THE OUTCOME OF HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

BY

DR SHAHARUDIN ABDULLAH

PUM 1016

Dissertation Submitted In Partial Fulfillment of The Requirement for The Degree of Master of Medicine (Internal Medicine)

UNIVERSITI SAINS MALAYSIA

2006

ACKNOWLEDGEMENTS

I would like to thank all lecturers in Medical Department, Hospital University Science Malaysia (HUSM) for their support in completing this dissertation and for all kind help during my postgraduate training. Special thanks to Associate Professor Dr. Zainal Darus for the advice and supervision in finishing this task. My appreciation also goes to Dr. Che Wan Aminud-din Hashim for the inspiration, ideas and for giving a chance to pursue my future dreams. My gratitude also goes to Dr. Than Winn from Department of Community Medicine (HUSM) for the advice on statistical aspect.

To my parents who inspired me a lot of their hardship and for their ever lasting support. Special thanks to my heroes – Dzafran and Ikhwan for their support and often cherished me with their thought and action.

Finally to my beloved wife, Dr Tengku Fatimah Murniwati Binti Tengku Muda, for the full support and understanding during these stressful years.

TABLE OF CONTENT

CHAPTER 2: OBJECTIVES

CHAPTER 3: METHODOLOGY

CHAPTER 4: RESULT

CHAPTER 8: STUDY IMPACT AND RECOMMENDATION

LIST OF TABLES

LIST OF FIGURE

ABBREVIATIONS

AST	Aspartate amino-transferase
ATS	American Thoracic Society
BAL	Bronchoalveolar Lavage
BALF	Bronchoalveolar Lavage Fluid
BTS	British Thoracic Society
BTSr	British Thoracic Society rule
CAP	Community-Acquired Pneumonia
CFU	Colony Forming Unit
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CTS	Canadian Thoracic Society
CURB	Confusion, Urea, Respiratory Rate, Blood pressure
ESRD	End Stage Renal Disease
HTN	Hypertension
IDSA	Infectious Disease Society Association
IHD	Ischaemic Heart Disease
IL	Interleukin
IQR	Interquartile Range
mBTSr	Modified British Thoracic Society rule
PaO_2	Partial Pressure arterial Oxygen
$PaCO_2$	Partial Pressure arterial Carbon Dioxide
PCT	Procalcitonin
PSB	Protacted Specimen Brush

PSI	Pneumonia Severity Index
RBS	Random Blood Sugar
ROC	Receiver Operating Characteristic
TNFα	Tumor Necrosis Factor alpha
UMMC	University Malaya Medical Centre
WCC	White Cell Count

ABSTRAK

Kesudahan pesakit akibat jangkitan paru-paru perolehan komuniti di Hospital Universiti Sains Malaysia.

Latar belakang:

Penyakit jangkitan paru-paru perolehan komuniti masih merupakan penyebab utama kemasukan ke hospital. Hasil daripada beberapa keputusan kajian yang telah dibuat, kadar kematian yang dialami oleh pesakit di hospital adalah tinggi. Kadar kematian ini dipengaruhi oleh sebilangan faktor-faktor klinikal semasa kemasukan ke hospital. Walaubagaimanapun, kajian terhadap kadar kematian dan faktor-faktor yang mempengaruhinya masih sedikit. Tujuan utama kajian ini adalah untuk menilai kadar kematian akibat jangkitan paru-paru perolehan komuniti di Hospital Universiti Sains Malaysia dan mengenal pasti faktor yang mempengaruhi kadar kematian.

Metodologi:

Ini merupakan kajian retrospektif yang dilakukan dari Januari 2004 hingga Disember 2004. Semua rekod pesakit jangkitan paru-paru perolehan komuniti disemak. Data-data pesakit yang memenuhi syarat-syarat kajian direkodkan. Maklumat yang diambil adalah data demografi, penemuan klinikal, hasil keputusan penyiasatan makmal dan jenis rawatan antibiotik. Analisa terhadap data ini dilakukan untuk menilai kadar kematian dan

seterusnya dianalisa untuk menentukan kaitannya dengan kematian akibat jangkitan paru-paru perolehan komuniti.

