THE PROGNOSTIC ABILITY OF CURB-65 IN PREDICTING OUTCOMES OF HOSPITALISED PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

By:

DR NURUL MAJIDAH BINTI ABDUL RAZAK

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE)

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LIST OF ABBREVIATIONS

ATS	American Thoracic Society
AUC	Area under curve
AUROC	Area under receiver operating characteristic curve
BPM	Beats per minute
BTS	British Thoracic Society
CAP	Community Acquired Pneumonia
CURB	Confusion, urea, respiratory rate, blood pressure
CURB-65	Confusion, urea, respiratory rate, blood pressure, age more than 65 years old
COPD	Chronic obstructive pulmonary disease
CRB-65	Confusion, respiratory rate, blood pressure, age more than 65 years old
CRP	C-reactive protein
HAP	Hospital Acquired Pneumonia
HCAP	Healthcare Associated Pneumonia
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
ICT	Immunochromatography

IDSA	Infectious Disease Society of America
NPV	Negative predictive value
PCR	Polymerase chain reaction
PCT	Procalcitonin
PPV	Positive Predictive value
PSI	Pneumonia Severity Index
ROC	Receiver operating characteristic
SCAP	Severe Community Acquired Pneumonia
SIR	Systemic inflammatory response syndrome
SLR	Simple logistic regression
UMMC	University Malaya Medical Centre

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ABSTRAKS (VERSI BAHASA MELAYU)

Latar belakang

Jangkitan paru-paru perolehan komuniti (CAP) merupakan penyakit yang biasa dan sebanyak 20-40% pesakit ini memerlukan rawatan lanjut. Ia juga mempunyai kadar morbiditi dan kematian yang tinggi.CAP masih lagi menjadi salah satu punca utama kematian daripada penyakit berjangkit. Terdapat beberapa ujian yang telah dikemaskini untuk mengukur keterukan penyakit, meramal kematian pesakit dan sebagai panduan keputusan klinikal mengenai tahap intervensi yang diperlukan untuk pemantauan yang lebih baik.

Tujuan kajian ini adalah untuk mengenalpasti kebolehan prognostikasi CURB-65 dalam meramal kebarangkalian untuk mendapat komplikasi di kalangan pesakit yang dirawat di wad.

Kaedah Kajian

Kajian ini merupakan kajian pemerhatian kohort retrospektif yang dijalankan ke atas pesakit yang dimasukkan ke wad perubatan dan unit rawatan rapi HUSM yang memenuhi kriteria-kriteria yang telah ditetapkan, bermula Jun 2012 hingga Mei 2014. Profil pesakit dan penyakit jangkitan paru-paru dilihat dalam kajian deskripsi. Komplikasi yang dikaji dalam kajian ini adalah penggunaan bantuan inotropik, keperluan untuk bantuan ventilasi, kemasukan ke unit rawatan rapi dan kematian di hospital. Kebolehan prognostikasi CURB-65 dalam menjangkakan komplikasi-komplikasi tersebut dianalisis mengunakan 4 ujian iaitu Ujian Chi-Squre, SLR, analysis lengkuk ROC, sensitiviti, spesifisiti dan nilai kebolehan negatif dan positif. Nilai yang diletakkan untuk menandakan CURB-65 tinggi adalah 3 hingga 5.

Keputusan

Majoriti pesakit merupakan Melayu (95.4%) dengan agihan yang hampir bagi lelaki dan perempuan dan min usia adalah 63.29 (SD±16.55) tahun. Presentasi utama pesakit adalah demam, diikuti oleh batuk berkahak. Kadar kematian di hospital adalah 8.8%, penggunaan bantuan inotropik ialah 11.1%, keperluan untuk bantuan ventilasi ialah 12.6% dan kemasukan ke unit rawatan rapi ialah 6.9%. Skor CURB-65 menunjukkan sensitiviti (89-100%), specifisiti (84-88%), nilai kebolehan negatif dan kawasan bawah lengkuk ROC yang tinggi serta mempunyai hubungan yang signifikan dengan semua komplikasi. Ia juga mempunyai nilai diskriminasi yang bagus ke cemerlang (0.853-0.938).

Kesimpulan

Kajian kami menunjukan CURB-65 mempunyai kebolehan prognostikasi dalam menjangkakan komplikasi seperti penggunaan bantuan inotropik, keperluan untuk bantuan ventilasi, kemasukan ke unit rawatan rapi dan kematian di hospital di kalangan pesakit yang dimasukkan ke wad untuk jangkitan paru-paru dengan nilai sensitiviti dan specifisiti yang tinggi.

ABSTRACT (ENGLISH VERSION)

Background

Community Acquired pneumonia (CAP) is a common disease and many patients require admission, which is about 20-40% of patients. It also has high morbidity and mortality. CAP still remains one of the leading causes of death from infectious diseases. There are several validated tools to assess severity, predict mortality in patients admitted with CAP and guide clinical decision about the level of intervention required for better monitoring and treatment.

The purpose of this study is to determine the prognostic ability of CURB-65 as a pneumonia severity score in predicting outcomes in hospitalized patients with CAP.

