PROSPECTIVE STUDY OF THE AETIOLOGY OF ADULT COMMUNITY ACQUIRED BACTERIAL PNEUMONIA NEEDING HOSPITALISATION IN SINGAPORE

K P Hui, N K Chin, K Chow, A Brownlee, T C Yeo, G Kumarasinghe, T B Chan, W C Tan

ABSTRACT

A prospective survey of 96 consecutive adult patients with community acquired pneumonia requiring hospitalisation was carried out at National University Hospital, Singapore. Causative pathogens were identified in 58% of patients. Mycobacterium tuberculosis was the most common pathogen (21%), followed by Streptococcus pneumoniae (12%), Haemophilus influenzae (5.2%), Mycoplasma pneumoniae (5.2%) and Staphylococcus aureus (4.2%). Gram-negative organisms (apart from Haemophilus influenzae) were found in 10% of pneumonia patients. More than half of the patient had pre-existing illness, the most common was diabetes mellitus (21%).

Keywords: *community acquired bacterial pneumonia, aetiology, Singapore*

SINGAPORE MED J 1993; Vol 34: 329-334

INTRODUCTION

Pneumonia acquired in the community remains a common cause for hospital admissions in both developed and third world countries. Despite the advent of potent antibiotics over the last 3 decades, significant mortality is still associated with community acquired pneumonia requiring hospitalisation. The pattern of microbiological organisms causing pneumonia in the community of the developed countries have been well studied[1-5]. In Singapore, there is no previous report of the pattern of organisms causing pneumonia in the community. A knowledge of the local pattern of pathogens is essential to provide a guide to empirical antibiotics therapy.

We therefore carried out a prospective survey on the pattern of causative microbial organisms of community acquired pneumonia needing hospitalisation. In addition, we analysed the clinico-pathological features that might differentiate between the different causative organisms.

Division of Respiratory Medicine
Department of Medicine
National University of Singapore
Kent Ridge
Singapore 0511

K P Hui, MD(UK)
Teaching fellow

N K Chin, M Med (Int Med)
Registrar

T C Yeo, MRCP (UK)
Resident

T B Chan, M Med (Int Med), FAMS
Associate Professor

W C Tan, FRCP (UK)
Associate Professor

Department of Microbiology
National University Hospital
Lower Kent Ridge Road
Singapore 0511

K Chow, MSc (ROC)
Senior Technician

A Brownlee, BSc (UK)
Senior Technician

G Kumarasinghe, FRCPath(UK)
Consultant

Correspondence to: Dr K P Hui

Table I - Diagnostic criteria of community acquired pneumonia

Pneumonia was defined as requiring
pneumonic consolidation on chest radiograph (on admission)
with at least 2 of the following
cough
fever (>38°) within 24 hours of admission
leucocytosis (white cell counf > 12 000 / ml)
response to antibiotics
Exclusion criteria
other causes of the pneumonic consolidation
isolated pleural effusion
hospital admission within the preceding 2 weeks

Table II - Investigations of patient with pneumonia

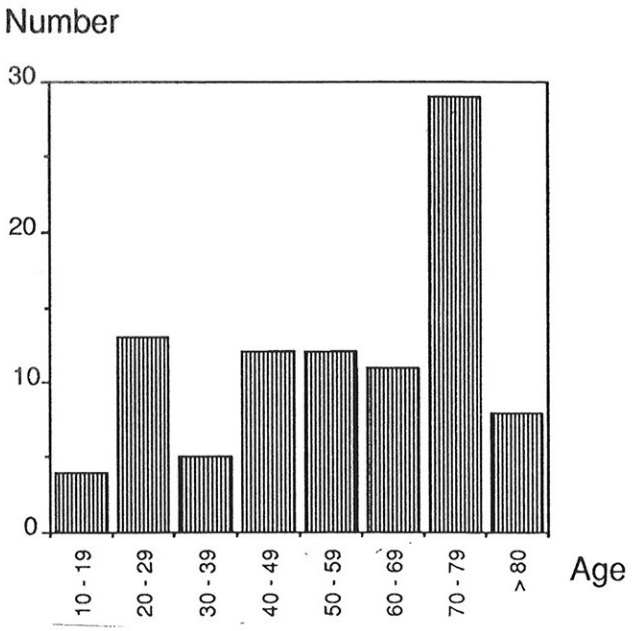
Microbiology	Sputum culture for pyogenic organism smear and culture for acid-fast bacilli pneumococcal antigen assay Blood culture serology for Mycoplasma pneumoniae and Legionella pneumophilla
Haematology	White cell count with differential Haemoglobin Platelet
Biochemistry	Urea and creatinine Sodium and potassium Liver function tests : alanine trans- aminase, alkaline phosphatase, total bilirubin Glucose Protein and albumin

