EVALUATION OF ANTIBIOTIC THERAPY AMONG PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITAL PULAU PINANG

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by

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LIST OF ABBREVIATIONS

AFB	Acid-Fast Bacilli
ATS	American Thoracic Society
BTS	British Thoracic Society
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
CRC	Clinical Research Centre
DBP	Diastolic Blood Pressure
DRSPTWG	Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group
g (s)	Gram(s)
HAP	Hospitalized-Acquired Pneumonia
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IV	Intravenous
LOS	Length of Stay
LRTIs	Lower Respiratory Tract Infections
mg (s)	Milligram (s)
MOH	Ministry of Health
NMRR	National Medical Research Register
SBP	Systolic Blood Pressure

SOB	Shortness of Breath
WBC	White Blood Cell
WHO	World Health Organization

PENILAIAN TERAPI ANTIBIOTIK DALAM KALANGAN PESAKIT YANG MENGALAMI PNEUMONIA JANGKITAN DARI KOMUNITI DI HOSPITAL PULAU PINANG

ABSTRAK

Pneumonia jangkitan dari komuniti adalah salah satu penyakit berjangkit yang menyebabkan morbiditi dan mortaliti, terutamanya di rantau Asia-Pasifik. Garis panduan antibiotik diperlukan untuk mencapai penggunaan antibiotik yang sesuai dalam pengurusan pneumonia jangkitan dari komuniti, termasuk Malaysia. Hasil terapi masih perlu dipantau untuk menilai penggunaan antibiotik untuk pesakit dengan pneumonia jangkitan dari komuniti yang dimasukkan ke hospital. Oleh itu, kajian ini bertujuan untuk menilai penggunaan antibiotik untuk pneumonia jangkitan dari komuniti di wad perubatan Hospital Pulau Pinang, Malaysia.

Kajian ini ialah kajian cross-sectional. Data dikumpulkan daripada rekod perubatan pesakit yang telah didaftarkan dan disahkan menghidap pneumonia jangkitan dari komuniti di Hospital Pulau Pinang, Malaysia dari 1 Januari, 2008 hingga 31 Disember, 2011. Tiga ratus dua puluh tiga (323) pesakit dipilih berdasarkan kriteria penyertaan dan kriteria pengecualian. Antara 323 pesakit, terdapat 188 (58.20%) pesakit yang dirawat dengan antibiotik yang mengikuti garis panduan dan 135 (41.80%) pesakit dirawat dengan antibiotik yang tidak mengikuti garis panduan. Dalam kumpulan pesakit yang mendapat antibiotik mengikuti garis panduan, antibiotik yang paling banyak diberikan adalah amoxicillin/clavulanate + azithromycin (77.1%), diikuti oleh ampicillin/sulbactam + azithromycin (16.5%). Dalam kumpulan pesakit yang mendapat antibiotik tidak mengikuti garis panduan, antibiotik yang diberikan adalah amoxicillin/clavulanate secara monoterapi (37.8%),

diikuti oleh ampicillin/sulbactam secara monoterapi (18.5%), macrolide sahaja (8.1%), tetracycline + β-lactam/penghalang β-lactamase (9.6%). Hasil kajian menunjukkan bahawa terdapat perbezaan yang signifikan dalam pemulihan denyutan jantung (p=0.041) dan penurunan sel darah putih (p=0.040) di antara kumpulan pesakit yang mendapat antibiotik mengikuti garis panduan dan tidak mengikuti garis panduan. Berdasarkan ujian kultur dan pengubahsuaian antibiotik, kajian menunjukkan bahawa pemulihan dalam nilai urea (p=0.002) menunjukkan perbezaan yang ketara antara enam kumpulan. Tempoh penginapan dalam kumpulan pesakit yang mendapat antibiotik mengikuti garis panduan adalah 4.72 ± 2.06 hari, sedangkan kumpulan pesakit yang mendapat antibiotik tidak mengikuti garis panduan menunjukkan tempoh penginapan 4.90 ± 2.26 hari. Mortaliti hanya didapati dalam kumpulan pesakit yang mendapat antibiotik tidak mengikuti garis panduan, iaitu sejumlah tiga orang pesakit.

Penemuan menyimpulkan bahawa antibiotik yang paling banyak diberikan kepada pesakit adalah gabungan amoxicillin/clavulanate dan azithromycin. Kepatuhan terhadap garis panduan antibiotik menunjukkan keberkesanan dalam mengurangkan sel-sel darah putih, memulihkan denyutan jantung pesakit, memendekkan tempoh penginapan dan kematian; ujian kultur dan pengubahsuaian antibiotik mempengaruhi pemulihan dalam nilai urea.

EVALUATION OF ANTIBIOTIC THERAPY

AMONG PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

IN HOSPITAL PULAU PINANG

ABSTRACT

Community-acquired pneumonia (CAP) is one of infectious diseases that cause morbidity and mortality, especially in Asia-Pacific regions. Antibiotics guideline is needed in order to achieve appropriate use of antibiotics for CAP management, including Malaysia. Outcome of therapy still needed to be monitored to evaluate the antibiotics use for hospitalized patients with CAP. Therefore, this study was aimed to evaluate antibiotics use for community-acquired pneumonia (CAP) in medical ward of Hospital Pulau Pinang, Malaysia.

