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Research Report **MSc (Pharmacotherapy) 2012**

A Retrospective Study to Evaluate Adherence to the South African Guideline on the Management of Community-Acquired Pneumonia in Adults

Anastacia Chetty

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Pharmacotherapy

Johannesburg, 2012

FINAL Version 1.0

Anastacia Chetty **Research Report** **MSc (Pharmacotherapy) 2012**
Student no.: 0401210k

Candidate's Declaration

I, Anastacia Chetty, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Pharmacotherapy in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Chetty

24 day of April 2012

Dedication

To my parents

Leonard and Venothie Chetty

For all the sacrifices you have made in life,

your infinite wisdom, guidance, understanding and patience

"Medicine, the only profession that labours incessantly to destroy the reason for its existence." - James Bryce

Anastacia Chetty
Student no.: 0401210k

Research Report **MSc (Pharmacotherapy) 2012**

Abstract

Introduction: Community-acquired pneumonia (CAP) is consequence of infection, causing morbidity and mortality, leading to healthcare resource expenditure. Guidelines have been published by societies indicating the optimal antibiotic treatment of patients with CAP; however, few studies have confirmed whether guidelines are being adhered to, or if they lead to improved outcomes in patients in South Africa.

Study objectives and Design: This was a retrospective record review to determine levels of adherence to the 2007 South African Thoracic Society Guideline for CAP management in adults at an academic teaching hospital, and to confirm whether guideline adherence leads to improved patient outcome, shorter length of hospital stay and shorter time to clinical stability.

Results: 181 patients consisting of 101 females; 109 HIV positive (42 HIV status unknown) and 1 mortality had data recorded, out of 1073 files who met the criteria (297 excluded due to TB/PCP infection or underage and 595 not provided). Of these 181, 47 had CURB-65 scores ranging from 2-4. The majority (66%) of patients received antibiotic treatment adherent to the guideline. Patients that received treatment non-adherent to the guideline were found to have been over-treated (broader spectrum antibiotics used). There was no significant difference in the length of hospital stay among the two patient groups; however a significantly longer time to clinical stability was found in patients who had received treatment adherent to the guideline.

Conclusion: This study found a much higher level of SATS guideline adherence than other studies and a lower mortality.

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1. List of Abbreviations

AIDS:	Acquired Immunodeficiency Syndrome
ATS:	American Thoracic Society
BTS:	British Thoracic Society
CAP:	Community acquired pneumonia
COPD:	Chronic obstructive pulmonary disease
ERS:	European Respiratory Society
LOHS:	Length of hospital stay
HIV:	Human immunodeficiency virus
ICU:	Intensive care unit
IDSA:	Infectious Diseases Society of America
PCP:	*Pneumocystis jirovecii* Pneumonia
SATS:	South African Thoracic Society
TB:	Tuberculosis

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5 CHAPTER ONE

5.1 Introduction

Community-acquired pneumonia (CAP) is a consequence of infection, known to cause profound morbidity and mortality throughout the world, leading to significant health care resource expenditure (Calzada *et al.*, 2007; Feldman, 2004).

CAP is defined as an acute infection associated with inflammation of the lung parenchyma distal to the terminal bronchioles (Bartlett *et al.*, 2000; Klugman *et al.*, 2004; Feldman *et al.*, 2007; Black, 2008). CAP is normally accompanied by clinical and/or radiological signs of consolidation of part or parts of one or both lungs (Bartlett *et al.*, 1998; Klugman *et al.*, 2004; Feldman *et al.*, 2007; Black, 2008). CAP distinctively refers to pneumonia acquired within the general community (Black, 2008). Diagnosis of CAP is mainly based on signs and symptoms such as fever, rigors, sweats, increased cough or new cough, with or without sputum production or change in the colour of respiratory secretions in a patient with chronic cough, rapid respiratory rate, chest discomfort, or the onset of dyspnoea (Bartlett *et al.*, 1998; Klugman *et al.*, 2004). Patients may also have nonspecific symptoms such as fatigue, myalgias, abdominal pain, anorexia, and headache (Bartlett *et al.*, 1998).

In spite of progress in antibiotic therapy, CAP remains a frequent and potentially fatal infectious disease, becoming the fifth-largest killer in South Africa in 2000, accounting for 3,9% of all deaths (Black, 2008; Bradshaw *et al.*, 2000). A recent South African

study reported a 20% mortality rate for patients hospitalized with CAP (Nyamande and Lalloo, 2007).

5.2 Epidemiology

CAP is a common disorder and represents a major cause of healthcare utilisation (Mpe *et al.*, 2005; Butler, 2009). CAP will continue to be a significant danger to patients in the future as the number of patients at risk increases, such as people infected with the human immunodeficiency virus (HIV), the elderly population and patients with co-morbid diseases (Mpe *et al.*, 2005; Feldman *et al.*, 2007; Johnstone *et al.*, 2008).

The impact of HIV is particularly burdensome in resource-poor countries, particularly sub-Saharan Africa, where the prevalence of HIV infection is much higher than in developed countries (Feikin *et al.*, 2004). Pulmonary diseases, and in particular respiratory tract infections, are a major cause of significant morbidity and mortality in HIV infected patients (Feldman *et al.*, 2007). Bacterial infections, including tuberculosis and pneumococcal pneumonia and the complications thereof, have been noted to be the most serious lower respiratory tract infection in HIV infected patients compared with non-HIV infected patients (Feldman *et al.*, 2007; Feikin *et al.*, 2004). In HIV positive patients there is an inverse relationship between the CD4 cell count and the incidence of pneumonia. CAP is more commonly found when the CD4 cell count is less than 200 cells/µl; nevertheless CAP may occur at any stage in HIV positive patients (Feldman *et al.*, 2007). The risk of other opportunistic infections also increases as the CD4 cell count decreases (Feldman *et al.*, 2007).

CAP requiring hospitalization is a common and serious illness that also affects patients who are 65 years of age and older (Johnstone *et al.*, 2008). It is well known that over the past 15 years the rate of hospitalization for CAP among this age group have increased (Johnstone *et al.*, 2008).

5.3 Aetiology

Many microorganisms may cause pneumonia; however, only a few organisms are associated with the majority of cases (Feldman *et al.*, 2007; Black, 2008). The causative organisms cannot be identified on clinical and radiographic finding's alone, which makes selecting the appropriate antibiotic challenging (Menendez *et al.,* 2005). Antibiotic selection is initially empiric, after CAP confirmation on a chest radiograph, and this eliminates a delay in the pharmacotherapy of a CAP patient. Empiric therapy eliminates the need to first perform extensive investigations to identify the causative pathogen in a CAP patient and then selecting the antibiotic to which the microorganism is susceptible to. This is important since the disease is severe and delays in antibiotic therapy are associated with increased mortality (Black, 2008). Nevertheless, some investigations are performed to identify the causative agent in order to ensure that the antibiotic used is appropriate. If the empiric treatment is not appropriate it can then be changed, re-defined or de-escalated by the treating physician. It has been shown that the shorter the period between diagnosis of CAP and initiation of antibiotic treatment, the better the impact on patient outcome (Menéndez *et al.,* 2005).

Prospective studies assessing the causes of CAP in adults have shown that in 40 – 60% of patients the cause of CAP is not identified (Bartlett *et al.*, 2000). Only approximately 11% of patients with CAP will have positive blood cultures, more commonly associated with severe disease (Mpe *et al.*, 2005). The most common microbial aetiology identified in nearly all studies of CAP is *Streptococcus pneumoniae;* this microorganism accounts for roughly two thirds of all cases of bacterial pneumonia in which a microorganism is isolated (Bartlett *et al.*, 2000; Klugman *et al.*, 2004). The occurrence of other pathogens varies in a predictable manner, depending on age, co-morbidity and severity (Black, 2008). Other pathogens found less frequently include *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Streptococcus pyogenes, Neisseria meningitidis, Moraxella catarrhalis, Klebsiella pneumoniae* and other Gram negative rods, *Legionella* species, influenza virus (depending on the time of year), respiratory syncytial virus, adenovirus, parainfluenza virus and other microbes (Bartlett *et al.*, 1998; Klugman *et al.*, 2004). Additionally, previous studies have reported mixed aetiology in up to 30% of infections (Klugman *et al.*, 2004). *M. pneumoniae* is frequently seen in mild CAP while *Legionella* spp., *S. aureus* and Gram-negative organisms such as *K. pneumoniae* are more commonly seen in severe CAP (Black, 2008). *H. influenzae* is commonly found in patients with chronic obstructive airways disease (COPD) and in patients with HIV infection (Table 1) (Black, 2008; Feldman *et al.*, 2007). In a recent South African study, *S. pneumoniae* was found to be the causative pathogen in 50% of isolates (Nyamande and Lalloo, 2007). Furthermore, the study also found atypical microorganisms in 21% of hospitalized patients (Nyamande and Lalloo, 2007). In South Africa, the incidence of

CAP caused by atypical pathogens is unclear, although, a cyclical variation occurs over time and an association with CAP outbreaks has been displayed (Black, 2008). Previous studies to determine aetiology of mild CAP in patients treated as outpatients have not been comparable but show a greater geographical variability (Black, 2008). Viral pathogens, mostly Influenza A, may play a greater role in patients with mild CAP, treated as outpatients, and approximately 20 – 50% of such CAP cases may be viral (Black, 2008). Influenza pneumonia caused by influenza viruses type A or B can present as mild/moderate or as a severe 'flu' or 'flu-like' illness (Feldman *et al.*, 2007). Prognosis of viral infections is worse if complicated by bacterial pneumonia (Feldman *et al.*, 2007). *M. pneumoniae* is most commonly found in patients 2 - 7 years of age and young adults (Bartlett *et al.*, 2000).

