INVASIVE PNEUMOCOCCAL INFECTION IN CHILDREN

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Abstract. *Streptococcus pneumoniae* infections can involve multiple organs and cause high mortality and morbidity. In this retrospective study, we reviewed patients with invasive pneumococcal infection in the pediatric department of a teaching hospital in Taipei. From 1984 to 1998, 81 children with invasive pneumococcal infection were hospitalized. Twenty-eight patients had meningitis, 27 had pneumonia with pleural effusion, 60 had sepsis, and 4 had arthritis. Thirty-eight patients had more than one site of infection. Most of our patients (81.7%) were below 5 years of age. Pneumococcal infections were more common from October to March. Eight patients had a history of trauma that correlated with the site of infection. Thirteen patients (16.0%) expired and 20 (24.7%) had severe sequelae. Multi-regression analysis found that meningitis and complications were independent variables that affected the outcome. The percentage of penicillin-resistant strains increased beginning in 1990 and accounted for about four-fifths of the infections in the final 2 years of the study. Since invasive pneumococcal infections in children may have a poor prognosis and penicillin-resistant strains have become increasingly common, early and adequate antibiotic therapy should be given as soon as possible.

INTRODUCTION

Ninety serotypes of *Streptococcus pneumoniae* have been identified. This pathogen frequently causes pneumonia, sinusitis, and otitis media, as well as more invasive diseases, such as sepsis, meningitis, arthritis, and a variety of other infections. High morbidity and mortality caused by pneumococcal infection in children and adults have been reported (Breiman *et al*, 1994; Duchin *et al*, 1995; Tomasz, 1997). Epidemiologic data on pneumococcal infections in a particular area is important to assist physicians practicing in that locale in prevention and treatment. We retrospectively reviewed our pediatric patients with invasive pneumococcal infection over the past 15 years and report our experience in managing this disease.

MATERIALS AND METHODS

The study was conducted in the Department of Pediatrics in Mackay Memorial Hospital, a teaching hospital in Taipei. Children eligible for inclusion were 18 years of age and younger, had had *S. pneumoniae* isolated from a normally sterile body fluid or had had an invasive infection with a positive finding on a latex particle agglutination test for pneumococcal antigen. Invasive infection was defined as sepsis, meningitis, arthritis, or pneumonia with pleural effusion. All the children were hospitalized between 1984 and 1998.

Clinical information collected included age of the patient, time of disease onset, underlying diseases, duration of fever before admission, hemoglobin, total white blood cell and differential count, erythrocyte sedimentation rate (ESR), complications during hospitalization, penicillin susceptibility of the isolated pathogen, and outcome.

The susceptibility test was performed with a 1 μg oxacillin disk according to the recommendations of the National Committee for Clinical Laboratory Standards (1993). An inhibition zone of less than 19-mm indicated resistance. Minimum inhibitory concentrations (MICs) for *S. pneumoniae* were determined by either the E-test (AB Biodisk, Solna, Sweden) or the microdilution method using cation-adjusted

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Mueller-Hinton broth supplemented with 3% lysed horse blood (Swenson *et al*, 1986).

Outcome variables were analyzed by a chi-square test and multi-regression analysis. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 81 patients were eligible for the study, including one patient with recurrent meningitis who had Mondini dysplasia with cerebrospinal fluid leakage. Twenty-eight patients (34.6%) had meningitis, 27 (33.3%) had pneumonia with pleural effusion, 60 (74.1%) had sepsis, and 4 (4.9%) had arthritis. Thirty-eight patients (46.9%) had sepsis with other sites of infection (23 with meningitis, 14 with pneumonia with pleural effusion, and 1 with arthritis). One patient with meningitis and six with pneumonia were diagnosed as having pneumococcal infection only by a positive latex particle agglutination test, without positive culture results.

The age distribution is shown in Fig 1. The percentage of patients below age 5 was 81.7%, and below age 2 was 39.0%. Pneumococcal infections were more common in the cooler season, *ie* from October to March (70.7%) (Fig 2).

Underlying diseases included a history of trauma (8 patients), cerebral palsy (4), complex congenital heart disease (3), malignancy (2), immunodeficiency (2), and congenital anomalies (2). Of the 8 with recent trauma, 7 had head injury that was followed by meningitis in 5 (17.2% of all meningitis cases) and sepsis in 2, and 1 had hip injury that was followed by arthritis (Table 1). The trauma had all occurred within two weeks before the onset of pneumococcal infection.

The average duration of hospitalization was 20.0 days. Forty patients had been managed

Table 1
Underlying diseases of patients with invasive pneumococcal infections.

