Invasive pneumococcal disease in Hong Kong children

Iris Mei-Ching CHAN 陳美貞,1* Daniel Kwok-Keung NG 吳國強,1 Ting-Yat MIU 繆定逸,2 Ping LAM 林萍,2 Cindy Wing-Sze TSE 謝詠詩,3 Chung-Hong CHAN 陳仲康,1 POK-Yu CHOW 周博裕,1 Sharon Wan-Wah CHERK 卓薈樺1

1Department of Paediatrics, Kwong Wah Hospital; 2Department of Paediatrics and Adolescent Medicine, Queen Elizabeth Hospital; 3Department of Paediatrics and Adolescent Medicine, Caritas Medical Centre; 4Department of Pathology, Kwong Wah Hospital, Hong Kong

*Author to whom correspondence should be addressed.
Email: cmc037@ha.org.hk

Abstract

Objective: Invasive pneumococcal disease (IPD) carries a significant disease burden worldwide. Since clinical details about IPD in Hong Kong are limited, the aim of our retrospective descriptive case study is to provide additional information on this area about IPD in Hong Kong. Methods: Clinical data were collected from three local district hospitals including Caritas Medical Centre, Kwong Wah Hospital and Queen Elizabeth Hospital during the period of 1995 to 2007. Results: Forty cases of IPD were identified and reviewed, including bacteraemia without focus (20), pneumonia (12), meningitis (7) and endocarditis (1). The median age was 3-year. The epidemiological data, clinical features, complications and long term sequelae of the disease were further analysed. Our data showed that 85% of IPD occurred between September and March. Convulsion was the commonest feature during the illness, occurring in 32.5% of the total cases. Convulsion was associated with a 5-fold increase in risk of severe morbidity and/or mortality. Conclusion: High index of suspicion to diagnose IPD is needed, especially in children under the age of 2 years or those with chronic medical illness because the presenting symptoms could mimic upper respiratory tract infection. Furthermore, they were associated with a significantly higher risk of mortality and morbidity.

Keywords: Bacteremia; Child; Meningitis, pneumococcal; Pneumococcal infections; Pneumonia, pneumococcal

Introduction

Streptococcus pneumoniae is a leading cause of bacterial infection amongst children worldwide, being the most common cause of bacterial pneumonia and an important cause of meningitis and bacteraemia.1,2 Infection caused by S. pneumoniae produces significant morbidity, mortality and long term sequelae in children.2,3 The incidences for invasive pneumococcal diseases (IPD) in Hong Kong were reported to be 18.8 and 15.6 per 100 000 for children aged ≤2 and ≤5 years respectively.4 However, data on the clinical features of IPD in Hong Kong children is limited. To address the foresaid issue, a retrospective review was conducted for children with invasive pneumococcal disease admitted to three public non-teaching hospitals in Hong Kong.

Methods

This retrospective descriptive case review study was conducted at the Departments of Paediatrics in Caritas Medical Centre, Kwong Wah Hospital and Queen Elizabeth Hospital. These 3 hospitals are located in Kowloon, Hong Kong. All clinical records of patients with positive culture of Streptococcus pneumoniae in normally sterile body fluid, i.e. blood, pleural fluid, cerebrospinal fluid, were retrieved. The study periods were slightly different between the three hospitals, Kwong Wah Hospital (KWH) between 1995 and 2007, Queen Elizabeth Hospital (QEH) between 1997 and 2007, and Caritas Medical Centre (CMC) between 2000 and 2006. Their case summaries, clinical notes, blood tests, bacteriological culture...
results and radiological imaging reports were retrieved and reviewed by the authors with entry to a standard form.

Clinical definitions
IPD was defined as the isolation of *S. pneumoniae* in blood, cerebrospinal fluid or other normally sterile sites. Bacteraemia without focus (BWF) was defined as isolation of *S. pneumoniae* from blood without a focus of infection. A child was considered to have pneumococcal meningitis when the clinical course was consistent with meningitis and *S. pneumoniae* was isolated from cerebrospinal fluid. The diagnosis of pneumococcal pneumonia was defined when clinical course and radiographic findings were consistent with pneumonia with isolation of *S. pneumoniae* from blood, pleural fluid or bronchoalveolar lavage. The diagnosis of pneumococcal endocarditis was considered definite when there was a consistent clinical course with suggestive echocardiogram and *S. pneumoniae* was isolated from the blood. Long term sequelae were defined as neurological deficits (e.g. neurosensory hearing loss, blindness, abnormal visual evoked potential, cerebrovascular accident), epilepsy, heart failure and death.

Identification of *Streptococcus pneumoniae*
Colonies of alpha haemolytic streptococcus with colony morphology suspected of *S. pneumoniae* were subcultured onto the blood agar plate with an optochin disc applied and incubated at 35°C in 5% CO₂. Most *S. pneumoniae* would have a >14 mm zone of inhibition. The identification was further confirmed with its bile solubility with 2% sodium deoxycholate on the agar plate after incubation.