Keputusan:

155 rekod pesakit yang memenuhi syarat-syarat kajian telah dianalisa. Usia min pesakit adalah 62 ± 17 tahun. Kadar kematian akibat jangkitan paru-paru perolehan komuniti adalah 19.4%. Faktor-faktor yang mempengaruhi kadar kematian ialah komposisi komorbid utama (OR11.1; p=0.001), kekeliruan (OR 18.7;p=0.001) dan hipoksemia (OR 10.6;p=0.002). Faktor lain yang dikenal pasti adalah tekanan darah diastoli yang rendah dan hiperglisemia ≥ 13 mmol/l dengan kebarangkalian(OR)1.1(p=0.002)dan 6.4(p=0.007).

Pesakit mempunyai risiko kematian setinggi 46.3 kali ganda sekiranya terdapat tiga daripada faktor-faktor berikut; mempunyai komposisi komorbid utama, kekeliruan, tekanan darah diastoli rendah, hipoksemia dan hiperglisemia. Analisa terhadap kriteria keterukan telah mengenalpasti 21 daripada 27 pesakit dalam kajian ini mengalami jangkitan paru-paru yang serius. Sensitiviti kriteria yang dicadangkan untuk meramal tahap keterukan penyakit adalah 0.70 dan tahap penilaian negatif 0.93.

Rumusan:

Kadar kematian akibat jangkitan paru-paru perolehan komuniti di HUSM adalah setara dengan kajian yang lampau. Faktor yang boleh mempengaruhi

kadar kematian ini juga adalah hampir sama. Sebilangan daripada faktor-faktor ini dapat digunakan untuk menentukan tahap keterukan penyakit jangkitan paru-paru. Kehadiran tiga daripada factor ini dapat membantu mengenal pasti sebilangan pesakit yang berisiko tinggi, seterusnya perawatan yang optimum dapat diberikan.

ABSTRACT

The outcome of hospitalized patients with Community- Acquired Pneumonia in HUSM.

Background:

Community-acquired pneumonia (CAP) remains an important cause of hospital admission. Studies have shown that the mortality of patients admitted with community-acquired pneumonia is high. The outcomes have been shown to be influenced by various clinical variables at presentation. Applications of these variables as predictor of severity have been shown to improve patients management outcome. The outcome of patients admitted due to CAP has not been studied in Hospital University Science Malaysia (HUSM). The main purpose of this study was to evaluate outcome in patients who required admission due to community acquired pneumonia in HUSM and to determine factors that influenced their poor outcome.

Methodology:

This was a retrospective cohort study between January 2004 to December 2004. Records of patients with community-acquired pneumonia admitted to HUSM were screened. This study included all patients aged more than 12 years old who met the inclusion criteria. The following information; demographic data, initial

clinical findings, laboratory investigations and type of antibiotics regime given were recorded into customized data collection sheet. Variables obtained were examined for association with mortality. Severity prediction criteria were formulated from identified variables that showed significant association with mortality.

Results:

Records of 155 patients' that met the inclusion criteria were evaluated. The mean age at presentation was 62 ± 17 years. The mortality rate was 19.4%. Variables that significantly influenced the mortality on multivariate analysis at presentation were presence of important co-morbid illnesses (OR 11.13; p = 0.001), confusion (OR 18.72; p = 0.001) and hypoxaemia (OR 10.62; p = 0.002). Other factors identified were low diastolic blood pressure and random blood sugar greater than 13 mmol/l with odds ratio of 1.08 (p=0.002) and 6.37 (p=0.007) respectively.

The presence of any three of following variables on admission; presence of co-morbid illness, confusion, low diastolic blood pressure of ≤ 60 mmHg, low oxygen saturation and random blood sugar equal or greater than 13 mmol/l was associated with a 46.3 fold increase in death.

The suggested predictive severity rule identified 21 of the 27 patients who died as having severe community acquired pneumonia. The sensitivity of the suggested severity model for predicting death was 0.70 and specificity of 0.95. The rule had a negative predictive value of 0.93.

Conclusion:

The mortality from community-acquired pneumonia requiring hospitalization in our centre is high compared to previous studies. We found that certain factors that influenced the outcome of our patients were almost similar with other previous studies. We found that the presences of three of the five variables (co-morbid illness, confusion, low diastolic blood pressure, hypoxaemia and hyperglycaemia) would allow us to detect patients who at risk of poor outcome.

STUDY BACKGROUND

Community-acquired pneumonia is a major health concern throughout the world as it has high morbidity and mortality. This inevitably leads to increase in health care cost and economic burden. It is estimated that USD 400 million is spent for the management of these patients. Each year in the United States, an estimated 4 million cases occur. Most patients are managed in the community whereas admission to hospital is required in 20 to 40% of patients. (Hoare and Lim, 2006).