METHOD

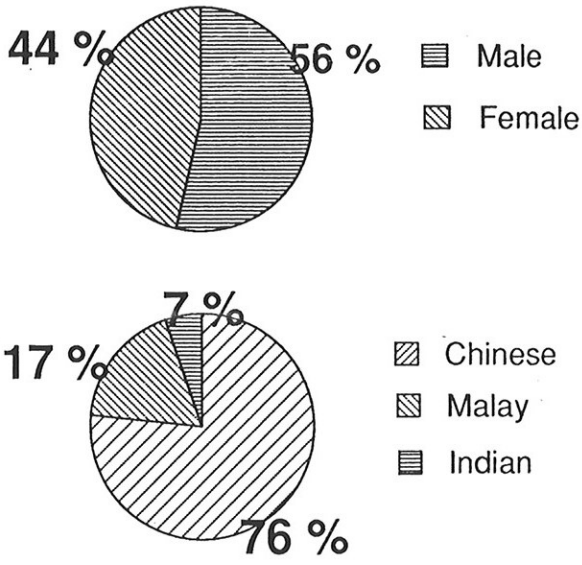
All patients admitted to National University Hospital from 1 March to 31 August 1991 with community acquired pneumonia were recruited into the survey. Definition of community acquired pneumonia was as outlined in Table I. Patients who had symptoms of cough with sputum production, but without radiological features of pneumonic consolidation were not considered to have pneumonia. Pneumonia that developed distal to airway obstruction in patients who had known carcinoma of the lung were also excluded. Patients with severe immunosuppression (such as immuno-suppressive chemotherapy, haematological malignancies, neutropenia) were excluded.

Fig 1 - Demographic data of patients with community acquired pneumonia needing hospitalisation : (a) Age distribution, and (b) sex and race distribution.

1(a)



1(b)



On admission, clinical variables of the patients that were collected included age, sex, racial group, history of smoking, past medical history, systolic blood pressure and heart rate on admission, and maximum temperature within 24 hours of admission. Microbiological, haematological and biochemical investigations were as in Table II. Sputum was sent for routine bacterial culture as well as *Mycobacterium tuberculosis* smear and culture. For a routine bacterial culture, sputum specimens were inoculated onto both chocolate and blood agar plates. A semi-quantitative count was made as heavy, moderate, or light growth when the pathogenic organisms were isolated from the primary, secondary, and tertiary streaking areas. An organism grown in pure culture or predominant among a scanty mixed growth was considered to be the primary pathogen. In addition, only specimens with greater than 25 white blood cells and less than 25 epithelial cells per low power field seen with Gram-stain were selected for the study[6]. Pneumococcal antigen assay were performed on sputum using the Wellcogen assay kit (Welcome, ZL 22). Sputum samples were prepared by autoclaving at 120°C 15 lb/in^2 for 15 minutes, then centrifuged at 10,000 rpm for 5 minutes. The supernatant was removed and latex agglutination performed. A definite agglutination after 3 minutes was considered positive for *S pneumoniae* antigen. For *Mycobacterium tuberculosis*, a Ziehl-Neelsen stain was performed, and followed by culture. Blood samples were taken for aerobic and anaerobic cultures, and organisms grown were considered to be significant pathogens of pneumonia in the absence of any other source of infection. *Mycoplasma pneumoniae* and *Legionella pneumophilia* serology were tested in paired samples 2 weeks apart. *Mycoplasma pneumoniae* serology was tested with passive particle agglutination quantitative test (Serodia-Myco II) providing 2-fold dilution from 1/40. A four-fold increase in titre or an initial titre of >1/160 with compatible clinical signs was considered positive for recent *Mycoplasma pneumoniae* infection. *Legionella pneumophilia* serology was tested with indirect fluorescent antibody test (antigen obtained from PHLS, Colindale, UK) from dilution of 1/16, and diagnosis of infection was made when there was at least a 4-fold rise in titre. Results of routine haematological (white cell count with differential, haemoglobin and platelet count) and biochemical (serum urea and electrolytes, blood glucose, serum protein and albumin levels, liver function tests) investigations were also noted.

