Pediatric invasive pneumococcal disease in a teaching hospital in Bangkok

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Background: Increased problems with drug-resistant Streptococcus pneumoniae (SP) and the dearth of epidemiologic and clinical information on invasive pneumococcal disease in children in Asia formed the basis for this study.

Methods: A periodic retrospective review of the records of 0–15-year-old patients was conducted at a teaching hospital in Bangkok, during 1971–2000.

Results: Infections with penicillin-non-susceptible SP (PNSSP) strains rapidly increased after they first appeared in 1988, and they accounted for 71% (29/41) of the total cases during 1996–2000. Of 137 patients, 74% were <60 months old, and 66% had an underlying condition. Infections included: bacteremia without focus 51; pneumonia 38; meningitis 32; peritonitis 13; and bone/joint infection 2. Two patients had two foci of infection. Eight of 10 episodes in patients with AIDS were bacteremic pneumonia. Median ages (range) in months for patients with and without an underlying condition were 24 (1–174) and 10 (0–160), and for the patients without an underlying condition they were: pneumonia 23 (4–156); bacteremia without focus 12 (0–160); and meningitis 7 (2–156). Case-fatality rates were 18% and 2% for patients with and without an underlying condition. The study also examined factors associated with PNSSP infection and death. During 1991–2000, 74% (43/58) of the total cases occurred from November to April, which are dry months.

Conclusions: This study population contained a high proportion with both an underlying condition and infection with PNSSP, and a moderately low proportion with bacteremia without focus. The disease was two to three times more common in dry months than in rainy months.

INTRODUCTION

The high prevalence of penicillin-resistant Streptococcus pneumoniae (SP) in Asia, as recently reported in the Asian Network for Surveillance of Resistant Pathogens Study, is alarming. Although there is an abundance of information from other parts of the world, there are only a few studies describing the epidemiology and clinical features of invasive pneumococcal disease in children in Asia. This information is important for better understanding of this serious childhood disease, for prevention of inadequate treatment, and for planning of preventive measures.

This study assessed epidemiologic and clinical data of Bangkok children who had invasive SP infections during the past three decades and who were cared for at a teaching hospital. The study also examined factors associated with infection by penicillin-non-susceptible SP (PNSSP) or with death. Since the characteristics of the disease seemed to be changing, we therefore evaluated any changes during the 30-year period.

METHODS

Patients

This retrospective study was performed at Ramathibodi Hospital, a teaching hospital in Bangkok which provides both primary and tertiary care. The study included all 0–15-year-old children from whom SP strains were isolated from a normally sterile body site between January 1971 and December 2000. There was no substantial change in criteria for obtaining clinical specimens for culture from pediatric patients at this hospital during the study period, but in the later years of the study, the hospital was providing care for an increasing proportion of children who were immunocompromised.

Data collection

Patients were identified from microbiological records. Throughout the 30-year period, data were collected periodically by medical record and microbiological record review.

Bacteriology

SP organisms were identified according to standard laboratory procedures. Before 1998, resistance to
An infection was considered invasive if SP isolates were recovered from normally sterile body specimens such as blood, pleural fluid, cerebrospinal fluid (CSF), ascites, bone tissue, or joint fluid. The invasive infections were then grouped according to their localization and predominant clinical features (i.e., bacteremia without focus, pneumonia, meningitis, primary peritonitis, and bone or joint infections). Death within 1 week of a positive culture result was regarded as being related to that infection.

Meteorological Information

The meteorological data for Bangkok during 1991–2000 were obtained from the Climatology Section, Meteorological Department, Ministry of Transport and Communications, Bangkok.

Analysis

Stata statistical software was used for all calculations. The chi-square test or Fisher’s exact test (for expected cell frequencies of <5) was used for univariate examination of categorical data. Continuous variables that were not normal distributions were described using median and range, and were analyzed with the Mann–Whitney test for comparing two groups, or with the Kruskal–Wallis test for comparing >2 groups. A multiple logistic regression model was used to estimate the independent effects of the study variables on the risk of PNSSP infection or death. A significant difference between the compared groups was assumed if P<0.05.