This was cross-sectional study. Data were collected from medical record of patients that had been registered and diagnosed with CAP in Hospital Pulau Pinang, Malaysia from January 1, 2008 until December 31, 2011. Three hundred and twenty three (323) patients were selected based on inclusion and exclusion criteria. Among 323 patients, there were 188 (58.20%) patients treated with antibiotics according to the guideline and 135 (41.80%) patients received antibiotics discordant to guideline. In guideline-adherent group, the most prescribed antibiotics were amoxicillin/clavulanate + azithromycin (77.1%); followed by ampicillin/sulbactam + azithromycin (16.5%). While in guideline-discordant group, the most commonly prescribed antibiotics were amoxicillin/clavulanate monotherapy (37.8%); followed by ampicillin/sulbactam monotherapy (18.5%), macrolide alone (8.1%), tetracycline + β-lactam/β-lactamase inhibitor (9.6%). Study findings also showed that there were significant differences in the improvement for heart rate (p=0.041) and white blood

cell (WBC) reduction (p=0.040) between guideline-adherent and guideline-discordant group. Based on culture tests and modification of antibiotics, findings suggested; patients' improvement in urea level (p=0.002) were significantly different among six groups. Length of stay (LOS) in guideline-adherent group was 4.72 ± 2.06 days, while guideline-discordant group showed length of stay (LOS) of 4.90 ± 2.26 days. Deaths were only found in guideline-discordant group with three patients.

Study findings concluded that the most common antibiotic that had been prescribed was combination of amoxicillin/clavulanate and azithromycin. Application of available antibiotic guideline of CAP showed effectiveness in reducing white blood cells (WBC) count, improving heart rate of patients, shortening length of stay (LOS) and no mortality; culture tests and modification of antibiotics affected patients' improvement in urea level.

CHAPTER 1

INTRODUCTION

1.1. Background

Community-acquired pneumonia (CAP) is one of infectious diseases that cause morbidity and mortality, especially in Asia-Pacific regions (Song *et al.*, 2011). It is one of pulmonary infections that ranging from self-limited processes to life-threatening infections and from acute diseases to chronic inflammatory diseases (Simon, 2003). It is inflammation or infection of lungs that causes lungs dysfunction (Lutfiyya *et al*., 2006).

The choice of antibiotics therapy ensures appropriate coverage of causative microorganisms in hospitalized patients with CAP (Ho *et al.*, 2009). Selection of antibiotics based on severity of illness, presumptive microorganisms, local resistance patterns of the microorganisms and co-morbid conditions (Lutfiyya *et al*., 2006; MOH, 2008; Ho *et al.*, 2009). The physician should decide the need and reason for therapy, select the appropriate antibiotics, dose, frequency, route of administration and duration of use (Guven and Uzun, 2003). Therefore, a specific antibiotic guideline is needed in order to achieve appropriate use of antibiotics for CAP management.

Some guidelines had been made by several organizations such as American Thoracic Society (ATS), British Thoracic Society (BTS), Canadian Society of Infectious Diseases and others. However, treatment for CAP in Asian countries, including Malaysia, should be based on epidemiological data of microorganisms and antibiotics resistance (Song *et al.*, 2008). As the most common causative microorganism for CAP, *Streptococcus pneumoniae* resistance to β-lactams is

increasing (Song *et al.*, 2004a; Song *et al.*, 2004b; Song *et al.*, 2008). But, *Streptococcus pneumoniae* isolates are still susceptible to β-lactams in some CAP studies in Asia, including Malaysia. Therefore, β-lactams still become the choice of antibiotic for CAP guideline therapy due to their sensitivity against *Streptococcus pneumoniae* (Rohani *et al.*, 1999; Wattanathum *et al.*, 2003; Song *et al.*, 2008; Ishida *et al.*, 2008).

The occurrence of atypical microorganisms that cause CAP is increasing (Shevet *et al.*, 2005). Even though a review defines that antibiotics for atypical microorganisms in hospitalized CAP patients do not give benefit for survival or clinical efficacy (Shevet *et al.*, 2005), current guidelines recommend the use of antibiotics that may cover atypical microorganisms (Mandell *et al.*, 2000; Mandell *et al.*, 2007; MOH, 2008; Lim *et al.*, 2009). Those antibiotics are consisted of combination of β-lactam and macrolide or fluoroquinolone monotherapy (Mandell *et al.*, 2000; Mandell *et al.*, 2007; Calzada *et al.*, 2007; MOH, 2008; Lim *et al.*, 2009; Tessmer *et al.*, 2009). Addition of macrolide to a β-lactam regimen or fluoroquinolone monotherapy for CAP treatment may improve survival and length of stay (LOS) (Martinez, 2004). But, some guidelines restrict the use of fluoroquinolone regarding increased number of microorganisms that become resistant to fluoroquinolone (Song *et al.*, 2004b; Mandell *et al.*, 2007; MOH, 2008; Lim *et al.*, 2009).

In some studies, patients that received antibiotics according to guideline showed better outcomes than those who received antibiotics discordant to guideline (Arnold *et al.*, 2009; Tessmer *et al.*, 2009). Outcomes included time to reach clinical stability, length of stay (LOS) and mortality (Arnold *et al.*, 2009; Tessmer *et al.*, 2009). Treatment failure was also lower in guideline-adherent group (Arnold *et al.*,

2009; Tessmer *et al.,* 2009). Otherwise, some studies showed that length of stay (LOS) and mortality in guideline-adherent group were not significantly different between guideline-adherent group and guideline-discordant group (Marras *et al.,* 2004; Calzada *et al.,* 2007). It is important to evaluate the outcome therapy of CAP even though some studies do not show better outcomes from the impact of applied guideline in treating hospitalized patients with CAP. However, antibiotics guideline must be taken into consideration when selecting the appropriate antibiotics for therapy of CAP, including Malaysia. Outcome of the therapy still needed to be monitored to evaluate the antibiotics use for hospitalized patients with CAP.

1.2. Epidemiology of Community-Acquired Pneumonia (CAP)

Lower respiratory tract infections (LRTIs), including CAP, was placed third among 20 leading causes of death (WHO, 2008). There was a study that included 4337 patients from four regions. The study showed the incidence of CAP due to atypical pathogens for 22% in North America, 28% in Europe, 21% in Latin America and 20% in Asia and Africa (Arnold *et al.*, 2007). Community-acquired pneumonia (CAP) infections were endemic in the Asia region (Ngeow *et al*., 2005).

