ORIGINAL ARTICLE

A Study on Community Acquired Pneumonia in Adults Requiring Hospital Admission in Penang

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Summary

A study was carried out to determine the pattern of microbiological organisms causing community acquired pneumonia in adult patients admitted to Penang Hospital between November 1999 and August 2000. Altogether, 98 patients (64 males, 34 females) with a mean age (± S.D.) of 55.9 (± 19.0) (range 15 to 87) years were included in the study. Causative organisms were identified in 42 patients (42.9%). *Mycobacterium tuberculosis* was the commonest pathogen being identified in 15.3 % of cases, followed by *Klebsiella pneumoniae* (7.2%), *Pseudomonas aeruginosa* (6.1%) and *Staphylococcus aureus* (5.1%). *Streptococcus pneumoniae* and *Acinetobacter* spp accounted for 3 cases each (3.1%) and *Haemophilus influenzae*, non-haemolytic *Streptococcus*, *Mycoplasma pneumoniae*, *Salmonella typhi*, *Escherichia coli*, *Klebsiella* spp and *Pseudomonas* spp for 1 case each (1.0%). Four patients (4.1%) had dual infections and no case of legionella pneumonia was found in this series.

Key Words: Community acquired pneumonia, Aetiology, Malaysia

Introduction

Community acquired pneumonia is a common clinical problem which causes significant morbidity and mortality. With regard to the pattern of aetiological organisms there have been many reports from developed countries[1-6], and some data from other Asian countries[7-9] showing that considerable differences may exist in the type and frequency of causative organisms in different communities. Since little is known about the local aetiological pattern to guide rational empirical treatment in Malaysia, we carried out a prospective study on the pattern of organisms causing community acquired pneumonia in adults requiring hospital admission to Penang Hospital, a 1236 bed government hospital.

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Materials and Methods

All patients aged 12 years and above admitted to Penang Hospital between 1st November 1999 and 16th August 2000 with community acquired pneumonia were considered for inclusion in the study. Those included had clinical features of acute lower respiratory tract infection and radiological evidence of consolidation or shadowing suggestive of infection which was neither preexisting nor of other known cause. The following were excluded from the study: patients with pneumonia distal to bronchial obstruction caused by a foreign body or tumour, patients with coexisting disease in whom pneumonia is an expected terminal event (such as aspiration pneumonia after stroke or coma),

immunocompromised patients, including those with haematological malignancy, acquired immunodeficiency syndrome (AIDS), or coexisting solid organ malignant neoplasms and those admitted to hospital within the preceding four weeks or transferred from another hospital.

The following clinical data were obtained: age, sex, ethnic group, smoking history, past medical history, blood pressure and heart rate on admission and maximum temperature within 24 hours of admission. Sputum, blood and urine specimens were collected as soon as possible after admission. Sputum was collected with the help of physiotherapy if necessary, and sent for Gram stain, routine bacterial culture and antibiotic sensitivity testing, and smear and culture for *Mycobacterium tuberculosis*. Only specimens with greater than 25 white blood cells and less than 25 epithelial cells per low power field on Gram stain were selected for the study[10]. For routine bacterial culture, sputum specimens were inoculated onto chocolate and blood agar as well as MacConkey agar plates. For *Mycobacterium tuberculosis*, Ziehl-Neelsen staining was performed followed by culture. Blood was taken for culture, pneumococcal antigen and serological tests. Two blood samples were taken for aerobic cultures using the BACTEC system. *Mycoplasma pneumoniae* and *Legionella pneumophila* serology were tested in paired samples 2 to 3 weeks apart. *Mycoplasma pneumoniae* serology was tested by passive particle agglutination test (Serodia-Myco II, Japan) and *Legionella pneumophila* (serogroups 1 - 6) serology was tested by indirect fluorescent antibody test (SCIMEDX Corporation, United States of America). Urine was sent for microscopy and detection of pneumococcal antigen. Pneumococcal antigen assay was performed on blood and urine using the *Streptococcus pneumoniae* latex agglutination test (Wellcogen assay kit, United Kingdom). Routine haematological tests (haemoglobin, total white count with differential and platelet count) and blood biochemistry (blood urea and electrolytes, blood glucose, liver function tests) were also performed and arterial blood gas analysis was done when deemed appropriate.