Condition	**Common Pathogen**
Alcoholism	*S. pneumoniae*, anaerobes
COPD and/or smoking	*S. pneumoniae, H. influenzae, M. catarrhalis, Legionella* species
HIV infection (early stage)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV infection (late stage)	*S. pneumoniae, H. influenzae, M. tuberculosis, P. jirovecii, C. neoformans, Histoplasma*
Structural disease of lung (bronchiectasis, cystic fibrosis etc)	*P. aeruginosa, S. Aureus*
Airway obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
Elderly (≥ 65 years)	*S. pneumoniae*, Gram-negative organisms e.g. *K. pneumoniae*, Anaerobic organisms,
Young adults	*M. pneumoniae*

Table 1: Epidemiological conditions related to specific pathogens in patients with selected community-acquired pneumonia (Adapted from Bartlett *et al.*, 2000.)

In elderly patients more infections with Gram-negative organisms occur (Feldman *et al.*, 2007). Severely ill patients are also infected more frequently with *K. pneumoniae* and *S. aureus* (Feldman *et al.*, 2007). Mixed aetiology infections are relatively common, particularly in the elderly and severely ill patients (Feldman *et al.*, 2007). Anaerobic infections occur more commonly in the elderly and in patients with increased risk of aspiration (e.g. alcoholism, epilepsy, cerebrovascular accident) (Feldman *et al.*, 2007).

The same causative CAP pathogens found in HIV negative patients are also found in HIV positive patients (Feldman *et al.*, 2007). The most common risk factor for pneumonia is the stage of HIV disease; bacterial pneumonia tends to occur earlier in the course of HIV infection than other opportunistic infections (Feikin *et al.*, 2004). As in the general population, *S. pneumoniae* is the most common bacterial cause of CAP among HIV infected adults, implicated in approximately 20% of all bacterial pneumonias (Feikin *et al.*, 2004). *S. pneumoniae* is second only to *Pneumocystis jirovecii* as the common identifiable cause of acute pneumonia in AIDS patients (Bartlett *et al.*, 2000). However, the possibility of infection with *M. tuberculosis* should also always be considered in these patients (as discussed below) (Feldman *et al.*, 2007). Any of these infections may occur alone or in combination with the usual bacterial pathogens (Feldman *et al.*, 2007).

Pseudomonal infections are most commonly seen in CAP patients with structural lung disease, in particular cystic fibrosis and /or bronchiectasis, in patients who have received broad-spectrum antibiotic therapy for more than 7 days in the previous month,

and in patients who have recently been hospitalized (because of nosocomial colonization) (Feldman *et al.*, 2007). *Legionella,* an opportunistic pathogen, is usually seen in organ transplant recipients, renal failure patients, chronic lung disease, smokers and AIDS patients (Bartlett *et al.*, 2000).

The possibility of infection with *M. tuberculosis* is especially common in immunocompromised patients, such as those with concurrent HIV infection, and may present as an acute infection (Feldman *et al.*, 2007). Tuberculosis should also be considered as a possible cause of pneumonia in immunocompetent individuals, particularly in those who are not responding to conventional antibiotic therapy (Feldman *et al.*, 2007).

5.4 CAP Guidelines

CAP was one of the first diseases to have guidelines written for the management of patients internationally (Ewig and Welte, 2008). The frequency of infection, causative microorganism involved, increased antimicrobial resistance, and the costs related to managing CAP patients have encouraged numerous specialist committees to publish treatment guidelines aimed at improving the care of patients with CAP (Cazzola *et al.*, 2002). The objectives of guidelines are to improve the efficiency and the effectiveness of health care by decreasing variations in key methods of patient care (Nathwani *et al.*, 2001). Guidelines are ideally methodically developed, and often represent expert opinion and are developed to assist doctors in making decisions about health care for

specific clinical circumstances (Nathwani *et al.*, 2001). Guidelines can influence outcome only if there is evidence that links a certain process to an outcome and evidence that there are potentially important variations in routine care (Nathwani *et al.*, 2001). By improving patient outcomes, total costs of illness may be decreased, mainly as a result of a decrease in hospitalization, the most costly factor of healthcare for patients with CAP (Cazzola *et al.*, 2002).

Antimicrobial agents are important in the treatment of patients with CAP (Mpe *et al.*, 2005). Until swift diagnostic methods improve, most patients will be treated empirically, at least initially (Mpe *et al.*, 2005). Specific recommendations for empiric therapy for CAP have been widely published (Mpe *et al.*, 2005). Studies have found that mortality is improved by early initiation of antibiotics to which the organism is sensitive to and adversely affected by delayed or improper initial therapy (Mpe *et al.*, 2005).

Since the development of guidelines for the management of CAP, multiple national guidelines, such as the American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA), the European Respiratory Society (ERS), the British Thoracic Society (BTS) and the South African Thoracic Society (SATS) have been released and repeatedly updated (Ewig and Welte, 2008). However, the question still remains as to whether guidelines are being adhered to and furthermore whether adherence to these guidelines leads to improved patient outcome. Studies conducted in several countries have attempted to answer these questions.

A study conducted by Blasi *et al.,* in 2008, assessed whether adherence to the Italian CAP guideline improved patient outcome, with the primary end point being treatment failure and mortality. In their study Blasi *et al.,* found that adherence to the guideline was associated with a significantly lower rate of treatment failures and a non-significant trend to lower mortality. However, the study also found that overall guideline adherence was extremely low. According to the authors, the results from their study either indicate that adherence to guidelines leads to significantly improved outcomes, or that guidelines could be inappropriate in the general practitioner setting.

A study conducted in Spain, using the 2001 ATS guidelines, found that adherence to guidelines was significantly associated with a shorter hospital stay as well as a trend towards lower mortality (Ewig and Welte, 2008; Dambrava *et al.,* 2008). Furthermore, a study conducted by Wu *et al.,* in 2004, investigating IDSA guideline adherence in CAP patients in an ambulatory setting, found that in 52,9% of the patients treatment was adherent to the guideline recommendations for the management of CAP. The results of their study also showed that when guidelines were followed, patients had significantly fewer respiratory infection-related hospital admissions within 30 days after antibiotic treatment compared with patients whose antibiotic regimen did not reflect the guidelines.

A study in South Africa conducted by Mpe *et al.*, in 2005 whose main objective was to assess mortality from CAP in a teaching hospital, found that only 8,7% of patients with severe pneumonia received SATS 1996 guideline recommended antimicrobial therapy.

However, there were no significant differences in the mortality rates amongst patients who received guideline recommended antibiotic treatment compared with patients who received antibiotic treatment non-adherent to the guideline.

Nyamande and Lalloo (2007) also conducted a similar study, in this case to assess whether the South African 2002 CAP guideline was being adhered to and whether adherence to the guideline reduced the length of hospital stay and mortality in patients with severe CAP at King Edward VIII Hospital in Durban. Their study found very poor adherence to the guideline. The authors of this study stated possible reasons for the poor adherence could include lack of awareness, attitude, lack of knowledge of the guideline and local barriers to implementation of the guideline. Because in their study the number of patients receiving treatment according to the SATS guideline was so small they were unable to confirm, confidently, whether adherence could have resulted in a clinical benefit.

Interestingly, a study conducted by Halm *et al.,* (1999) assessed the response of physician's to the implementation of CAP practice guideline in an emergency department and investigated whether the guideline changed physician's knowledge and attitudes about pneumonia (Cazzola *et al.,* 2002). More than 73% of the physicians reported the guideline as being helpful and more than 94% wanted it to be continued in future (Cazzola *et al.,* 2002). Most physicians reported that the guideline would decrease costs and improve quality without any increase in harmful outcomes (Cazzola *et al.,* 2002).

In December 2007, the South African Thoracic Society (SATS) published a revised guideline for the management of CAP in adults. The main purpose of the SATS guideline was *"to provide rational and cost-effective recommendations regarding choice of initial empiric antibiotic therapy that is likely to improve patient survival"* (Feldman *et al.*, 2007). The guideline was revised due to increasing antibiotic resistance, availability of new antimicrobial agents and international trends based on evidence published since the previous guideline (Feldman *et al.*, 2007). Advice was given for CAP patients based on age, the severity of the infection and the presence or absence of underlying/ coexistent disorders. Categories considered were adults without co-morbid disease, the elderly and/or adults with co-morbid disease, including HIV infection, and severely ill adults (Table 2) (Feldman *et al.*, 2007).