Statistical analysis

Values were presented as mean ± standard errors of mean (sem). Differences between any 2 groups were analysed by Student's unpaired t-test, whereas differences between groups were analysed with analysis of variance (ANOVA). In view of multiple tests, a statistical significance was considered when $p \leq 0.002$ (Bonferroni's correction). Proportions were analysed by chi-square test with Yates continuous correction.

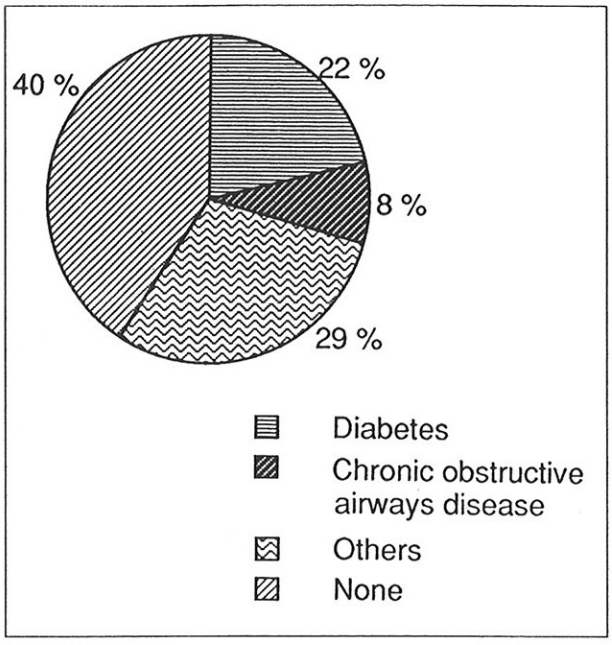
RESULTS

During the period, 96 patients were admitted with community acquired pneumonia. The demographical characteristics of age, sex and racial distributions were as in Fig 1. More than half of the patients had significant pre-existing medical illness (Fig 2), and diabetes mellitus was the single most common illness (21%).

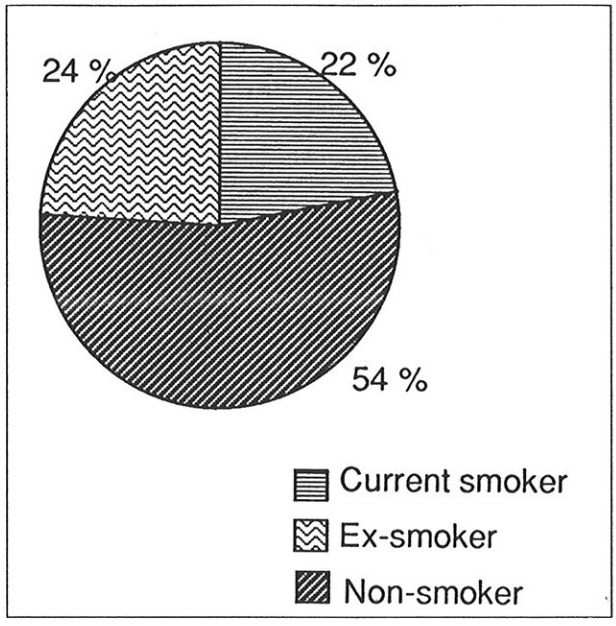
Microbiological investigations identified no pathogens in slightly less than half (42%) of the patients (Fig 3). Of the identified pathogens, *Mycobacterium tuberculosis* was the most common micro-organism causing pneumonia requiring hospital admission from the community (21%). One patient underwent fibreoptic bronchoscopy, and culture from the bronchoalveolar lavage showed *Mycobacterium tuberculosis*. For patients with non-tuberculosis pneumonia, the most common micro-organism identified was *Streptococcus pneumonia* (12%), of which 33% were culture positive. The other major groups of pathogens were *Haemophilus influenzae* (5.2%), *Mycoplasma pneumoniae* (5.2%) and *Staphylococcus aureus* (4.2%). Gram-negative organisms (excluding *Haemophilus influenzae*) caused 9.5% of the cases. A number of features were found to be useful in differentiating the various groups of pathogens (Fig 4 and 5). Patients with tuberculosis had higher platelet count than non-tuberculosis patients (ANOVA, p=0.001), but there was no significant difference in serum sodium levels or other laboratory investigations. Patients with *Mycoplasma pneumoniae* infection were much younger than the other groups (22.8 ± 2.4 years). Patient who were infected *with Streptococcus pneumoniae* tended to have higher total white cell count and