Criteria for laboratory diagnosis of infection

Pneumococcal infection was considered 'definite' if the organism was isolated from blood or pleural fluid or if pneumococcal antigen was detected in blood or urine, and 'probable' if the organism was isolated from sputum. Infection with other bacteria was considered 'definite' if the organism was isolated from blood or pleural fluid (excluding *Staphylococcus epidermidis*). If *Staphylococcus epidermidis* was cultured in the blood, the diagnosis was considered 'probable' if two positive blood cultures were obtained at separate sites and times[11]. For *Haemophilus influenzae* and *Staphylococcus aureus*, infection was considered 'probable' when the organisms were isolated from sputum. For other bacteria, 'probable' infection required that the organism was the predominant one on sputum Gram stain in addition to its isolation from sputum. A four-fold or greater increase in titre of any of the serological tests was considered 'definite' evidence of infection. The diagnosis of tuberculosis was considered to be 'definite' if *M. tuberculosis* was identified from culture of sputum or pleural fluid and it was considered 'probable' if more than one sputum direct smear was positive for acid fast bacilli (AFB) without subsequent confirmation by culture.

Statistics

Results were expressed as mean ± standard deviation. Differences between any two groups were analysed by Student's unpaired t-test for continuous variables and Chi-square test for categorical variables. Values of p below 0.05 were considered significant.

Table I
Age and Ethnic Distribution of Patients Admitted with Community Acquired Pneumonia

	Malay	Chinese	Indian	Others	No. (%)
12 - 19 years	2	1	1	1	5 (5.1)
20 - 29 years	2	1	3	1	7 (7.1)
30 - 39 years	2	5	2	1	10 (10.2)
40 - 49 years	5	0	2	1	8 (8.2)
50 - 59 years	3	11	6	0	20 (20.4)
60 - 69 years	5	8	6	0	19 (19.4)
70 - 79 years	5	12	4	0	21 (21.4)
≥ 80 years	1	5	1	1	8 (8.2)
TOTAL	25	43	25	5	98 (100)

Results

Altogether, 98 patients with community acquired pneumonia were included in the study. There were 64 male patients (65.3%). The mean age was 55.9 (± 19.0) years and the age range was 15 to 87 years. The age and ethnic distribution of the patients are as shown in Table I. Coexisting illness was present in 69.4% of the patients studied (Table II).

There were 35 current smokers in this group of patients (35.7%), 20 were ex-smokers (20.4%), 42 had never smoked (42.9%) and the smoking history could not be obtained in one patient (1.0%) who was admitted in a drowsy almost comatose state. Out of the 98 patients, 13 admitted to drinking alcohol but the average intake was difficult to quantify; two of these patients were known to have alcoholic liver disease. Seven patients admitted to intravenous drug abuse and another two admitted to smoking illegal drugs.

Eight patients gave a history of antibiotic administration before admission and four had admission to hospital for pneumonia in the past. Causative organisms were identified in 42 patients (42.9%), and their distribution is shown in Table III. The commonest pathogen identified was *Mycobacterium tuberculosis* in 15 patients

Table II
Coexisting Illnesses in Patients Admitted with Community Acquired Pneumonia

	No.	Percentage
Respiratory illness		
Chronic obstructive pulmonary disease	21	21.4
Old tuberculosis	14	14.3
Asthma	11	11.2
Bronchiectasis	2	2.0
Sinusitis	1	1.0
Non-respiratory illness		
Hypertension	23	23.5
Diabetes mellitus*	19	19.4
Cardiovascular disease	15	15.3
Renal disease	5	5.1
Neurological disease	3	3.1
Hepatic disease	3	3.1
Other	7	7.1
Both respiratory and non-respiratory coexisting illness	19	19.4
Either respiratory or non-respiratory coexisting illness	49	50.0
No coexisting illness	30	30.6