Methodology

The study was an observational retrospective cohort study performed for patients admitted to medical ward and intensive care unit (ICU) HUSM that fulfilled diagnosis for CAP, from June 2012 till May 2014. The clinical profiles for CAP in HUSM were elaborated in a descriptive study. The adverse outcomes that were investigated in this study were use of inotropic support, need of ventilation support, ICU admission and in hospital mortality. The prognostic ability of CURB-65 in predicting outcomes were analysed using 4 tests, i.e: Chi square test, SLR, ROC curve analysis and sensitivity, specificity and predictive values. The recommended cut off points to indicate higher CURB-65 score was 3 to 5.

Results

The majority of patients were Malay (95.4%) with almost equal male to female distribution and mean age of 63.29 (SD$\pm$16.55) years. The proportion of in hospital

mortality was 8.8%, use of inotropic support was 11.1% , need of ventilation support was 12.6% and need of ICU admission was 6.9%. CURB-65 score severity category demonstrated high sensitivity (89-100%), specificity (84-88%), negative predictive value (99-100%) and area under ROC curve; and significant association with all the adverse outcomes. It also had good to excellent discriminative values (0.853-0.938).

Conclusion

Our study showed CURB-65 had a prognostic ability in predicting outcomes i.e: used of inotropic support, need of ventilation support, need of ICU admission and inhospital mortality for hospitalised patients with community acquired pneumonia with high sensitivity and specificity.

CHAPTER ONE

INTRODUCTION

1.1 Study Background

Community acquired pneumonia (CAP) is a common disease, in which about 15-50% of these patients require admission, and about 5-10% of those admitted patients require management in an intensive care unit (ICU) (Hoare et al, 2006; Hoogewerf M et al, 2006). It also has high morbidity and mortality (Andrew J et al, 2003). CAP still remains one of the leading causes of death from infectious diseases worldwide (Ramirez JA, 2003; Song JH et al, 2009).

This disease inevitably imposes a heavy burden on the healthcare system in terms of its high cost both for diagnosing and managing the disease, whether for ward or ICU admission, (Moran GJ et al, 2009; Xu F et al, 2008) in which, pointing out the importance of predicting the need for hospitalization, whether to ICU or general medical ward, as well as the outcome of the patient during treatment course (Lim WS, 2003).

The British Thoracic Society (BTS) (Macfarlane JT et al, 2001), Infectious Diseases Society of America (Bartlett JG et al, 2000) and the Canadian Thoracic Society (Mandell LA et al, 2000) guidelines recommend the use of validated prognostic tools on admission to hospital as adjuncts to clinical judgement in managing CAP (Fine MJ et al, 1997; Lim WS et al, 2003). It is important to assess the severity of pneumonia, particularly on presentation as this can be used to guide physician in treatment plan,

further intervention and level of care, as well as allow predictions about progression of the disease and prognosis (Carol P et al, 2008).

There are several validated tools or scoring system to assess severity, predict mortality in patients admitted with CAP and guide clinical decision about the level of intervention required (Macfarlane JT et al, 2001; Bartlett JG et al, 2000; Mandell LA et al, 2000; American Thoracic Society, 2001).

These severity scoring systems were developed to improve the efficiency and effectiveness of health care. The ability of prediction tools to assess outcome of CAP helps physicians in identifying high risk patients for better monitoring and treatment as well as to prevent adverse outcome.

Internationally, several guidelines currently recommend the use of the Pneumonia Severity Index developed by Fine et al and / or the CURB-65 score developed by Lim and colleague as severity scoring tools. (BTS Standards of Care Committee, 2001; Mandell LA et al, 2007)

The purpose of this study is to determine the ability of CURB-65 as a pneumonia severity score in predicting outcomes in hospitalized patient with CAP.

Although many studies reported that severity scoring system helps clinicians in managing patients with CAP, this scoring system is still not aggressively used in our population. Hopefully this study can convince clinicians that a simple scoring system which is CURB-65 is applicable and useful in predicting outcomes of CAP, especially need of ventilator support, need of inotropic support, need of ICU admission and mortality.

The accuracy of the CURB-65 score is now well established but it has not been universally accepted. Although simpler than the PSI, still large majority doctors were unable to name its components properly.

Despite increasing publicity and programme to promote severity assessment, a few studies showed that only 13% of patients received severity assessment on admission (Collini P et al, 2007; James D Chalmers et al, 2008). The study in United Kingdom by Barlow GD et al (2003) showed that junior doctors have poor awareness of the BTS recommendations. In a survey of 83 junior and middle grade doctors, only 4% could correctly state all four prognostic markers of the BTS CURB tool.

The clinical application of severity tools has been described as dependent on three factors: 1) the accurate prediction of the outcome of interest; 2) the ability to classify patients into clinically useful groups (e.g by level of risk); 3) simplicity. (Chalmers JD et al, 2012; Relly BM et al, 2006) All these criterias are fulfilled by the CURB-65 severity score.

Additionally, the basic information required to determine the CURB-65, are routinely documented in medical record at the initial hospital assessment, four of the five required criteria are assessable clinically and fifth (blood urea) is a simple laboratory test available even in low technology setting, making it possible to generate a prediction rule for each patient at the point of care, before determining further active intervention.

The severity scoring could be used along with clinical judgement in therapeutic decision making. It is necessary to promptly identify high risk patients to aid therapeutic decision making, and guide prognosis. Therefore, the data collected in this study will justify the need and usefulness of severity scoring system for

community acquired pneumonia and at the same time guide us for further aggressive intervention for high risk patients. In addition, this score is easy to apply in day-to-day clinical practice.