A systematic review of the literature on pneumonia prognosis has identified a variety of demographic factors, symptoms, physical examination findings, co-morbid illnesses, laboratory abnormalities, and aetiologic agents that are independently associated with mortality in patients who required hospitalization. By combining these prognostic factors, investigators have developed a variety of indices to predict short-term mortality. These predictive instruments vary with respect to the patient populations studied, number of predictor variables included and statistical methods used.

There is not much data on mortality associated with community-aquired pneumonia in Malaysia. This study is to look at the outcome of patients who required hospitalization for pneumonia in Hospital University Science Malaysia (HUSM) and to study the factors associated with mortality. We hope that the data collected in this study would benefit physician managing these cases in this region.

INTRODUCTION

1.1 OVERVIEW OF PNEUMONIA

1.1.1 Definition

Pneumonia is generally defined as inflammation of lung parenchyma characterized by consolidation of the affected area. In this condition the alveolar spaces being filled with exudates, inflammatory cells and fibrin. Distribution may be lobar, segmental or lobular. It can be defined pathologically as lobar pneumonia or bronchopneumonia. It can also be defined clinically as community acquired, hospital-acquired pneumonia and ventilator-associated pneumonia.

Community-acquired pneumonia is defined as an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community. Patients usually present with symptoms and signs consistent with an acute lower respiratory tract infection, with at least one systemic feature i.e. either a symptom complex of sweating, fever, rigor and/or temperature of 38°C or more (MacFarlane et al, 2001).

Hospital-acquired pneumonia is defined as infection of lung parenchyma occurring more than 48 hours after hospitalization. Where pneumonia occurs in the subset of patients receiving mechanical ventilation, it is termed as ventilator-associated pneumonia.

1.1.2 Pathogenesis

Micro-organisms are deposited in terminal bronchioles and alveolar spaces via several mechanisms. These include aspiration of oropharyngeal or gastric contents, inhalation of bacterial laden aerosols and haematogenous spread from a distant infected site to the lung. Most of cases are due to aspiration and inhalation mechanism (Leeper and Moss, 2003).

Inhalational entry of organism is associated with specific pathogens that are able to reach the lower airway. These pathogens include *Legionella* species, *Mycoplasma pneumoniae, Chlamydia* species and *Coxiella burnetti*. These pathogens share common ability to resist phagocytosis or to survive intracellularly within phagocytes.

Depending on the balance between the virulence of the pathogen and the patient's host defense system, an intense inflammatory process ensues after propagation of organisms in the lower respiratory tract system. Exudation of protein-rich fluid in alveolar spaces then cause ventilation perfusion mismatch; contributing to increased work of breathing and hypoxia (Leeper and Moss, 2003).

1.1.3 Incidence

It is difficult to determine the true incidence of community acquired pneumonia (CAP) in a given population because it may range from mild infection which goes unreported by the patient to severe illness requiring hospitalization. The incidence might be under reported in less developed countries. It is estimated that up to 5.6 million cases of CAP occur annually in United States and as many as 1.1 million of these cases require hospitalization (Ramirez, JA 2003).

Incidence of community-acquired pneumonia (CAP) also varies according to age group and study centers. Hoare and Lim (2006) reported that the annual incidence rate was 6 per 1000 in the 18 to 39 age group. This incidence rose to 34 per 1000 population in those aged more than 75 years old. The incidence was similar in a study done by Jokinen and colleague, where the frequency of CAP occurred in the elderly age group was 34 per 1000 population (Jokinen et al, 1993).

Based on three prospective population studies from United Kingdom, Finland and North America, the annual incidence of CAP ranges between 5 and 11 per 1000 adult population (BTS, 2001). A Recent prospective observational study by O'Meara et al (2005) showed the incidence of hospitalization for pneumonia was 11.1 per 1000 person per year following median of 10.7 years follow up study. In 1997, based on the Malaysian second national health survey, Malaysia had a total of 19,827 reported hospital admissions due to pneumonia with 12.4% mortality.