RESULTS

In total, 138 episodes of invasive SP infection in 137 children were treated at this hospital during 1971–2000. For the one patient who had two episodes of SP infection, only the first episode was included. Forty patients gave positive cultures from more than one site. Positive blood cultures were obtained from 118 patients (86%). Other positive clinical specimens were: CSF 34, ascites 11, pleural fluid 11, bone tissue 1, and joint fluid 1. None of the patients had received a pneumococcal vaccine.

One AIDS patient had two attacks of invasive pneumococcal infection, pneumonia with pleural empyema at the age of 15 months, and bacteremia without focus at the age of 3 years. Three non-AIDS patients were referred to this hospital because of recurrent SP meningitis. Anatomic defects of the skull were detected as the responsible factors in each of these three cases.

Epidemiologic changes

Table 1 shows epidemiologic changes in 5-year periods. The number of cases was at its lowest during 1986–90, and the increased numbers of total cases in each of the two following periods were comparable to the numbers of cases infected with PNSSP for each of those respective periods. The first case of PNSSP infection appeared in August 1988, with the prevalence of PNSSP infections increasing dramatically from 9% (1/11) during 1986–90 to 71% (29/41) during 1996–2000. The percentage of patients who were <60 months old ranged between 68% and 88% for all periods, with the exception of 45% during 1986–90. The first case with acquired immunodeficiency syndrome (AIDS) as an underlying condition occurred in April 1994, and 22% (9/41) of all cases during 1996–2000 had AIDS as an underlying illness. The mortality did not significantly change with time by 5-year periods (P=0.684).

Seasonal variation

The disease as a whole had a yearly nadir from June to August, the middle of the rainy season. During 1991–2000, the disease had a high frequency from November to April, which is the dry season (average monthly rainfall 2–75 mm, and relative humidity 69–72%); the monthly case totals of 6–9 during that half of the year accounted for 74% (43/58) of the total cases. The frequency was low during the rainy season from May to October (average monthly rainfall 161–374 mm, and relative humidity 73–80%), with monthly case totals of two or three accounting for only 26% (15/58) of the total cases.

Underlying conditions, and types of infection

Sixty-six per cent (90/137) of the patients had an underlying condition. These were: nephrotic syndrome 23, congenital heart disease 10, malignancy 10, AIDS 10, liver disease 8, thalassemia 10 (7 had splenectomy), systemic lupus erythematosus 3, malnutrition 6, and others 11 (agammaglobulinemia 1, pure red cell aplasia...
Of the patients with an underlying condition, 21% (19/90), 43% (39/90) and 69% (62/90) were, respectively, <12, <24 and <60 months old (Figure 1B). The median ages were as follows: pneumonia, 16 months (range: 3–122 months); bacteremia without focus, 21 months (range: 0–160 months); meningitis, 24 months (range: 2–174 months); and peritonitis, 96 months (range: 24–168 months). There was no significant difference in age distribution between patients with pneumonia, bacteremia without focus, or meningitis (P=0.278), but patients with peritonitis were significantly older than those with other types of infection (P<0.001).

Infection with penicillin-non-susceptible S. pneumoniae

Thirty-seven patients were infected with PNSSP strains, with 97% (36/37) of those infections occurring during the last decade of the study. Of 37 PNSSP isolates, a penicillin MIC was available for review in 31. Forty-two per cent (13/31) were intermediately resistant and 58% (18/31) were completely resistant to penicillin. Susceptibility data for ceftriaxone were available for review for only 11 PNSSP isolates, of which three had an MIC ≥1.0 mg/L. The clinical characteristics of the patients in relation to PNSSP infection are presented in Table 2.

A univariate analysis (Table 2) suggested that there was no statistically significant association between infection with PNSSP and age <24 months, sex, or presence of an underlying condition. There was a statistically significant association between AIDS and PNSSP infection when all cases were included in the analysis (9/10 versus 28/127, P=0.000), but an association was not detected when only cases from the AIDS era (i.e. 1996–2000) were included (8/9 versus 21/32, P=0.240). The prevalence of PNSSP infection was higher in patients with pneumococcal pneumonia or meningitis than in patients who had other types of pneumococcal disease (25/72 versus 12/65, P=0.032). When the potentially associated factors were entered into a logistic regression model, variables which had a statistically significant association with PNSSP infection included infection during 1991–2000 (odds ratio (OR) 120.6; 95%
CI 14.9–975.0) and pneumonia or meningitis (OR 3.2; 95% CI 1.0–9.7), but not AIDS (OR 5.3; 95% CI 0.6–47.4).