1.2 Epidemiology Of Community Acquired Pneumonia

Pneumonia is one of the commonest causes of admission to the hospital especially in medical ward with lifetime prevalence of 20-30% in developing countries and 3-4% in developed countries (Shah BA et al, 2010).

It is associated with significant adverse outcomes and complications including mortality. (Feagan BG et al, 2000; Fine JM et al, 1999; Lim WS et al, 2000). The disease imposes a major burden on the healthcare resources in terms of its high cost both for diagnosing and managing the disease (Moran GJ et al, 2009; Mandell LA et al, 2007).

In view of the clinical importance of CAP, many countries have developed national guidelines for the management of this condition (Task force on CAP, 1998; Heffelfinger JD et al, 2000; Bartlett JG et al, 2000; Mandell LA et al, 2003; Mandell LA et al, 2000; Niederman MS et al, 2001; British Thoracic Society, 2001). By the way, the most widely used guideline is the BTS Guideline for Management of CAP 2009.

Pneumonia is also a common cause of death among hospital admissions. Pneumonia was ranked the 6th main cause of death for patients hospitalized in Penang government hospitals in year 2005 (Hooi LN et al, 2001) and it remains the leading cause of death in many developed and developing countries. It is the 7th leading cause

of death in the United States in 2000, after heart disease, malignant neoplasm, cerebrovascular disease, chronic lower respiratory tract disease, unintentional injuries and diabetes mellitus.

According to Malaysia Ministry of Health Annual Report 2012, the second principal cause of hospitalization in Ministry of Health hospitals in 2012 is disease of respiratory system including community acquired pneumonia. It accounts for 11.02% of total admissions. Disease of respiratory system is also the second principal cause of death in Ministry of Health hospitals in 2011 (18.80%), after disease of the circulatory system (24.69%). (Annual Report Ministry of Health 2012).

Severity assessment and site-of-care decisions for patients with CAP are pivotal for patients' safety and adequate allocation of resources.

A retrospective study by Shaharudin and colleagues (2011) from Hospital Universiti Sains Malaysia (HUSM) in 2004, from one hundred and fifty-five patients hospitalized with CAP, the inpatient mortality was 19.4%. Loh et al (2001) reported a 12% mortality rate in 2001 in Seremban Hospital while Liam et al (2000), at the University Malaya Medical Centre (UMMC) reported a mortality of 13.7% in 2000.

In the United Kingdom, death from CAP has been reported to be 5.7% to 12% (BTS, 2001), while a meta-analysis by Fine and colleagues (1996) showed a 13.6% mortality rate in hospitalized patients to 36.5% mortality rate for patients admitted to intensive care unit (ICU).

It is now recognized that prognosis significantly depends on early treatment taken in approaching this disease. Due to the high rate of mortality among patients with CAP, there is a need for an accurate predictive tool for the physicians to make the decisions on appropriate therapy.

There are several validated tools to assess severity and predict mortality in patients admitted with CAP. These severity scoring systems are developed to improve the efficiency and effectiveness of health care. The ability of a prediction tool to assess mortality of CAP helps physicians in identifying high risk patients for better monitoring and treatment.

1.3 Definition of Pneumonia

Pneumonia is defined as an infection of the lungs involving alveoli, distal airways and interstitium of the lung. The infection is manifested by replacement of the normal lung sponginess by consolidation. The alveoli also filled with red blood cells, white blood cells and fibrin.

Infectious Disease Society of America (IDSA) defined pneumonia as an acute infection of the lung parenchyma accompanied by acute infiltrates on chest radiograph or an auscultatory finding consistent with pneumonia which are presence of altered breath sounds and / or localized rales, with two of the following: fever or hypothermia, rigors, sweating, new cough with or without sputum or change in color of respiratory secretions in a patient with chronic cough, chest discomfort and dyspnea. In the elderly, it is more common to be afebrile or hypothermic. In elderly also, sometimes altered mental status is the only complaint.

1.4 Classification of Pneumonias

Pneumonia can be divided into several different classifications depending on clinical characteristics, source of infection, aetiological factors or morphological factors.

Based on source of infection, pneumonia can be divided into:

1) Community-acquired pneumonia (CAP). It is defined as an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community. The common organism for this pneumonia will be elaborated on in the part on aetiology.
2) Hospital-acquired pneumonia (HAP) or Nosocomial pneumonia. This is a respiratory infection that begins in a nonintubated patient after 48 hours of admission or within 90 days of admission.
3) Healthcare associated pneumonia (HCAP). It is defined as a respiratory infection that occurs:
    - within 90 days of a hospitalization that lasts 2 days or more, or
    - in a patient that stays at a nursing home, or
    - in a patient that has a visit to an intravenous puncture care facility or a hospital-based clinic or hemodialysis facility, or
    - within 3 days of receiving antibiotics, chemotherapy, or any type of wound care.
4) Ventilator associated pneumonia (VAP). This is a nosocomial pneumonia that begins more than 48 hours after the patient is intubated.
5) Aspiration pneumonia. Aspiration pneumonia is broadly defined as the pulmonary sequelae of abnormal entry of material from the stomach or upper respiratory tract into the lower airways. The term generally applies to large-volume aspiration. There are at least 3 distinctive forms, based on the nature of the inoculum, the clinical presentation, and management guidelines: toxic injury of the lung (such as due to gastric acid aspiration or Mendelson’s syndrome), obstruction (with a

foreign body or fluids), or infection. (Barlett JG et al, 1975; Barlett JG et al, 1993; Matthay MA et al, 1996).