1.1.4 Aetiology of Community Acquired Pneumonia

The reported prevalence of specific pathogens varies depending on the methods by which the aetiological diagnoses were determined and the patient population studied. In most cases, there was a small range of key pathogens that were associated with community-acquired pneumonia. Most literature in western studies found *Streptococcus pneumoniae* as the most frequently identified pathogen (Farber 1999; BTS 2001; ATS 2001; Apisanithar and Murdy 2005). Other key pathogens reported were *Haemophilus influenzae*, *Mycoplasma pneumonia, Legionella pneumophilia and Chlamydia pneumoniae* (Ruiz, Ewig, Marcos et al 1999; Waltanathum, Chaoprasong, Nunthapisud et al 2003).

In the local setting, a study by Liam et al (2001) at University Malaya Medical Center Kuala Lumpur showed the most frequent isolated pathogens were gram-negative bacilli. *Klebsiella pneumoniae* was the most frequently isolated which caused 10.2% of all cases, followed by *Streptococcus pneumoniae* and *Haemophilus influenzae* in 5.5% cases, *Mycoplasma pneumoniae* and *Pseudomonas aeruginosa* (3.9%) were isolated in 3.9% cases respectively.

A great deal of atypical pathogens causing CAP has been studied. Ngeow YF et al found that the overall infection rate for atypical pathogens in Asia-pacific region was 19.9% (Ngeow YF, 2001). This study which involved Malaysia (Kuala Lumpur and Petaling Jaya), found the infection rates for *Mycoplasma*

pneumoniae was 9.4%. While the infection rate for *Legionella pneumophilia* and *Chlamydia pneumoniae* was 6.2% and 4.3% respectively.

Burkholderia pseudomallei should be considered as one of the causative organism in community-acquired pneumonia in Southeast Asia especially in patients with diabetes mellitus. In Northeastern Thailand, *Burkholderia pseudomallei* were identified in 11% of patients hospitalized for CAP (Reechaipichitkul and Tantiwong, 2002).

In a study conducted in Malaysia, *Burkholderia pseudomallei* was identified as the causative microorganism for CAP in 1.6% of cases (Liam et al, 2001). Whereas in a recent study by How and colleague conducted in Pahang over three years, 40% of confirmed cases of meliodosis presented with pneumonia (How et al 2005).

1.1.5 Risk factors for pneumonia

1.1.5(a) Age

Community-acquired pneumonia (CAP) is a frequent cause of hospital admission and has significant morbidity and mortality in the elderly. The important effect of age on symptoms and clinical presentation of pneumonia were first described by Sir Wiliam Osler many years ago (Feldman 1999). Many studies had shown an increased incidence and fatality rate in the elderly. The cardinal risk factors for high incidence of pneumonia in elderly are presence of co-morbidity and malnutrition (Schafer H. and Ewig S. 2000).

The incidence of community acquired pneumonia in persons 65 years or older ranged between 51.1 and 55.6 per 1000 persons per year (Feldman, 1999). The incidence of hospitalized elderly patients with community-acquired pneumonia also rose to five-fold as age increases from 65-69 to more than 90 years (Kaplan, Angus, Griffin, et al 2002).

There is no simple explanation for the increased susceptibility of the elderly to pneumonia. Many age related changes are thought to increase the risk. These include systemic disease such as diabetes, lung disease, cardiac disease or rheumatism in addition to various age-associated changes in lung structure and function accompanied by age associated alterations in the immune system.

There is a change in subpopulations of T lymphocytes in the circulation with increase in percentage of immature cells in the elderly. T lymphocytes in elderly patients have an attenuated mitogenic response to antigen and a reduced capacity to produce or respond to cytokines such as interleukin-2 (Feldman 1999).

The elderly have been shown to have an increase in oropharyngeal colonization rate with pathogens such as *Staphylococcus aureus* and aerobic gram-negative bacilli such as *Klebsiella pneumonia* and *Escherichia coli* (Feldman 1999). A study by Liam et al (2001), had confirmed that gram-negative bacilli were more frequently identified in patients age 60 years or older.

Although this colonization may be transient, it may increase the risk of pneumonia caused by these pathogens. Colonization occurred particularly in patients who are unable to ambulate without assistance, who have difficulty performing their daily activity of living, who have bladder incontinence, chronic cardiac or respiratory disease.

1.1.5(b) Alcoholism

High alcohol intake is the main risk factor for developing pneumonia in middle-aged people. Ethanol adversely affects many properties of the respiratory tract defense mechanism. Alcohol directly inhibits the ability of lung immune

cells to kill bacteria and excessive ethanol ingestion suppresses the normally protective acute inflammatory response to infection, resulting in defective recruitment of additional innate immune cells.

