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Clinical outcome of invasive pneumococcal infection in children: a 10-year retrospective analysis

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A retrospective study was conducted on 72 children admitted to a medical center in Taiwan due to invasive pneumococcal infections diagnosed between January 1990 and April 2000. Of these patients, 28 had meningitis and 44 had other invasive diseases. Forty-one (56.9%) strains of *Streptococcus pneumoniae* showed reduced susceptibility to penicillin by the oxacillin disc diffusion method. The total mortality was 20.8%, 32.1% for meningitis, and 13.6% for other invasive diseases. Ten (52.6%) of the patients survived from meningitis had long-term sequelae. Statistical analysis showed that initial presentation of coma, shock, respiratory distress requiring mechanical ventilation, and leukopenia (leukocyte <4000 /mm^3) were associated with mortality of invasive pneumococcal infections. Low cerebrospinal fluid leukocyte count (<50 /mm^3) and high cerebrospinal fluid protein level (≥660 mg/dL) were also associated with mortality of meningitis. The presence of underlying diseases and high alanine aminotransferase level (≥100 U/L) were associated with fatal non-meningitic invasive diseases. Patients with shock and high alanine aminotransferase level but without high C-reactive protein level (≥20 mg/dL) were associated with rapidly fatal outcome. The outcome of invasive pneumococcal diseases was not associated with penicillin susceptibility.

Key words: Invasive pneumococcal infection, mortality, rapidly fatal outcome

Streptococcus pneumoniae is a common pathogen of pneumonia, bacteremia, and meningitis in infants and children. It has long been recognized as one of the major causes of morbidity and mortality in children, especially in those with meningitis. The severity of disease is related to the virulence and the number of organisms causing the bacteremia, the integrity of specific host defense, and the sites of infection [1]. Despite prompt diagnosis, effective antimicrobial therapy, and intensive supportive care, little improvement can be achieved in the outcome of children with invasive pneumococcal infections. Several prognostic factors have been reported, including the presence of underlying medical conditions, shock, coma, respiratory failure, leukopenia, thrombocytopenia, and changes in various parameters of cerebrospinal fluid (CSF) [2-7]. Hsueh *et al* [8] reported that the presence of underlying disease, septic complication, bacteremic pneumonia, and serotype 3 were significant prognostic indicators for adults with invasive pneumococcal diseases in Taiwan. To our knowledge, no similar data for children has been reported in Taiwan. We conducted this study to investigate the prognostic indicators of invasive pneumococcal diseases in Taiwan children.

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Patients and Methods

Patient collection

All isolates identified as *S. pneumoniae* from blood or other sterile body sites in the microbiology laboratory of the Taichung Veterans General Hospital between January 1990 and April 2000 were reviewed. Children younger than 14 years were enrolled; all of them were admitted during their course of illness. The definitions for individual invasive pneumococcal infections were as previously reported [9]. Isolates from sputum, nasopharyngeal swabs, and ear discharge were excluded from the study. Patients died within 48 h of hospitalization were referred to as following rapid fatal outcome. We reviewed the medical records and analyzed the demographic data, clinical features, laboratory data, and outcome.

Microbiological study

S. pneumoniae was identified by a reference method adopted from the literature [10]. Isolates of *S. pneumoniae* were routinely screened for penicillin

susceptibility using the 1-μg oxacillin disc diffusion method. Isolates with inhibitory zones less than 20 mm were presumed to be penicillin non-susceptible, whereas those with zones greater than or equal to 20 mm were considered penicillin susceptible [11].

Statistical analysis

Chi-square method and Fisher exact test were used for analysis. A p value less than 0.05 was considered statistically significant.

Results

Population

A total of 95 isolates from 72 children were identified during the study period. *S. pneumoniae* was isolated from a variety of clinical specimens, including blood (51 isolates), CSF (27), pleural effusion (11), abscess (3), urine (1), skin (1), and synovial fluid (1). Isolates obtained from the same patient during a single episode of infection were regarded as the same strain. Of these 72 children, 28 had meningitis, 13 had primary bacteremia, 11 pleural empyema, 10 bacteremic pneumonia, 4 arthritis, 2 periorbital abscesses, one deep neck infection, one psoas muscle abscess, one peritonitis, and one cutaneous infection. The mean age was 32.4 ± 33.4 months, with a range of 1 day to 14 years. Boys outnumbered girls with a male to female ratio of 5:4; however, there is a trend of increasing female proportions in this study population. Fifteen (20.8%) patients had documented underlying medical conditions, including leukemia (3 cases), immunoglobulin G 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), and prematurity (1).