2007 SATS Guidelines for the Management of Community-Acquired Pneumonia in Adults	
Patients Treated at home	
Patients < 65 years, without co-morbid disease	High dose amoxicillin ± macrolide/azalide/tetracycline
≥ 65 years &/or adults with co-morbid disease including HIV infection	Amoxicillin/clavulanic acid or 2nd generation cephalosporin (cefuroxime axetil or cefpodoxime) ± macrolide/azalide/tetracycline Alternative: Fluoroquinolone
Hospitalized Patients	
Patients < 65 years, without co-morbid disease	Parenteral penicillin G or amoxicillin/ampicillin ± macrolide/azalide Alternative: Fluoroquinolone
≥ 65 years &/or adults with co-morbid disease including HIV infection	Amoxicillin/clavulanic acid or 2nd or 3rd generation cephalosporin ± macrolide/azalide Alternative: Fluoroquinolone
Severely ill adults	Amoxicillin/clavulanic acid or 2nd or 3rd generation cephalosporin and aminoglycoside and macrolide/azalide Alternative: Fluoroquinolone together with another agent

Table 2: SATS guidelines for the treatment of CAP in adults

6 CHAPTER TWO

6.1 Study Rationale

Guidelines for the management of CAP have been published by a number of thoracic societies; however, few studies have been performed to confirm whether guidelines are being adhered to and/or whether adherence to guidelines leads to improved patient outcomes in South Africa.

As previously stated, Mpe *et al.*, (2005) briefly assessed adherence to the 1996 South African guideline and found that only 8,7% of patients with severe pneumonia received SATS guideline recommended antimicrobial therapy. The only other study from South Africa, conducted by Nyamande and Lalloo (2007) showed poor adherence to the SATS 2002 guideline; however, because the sample population receiving antibiotic treatment according to the guidelines was so small, a direct comparison of patient outcomes between the group of patients receiving treatment according to the guideline and those who were not receiving treatment according to the guideline could not be made. That study was conducted in only one hospital in South Africa. Also it should be noted that a revised SATS guideline was released in December 2007, and the study conducted by Nyamande and Lalloo investigated the 2002 SATS guideline in the treatment of CAP patients.

No study, to date, has been performed to assess whether the 2007 revised SATS guideline is being adhered to and/or whether adherence to the guideline leads to improved patient outcomes, length of hospital stay and time to clinical stability.

Why would a study such as this be important in South Africa? The answer to this is simply that South Africa is a middle income, resource-limited country, with the highest HIV population in the world, and any recommendations that results in appropriate use of the resources of this country, coupled with better patient outcome, decreased length of hospital stay and decreased hospital expenditure, would be important. This would, in theory, result in our healthcare system being able to cope with the demands and illnesses of the public, as well ensure that the resources are being distributed among more patients.

6.2 Study Objectives

- To determine the level of adherence to the 2007 South African Thoracic Society Guideline for the management of CAP in adults.
- To determine whether adherence to the 2007 South African Thoracic Society Guideline leads to improved patient outcome (lived/died).
- To determine whether adherence to the 2007 South African Thoracic Society Guideline leads to a shorter length of hospital stay by patients.
- To determine whether adherence to the 2007 South African Thoracic Society Guideline leads to a shorter time to clinical stability in patients.

6.3 Study Design

6.3.1 Methodology

Records were reviewed retrospectively for all hospitalized patients with a confirmed diagnosis of CAP admitted to the Helen Joseph Hospital in Johannesburg during the period January 2009 to December 2009. Helen Joseph Hospital is an academic teaching hospital, which has approximately 700 beds with medical, surgical, orthopaedic and psychiatric wards. Retrospective data were reviewed in order to prevent any unwanted influence over the treating physician's choice of antibiotic.
The initial study methodology involved the retrospective review of patients admitted to Helen Joseph Hospital during the period January 2008 to December 2009. However, after reviewing patient files for the period January 2009 to December 2009, and a total of 181 cases being included into the study for that year, the statistician indicated that there were sufficient numbers for a statistical power to be calculated.

In this study CAP was defined as the presence of an acute infiltrate on a chest radiograph as well as two or more of the following signs and symptoms: altered breath sounds and/or signs of lung consolidation, fever or hypothermia, rigors, sweats, cough with or without sputum production, pleuritic chest pain, cyanosis, shortness of breath and rapid respiratory rate (Bartlett *et al.*, 2000; Hoare and Lim, 2006).

CAP severity was determined using the CURB-65 scoring system. This scoring system assesses the patient on presentation and is derived from the British Thoracic Society

rule (Lim *et al.*, 2003). CURB-65 uses five components: confusion, urea > 7 mmol/l, respiratory rate ≥ 30 breaths/min, low blood pressure (systolic < 90 mmHg and/or diastolic ≤ 60 mmHg and age ≥ 65 years (Lim *et al.*, 2003). Each patient is given 1 point for each parameter if present (Lim *et al.*, 2003). Patients with scores of 0 and 1 are thought to be mild and potentially suitable for management as outpatients (Lim *et al.*, 2003). Patients with scores of 2 are considered moderately ill and need to be observed in hospital, at least initially (Lim *et al.*, 2003). Patients with scores of ≥ 3 are thought to be severely ill, and need consideration for admission to a high-care or even intensive care unit (Lim *et al.*, 2003).

This study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand on the 31 May 2010 (Appendix 1). Approval to conduct this study at Helen Joseph Hospital was granted by the CEO of Helen Joseph Hospital, Ms GM Bogoshi (Appendix 2).

6.3.2 Inclusion Criteria

- Patients with confirmed CAP admitted to Helen Joseph Hospital during the period January 2008 to December 2009 for CAP (Enough patients were found in 2009 alone to perform statistical analysis; therefore it was decided to restrict the analysis to these cases only).
- Patients ≥ 18 years of age
- CAP defined as the presence of two or more of the following:
    - Altered breath sounds and/or signs of lung consolidation

- Fever or hypothermia
- Rigors
- Sweats
- Cough with or without sputum production
- Pleuritic chest pain
- Cyanosis
- Shortness of breath
- Rapid respiratory rate

- All patients have had radiological confirmation of the diagnosis of pneumonia
- Cases considered sick enough for admission to hospital by way of the following:
  - Co-morbid illness
  - Cyanosis
  - Multilobar consolidation
  - Complications
  - Perceived need for ICU admission
  - High CURB-65 severity score, based on
    - Confusion
    - Urea > 7 mmol/l
    - Respiratory rate ≥ 30 breaths/min
    - Low blood pressure (SBP < 90 mmHg and/or DBP ≤ 60 mmHg)
    - Age ≥ 65 years

6.3.3 Exclusion Criteria

- Age < 18 years
- Patients suspected or confirmed to have *Pneumocystis jirovecii* infection
- Patients suspected or confirmed to have pulmonary TB
- Patients hospitalized simply due to poor socioeconomic status or transport problems

Patients who were hospitalized due to poor socioeconomic status or transport problems alone were excluded from this review as these patients may be young, otherwise healthy patients, who would, under normal circumstances, not be hospitalized.

6.3.4 Data Collection and Capture

The 2009 ward discharge books from all the medical wards at Helen Joseph Hospital were reviewed to identify all CAP patients who had been admitted and subsequently discharged or who had died. The patient files were retrieved from the record room and archives. Parameters that were recorded were: age, gender, date of hospitalization, presence of altered breath sounds, fever or hypothermia, rigors, sweats, cough and/or sputum production, pleuritic chest pain, cyanosis, shortness of breath, rapid respiratory rate, co-morbid disease, HIV status, unilobar or multilobar pulmonary consolidation, complications, perceived need for ICU, presence of cyanosis, pulse rate, partial pressure of arterial oxygen, albumin results, day of symptom resolution, ICU admission, presence of confusion, urea results, temperature, pulse rate, white cell count, platelet

count, presence of CURB-65 factors, chest radiograph, microbiology specimen results, antibiotic treatment regimen and date of death, hospital discharge or resolution of symptoms (Appendix 3).

Compliance with the SATS 2007 guideline was based on the antibiotic regimen used during the first 48 hours of hospital admission as antibiotic regimens are sometimes changed very early on in patient treatment.

Time to clinical stability was determined according to a validated rule that defined clinical stability as the first day that one or more of the following criteria were simultaneously achieved: systolic blood pressure ≥ 90 mm Hg; respiratory rate ≤ 24 breaths/min; oxygen saturation ≥ 92%, temperature ≤ 37,2 °C; ability to tolerate oral intake; and baseline mental status (Frei *et al.*, 2010). Time to clinical stability was calculated by subtracting the admission date from the first date that the patient was determined to be clinically stable (Frei *et al.*, 2010). Length of hospital stay (in days) was calculated by subtracting the hospital admission date from the hospital discharge date (Frei *et al.*, 2010).

6.3.5 Statistical Analysis

A Chi-squared test was used to determine whether adherence to the SATS guideline lead to improved patient outcomes (lived/died). The Chi-squared test was used to test for an association between two categorical variables. The length of hospital stay and time to clinical stability were compared between patients who received antimicrobial

treatment adherent to the CAP guideline and those who received treatment non-adherent to the CAP guideline initially using the Analysis of Variance statistical model. The length of hospital stay and time to clinical stability were found not to be normally distributed and so a nonparametric test, the Wilcoxon Rank Sum test, was used for comparison between the two groups.