6) Pneumonia in the immunocompromised host or opportunistic pneumonia. This group includes patients on chemotherapy, on immunosuppressant treatment such as high dose steroid or retroviral disease. Main pathogens are cytomegalovirus, Pneumocystis jiroveci, Mycobacterium avium-intracellulare, invasive aspergillosis and invasive candidiasis.

Pneumonia also can be classified by clinical characteristics. This divides them into acute (less than three weeks duration) and chronic pneumonias. Acute pneumonias are further divided into the classic bacterial bronchopneumonias (such as *Streptococcus pneumoniae*), the atypical pneumonias (such as the interstitial pneumonitis of *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*). Chronic pneumonias tend to be either non-infectious, mycobacterial, fungal, or mixed bacterial infections caused by airway obstruction. The most common cause of chronic pneumonias include *Nocardia*, *Actinomyces* and *Blastomyces dermatitidis*, as well as the granulomatous pneumonias (*Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum* and *Coccidioides immitis*).

With the advent of modern microbiology, classification based upon the causative microorganism become possible. Determining which microorganism is causing an individual's pneumonia is an important step in deciding treatment type and length.

Other than that, pneumonia also can be classified based on anatomical or morphological type. It can be classified as lobar pneumonia (infection that only involves a single lobe of a lung). Lobar pneumonia is often due to *Streptococcus*

pneumoniae (though *Klebsiella pneumonia*e is also possible). Multilobar pneumonia involves more than one lobe, and it often causes a more severe illness.

1.5 Aetiology Of Community Acquired Pneumonia (CAP)

Although many microorganisms have been associated with CAP, it is a small range of key pathogens that cause most cases that can be identified. Streptococcus pneumoniae (pneumococcus) is the most frequently identified pathogen, with the highest incidence of this organism reported in studies that used urinary antigen detection. Apart from Streptococcus pneumoniae, a great deal of literature in Western countries have reported Haemophilus influenza; atypical pathogens such as Chlamydia pneumoniae, Mycoplasma pneumonia and Legionella pneumophila; and viruses (influenza virus, adenovirus, respiratory syncytial virus, parainfluenza virus and coronavirus) as common pathogens of CAP (Bartlett JG et al, 2000; British Thoracic Society, 2001; Jokinen C et al, 2001; Dowell SP et al, 1996; Marx A et al, 1999; Peiris JSM, 2003).

Gram-negative bacilli (Enterobacteriaceae and pseudomonas) are the common cause of CAP in patients who have had previous antimicrobial treatment or who have pulmonary comorbidities such as chronic lung disease, lung fibrosis or chronic obstructive pulmonary disease (Aranclfla F et al, 2002).

In one study, 33% of hospitalized CAP patients with unknown aetiology diagnosed by routine methods were found to be due to Streptococcus pneumoniae based on findings from transthoracic needle lung aspiration, suggesting that many patients without a known pathogen have pneumococcal infection (Ruiz-Gonzalez A et al, 1999).

The microbial aetiological distribution of CAP reported in the literature depends on the patient population, the geographical region, the intensity of investigations carried out and the occurrence of epidemics of infection.

Even when carefully sought for in large prospective studies, the putative causative organism remains unknown in about half of all patients with CAP. Reasons for failure to identify the aetiological agent include presence of fastidious organism, prior treatment with antibiotics, unusual pathogens that were unrecognized, viral infections, non-infectious mimic of CAP, and pathogens that are currently not identified or recognized. The differences in the microbiology of CAP as compared to what is reported in the West must be taken into consideration when selecting the appropriate antibiotics for initial empirical therapy of CAP in this region.

A number of studies in Asia, where the prevalence of tuberculosis is high have shown that infection due to Mycobacterium tuberculosis may commonly present as an apparent CAP, which is about 4.8-15.3% of cases. (Chan CH et al, 1992; Hui KP et al, 1993; Hooi LN et al, 2001; Liam CK et al, 2003). Although pulmonary tuberculosis is a chronic respiratory infection, it can present as CAP and it should be a differential diagnosis in areas where tuberculosis is endemic.

In studies conducted in Malaysia, 2 out of 127 (1.6%) patients in the Kuala Lumpur series had melioidosis, (Liam CK et al, 2001) while Burkholderia pseudomallei was not isolated in any patient in the Penang series (Hooi LN et al, 2001). Burkholderia pseudomallei should be considered a causative organism in patients with CAP in rural Southeast Asia particularly if the patient has diabetes mellitus. (Reechaipichitkul W et al, 2002).

