 14 to 60 years, and 58 (28.3%) were over 60 years of age. From 1992 to 1997, the total number of cases admitted between January and March was 71 (36.4%), between April and June, 39 (20.0%), between July and September, 40 (20.5%), and between October and December, 45 (23.1%). The ranges of annual admission rates for the same period were 20 to 45% for January to March, 10 to 33% for April to June, 15 to 31% for July to September, and 12 to 36% for October to December (Table 1).

The clinical manifestations of the study cases were as follows: acute pneumonia, 104 (50.7%) cases, acute exacerbation of chronic obstructive pulmonary disease or infected bronchiectasis or bronchopneumonia, 43 (21.0%), meningitis, 30 (14.6%), primary septicemia without initial obvious nidus, 17 (8.3%), primary peritonitis, 8 (3.9%), septic arthritis, 2 (1.0%), and thoracic empyema 1 (0.5%) case.

A variety of diseases were associated with the infection in 91 (44.4%) of the 205 cases. Specifically, alcoholism was diagnosed in 23 (11.2%) cases; nephrotic syndrome in 14 (6.8%) cases; systemic lupus erythematosus in 12 (5.9%) cases; diabetes mellitus and acute leukemia in 11 (5.4%) cases each; HIV infection in 10 (4.9%) cases; hypertension in 9 (4.4%) cases; thalassemia in 6 (2.9%) cases; congestive heart failure due to ischemic heart disease or valvular heart disease in 6 (2.9%) cases; splenectomy in 4 (2.0%) cases; and multiple myeloma and chronic renal failure in 3 (1.5%) cases each (see Table 1).

Table 1. Demographic and Clinical Data in 205 Cases

Parameter	*Number of Cases (%)*	*Range (%)*
Male:female ratio 1.7:1		
Age group (y)		
< 2	19 (9.3)	
2–13	29 (14.1)	
14–60	99 (48.3)	
> 60	58 (28.3)	
Admission rate*		
January–March	71 (36.4)	(20–45)
April–June	39 (20.0)	(10–33)
July–September	40 (20.5)	(15–31)
October–December	45 (23.1)	(12–36)
Type of Infection		
Pneumonia	104 (50.7)	
Acute exacerbation of COPD/ infected bronchiectasis/ bronchopneumonia	43 (21.0)	
Meningitis	30 (14.6)	
Primary septicemia	17 (8.3)	
Primary peritonitis	8 (3.9)	
Septic arthritis	2 (1.0)	
Thoracic empyema	1 (0.5)	
Association with study diseases	91 (44.4)	
Alcoholism	23 (11.2)	
Nephrotic syndrome	14 (6.8)	
Systemic lupus erythematosus	12 (5.9)	
Leukemia	11 (5.4)	
Diabetes mellitus	11 (5.4)	
HIV infection	10 (4.9)	
Hypertension	9 (4.4)	
Thalassemia	6 (2.9)	
Congestive heart failure	6 (2.9)	
Splenectomy	4 (2.0)	
Multiple myeloma	3 (1.5)	
Chronic renal failure	3 (1.5)	

*Admission rate calculated for each year and on average using cases admitted during 1992 to 1997 only. COPD = chronic obstructive pulmonary disease.

The susceptibility results by disk diffusion method were available for most isolates (Table 2). Intermediate resistance to penicillin was detected in 17 to 34% of blood isolates and 47 to 73% of isolates from sputa during 1994 to 1997. The MICs determined by E-test were available for 14 strains of PRP isolated from blood specimens and ranged from 0.1 to 1.5 mg/L. Five isolates showed the MICs to be less than 0.5 mg/L and eight isolates at 0.5 mg/L. One strain isolated from blood in 1997 exhibited MICs for penicillin and cefotaxime at 1.5 and 1.0 mg/L, respectively. All cerebrospinal fluid (CSF) isolates were susceptible to cefotaxime or ceftriaxone.