6.4 Results

A total of 1073 patients were admitted to Helen Joseph Hospital for CAP during the period January 2009 to December 2009. These files were all selected to be reviewed. Of the 1073 patients, 595 patient files were not provided for review, as they could not be found and 297 were excluded due either to proven *Mycobacterium tuberculosis* infection or PCP, underage of patients or patients who were being treated empirically for PCP or pulmonary TB, or patient files that did not contain enough information to be included into the study. A final total of 181 patients fulfilled the study criteria and were included into the study. This breakdown is shown in figure 1.

As mentioned earlier, the number of patients included into the study for January 2009 to December 2009 was discussed with the statistician and it was decided that there were enough patients included into the study to conduct a statistical analysis, without including the cases from 2008.

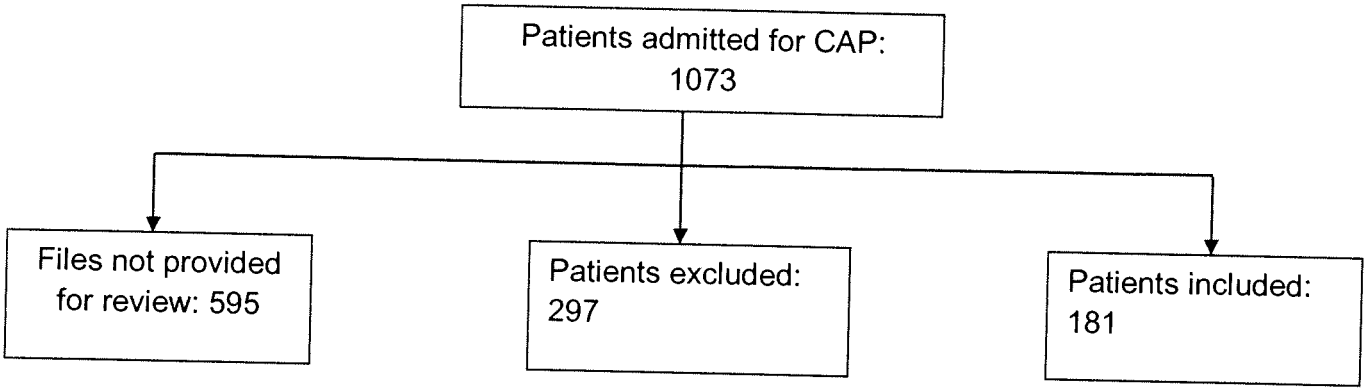


Figure 1: Breakdown of patients admitted for CAP during January – December 2009.

6.4.1 Demographic Features

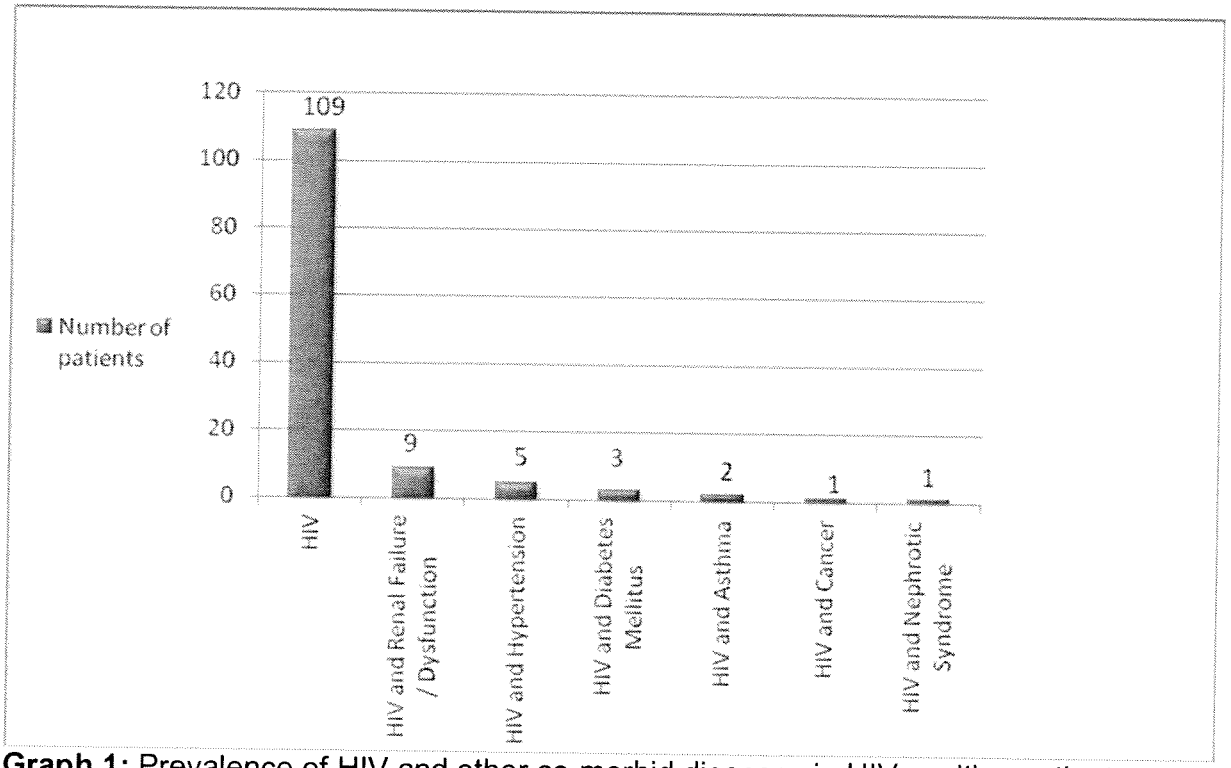
The clinical features of the patients included in this study are listed in Table 3. Of the 181 patients, 80 were male and 101 were female. The patient's ranged in age from 18 – 85 years, with a mean age of 41 years and a median age of 37 years. 21 patients included in the study were found to be 65 years of age or older.

Clinical Features	Number
Mean age (years)	41
Median age (years)	37
Older than 65 years	21
Younger than 65 years	160
Female	101
Male	80

Table 3: Clinical features of patients included into the study.

6.4.2 Co-morbid diseases:

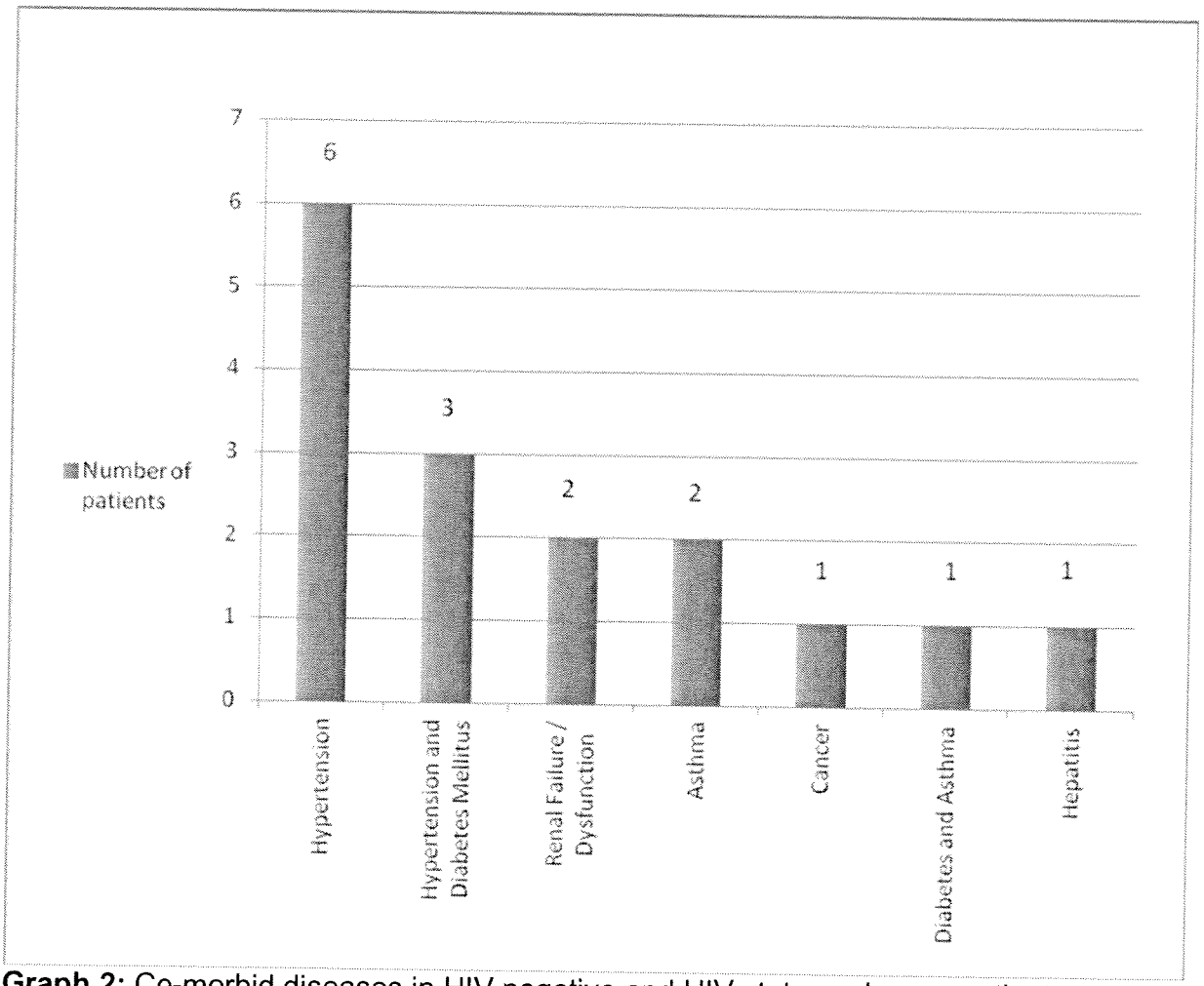
Overall 60% (109 patients) of the patients included in this study were HIV positive. It was also noted that most of these HIV positive patients also had other co-morbid diseases, listed in Graph 1, such as asthma, renal failure or dysfunction, diabetes mellitus, hypertension and nephrotic syndrome.



