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Invasive *Streptococcus pneumoniae* infections of children in central Taiwan

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We carried out a retrospective study on childhood invasive pneumococcal infections (IPI) diagnosed from the January 1990 through the April 2000 at a medical center in central Taiwan. Their clinical features, outcome of the patients and the resistance patterns of the isolates were analyzed. A total of 95 clinical isolates from 72 patients younger than 14 years of age were included in this study. Of these 72 patients, 51 had bacteremia, 28 meningitis, 14 bacteremic pneumonia, 12 pleural empyema, eight otitis media, four arthritis, three sinusitis, two periorbital abscesses, one deep neck infection, one psoas muscle abscess, one peritonitis, one urinary tract infection, and one cutaneous infection. Ancillary diagnostic tests, including Gram stain smears and latex agglutination tests, were applied and the sensitivities were 86.2% and 54.3%, respectively. The prevalence rate of penicillin nonsusceptible *Streptococcus pneumoniae* has increased dramatically since 1995 in central Taiwan, with rates of 5.6% and 74.1% before and after 1995, and the overall mortality rate was 20.8% and 53.3% respectively. Ten of 19 children (52.6%) with pneumococcal meningitis who survived had long-term sequelae.

Key words: Invasive pneumococcal infections, penicillin nonsusceptible *Streptococcus pneumoniae*

Streptococcus pneumoniae infection has long been recognized as one of the major causes of morbidity and mortality in children [1]. The spectrum of the disease includes bacteremia, meningitis, pneumonia, otitis media, sinusitis, and suppurative infection of other sterile body sites. Pneumococcus is universally susceptible to penicillin until penicillin nonsusceptible *S. pneumoniae* (PNSSP) was first isolated in 1967 [2]. The prevalence of PNSSP is increasing worldwide and has led to a new challenge for clinical physicians [1]. In Taiwan, the first isolate of PNSSP was reported by Hsio *et al* in 1986 [3]. Huang *et al* reported two patients with PNSSP meningitis in 1991, and it was the first report about PNSSP infection in Taiwan [4]. To our knowledge, the prevalence of PNSSP infection in Taiwan has become one of the highest in the world [1]. An extremely high prevalence (71%) of nasopharyngeal carriage of PNSSP was reported among preschool children in southern Taiwan [5]. Lu *et al* also showed a similar pattern of reduced penicillin susceptibility (65.3%) in invasive pneumococcal infections (IPI) of children in northern Taiwan [1]. Comparable data for central Taiwan have been relatively scanty. We conduct this study to present the clinical features and outcome of pediatric IPI and the resistance patterns of the isolates in central Taiwan.

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Patients and Methods

Children younger than 14 years of age with IPI between January 1990 and April 2000 at Taichung Veterans General Hospital were identified retrospectively. All the patients enrolled in this study had been hospitalized during their illness. IPI was defined as an acute illness caused by *S. pneumoniae*, isolated from either blood or other sterile body sites. The definitions of individual disease entities have been mentioned in detail elsewhere [1]. Because percutaneous sinus aspiration and tympanocentesis were not routinely performed, the patients with sinusitis or otitis media had concurrent pneumococcal bacteremia were regarded to have pneumococcal sinusitis or otitis media. Isolates from sputum, nasopharyngeal swabs and ear discharge were excluded from the study. The patients died within 48 h of admission were defined to have rapidly fatal outcome. The following information was analyzed: age, gender, underlying conditions, source of the isolates, clinical diagnosis, laboratory data, and outcome.