From previous study in HUSM by Sanihah et al in 2007, only 38.5% from 142 patients noted to have pathogen isolated. The most common organism isolated were *Haemophilus influenza* and *Mycobacterium tuberculosis.*

Other than that, different centres have different common organisms. Different categories of pneumonia also have their own common pathogens. For example:

a. Patients with minimal comorbidities, *S. pneumoniae, M. pneumoniae, C. pneumoniae* and viruses.
b. Patients with underlying chronic pulmonary or cardiovascular disease, most common pathogens are resistant *S. pneumonia, H. Influenzae, M. Catarrhalis* and *Legionella pneumophila*.
c. Nosocomial patients (hospitalized or nursing home patient), most common pathogens are resistant gram negative rods, *P. aeruginosa, methicillin resistant staph aureus* and anaerobes (due to aspiration).
d. Alcoholics patients, most common pathogens *K. pneumoniae,* anaerobes and tuberculosis.
e. Intravenous drug users, most common pathogens are *S. aureus, P. jerovoci* and anaerobes.
f. Post splenectomy patients, most common pathogens are *S. pneumoniae* and *H. influenzae.*
g. HIV / AIDS patients, most common pathogens are *P. jerovoci, S. pneumoniae,* tuberculosis and fungal.
h. Leukaemic or bone marrow transplant patients, most common pathogens are *aspergillu fumigatuss, legionella pneumophila*, cytomegalovirus and other fungal organisms.

i. Post influenza infection, most common pathogens are *S. pneumoniae* and *S. aureus.*

j. Cystic fibrosis patients, most common pathogens are *P. aeruginosa* and *S. aureus*.

k. Patients with animal exposure, most common pathogens are *C. psittaci*, *C. neoformans, H. capsulatum* (from exposure to birds); *hantavirus* (from exposure to rats); *C. burnetti* (from exposure to farm animals

Table 1 shows the most common pathogens associated with CAP as derived from collective results of various studies conducted in the west and in the Asia Pacific region. (British Thoracic Society, 2001; Jokinen c et al, 2003; Aranclfla F et al, 2002; Ruiz-Gonzalez A et al, 1999; Ishida T et al, 1998; Miyashita N et al, 2000; Woo JH et al, 2001; Chan CH et al, 1992; Reechaipichitkul W et al, 2002; Wattanathum A et al, 2003; Liam CK et al, 2001; Hooi LN et al, 2001; Liam CK et al, 2003; Hui KP et al, 1993; Ngeow YF et al, 2003; Luna CM et al, 2000; El Solh AA et al, 2001; Lee KH et al, 1996; Tan YK et al, 1998; Bochud PY et al, 2001; Marrie TJ et al, 1996)

Table 1: Microbiological pattern of CAP in patients requiring hospitalization.

Location	No. of patients	Frequency / rank of microbial cause (%) 1	2	3	4	5	6	Unknown
HUSM (Sanihah et al, 2009)	**143 (%)**	**H. influenzae 6.3**	**M. tuberculosis 6.3**	**K. pneumoniae 4.9**	**Candida Albicans 3.5**	**Streptococcal sp. 2.8**	**M. pneumoniae 2.8**	**61.5**
Kuala Lumpur (Liam CK et al, 2001)	127	K. pneumoniae	S. pneumoniae	H. influenzae	M. pneumoniae	Ps. aeruginosa	Burkholderia pseudomallei	
	(%)	10.2	5.5	5.5	3.9	3.9	1.6	58.3
Penang (Hooi LN et al, 2001)	1137	M. tuberculosis	K. pneumoniae	Ps. aeruginosa	S. aureus	S. pneumonia	Acinetobacter spp.	
	(%)	15.3	7.2	6.1	5.0	3.0	3.0	57.1
Singapore (Hui KP et al, 1993)	96	M. tuberculosis	S. pneumonia	Gram negative bacilli	H. influenzae	M. pneumoniae	S. aureus	
	(%)	21.0	12.0	10.0	5.2	5.2	4.2	42.0
United Kingdom (5 studies) (BTS, 2001)	1137	S. pneumoniae	C. pneumoniae	M. pneumoniae	Influenza A & B	H. influenza	Legionella spp.	
	(mean %)	39	13.1	10.8	10.7	5.2	3.6	30.8
Other part of Europe (23 studies) (BTS, 2001)	6026	S. pneumoniae	C. pneumoniae	M. pneumoniae	Influenza A & B	Legionella spp.	Gram negative enteric bacilli	
	(mean %)	19.4	6.3	6	5.3	5.1	3.3	50.7
Australia & New Zealand (3 studies) (BTS, 2001)	453	S. pneumoniae	M. pneumoniae	H. influenza	Legionella spp.	Gram negative enteric bacilli	C. pneumonia	
	(mean %)	38.4	14.6	9.5	7.5	4.6	3.1	31.6
North America (4 studies) (BTS, 2001)	1306	S. pneumoniae	H. influenza	C. pneumoniae	Influenza A & B	Gram negative enteric bacilli	Legionella spp.	
	(mean %)	11.3	6.3	5.9	5.9	5.3	4.3	40.7

Table 2: Microbiological pattern of CAP in patients requiring hospitalization (cont.).