** 4 of these patients had newly diagnosed diabetes mellitus*

Table III
Causative Organisms in Patients with Community Acquired Pneumonia*

Organism	Number	Definite/probable	Percentage
Mycobacterium tuberculosis	15	14/1	15.3
Klebsiella pneumoniae	7	0/7	7.2
Pseudomonas aeruginosa	6	0/6	6.1
Staphylococcus aureus	5	5/0	5.1
Streptococcus pneumoniae	3	1/2	3.1
Acinetobacter spp	3	0/3	3.1
Haemophilis influenzae	1	0/1	1.0
Non-haemolytic *Streptococcus*	1	1/0	1.0
Salmonella typhi	1	1/0	1.0
Escherichia coli	1	0/1	1.0
Klebsiella spp	1	0/1	1.0
Pseudomonas spp	1	0/1	1.0
Mycoplasma pneumoniae	1	1/0	1.0
Aetiology determined	42*	23/23	42.9
No organism identified	56	-	57.1

**Includes 4 patients with two identified aetiological organsisms*

(15.3%). Ten patients had positive sputum smears for AFB and all but one of these patients also had positive sputum culture for *Mycobacterium tuberculosis*. Another four patients were smear negative but culture positive for *M. tuberculosis*, and the remaining patient had the diagnosis of tuberculosis made from positive culture of pleural biopsy.

Klebsiella pneumoniae was cultured from sputum in seven patients, *Pseudomonas aeruginosa* in six patients, *Acinetobacter* spp in three patients, *Escherichia coli* in one, *Klebsiella* spp in one, *Pseudomonas* spp in one and *Haemophilus influenzae* in one. *Staphylococcus aureus* was cultured from blood in five patients and in one of these patients, the organism was also cultured from sputum. Two other patients had positive blood cultures: one grew a non-haemolytic *Streptococcus* and *Salmonella typhi* was grown in the other patient.

Streptococcus pneumoniae was detected in three patients; the diagnosis was definite in one patient who had positive blood culture as well as pneumococcal antigen detected in the blood, whereas in two others a probable diagnosis of pneumococcal infection was made based on positive culture of the organisms from sputum. No patient had pneumococcal antigen detected in urine. *Mycoplasma pneumoniae* was found to be the cause of pneumonia in one patient, the only patient in whom diagnosis was made from testing on paired sera. No case of pneumonia caused by *Legionella pneumophila* was identified in this study. Two organisms were detected in 4 patients (4.1%) as shown in Table IV

An aetiological diagnosis was established in a significantly higher proportion of patients less than 60 years of age compared to those aged 60 years and above (54.0% vs. 31.3%, $p<0.05$). *Mycobacterium tuberculosis* was the commonest

Table IV
Patients with Dual Infections

Assumed Primary Infection	Assumed Secondary Infection	Number of Patients
Staphylococcus aureus	*Klebsiella pneumoniae*	1
Mycobacterium tuberculosis	*Klebsiella pneumoniae*	1
Mycobacterium tuberculosis	*Acinetobacter* spp	1
Salmonella typhi	*Pseudomonas aeruginosa*	1
Total		4

organism detected in those less than 60 years of age (12/50, 24.0%), in patients with no coexisting illness (8/30, 26.7%) and in those with diabetes mellitus (4/19, 21.1%). Gram-negative bacilli were the commonest pathogens isolated from patients aged 60 years or more (8/48, 16.7%), those with coexisting illnesses (14/68, 20.6%) and in those with chronic obstructive pulmonary disease (3/21, 14.3%). *Staphylococcus aureus* was the commonest causative organism in intravenous drug abusers (3/7, 42.9%); all the three intravenous drug abusers with *Staphylococcus aureus* pneumonia had bacteraemia and two of them had right-sided infective endocarditis as well.