For susceptibility testing, E-test strips of penicillin and cefotaxime (AB Biodisk, Solna, Sweden) were used to determine the minimum inhibitory concentration (MIC) of the isolates to penicillin and cefotaxime. E-test MICs were determined following the manufacturer’s recommendations. Test inocula were prepared from pneumococcal colonies grown on horse blood agar that had been incubated for 20 to 24 hours in 5% CO₂. Colonies were suspended in 0.9% saline to obtain a suspension equivalent to a 0.5 McFarland standard of turbidity. From this suspension, E-tests were performed on Mueller-Hinton agar with 5% horse blood (BBL, Becton Dickinson Microbiology Systems, Cockeysville, MD). The plates were incubated at 35°C in 5% CO₂ for 20 to 24 hours. MICs falling between two marks on the E-test strip were rounded up to the next higher twofold dilution, as recommended in the instructions. Results were interpreted according to the published breakpoints of the Clinical and Laboratory Standards Institute (CLSI). The term non-susceptible was used to denote both intermediate and resistant isolates. For penicillin, the criteria were susceptible, ≤0.06 µg/mL; intermediate, 0.12-1µg/mL; resistant, ≥2 µg/mL. For cefotaxime, the criteria were susceptible, ≤1 µg/mL; intermediate, 2 µg/mL; resistant, ≥4 µg/mL.

Data analysis
Statistical analyses were performed using SPSS 11.0 (Mac OS X, SPSS Inc, Chicago, IL) Data were summarized as percentage for categorical variables and median for continuous variables. The associations between mortality and morbidity related to IPD and selected risk factors (age <2-year and seizure) were studied by Fisher Exact test. Odds ratios with 95% confidence intervals were calculated. Two tailed p value of less than 0.05 was considered statistical significant.

Results
Forty cases of IPD were identified in the study period, 21 cases from KWH (52.5%), 14 cases from QEH (35%) and 5 cases from CMC (12.5%). There was a slight female preponderance with a male: female ratio of 1:1.2. The age ranged from 2-month-old to 13-year-old. The median age was 3-year. Twenty-six cases were older than 2-year (65%). Fourteen cases were below or equal to the age of 2-year (35%). Thirty-eight children were Chinese (95%) and 2 of them were South Asian (5%). Thirty-four cases (85%) occurred in cooler weather, i.e. from September to March, (Figure 1) which was similar to Ho et al.’s study.*

Figure 1. Monthly distribution of 40 cases of invasive pneumococcal disease.
Most of the cases presented as pneumonia (n=12, 30%), fever without focus (n=11, 27.5%), febrile convulsion (n=7, 17.5%), upper respiratory tract infection (n=6, 15%) and meningitis (n=4, 10%). Final diagnoses included: 20 (50%) bacteraemia, 12 (30%) pneumonia, 7 (17%) meningitis, and 1 (2.5%) endocarditis (Table 1).

The most common presentation was convulsion (13/40, 32.5%). Only 6 out of these 13 convulsion cases had meningitis. The 7 convulsion patients without meningitis had no long term sequelae. Convulsions occurred significantly more frequent in patients under 2-year (11/13), the odds ratio was 5.6 (95% CI=1.33 to 23.6). Amongst those 13 cases under 2-year, 6 were diagnosed to have meningitis (6/13, 46%), 7 cases had bacteraemia (7/13, 54%). Patients under 2-year and having convulsion (n=11) had a 15-fold increase in risk for long term sequelae or mortality (95% CI=2.1-109.99).

Most patients who suffered from pneumonia recovered fully without any sequelae. Pleural effusion/empyema were identified in 2 out of 12 cases (17%). One of these 2 cases presented with shock, pericardial effusion and disseminated intravascular coagulopathy. Both of them recovered without any long term sequelae.

Pneumococcal meningitis was associated with poor outcome. In the current study, there were seven cases of pneumococcal meningitis. Six of them had convulsion during the illnesses and the remaining one had obvious clinical features of meningitis i.e. neck stiffness, headache and fever. Three out of 7 meningitis patients recovered completely whilst 3 had long term neurological deficits (deafness, blindness, cerebral palsy, epilepsy, abnormal visual evoked potential) and 1 died.

Pneumococcal endocarditis was a rare and unusual complication in IPD that usually occurred in patient with pre-existing heart structural lesion, which carried significant morbidities and mortality. However, our case, a 39-month-old, had normal heart structure and good past health. The endocarditis was complicated by perforation of the anterior mitral valve leaflet resulting in severe mitral regurgitation and heart failure. The patient also suffered a stroke due to the septic embolism to the left middle cerebral artery resulting in right hemiparesis.

Four patients (10%) had complications due to IPD including pleural effusion/empyema, subdural effusion, syndrome of inappropriate ADH secretion (SIADH), central diabetic insipidus, shock, disseminated intravascular coagulopathy, neurological deficits, perforated mitral valve and cerebrovascular event (Table 2).