Location	No. of patients	Frequency / rank of microbial cause (%) 1	2	3	4	5	6	unknown
Okayama (Ishida T et al, 1998)	318	S. pneumoniae	H. influenzae	M. pneumoniae	K. pneumoniae	S. Milleri	C. pneumoniae	
	(%)	23	7.4	4.9	4.3	3.7	3.4	39
Okayama (Miyashita N et al, 2000)	200	S. pneumoniae	H. influenzae	M. pneumoniae	C. pneumoniae	S. aureus	Anaerobs	
	(%)	20.5	11.0	9.5	7.5	5.0	4.0	41.5
Korea (Woo JH et al, 2001)	562	S. pneumoniae	K. pneumoniae	Ps aeruginosa	S. aureus	Streptococcus Viridans	Enterobacter Cloacae	
	(%)	21.7	14.8	9.8	9.5	5.7	4.2	61.7
Hong Kong (Chan CH et al, 1992)	1137	M. Tuberculosis	S. pneumonia	Chlamydia spp.	Viral	H. influenza	M. pneumonia	
	(%)	12.0	12.0	6.0	6.0	4.0	3.0	59.0
Bangkok (Watanathum A et al, 2003)	147	S. pneumoniae	C. pneumoniae	M. pneumoniae	K. pneumoniae	L. pneumophila	H. influenza	
	(%)	22.4	16.3	9.5	6.8	5.4	2.7	29.0

1.6 Pathophysiology Of Community Acquired Pneumonia

Pneumonia is an infectious process that occurs as a result of the invasion and overgrowth of microorganisms (as mentioned in aetiology part in this dissertation) in lung parenchyma, breaking down defense mechanisms. It further provokes intra-alveolar exudate production. Basically, the development of pneumonia requires the pathogen to reach the alveoli and that host defenses were overwhelmed by microorganism virulence.

The lungs are constantly exposed to particulate material and microbes that are present in the upper airway, from the air that is breathed in. The lower respiratory tract can be entered by microorganisms by several mechanisms which include gross aspiration or microaspiration of the oropharyngeal or gastric content, aerosolization of bacterial laden aerosol, haematogenous spread from a distant infected site and direct spread from a contiguous infected site.

There are many determinant factors that can cause changes in the normal flora of the upper respiratory tract that predispose to infection, such as underlying disease, loss of mechanical respiratory defenses with the use of sedatives, tracheal intubation and antibiotic treatments.

In pneumonia, lungs capillaries become leaky, and protein-rich fluid seeps into the alveoli. This can lead to a less functional area for oxygen-carbon dioxide exchange, causing relative oxygen deprivation, while retaining potentially damaging carbon dioxide. The alveoli fill further with fluid and debris from the large number of white blood cells that are being produced to fight the infection. Consolidation, a feature of bacterial pneumonias, occurs when the alveoli, which are normally hollow air spaces within the lung, instead become solid, due to fluid and debris.

Pathogenesis of pneumonia involves: 1) congestion, which occurs in day 1 of infection due to vasodilation of the capillaries, 2) red hepatisation, which occurs in day 2, with accumulation of red blood cells and exudative production, 3) grey hepatisation, which occurs on day 4 of infection, with accumulation of neutrophils and macrophages, and 4) resolution, which occurs after day 8 with presence of few macrophages & normalization of lung parenchyma.

The pathology of pneumonia manifests as four general patterns which are lobar pneumonia, bronchopneumonia, interstitial pneumonia and milliary pneumonia. Lobar pneumonia classically involves an entire lung lobe relatively homogenously, although in some patients, a small portion of the lobe may be unaffected or at an earlier stage of involvement.

Bronchopneumonia, a patchy consolidation involving one or several lobes, usually involves the dependent lower and the posterior portions of the lungs, a pattern that is attributable to the distribution of aspirated oropharyngeal content by gravity.

Interstitial pneumonia predominantly involves the interstitium, including alveolar walls and the connective tissue around the bronchovascular tree. Milliary pneumonia resembles the millet seeds in milliary tuberculosis due to haematogenous spread. Persistent and uncontrolled infection may lead to several complications such as abscess formation, necrotizing pneumonia, vascular invasion with infarction, cavitation and extension to the pleura with effusion, empyema or bronchopleural fistula. (Marrie TJ et al, 2005).

1.7 Risk Factors for Community Acquired Pneumonia

There are a lot of factors which increase the risk of developing CAP including extremes of age, immunosuppressive diseases (e.g. diabetes mellitus, neoplasms and HIV infection) respiratory disorders (e.g. bronchial asthma), use of drugs (e.g. oral steroids) and alcohol abusers.

Age and co-morbidities are known to be the risk factors for CAP. They are supported by many findings in other countries: (Johnson PDR et al, 2002; Cunha BA et al, 1998; Kaplan V et al, 2002) for example, studies at the University of Pittsburgh, USA, showed that the incidence rate of CAP rose five-fold as age increased from 65–69 years to more than 90 years (Kaplan V et al, 2002) and, in the Spanish Evan-65 study, the burden of CAP was found to increase with age. (Ochoa-Gonder O et al, 1993).

Aging is associated with a decline in lung performance due to increase in elastic recoil of the lung, chest wall compliance and respiratory muscle strength. The mucociliary clearance, cough reflex and oropharyngeal deglutition are also impaired in the elderly and the ability to mount an immune response is abnormal due to impairment of T-cell function. Oropharyngeal colonization rate with pathogens were also increased in the elderly. These abnormalities predispose to infection by microaspiration which is an important cause of pneumonia in the elderly. (Kikuchi et al, 1994) The presence of comorbidities and poor nutritional status in the elderly can lead to an increased susceptibility to infection.

Other than that, heart failure, chronic obstructive pulmonary disease (COPD), and malignancies were the leading co-morbidities found in several studies for CAP previously (Godwin C Mbata et al, 2013; Ewig S et al, 2004; Menendez R et al,

2008). Studies have shown an increased rate of lower respiratory tract infections in patients with heart failure and, in fact, CAP is known to be an exacerbating factor in patients with congestive cardiac failure (Bonan JT et al, 1999; Thompson WW et al, 2003).