Community-acquired pneumonia (CAP) showed incidence 3-5 cases per 1000 persons and mortality rate approximately of 5-15% in hospitalized patients (Kaplan *et al.*, 2002). Most patients with CAP were treated in ambulatory care, while 20% of CAP patients were hospitalized and 1% of CAP patients required treatment in an Intensive Care Unit (Glover and Reed, 2008). Mortality rate for hospitalized patients with CAP was estimated for 5.1-13.7% (Marston *et al*., 1997).

A prevalence study was conducted at 12 medical centers in Beijing, Shanghai, Hong Kong, Seoul, Taipei, Bangkok, Manila, Kuala Lumpur, Petaling

Jaya, Singapore, Jakarta, Surabaya. Most patients in this study were admitted to hospital for treatment of CAP. Among 1374 patients with CAP diagnosis, 821 (88.7%) patients were admitted to hospital and 56 (6%) patients required treatment in the Intensive Care Unit (ICU). This study stated that CAP infections were endemic in the region (Ngeow *et al.*, 2005).

Epidemiology study of *Streptococcus pneumoniae* infection was conducted in Malaysia. A study conducted by Rohani *et al* (1999) in the six study centers in Malaysia obtained 273 isolates of *Streptococcus pneumoniae*. Community-acquired pneumonia (CAP) was the main clinical manifestation of pneumococcal infections. A prospective study was conducted to predict in-patient mortality in 108 hospitalized patients with CAP in Malaysia. The study showed that 13 (12%) patients died in hospital while 95 (88%) patients survived (Loh *et al.*, 2004). There was a retrospective study that included 313 cases of *Klebsiella pneumoniae* infections. In-hospital mortality and requirement for ventilation were 14.3% and 10.8% respectively (Loh *et al*., 2007). Hence, CAP still causes morbidity and mortality in respiratory tract infections.

1.3. Clinical Manifestation of Community-Acquired Pneumonia (CAP)

Some microorganisms such as Gram-positive and Gram-negative bacteria can cause CAP, with similar clinical characteristics. *Pneumococcus, Staphylococcus*, the enteric Gram-negative rods may cause local irritation or destruction of blood vessels that can lead to rust-colored sputum or hemoptysis (Glover and Reed, 2008).

Bacterial pneumonia is caused by Gram-positive such as *Streptococci, Staphylococci* and Gram-negative organisms that inhabit the gastrointestinal tract (enterics), soil and water (non-enteric) (Lim *et al*., 2009). The chest radiograph

reveals a dense lobar or segmental infiltrate that indicate Gram-positive and Gram-negative bacterial infection. Sputum gram stain shows predominant organism, which is reflected as growth of a single species on culture (Glover and Reed, 2008). The complete blood count test shows leukocytosis with a predominance of polymorphonuclear cells. White blood cell (WBC) may increase or remain normal in bacterial infection. The patient also may suffer low oxygen saturation on arterial blood gas or pulse oximetry (Glover and Reed, 2008).

Table 1.1. Clinical Manifestation of Pneumonia (Simon, 2003; Lutfiyya *et al.*, 2006; Glover and Reed, 2008)

Signs and symptoms	Physical examination
1. Fever 2. Chills 3. Dyspnea 4. Productive cough 5. Rust-colored sputum or hemoptysis 6. Pleuritic chest pain	1. Tachypnea and tachycardia 2. Dullness to percussion 3. Diminished breath sounds over affected area 4. Inspiratory crackles during lung expansion
Chest radiograph	**Laboratory tests**
1. Dense lobar 2. Segmental infiltrate	1. Leukocytosis with predominance of polymorphonuclear cells 2. Low oxygen saturation on arterial blood gas or pulse oximetry

1.4. Antibiotics Therapy for Hospitalized Patients with Community-Acquired Pneumonia (CAP)

Antibiotics therapy is needed in treating hospitalized patients with CAP. Antibiotics choices are classified into preferred and alternative recommendations based on clinical evidence of effectiveness and adverse effects (MOH, 2008). Antibiotics prescribing should be made based on the presumptive etiologic microorganisms, local susceptibility pattern and patients' co-morbidities. Information on pattern of antibiotics use is essential regarding management on antibiotics

prescribing (MOH, 2008). The use of guidelines can promote the appropriate management of CAP (File and Hadley, 2002).

In American guideline, antibiotics treatments for hospitalized patients with CAP are initially given fluoroquinolone alone or macrolide plus β-lactam (Mandell *et al.*, 2007). Patients with recent antibiotics therapy are given an advanced macrolide plus a β-lactam or fluoroquinolone alone (Mandell *et al.,* 2007). In Canadian guideline, the use of fluoroquinolone alone is recommended (Mandell *et al.*, 2000). Development of resistance to these fluoroquinolones has already been reported (Liam, 2005). Despite a high level of activity against *Streptococcus pneumoniae* and atypical organisms, fluoroquinolones are not recommended because of their overextended spectrum of coverage that include Gram-negative bacteria and the emergence of resistant *Streptococcus pneumoniae* (Liam, 2005). The use of a third-generation cephalosporin and a macrolide antibiotic provides better coverage for CAP without causing *Streptococcus pneumoniae* resistance but also of the emergence of many resistant Gram-negative organisms that are not related with the patient's pneumonia (Liam, 2005). Fluoroquinolones are used for certain conditions, such as patients who are allergic to first-line agents, failure in first-line therapy, or penicillin resistance (Liam, 2005). Community-acquired pneumonia (CAP) that caused by penicillin resistant *Streptococcus pneumoniae* can still adequately treated with β-lactams at the right dosage (Liam, 2005). In British guideline, initial antibiotics regimens for hospitalized patients with CAP include amoxicillin plus clarithromycin or benzylpenicillin plus clarithromycin (Lim *et al.,* 2009).