Underlying disease	Arthritis	Sepsis[a]	Meningitis	Pneumonia with pleural effusion	Total
Trauma history	1	2	5	0	8
Cerebral palsy	1	1	1	1	4
Complex congenital heart disease	0	1	2	0	3
Congenital anomaly	0	2	0	0	2
Malignancy	0	1	1	0	2
Immunodeficiency or immunosuppressive therapy	0	1	1	0	2

[a]Only patients who had sepsis without other sites of infection identified are included here.

Table 2
Outcome of 81 patients with invasive pneumococcal infections

Outcome	Arthritis	Meningitis	Sepsis[a]	Pneumonia with pleural effusion	Total	%
No sequelae	2	6	18	22	48	59.3
Sequelae	2	14	1	3	20	24.7
Death	0	8	3	2	13	16.0

[a]Only patients who had sepsis without other sites of infection identified are included here.

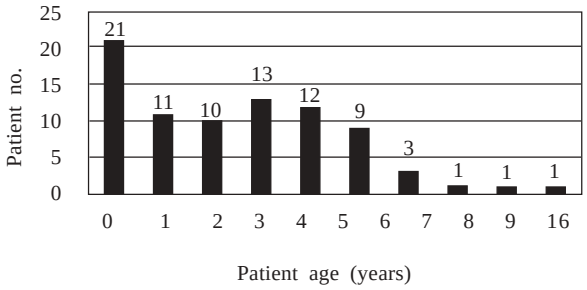

Fig 1–Age distribution of patients with invasive pneumococcal infections.

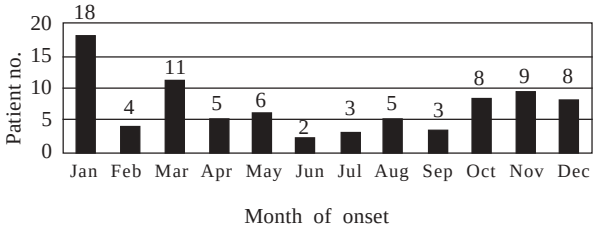

Fig 2–Seasonal variation of invasive pneumococcal infections.

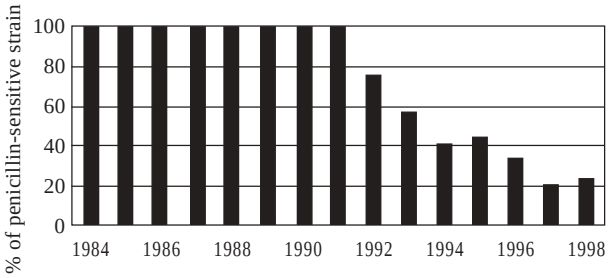

Fig 3–Susceptibility to penicillin of isolated pneumococcal strains.

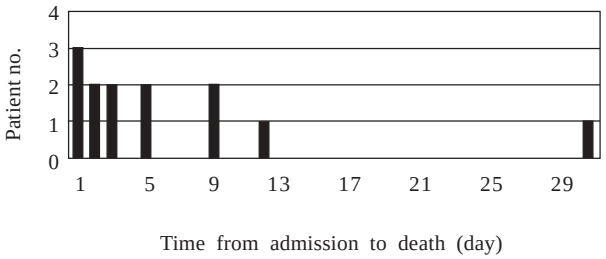

Fig 4-Time from admission to death.

in the intensive care unit, where the average duration of intensive care was 10.7 days. Complications during hospitalization included shock (20 patients), coma (18), ventilator use (17), seizures (16), disseminated intravascular coagulation (15), hepatic impairment (9), renal impairment (7), hypoalbuminemia (5), hearing impairment (4), and respiratory distress syndrome (2).

There were no penicillin-resistant strains isolated before 1992. The percentage of penicillin-resistant strains increased quickly thereafter, however, and approximated four-fifths of the isolates in the final 2 years (Fig 3).

Forty-eight patients fully recovered (59.3%), sequelae were noted in 20 patients (24.7%), and 13 patients died (16.0%). The morbidity and mortality in patients with meningitis were 50.0% and 28.6%, respectively (Table 2). The median duration between admission and death was 2.0 days (Fig 4).

There were no statistical differences among the three different outcomes with regard to age of patient, month of onset, duration of fever before admission, hemoglobin, ESR, or susceptibility of the organism to penicillin. Univariate analysis indicated a significant relationship between outcome and meningitis, complications during hospitalization, white blood cell count, and percentage of band-forms. However, only meningitis and complications during hospitalization were significantly correlated with outcome by multiple-regression analysis.