Fig 2 - Distribution of (a) pre-existing illness and (b) smoking history. The most common pre-existing illness was diabetes, and slightly more than half of the patients were non-smokers. Others included ischaemic heart disease, hypertension, epilepsy, thyrotoxicosis, hypothyroidism, etc.

2(a)



2(b)



absolute neutrophil count, though this was not statistically significant (ANOVA, p=0.02). Patients with *Staphylococcus aureus* pneumonia had higher urea levels (ANOVA, p=0.0004), but creatinine levels were not elevated. No other features were found to be significantly different amongst the different groups of pathogens. There were no associations between any group of medical illness and causative organisms.

DISCUSSION

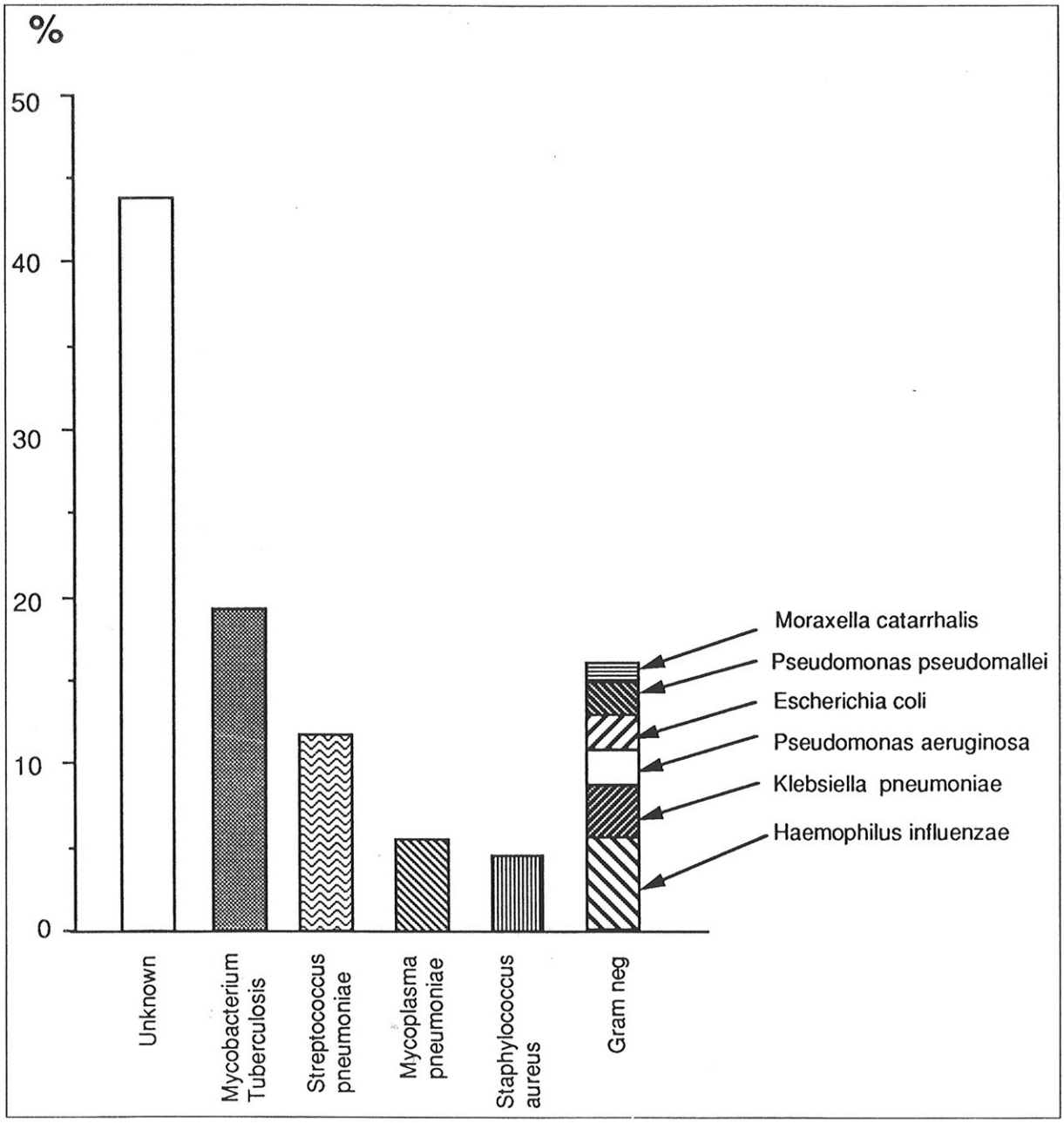
This is the first prospective survey of community acquired pneumonia needing hospitalisation in Singapore, and provides important information on the pattern of causative organisms and differentiating features on routine investigations. The essential feature for the diagnosis of pneumonia in our study is the presence of new radiographic pneumonic consolidation. This criterion excluded exacerbation of chronic obstructive pulmonary disease due to bronchitis, rather than pneumonia.

