Original Article

Early Predictors of Mortality in Pneumococcal Bacteraemia

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Abstract

Introduction: *Streptococcus pneumoniae* **bacteraemia is associated with significant mortality rates worldwide. The purpose of this study is to identify risk factors for predicting mortality in patients with** *S. pneumoniae* **bacteraemia.** **Materials and Methods:** **A retrospective cohort study was carried out in a university-affiliated acute tertiary care hospital in Singapore. Thirty-eight patients with blood cultures positive for** *Streptococcus pneumoniae* **over a 2-year period from January 2000 to December 2001 were recruited for the study.** **Results:** **The records of patients admitted to hospital with blood cultures positive for** *S. pneumoniae* **between January 2000 and December 2001 were reviewed. Thirty-eight patients were found positive for** *S. pneumonia***; this included 31 men (81.6%) and 7 women (18.4%) between the ages of 14 years and 90 years. Of this, 7 patients (18.4%) required admission to the intensive care unit, 5 of whom required mechanical ventilation. The factors that predicted mortality were the presence of septic shock ($P < 0.005$), leukopenia or leukocytosis ($P < 0.005$), the presence of an underlying malignancy ($P = 0.008$), anaemia ($P = 0.025$) and the presence of a high anion gap ($P = 0.047$) on admission.** **Conclusion:** **Of all the risk factors observed, those that predicted mortality in patients on initial presentation of** *S. pneumoniae* **bacteraemia were the presence of septic shock, leukopenia or leukocytosis, anaemia, a raised anion gap and the presence of an underlying malignancy.**

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Key words: Anaemia, Anion gap, Low leukocyte count, Malignancy, Mortality, *S. pneumoniae* bacteraemia, Septic shock

Introduction

Streptococcus pneumoniae infection is the most common cause of community-acquired pneumonia worldwide.[1] It has been associated with an approximately 10% rate of bacteraemia.[2-4] Despite the advances in antibiotics, pneumococcal bacteraemia still carries a significant mortality rate.[2-6]

Over the years, this illness has been studied and various risk factors, including the patients' history, clinical and laboratory findings, have been found to be associated with poor clinical outcome.[2-11] Only a few studies have looked at the predictors of poor clinical outcome at the time of admission.[2-5,7] We aimed to identify the factors associated with mortality in patients with *S. pneumoniae* bacteraemia in Singapore. We also sought to establish whether antibiotic resistance would affect mortality.

Materials and Methods

We conducted a retrospective study of patients admitted to Singapore General Hospital, a 1600-bed, university-affiliated acute tertiary care hospital in Singapore, who had been found to have *S. pneumoniae* bacteraemia. We enrolled patients who had been admitted between January 2000 and December 2001. All patients found to have at least 1 set of positive blood culture for *S. pneumoniae* were included in the study. We identified 38 subjects who had blood cultures positive *for S. pneumoniae*. These subjects were subsequently enrolled in our study. The case records of these 38 subjects were reviewed and analysed.

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Septic shock was defined as the presence of sepsis with hypotension (arterial blood pressure <90 mm Hg, or 40 mm Hg less than the patient's usual blood pressure), that is, unresponsive to fluid resuscitation, along with tissue hypoperfusion. This includes the presence of lactic acidosis, oliguria and change in mental state. Patients requiring inotropic support to maintain tissue perfusion were also included.[12] We then looked at the final outcome of the hospitalisation, which was either the patient's discharge from hospital or death.

The clinical, biochemical and radiological factors analysed are summarised in Table 1.