Additionally it disrupts the link between innate and adaptive pulmonary immunity further hindering the alcoholic patient's ability to eliminate invading pathogens (Happel and Nelson 2004). Alcohol facilitates bacterial colonization of the oropharynx with gram-negative bacilli, impairs cough reflexes, alters swallowing and mucociliary transport and impairs the function of lymphocytes, neutrophils, monocytes and alveolar macrophages. Each of these factors contributes to the reduced bacterial clearance from the airways found in these patients.

Infections caused by gram-negative bacilli and *Legionella pneumophilia* occur more frequently in heavy drinkers. Study by J.F. Sola et al (1995) found that high alcohol intake was an independent risk factor for developing community-acquired pneumonia. They also found that patients with chronic alcoholism had a higher incidence of pneumonia caused by gram-negative bacilli and Staphylococcus aureus.

Tumor necrosis factor-α (TNF-α) is one of the important cytokines produced by alveolar macrophages in pulmonary host defense against most key pathogens in community-acquired pneumonia. Alcohol intoxication has been shown to impair the pulmonary TNF-α response to bacterial endotoxin

lipopolysaccharide (cell wall component of bacteria) produced by these pathogens (Happel and Nelson 2005).

Acute ethanol exposure meanwhile prevents cleavage of TNF-α from the producing cells surface rendering it further ineffective. However acoholism is not a risk factor for the pneumonia severity except in the case of pneumococcal infection with leucopenia.

1.1.5(c) Smoking

Smoking alters mucociliary transport and function that may lead to impaired clearance of aspirated particles from lower respiratory tract. Smoking also affects humoral and cellular host defenses, epithelial cell function and increases the adhesion of *Streptococus pneumoniae* and *Hemophilus influenzae* to the oropharyngeal epithelium. Smoking also predisposes to infections by influenzae, *Legionella pneumophilia* and *Streptococcus pneumoniae* (Rabbat and Huchon 2004).

1.1.5(d) Associated Disease

Associated diseases or co-morbid illnesses are frequent in patients hospitalized due to community-acquired pneumonia, ranging from 46% to 80% (Rabbat and Huchon 2004). Although associated diseases do not

increase mortality, in most studies up to 70% of fatal cases due to pneumonia had comorbid illness compared to 40% among those who survived (Rabbat and Huchon 2004).

O'Meara in their study found that the risk for pneumonia was higher in patients with history of cardiovascular disease and chronic obstructive pulmonary disease (O'Meara et al, 2005).

1.1.5(e) Miscellaneous factors

Previous hospital stay increases the risk for pneumonia due to *Streptococcus pneumoniae* in particular. Exposure to stagnant water or to domestic water supply systems (Rabbat and Huchon 2004) may favor the development of legionnaires' disease.

A variety of medications may contribute to the development of pneumonia especially in elderly patients, morphine and atropine interfere with mucociliary clearance; sedatives alter the coughing reflex and epiglottic function whereas corticosteroids and salicylates act on phagocytosis functions (Rabbat and Huchon 2004). Infection with Legionella species may be more frequent in patient on oral steroids (BTS 2001).

1.1.6 Diagnostic Testing for Community-Acquired Pneumonia

1.1.6(a) Noninvasive Testing

The causative agent of community-acquired pneumonia can be identified by noninvasive microbiological investigation in majority of cases. In most instances, the causative agents were isolated from blood or expectorated sputum.

1.1.6(a) i Sputum Gram Stain

The gram stain of expectorated sputum has been widely used for the diagnosis of community-acquired pneumonia. The sputum gram stain can provide specific diagnostic information and serve as an early guide to therapy. However the use of sputum gram stains as a diagnostic tool can be misleading, as it needs to be interpreted according to strict criteria. A specimen with fewer than 10 squamous epithelial cells and more than 25 neutrophils per low power field with evidence of a predominant bacteria morphotype examined under high power field is an accurate indicator of the cause of pneumonia.

1.1.6(a) ii Blood Culture

Blood cultures are positive in 4% to 18% in hospitalized patients with community-acquired pneumonia (S.J. Skerrett 1999). The yield of blood culture is strongly influenced by prior antibiotic therapy. Blood cultures are positive in less than 5% of patients who have received prior antibiotics before the blood specimen is drawn.