Microbiological study

S. pneumoniae was identified by the reference method shown elsewhere [6]. These isolates were routinely screened for penicillin susceptibility using 1 μg oxacillin disc diffusion method. Isolates with inhibitory zones of less than 20 mm were presumed penicillin nonsusceptible, whereas those with zones of no less than 20 mm were presumed penicillin susceptible [7]. The minimum inhibitory concentration (MIC) to penicillin was measured by the E-test for 28 isolates. The E-test was performed according to the recommendations of the manufacturer using the E-test strips (AB Biodisk, Solna, Sweden) placed on Mueller-Hinton blood agar (BBL, Microbiology System, Cockysville, MD, USA) and incubated under 5% CO_2 at 35 °C for 18 to 24 h. An intersection falling between two MIC markings was interpreted as the next higher value. An isolate with a MIC of penicillin ≤ 0.06 μg/mL was defined as susceptible; of 0.12 to 1 μg/mL, intermediate; and of ≥ 2 μg/mL, highly resistant [8]. Gram stain smears and polysaccharide antigen detection were also performed as ancillary diagnostic tests. Latex agglutination tests for pneumococcal antigens were done by using the commercial kit, Pastorex® Meningitis (Sanofi Diagnostics Pasteur, France), and these tests were applied in 46 specimens, including cerebrospinal fluid (CSF), pleural effusion fluid, synovial fluid, urine, and blood. A positive reaction is determined by the formation of clumps visible to the naked eye [9].

Statistical analysis

Chi-square method was used for analysis. A p value less than 0.01 was considered as statistically significant.

Table 1. Clinical features of 72 patients with IPI

Age (mo), mean/range	32.4 ±33.4/0.03-168
Gender (male : female)	5:4
Underlying condition	15 (20.8%)
ALL	3
IgG deficiency	2
Congenital heart disease	2
Nephrotic syndrome	1
Recurrent meningitis	1
Chickenpox	1
Osteogenesis imperfecta	1
Aplastic anemia	1
Liver cirrhosis	1
Neuroblastoma	1
Cerebral palsy	1
Prematurity	1
Previous URI	51 (70.8%)
White blood cell[a] (/μL)	17682 ±11699
Neutrophil (%)	73.2 ±18.4
C-reactive protein (mg/dL)	17.5 ±12.3
Mortality	15 (20.8%)
Meningitis	9 (32.1%)
Other disease	6 (13.6%)
Long-term sequelae	10 (17.5%)
Meningitis	10 (52.6%)
Epilepsy	5
Mental retardation	4
Hydrocephalus	3
Hearing impairment	2
Visual impairment	1
Cerebral palsy	1
CSH	1
Other disease	0

Abbreviations: URI = upper respiratory infection; ALL = acute lymphoblastic leukemia; CSH = chronic subdural hematoma
[a]2 leukemic patients and 1 aplastic anemia with leukopenia (leukocyte count < 4000/μL) were excluded.

Results

Population

A total of 95 isolates from 72 children were included in this study. *S. pneumoniae* was isolated from a variety of clinical specimens, including blood (51), CSF (27), pleural effusion fluid (11), abscesses (3), urine (1), skin (1) and synovial fluid (1). The isolates obtained from a given patient during a single episode of infection were regarded as the same strain. Of these 72 enrolled children, 51 patients had bacteremia, 28 meningitis, 14 bacteremic pneumonia, 12 pleural empyema, eight otitis media, four arthritis, three sinusitis, two periorbital abscesses, one deep neck infection, one psoas muscle abscess, one peritonitis, one urinary tract infection (UTI), and one cutaneous infection. The clinical features, including the characteristics of the patients, laboratory data, and outcome are shown in Table 1.

Thirty-seven of the 72 patients (51.4%) were 2 years old or younger (Fig. 1). About 70% of patients occurred in the cold season between October and the next March (Fig. 2). Precedent upper respiratory tract infection (URI), including otitis media, within 2 weeks of hospitalization could be traced in 70.8% of our patients. Fifteen (20.8%) patients had documented underlying medical conditions.

A 7-year-old girl with acute lymphoblastic leukemia (ALL) had suffered from fever and paronychia. The viral and bacterial cultures of the pus aspirated from paronychia yielded Herpes simplex virus and *S. pneumoniae*, respectively. Two neonates were included in this study, one having pneumococcal septic shock and the other pneumococcal meningitis. A 14-year-old girl had been suffered from four episodes of bacterial meningitis during a period of 5 years. *S. pneumoniae*

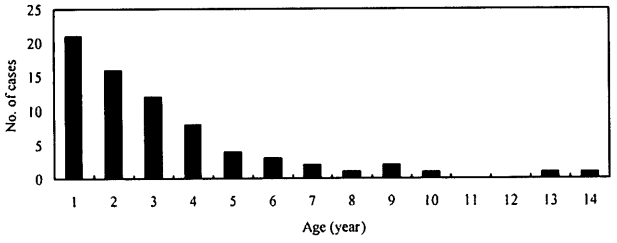

Fig.1. Age distribution of patients with IPI.