A comparison of some of the characteristics of patients with tuberculosis with those found to have pneumonia caused by other pathogens is shown in Table V. At the time of initial assessment, patients with tuberculosis were more likely to have involvement of upper lobe(s) and evidence of cavitation on chest radiograph than those with pneumonia caused by other pathogens. None of the other factors looked at, such as age, maximum temperature within the first 24 hours of admission and results of routine haematological and biochemical tests helped to differentiate these two groups of patients.

Nine patients (seven male, two female) died, giving an overall mortality rate of 9.2%. No pathogen was identified in four of these patients. In the other five patients, one had relapsed pulmonary tuberculosis and his sputum grew *Mycobacterium tuberculosis* (sensitive to rifampicin, kanamycin and pyrazinamide but resistant to streptomycin, ethambutol and isoniazid) as well as Acinetobacter spp; in the other patients, *Haemophilus influenzae, Escherichia coli, Staphylococcus aureus* and non-haemolytic *Streptococcus* were the causative organisms.

Patients who died were more likely to be aged over 65 years compared to those who survived (55.6% vs. 34.8%) and they were also more likely to have coexisting illnesses (88.9% vs. 67.4%) but these differences were not statistically significant. Bacteraemia was found in 22.2% of those who died compared to 7.9% of those who survived. Out of five patients who had assisted ventilation, four succumbed to their illness. A significantly higher proportion of patients who died had adverse prognostic factors of multilobar involvement on chest x-ray (88.9% vs. 50.6%, $p<0.05$), raised blood urea of over 7 mmol/L on admission (77.8% vs. 23.0%, $p<0.01$) and low arterial oxygen tension of less than 8 kPa on admission (66.7% vs. 22.1%, $p<0.01$) compared to those who survived. There were no significant differences between those who died and those who survived with respect to blood pressure on admission (systolic and diastolic), haemoglobin concentration, total white cell count and maximum temperature within the first 24 hours of admission.

Discussion

Accurate epidemiological data on pneumonia in Malaysia is lacking. However, it is known to be a common cause of hospital admission and

TableV
Comparison of Characteristics of Patients with Tuberculosis and Those with Pneumonia Caused by other Organisms (at Initial Assessment)

Characteristic	Tuberculosis (n = 15)	Non-tuberculous aetiology (n = 27)
Age, years	43.3 ± 17.6	53.4 ± 19.1
Involvement of upper lobe(s), number of patients	8 (53.3%)	4 (14.8%)*
Cavitation on chest radiograph, number of patients	8 (53.3%)	3 (11.1%)*
Maximum temperature in the first 24 hours, ° C	37.2 ± 0.5	37.8 ± 0.9
Haemoglobin, g/dL	12.3 ± 1.9	12.1 ± 1.6
Total white count, x 10^9/L	10.5 ± 2.9	14.3 ± 6.7
Platelet count, x 10^9/L	317.5 ± 120.3	287.3 ± 132.7
Blood urea, mmol/L	3.8 ± 1.5	5.7 ± 4.4
Serum creatinine, μmol/L	88.8 ± 15.5	100.0 ± 22.5
Serum sodium, mmol/L	134.1 ± 4.6	135.0 ± 6.3
Serum potassium, mmol/L	3.9 ± 0.6	3.8 ± 0.6
Blood glucose, mmol/L	10.5 ± 8.0	7.3 ± 2.5
Total protein, g/L	73.4 ± 7.0	72.8 ± 11.7
Serum albumin, g/L	37.8 ± 5.3	36.4 ± 5.8
Serum bilirubin, μmol/L	10.4 ± 5.1	13.0 ± 5.3

** $p < 0.01$*

attendance in outpatient clinics. According to Ministry of Health annual reports, respiratory diseases is the commonest cause of medical consultations and the fourth leading cause of hospital admission[12]. From the 1999 annual report of the Penang State Health Department, respiratory diseases ranked as the leading cause of outpatient clinic attendance and the seventh leading cause of hospital admission[13]. Pneumonia ranked the fifth leading cause of death in patients admitted to government hospitals in Penang in 1999. Statistics from developed countries show that community acquired pneumonia is a common clinical entity that results in significant morbidity and mortality as well as cost of treatment[1].