Table 1.2. Antibiotics Therapy for Hospitalized Patients with Community-Acquired Pneumonia (CAP) That Recommended by American, British and Canadian Guideline

Guideline	Preferred therapy	Alternative therapy
American Guideline (Mandell *et al.*, 2007)	Fluoroquinolone alone or macrolide (azithromycin, erythromycin or clarithromycin) **plus** β-lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam)	
British Guideline (Lim *et al.*, 2009)	Amoxicillin 500 mg –1.0 g three times in a day given orally plus clarithromycin 500 mg twice a day given orally (If drugs may not be given orally, use IV amoxicillin 500 mg three times in a day or IV benzylpenicillin 1.2 g four times in a day plus IV clarithromycin 500 mg twice in a day)	Doxycycline 200 mg loading dose then 100 mg given orally or levofloxacin 500 mg once in a day orally or moxifloxacin 400 mg once in a day given orally
Canadian Guideline (Mandell *et al.*, 2000)	Fluoroquinolone (Third-generation levofloxacin, fourth-generation gatifloxacin and moxifloxacin, are prohibited due to severe hepatotoxicity)	Second, third or fourth generation of cephalosporin + macrolide

Based on Ministry of Health, Malaysia, preferred therapy includes IV or oral azithromycin or IV/oral erythromycin ethylsuccinate plus third-generation of cephalosporins or β-lactams/β-lactamase inhibitors. While CAP which is caused by *Pseudomonas aeruginosa*, preferred treatment includes piperacillin/tazobactam or cefepime plus gentamicin plus azithromycin (MOH, 2008).

Table 1.3. Guideline of Antibiotics for Hospitalized Patients with Community-Acquired Pneumonia (CAP) Management in Malaysia (MOH, 2008)

Infection/Condition and Likely Organism	**Recommended Therapy**		**Notes**
	Preferred	**Alternative**	
CAP requiring hospitalization (not requiring mechanical ventilation) *Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenza* *Klebsiella pneumoniae* *Legionella* *Staphylococcus aureus* Other Gram Negative Bacilli (*Enterobacter*, *Escherichia coli*).	Azithromycin 500 mg IV/PO once in a day **or** Erythromycin 500 mg IV four times in a day/ erythromycin ethylsuccinate 800 mg PO twice a day **plus** Third-generation of cephalosporins, such as ceftriaxone 1-2g IV once in a day **or** Lactam/β-lactamase inhibitors, such as amoxycillin/clavulanate or ampicillin/sulbactam Duration : 1 week	Levofloxacin 500 mg IV/PO once in a day for 1 week	1. Empirical therapy for melioidosis should be considered if patient has diabetes mellitus. 2. Quinolone is used when patients failed first line regimens or allergic to alternative.
Pseudomonas aeruginosa infection	Piperacillin/tazobactam 4.5 g IV three times in a day for 1 week **or** cefepime 2 g IV twice a day for 1 week **plus** Gentamicin 5 mg/kg IV once in a day **plus** Azithromycin 500 mg IV once in a day for 1 week	Piperacillin/tazobactam 4.5 g IV three times in a day for 1 week **or** Cefepime 2 g IV twice a day for 1 week **plus** Ciprofloxacin 500 mg IV twice a day for 1 week	

The main goals of CAP management include eradicating the causative microorganisms, resolving signs and symptoms of CAP, reducing hospitalization and preventing relapse (Lutfiyya *et al.*, 2006). Appropriate clinical parameters should be evaluated to ensure the efficacy and safety of the therapy (Glover and Reed, 2008). Improvement of CAP symptoms such as cough and fever, are important to be evaluated. Improvement of symptoms should be observed within the first two days (Glover and Reed, 2008). Initial antibiotics therapy should be evaluated if patient's condition is deteriorating within two days (Glover and Reed, 2008). Heart rate, blood pressure, respiratory rate, body temperature, oxygen saturation and mental status should be measured initially at least twice daily (Lim *et al*., 2009). The median time

for improvement in heart rate and blood pressure is two days and for temperature, respiratory rate and oxygen saturation is three days (Lim *et al*., 2009). Risk factors for failure in therapy include multi lobar involvement, occurrence of pleural effusion, co-existing liver disease, cancer or neurological disease, *Legionella*, leucopenia, high disease severity on admission and inappropriate antibiotics therapy. Failure may increase mortality and length of hospital stay (Lim *et al*., 2009).

CHAPTER 2

LITERATURE REVIEW

2.1. Introduction

Community-acquired pneumonia (CAP) still causes morbidity and mortality (Loh, 2006). An awareness of the presumptive causative microorganisms of CAP treated in certain settings is important to start initial antibiotics therapy (Liam, 2005). The choice of antibiotics in treating hospitalized patients with CAP is important as it may influence outcomes of therapy (Loh, 2006).

The use of guidelines may lead to appropriate antibiotics management of CAP (File, 2004). Development and application of treatment guidelines should help reduce inappropriate prescribed antibiotics (File, 2004). The National Antibiotic Guideline 2008, published by Ministry of Health Malaysia, can be important guidance for physicians towards making appropriate antibiotics choices for CAP (MOH, 2008). Information on pattern of antibiotics use in hospitalized CAP is also essential towards control measures on antibiotics that being prescribed (MOH, 2008).