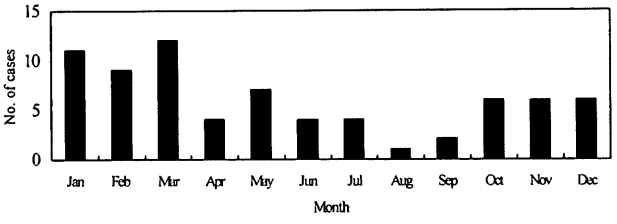

Fig.2. Seasonal distribution of patients with IPI.

was isolated from CSF in two of the episodes, while no organism was isolated from the rest. However, all the four episodes of meningitis responded well to intravenous penicillin therapy. We failed to demonstrate any risk factor for recurrent pneumococcal infection. The girl did not experience any further episode of meningitis and remained well.

Ancillary diagnostic tests

S. pneumoniae could be demonstrated by Gram stain smears in 25 of 29 sterile specimens, which consisted of 20 CSF specimens, eight pleural effusion specimens, and one drainage of a periorbital abscess. Three of the four negative specimens were obtained 6 to 8 days after antimicrobial therapy. The sensitivity of Gram stain smears was 86.2% totally, 90% for CSF specimens, and 75% for pleural effusion fluid specimens. Latex agglutination tests were applied in 46 specimens, including CSF (23), urine (11), pleural effusion fluid (9), serum (2), and synovial fluid (1). The sensitivity was 54.3% totally, 82.6% for CSF, 27.3% for urine, and 33% for pleural effusion fluid. All the tests for serum and synovial fluid revealed negative results. The longest interval between initiating antimicrobial therapy and positive latex results was 20 days for CSF, 18 days for urine, and 10 days for pleural effusion fluid.

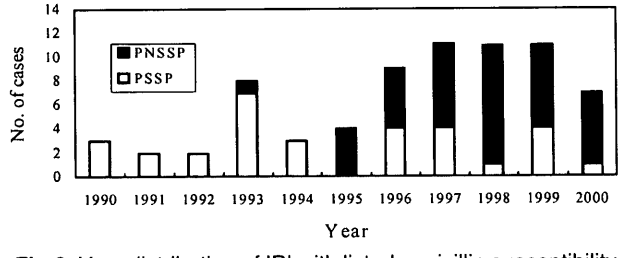

Fig.3. Year distribution of IPI with listed penicillin susceptibility. (PNSSP = penicillin nonsusceptible *S. pneumoniae*; PSSP = penicillin susceptible *S. pneumoniae*)

Antimicrobial susceptibility tests

Forty-one strains (56.9%) showed reduced susceptibility to penicillin with screening by the oxacillin disc diffusion method. All these PNSSP strains were isolated after 1994 with one exception, which was isolated in 1993 (Fig. 3). The first isolate of PNSSP was obtained from a leukemic patient suffering from chicken pox complicated with subsequent septic shock, fulminant hepatitis, and disseminated intravascular coagulation, and the MIC value was 2 μg/mL. The prevalence of PNSSP increased dramatically after 1994, with rates of 100% (4/4), 55.6% (5/9), 75% (8/12), 90.9% (10/11), 63.6% (7/11), and 85.7% (6/7) for the years 1995, 1996, 1997, 1998, 1999, and 2000, respectively. The average prevalence rate of PNSSP was 74.1% after 1995. The MIC data were available for 28 patients with PNSSP infection and 17.8% of them were defined as being penicillin highly-resistant (MIC ≥ 2 μg/mL).