Empirical antimicrobials were penicillin G sodium (36.6%), cefotaxime (14.1%), ceftriaxone (9.8%), ampicillin (8.8%), cefuroxime (4.3%), co-amoxiclav (3.9%), ceftazidime (3.4%), imipenem (0.5%), vancomycin (0.5%), ciprofloxacin (2.0%), erythromycin (1.0%), co-trimoxazole (0.5%), and no antimicrobial (2.0%). The antimicrobials were started on the first day of hospitalization in 175 (85.4%) cases, the second day and third day in 9 (4.4%) cases each, the fourth day in 4 (2.0%) cases, and the fifth day or later in 8 (4.0%) cases. If appropriate, the antibiotic

Table 2. Percentage Susceptible of Pneumococci by Antimicrobial, Type of Specimen, and Year

Year and Specimen (Number of Strains Tested)	*Antimicrobial*				
	Pen	*Ery*	*Amox*	*Cefo*	*Ceft*
1994					
Blood (49)	76	86	98	100	100
Sputum (2)	100	100	100	100	100
CSF(1)	100	100	100	100	100
1995					
Blood (47)	81	88	94	100	100
Sputum (15)	53	67	100	100	100
CSF(7)	43	43	100	100	100
1996					
Blood (40)	83	88	96	100	100
Sputum (10)	30	60	60	90	90
CSF (5)	40	60	60	100	100
1997					
Blood (41)	66	73	81	98	100
Sputum (30)	27	57	70	100	100
CSF (3)	33	33	100	100	100

Pen = penicillin; ery = erythromycin; amox = amoxicillin; cefo = cefotaxime; ceft = ceftriaxone; CSF = cerebrospinal fluid.

therapy was changed when the results of culture and susceptibility testing were reported.

Complete recovery or improvement was achieved in 122 (59.5%) cases. Two (1%) cases were transferred to succumb at home. Death occurred within day 1 to 7 of hospitalization in 59 (28.8%) cases and after more than 7 days in 24 (11.7%) cases. Thus total mortality was 83 (40.5%) cases. The mortality rates during the first 5 and 7 days of hospitalization were 25.2% and 28.8%, respectively. Death after 7 days of hospitalization was found to be 11.7%. Among the four age groups, mortality rate was found to be highest (63%) in the age group of 61 years or older. The mortality rate was highest (56%) during October to December; in other periods it ranged from 30% to 36%. Primary septicemia and alcoholism were associated with the highest death rates (65% and 78%) by type of infection and associated disease, respectively. As shown in Table 3, differences in mortality rates between different age groups were statistically significant.

Univariate analysis of all cases revealed that relative risk increase for death (RRI) was 2.7-fold for alcoholism, 2.7-fold for congestive heart failure, and 2.0-fold for advanced age. By logistic regression analysis, the derived equation was 72% accurate for prediction of death. The RRI of old age for death was 3.4 (95% CI = 1.4–8.2), of alcoholism was 8.0 (95% CI = 3.1–20.9), and of congestive heart failure was 8.6 (95% CI = 0.97–76.1). In separated analysis for 104 patients with pneumonitis, 10 (76.9%) of 13 cases with alcoholism died, whereas 36 (39.6%) of 91 cases without alcoholism died, and the difference in the mortality rates between the two groups reached statistical significance (P = 0.025).

By observation, the prognosis was grave in cases with onset of shock occurring within 7 days of illness among alcoholics, with peripheral leukocyte counts of less than 1500 cells/mm^3 (2 cases), and with numerous bacteria (over 50 cells/oil-field) seen under microscopy with no or very few neutrophils in Gram-stained smears of CSF (2 cases).

DISCUSSION

It is clear that admissions to a tertiary-care hospital for pneumococcal infection represent only a small portion of the spectrum of the infection. Siriraj Hospital is the oldest tertiary-care government hospital in Thailand, where 1.2 million patients are treated each year by the outpatient department. Although 2500 hospital beds exist, the waiting list for admission is long for nonemergency cases. Patients presenting with infections or pyrexia, must have moderate to severe symptoms to be selected for admission. Thus, other cases with noninvasive pneumococcal infections, such as acute otitis media, sinusitis, orbital cellulitis, or with culture-negative pneumococcal infection were not included in this study.