Antimicrobial susceptibility

Forty-one (56.9%) strains showed reduced susceptibility to penicillin as detected by the oxacillin disc diffusion method. Young age (<5 years old), sex, and the presence of underlying diseases were not associated with the susceptibility of pneumococcus to penicillin.

Clinical outcome

Fifteen (20.8%) patients died and 8 (53.3%) of them followed rapidly fatal outcome. The mortalities of meningitic and non-meningitic pneumococcal infections were 32.1% and 13.6%, respectively. All 2 neonates enrolled in this study died; one (age at onset, 1 day) with septic shock died on his first day of life and the other (age of onset, 12 days) with meningitis succumbed to the complications of hospitalization on the 86th postadmission day. Ten (52.6%) among 19 patients survived from meningitis had long-term sequelae, including epilepsy (5 cases), mental retardation (4), hydrocephalus (3), hearing impairment (2), visual impairment (1), cerebral palsy (1), and chronic subdural hematoma (1). Eight (75%) of the 12

Table 1. Risk factors for mortality in pneumococcal meningitis

Category	Fatal n = 9	Non-fatal n = 19 (%)	p
Age <2 years	8	12 (63)	NS
Male	6	11 (58)	NS
Underlying conditions	2	3 (16)	NS
Coma	7	3 (16)	0.001
Mechanical ventilation	9	10 (53)	0.01
Shock	4	0	0.002
Leukopenia (<4000 /mm^3)	5	3 (19)	0.03
High CRP (≥20 mg/dL)	4	10 (n = 18)	NS
Thrombocytopenia (<10^5 /mm^3)	3	1 (5)	0.05
Low CSF leukocyte (<50 /mm^3)	7 (n = 8)	4 (21)	0.001
High CSF protein (≥660 mg/dL)	5 (n = 8)	3 (19)	0.02
Low CSF sugar (≤30 mg/dL)	5 (n = 8)	16 (84)	NS
High ALT (≥100 U/L)	2 (n = 8)	2 (n = 15)	NS
PNSSP	6	7 (38)	NS
Vancomycin[a]	6	7 (38)	NS
Steroid[b]	3	10 (53)	NS

Abbreviations: NS = not significant; CRP = C-reactive protein; CSF = cerebrospinal fluid; ALT = alanine aminotransferase; PNSSP = penicillin non-susceptible *S. pneumoniae*

[a]Vancomycin was included in the initial antimicrobial therapy.

[b]Intravenous steroid was initiated just before or simultaneously with the antimicrobial therapy and continued for 2 to 3 days.

Table 2. Risk factors for mortality in non-meningitic invasive pneumococcal diseases

Category	Fatal n = 6	Non-fatal n = 38 (%)	*p*
Age <2 years	2	15 (41)	NS
Male	4	19 (50)	NS
Underlying conditions	4	6 (16)	0.006
Coma	3	0 (0)	<0.0001
Mechanical ventilation	6	3 (8)	<0.0001
Shock	6	0 (0)	<0.0001
Leukopenia (<4000 /mm^3)	3	4 (n = 35)	0.02
High CRP (≥20 mg/dL)	2	16 (n = 37)	NS
Thrombocytopenia (<10^5 /mm^3)	2	3 (8)	NS
High ALT (≥100 U/L)	2 (n = 3)	1 (n = 15)	0.01
PNSSP	4	24 (63)	NS
Vancomycin[a]	0	2 (5)	NS

Abbreviations: NS = not significant; CRP = C-reactive protein; ALT = alanine aminotransferase; PNSSP = penicillin non-susceptible *S. pneumoniae*

[a]Vancomycin was included in the initial antimicrobial therapy.

patients with pleural empyema underwent decortication and drainage by thoracotomy or thoracoscopy.

Risk factors for mortality and long-term sequelae of these patients were analyzed and listed in Tables 1, 2, 3, and 4. Quantitative variables were dichotomized and the cutoff values for quantitative variables were determined based on results of previous studies [2-7].