Twenty-seven children (68.5%) were previously healthy. One or more underlying diseases were identified in 13 (32.5%) children. Seven (17.5%) had an Advisory Committee on Immunization Practices (ACIP) defined high risk medical condition including 1 congenital immunodeficiency (i.e. X-linked agammaglobulinaemia); 3 acquired immunocompromised conditions (i.e. malignancy on chemotherapy, systemic lupus on systemic steroid and nephrotic syndrome on systemic steroid); 3 congenital heart diseases (2 of them were

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Table 1. Distribution of sites of invasive pneumococcal diseases and the respective age groups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
<th>Age group, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;= 2-year</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (30)</td>
<td>3</td>
</tr>
<tr>
<td>Meningitis</td>
<td>7 (17)</td>
<td>5</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>20 (50)</td>
<td>10</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40 (100)</td>
<td>19 (47.5%)</td>
</tr>
</tbody>
</table>

Table 2. Mortality and morbidity of invasive pneumococcal diseases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
<th>Significant morbidity (%)</th>
<th>Mortality (%)</th>
<th>Full recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>12 (30)</td>
<td>0</td>
<td>0</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>7 (17)</td>
<td>3 (42.9)</td>
<td>1 (14.3)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>20 (50)</td>
<td>0</td>
<td>1 (5)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (2.5)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40 (100)</td>
<td>4 (10)</td>
<td>2 (5)</td>
<td>34 (85)</td>
</tr>
</tbody>
</table>
associated with syndromal disorder and other co-

morbidities). Two cases had other chronic medical
conditions not defined as conferring a high risk for
pneumococcal infection including systemic lupus
erythematous not on systemic steroid, congenital
CMV infection with cerebral palsy and epilepsy. Four
cases were born preterm. For these 13 children with
pre-existing diseases, 7 had bacteraemia, 5 had
pneumonia and 1 had meningitis.

There were 2 deaths reported in the current case
series. One died of meningitis and the other died of
septicaemia. The mortality rate was 5% in the current
IPD series. Both of them were under the age of 2
years, giving a mortality rate of 14.3% in patient
under 2 years, compared to no mortality in older
patients. One child did not have any risk factor
whereas the other had velo-cardio-facial syndrome
and repaired congenital heart disease. Both patients
succumbed within 24 hours after admission.

Blood culture was positive for *S. pneumoniae* in
33 cases (82.5%). Amongst 7 cases of meningitis, 6
cases had positive culture in both blood and CSF
culture; whereas 1 case was positive only in CSF
culture. Around 58% of *S. pneumoniae* isolates were
susceptible to penicillin; 42% were penicillin non-
susceptible strains (PNSS). For erythromycin, 16%
(4 out of 25) were susceptible and 84% were non-
susceptible. Forty-one percent were trimethoprim-
sulfamethoxazole susceptible. The high incidence of
macrolide and trimethoprim-sulfamethoxazole
resistance among clinical isolates of *S. pneumoniae*
was similar to that reported from Taiwan and Hong
Kong. All strains isolated in the current study were
sensitive to cefotaxime and vancomycin.

Discussion

IPD is predominantly a disease of young children
worldwide, affecting mainly children younger than 5
years of age. Similar to other reports, our report
confirmed that children in Hong Kong younger than
2 years were more likely to suffer from any morbidity
(e.g. heart failure, neurological deficits) or mortality
with the odds ratio being 14 (95% CI=1.42-135.5).

The current study showed that convulsion is the
commonest presenting feature of IPD, accounting for
32.5% of the total cases. Patients under 2-year-old
who presented with convulsion had a 15-fold increase
in risk for long term sequelae or mortality (p=0.01,
95% CI=2.1-109.99). The other novel finding was that
15% of the IPD cases in the current series presented
with symptoms of upper respiratory tract infection.
This highlights the need for a high index of suspicion
for diagnosis of IPD especially in children below the
age of 2 years or those with chronic medical illness
as they are more likely to suffer from mortality and
morbidity as a result of IPD.

Meningitis and endocarditis were associated with long
term sequelae in the current study. The long term
sequelae included neurological deficits, heart failure,
cerebral palsy and epilepsy. Pneumonia usually
recovered without any sequelae. The mortality in this
study was 5%. All the deaths occurred in those below
the age of 2-year.

In recent years, *Pneumococcal sp.* resistance to
penicillin and other antibiotics were reported in several
countries including North America, Hong Kong and Taiwan. The penicillin resistance rate was
increasing as it rose from 0.2% (1988) to 7.6% (1992)
to 28.9% (1994). In the current study, the penicillin
resistance rate was 42%, comparable with previous
study that yielded 41%. In order to decrease the morbidity and mortality in
these young children, 2 types of Pneumococcal
vaccines: pneumococcal conjugated and
polysaccharide vaccine were developed and
advocated recently. Decline in incidence, disease
burden of IPD was noted in many places after
introduction of the new conjugate vaccine. The
disease burden in Hong Kong children aged below
2 years old can also be potentially reduced by
vaccination. The use of new conjugate vaccine has
also showed reduced antimicrobial resistance in some
places already e.g. Israel, South Africa. Therefore,
vaccination should be considered in those high risk
groups as recommended by ACIP.

In conclusion, the current study demonstrated the
increased susceptibility to IPD in children under the
age of 2 years or those with chronic medical illness
and IPD may present only with symptoms of upper
respiratory tract infection. A high index of suspicion
is required to allow early diagnosis and treatment that
prevent mortalities and morbidities associated with
IPD.
References


