Paediatric invasive pneumococcal disease from two tertiary hospitals in Malaysia

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ABSTRACT

Introduction: Invasive pneumococcal disease (IPD) a leading cause of death and morbidity in children below five-years-old. This study aims to compare the varied presentation and clinical course of IPD in two different tertiary hospitals in Malaysia.

Methodology: A retrospective study of all positive *Streptococcus pneumoniae* isolates consistent with invasive disease from children below 14 years of age hospitalised in two tertiary hospitals; between year 2012 and 2016 was conducted. IPD cases were defined as isolates of *S. pneumoniae* from a normally sterile body fluid site.

Results: Fifty-four patients were identified in both centres, 35 (65%) from HRPB as compared to 19 (35%) from HS. Majority of cases (14/35, 40 %) in HRPB were of Orang Asli in comparison to Malay children (16/19, 84%) in HS. Septicaemia, pneumonia and meningitis were the most common clinical presentation of IPD in both centres. There was a noticeably higher percentage of isolates found to be non-susceptible (NS) in HS (62.5%) as compared to HRPB (37.5%) although of no statistical significance. Mortality rate was higher in HRPB (26%) in comparison to 11% in HS.

Conclusion: This study highlighted the varied presentation of IPD in two different hospital settings. Although both deemed as urban centres, this study emphasises the importance of understanding socio-demography, health facility availability and primary care practices as it significantly alters the clinical course of a disease.

KEY WORDS:
invasive pneumococcal disease, paediatric, Malaysia, Streptococcus pneumoniae

INTRODUCTION

South-East Asia lags decades behind the rest of the world as the pneumococcal vaccine is yet to be implemented in the National Immunisation Schedule in these countries with an exception of Singapore, where the country pioneered the introduction since 2009.[1] Pneumococcal disease is known to infect and cause significant mortality in children below two-years of age. It is also the leading cause of preventable death in children below five-years of age.[2] Invasive pneumococcal disease (IPD) alone is said to contribute to approximately one million deaths annually.[3] The causative organism is a major cause of serious invasive diseases, such as meningitis, bacteraemia, and pneumonia, with young children in the first two years of life being particularly susceptible.[4]

In Malaysia, it is estimated that 4% of 7000 deaths in children below the age of five is due to IPD.[5] This disease which is preventable by vaccine, not only causes significant mortality but also has significant morbidity, particularly in survivors of pneumococcal meningitis with severe neurological sequelae. The pneumococcal vaccine was only made available in 2005. However, it is yet to be incorporated into the Malaysian immunisation programme.[6] Over the last decades, the rate of non-susceptible strains in Malaysia has increased from 2% to an alarming 50% in the year 2011.[7] There is also limited published data on the clinical spectrum associated with antibiotic resistance in IPD after the pneumococcal vaccine was made available in Malaysia in 2006. Furthermore, previous studies focused on a single hospital setting within the Klang valley in Malaysia.[6,8] These have prompted us to conduct this study to compare the occurrences, socio demography, and clinical characteristics including its outcome, in two hospital settings in different states in Malaysia.

MATERIALS AND METHODS

Study design

A retrospective study of all positive *Streptococcus pneumoniae* isolates consistent with invasive disease from children below 14 years of age hospitalised in two tertiary hospitals; Hospital Serdang (HS), Selangor and Hospital Raja Permaisuri Bainun (HRPB) between 2012 and 2016 was conducted. A proforma sheet was used to record socio-demographic information, clinical presentation, treatment which included antibiotic usage, resuscitative treatment, ventilatory support, clinical complications and outcome. Concomitant mixed infection with *S. pneumoniae* and recurrent infection in the same patient were excluded.

Settings

Both hospitals are government-funded multi-speciality tertiary hospitals. HS is located in the district of Sepang in the state of Selangor serving an estimated population of 570,000

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within its vicinity covering other areas such as Putrajaya, Bangi and Kajang. HS treats an average of 10,500 hospitalised children annually. HRPB is located in the district of Kinta in the state of Perak serving an estimated population of 2.3 million for the whole state of Perak. It treats an average of 10,885 hospitalised children annually.