Graph 1: Prevalence of HIV and other co-morbid diseases in HIV positive patients.

Overall 30 patients were found to be HIV negative. The HIV status of 42 patients was unknown, as their HIV status was not documented in their hospital files and there was no record of HIV testing having been performed on these patients during their time of hospitalisation. The co-morbid diseases found in both these two groups of patients are

listed in Graph 2, included asthma, diabetes, cancer, hypertension, renal failure/dysfunction.



Graph 2: Co-morbid diseases in HIV negative and HIV status unknown patients

6.4.3 CURB-65 Scoring

The CURB-65 scoring system was used to assess CAP severity in patients included in this study, shown in Table 4. Patients had CURB 65 scores ranging from 0 – 4, with a median CURB score of 1.

CURB-65 Scores	Number of patients
0	71
1	63
2	33
3	13
4	1
Total	**181**

Table 4: CURB-65 scores of patients included into the study.

6.4.4 Microbiology

In 34 patients, bacterial isolates were identified, listed in Table 5. The major organism identified was *Streptococcus pneumoniae*, and other organisms identified included *H. influenzae*, *K. pneumoniae*, *S. aureus*, *Serratia marcescens* and *C. neuii*. Two patients were found to be infected with two microorganisms, of whom one was infected with *S. pneumoniae* and *H. parainfluenzae* and the other infected with both *S. pneumoniae* and *K. pneumoniae*.

Bacterial Isolate	Number identified	Source
S. pneumoniae	21	Blood
H. influenzae	5	4 blood 1 sputum
K. pneumoniae	2	Sputum
S. marcescens	2	Blood and sputum
S. pneumoniae and *H. parainfluenzae*	1	Blood and sputum
S. pneumoniae and *K. pneumoniae*	1	Blood and sputum
S. aureus	1	Blood
C. neuii	1	Blood
Total	**34**	

Table 5: Bacterial isolates identified.

6.4.5 SATS Adherence

In this study the majority of patients (66%) were found to have received treatment that was adherent to the SATS guideline, shown in Table 6. Overall 61/181 (34%) patients received treatment for CAP with drugs that were non-adherent to the SATS guideline. Most patients received either amoxicillin/clavulanic acid monotherapy (54%), or amoxicillin/clavulanic acid in combination with other antibiotics (40%). A small group of patients received ampicillin, amoxicillin, ceftriaxone alone or in combination with other antibiotics.

Treatment	Number of patients	Percentage	Number adherent to guideline
Amoxicillin/clavulanic acid	83	45,9	64
Amoxicillin/clavulanic acid, erythromycin	57	31,4	37
Amoxicillin/clavulanic acid, amoxicillin	14	7,7	11
Amoxicillin/clavulanic acid, erythromycin, gentamycin	6	3,3	1
Amoxicillin/clavulanic acid, gentamycin	4	2,2	0
Amoxicillin/clavulanic acid, amoxicillin, erythromycin	3	1,7	3
Piperacillin, tazobactam	3	1,7	0
Amoxicillin	2	1,1	0
Ceftriaxone	2	1,1	2
Piperacillin, tazobactam, erythromycin	2	1,1	0
Ampicillin	1	0,55	1
Amoxicillin/clavulanic acid, ceftriaxone	1	0,55	0
Amoxicillin/clavulanic acid, piperacillin, tazobactam	1	0,55	0
Ceftriaxone, erythromycin	1	0,55	0
Ceftriaxone, azithromycin	1	0,55	1
Total	**181**	**100**	**120**

Table 6: Antibiotic treatment received by patients.

6.4.6 Outcome

In this study the patient outcome was defined as whether the patient lived or died after receiving antibiotic treatment. Of the 181 patients, only 1 patient died; however this patient received treatment adherent to the SATS guideline and had a CURB-65 score of 2. There was no significant association between adherence to the guideline and patient outcome. However, as only 1 patient in this study had died, there were insufficient numbers for the test to be valid.

6.4.7 Length of hospital stay

The length of hospital stay was calculated by subtracting the hospital admission date from the hospital discharge date. The length of hospital stay ranged from 1 – 29 days. Eight patients refused hospital treatment and were discharged from hospital, and 16 patients were stepped down to Selby Park Hospital. These 24 patients were excluded from the analysis of the length of hospital stay, as these patients would ordinarily have had a longer length of hospital stay. The mean length of hospital stay in patients who received treatment that was adherent to the guidelines was 6,4 days, while it was 6,7 days for patients who received treatment that was non-adherent to the SATS guideline (not significantly different; p = 0,6838). Figure 2 below indicates the differences in LOHS between the two groups. . In this case, it can clearly be seen that the diamonds for non-adherent and adherent patients are the same, indicating no difference between the two groups.

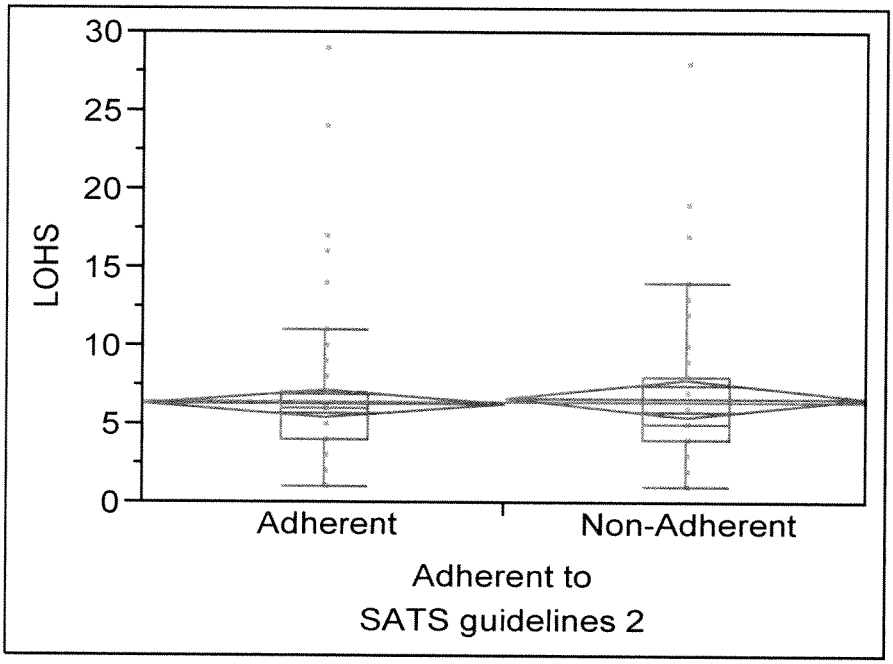


Figure 2: Length of hospital stay in patients adherent and non-adherent to the guideline.
* The diamonds can be interpreted in the following way: The middle line in the diamond is the mean of the group. The vertical endpoints form the 95% confidence interval of the mean.

6.4.8 Time to clinical stability

The range for the time to clinical stability was 1 – 8 days. There was a significantly longer time to clinical stability in patients whose therapy was adherent to the guideline (1,6 days) compared to those whose treatment was non-adherent to the guideline (1,3 days)(p = 0,0171). This can also be seen in Figure 3: in this case, it can clearly be seen that the diamond for those patients whose treatment was adherent is much higher than the diamond for those patients whose treatment was non-adherent.