2.2. Etiology of Community-Acquired Pneumonia (CAP)

Microorganisms that cause CAP could be different in each region. The most common causative microorganism worldwide is *Streptococcus pneumoniae.* Other common microorganisms include *Mycoplasma pneumoniae, Legionella, Chlamydophila pneumoniae, Haemophilus influenzae,* and viruses (Glover and Reed, 2008; Watkins and Lemonovich, 2011). High prevalence of mixed infections by bacteria and atypical pathogens also occurred (Almirall *et al*., 2007; Song *et al*.,

2008). Mixed infections occur more in patients with underlying diseases (Gutierrez *et al.*, 2005; Almirall *et al*., 2007).

Streptococcus pneumoniae was still the most common microorganism that caused CAP in some countries in Asia (Ishida *et al.,* 1998; Wattanathum *et al.,* 2003; Miyashita *et al.,* 2005; Ngeow *et al.,* 2005; Song *et al.,* 2008). Table 2.1 showed common microorganisms etiology for hospitalized patients with CAP in some countries in Asia, including Malaysia. Song *et al* conducted a study in China, South Korea, Hong Kong, India, Singapore, Vietnam, Philippines, Taiwan, regarding microorganisms that caused hospitalized CAP patients. This study showed *Streptococcus pneumoniae* (29.2%), *Klebsiella pneumoniae* (15.4%), *Haemophilus influenza* (15.1%), *Pseudomonas aeruginosa* (6.7%) as the most common causative microorganisms of CAP in the region (Song *et al.,* 2008). Studies that conducted by Miyashita and Ishida stated that *Streptococcus pneumoniae, Haemophilus influenzae* and *Mycoplasma pneumoniae* were the etiology of CAP in Japan (Miyashita *et al.,* 2005; Ishida *et al.,* 1998). In Thailand study, the most common causative microorganisms for CAP were *Streptococcus pneumoniae* (22.4%), *Chlamydophila pneumoniae* (16.3%), *Klebsiella pneumoniae* (9.5%), *Mycoplasma pneumoniae* (6.8%) (Wattanathum *et al.,* 2003; Ngeow *et al.,* 2005). However, etiology for CAP in Malaysia were quite different to those in other countries in Asia; they were *Klebsiella pneumoniae* (17.8%), *Mycobacterium tuberculosis* (15.1%), *Acinetobacter* (4.1%), *Pseudomonas* (2.7%) (Loh *et al.,* 2004).

Table 2.1. Common Causative Microorganisms for Hospitalized Patients with Community-Acquired Pneumonia (CAP)

Literature	No. of patients	Etiology of CAP
Song *et al.*, 2008	955	*Streptococcus pneumoniae* (29.2%), *Klebsiella pneumoniae* (15.4%), *Haemophilus influenzae* (15.1%), *Pseudomonas aeruginosa* (6.7%)
Miyashita *et al.*, 2005	400	*Streptococcus pneumoniae* (26.3%), mixed infection (14.0%), *Haemophilus influenzae* (13.0%), *Mycoplasma pneumoniae* (9.3%)
Ishida *et al.*, 1998	318	*Streptococcus pneumoniae* (23.0%), *Haemophilus influenzae* (7.4%), *Mycoplasma pneumoniae* (3.4%)
Wattanathum *et al.*, 2003; Ngeow *et al.*, 2005	147	*Streptococcus pneumoniae* (22.4%), *Chlamydophila pneumoniae* (16.3%), *Klebsiella pneumoniae* (9.5%), *Mycoplasma pneumoniae* (6.8%)
Loh *et al.*, 2004	108	*Klebsiella pneumoniae* (17.8%), *Mycobacterium tuberculosis* (15.1%), *Acinetobacter* (4.1%), *Pseudomonas* (2.7%)

Klebsiella pneumoniae was the highest number of causative microorganism in hospitalized CAP patients in Malaysia (Loh *et al.*, 2004). A study by Kin showed that common causative microorganisms in hospitalized patients with CAP (n=352) in Kuala Lumpur, were *Klebsiella pneumoniae* (11.4%), *Mycoplasma pneumoniae* (6.3%), *Mycobacterium tuberculosis* (4.8%), *Staphylococcus aureus* (3.7%), *Streptococcus pneumoniae* (3.4%), *Haemophilus influenzae* (3.1%). While common causative microorganisms in hospitalized patients with CAP (n=98) in Penang were *Mycobacterium tuberculosis* (15.3%), *Klebsiella pneumoniae* (7.2%), *Pseudomonas aeruginosa* (6.1%), *Staphylococcus aureus* (5.0%), *Streptococcus pneumoniae* (3.0%), *Acinetobacter* (3.0%) (Liam, 2005). Thus, it is important that the choice of antibiotics therapy ensures appropriate coverage of potentially causative microorganisms in hospitalized patients with CAP.

2.3. Initial Antibiotics Therapy for Hospitalized Patients with Community-Acquired Pneumonia (CAP)

Antibiotics therapy is needed for CAP patients that require hospital treatment. Initial antibiotics therapy should be given to these patients. Initial antibiotics may be administered through intravenous or oral administration (Loh *et al.,* 2004). Earlier administration of initial antibiotics was required in order to get better clinical outcome and improve survival rate (Restrepo and Anzueto, 2005).

Antibiotics therapy must cover *Streptococcus pneumoniae* and atypical microorganisms (Restrepo and Anzueto, 2005). A study showed that length of stay (LOS) was 8.8 ± 7.2 days for patients who received atypical coverage (n=2.220) and 9.6 ± 7.0 days for patients who did not receive atypical coverage (n=658). The mean difference was statistically significant. This study also showed decreased patient mortality in patients who received atypical coverage (Arnold *et al.,* 2007).

Antibiotics that had atypical coverage for hospitalized patients with CAP were also advantageous for patients with *Legionella* infection (Shevet, *et al.,* 2005). A meta-analysis showed that in moderate CAP the relative risk for treatment failure was significantly lower in patients with *Legionella* infection that received antibiotics against atypical microorganisms (Loh, 2006).