Case Definition

A case of confirmed IPD was defined as an isolation of *S. pneumoniae* from a normally sterile body fluid site.[9] Pneumococcal septicaemia was defined as the presence of the organism in the blood with clinical features of sepsis that fulfilled the international paediatric sepsis consensus as outlined by Goldstein.[10] The diagnosis of pneumococcal pneumonia was made with the presence of a positive culture of the organism in blood or pleural fluid compatible with a clinical manifestation of pneumonia (fever with tachypnoea or chest retraction or signs of lower respiratory tract infection, e.g., crepitation or reduced breath sounds) supported by radiographic evidence if available. Pneumococcal meningitis was defined when a child presented with a clinical syndrome of meningitis (e.g. fever >38.5°C, headache, neck stiffness, altered consciousness or other meningeal signs) with the isolation of *S. pneumoniae* from blood or cerebrospinal fluid.[11] The diagnosis of septic arthritis was confirmed with the presence of *S. pneumoniae* in blood or joint aspiration.[12] Pneumococcal abscess was diagnosed when there was evidence of deep-seated pus formation in confined spaces with the isolation of *S. pneumoniae* from pus swab or tissue culture[13]. The term susceptible and non-susceptible (NS) in this study refers to susceptibility to penicillin. This term is defined by minimum inhibitory concentration (MIC) level that is above the susceptible cut off point as defined by the CLSI 2008-2014 criteria.[14] NS strain to penicillin is defined if the strain is either intermediate or resistant on the MIC level.

Laboratory Methods

Blood cultures were performed using Bactec Paediatric system or Bactec/PF where one to two millilitres of blood was placed in a medium with resin. The presence of *S. pneumoniae* isolates was identified by colony morphology, Gram staining and catalase reaction. It was further confirmed by optochin sensitivity (>5mm inhibition) and bile solubility by using standard microbiological methods according to guidelines from the Clinical and Laboratory Standards Institute (CLSI) recommendations.[14,15] The antibiotic susceptibility pattern of the isolates was determined by the standard Epsilometer test (E-test) method. MIC level breakpoints in this study were based on CLSI 2008-2014 criteria.[14]

Statistical analysis

All data obtained were analysed using IBM SPSS Statistics 21.0. Univariate analysis was used to analyse descriptive data for all variables. Results were presented as percentages and frequencies for categorical variables, and as mean and standard deviation for continuous variables. Chi-square test was used to determine the association between categorical variables, whereas, Pearson's product-moment correlation test was used to determine correlation between continuous variables. Fisher's exact test was used with frequencies less than five. Logistic regression analysis was used to determine the contribution of the factors on the severity and outcome of IPD in children. The acceptable level of statistical significance for all tests was set at $p<0.05$.

RESULTS

Socio-demographic background

Over the five-year retrospective study, 54 children were afflicted with IPD. Thirty-five children were identified in HRPB, which comprised 65% of total IPD case as compared to 19 (35%) from HS as shown in Table I.

Almost three-fifths of the study population (30/54, 56%) were less than two-years. None was in the age category of 12 to 14-years old. Two obvious discrepancies were present between the two hospitals. First, there was a higher percentage of Malay children in HS (84%) with IPD contrasting from HRPB where Orang Asli children were the largest population (40%) followed by Malay children (37%). All of the infected Orang Asli children were from HRPB. Secondly, there were no Chinese cases in HS.

Overall there was a slow gradual increase of IPD cases in HRPB (except in 2015) peaking in the year 2016 (17 cases) as shown in Figure 1. However, the occurrence levelled in HS ranging from two to six cases annually.

Clinical presentation and outcome

There was no difference in clinical presentation of IPD in both hospitals. Septicaemia (HRPB 80%, HS 79%), pneumonia (HRPB 63%, HS 63%) and meningitis (HRPB 26%, HS 21%) were the three most common presentations. The number of children with IPD requiring intensive care and ventilator support was almost similar in both centres. Mean duration of admission was comparatively higher in HS (17days) versus nine days in HRPB. Cases in both centres had a mean of three days of ICU admission. The morbidity rate was higher in HS (31%) as compared to HRPB (20%).The neurological sequelae in this cohort of patients included seven cerebral palsy (including one hemiparesis) and one speech delay. Of the respiratory sequelae, three developed bronchiectasis and two hyperactive diseases respectively, the latter requiring intermittent home oxygen monitoring. Among the Orang Asli children, four developed significant post IPD complications. Out of the four affected children, three had respiratory sequelae and one neurological impairment. The contributing factors for severity of disease and outcome were found to be not significant on logistic regression analysis (not shown). The mortality rate was higher in HRPB (26%) in contrast to 11% in HS, however, it was not statistically significant.

Antibiotic treatment, antibiogram and MIC levels

The percentage of isolates found to be non-susceptible to penicillin (NS) was higher in HS (62.5%) as compared to HRPB (37.5%) although no statistical significance was found. This correlates with a higher resistance pattern in the former hospital, and a parallel higher usage of second and third-line antibiotics in this centre. On the contrary, utilisation of penicillin was higher in HRPB. A similar trend was noted for both erythromycin ($p=0.012$) and tetracycline ($p=0.011$) resistance on the antibiogram. These results suggest the possible presence of multi-drug resistance (MDR) *S. pneumoniae* in HS.