Infection in adults constituted nearly half and the elderly 28.3% of total cases. Longevity among the Thai people puts the elderly at risk of development of pneumococcal infection, as found in developed countries. Unexpectedly, the admission rate during January to March was higher than during other periods; but this possibly is related to two festivals in January and February. Conventional New Year and Chinese New Year are the times when laborers work hard to produce goods for sale. Inadequate physical rest may increase susceptibility to infection. Approximately half of the cases manifested as acute pneumonia. Primary septicemia developed in 17 patients who initially had negligible focal symptoms, although the upper and lower respiratory tract often is claimed to be the nidus. Systemic reaction was exhibited more strikingly than local symptoms in these cases and may be related to an invasive virulence factor or factors of the organism rather than to poor host defense. Heavy bacteremia may occur subsequently and result in positive blood cultures.[7] Unfortunately, virulence factors or serotype of these isolates were not studied to confirm the hypothesis. Virulence factors may have been implicated in the cases of leukopenia, serious complications (e.g., adult respiratory distress syndrome or disseminated intravascular coagulation), or in cases in which numerous bacteria with few or no leukocytes were observed in the CSF. This study revealed alcoholism was commonly associated with pneumococcal infection, and it provided an opportunity to study the contribution of alcoholism to therapeutic outcome in some types of infection. Pneumococcal infection was found in 10 HIV-infected patients. Since serologic testing for HIV infection is voluntary, it is possible that other HIV-infected cases with concomitant pneumococcal infection were missed. This finding is the

Table 3. Percentage of Mortality by Age Group, Admission Period, Type of Infection, and Associated Disease among 205 Cases

	Mortality Rate (%)			
	*1–7 day**	*> 7 day**	*Total (%)*	*P-Value*
Total death	28.8	11.7	40.5	
Age group (y)				0.004
< 2	5	5	10	
2–13	10	3	13	
14–60	37	2	39	
> 60	41	22	63	
Admission period				0.322
January–March	30	6	36	
April–June	20	16	36	
July–September	23	7	30	
October–December	40	16	56	
Type of infection				0.743†
Pneumonia	35	11	46	
Acute exacerbation of COPD, infected bronchiectasis, bronchopneumonia	14	7	21	
Meningitis	40	3	43	
Primary septicemia	65	0	65	
Primary peritonitis	12	12	24	
Septic arthritis	0	0	0	
Thoracic empyema	0	0	0	
Association with study diseases				0.838
No (n = 114)	30	8	38	
Yes (n = 91)	34	10	44	
Alcoholism	65	13	78	
Nephrotic syndrome	14	7	21	
Systemic lupus erythematosus	25	0	25	
Leukemia	27	9	36	
Diabetes mellitus	36	19	55	
HIV infection	20	0	20	
Hypertension	22	11	33	
Thalassemia	33	0	33	
Congestive heart failure	67	16	83	
Splenectomy	50	0	50	
Multiple myeloma	0	33	33	
Chronic renal failure	67	–	67	

*Hospitalization day; †primary peritonitis and septic arthritis were excluded from the analysis due to small sample size.

first report in Thailand that confirms the predisposition of HIV infection to pneumococcal infection in Thai patients.