In common with nearly all the other described series, the largest group of patients had no identifiable organisms accounting for pneumonia. This may in part be due to pre-hospitalisation treatment with antibiotics prescribed by general practitioners and lack of sensitivity of conventional laboratory investigations. The proportion of undiagnosed pneumonia is comparable to other studies, showing undiagnosed proportion between 33 to 51%[1-5].

In our survey, *Mycobacterium tuberculosis* was the most commonly identified causative organism causing pneumonia acquired in the community. This is in contrast to the United Kingdom, where *Mycobacterium tuberculosis* was only found in 1% of a recent survey of pneumonia in the community[7]. This suggests that tuberculosis is still wide-spread in the Singapore community. This is supported by a recent report that the 1987 incidence rate of pulmonary tuberculosis in Singapore was 57 per 100,000 population[8], which is about six times the incidence rate in the USA in 1985 of 9.4 per 100,000[9]. We found that patients with tuberculosis had significantly higher platelet counts than non-tuberculosis patients. Although disseminated tuberculosis had been well-known to be associated with various blood disturbances, localised pulmonary tuberculosis had not been consistently found to be associated with changes in haematological profile[10]. At times, it may be difficult to distinguish tuberculosis from other bacterial pneumonia, the presence of relative thrombocythaemia may serve as a useful differential diagnosis feature. No other laboratory investigations were found to be helpful in differentiating tuberculosis and non-tuberculosis pneumoniae. In particular, serum sodium level was not significantly lower in tuberculosis despite the well-described association of inappropriate antidiuretic hormone secretion[11].

Amongst the non-tuberculosis patients, *Streptococcus pneumoniae* was the organism identified most commonly, as in accordance with the observations in other parts of the world. Sputum culture detected less than half of the cases of pneumococcal pneumonia, confirming that it is an insensitive test, as had been observed in previous studies[2,12]. Even with increased diagnostic yield with the pneumococcal antigen assay, it is likely that the true incidence of *Streptococcus pneumoniae* infection was higher as the sensitivity of the assay has been reported to be about 80%[1,2]. Patients with pneumococcal pneumonia tended to have higher total white cell and neutrophil counts compared to the other groups, although this was not statistically significant. Gram-negative organisms (excluding *Haemophilus influenzae*) accounted for about 10% of all the cases, a frequency that appeared higher than most other reported series. The British Thoracic Society survey of 25 British hospitals reported an incidence of only 3%[2]. Another multi-centre study in Spain found less than 5% of community acquired pneumonia were due to gram-negative organisms. Studies in the USA found incidence ranging from 2.4%[13] to 11.4%[3]. The higher incidence seen in our study may truly represent the pattern of local flora, not surprisingly, as some of the gram-negative bacilli (such as *Pseudomonas pseudomallei*) are endemic in South-East Asia. Should this higher prevalence of gram-negative organisms be confirmed by subsequent studies, there would be important implications in the choice of antibiotics therapy. Antibiotics resistance in