1.1.6(a) iii Antigen Detection

Methods for the detection of microbial antigens in respiratory secretions or other body fluids can be used for rapid aetiologic diagnosis of community-acquired pneumonia. Commonly used test can detect antigens for *Streptococcus pneumoniae*, *Legionella pneumophilia* and respiratory viruses. The specificity of these tests are generally more than 90% whereas the sensitivity are varies (table 1).

Organism	Specimen	Sensitivity(%)	Specificity(%)
Streptococcus pneumoniae	Sputum	42-90	73-100
	Serum	9-62	>90
	Urine	0-58	>90
Legionella pneumophilia	Sputum, BALF	22-75	>90
	Urine	55-90	>95
Respiratory viruses	Throat swab	50-90	>90
	BALF	50-90	>90

Table 1: Antigen detection for diagnosis of community-acquired pneumonia.

1.1.6(a) iv Serological Antibody detection

The serological measurement of a specific antibody response has limited value in establishing the aetiology of community-acquired pneumonia. The main reason is the lag of time response for a positive result, which may be up to several weeks. However, the detection of increased levels of specific immunoglobulin M antibody in a single serum sample can be use in the early diagnosis of pneumonia caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophilia* and *Coxiella burnetti* (Skerrette 1999). These tests, however, are less sensitive and specific if there was less than four-fold increase in antibody titers between paired serum specimens taken several weeks apart.

1.1.6(b) Invasive Procedures

Invasive procedures are rarely required for early microbiological investigation in community-acquired pneumonia except for thoracocentesis. Thoracocentesis is an important step in evaluation of pleural effusion associated with pneumonia (parapneumonic effusion). However, other invasive procedures can be very useful in cases of severe pneumonia and when there is suspicion of resistant pathogen.

The yield of bacterial cultures obtained via invasive procedures varies according to the type of procedures (table 2). For most of these procedures,

the diagnostic yield can be augmented by testing for microbial antigens or nucleic acids.

Procedure	Sensitivity(%)	Specificity(%)
Thoracocentesis	5-56	>95
Transtracheal aspirate	44-95	68-100
Transthoracic aspirate	33-80	>95
Bronchoscopy		
PSB $\geq 10^3$ CFU/mL	54-85	≥ 85
BAL $\geq 10^4$ CFU/mL	38-58	≥ 85

Table 2: yield of bacterial cultures from invasive procedure

1.1.7 Impact on health system

From prevalence base burden of illness study in United Kingdom estimated that CAP caused a direct health care cost of 441 million pounds annually during the 1992 to 1993 study period (Guest JF and Morris A, 1997). The average cost for managing pneumonia in the out patient community was estimated at 100 pounds per episode and those required hospitalization accounted for 87% of the total annual cost.

The economic impact of the illness reported in the United States was estimated to be 8.4 billion USD in direct costs; 400 million USD was spent on the care of 4.5 million outpatients while 8 million USD was spent on the care of 1.1 million hospitalized patients with community-acquired pneumonia (Niederman et al, 2001).

Increase health care utilizations have been shown to be due to improper used of antibiotic hence lead to antibiotic resistance and failure (Wu et al, 2004). A study by Wu found increase in health care cost in patients with community-acquired pneumonia who failed with initial macrolide treatment within four weeks of therapy. These patients had used more medical care services and received a second antibiotic within 4 weeks of initial macrolide therapy. Substantial saving in cost could probably be made by strategies to reduce the requirement for hospital admission and shorten the length of hospital stay for patients with non-severe community acquired pneumonia.

1.1.8 Measures to reduce health burden

Various treatment protocols were developed to guide management of patients with community-acquired pneumonia. Management concordant to the protocol will improve health care cost and socio-economic impact associated with this disease. Among the protocols developed were antibiotic prescribing protocol, pneumonia severity tools and management algorithm.

Al-Eidan et al (2000) reported that by using a specific antimicrobial prescribing protocol, there was a significant reduction in length of hospital stay, duration of intravenous antibiotic and treatment failure. These changes were significantly associated with reduction in healthcare related cost.

A study by Brown et al (2003) assessed the impact of initial antibiotic choices on total hospital cost and length of hospital stay. This hospital claim-made database study had confirmed the value of dual therapy in reducing mortality, total length of stay and hospital charges.

Identifying patients with less severe or mild pneumonia will reduce unnecessary hospitalization and subsequently reduce healthcare cost. Applying disease specific prediction rules will help physicians in deciding whether a patient can be safely treated at outpatient setting. One of most widely used and validated prediction rules is the pneumonia severity index proposed by American Thoracic Society 2001 clinical guideline for the management of adults with community-acquired pneumonia (Niederman MS et al 2001).