Discussion

The increasing prevalence of pneumococcal resistance to penicillin and other antimicrobial agents has become a worldwide problem, as it limits the available treatment options. Young age (<5 years old), previous use of β-lactam antibiotics, presence of underlying diseases, and non-invasive disease have been reported to be associated with penicillin non-susceptible *S. pneumoniae* infections [12,13]. In this study, however, young age (<5 years old), sex, and the underlying condition were not associated with penicillin non-susceptibility. Many studies have come to consensus that the clinical outcome of invasive pneumococcal diseases shows no correlation to antimicrobial susceptibility [2,14,15]. This study demonstrated the same results about penicillin susceptibility.

The mortality of pneumococcal meningitis in children is reported as 3% to 18% in developed countries, and is higher in developing countries and adults [4,16-20]. The mortality found in this study (32.1%) is compatible with those reported in other studies in Taiwan (25%-33%), but is much higher than those of the Western countries [3,9,21-23]. The reasons for the higher mortality in Taiwan are not clear at

Table 3. Risk factors for rapidly fatal outcome in invasive pneumococcal diseases

Category	Rapidly fatal n = 8	Non-rapidly fatal n = 7	*p*
Age <2 years	5	5	NS
Male	4	6	NS
Underlying conditions	5	1	NS
Meningitis	3	6	NS
Coma	5	5	NS
Shock	8	2	0.003
Leukopenia (<4000 /mm^3)	5	3	NS
High CRP (≥20 mg/dL)	1	5	0.02
Thrombocytopenia (<10^5 /mm^3)	4	1	NS
High ALT (≥100 U/L)	4 (n = 5)	0 (n = 6)	0.006
PNSSP	6	4	NS
Vancomycin[a]	2	4	NS

Abbreviations: NS = not significant; CRP = C-reactive protein; ALT = alanine aminotransferase; PNSSP = penicillin non-susceptible *S. pneumoniae*.

[a]Vancomycin was included in the initial antimicrobial therapy.

Table 4. Risk factors for long-term sequelae in pneumococcal meningitis

Category	LTS n = 10	No LTS n = 9	*p*
Age <2 years	9	3	0.01
Male	6	5	NS
Underlying conditions	2	1	NS
Coma	3	2	NS
Mechanical ventilation	4	3	NS
Leukopenia (<4000 /mm^3)	4	0	0.03
High CRP (≥20 mg/dL)	6	5	NS
Thrombocytopenia (<10^5 /mm^3)	1	0	NS
High CSF protein (≥660 mg/dL)	6 (n = 9)	0	NS
Low CSF sugar (≤30 mg/dL)	3	7	NS
High CSF leukocyte (≥1000 /mm^3)	2	2	NS
High ALT (≥100 U/L)	1 (n = 8)	1 (n = 8)	NS
PNSSP	5	2	NS
Vancomycin[a]	4	3	NS
Steroid[b]	8	3	0.04

Abbreviations: LTS = long-term sequelae; NS = not significant; CRP = C-reactive protein; CSF = cerebrospinal fluid; ALT = alanine aminotransferase; PNSSP = penicillin non-susceptible *S. pneumoniae*

[a]Vancomycin was included in the initial antimicrobial therapy.

[b]Intravenous steroid was initiated just before or simultaneously with the antimicrobial therapy and continued for 2-3 days.

present, but serotypes, virulence of pneumococcus, and genetic diversity of hosts may have some roles in it [3]. Some critical prognostic factors reported in several studies include the presence of underlying conditions, coma, shock, respiratory distress requiring mechanical ventilation, leukopenia (leukocyte <4000 /mm^3), thrombocytopenia (platelet count <100 000 /mm^3), low CSF glucose level (<30 mg/dL), high CSF protein level (≥660 mg/dL), and low CSF leukocyte count (<50 / mm^3) [2-7]. Delay in therapy is believed to be associated with poor outcome of pneumococcal meningitis; however, it is difficult to determine the critical time for starting the adequate antimicrobial therapy due to a lack of conclusive presentations and the rapidly progressive nature of the disease. The presence of coma, shock, respiratory distress requiring mechanical ventilation, low CSF leukocyte count, and high CSF protein level were associated with mortality in meningitis. In this study, patients with thrombocytopenia have higher mortality, but it is not statistically significant.