Fig 3 - Distribution of causative micro-organisms in patients with community acquired pneumonia. Total number of patients = 96



gram-negative organisms can develop rapidly[14], such that the emergence of multi-resistant strains have been seen in many other parts of the world. *Chlamydia pneumoniae*, the TWAR agent, was recently recognised to be an important cause of pneumonia in adults[15]. Serology for TWAR antibody was not performed in our study as there are still controversies about the reliability, specificity and interpretation of the commercially available assay kits. No cases of *Legionella pneumophilia* was found, as with a recent study from Hong Kong[16]. Perhaps *Legionella pneumophilia* infection is uncommon in Singapore, except in outbreaks in the community that was not within the time span of our study.

More than half of the patients had pre-existing illnesses, with diabetes mellitus being most common. The prevalence of diabetes mellitus in Singapore was less than 5% in a recent population-based survey[17]. The four-fold increase in prevalence of diabetes in our study population suggests that diabetic patients are predisposed towards pneumonia in the community. Increased susceptibility to pneumonia may be related to impaired granulocyte phagocytic functions found in diabetic patients[18]. In diabetic patients, the frequency of tuberculosis was no more than the other organisms.

As this survey was only carried out in the National University Hospital, it may still not be truly representative of the pattern throughout the whole island of Singapore. Nevertheless, there was no evidence that the local geographical features and admission pattern should bias the selection of causative pathogens. This was reflected in the even distribution of patients in the age and sex groups, and the racial distribution that was similar to that seen in the multi-ethnic population of Singapore. The survey was only over the period of 6 months, and thus some pathogens may be under-represented due to seasonal variations.

Fig 4 - Comparison of haematological and biochemical variables between tuberculosis and non-tuberculosis patients. Units : White cell count, platelet(x1000/ml);sodium, potassium, creatinine, urea, glucose and bilirubin levels (mmol/L);protein and albumin levels(g/dL) *p<0.001