By applying the algorithm, patients in low risk class i.e. risk class I, II and III are at low risk of death and can be safely treated as outpatients (Fine et al, 1997). Orrick found patients treated with preferred antibacterial therapy as recommended by Infectious Disease Society Association (IDSA), had a shorter mean length of hospital stay, a lower total cost of hospitalization and lower antibacterial cost compared with patients who did not receive preferred therapy (Orrick JJ *et al* 2004).

Variations in clinical practice have a major influence on cost of care, although there is no evidence that it changes the patient's outcome. Laing *et al* (2004) identified that variations in management of hospitalized CAP patients

outweighed the influence of patient's factors on the duration of intravenous antibiotic therapy. This variation, in turn was the major determinant for length of stay for hospitalized patients and has correlation with total health care cost.

1.1.9 Pneumonia Vaccination

Influenza vaccination is recommended for those at high risk of mortality from influenza or pneumonia complications. These high-risk groups include those with chronic lung disease, heart, renal and liver disease, patients with diabetes mellitus, those who are immunosuppressed due to disease or treatment and those patients aged over 65 years (BTS 2001) of age.

Pneumococcal vaccination is recommended in all elderly person age 65 years or older (BTS guideline 2001; Gross 2001). Vaccination is also recommended in other patients who have risk for pneumococcal infection. These groups of patients include those who have severe dysfunction of the spleen e.g. patients with sickle cell disease and celiac disease or anatomic asplenia and those patient's with chronic illnesses (congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, alcoholism and cirrhosis). A study by Fisman and colleagues showed prior vaccination against pneumococcus is associated with improved survival, decreased chance of respiratory failure and decreased length of hospital stay among patients with community-acquired pneumonia (Fisman DN, Abrutyn E, Spaude KA et al 2006).

1.2 COMMUNITY-ACQUIRED PNEUMONIA MORTALITY

1.2.1 Frequency

The mortality from community-acquired pneumonia in patients treated as outpatients ranged from 1% to 5%. While for hospitalized patients the mortality rate ranged from 15% to 30%, making it the seventh leading cause of death in United States of America (Mokdad et al, 2000). Those requiring intensive care were found to have mortality as high as 50% (Gibson et al 2003). A local study by Liam CK (2005) found that the overall in-hospital mortality in adult patients to be as high as 11%.

1.3 RISK FACTOR FOR PNEUMONIA MORTALITY

1.3.1 Age

Respiratory tract infections are a major cause of disease and death in the elderly. In 1995, from weekly morbidity and mortality report in the United State, 89% of all pneumonia deaths were attributed to patients aged 65 years or more. There was an increment of 44% pneumonia deaths in this age group from 1975 to 1992.

A Finnish study found that increasing age (for age more than 70 vs. 60-69 years) is one of the independent risk factors for pneumonia related mortality (Koivula 1994). An epidemiological study by Feikin identified advanced age as

among factors associated with mortality together with presence of underlying disease and Asian race (Feikin *et al* 2000). A study by Liam found a similar trend of mortality in elderly patients. He found mortality rate in patients aged more than 65 years old was as high as 53% (Liam CK 2005).

Elderly individuals may be at increased risk of death due to progressively impaired immune-surveillance, depressed ability to mount an appropriate immune response or dysregulated immune responses (Meyer, KC 2001).

Frequently, elderly patients had associated medical illnesses that can account for higher mortality in pneumonia. In patients with cardiac disease, the risk of death from community-acquired pneumonia is multiplied by 5-fold (Rabbat and Huchon 2004). Another study by O'Meara found that elderly patients with age more than 65 years old with co-existing chronic obstructive pulmonary disease had higher risk of death from pneumonia (O'Meara et al 2005).

1.3.2 Pre-hospitalization Functional status

Marrie and Wu in their study found that functional status at the time of admission was an independent predictor of mortality. Patients who were wheelchair bound or bedridden were more likely to die compared to patients who are able to walk unaided (Marie TJ and Wu LL, 2005).

Similarly Salive *et al* also found limitations in activities of daily living and cognitive impairment was independently associated with a significantly increased risk of pneumonia mortality (Salive *et al*, 1993).