Combination of β-lactams and macrolides showed better outcomes than β-lactams monotherapy. A prospective study was conducted between 2002 and 2004 of 141 adult patients with CAP hospitalized in Seremban Hospital, Malaysia. Sixty-three (44.7%) patients received a macrolide-containing antibiotic regimen while 78 (55.3%) patients received single non-macrolide broad spectrum antibiotics. However, there were no significant differences in mortality, need of ventilation and median length of hospital stay between the two treatment groups (Loh, 2006). Otherwise, there were studies that gave different outcome. A review that conducted by Caballero

and Rello stated that combination therapy of cephalosporin (β-lactam) and macrolide for hospitalized patients with CAP was related to decreased mortality and shorter length of stay (LOS) than treatment with cephalosporin (β-lactam) monotherapy (Caballero and Rello, 2011). The other study that showed the superiority of β-lactam plus macrolide was conducted by Martinez *et al* (2003). The study included 409 hospitalized patients with CAP diagnosis. Two hundred and thirty eight (58%) patients received β-lactam plus macrolide and 171 (42%) patients received β-lactam without macrolide. Multivariate analysis revealed that one of the variables, no inclusion of macrolide in the initial antibiotics regimens, was associated with death. Patients with bacteremic pneumococcal pneumonia, not adding macrolide to β-lactam-based initial antibiotics regimens may cause in-hospital mortality (Martinez *et al.,* 2003).

Antibiotics therapy that used β-lactam monotherapy did not give better outcomes than β-lactam plus macrolide or fluoroquinolone monotherapy. A systematic review was conducted to evaluate whether β-lactam plus macrolide or fluoroquinolone monotherapy excel β-lactam monotherapy. Eight relevant studies were included in this review. The review showed that β-lactam plus macrolide or fluoroquinolone monotherapy reduced mortality, reduced length of stay (LOS) in one study and showed no beneficial effects in one study. This was caused by unrecognized role of atypical pathogens, anti-inflammatory effects of macrolide or resistance to β-lactam (Oosterheert *et al.,* 2003).

The use of fluoroquinolones in CAP management is also getting increase, due to its effectiveness. A meta-analysis of randomized controlled trials that conducted by Vardakas *et al* showed fluoroquinolones were more effective than a combination of β-lactams and macrolides. It was stated that fluoroquinolones showed higher

success in treating CAP. But, mortality rates between fluoroquinolones and other comparator antibiotics were not different (Vardakas *et al.,* 2008). Higher success in treating CAP with fluoroquinolones was caused by zero baseline resistance to these antibiotics compared to higher resistance for β-lactams and macrolides. Unfortunately, resistance to fluoroquinolones might increase in the future (Vardakas *et al.,* 2008).

There were studies that supported the equal effectiveness of combination of β-lactams and macrolides, compared to fluoroquinolones. A study conducted at Veterans Affairs Hospital revealed that mortality rates were lower among PSI Class V patients in combination of β-lactams and azithromycin than in levofloxacin monotherapy group. But, the mortality rates among PSI Class I-IV patients were not different between two groups (Lodise *et al.,* 2007). The other retrospective study of 12945 inpatients showed that initial treatment of CAP with second-generation cephalosporin plus macrolide, third-generation cephalosporin plus macrolide or fluoroquinolone monotherapy was associated with reduction of 30-day mortality in patients with PSI classes IV and V (Gleason *et al.,* 1999).

The other study also pointed the use of cephalosporin group and doxycycline as initial antibiotics for CAP requiring hospitalization. A total of 216 patients of hospitalized CAP were treated with ceftriaxone plus doxycycline and 125 received other appropriate initial antibiotics. The result showed that ceftriaxone plus doxycycline could reduce inpatient mortality and 30-day mortality. However, ceftriaxone and doxycycline therapy did not reduce length of stay (LOS) and readmission rates (Flanders *et al.,* 2006).

2.4. Antibiotics Modification in Community-Acquired Pneumonia (CAP) Management

Positive blood culture results could be useful in CAP management. Antibiotics modification may occur due to positive blood culture results. But, cost-effectiveness needs to be assessed in prospective clinical trials (Waterer *et al.,* 1999).

Initial broad-spectrum antibiotics are given to hospitalized patients with CAP. Therefore, the possible influence to antibiotics modification for CAP is either reduction or narrowing antibiotics therapy. Antibiotics modification was consisted of any change in the dose of antibiotic, addition or discontinuation of one or more antibiotics (Waterer *et al.,* 1999). Seventy-four patients with pneumococcemia admitted into a study. Blood culture results altered management in 31 (41.9%) patients; two of patients had antibiotics modification due to antibiotics resistance. Antibiotics modification was consisted of macrolide stopped, change to penicillin, other antibiotics stopped, add vancomycin or change dose of cephalosporin (Waterer *et al.,* 1999).

Patients (N= 2039) were recruited from 128 centers in ten countries (Belgium, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Turkey, UK). Initial antibiotic treatment modification occurred in 28.9% of patients and was more likely in patients with co-morbidities; severely ill patients; patients with immune disorders or patients with recurrent episodes of CAP. The most common reasons for initial antibiotic treatment modification were insufficient response to treatment (12.0%) and adverse events (2.0%) (Blasi *et al.,* 2013).

Antibiotics therapy for hospitalized patients with CAP must be switched from intravenous to oral administration. An evaluation study stated that this modification is associated with significant reduction in the mean of length of hospital stay

(Restrepo and Anzueto, 2005). Patients could be discharged directly after changing from intravenous to oral administration (van der Eerden *et al.*, 2005).