In a population based case-control study of risk factors for CAP of 74610 adults patient in Spain, previous respiratory infection and chronic bronchitis significantly increase risk of CAP (Admiral J, 1996). COPD is a known frequent co-morbidity in patients admitted to hospital for CAP and respiratory failure. While a study of severe CAP in 529 patients in 33 intensive care units in Spain found COPD to be the most frequent co-morbidity (Fine MJ et al, 1997; Godwin C Mbata et al, 2013).

Not to forget, smoking is also one of the risk factors for getting the pneumonia. Smoking alters the mucociliary transport, epithelial cell function and increase risk of adhesion of certain pathogens such as S. pneumonia and H. influenza. A recent large population based study by Almirall J et al (2000) showed that, both current smokers and ex-smokers had a higher risk for CAP.

Other than that, heavy alcohol use causes alterations of the immune system, impairs the function of lymphocytes, neutrophils and other inflammatory cells, increasing host susceptibility to infectious disease, especially bacterial pneumonia.

1.8 Diagnosis Of Community Acquired Pneumonia

For diagnosing CAP, patient may present with fever or hypothermia, rigors, sweating, new cough with or without sputum (or change in color), chest discomfort, pleuritic chest pain, chills, rigors and dyspnea. Most patients also have nonspecific symptoms,

such as fatigue, myalgias, abdominal pain, anorexia, nausea, vomiting, diarrhea, arthralgia and headache. The presentation can range from mild to fatal disease. The onset may be sudden or insidious.

In the elderly, it is more common to be afebrile or hypothermic, and sometimes altered mental status is the only complaint.

From clinical examination, the findings include tachypnea and dull to percussion over the lungs. The auscultatory findings consistent with pneumonia are such as altered breath sounds, increase vocal resonance, bronchial breath sounds, pleural friction rub and/ or localized rales. In severe cases, patients might be reduced in conscious level and have respiratory failure (British Thoracic Society, 2009).

A diagnosis of pneumonia based on clinical features has a sensitivity of 47-69% and a specificity of 58-75% (Marrie TJ et al, 2005).

1.9 Laboratory Investigations for Community Acquired Pneumonia (CAP)

In investigating this disease, chest radiography is considered important for establishing the diagnosis of pneumonia and for distinguishing this condition from acute bronchitis, which is a common cause of antibiotic abuse. Other than that, it also can be used to detect associated lung diseases, to gain insight into the causative agent (in some cases), to assess severity, and as a baseline to assess response.

Other than that, we also need sputum microscopy and culture. Sputum need to be collected in sterile screwed containers. Adequacy of sputum was defined as more than 2ml of sputum containing of less than 15 epithelial cells on microscopy (Restrepo MI et al, 2006). A study by Niazlin et al in Kuala Lumpur (2012), showed that the

highest yield from the sputum culture were normal mouth flora (83%) followed by enterobacter spp., Group G streptococcus and Pseudomonas aeruginosa. Immunochromatography (ICT) method and molecular method such as polymerase chain reaction (PCR) improved the detection of *S. pneumoniae* in CAP patients as compared to conventional culture.

Other laboratory values that should be determined for patients who are hospitalized are: complete blood cell count and differential, serum creatinine, blood urea nitrogen, glucose, electrolytes, and liver function tests.

Besides that, oxygen saturation should be assessed. The BTS guidelines recommend arterial blood gas measurement only when the patient's oxygen saturation is less than 92% or other features of severe pneumonia are present (Macfarlane JT et al, 2001) or when there are signs and symptoms suggestive of carbon dioxide retention.

There should be two pretreatment blood cultures, as well as Gram staining and culture of expectorated sputum. Selected patients should have microbiological studies for tuberculosis and legionella infection.

The rationale for performing microbiological studies is to establish an aetiologic diagnosis is based on attempts to improve care of the individual patient with pathogen-specific treatment; to improve care of other patients and to advance knowledge by detecting epidemiologically important organisms (*Legionella pneumophila*, penicillin-resistant *Streptococcus pneumoniae*, and methicillin-resistant *Staphylococcus aureus*); to implement contact tracing and antimicrobial prophylaxis in appropriate settings (such as cases of *Neisseria meningitidis* infection, *Haemophilus influenzae* type B infection, and tuberculosis); to prevent antibiotic

abuse as well as development of antibiotic resistance; and to reduce antibiotic expense because as we know, CAP is one of the major healthcare burdens.

Currently, biomarkers have been increasingly proposed as useful tools in identifying patients with infection and guiding therapy. The two serum markers that have been most widely studied to prognosticate outcome are C-reactive protein (CRP) and procalcitonin (PCT). PCT, the precursor of calcitonin, arises in severe bacterial infection, but not in viral illness. However, this biomarker is not yet widely available and is expensive, and the added value of using PCT across inpatient populations has not yet been demonstrated. (Michael S et al, 2007; Christ-Crain M et al, 2006; Masia M et al, 2005) One study found that commonly measured and widely available inflammatory protein, CRP, improved the CURB-65 AUROC for 30 day mortality among CAP patients (Menendez R et al, 2009), but this requires validation in further study (Chalmers JD, 2012).