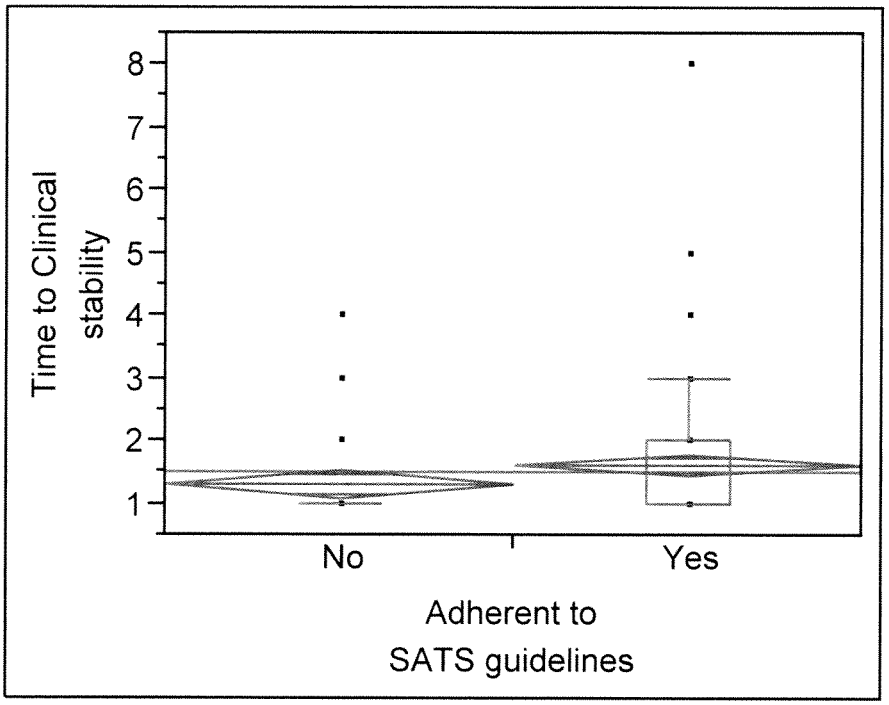


Figure 3: Time to clinical stability in patients adherent and non-adherent to the guidelines.
* The diamonds can be interpreted in the following way: The middle line in the diamond is the mean of the group. The vertical endpoints form the 95% confidence interval of the mean.

6.4.9 Additional analysis

As CURB-65 was used to assess disease severity, the time to clinical stability and length of hospital stay were also determined among the different CURB-65 score groups. The results indicate that the higher the CURB-65 score, the longer the LOHS (Table 7). Analysis could not be performed on the patient who had a CURB-65 score of 4 as statistical analysis cannot be performed on one patient. There was a significant difference in the mean LOHS among the different CURB-65 scores (p = 0,0001). There was also a slight increase in the time to clinical stability as the CURB-65 score increased; however this was found to be non-significant (p = 0,051).

	LOHS	Level of significance	Time to clinical stability	Level of significance
CURB-65 score comparison				
CURB-65 score = 0	5	0,0001	4	0,051
CURB-65 score = 1	6		1,5	
CURB-65 score = 2	9		1,7	
CURB-65 score = 3	9		1,9	
HIV status comparison				
HIV positive	6,1	0,1894	1,6	0,3952
HIV negative	6,3		1,5	
Age group comparison				
< 65 years	6	0,0121	1,5	0,5562
≥ 65 years	9		1,4	

Table 7: Length of hospital stay and time to clinical stability found in the additional analysis.

The LOHS and time to clinical stability were also compared amongst HIV positive (109 patients) and HIV negative patients (30 patients). HIV positive patients had a mean LOHS of 6,1 days, while HIV negative patients had a mean of 6,3 days (not significantly different; p = 0,1894). The mean time to clinical stability for HIV positive patients was also found to be no different (1,6 days) compared to HIV negative patients (1,5 days)(p = 0,3952)

The LOHS and time to clinical stability was also compared amongst patients 65 years and older (21 patients) and patients younger than 65 years (160 patients). Patients 65 years and older had a significantly longer mean LOHS of (9 days) than the patients younger than 65 years (6 days)(p = 0,0121). However there was no significant difference in the time to clinical stability of the patients 65 years and older (1,4 day) compared with the patients younger than 65 years (1,5 days)(p = 0,5562).

7. CHAPTER THREE

7.1 Discussion

In an attempt to decrease the morbidity and mortality associated with CAP, numerous societies and working groups have published guidelines to direct and assist physicians in choosing suitable antibiotics for empiric treatment of patients with CAP (Frei *et al.*, 2006; Menendez *et al.*, 2002). These guidelines take into account different risk factors, such as age, co-morbidity, and initial clinical severity (Menendez *et al.*, 2002). Guidelines should be implemented at a local level in each country (Menendez *et al.*, 2002).

Appropriate initial antibiotic selection for patients with CAP has been associated with decreased mortality and length of hospital stay (Frei *et al.*, 2006). Until recently there has been little proof of the impact of most guidelines on patient prognosis, including their influence on patient mortality, length of hospital stay and time to clinical stability (Frei *et al.*, 2006). This study is the first to analyze the potential impact that the South African Thoracic Society CAP 2007 guideline has had on length of hospital stay, time to clinical stability and mortality of CAP patients.

Between January 2009 and December 2009, a total of 1073 patients were admitted to Helen Joseph Hospital with a diagnosis of CAP. This would mean that approximately 89 patients were seen every month presenting with features of CAP that were considered severe enough by the treating physician to warrant hospital admission. This number does not include patients with CAP that were treated as outpatients. Although

some of the 1073 patients were found to be infected with TB or PCP and were subsequently excluded from this study, this study confirms the high incidence of CAP seen in our community. While it is not possible from the current study to determine the prevalence of CAP in the population, previous studies have found that the incidence of CAP was approximately three to five adults per thousand, of which 30% of patients require hospital admission (Menendez *et al.*, 2002; Marrie and Wu, 2005).

7.1.1 Demographic Features

More than half the patients admitted into this study were female patients, accounting for 56% of the total number of patients.

CAP is a common disease and a frequent cause of hospitalization and death among the elderly (patient's ≥ 65 years) (Fung and Monteagudo-Chu, 2010). The prevalence of CAP increases considerably with age, with patients older than 60 years of age comprising 81,2% of all cases (Fung and Monteagudo-Chu, 2010). Overall 21 patients out of the total 181 patients included into this study were 65 years and older and the majority of patients were younger than 65 years of age.

7.1.2 Co-morbid diseases

The majority of the patients in the study (126/181 patients; 70%) had co-morbid diseases, indicating that these patients had underlying health problems potentially contributing to their CAP risk. A particularly notable co-morbid disease found in this study was the presence of HIV infection. Overall 109 of the 181 patients (60%) were

found to be HIV positive. The stage of HIV disease, as well as whether these patients were on antiretroviral treatment, were not recorded. There is limited clinical information available comparing HIV negative and HIV positive patients with CAP (Park *et al.*, 2001). Results are contradictory and most published CAP guidelines do not include HIV positive patients (Park *et al.*, 2001; Malini *et al.*, 2010). The SATS guideline is one of the very few CAP guidelines which take HIV positive patients into consideration. This is due to the high incidence of HIV infection found in the South African population. HIV infection has been associated with an increased risk of bacterial pneumonia and CAP has been reported to be the most common cause of hospitalization among HIV infected patients, being linked to considerable mortality (Feikin *et al.*, 2004; Malini *et al.*, 2010).

Previous studies have found the incidence of HIV infection to be similar to that found in this study. In the study conducted by Nyamande and Lalloo (2007), 84% of patients included in their study were HIV positive.

7.1.3 CURB-65 scoring

The CURB-65 score has previously been described as being ideal for identifying patients with more severe CAP infection, who as a result have a higher risk of mortality (Niederman, 2007).

In this study 134 patients had CURB-65 scores of 0 – 1. These patients would potentially have been recommended for treatment as outpatients as they are considered low risk patients in terms of the CURB-65 scoring system (Lim *et al.*, 2003). Overall 47

patients had CURB-65 scores of 2 – 4 and these patients have a higher risk of mortality when analyzing the CURB-65 score and would have been recommended for hospital admission (Lim *et al.*, 2003).

In assessing the patients admitted for CAP during this study period, a possible reason for the attending physicians' decision to admit patients that may be considered low risk could be the high prevalence of co-morbid diseases found in this patient group, particularly HIV infection. Also what needs to be noted is that the CURB-65 scoring system does not take into account co-morbid diseases in patients with CAP. So while a patient may have a low CURB-65 score they may present to hospital in a very sick state due to their co-morbid disease and due to this the attending physician may opt to admit these patients.

7.1.4 Microbiology

Sputum and blood culture testing were performed on the majority of patients in this study. However, a causative organism was identified in only 34 cases. The low frequency of positive blood cultures is also consistent with blood culture yields in other studies (Mpe *et al.*, 2005). Also consistent with other studies was that *S. pneumoniae* was found to be the predominant causative organism in the patients in whom a positive blood culture was obtained, accounting for approximately 62% of the microorganisms identified. Mixed bacterial infections were also observed, one patient was co-infected with *S. pneumoniae* and *H. parainfluenzae* and another patient was co-infected with *S. pneumoniae* and *K. pneumoniae.*

7.1.5 SATS guideline adherence

This study has found that more than half of patients with CAP that were considered severe enough for hospital admission were treated with antibiotic regimens that were adherent to the SATS guideline (66%). The majority of patients were treated with amoxicillin/clavulanic acid, either alone or in combination with other antibiotics as seen in Table 7. Also noted in this study was that 44% of patients received combination antibiotic therapy. This could be due to concerns of the emergence of drug resistant strains of microorganisms causing CAP, as well as the increasing incidence of patients who are infected with more than one CAP causing microorganism (Mpe *et al.*, 2005). More likely, however, is the fact that according to the SATS guideline there is evidence that in patients with severe pneumonia, combination antibiotic therapy may be associated with a better outcome than monotherapy and therefore the SATS 2007 recommends combination antibiotic therapy in severely ill patients with pneumonia admitted to hospital.