Neurologic sequelae occur in 25% to 56% of children with pneumococcal meningitis, and hearing impairment is the most common as reported in the literature [4,16,18]. Long-term sequelae developed in 52.6% of patients surviving from meningitis in this study. Epilepsy and mental retardation comprise the majority of sequelae (70%), and only 20% of patients had hearing impairment. These patterns are inconsistent with other reports, and the reasons remain unclear. Young age (<2 years), respiratory failure, coma, prolonged seizure (>72 h after admission), low level of CSF glucose, high levels of CSF protein, lactate, leukocyte, and antigen load are suggested to be associated with neurological sequelae in previous studies [2-4,6,16]. Children younger than 2 years who had leukopenia, were receiving ventilatory support and intravenous steroid therapy had higher incidences of long-term sequelae, but it is not statistically significant. The use of steroid has been suggested to provide some protection from neurological sequelae; however, contradicting results exist and the issue remains controversial [2,24,25]. Nonetheless, current recommendations of the American Academy of Pediatrics suggest that dexamethasone be considered for children with pneumococcal meningitis [26].

The prognosis of non-meningitic pneumococcal invasive infection is better than that of meningitis except in patients with specific risk factors. The mortality is reported as 0.5% to 7% in developed countries [18,19,27]. In this study, the mortality is 13.6%, compatible with the 16.7% reported by Huang *et al* [23] and the 10.7% by Lu *et al* [9], and is higher than those of developed countries. The relevant prognostic indicators are reported scantily in the literature. Patients with underlying medical conditions with initial presentation of coma, shock, respiratory distress requiring mechanical ventilation, leukopenia, and high alanine aminotransferase level had significant high mortality in this study.

A significant proportion (53%) of the patients with

invasive pneumococcal infections follow a rapidly fatal outcome. Serotype 3, advanced age, presence of underlying disease, shock, and leukopenia have been reported to correlate with rapidly fatal outcome; however, few of these reports are supported by statistical analysis [8]. In this study, the presence of shock, high alanine aminotransferase levels, and the absence of high C-reactive protein (≥20 mg/dL) were associated with rapidly fatal outcome. This phenomenon may be partially explained by the fact that C-reactive protein has a demonstrated defensive role against invasive infections by *S. pneumoniae* [28].

Pleural empyema occurs in about 1% to 13.8% of patients with pneumococcal pneumonia and remains the most common complication [29]. The appropriate management of childhood empyema is controversial. Most cases can be adequately controlled with conventional therapy; however, some children necessitate surgical drainage procedures to treat refractory empyema. In this study, 8 of 12 children who had empyema underwent surgical drainage procedures. Most of them were referred from other hospitals due to persistent fever and loculated empyema despite adequate antimicrobial therapy. Excellent clinical responses to surgical drainage were observed in these patients.

Invasive pneumococcal infection in neonates is a rare but serious disease, and it accounts for 1% to 8% of neonatal sepsis with a mortality of 35% to 54%. *S. pneumoniae* is more likely to be associated with early-onset neonatal sepsis, and the prognosis is poorer than that of late-onset sepsis [30]. In this study, one neonate with early-onset pneumococcal septic shock died on his first day of life, and the other who had late-onset sepsis (age at onset, 12 days) with meningitis died of complications related to prolonged hospitalization of nearly 3 months. The increasing incidence and high mortality of invasive pneumococcal infection in neonates are alerting physicians to consider it as one of the possible causes when neonatal invasive infections were encountered.

The initial use of vancomycin has been reported as not associated with the outcome of pneumococcal meningitis by multivariate analysis [31], which is compatible with data in this study. Nonetheless, further investigations are necessary to determinate the impact of vancomycin use on the outcome of pneumococcal invasive disease.

In conclusion, prognosis of invasive pneumococcal infection in children is strongly associated with the initial critical presentations. The main shortcomings of this study are its retrospective nature and the lack of appropriate multivariate analysis of every prognostic indicator. This study presented some characteristic features about the outcome of pediatric invasive pneumococcal diseases in Taiwan, but some problems remain unanswered with the current knowledge about pneumococcal disease. Further investigations are essential to disclose the pathogenesis of pneumococcal disease, to lead to new concepts of its management, and finally to improve the outcome of invasive pneumococcal disease. At present, generalized immunization with conjugate pneumococcal vaccines seems to be the most cost-effective strategy in preventing childhood invasive pneumococcal diseases.

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