Data obtained were entered into a database file and statistical analysis was performed using the Statistical Package for Social Sciences version 10.0.5 (SPSS Inc, Chicago, IL). Univariate analysis involving continuous

Table 1. Factors that may be Used to Predict Clinical Outcome

History
    Gender
    Age
    Ethnicity
    Pleuritic chest pain
    Coughing
    Ischaemic heart disease
    Hypertension
    Diabetes mellitus
    Renal failure
    Liver failure
    Previous pulmonary tuberculosis
    History of malignancy
    History of alcohol abuse
    Smoking
    Duration of hospital stay
Clinical
    Fever (temperature >37.4°C)
    Tachycardia (pulse rate 100 beats/min)
    Tachypnoea (respiratory rate 20/min)
    Septic shock
    Systolic blood pressure
Laboratory
    Biochemical
    - blood urea nitrogen
    - serum sodium
    - serum potassium
    - serum bicarbonate
    - serum chloride
    - anion gap $[Na - (HCO_3 + Cl)]$
    - serum creatinine
    - serum glucose (random)
    Haematological
    - haemoglobin
    - leukocytes
    - platelets
    Radiological
    - consolidation
    - presence of pleural effusion

parameters was carried out using the Mann-Whitney U test. The chi-square test was used to compare the distribution of categorical data in various groups. A multivariate analysis was then performed. Statistical significance was taken as $P <0.05$.

Results

Over the 2-year period from 1 January 2000 to 31 December 2001, 38 patients were found to have blood cultures positive for *S. pneumoniae*. Thirty-one of these patients were male (81.6%) and 7 were female (18.4%). Of these 38 subjects, 7 (18.4%) required treatment in our medical intensive care unit (MICU), 5 of whom required mechanical ventilation. The antibiotic sensitivities of *S. pneumoniae* from every subject were also obtained, together with the minimum inhibitory concentration (MIC) values.

The subjects in our study were between the ages of 14 years and 90 years, with a median age of 57 years. Twenty-five were Chinese (65.8% of our study population), 9 were Malay (23.7%), 3 were Indian (7.9%) and 1 of other race (2.6%). The racial distribution in our study was reflective of the ethnic population distribution in our country. The

Table 2. Patient Demographics (n = 38)

	No.	%
Premorbid conditions		
Ischaemic heart disease	6	15.8
Hypertension	9	23.7
Diabetes mellitus	7	18.4
Renal failure	6	15.8
Liver failure	3	7.9
Previous pulmonary tuberculosis	3	7.9
Malignancy	6	15.8
History		
Smoking	16	42.1
Alcohol	6	15.8
Travel history	5	13.2
Fever	20	52.6
Pleuritic chest pain	15	39.5
Coughing	32	84.2
Tachycardia (pulse rate >90/min)	18	47.4
Tachypnoea (respiratory rate >20/min)	27	71.1
Septic shock	6	15.8
Number of antibiotics started		
1	12	31.6
2	21	55.3
≥3	5	13.2
Class of antibiotics started		
Penicillin	6	15.8
Third-generation cephalosporin	28	73.7
Macrolides	16	42.1
Fluoroquinolones	3	7.9
Others	16	42.1

demographics of our patients are summarised in Table 2.

The duration of hospital stay for our subjects was between 1 day and 30 days, with a median of 9 days. Two subjects stayed in hospital for 1 day but both died within 24 hours of admission. Of the 38 subjects, 6 (15.8%) were in septic shock at the time of admission. The 7 subjects admitted to the ICU were between the ages of 27 years and 70 years, with a mean of 47.4 years. The duration of ICU stay was between 1 day and 14 days, with a mean of 5.7 days. Five required mechanical ventilation (MV). The duration of ventilation ranged between 1 day and 12 days, with a mean of 7.2 days. Of the 5 subjects who required MV, 1 died within 24 hours of admission.

Of the total number of 38 subjects, 5 died (13.1% mortality rate). They were between the ages of 43 years and 87 years, with a mean age of 62.6 years. Only 1 died in the MICU while being mechanically ventilated. The remaining 4 out of 5 died within 48 hours of admission. Four subjects who died had an underlying malignancy. Table 3 shows the profile of the subjects who died in our study.