2.5. Antibiotics Therapy for Identified Microorganisms

As stated before, either typical microorganisms (Gram-positive and Gram-negative bacteria) or atypical microorganisms could cause CAP. As β-lactamase production by both Gram-positive and Gram-negative bacteria became major concern in CAP management, β-lactamase inhibitors such as clavulanate, sulbactam and tazobactam were developed (White *et al.*, 2004). Besides that, newer generation of cephalosporins that could endure β-lactamase production was also developed, such as third-generation and fourth generation of cephalosporins (Garau, 2005). Macrolides were used as alternative therapy for those who had allergy to penicillin (Garau, 2001). In CAP management, macrolides were used in combination with β-lactams/β-lactam inhibitors, due to its activity against atypical microorganisms (Flanders *et al.*, 2006).

A prospective randomized open study performed between 1998 and 2000 which included 262 hospitalized patients with CAP diagnosis. The two groups consisted of empirical broad spectrum antibiotics treatment and pathogen directed treatment approach. The study showed that there were no significant differences between two groups in LOS, 30-day mortality, clinical failure or resolution of fever. This study stated that empirical antibiotics therapy for hospitalized patients with CAP has equal clinical efficacy to pathogen directed treatment approach (van der Eerden *et al.*, 2005). However, once the pathogen could be identified, adjusted antibiotics must be administered (Restrepo and Anzueto, 2005).

Identification of specific causative microorganisms within 24–72 hours could still be useful for guiding continued treatment. Therapy could be conducted by selecting narrow spectrum antibiotics, so that it could reduce the risk of higher resistance (File, 2003; Charles, *et al.,* 2008). There are no clear advantages of intravenous therapy over oral therapy for antibiotics therapy based on identified microorganisms. However, CAP patients who require hospitalization, receive intravenous administration (File, 2003).

2.6. Outcome of Community-Acquired Pneumonia (CAP) Management

Application of available antibiotic guideline of CAP shows better outcome of therapy. These were supported by some CAP studies. One of these studies was a study conducted by Tessmer *et al* (2009) in German that included 1854 hospitalized patients with CAP. These patients were treated with antibiotics accordant to guideline, either combination of β-lactam and macrolide (51.0%) or β-lactam monotherapy (49.0%) Combination of β-lactam and macrolide was associated with decreased 14 day mortality and treatment failure at 14 days therapy (Tessmer, *et al.,* 2009). The other study was conducted by Arnold *et al* (2009) in order to define the outcome therapy of geriatric patients hospitalized with CAP who were treated with antibiotics according to 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guideline. This study included 1725 hospitalized patients. Guideline-adherent group showed decreased time to achieve clinical stability, shorter length of stay (LOS), and decreased in-hospital mortality than guideline-discordant group. In guideline-adherent group, the most common antibiotics were combination of β-lactam and macrolide (58.6%) and quinolone

monotherapy (39.7%). In guideline-discordant group, the most common antibiotics were β-lactam monotherapy (52.0%) (Arnold *et al.,* 2009).

Otherwise, application of available antibiotic guideline of CAP did not show better outcome of therapy in some CAP studies. Marras *et al* (2004) reviewed 698 cases of CAP in Canada, 91.0% (636 cases) were accordant to Canadian Guideline. The study stated that there was no significant difference in mortality and length of stay (LOS) between guideline-adherent and guideline-discordant group. The most common antibiotics were quinolone monotherapy and cephalosporin monotherapy (Marras *et al.,* 2004). There was also one study in Spain that pointed the outcome of guideline-adherent for antibiotics therapy of CAP. Mortality was analyzed as the outcome. But, the mortality rate was higher in non-adherent group than adherent group. It was a prospective study with 425 hospitalized patients with CAP. The overall mortality was 8.2%. Mortality in adherent group was 26 (8.2%) while in non-adherent group was 9 (8.5%). Adherent level to guideline was 76.5% with the predominance of combination of β-lactam and macrolide (57.4%). The median length of stay was 8 ± 5 days and the re-admission rate was 7.6% (Calzada *et al.,* 2007).

Mortality, length of stay (LOS), admission rate to intensive care unit (ICU) was higher in patients with Gram-negative infections than those with Gram-positive infections (Wattanathum *et al.,* 2003; Loh *et al.,* 2007; Falguera *et al.,* 2009). A study enrolled 313 hospitalized patients with CAP and *Klebsiella pneumoniae* isolates. Death was found most common in patients with antibiotic-resistant, compared to antibiotic-susceptible patients (10.8% vs 23.3%). But, there were no significant differences in length of stay (LOS) between antibiotic-resistant patients and antibiotic-sensitive patients (Loh *et al.,* 2007). The other study conducted in

Thailand with 147 adult hospitalized patients with CAP. The mortality rate was 16.3% in the non-ICU hospitalized patients. Mortality rate of Gram-negative infections was significantly higher than those Gram-positive infections or atypical pathogen infections (53.8% vs 24.4% vs 12.1%) (Wattanathum *et al.*, 2003). A study with 3272 episodes of CAP showed that sixty-one patients (2%) were infected by Gram-negative bacilli. Among 61 patients that infected by Gram-negative bacilli, 12 patients (20%) required intensive care unit (ICU) admission, and the rest of 287 patients (9%) that not infected with Gram-negative bacilli also required ICU admission. Gram-negative bacilli pneumonia patients were also related to increased mortality (22 of 61 patients, 36%) compared to patients that not infected with Gram-negative bacilli (236 of 3211 patients, 7%). Gram-negative bacilli pneumonia patients were also related to increased length of stay (LOS), compared to patients that not infected with Gram-negative bacilli (16 days vs 9 days) (Falguera *et al.*, 2009).