TREATMENT

All 137 patients were hospitalized. During the first two decades of this study (1971–90), most of the medication administered to patients with invasive SP infection comprised penicillin G or ampicillin. However, after 1990, when PNSSP infections began to appear, the treatment of choice became cefotaxime or ceftriaxone, although high doses of penicillin G or ampicillin, chloramphenicol or cefuroxime were used in some patients. Treatment with vancomycin was begun in this group of patients in December 1995, and has been used for only six patients. Two patients died on admission before antimicrobial treatment could be started.

Mortality

Tables 1 and 2 show patient information in relation to death. The overall case-fatality rate was 12% (17/137), with a higher rate for patients with an underlying condition (18%, 16/90) than for patients without an underlying condition (2%, 1/47). Ninety-four per cent (16/17) of the patients who died had an underlying condition. All eight of the patients who died during the first half of the study period (1971–85) had an underlying condition and were infected with penicillin-susceptible SP. Eighty-nine per cent (8/9) of the patients who died during 1991–2000 had an underlying condition, and 75% (6/8) of these were infected with PNSSP. The only patient who died without an underlying condition was a 3-month-old infant who was found asphyxiated at home and was comatose on admission. No localized infection was detected, and her blood culture, taken on admission, grew SP.

A univariate analysis (Table 2) suggested that death was associated significantly with both the presence of an underlying condition (P = 0.007) and bacteremia without focus (P = 0.002). There was no significant association between death and either age <24 months, peripheral white blood cell counts of ≤ 10,000 cells/mm³, or PNSSP infection. When the potential parameters were entered into a logistic regression model, it was found that the factors which were independently associated with death included: presence of an underlying condition (OR 8.6, 95% CI 1.1–68.1), and bacteremia without focus (OR 4.4, 95% CI 1.4–13.6).

DISCUSSION

This study demonstrates the impact of two recently emerging infectious problems, PNSSP and AIDS, on the epidemiology of invasive pneumococcal disease in children in Bangkok. The prevalence of PNSSP infection in our study reached its height during 1996–2000 (71%), and is similar to figures from Taiwan (74%,③ 80%④ during those same years, and from Korea (77%)② during 1995–96. The prevalence is much higher than that found in two US studies (37%,⑩ 42%,⑪) during 1998–99 and in a South African study (39%)⑫ during 1996–97. The introduction and spread of international epidemic clones, such as the serotype 23F Spanish clone, into Asian
Table 2. Characteristics of 137 children with invasive pneumococcal infections, and association with penicillin-non-susceptible Streptococcus pneumoniae (PNSSP) infection, or with death