Table I: Socio- demography of Invasive Pneumococcal Disease in HRPB and HS

Characteristics	HRPB (Ipoh) N = 35	H.S N =19	p value
Gender			
Female/Male	21(60%)	8(40%)	0.208
Ethnicity			
Malay	13(37%)	16(84%)	0.001**
Chinese	5(14%)	0(0%)	0.149
Indian	3(9%)	1(5%)	1.000
Indigenous	14(40%)	0	0.001**
Others	0	2(11%)	0.119
Age			
0 to <6 Months	3(8.5%)	3(16%)	0.653
0 to <1 Years Old	8(23%)	6(32%)	0.345
0 to <2 years Old	19(54%)	11(58%)	1.000
0 to <5 Years Old	28(80%)	17(89%)	0.236
>5 Years Old	7(20%)	1(5%)	0.236
Comorbidities			
Malnourished	8(23%)	6(32%)	0.623
Undernourished	16(46%)	9(47%)	0.907
Obese	2(6%)	0(0%)	0.535
Heart Disease	1(3%)	1(5%)	1.000
Prematurity	4(11.5%)	2(10%)	0.169
Syndromes	3(9%)	0(0%)	0.54

(Fisher's Exact Test was used when more than 20% of cells have expected frequencies <5)

Table II: Clinical Characteristics of Invasive Pneumococcal Disease in HRPB and HS

Characteristics	HRPB N=35	H.S N =19	p value
Clinical Diagnosis			
Pneumonia	22(63%)	12(63%)	0.983
Parapneumonic Effusion	7(20%)	6(32%)	0.506
Meningitis	9(26%)	4(21%)	1.000
Septicaemia	28(80%)	15(79%)	1.000
Abscess	4(11.5%)	1(5%)	0.646
Antibiogram (Resistance Pattern)			
Penicillin	1(3%)	0(0%)	1.000
Vancomycin	-	-	0.011**
Tetracycline	7(20%)	10(53%)	1.000
Trimetroprim	4(11.5%)	2(11%)	0.012**
Erytromycin	3(8.6%)	14(74%)	
Non Susceptible (MIC)	3(37.5%)	5(62.5%)	0.089
Antibiotics(Treatment)			
Penicillin	20(57%)	5(26%)	0.023
Cephalosporin	18(51%)	14(74%)	0.158
Carbapenem	2(6%)	4(21%)	0.172
Macrolides	3(9%)	6(32%)	0.059
Vancomycin	1(2%)	2(11%)	0.546

Table III: The outcome of Invasive Pneumococcal Disease in HRPB and HS

Characteristics	HRPB N =35	H.S N=19	P Value
ICU admission	16(46%)	10(53%)	0.627
Assisted Ventilation	13(37%)	7(37%)	1.000
Inotropes/Fluid Bolus	14(40%)	9(47%)	0.774
Respiratory Sequelae	2(6%)	3(16%)	0.332
Neurological Sequelae	5(14%)	3(16%)	1.000
Death	9(26%)	2(11%)	0.292

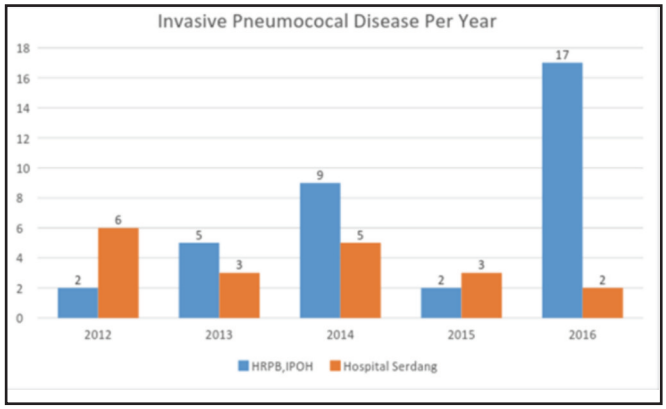

Fig. 1: Occurrence of Invasive Pneumococcal Disease per year in HRPB and HS 2012-2016.

DISCUSSION

Although the demographic data pertaining to age, gender and clinical manifestations were same in the two tertiary hospitals, our study showed that there were important differences in other aspects.