The chest X-rays of all 38 subjects enrolled were noted at the time of admission. Thirty (78.9%) had obvious radiological evidence of consolidation on their chest X-rays on admission, with involvement of at least 1 lobe. Of these 30 patients with consolidation, 7 (23%) had associated para-pneumonic effusion, as shown on their chest X-rays. The remaining 8 patients had unremarkable chest X-rays, despite having respiratory tract symptoms and clinical signs suggestive of pneumonia.

The clinical factors that were significant in predicting mortality were the presence of septic shock on admission (P <0.005) and an underlying malignancy (P = 0.008). Significant laboratory factors that predicted mortality were the presence of leukopenia (median, 2.37 x 10^9 L^{-1} ± 1.79 SD) or leukocytosis (median, 14.90 x 10^9 L^{-1} ± 7.55 SD) (P <0.005), anaemia (median haemoglobin value, 9.2 gdL^{-1} ± 2.51 SD) (P = 0.021) and high anion gap greater than 12 $mmolL^{-1}$ (P = 0.047). Although we found the presence of hypochloridaemia less than 110 $mmolL^{-1}$ to be significant (P = 0.045), we felt that it could be better explained by the role of chloride in the anion gap.

Table 4 shows the significant clinical risk factors for *S. pneumoniae* bacteraemia.

Antibiotic Susceptibility

We also obtained the antibiotic sensitivity results of *S. pneumoniae* from every patient. We examined the MIC value of penicillin of all strains cultured. Of the 38 isolates, 36 (94.7%) grew *S. pneumoniae* sensitive to penicillin (MIC, <0.1 μg/mL). Two (5.3%) had strains with intermediate resistance (MIC, 0.1 μg/mL to 2.0 μg/mL). None had highly resistant strains (MIC, >2.0 μg/mL). The MIC for ceftriaxone was <0.5 in all strains. These MIC values were based on the guidelines set by the National Committee for Clinical Laboratory Standards.[13]

For these 38 subjects, we obtained a total of 40 sets of *S. pneumoniae* isolates as a few subjects had more than 1 set of blood culture done. Each set consisted of an aerobic and an anaerobic blood culture. In total, 76 isolates (95.0%) were sensitive to penicillin while 4 isolates (5.0%) had intermediate resistance. None of the isolates had high resistance. We investigated the susceptibility of *S. pneumoniae* obtained from all sources cultured in our hospital in 2001. This included cultures from fluids such as blood, urine, cerebrospinal fluid and also tissue cultures. From this data, we found out that the overall resistance rate (intermediate and high) to penicillin was 29%. We also investigated the susceptibility of isolates from *S. pneumoniae* bacteraemia from all hospital admissions in 2001 and found that out of 40 isolates, only 4 (10%) had intermediate resistance. Nevertheless, this illustrates that bacteraemia is inversely associated with resistance, as shown in previous studies.[14-18]

Discussion

S. pneumoniae is the most common cause of community-acquired pneumonia worldwide. *S. pneumoniae* bacteraemia is also associated with a significant mortality rate, of which 19% was reported in Ohio,[2] 21% in London[3] and 36% in Washington DC.[4] Few studies have looked at predictors of mortality at time of admission[11,13] and yet fewer have looked at *S. pneumoniae* bacteraemia in particular.[3,4,7] In our study, we attempted to investigate both clinical and laboratory risk factors that would predict hospital mortality in patients who had *S. pneumoniae* bacteraemia at the time of admission.