DISCUSSION

The incidence of pneumococcal infection is high in neonates, infants, and toddlers, low in adolescents and young adults, and then increases again in the elderly (Burman *et al*, 1985). In our study, nearly 80% of the patients were below 5 years of age and 40% were younger than 2. Pneumococci may colonize the respiratory tract and spread via droplet aerosolization. Viral respiratory tract infections may predispose to pneumococcal infections

(Hodges and MacLeod, 1946). Our patients more commonly developed pneumococcal infection from October to March.

According to previous reports, the frequency and severity of pneumococcal infection are increased in patients with sickle cell disease, asplenia, splenosis, deficiencies in humoral (B cell) immunity, acquired immunodeficiency syndrome, malignancy (*eg* leukemia, lymphoma), and complement deficiencies (Aavitsland *et al*, 1994; Weisholtz *et al*, 1983). However, in our series, we had only 2 patients with malignancy and 2 with immunodeficiency, none of the other above risk factors being present. Instead, trauma was common (8 patients). The high incidence of predisposing trauma was especially noticeable in the patients with meningitis (17.2%). In the report of Aisa *et al* (1991) of 27 patients with pneumococcal meningitis, an underlying disease or condition was present in 81.5%, and in 55.5% there was an anatomical defect, either congenital, or acquired in origin. Other reports have also noted the association between brain injury and bacterial meningitis (Jones *et al*, 1973; Roming *et al*, 1973). Levin *et al* (1972) suggested pneumococcal meningitis may be caused by an unseen cerebrospinal fluid leak. Pneumococcal infection should be considered in patients with meningeal signs or suspected sepsis after a recent head injury.

Invasive pneumococcal infection may progress quickly. Nearly half of our patients were sent to the intensive care unit directly from the emergency room or were transferred there from the general ward in the first few days of hospitalization. For patients who died, the median duration from admission to death was only 2 days, indicating rapid deterioration in the face of overwhelming infection. Acute complications, such as shock, coma, seizures, disseminated intravascular coagulopathy, hepatic and renal impairment were common and might contribute to a rapid downhill course.

Pneumococcal infection had high mortality and morbidity in our study, especially in patients with meningitis, of whom 50.0% had sequelae and 28.6% died. The disastrous outcome of these infections has also been reported in a prospective multi-center hospital surveillance of *S. pneumoniae* disease in India (IBIS, 1999). Their total case-fatality rate was 21.3% (meningitis: 34%, pneumonia: 19%, septicemia: 21%).

Rios *et al* (1999) reported on risk factors associated with mortality in children with invasive pneumococcal disease, finding no significant differences in age, gender, underlying disease, or antimicrobial treatment. Variables associated with mortality by univariate analysis were a diagnosis of meningitis; antimicrobial resistance to penicillin, trimethoprim-sulfamethoxazole (TMS), or erythromycin; multidrug resistance; and serotypes. In the logistic regression analysis, serotypes, meningitis, and TMS resistance were significantly associated with mortality. However, Tan *et al* (1998) in reviewing 254 patients with pneumococcal pneumonia, did not find a significant difference in outcome between patients with penicillin-susceptible and those with nonsusceptible isolates of *S. pneumoniae*. In our logistic regression analysis, only meningitis and complications during hospitalization were significant variables predicting outcome. Age, white blood cell count, and susceptibility to penicillin were not significant variables.

Since the first penicillin-resistant *Streptococcus pneumoniae* (PRSP) was reported in Australia in 1967 (Hansman and Bullen, 1967), the frequency has been increasing around the world (Friedland, 1995; Centers for Disease Control and Prevention, 1996; Applelbaum, 1992; Health Canada, 1996; Freidland and McCracken, 1994). Several reports on PRSP in Asia have been published. In Hong Kong, the prevalence was 69.1% in 1999 (Ho *et al*, 1999); 59.3% in Japan in 1995 (Tsunoda and Tanimura, 1997); and 68~77% in Korea in 1995 (Song, 1998). In Taiwan, Huang *et al* (1991) reported the first two cases of penicillin-resistant pneumococcal meningitis in 1991. An extremely high prevalence (71%) of nasopharyngeal carriage of PRSP among children (Chiou *et al*, 1998) and a high incidence of multi-resistant strains of *S. pneumoniae*

among clinical isolates (Hsueh *et al*, 1999a,b) have subsequently been reported. In our hospital, the prevalence of PRSP was less than 10% from 1990 to 1991, but increased dramatically to 45% from 1994 to 1995 (Huang *et al*, 1997). Unfortunately, by the time of this study (1997 and 1998), 80% of our isolates were resistant. The high prevalence of resistance makes choosing an antibiotic for invasive pneumococcal infection difficult. Wide-scale anti-pneumococcal immunization may in fact be the best method of preventing this infection.

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