There are some risk factors that can lead to death due to CAP. A study with 955 hospitalized patients with CAP showed that malignancy, cardiovascular diseases, respiratory rate > 30/min and hyponatremia were risk factors that led to death of patients (Song *et al.,* 2008). Sepsis had become one of causative conditions that could lead death to hospitalized CAP patients (Dionaldo *et al.,* 2007). An observational study with 52 hospitalized patients with CAP. Among 52 patients, three (6%) died due to sepsis and others were discharged with improved condition. Mean of length of stay (LOS) was 9.0 ± 5.0 days (Dionaldo *et al.,* 2007). Other study with 3523 patients with CAP; 514 (15%) outpatients, 2521 (72%) patients in ward and 488 (14%) patients in intensive care unit (ICU), showed that *Streptococcus pneumoniae* has the highest number for mortality. Besides that, mixed etiologies also

caused high mortality with 32.2% of mixed bacteria with bacteria and 29.3% of bacteria and viruses (Cilloniz *et al.,* 2011). Among 318 hospitalized patients with CAP that enrolled in a Japan study, 20 (6.1%) patients died during hospitalization. Results of culture test of these patients were *Streptococcus pneumoniae* in three patients, *Klebsiella pneumoniae* in three patients, *Streptococcus milleri* in two patients, *Mycobacterium tuberculosis* in two patients, *Staphylococcus aureus* in one patient, *Staphylococcus aureus* + *Streptococcus pneumoniae* in one patient, *Klebsiella pneumoniae* + *Pseudomonas aeruginosa* in one patient (Ishida *et al.,* 1998).

Death was found most common in patients with antibiotic-resistant, compared to antibiotic-susceptible patients (Loh *et al.,* 2007). In one study, antibiotic resistance did not influence clinical outcomes and death (Song *et al.,* 2004a). A study with 233 adults with pneumococcal pneumonia showed that among 233 patients, 202 (86.7%) patients showed clinical improvement, 31 (13.3%) patients died within 30 days after diagnosis. Mortality rates among patients with penicillin resistance, cephalosporin resistance or macrolide resistance were not higher than patients with antibiotic-susceptibility (Song *et al.,* 2004a). A review of CAP amongst adults in the Asia-Pacific region stated that antibiotics resistance did not affect mortality rates significantly (Song *et al.,* 2011).

2.7. Problem Statements

Antibiotics selection for community-acquired pneumonia (CAP) needs thorough consideration, due to various microorganisms that may cause CAP. Guideline may help antibiotics prescribing for CAP. However, antibiotics prescribing that accordant to available guideline need to be evaluated. Antibiotics modification

may also occur during CAP management, due to inappropriate initial antibiotics therapy, patients' health status or identified microorganisms. Therefore, antibiotics modification also needed to be evaluated. Antibiotics therapy for CAP according to guideline should represent better outcome than guideline-discordant therapy. Outcome of the therapy should be evaluated, between guideline-adherent therapy and guideline-discordant therapy.

2.8. Rational of Study

Community-acquired pneumonia (CAP) is an infectious disease that can cause increasing morbidity and mortality. Antibiotics therapy is needed in hospitalized patients with CAP. Antibiotics selection for CAP management may experience some constraints due to various causative pathogens and patients' health status. Choice of antibiotics is important as it can influence its outcome of CAP management.

Many countries have developed guideline for antibiotics therapy in CAP treatment, including Malaysia. The National Antibiotic Guideline, published by Ministry of Health, Malaysia, can be important guideline for prescribers to make appropriate antibiotics choices for CAP. Guideline-adherence in giving antibiotics prescription may increase outcome of CAP management.

Information on pattern of antibiotics prescriptions is also essential to arrange control measurement on antibiotics prescribing and its effectiveness. Effectiveness of antibiotics therapy that made based on National Antibiotic Guideline, published by Ministry of Health, Malaysia need to be evaluated. As comparison, effectiveness of antibiotics therapy that made discordant to this guideline also needed to be evaluated.

Hopefully, this comparison may help in representing some output to achieve better outcome for CAP management.

2.9. Objectives

2.9.1. General Objective

This study is aimed to evaluate antibiotics use for community-acquired pneumonia (CAP) patients in medical ward of Hospital Pulau Pinang, Malaysia.

2.9.2. Specific Objectives

1. To identify causative microorganisms of community-acquired pneumonia (CAP) in medical ward of Hospital Pulau Pinang, Malaysia.
2. To evaluate initial antibiotics that being prescribed for community-acquired pneumonia (CAP) in medical ward of Hospital Pulau Pinang, Malaysia.
3. To evaluate antibiotics modification for community-acquired pneumonia (CAP) management in medical ward of Hospital Pulau Pinang, Malaysia.
4. To evaluate antibiotics that being prescribed based on identified microorganisms in community-acquired pneumonia (CAP) patients in medical ward of Hospital Pulau Pinang, Malaysia.
5. To evaluate outcome related to community-acquired pneumonia (CAP) management in medical ward of Hospital Pulau Pinang, Malaysia.

CHAPTER 3

METHODOLOGY

3.1. Study Design

This was cross-sectional study. Data were collected from medical record of patients that had been registered and diagnosed with CAP. Patients' list was obtained from Chest Ward and Medical Record Office.

3.2. Study Period and Location

This study was conducted from May -November 2012. It was conducted at Hospital Pulau Pinang, Malaysia.

3.3. Population and Sampling Procedure

3.3.1. Sample Size Calculation

Sample size calculation was calculated with the pattern below:

$$X = Z(c/100)^2 r(100-r)$$
$$n = Nx/((N-1)E^2 + x)$$
$$E = \text{Sqrt}[(N-n)x/n(N-1)]$$

n was the sample size, N was the population size, r was the fraction of response and $Z(c/100)$ was the critical value for the confidence level c (Raosoft, 2004).

Sample size was calculated with population of patients treated with CAP management that counted approximately 1000 patients in medical ward of Hospital Pulau Pinang, Malaysia and with confidence level of 95%. Hence, the recommended sample size was 278 patients.