We found that the best predictors of mortality were the presence of septic shock (P <0.005), the presence of leukopenia or leukocytosis (P <0.005) and the presence of an underlying malignancy (P = 0.008). The other 2 factors that were found to be significant were the presence of anaemia (haemoglobin level <10 g/dL) (P = 0.021) and the presence of a high anion gap (P = 0.047). The presence of a high anion gap may be a surrogate marker for underlying acidosis, which is a risk factor in predicting mortality, as shown in previous studies.[4,12,19]

Our study had a mortality rate of 13.1%. This finding is similar to other studies, which quoted mortality rates between 15% and 25%.[2-4] It has been quoted in previous studies that at least 50% of mortality resulting from *S. pneumoniae* bacteraemia occurred within the first 48 hours of admission.[3,4] This is consistent with our study, where 4 out of 5 (75%) deaths occurred within the first 48 hours. We also observed that 80% of those who died had a history of

Table 3. Profile of Patients who Died in our Study

Age (y)	Gender	Duration after admission	Medical condition	Neutrophils (x $10^9 L^{-1}$)	Septic shock
43	Male	Within 48 h	Metastatic nasopharyngeal carcinoma	4.33	Yes
56	Male	Within 24 h	Relapsed acute myeloid leukaemia	4.22	Yes
61*	Male	Within 48 h	Nasopharyngeal carcinoma (given radiotherapy previously)	0.44	Yes
66	Male	Within 5 days	Right lung upper lobe non-small cell carcinoma with SVCO	17.06	No
87	Male	Within 24 h	Diabetes mellitus, vascular dementia	1.2	No

SVCO: superior vena cava obstruction
* Patient died in intensive care; minimum inhibitory concentration value >0.1 µg/mL

Table 4. Clinical Risk Factors for *S. pneumoniae* Bacteraemia

Diagnostic arm	Parameter		Cases	*P* values
History	Age			0.711
	Gender	Male	31	0.777
		Female	7	
	Ethnicity	Chinese	26	0.389
		Malay	8	
		Indian	3	
		Others	1	
	Pleuritic chest pain		15	0.332
	Coughing		32 (27 productive)	0.88
	Ischaemic heart disease		6	0.401
	Hypertension		9	0.237
	Diabetes mellitus		7	0.777
	Renal failure		6	0.831
	Liver failure		3	0.647
	Previous pulmonary tuberculosis		3	0.292
	Malignancy*		6	0.008
	Smoking		16	0.108
	Alcohol		6	0.831
Clinical	Fever		20	0.123
	Tachycardia		18	0.076
	Tachypnoea		27	0.310
	Septic shock*		6	<0.005
Haematological	Haemoglobin*	<12 gdL^{-1}	19	0.021
		≥12 gdL^{-1}	18	
	Leukocytes*	<4 x 10^9 L^{-1}	3	<0.005[†]
		>10 x10^9 L^{-1}	24	
	Platelets	<140 x 10^9 L^{-1}	8	0.252
Biochemical	Blood urea nitrogen	>7.7 mmolL^{-1}	20	0.802
	Sodium	<135 mmolL^{-1}	23	0.501
	Potassium	<3.5 mmolL^{-1}	6	0.834
		>5.0 mmolL^{-1}	1	
	Bicarbonate	<9.0 mmolL^{-1}	5	0.715
		>31.0 mmolL^{-1}	1	
	Chloride	<110 mmolL^{-1}	5	0.045
	Anion gap*	>12 mmolL^{-1}	15	0.047
	Creatinine	>141 mmolL^{-1}	16	0.738
	Glucose	<4.0 mmolL^{-1}	3	0.387
		>11.0 mmolL^{-1}	5	
Radiological	Effusion		7	0.777
	Consolidation		31	0.777

* Significant risk factors
† Accounts for leukopenia (<4 x 10^9 L^{-1}) and leukocytosis (>4 x 10^9 L^{-1})

Table 5. Penicillin Sensitivity of *S. pneumoniae* in our Study

Year	No. of patients	No. of isolates (blood)	Sensitive (MIC, <0.1 µg/mL) (No. of isolates,%)	Intermediate (MIC, 0.1-2.0 µg/mL) (No. of isolates,%)	Resistant (MIC, >2.0 µg/mL) (No. of isolates,%)
2000	12 (33.3%)*	40	40 (100%)[†]	–	–
2001	26 (66.7%)*	40	36 (90.0%)[‡]	4 (10.0%)[‡]	–
Total	38	80	76 (95.0%)[§]	4 (5.0%)[§]	–

MIC: minimum inhibitory concentration values
* Expressed as percentage of total number of patients
† Expressed as percentage of isolates in year 2000
‡ Expressed as percentage of isolates in year 2001
§ Expressed as percentage of total isolates

an underlying malignancy. In 1995, Afessa et al[4] found that the presence of malignancy was associated with a higher mortality rate. Seventy per cent of his case fatalities had an underlying malignancy.