Clinical outcome

The overall mortality rate was 20.8%, and eight (53.3%) of them followed rapidly fatal outcome. All the patients with rapidly fatal outcome were associated with septic shock and 62.5% of them presented with leukopenia (leukocyte count < 4000/mm^3). All the patients with septic shock, with or without meningitis, died within 10 days of admission. The fatality rates of meningitic and nonmeningitic pneumococcal infection were 32.1% and 13.6%, respectively. A male newborn baby with pneumococcal septic shock died on the first day of his life and another 12-day-old female baby with pneumococcal meningitis succumbed to the complications of hospitalization on the eight-sixth day after admission. Eight of 12 patients (75%) with pleural empyema underwent decortication and drainage by thoracotomy or thoracoscopy. Pneumococcal bacteremia was found incidentally in four patients with only mild URI symptoms. They did not receive antimicrobial therapy initially and remained afebrile without new focal infection during follow-up. The repeated blood cultures were all sterile. Long-term sequelae occurred in 10 (52.6%) of the patients who survived from pneumococcal meningitis. Eleven of 42 patients with PNSSP infections and four of 30 patients with penicillin-susceptible pneumococcal infections died in

the present study. The mortality rates showed no significant difference between the two groups (p = 0.19).

Discussion

S. pneumoniae is a common inhabitant of the upper respiratory tract and it must invade the respiratory epithelium to produce disease. In our study, the high prevalence (69.4%) of IPI in cold season may have reflected the pathogenesis because the common viral URI helps pneumococcal invasion. The severity of the disease is related to the virulence and number of organisms causing bacteremia, the integrity of specific host defenses, and the sites of infection.

IPI are relatively common in children younger than 2 years of age, and much less in teenager and young adults, again increasing in adults older than 65 years of age [10]. In the present study, 53.6 % of the patients are younger than 2 years of age. Boys were more predominant than girls with a ratio of 5 to 4 in our study, which is comparable to other studies (1-2:1) [11,12]. The majority of our patients with IPI did not have any identifiable risk factor except a history of previous URI. The spectrum of disease was similar to that of children in Finland and Israel, however, the proportion of cases of bacteremia without an apparent focus was much lower in our patient population [11,12]. The correlation between this finding and the widespread use of antibiotics in Taiwan requires further investigation.

The demonstration of pneumococcal infection is usually difficult due to the frequent autolysis of these bacteria. Some ancillary tests have been used for identifying the etiology of the disease and the Gram stain smear remains the most sensitive diagnostic tool among them. The latex agglutination test is not so sensitive for pneumococcal infections as to other bacteria, especially those with localized disease (e.g., pneumonia and otitis media) [13]. In our study, we demonstrated that the polysaccharide antigen could persist in sterile body fluid for a relatively long period after antimicrobial therapy and could be detected by the latex agglutination tests. This data may help physicians to make a presumptive diagnosis of partially treated pneumococcal infection.

The emergence of pneumococcal resistance to penicillin and other antimicrobial agents has become a worldwide problem, as it limits the options available for the treatment of IPI. PNSSP has been associated with 70% and 65.3% of pediatric IPI occurring in the southern and northern parts of Taiwan in recent years [1,5]. In this study, we found a trend of increasing PNSSP prevalence, with rates of 5.6% and 74.1% before and after 1995, respectively. The latter data approximates the rate (79.7%) reported in Korea, the most PNSSP prevalent country in Asia [14]. An increasing proportion (13-44%) of penicillin highly-resistant *S. pneumoniae* has been reported in Taiwan recently [5,15,16,17-19]. At the same time, multicenter surveillance studies also have shown that *S. pneumoniae* is not susceptible to other antimicrobial agents (Table 2) [1,5,15-24]. It is possible that abuse of antimicrobial agents may contribute to the high resistance rates in Taiwan.

S. pneumoniae is the most common cause of childhood community-acquired pneumonia. Pleural empyema occurs in about 1% to 13.8% of patients and remains the most common complication [25]. Most children can be adequately treated without surgical drainage but some with refractory empyema may require invasive procedures such as thoracotomy and thoracoscopy with adhesiolysis [26]. In our series, about three-fourths of children with empyema underwent surgical drainage procedures. Our hospital is the referral center in central Taiwan and it may account for the relatively high percentage in comparison with other series. The mortality rate of pneumococcal pneumonia varies from 0.5% to 12% in different reports in the literature [12,27] and none of the patients with uncomplicated pneumonia died in this study.