1.10 Severity Score for Community Acquired Pneumonia

The most important step in management of CAP is the initial assessment of the severity of the disease. Assessment of severity of the disease in CAP is very important for further optimum care of the patient. An accurate assessment helps the clinician to determine the site of care, the extent of diagnostic testing and the type and intensity of treatment especially antibiotics of choice. (Capelastegui A. et al, 2006; Huang DT et al, 2008; Liapikau A et al, 2009; Myint PK et al, 2009).

However, a number of studies suggest that routine clinical judgement is subjective and often not sufficient for assessing the severity of the CAP. Clinical judgement alone is prone to error in stratifying mortality risk and may underestimate its severity.

This may result in under treatment and poor outcomes. (Neil Am et al, 1996; Neill AM et al, 1996; Woodhead MA, 1987; Almirall J et al, 2000).

Therefore clinical prediction rules for CAP management offer a useful adjunct to the art of clinical practice. There are several pneumonia severity scoring systems that have been proposed as a tool for augmenting clinical judgement for stratifying patients with CAP into different management groups of patients for further active treatment and prevent insufficiently aggressive interventions for patients at high risk of complications. (Tang CM et al, 1993; Neil AM et al, 1996).

Chun Shing Kwok et al (2013) already identified 20 different published risk prediction models for mortality in CAP. Four models relied on clinical variables that could be assessed in community settings. Nine models required laboratory tests in addition to clinical variables, and the best performance levels among the validated models were CURB and CURB-65. The PSI was the only validated model with good discriminative ability among the four that relied on clinical, laboratorial and radiological variables.

However, there has yet to be a clear consensus on which model that should be used (Singanayam A et al, 2009).

The severity scoring systems available are:

1) BTS score (BTS and the public health lab service, 1987; Farr M et al, 1991),
2) Mortality Risk Index (Leroy O et al, 1996),
3) CURB (Neill AM et al, 1996),
4) PSI (Fine MJ et al 1997),

5) CURB-65 ((Lim WS et al, 2003; Barlow G et al, 2007; Ewig S et al, 2004)

6) CRB-65 (confusion, respiratory rate, blood pressure, age more than 65 years old) (Lim WS et al, 2003),

7) Modified American Thoracic Society (ATS) Rule (Ewig S et al, 2004),

8) SOAR (systolic blood pressure, oxygenation, age, respiratory rate) (Myint PK et al, 2006),

9) CURB age (confusion, urea level, respiratory rate, blood pressure, age) (Myint PK et al, 2007),

10) A-DROP [(i) Age (male $\geq$ 70 years, female $\geq$ 75 years); (ii) Dehydration (blood urea nitrogen (BUN) $\geq$ 210 mg/L); (iii) Respiratory failure (SaO2 $\leq$ 90% or PaO2 $\leq$ 60 mm Hg); (iv) Orientation disturbance (confusion); and (v) low blood Pressure (systolic blood pressure $\leq$ 90 mm Hg)].) (Shindo Y et al, 2008),

11) CURSI (confusion, urea, respiratory rate and shock index) (Nullman et al, 2014),

12) CURASI (confusion, urea, respiratory rate and adjusted shock index) (Myint PK et al, 2009),

13) PIRO score(predisposition, insult, response and organ dysfunction). This score including the presence of the following variables: comorbidities (chronic obstructive pulmonary disease, immunocompromise), age >70 years, multilobar opacities in chest radiograph,shock, severe hypoxemia,acute renal failure,bacteremia, acute respiratory distress syndrome. (Rello et al, 2009)

14) IDSA/ATS 2007 (American Thoracic Society/Infectious Disease Society of America 2007) (Lipikou A, 2009),

15) PARBscore (presence of pleural effusions, albumin <3.0 g/dl, respiratory rate >30 breath /minute, blood urea level >25 mg/dl) (Uchiyama N et al, 2010),

16) AFSS (Abbreviated Fine Score) (Escobar GJ et al, 2008),

17) CARSI (confusion, age, respiratory rate and shock index) (Musonda P et al, 2011)

18) CARASI (confusion, age, respiratory rate and adjusted shock index) (MusondaP et al, 2011)

19) SMART-COP. This criteria consists of low **s**ystolic blood pressure, **m**ultilobar chest radiography involvement, low **a**lbumin level, high **r**espiratory rate, **t**achycardia, **c**onfusion, poor **o**xygenation and low arterial **p**H.

20) SWAT-Bp. This criteria consists of male sex (S), wasting (W), non-ambulatory (A), Temperature of more than 38*C or less than 35*C (T) and blood pressure of less than 100/60 (Bp). Mortality for scores 0-5 was 0%, 3.3%, 7.4%, 29.2%, 61.5% and 87.5% respectively (Edmund Birkhamshaw et al, 2013).

Among these severity scores, the CURB-65 and PSI are two of the most prominent methods in regards of assessing the severity of community acquired pneumonia. (Lim WS, 2003; Moran GJ et al, 2009; ATS / IDSA, 2005; Mandell LA et al, 2007; Charles PG et al, 2008; Yu KT et al, 2008; Waterer GW et al, 2006).

First, the CURB-65 score, a simple method of assessing and risk stratifying CAP patients, is composed of five separate criterias, namely, confusion, uremia (blood urea