In our study, we obtained information regarding the antibiotic susceptibility of *S. pneumoniae* and made the following observations. A total of 29% of *S. pneumoniae* cultured from all isolates in our hospital in 2001 were resistant to penicillin. These included isolates from the blood, urine, sputum, cerebral spinal fluid and tissue cultures. In 2001, out of 40 isolates of bacteraemic *S. pneumoniae* in our hospital, 4 isolates (10%) were strains of intermediate resistance (MIC, 0.1 µg/mL to 2.0 µg/mL). None were highly resistant, with MIC >2.0 µg/mL. This suggests that bacteraemia was associated with a lower rate of resistance. Previous studies have reported a resistance rate of 15% to 30%. However, interestingly, most studies have reported that despite the high resistance rate, the presence of bacteraemia is inversely related to the rate of resistance.[19-21] The strains in our study were very susceptible to penicillin. Furthermore, the strains cultured in our study were all sensitive to ceftriaxone, a third-generation cephalosporin, which was the antibiotic of choice in 73.7% of patients. All 4 isolates of intermediate resistance were from 2 patients. These 2 patients had concomitant medical conditions that predisposed them to recurrent infections; 1 had an underlying malignancy while the other had had a previous cerebral vascular accident resulting in the patient being bedbound. These may have predisposed them to frequent infections and prior antibiotics usage and hence, increased rates of resistance. Based on the entries in the case records, there was no delay in the institution of antibiotics. All antibiotics were administered within the first 2 hours of admission to the ward. However, we did not look for any relationship between the time of antibiotic administration and mortality.

Our study illustrated that mortality among patients with *S. pneumoniae* bacteraemia is related to host factors rather than antibiotic sensitivity. Among our case fatalities, 4 out of 5 subjects were infected by strains sensitive to penicillin. The remaining subject grew *S. pneumoniae* with intermediate resistance. However, all 5 subjects grew strains that were sensitive to ceftriaxone. Although we do not have strains of high resistance from January 2000 to December 2001, our mortality rate resulting from *S. pneumoniae* bacteraemia was similar to previously reported studies. Those studies had strains ranging from sensitive to highly resistant ones. These studies also showed that mortality was not affected by the rate of resistance.[14-18] As we had very few strains of *S. pneumoniae*, we did not look for a relationship between mortality and antibiotic resistance. Therefore, what was proven in previous studies could not be concluded in ours.

Our study had certain limitations. Firstly, it was a retrospective study. All information obtained was based on case records. Previous studies have shown low albumin levels to be related to mortality.[2-10] In our study, not all cases had a serum albumin performed. This illustrates that the information gathered is based on what was available in the case records. Secondly, we had a small sample size. The small sample size makes it difficult for us to look for relationships in certain factors. One example would have been the relationship between resistance rate and mortality. As such results would have been debatable, we did not include this in our analysis.

Despite advances in antibiotics therapy, mortality associated with *S. pneumoniae* bacteraemia remains high. Data from our study suggest that host factors and responses to the illness play an important role in mortality. Despite our strains being fairly sensitive to penicillin, our mortality rate is similar to previous studies.[2-4] In addition, the presence of a high anion gap should alert the clinician to the severity of the illness in this group of bacteraemic patients. Appropriate antibiotics and good supportive care remain the mainstay of management of patients with *S. pneumoniae* bacteraemia.

Acknowledgement

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