A total of 14 patients had CURB-65 scores of 3 or more; however only one of these patients received treatment adherent to the guideline which recommends a combination of amoxicillin/clavulanic acid, erythromycin and an aminoglycoside to be used in these patients. The other 13 patients received the following antibiotics: amoxicillin/clavulanic acid (1 patient), amoxicillin/clavulanic acid and erythromycin (9 patients), amoxicillin/clavulanic acid and gentamycin (1 patient), amoxicillin/clavulanic acid and piperacillin/tazobactam (1 patient) or ceftriaxone and erythromycin (1 patient). 41 patients included into this study had no co-morbid diseases and were younger than 65

years of age. The SATS guideline recommends that these patients be treated with amoxicillin or ampicillin with the addition of a macrolide if necessary. However, this study found that only 1 patient received treatment that was adherent to the guideline (patient received ampicillin). The other 40 patients received treatment that was non-adherent to the SATS guideline. Most of these patient received amoxicillin/clavulanic acid either alone or in combination with other antibiotics. Also found in this study was that a few patients were treated with amoxicillin/clavulanic acid and amoxicillin was added to the treatment regimen. The reason for this is to increase the amoxicillin concentration in the patient's treatment regimen in order to cover for potential beta-lactam resistance and is compatible with the SATS guideline.

The level of adherence to the CAP guideline found in this study is higher than the findings in the other South African studies, which found that most patients received treatment that was non-adherent to the CAP guideline. For example, Mpe *et al.*, in 2005, investigated the mortality rate amongst patients hospitalized for CAP. In their study Mpe *et al.*, found that only 8,7% of patients received treatment adherent to the 1996 CAP guideline. Mpe *et al.*, (2005) stated that a likely cause for non-adherence to the guideline could be differences in the assessment of cases amongst the attending physicians, low levels of awareness and use of guidelines for the management of CAP and conflicting advice among the guidelines. Nyamande and Lalloo investigated the level of adherence to the 2002 SATS guideline in their 2007 study, they found that 92% of patients admitted to King Edward VIII Hospital in Durban for CAP received treatment that was non-adherent to the guideline, while only 8% of patients were found to have

received treatment that was adherent to the guideline. Nyamande and Lalloo stated that the possible reasons for non-adherence to the SATS guideline include lack of awareness, attitude, lack of knowledge of the guideline and local barriers to implementation of the guideline. Nyamande and Lalloo also stated that physicians may feel that guidelines restrict their autonomy, freedom and clinical judgement. This study also found that patients who received treatment that were non-adherent to the guideline tended to be over-treated (broader spectrum antibiotics were more commonly used).

Therefore it would be interesting to presume that the reasons for the level of adherence found in the current study could be due to awareness and education of the CAP guidelines among the attending physicians. Another contributing factor to adherence to the CAP guideline may be the high case load of CAP found at Helen Joseph Hospital. It may also be said that since CAP is a relatively common disease encountered by physicians at Helen Joseph Hospital one would therefore expect all staff to be trained and familiar with the recommended pharmacological treatment to be administered empirically in order to improve patient outcome. A similar finding was noted in a study conducted by Marrie and co-workers in 2003, which found that clinicians who treat a higher volume of patients with pneumonia achieved better outcomes.

7.1.6 Outcome

Mortality was only observed in one patient in this study, who had been given treatment adherent to the South African guideline. This patient had a CURB-65 score of 2. The remaining 180 patients all lived. This may be attributed to the experience of the doctors

at Helen Joseph Hospital and what also should be taken into account is that 595 files were not provided and there may have been more patients who died in this study had these files been provided and included into this study. Also patients who received treatment that was non-adherent to the guideline were over-treated rather than under-treated and therefore would not have been expected to have a worse outcome. This mortality rate of hospitalised patients with CAP was very low in comparison to other studies. Previous studies have stated that CAP mortality ranges from 1-5% among hospitalised patients (Dambrava *et al.*, 2008). However, it should also be noted that when analysing the mortality rates found in previous studies, significant differences amongst these studies existed.

A previous South African study conducted by Mpe *et al.,* in 2005, who investigated the mortality rate amongst patients hospitalized for CAP, found that the mortality rate (7,8%) was similar between patients who received guideline adherent therapy compared to guideline non-adherent therapy. This was also found in the study conducted by Nyamande and Lalloo (2005). In the study conducted by Nyamande and Lalloo (2005), a total of 36 patients were noted to have died, 4 patients in the group that received treatment according to the guideline and 32 patients in the group that received treatment non-adherent to the guideline. However, the difference in mortality was not found to be significant.

In 2001, Malone and Shaban investigated adherence to the ATS guideline for hospitalised patients with CAP. In their study, Malone and Shaban found that patients

with CAP treated non-adherent to the ATS guideline had a 4,46 higher risk of inpatient mortality and a significantly longer length of hospital stay. Marras and Chan, in their 1998 study, investigated the usefulness of guidelines (ATS, CTS and Canadian Infectious Disease Society) in treating CAP. They were unable to demonstrate any significant differences in mortality or length of hospitalization in relationship to guideline adherence or not. In comparison, a study conducted by Menendez *et al.,* (2002), who studied the influence of guideline non-adherent treatment on the outcome of CAP, found that mortality in patients with the most severe CAP (Fine risk class V) was much higher when guidelines were not followed.

A possible contributing factor to the low mortality found in this study is that the majority of patients had low CURB-65 scores, would normally be treated as outpatients, but for some reason or the other these patients were admitted into hospital. As stated earlier, a possible reason for admission of patients that were at a lower risk of mortality could be the co-morbid diseases found in this patient population and in particular HIV infection. Another possible reason is that more experienced clinicians who followed the guideline may be less likely to discharge their patients.

Previous studies have been performed to analyze the outcome of CAP in hospitalized HIV positive and HIV negative patients. These studies have reported differing clinical outcomes (Malinis *et al.*, 2010). Malinis *et al.*, in 2010 investigated the clinical outcomes of HIV-infected patients hospitalized with bacterial CAP. The laboratory data and clinical data found in their study implied that the host responses to bacteria is

similar among HIV positive and HIV negative patients regardless of the higher risk of developing bacterial CAP in HIV positive patients. Malinis *et al.*, (2010) found that clinical outcomes were similar in hospitalized HIV positive and HIV negative patients. This is consistent with the findings in the current study.

However, a study conducted by Feldman *et al.*, in 2007, investigated the impact of HIV on clinical presentation and outcome of patients with bacteraemic pneumonococcal pneumonia. In their study, Feldman *et al.*, adjusted for age and severity of illness by multivariate analysis and found that there was a considerably higher 14-day mortality in HIV patients, which was partly related to their level of immunocompromise (indicated by CD4 counts). Their study also found that when stratified by the Pitt bacteraemic score, critically ill HIV patients had a 4-fold risk of death compared to critically ill HIV negative patients. Therefore when taking this study into account we would have expected to have found a greater mortality rate due to the majority of patient included in this study in patients co-infected with HIV.

Another possible reason for the low mortality found in the current study could be attributed to the appropriateness of the antibiotic selection by the attending physician. Clearly more than half the patients were being treated with guideline concordant treatment by the attending physician. Furthermore in this study it was important to note that in those patients that had received treatment that was non-adherent to the guideline, most were being over-treated, rather than under-treated i.e. a broader spectrum antibiotic was always used in the non-adherent patients rather than a narrow

spectrum antibiotic, and this may also have contributed to the overall good outcome. This was also found in the study conducted by Nyamande and Lalloo, (2007). Since the majority of patients were treated with antibiotic regimens adherent to the SATS guideline we could assume that the low mortality found in this study was due to the high level of adherence to the SATS guideline.

7.1.7 Length of Hospital stay

The association between guideline adherent antibiotic therapy and time to clinical stability or length of hospital stay is important as it helps to identify a clinical intervention (e.g. appropriate empiric antibiotic therapy) that could result in decreased length of hospital stay (Frei *et al.*, 2006). In this study the length of hospital stay ranged from 1 – 29 days. Patients who received treatment that was adherent to the SATS guideline had a mean length of hospital stay of 6,3 days and patients whose treatment was non-adherent had a mean length of hospital stay of 6,7 days. However, this was not significantly different (p= 0,6838).

The findings in this study are also consistent with the findings of Nyamande and Lalloo (2007), who also found no statistically significant difference in the length of hospitals stay among patients who received treatment adherent to the 2002 guideline and those who received treatment non-adherent to the guideline.

Length of hospital stay for CAP may be influenced by many factors, including initial clinical severity of the disease, different clinical practices, presence of co-morbidity, and

characteristics of the hospital which may override the potential effect of a specific antibiotic regimen on length of hospital stay (Menendez *et al.*, 2002).