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total no. (n= 137)</th>
<th>PNSSP infection (n=37)</th>
<th>No. (%)</th>
<th>P-value</th>
<th>Death (n=17)</th>
<th>No. (%)</th>
<th>P-value</th>
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<td><strong>Year period</strong></td>
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<tr>
<td>1971–1990</td>
<td>79</td>
<td>1 (1)</td>
<td>0.000</td>
<td>8 (10)</td>
<td>0.344</td>
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<td>1991–2000</td>
<td>58</td>
<td>36 (62)</td>
<td>0.078</td>
<td>9 (15)</td>
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<td><strong>Age</strong></td>
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<tr>
<td>&lt;24 months</td>
<td>71</td>
<td>16 (22)</td>
<td>0.221</td>
<td>10 (14)</td>
<td>0.537</td>
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<td>≥24 months</td>
<td>66</td>
<td>21 (32)</td>
<td>0.059</td>
<td>7 (11)</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>72</td>
<td>21 (29)</td>
<td>0.549</td>
<td>7 (10)</td>
<td>0.315</td>
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<tr>
<td>Female</td>
<td>65</td>
<td>16 (25)</td>
<td></td>
<td>10 (15)</td>
<td></td>
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<td><strong>Host status</strong></td>
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<tr>
<td>Without an underlying condition</td>
<td>47</td>
<td>10 (21)</td>
<td>0.275</td>
<td>1 (2)</td>
<td>0.007</td>
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<td>With an underlying condition</td>
<td>90</td>
<td>27 (30)</td>
<td></td>
<td>16 (18)</td>
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<td>No</td>
<td>127</td>
<td>28 (22)</td>
<td>0.000</td>
<td>14 (11)</td>
<td>0.110</td>
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<tr>
<td>Yes</td>
<td>10</td>
<td>9 (90)</td>
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<td>3 (30)</td>
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<td><strong>Types of infection</strong></td>
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<tr>
<td>Bacteremia without focus</td>
<td>51</td>
<td>9 (18)</td>
<td>0.169</td>
<td>12 (23)</td>
<td>0.060b</td>
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<td>Pneumonia</td>
<td>38</td>
<td>14 (38)</td>
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<td>3 (8)</td>
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<td>Meningitis</td>
<td>35</td>
<td>11 (31)</td>
<td></td>
<td>2 (6)</td>
<td></td>
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<td>Peritonitis, primary</td>
<td>13</td>
<td>2 (15)</td>
<td></td>
<td>0 (0)</td>
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<tr>
<td>Bone/joint infection</td>
<td>2</td>
<td>1 (50)</td>
<td></td>
<td>0 (0)</td>
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<td><strong>Peripheral white blood cell count</strong></td>
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<td>(cells/mm³)</td>
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<tr>
<td>≤10,000</td>
<td>33</td>
<td>10 (30)</td>
<td>0.625</td>
<td>7 (21)</td>
<td>0.078</td>
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<tr>
<td>&gt;10,000</td>
<td>104</td>
<td>27 (26)</td>
<td></td>
<td>10 (10)</td>
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<tr>
<td><strong>PNSSP infection</strong></td>
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<tr>
<td>Yes</td>
<td>37</td>
<td>NAc</td>
<td>–</td>
<td>6 (16)</td>
<td>0.397</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>100</td>
<td>NAc</td>
<td></td>
<td>11 (11)</td>
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</table>

a Two patients had two sites of infection each; one had meningitis plus pneumonia, the other had meningitis plus peritonitis.
b For comparison of death rates in bacteremia without focus (12/51) and other types (5/86), P=0.002.
c NA=not applicable.

countries, together with selective pressure resulting from antibiotic use, are the likely responsible factors.

Patients with an underlying condition accounted for 66% in our study, which is similar to what was found in a Korean study (64%) and in two South African studies (64%, 73%), and much higher than what was found in studies from the USA (4%, 5%), and Canada (23%). Lower proportions of patients with an underlying condition in the USA and Canadian reports probably result from more effective treatment of underlying conditions and the use of pneumococcal vaccine in patients susceptible to invasive SP infection in the reported populations.

Our findings for the age distribution of patients without an underlying condition are very similar to those of the studies in the USA, and in two South African studies, and in Israel, in that all studies reported that 61–74% were <24 months old, and only 10–13% were >5 years old. These findings agree with reports from North America, and Israel, that the children and Africa and South Africa that the patient with meningitis tend to be younger than those with either bacteremia without focus or pneumonia. The reported median ages in children without an underlying condition were as follows: meningitis 6.5 months, 6.7 months and 12 months, bacteremia without focus 15 months and 19 months, and pneumonia 21 months, 22 months and 12 months. In our study, there was no difference in age distribution by type of infection in patients with an underlying condition.

In our study, meningitis was the most common type of infection in patients without an underlying condition, while bacteremia without focus accounted for the highest proportion in patients with an underlying condition. Studies from North America, and Finland found that the most common clinical entity of invasive SP infection was bacteremia without focus, which occurred in 56–70% of patients. This clinical entity is almost absent in studies from Africa, Uruguay and Argentina, and Chile. Thirty-seven per cent of the patients in our study had bacteremia without focus, which is comparable with the findings of studies from Taiwan, and Israel, and Korea (45%). A difference in blood culture practice is a possible explanation for these differences.