Overall, our study highlighted the contrasting occurrence in the two centres. A higher burden rate was noted in HRPB which was slightly more than double in this hospital as compared to HS. The annual occurrence seemed to show an increased rate in HPRB over the studied years as compared to an almost plateau pattern observed in HS. One could not make a generalized conclusion as the true occurrence of IPD cases were likely scattered within the several centres in the vicinity and not captured in a single centre, especially with HS. On the other hand, Selangor had higher GDP per capita as compared to Perak that could have attributed to the difference in occurrence.[17] This would be translated to increased affordability to vaccine uptake and hence enhanced herd immunity. The herd immunity generated within the urban community could further contribute to the stagnation of IPD cases in HS.

This study found that the Orang Asli children were vulnerable to the infection and they were confined to HPRB. The minority group becomes an outlier in terms of racial distribution, as they make up a significant 25% in this cohort in terms of racial distribution, in contrast to the 0.5% it represents in the national population.[18] It is understandable that the cases were seen in HRPB as Perak state houses 30% of Malaysian Orang Asli communities while Selangor only comprised 6% of the total population.[19] In addition, HRPB is also the main referral hospital for Orang Asli children from West Pahang and Ulu Kelantan apart from Perak.

This study also highlighted that the Orang Asli children were susceptible to contracting IPD as compared to the other races. This corroborates with previous findings[20] that the natives were at higher risk of the infection. Cortese MM et al., revealed that the Alaskan and Australian natives were 10 to 50 times at higher risk of IPD.[21,22] The elevated risk among Orang Asli children has been attributed to various underprivileged socioeconomic factors. Low income may represent limited access to health care; increased household crowding with resultant poorer quality housing and hygiene, increased exposure to cigarettes and undernutrition; which are all potential mechanisms by which this poverty-driven community may contribute further to the increased risk of IPD.[23,11]

Our study also showed that a proportion of cases that were sensitive to penicillin on antibiogram were non susceptible on E-testing. This discrepancy raises concern as it may implicate delay in adequately treating resistant pneumococcal meningitis and disseminated infection, as vancomycin is warranted. Antibiogram is an important tool, however MIC testing is more sensitive. This study highlighted the E-testing should be performed for all *S. pneumoniae* isolates.

A different pattern of antibiotic resistance was shown in both centres. HS recorded an alarming rate of 62.5 % of penicillin NS strains versus 37.5% in HRPB. Similarly, higher rates of resistance to erythromycin and tetracycline were observed in HS, which could indicate possible increased rates of MDR in this setting. The high penicillin-resistant rate in HS corresponds with previously high rates of between 50% to 61% during the period 2004 to 2007 in Klang Valley, Malaysia.[5] The higher penicillin NS rate and the possibility of the presence of MDR *S. pneumoniae* in HS could also reflect the overzealous antibiotic usage in the primary care for children within Klang Valley.[23] Furthermore, with the presence of a more virulent organism, the preference of second-line antibiotic usage in this centre is thus justified.

The overall fatality rate was 20% (11/54); a figure which is much higher in comparison to the global pneumococcal fatality in children of 11%.[24] In this study, HRPB (26%, 9/25) documented a higher fatality rate compared to HS (11%, 2/19). This may not be surprising as the burden of the disease was twice in the former in comparison to the latter hospital. Higher fatalities in the former centre could also be attributed to a delayed and more severe form of presentation of cases to HRPB. This was reflected as four children from HRPB succumbed to their illness within twelve hours of admission to the hospital. Moreover, HRPB is a state referral centre with a vast area of coverage from thirteen districts may have further contributed to delayed access to health facilities in comparison to more than 100 hospitals (both public and private) in the vicinity of HS.

There were a few limitations in this study. First, this study is unlikely to reflect the true occurrence of IPD among Malaysian children as it is confined to two hospitals in urban Malaysia. The study population reflects selection bias and involvement of a relatively small number of isolates. Furthermore, isolate serotype data were not available for the majority of samples. Serotyping data would have added valuable information in terms of clinical relevance, especially in the decision-making of type of pneumococcal vaccine to be introduced in Malaysia. The retrospective nature of the study has disadvantages including missing data, recall bias and reliance on others for accurate record keeping.

CONCLUSION

IPD remains a disease of significant morbidity and mortality in Malaysia. This study highlights the varied presentation of IPD in two different hospital settings. Although both districts are deemed as urban centres, this study emphasises the importance of understanding socio-demography, availability of health facilities and primary care practices as it significantly alters the clinical course of diseases. This study further highlights the role of herd immunity mounted by the use of PCV, which impedes the fluctuating occurrences of IPD in a highly mobilised population. Clinicians should be vigilant in determining susceptibility and sensitivity of IPD as the choice of antibiotic treatment differs and ultimately favours improved outcome.

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