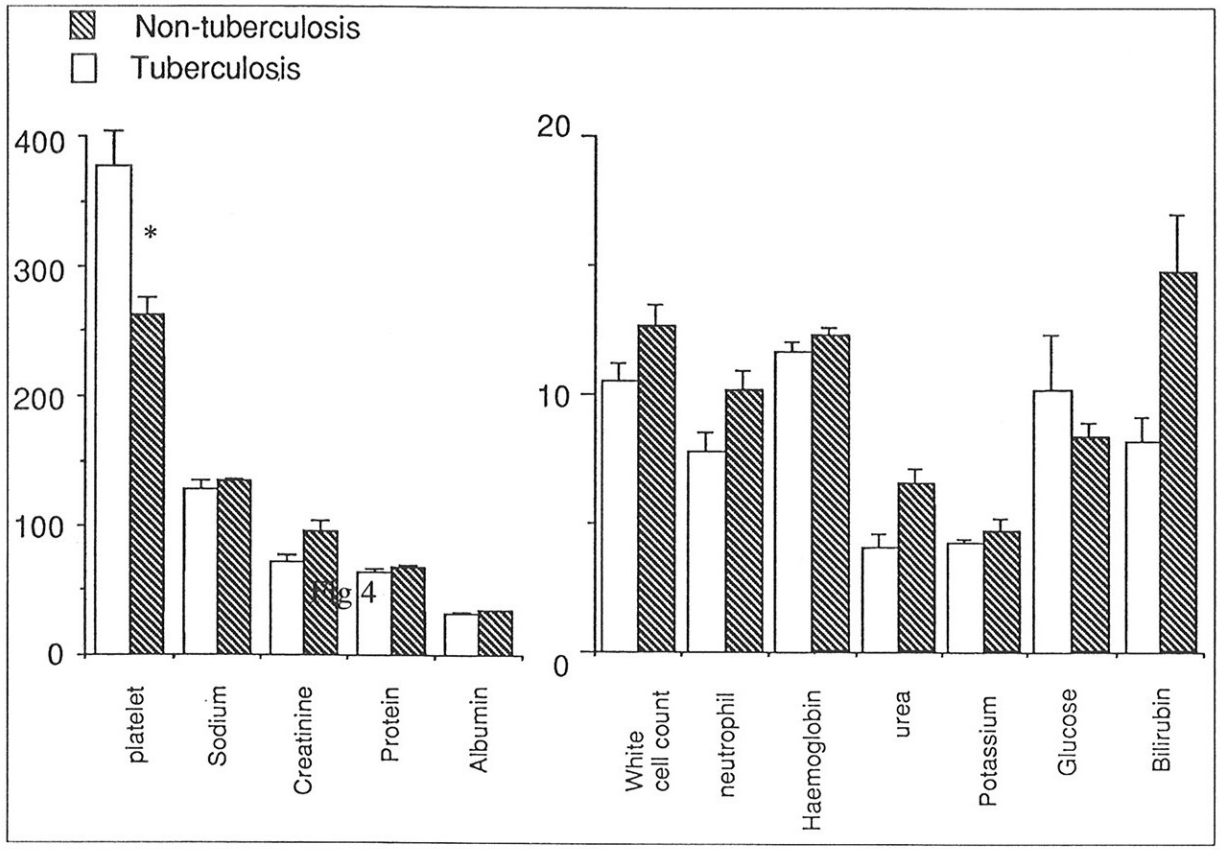
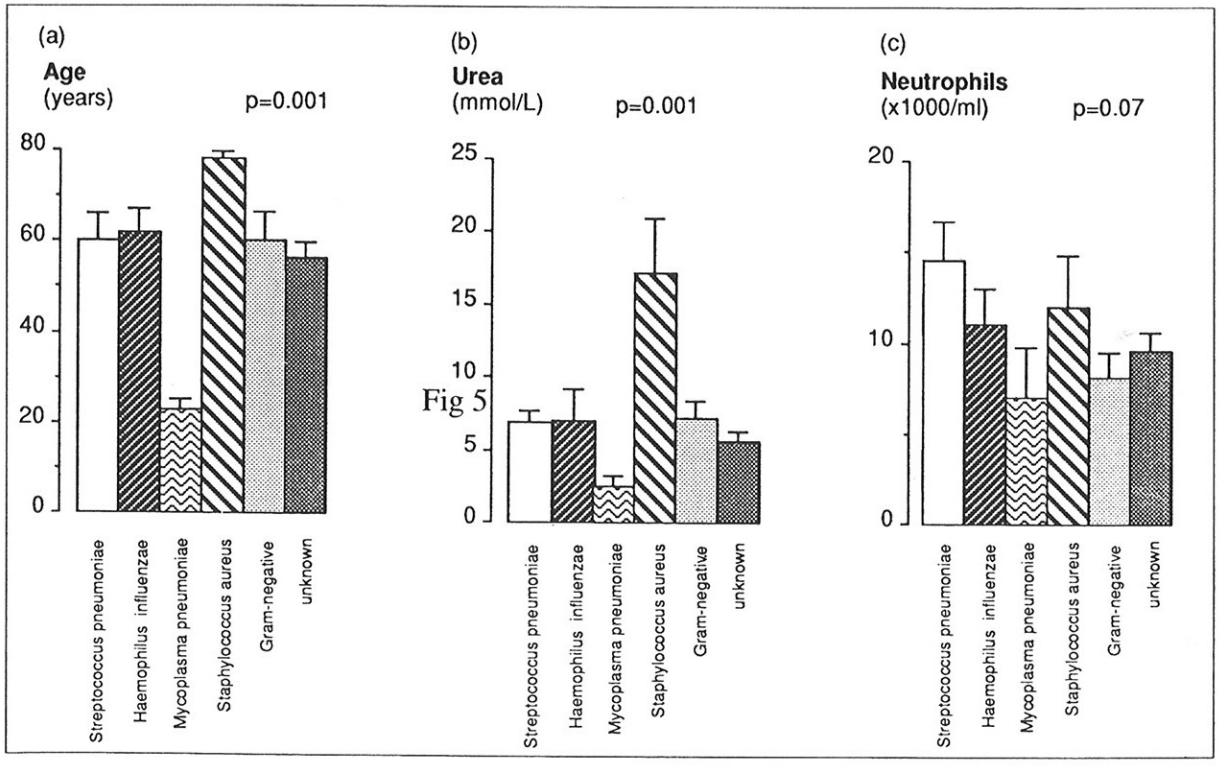


Fig 5 - Comparison of different groups of organisms for (a) age, (b) urea level and (c)neutrophil count.