Pneumococcal peritonitis occurred in 9% (13/137) of our patients, which is comparable to the 17% (18/106) found in a Korean study, and is much higher than the 0–1.4% found in the other studies from Taiwan, Israel, and Africa.
infected patients. Although AIDS was not detected as an infection in HIV-infected children. Madhi et al.\textsuperscript{25} also reported that the HIV-infected patients had a higher incidence of bacteremic lower respiratory tract infection, which is in agreement with two studies that had bacteremic pneumonia or pneumonia with pleural empyema. An association between HIV infection and PNSSP has been previously reported.\textsuperscript{12,14,25} It was also found in our study that PNSSP-infected patients formed a greater proportion of the patients with either pneumonia or meningitis (35%) than of those with either bacteremia without focus or peritonitis (17%), which is in agreement with the findings of some studies.\textsuperscript{12,26} However, our finding does not agree with a study in Uruguay and Argentina,\textsuperscript{21} in which children with meningitis were less likely to have drug-resistant SP than those with other forms of invasive infection. Furthermore, a study in the USA\textsuperscript{10} found no difference in the rates of PNSSP among children with bacteremia without focus, pneumonia, or meningitis. Age in our study was not found to be an independent risk factor for PNSSP infection, which is consistent with the findings of some studies,\textsuperscript{10,21} but not with others.\textsuperscript{2,16,27} Unadjusted effects of some confounding factors, such as previous antimicrobial treatment,\textsuperscript{10} may have been responsible for this discrepancy. The presence of SP isolates which were resistant to cefotaxime or ceftriaxone is an alarming aspect of our study.

There was no significant change in the overall case-fatality rate over the three decades covered by this study. Our findings are consistent with previous reports that there is no increase in mortality for patients infected with PNSSP.\textsuperscript{2,10,21} The availability of alternative effective antimicrobial drugs (cefotaxime or vancomycin) to penicillin is the likely explanation. While bacteremia without focus seems to be a mild disease, and a large proportion of the patients had been treated as outpatients in some developed countries such as Canada,\textsuperscript{21} it was unexpectedly found in our study that this type of disease was independently associated with increased risk of death (OR 4.4). Selective blood culture practices in more seriously ill febrile patients who are without focus of infection is a likely explanation for this finding. All 17 patients who died from bacteremia without focus of infection in our study had an underlying condition.

It was noticed in our study that the invasive pneumococcal disease in Bangkok peaked in the dry months (November to April) and declined strikingly in the rainy months (May to October), which is very similar to the findings of studies in Taipei, Taiwan\textsuperscript{4} and Houston, Texas,\textsuperscript{20} both of which have relatively warm climates. The Taipei report proposed an association of invasive SP infection with the cooler season,\textsuperscript{4} while the Houston report\textsuperscript{28} suggested an association with air pollution or viral infection in winter. Studies from the temperate and cooler parts of the world (Michigan, USA,\textsuperscript{15} Finland,\textsuperscript{18} and Winnipeg, Canada\textsuperscript{29}) also showed that invasive pneumococcal infection had its nadir during June to August, which is their summer. The study by Bell et al.\textsuperscript{20} in Malawi in southern Africa also showed that people were more susceptible to invasive SP infection in the dry season than in the rainy season. All of the above reports found peak months of invasive SP diseases in the dry season.\textsuperscript{4,15,18,28–30} Dowell\textsuperscript{31} has proposed that dry weather causes dryness of nasal mucus, which probably enhances the invasiveness of SP.

The findings for children in Bangkok agree with those of other studies,\textsuperscript{10,15–17} in that those most susceptible to invasive pneumococcal infection were infants <24 months of age and individuals with host defense abnormalities. Children with pneumococcal meningitis were younger than children with bacteremia without focus or pneumonia. High proportions of our patients had both underlying conditions and infection with PNSSP. The proportion of patients with bacteremia without focus in this study was moderately low. It was also found that children in Bangkok were more susceptible to invasive SP infection in the dry season. Increasing problems with PNSSP infection and AIDS are accompanied by increasing numbers of cases of invasive SP infection. There has been no information on serotypes of invasive SP strains in Thailand, and this is needed for future pneumococcal immunization programs.

A national study conducted by the National Institute of Health, Department of Medical Sciences, Ministry of Public Health has been recently started.

**ACKNOWLEDGEMENT**

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REFERENCES