1.3.3 Markers of inflammatory response

The usefulness of the inflammatory markers to assess the outcome of CAP is still unclear. The use of inflammatory markers may help to identify those patients with poor prognosis and may help to establish different therapeutic strategies. Multiples profiles of inflammatory markers have been studied. These include pro-inflammatory markers such as tumor necrosis factor alpha (TNF-α), interleukin 1β (IL-1β), IL-6, IL-8 and anti-inflammatory cytokine (IL-10).

Higher concentrations of pro-inflammatory and anti-inflammatory cytokines were found in Legionella pneumonia, in bacteremic pneumonia episodes, those patients who required mechanical ventilation and as well as in non-survivors from severe pneumonia (Fernendez-Serrano *et al* 2003). In the study, Fernendez also found that serum IL-6 and IL-10 concentrations greater than 87 pg/mL and 14.7 pg/mL, respectively at 48 hours after admission, predicted a higher mortality rate. An increase in serum level of IL-6 between day 1 and day 3 signifies non-responders group of patients with severe CAP following empirical antibiotic therapy (Igonin *et al* 2004).

Procalcitonin (PCT) is a peptide consisting of 116 amino acids, and has been found to be elevated in patients with sepsis and severe infections. In a study of community-acquired pneumonia, PCT is elevated in infective cases with typical bacterial etiology rather than pneumonia caused by atypical organism (Hedlund 2000).

Correlation of PCT with the clinical status of patients with pneumonia and prognosis of the disease has been studied by Brunkhorst and colleague (Brunkhorst *et al* 2002). In this study, they found that the determination of PCT has slight but limited prognostic value in patients with pneumonia. In the later course of the disease, they found that non-survivor groups showed higher levels of PCT (Brunkhorst *et al* 2002).

1.3.4 Presence of Co-morbid illness

Various clinical guidelines (CTS 2000, ATS 2001, BTS 2001 and IDSA 2003) addressed the importance of pre-existing co-morbidity on severity of community-acquired pneumonia and its association with in hospital mortality.

A study in University Malaya Medical Center found that mortality from CAP was more likely in patients with co-morbid illness. Twelve of 13 patients who died from CAP had other co-morbid illnesses compared to 63 of 114 patients who survived (Liam 2001). A more recent study by the same author found that

hospitalized patients due to CAP with co-existing congestive cardiac failure was independently associated with an increased mortality risk (Liam 2005).

Other co-morbid illnesses that had been associated with increased risk of mortality in patients hospitalized due to CAP are cerebrovascular accident and co-existing infectious disease (O'Meara et al 2005 and Fine 2001), diabetes mellitus, neoplastic disease, history of liver disease and presence of renal impairment (Fine 2001). Increased risk of mortality in patients with underlying liver disease is due to increase likelihood of treatment failure among this group of patients (Menendez 2004).

1.3.5 Physical and Laboratory findings

Several studies in CAP found that classic constitutional symptoms such as fever may not be present especially in the elderly. Lack of fever on hospitalization may be related to poor systemic inflammatory response in the elderly. A few studies have shown that apyrexia was a statistically significant adverse prognostic factor.

In a study of 359 patients with CAP, Fang *et al* (1990) found that mortality for febrile patients was 12% as compared with 31% for afebrile patients. Sunket *et al* (2004) reported in their prospective clinical study that mortality was 29%

in the group without fever compared to 4% in those with fever. They concluded that mortality rate in the afebrile group with leukocytosis was seven times higher than in the group with fever and leucocytosis.

ATS (2001) CAP guideline reported that certain physical findings are associated with higher mortality or a more complicated course in patients hospitalized with pneumonia. These physical findings include respiratory rate more or equal than 30 breaths/min, diastolic blood pressure less than 60 mm Hg or systolic blood pressure less than 90 mm Hg, pulse rate more than 125/min and fever less than 35°C or more than 40°C. However guideline from BTS (2001) reported only temperature less than 37°C and respiratory rate more than 24 breaths/min were predictors of unfavourable outcome for hospitalized patients with CAP.

In a study by Marrie *et al* (2005) which involved 3043 patients, in which 246 patients died (8.1%), they found that hyperkalemia and lymphopenia were associated with early mortality (less than 5 days hospitalization).

As respiratory failure is the leading cause of death among patients admitted with CAP, measurement of partial pressure arterial oxygenation (PaO2) and arterial carbon dioxide pressure (PaCO2) is important in the initial evaluation of patients with CAP. Hypoxaemia has been associated with impending respiratory failure with subsequent intensive care unit admission and mortality.