This is the first study on community acquired pneumonia to be carried out in Penang on adult patients requiring admission to hospital. No causative organisms were identified in a significant proportion of patients (57.1%). The possible causes for the inability to determine aetiology in the majority of patients are lack of sensitivity of laboratory investigations, prior antibiotic treatment and lack of more sophisticated investigations which are expensive and require highly trained personnel. Other prospective studies for evaluating the causes of community acquired pneumonia in adults have failed to establish an aetiologic diagnosis in 40 - 60% of cases[14], even with extensive diagnostic testing.

It is not surprising that *Mycobacterium tuberculosis* was found to be the commonest pathogen causing community acquired pneumonia in hospitalised patients in Penang Hospital. The incidence of tuberculosis remains high in Malaysia; in 1999, the reported incidence was 65.6 per 100 000 for all forms of tuberculosis and 36.1 per 100 000 for

bacteriologically positive cases of pulmonary tuberculosis[15]. Penang has a high tuberculosis incidence compared to other states in Peninsular Malaysia; in 1999, the incidence of tuberculosis in the North-east district of Penang Island was 132 per 100 000[16], the highest rate for any district in Peninsular Malaysia. This study has shown that pulmonary tuberculosis can be difficult to distinguish from other causes of acute pneumonia. Studies from Hong Kong and Singapore on hospitalised patients also found that *Mycobacterium tuberculosis* was a common cause of community acquired pneumonia in these countries[7,8].

The gram-negative bacteria, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, were the most common causes of community acquired pneumonia after *Mycobacterium tuberculosis*. Overall, gram-negative organisms excluding *Haemophilus influenzae* were found in 19.4% of patients. Although mostly described as rare causes of community acquired pneumonia in other series, the role of aerobic gram-negative bacilli in community acquired pneumonia is being appreciated more in recent years, especially in those with comorbid illness, the elderly, and those with severe community acquired pneumonia requiring admission to hospital and possibly the intensive care unit[17]. The high proportion of patients with coexisting illnesses in this study (nearly 70%) may account to some extent for the higher prevalence of gram-negative pathogens identified.

Another possible reason for the high rate of isolation of aerobic gram-negative bacilli from the sputum of patients in this study is antibiotic treatment prior to admission since even short courses of antibiotics can drastically alter the mouth and upper respiratory flora resulting in a predominance of gram-negative bacilli[18].

In western series, community acquired staphylococcal pneumonia is said to be infrequent except during epidemics of influenza. However, in Penang, it is seen in a distinct subset of intravenous drug users who present with *staphylococcus aureus* septicaemia; there may be right-sided infective endocarditis with haematogenous seeding of the lungs. These patients often have severe pneumonia which can be rapidly fatal and in which abscess formation is common.

Streptococcus pneumoniae is the commonest bacterial pathogen identified in most series of community acquired pneumonia[1]. It is an elusive pathogen in Penang and was identified in only 3.1% of patients in this series. Pure culture of the organisms from sputum may be hindered by contamination of sputum by pharyngeal organisms and overgrowth of other bacteria resulting from delay of transport to the laboratory[19]. In this study, no additional cases were identified by testing for pneumococcal antigen in blood and urine. The diagnostic yield may have been further increased by pneumococcal antigen assay on sputum, which was not done in this study. However, antigen positivity in the sputum can result from pneumococcal carriership of the lower respiratory tract, especially in patients with chronic bronchitis, hence the results would have had to be interpreted with caution[20]. Since the diagnosis of pneumococcal pneumonia is one of the most difficult to document microbiologically using routine investigations, it is possible that it was the aetiological agent in some of the patients in whom no causative organism was found.