Resistance to antimicrobials, penicillin G in particular, is another emerging problem among recent pneumococcal isolates. Intermediate resistance to penicillin was detected in 17 to 34% of blood isolates and 47 to 73% of sputum isolates during 1994 to 1997. All CSF isolates were susceptible to cefotaxime or ceftriaxone. Until 1995, sputum isolates were assumed to be penicillin-susceptible at this hospital and posed no therapeutic problem, since penicillin G sodium at 300,000 units/kg may be effective with relatively resistant strains. Even meningitis due to PRP (MICs for penicillin, 0.1–0.3 mg/L) may be managed successfully with penicillin G sodium at this dosage, as evidenced by subsequent negative culture in a few cases. Because cefotaxime or ceftriaxone are the two empirical drugs used to treat meningitis at the hospital, both should be effective, since 94.3% of penicillin-resistant or intermediate-resistant pneumococci were reported to be susceptible to ceftriaxone.[8] This study did not correlate mortality rates with the susceptibility of pneumococcal isolates to the empirical antimicrobials, because the susceptibility result was not available in every case and, whenever available, confirmed that most of the empirical antimicrobials were active against PRP. In other studies, the mortality rates of infections due to penicillin-sensitive *S. pneumoniae* and PRP were similar.[9,10] Only one blood isolate in 1997 exhibited MICs for penicillin and cefotaxime at 1.5 and 1.0 mg/L, respectively by E-test. The finding of this isolate of nearly high-level PRP is a real threat to patients in Thailand. The role of microbiology laboratories in the detection of high-level penicillin-resistant pneumococci isolated from sterile sites is evident. Since PRP is frequently detected in nasopharyngeal isolates,[11] nasopharyngeal swab and culture is a sensitive and practical method for national surveillance of drug resistance.[12]

The overall mortality rate in the present study was rather high (40.5%) compared to 15 to 21% of bacteremic

patients in developed country.[1,2] When the cumulative mortality rate was broken down according to day of hospitalization, it was 25.2% at day 5 and 28.8% at day 7. After day 7, another 12.2% of patients succumbed. The authors chose to divide mortality rate by day 7 because the mortality rate reached a steady state after that day. The mortality rates of 25.2% or 28.8% do not differ significantly from previous reports. It is well known that proper antimicrobial treatment is rarely effective in altering the outcome or death that occurred within 1 to 7 days of hospitalization. However, the late mortality of 12.2 to 15.5% certainly contributes to the overall high mortality. Diabetes mellitus and multiple myeloma were found, in addition to advanced age and alcoholism, to contribute to the late mortality. The so-called referral bias also contributed, because more severe cases were referred to Siriraj Hospital and thus included in the analysis. Mortality was high during the winter season (October-December) when influenza is usually epidemic and known to contribute to pneumococcal disease predisposition and consequent mortality. This study strongly indicates that alcoholism was a major risk factor that increased the likelihood of death in pneumonia by twofold. In Thailand, alcoholics usually have a poor nutritional state that weakens immunity. Old age is another significant factor that increases risk of death. Due to the small sample size (n = 6), congestive heart failure was statistically insignificant as a prognostic factor, but the upper limit of the 95% confidence interval of its odds ratio was high (95% CI = 0.97-76.1).

Antimicrobials are generally regarded as ineffective in saving lives of those with rapidly progressive infection. Pneumococcal vaccination is an intervention that would reduce the incidence of invasive pneumococcal infection and prevent the early deaths. Although serotyping of pneumococci was not performed in this study, other studies in Thailand have revealed that approximately 87 to 90% of the isolates were included in the polysaccharide vaccine.[13,14] Efficacy of the vaccine exceeds 57% for prophylaxis of infection caused by serotypes represented in the vaccine.[15,16] Whether pneumococcal vaccination among the Thai patients with high risk of pneumococcal infection and poor prognosis is cost-effective in the era of economic crisis remains to be seen. Simultaneous immunization with influenza and pneumococcal vaccines also is a challenging strategy for Thailand to overcome the high mortality rate of pneumococcal infection in the elderly during the winter season.

In conclusion, severe pneumococcal infection still prevails with overall high mortality in developing countries. Empirical therapy with appropriate antimicrobials is unable to reduce the early mortality. Continuous laboratory monitoring of the susceptibility to penicillin and cephalosporins is needed to determine the situation of antimicrobial resistance and to provide a basis for guidelines for antimicrobial therapy. Preventive measures, such as reducing alcohol use, avoiding polluted or overcrowded environments,[17] and foremost, undergoing pneumococcal vaccination, should be seriously considered by those with high risk and poor prognosis, to avoid invasive pneumococcal infection.

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