S. pneumoniae represented 19% to 33% of the causative organisms of bacterial meningitis in children in recent surveillance studies in Taiwan [28-30]. It is also associated with the highest mortality and morbidity among bacterial meningitis in children. The mortality rate ranges from 3% to 18% for children in developed countries and is even higher in developing countries and adults [11,12,31]. The mortality rate (32.1%) in this study was comparable to other series (25-33%) in Taiwan [1,30-32]. The reason for the high fatality rate in Taiwan is unknown, but factors such as serotypes, virulence, and genetic diversity between hosts may play roles [30]. Neurological sequelae occurred in 25% to 56% of children with pneumococcal meningitis in the literature and our data (52.6%) remain the highest among them [33]. Recurrent bacterial meningitis is uncommon and most often caused by *S. pneumoniae*. Congenital or acquired anatomical communication, foci of infection, and immunodeficiency should be searched for carefully in these patients [34]. We failed to demonstrate any risk factor in the patient with recurrent meningitis.

S. pneumoniae was responsible for 2.4% of all cases with bacteremia in the study of Taiwanese children by Chiang *et al* in 1991 [35]. It represents the most common

Table 2. Antimicrobial susceptibility data of *S. pneumoniae* from multicenters in Taiwan, 1995-1999

Antimicrobial agent	% of non-susceptible isolates	Reference(s)
Penicillin	56-76	1,5,16,21,19,23
Ampicillin	40	23
Amoxicillin	33	23
AMC[a]	49	23
Cefazolin	9	18[b]
Cefaclor	46	5
Cefotaxime	13-39	5,15,16
Ceftriaxone	12-56	5,15,16,23
Cefixime	43	15
Tetracycline	83-88	5,16,21
Erythromycin	70-86	16,21,19,24
Clarithromycin	59-95	5,15,24
Azithromycin	70-94	16,21,23,24
Clindamycin	54	16
SMX/TMP[c]	65-87	15,21,23
Rifampicin	0-7	5,15,16
Chloramphenicol	22-48	5,16,21
Ciprofloxacin	96	18[b]
Ofloxacin	2	21
Imipenem	14-46	5,15,16,21
Meropenem	39	15
Vancomycin	0	5,15,16,21
Teicoplanin	0	15,16

[a]AMC= amoxicillin/clavulanic acid
[b]The population in reference 18 includes patients from 1989 through 1995.
[c]SMX/TMP= sulfamethoxazole/trimethoprim

cause (70-90%) of occult or unsuspected bacteremia in infants and young children [36]. There are four children who received no antimicrobial therapy in the present study with unsuspected pneumococcal bacteremia. Their second sets of blood cultures were sterile and they experienced no complication. It is contrary to the study of Harper *et al* and they have experienced a better outcome in the patients with initial antimicrobial therapy than those without therapy [37]. One study further demonstrates that parenteral therapy shows an even better clinical outcome than oral therapy [38].

Invasive infection with *S. pneumoniae* in neonates is a rare but serious disease and its incidence has increased in recent years. It has been reported to account for 1% to 8% of neonatal sepsis with a mortality rate of 35% to 54% [39]. Two neonates in our series died of pneumococcal septic shock and meningitis, respectively. The increasing incidence of PNSSP and the high mortality rate of neonatal pneumococcal infection should alert physicians to consider it as one of the possible pathogens of invasive neonatal infections.

Our overall mortality rate (20.3%) of IPI was one of the highest among those reported in the literature (1.3-25%) and the higher proportion of meningitis (38.9%) in our population may have accounted for it [1,11,12,40]. The strongest prognostic factors that have been presented for pediatric IPI include coma, shock, and respiratory distress requiring mechanical ventilation [40]. The outcome of IPI, whether meningitis or not, showed no correlation to penicillin susceptibility in our study and other studies [25,27]. Despite adequate management, little improvement can be achieved in the prognosis of IPI. Generalized immunization with pneumococcal vaccines, either conjugate or unconjugate, may be the most cost-effective strategy for the control of IPI at present. New concepts about its pathogenesis and specific therapeutic options may shed light on advances in the treatment of IPI in the future.

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