In summary, our survey has found that pulmonary tuberculosis remains common and is the most common cause for pneumonia requiring hospitalisation in Singapore. The pattern of pyogenic pathogens was similar to those observed in other parts of the world, although gram-negative organisms appeared to be more prevalent.

ACKNOWLEDGEMENTS

The authors would like to thank all the medical and laboratory staff who had helped in the study. This study was supported by NUS grant RP 910413.

REFERENCES

1. Macfarlane JT, Finch RG, Ward MJ, Macrae AD. Hospital study of adult community acquired pneumonia. Lancet 1982; ii; 255-8.
2. British Thoracic Society and Public Health Laboratory Service. Community-acquired pneumonia in adults in British Hospitals in 1982-1983: A survey of aetiology, mortality, prognostic factors and outcome. Q J Med 1987; 239: 195-220.
3. Sullivan RJ, Dowdle WR, Marine WM, Hierholzer JC. Adult pneumonia in a general hospital. Arch Intern Med 1972; 129:935-42.
4. Moore MA, Meson MH, Charache P, Shepard RH. The characteristics and mortality of outpatient acquired pneumonia. Johns Hopk Med J 1977; 140: 9-14.
5. Blanger J, Blanquer R, Borras R, Nanffai P, Morales P, Menendez R, et al. Aetiology of community acquired pneumonia in Valencia, Spain : a multicentre prospective study. Thorax 1991; 46: 508-11.
6. Barlett JG, Ryan KJ, Smith TF, Wilson WR. Laboratory diagnosis of lower respiratory tract infection. Am Soc Microbiology 1987; Cumitech 7A:9.
7. Woodhead MA, MacFarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1987; i: 671-4.
8. Aditama TY. Prevalence of tuberculosis in Indonesia, Singapore, Brunei Darussalem and the Philippines. Tubercules 1991; 72: 255-60.
9. PC Hopewell. Mycobacterial diseases. In: Murray JF, Nadel JA. eds. Textbook of Respiratory Medicine. Philadelphia: WB Saunders, 1988 :862.
10. Cameron SJ. Tuberculosis and the blood - a special relationship? Tubercle 1974; 55:55-72.
11. Chung DK, Hubbard WW. Hyponatraemia in untreated active pulmonary tuberculosis. Am Rev Respir Dis 1969; 99: 595-7.
12. Perlino CA. Laboratory diagnosis of pneumonia due to Streptococcus pneumoniae. J Infect Dis 1984; 150: 139-44.
13. Mufson MA, Chang V, Gill V, Wood SC, Romansky MJ. Role of viruses, mycoplasmas and bacteria in acute pneumonia in civilian adults. Am J Epidemiol 1967; 86:526-44.
14. Neu HC. Overview of mechanisms of bacterial resistance. Diagn Microbiol Infect Dis 1989; 12:109S-116S.
15. Thom DH, Grayston JT. Infections with Chlamydia pneumoniae strain TWAR. Clinics in Chest Medicine : Atypical pneumonia syndromes. Philadelphia : WB Saunders Co. 1991; : 245-6.
16. Chan CHS, Cohen M, Pang J. A prospective study of community-acquired pneumonia in Hong Kong. Chest 1992; 101: 442-6.
17. Thai AC, Yeo PPB, Lun KC, Hughes K, Wang KW, Sothy SP, et al. Changing prevalence of diabetes mellitus in Singapore over a ten year period. J Med Asso Thailand 1987; 70: 63-7.
18. Repine JE, Clawson CC, Goetz FC. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetics. J Infect Dis 1980; 142:869.