Atypical pathogens such as viruses, mycoplasma, chlamydia and rickettsia are not usually identified because of the cost of serological tests and difficulty in obtaining paired sera; the results are usually too late to be of therapeutic use. No tests were done to detect viruses, chlamydia and rickettsia as causes of community acquired pneumonia in this study. *Mycoplasma pneumoniae* is regarded as a respiratory tract pathogen of children and young adults[21] with those in enclosed populations being particularly prone to infection. The patient found to have mycoplasma pneumonia in this study was a prisoner who recovered with doxycycline. It is probable that atypical pathogens account for a

higher proportion of pneumonias in patients not admitted to hospital, especially young patients with no comorbidity[22].

No case of Legionnaires' disease was found in this study. *Legionella pneumophila* is difficult to culture and the diagnosis is usually made retrospectively by a four-fold increase in indirect fluorescent antibody in the serum. It has been isolated from water samples from air-conditioning systems which may account for outbreaks in hotels and hospitals. Sporadic cases of community acquired legionellosis have been reported from Singapore[23] and organisms belonging to legionella species have been isolated from cooling towers in Kuala Lumpur[24]. Although none of the organisms isolated in Kuala Lumpur belonged to the Pontiac subgroup of serogroup 1, which commonly causes human infections, it is possible that this disease is an unrecognised cause of community acquired pneumonia in Malaysia.

This study was conducted over a short period of just over nine months and it is possible that less common pathogens were not detected during the study. For example, melioidosis is not a common cause of pneumonia in Penang but it must be remembered that *Burkholderia pseudomallei* is endemic in Southeast Asia[8,25,26]. Melioidosis can cause abscess formation, acute necrotising pneumonia, chronic suppurative infections and septicaemia, and it may be clinically difficult to distinguish this disease from tuberculosis. Its occurrence in Malaysia is well documented and it must not be forgotten as a cause of pneumonia in this part of the world[26]. A larger multicentre study will need to be carried out in order to obtain accurate information on the epidemiology of community acquired pneumonia in Malaysia.

Patients with community acquired pneumonia treated in an ambulatory setting have a low mortality rate (less than 1%)[1]. The overall mortality for hospitalised patients is 10 - 20% whereas patients who need admission to an intensive care unit have mortality rates of up to 50%[27]. There have been many studies of risk factors for mortality in community acquired pneumonia[27-29]. In our study, 9.2% of the patients died and those who died were more likely to be aged over 65 years, more likely to have coexisting illnesses and suffer from bacteraemia than those who survived. Multilobar involvement on chest radiograph, raised blood urea of over 7 mmol/L and low arterial oxygen tension of less than 8 kPa were found to occur significantly more commonly in those who died in this study and these factors have also been found to be adverse prognostic factors in other studies.

The use of empirical therapy is often necessary in the management of community acquired pneumonia because of non-specificity of clinical and radiological findings, limitations of diagnostic testing and presence of the potential for fatality which is difficult to assess in the early phase. Selection of appropriate antibiotics is hindered by lack of epidemiological data on the local pattern of causative pathogens which may be different from that reported from developed countries. With respect to the present study, the pattern of organisms is different from most series from Europe and North America where the commonest pathogen identified is *Streptococcus pneumoniae*, followed by *Mycoplasma pneumoniae* and *Haemophilus influenzae*. Knowledge of the local pattern of organisms would be useful for the development of guidelines for management of community acquired pneumonia in this country.

In summary, *Mycobacterium tuberculosis* and gram-negative organisms were the commonest pathogens identified in this study. The aetiological pattern of community acquired pneumonia in adults requiring hospital admission in Penang is different from that reported in other series and this must be taken into account when selecting antibiotics for empirical therapy.

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