7.1.8 Time to clinical stability

The time to clinical stability was found to range between 1-8 days in this study. The median time to clinical stability was found to be 1,6 days in patients whose treatment was adherent to the guideline and 1,3 days for patients who received treatment that was non-adherent to the guideline (not significantly different). Another notable finding was that patients remained hospitalized for several days after achieving the criteria defined for clinical stability. Halm *et al.,* (1998) suggested that patients could be safely discharged within 24 hours of clinical stability being achieved. Frei *et al.*, (2006) stated that using this rule in future may lead to a shorter length of hospital stay and a decrease in health care expenditures. Once again, a possible reason for the long hospital stay even after achievement of clinical stability in the patients in the current study may be the high incidence of HIV and other co-morbid diseases found among patients, that themselves needed specific management. This finding is consistent with the study conducted by Fine *et al.*, 1997, who conducted a physician survey of the discharge decision in CAP patients, which indicated that 22% of pneumonia inpatients remained in the hospital after reaching clinical stability. According to the authors, the most common factors rated as being "very important" in delaying discharge were diagnostic evaluation or treatment of co-morbid illness, completion of a standard course of antimicrobials, and delays with arrangements for long-term care.

7.1.9 Additional analysis

A finding in this study which is consistent with other studies, is that as the CURB-65 score increased so did the length of hospital stay and to a lesser extent, the time to clinical stability ($p = 0,0001$ and $p = 0,0354$ respectively). These results support the use of the CURB-65 scoring system in assessing CAP severity. The same findings were observed by Capelastegui and colleagues in 2006, who used the CURB-65 approach to evaluate inpatients and outpatients with CAP in Spain. In their study, Capelastegui and colleagues (2006) found that the CURB-65 could accurately predict the 30-day mortality rate, the need for mechanical ventilation, and, the need for hospitalization. Capelastegui and colleagues also found that a high CURB-65 score was associated with a longer length of IV therapy, length of hospital stay and time to clinical stability.

The current study found that the median length of hospital stay amongst HIV positive was 6,1 days compared to 6,3 days in HIV negative patients (not significantly different). This is consistent with the study conducted by Malinis *et al.,* in 2010 who found that patients with HIV infection and patients without HIV infection had similar time to clinical stability, length of stay, all-cause mortality and CAP related mortality rates.

This finding is in contrast to a previous South African, study conducted by Feldman *et al.*, in 2007, which found that the length of hospital stay was less for the HIV patients compared to non-HIV patients (Feldman *et al.*, 2007). However, in their study Feldman *et al.*, suggested that a possible reason for the shorter length of hospital stay found in their HIV patient population may be because patients at their Hospital, once noticeably

improved medically and stable, are stepped down to a feeder hospital to continue their inpatient care and therefore would appear to have been discharged sooner than HIV negative cases that would have been discharged directly home.

No significant differences in the time to clinical stability was found in the HIV positive patients compared to the HIV negative patients (1,5 days) ($p = 0,3969$).

Also observed in this study, was that patients that were 65 years and older had a significantly longer mean length of hospital stay of 9 days compared to patients that were younger than 65 years who had a mean length of hospital stay of 6 days ($p = 0,0121$). Patients 65 years and older had a mean time to clinical stability of 1,4 days, while patients younger than 65 had a mean of 1,5 days (not significantly different).

7.2 Strengths and Potential Limitations of the Study

The strengths of this study are firstly that a large number of patients were included into the study which provided sufficient numbers for statistical analysis to validate the SATS 2007 guideline. Secondly, the data found in the hospital files of the patients included into the study was found to contain all the information necessary for this study. Thirdly, this study is the only one that has been conducted to-date which investigates adherence to the current SATS CAP guideline and its potential impact on patient outcomes.

This study has some potential limitations. In the first instance 595 files were not provided, secondly it was conducted at one academic hospital in the public sector and

so the findings may not be generalisable to district facilities, the country as a whole, or to the private sector patients. Thirdly, the data was collected retrospectively and so the quality of the information was reliant on the completeness of the case notes and clinicians who follow guidelines may be more attentive to detail or have other treating characteristics different to others. Fourthly, the number of patients that received treatment that was non-adherent with the guideline was very small and there was only one death overall, thus potentially limiting the ability of the analysis to identify differences.

7.3 Conclusions

This study is the first to analyze adherence to the South African Thoracic Society 2007 guideline for the treatment of community-acquired pneumonia among patients hospitalized with CAP at Helen Joseph hospital in Johannesburg. The results of this study indicate that the guideline was followed in more than half of the cases. This adherence may also be related to the lower mortality due to CAP found in this study compared to previous studies, in that only one of the patients died, much lower than that reported for such patients previously.

These results are in contrast to previous studies performed in South Africa. Mpe *et al.*, (2005) found that only 8,7% of patients received treatment according to the 1996 SATS guideline and a mortality rate of 7,8% was found. Nyamande and Lalloo (2007) also found low adherence (8%) to the 2002 SATS guideline and a greater mortality was found in their study, 28% and 19% in patients treated with guideline adherent and

guideline non-adherent therapy respectively. However, mortality was not statistically significant in their study.

No significant difference in the length of hospital stay was found in patients who received treatment adherent to the guideline and those who received treatment that was non-adherent to the guideline. This is consistent with the study conducted by Nyamande and Lalloo (2007). However, a significant difference was found in the time to clinical stability.

Prospective data to show outcomes are different between guideline treated and untreated patients would be ideal, however, guidelines are still useful and there are many persuasive reasons for the issue of guidelines to be pursued vigorously (Marrie and Chan, 1998; Nyamande and Lalloo, 2007). Firstly, guidelines offer a summary of available evidence and the opinion of a group of experts, and therefore give realistic direction in the management of a specific condition (Marrie and Chan, 1998). Other important motives include, cost effectiveness, rational prescribing, reducing the development of antibiotic resistance, improving patient satisfaction, and decreasing variability in treatment (Marrie and Chan, 1998; Nyamande and Lalloo, 2007).

The study has shown that the South African guidelines have significant influence in medical practice at a Helen Joseph Hospital. There are several possible explanations. These include awareness, attitude, knowledge of the guidelines, local implementation of the guidelines, as well as the high incidence of CAP.

7.4 Future studies

A possible step further into analyzing the adherence to and potential impact of the CAP guidelines is to conduct a larger, multicentre study, involving a number of provinces in South Africa, and including non-academic institutions and both the public and private sectors. As one of the intentions of guidelines is to reduce cost, a study comparing the costs involved in patients who receive treatment adherent to the guideline and those who receive treatment that is non-adherent to the guideline would also validate an important motive for guidelines.

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Appendix 1

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Anastacia Chetty

CLEARANCE CERTIFICATE	**M10559**
PROJECT	A Retrospective Study to Evaluate Adherence to the South African Guideline on the Management of Community Acquired Pneumonia in Adults
INVESTIGATORS	Anastacia Chetty.
DEPARTMENT	Pharmacy & Pharmacology
DATE CONSIDERED	28/05/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 31/05/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof C Feldman

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 2

DEPARTMENT OF HEALTH
&SOCIAL DEVELOPMENT
HELEN JOSEPH HOSPITAL
OFFICE OF THE CLINICAL EXECUTIVE
ENQ: Mrs.N. Sithole
TEL: (011) 489 0453
EMAIL:Naumi.sithole@gauteng.gov.za

TO: Anastacia Chetty

RE: MSc PHARMACOTHERAPY RESEARCH PROJECT.

Your request to conduct research at Helen Joseph Hospital has been approved.

Yours Sincerely

.....

Mrs. Naumi. Sithole
Clinical Executive
Date: 21/ 04/ 2010

Appendix 3

PROTOCOL CAP-001 **PID:**_____

Case Report Form

Gender: M / F					Age:					
Date of Hospitalization:										
Date										
Altered breath sounds/consolidation										
Fever / hypothermia										
Rigors										
Sweats										
Cough										
Sputum production										
Pleuritic chest pain										
Cyanosis										
Shortness of breath										
Rapid RR										

Co-morbid disease	
HIV status	
Multilobar consolidation	
Complications	
Perceived need for ICU	

Temperature										
Pulse rate										
White cell count										
Platelet count										
Partial pressure of arterial O_2										
Albumin										
CURB-65										
Confusion										
Urea> 7 mmol/l										
Respiratory rate≥ 30 breaths/min										
BP(SBP < 90 mmHg, DBP ≤ 60 mmHg)										
Age ≥ 65 years										
Total CURB-65 score										

PROTOCOL CAP-001 **PID:**_____

Case Report Form

Chest radiograph	
Confirmation of pneumonia:	
Description:	

Microbiology	
Causative micro.	
Source (sputum/blood)	
Drug sensitivity	
Antibiotic Regimen	
β-lactam	
Macrolide	
Aminoglycoside	
Fluoroquinolone	
Other	
SATS guideline Adherent	
Patient Outcome	
Lived/died	
ICU admission	
Date of ICU discharge	
Date of hosp. discharge	
Date of Death	
Resolution of symptoms/signs (clinical stability) most of following achieved:	
Date	
SBP ≥ 90mmHg	
RR ≤ 24 breaths / min	
O2 saturation ≥ 92 %	
Temperature ≤ 37.2 °C	
Tolerate oral meds?	