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Original Article

Adherence to SATS antibiotic recommendations in patients with community acquired pneumonia in Johannesburg, South Africa

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Abstract

Introduction: Antibiotic guidelines have been published by various societies indicating the optimal empiric antibiotic treatment of patients with community acquired pneumonia (CAP); however, no studies have been undertaken in South Africa investigating whether the most recent South African Thoracic Society (SATS) antibiotic CAP guideline, published in 2007, is being adhered to, or whether adherence is associated with improved patient outcomes.

Methodology: This was a retrospective record review over a one-year period undertaken to document levels of adherence to the 2007 SATS guideline for CAP management in adults at an academic teaching hospital.

Results: A total of 181 patients with CAP were included in the study, of whom 101 were female, and 109 were known to be HIV-seropositive. The majority (66%) of the patients received antibiotic treatment that was guideline-adherent. In those patients who received treatment that was non-adherent to the guideline recommendations, rather than receiving inadequate cover, they actually had received treatment that was in excess of what was recommended. 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 guideline-adherent treatment. Only one CAP patient died and therefore it was not possible to determine the impact of guideline adherence on patient mortality.

Conclusion: Results of this study indicated a relatively high level of SATS guideline adherence. Guideline adherence was not associated with improved patient outcomes.

Key words: adherence; antibiotic guidelines; community-acquired pneumonia

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Introduction

Community acquired pneumonia (CAP) is one of the diseases with the greatest morbidity and mortality in the world, and leads to substantial consumption of healthcare resources. Outcome of pneumonia is determined by three main factors, namely the characteristics of the infecting microorganism, the nature of the infected host and the choice of antibiotic treatment [1]. Of these, antibiotic therapy is a factor related to patient prognosis that can be modified and improved. However, in this regard, it is important to remember that prescription of antibiotics in CAP is initially empirical because the microorganisms are usually unknown at the time of diagnosis [2]. Furthermore, neither symptoms nor routine laboratory or radiological findings allow an accurate aetiological diagnosis [2].

For all these reasons, numerous CAP guidelines have been published by various national and international societies [3], including the South African Thoracic Society [2], which have recommendations for both overall patient management, as well as the choice of initial empiric antibiotic therapy. One question that always remains is whether adherence to these guidelines is associated with better patient outcomes, and to this end several studies have been undertaken [4-6]. These studies suggest not only that antibiotic regimens that are non-adherent to the guidelines may be associated with a higher mortality, but that therapy that is guideline-adherent is associated with a lower mortality, a more rapid time to clinical stability and lower overall treatment costs [4-6].

Only one previous study has investigated adherence to CAP guidelines in South Africa, applying the

guideline published in 1996, and what the authors documented was very poor adherence to that guideline and no evidence of benefit of guideline adherence on patient outcome [7]. Therefore, this study was designed and implemented to document the levels of adherence to the most recently (2007) published South Africa Thoracic Society CAP guideline [2], specifically with regard to the choice of initial empiric antibiotic therapy, and to determine if adherence to the guideline recommendations was associated with improved outcomes in patients hospitalized with CAP

Patients and Methods

This study was a retrospective record review of all adult cases (≥ 18 years of age) with CAP admitted to the Helen Joseph Hospital in Johannesburg, between January 2009 and December 2009. Patients were identified through the admission records of all the medical wards in the hospital. The study had been approved by the Human Research Ethics Committee of the University of the Witwatersrand.

In this study CAP was defined as a lower respiratory tract infection associated with an abnormal infiltrate on a chest radiograph, together with the presence of two or more of the following signs and symptoms: altered breath sounds and/or consolidation, fever or hypothermia, rigors, sweats, cough, expectoration, pleuritic chest pain, cyanosis, shortness of breath and tachypnoea, as previously described [8].

Patients with known or suspected *Pneumocystis jirovecii* pneumonia (PCP) and pulmonary tuberculosis were excluded. The other exclusion criteria were age younger than 18 years of age and those patients residing in nursing homes or long-term care facilities.

The parameters captured from the patient files were age in years, gender, date of hospitalization, presence of altered breath sounds, fever or hypothermia, rigors, sweats, cough, expectoration, pleuritic chest pain, cyanosis, shortness of breath, respiratory rate, pulse rate, temperature, co-morbid disease including HIV status, evidence of pulmonary consolidation on chest radiograph, additional parameters needed for calculating the CURB-65 score, ICU admission or not, results of microbiological studies, antibiotic regimens used within the first 48 hours, date of resolution of symptoms, date of hospital discharge or date of death. With regard to the microbiological investigations, the usual practice at Helen Joseph Hospital for patients with CAP is to have routine blood cultures, with sputum examination for microscopy, sensitivity and culture being performed in selected cases.

The CURB-65 score is a six- point score system, recommended in the South African Society guideline for assessing severity of illness of the patients. In this scoring system, one point is assigned for each of the following parameters, if present; confusion; urea >7mmol/l; respiratory rate ≥ 30/min; low systolic (<90mmHg) and/or low diastolic (≤ 60mmHg) blood pressure and age ≥ 65 years [2,9,10]. Thus the score may vary from 0 to 5. It is commonly recommended that patients with a score of 0-1 may be suitable for therapy at home; those with a score of 2 usually require a period of hospitalization; and those with a score ≥ 3 would be considered to be more severely ill and may even require a period of high care or intensive care unit admission. In addition to the CURB-65 score, the South African Thoracic Society guideline also indicates additional parameters that may require individuals to be admitted to hospital, including factors such as socio-economic status or home circumstances and the presence of co-morbidities [2].

The admitting registrar or physician had determined the initial empiric antibiotic(s) administered.

According to the South African Thoracic Society Guideline of 2007, recommendations for in-hospital antibiotic treatment of patients with CAP are as follows; in patients with no co-morbid illness and below the age of 65 years recommended treatment is a ß-lactam agent (penicillin or ampicillin/amoxicillin) with or without a macrolide or alternatively a fluoroquinolone; in patients 65 years of age or older and in those patients with co-morbidity, the recommended antibiotic treatment is a ß-lactam agent (amoxicillin-clavulanic acid or a second or third generation cephalosporin) with or without a macrolide or alternatively a fluoroquinolone; and in severely ill adults requiring intensive care the recommended treatment is a ß-lactam agent (amoxicillin-clavulanic acid or a second or third generation cephalosporin) plus an aminoglycoside and a macrolide or alternatively a fluoroquinolone plus a ß-lactam or an aminoglycoside [2]. These recommendations were the basis for determining whether antibiotic treatment in the current study was adherent or non-adherent to the guideline in each patient. All other antibiotic regimens were considered non-adherent to the guideline [2].

Thereafter the impact of adherence or non-adherence to the guideline on patient outcome was evaluated. The outcome measures studied were time to clinical stability, length of hospital stay (LOHS) and mortality. Time to clinical stability was determined according to the validated rule that defined clinical stability as the first day that one or more of the

following criteria were simultaneously achieved: systolic blood pressure ≥ 90mmHg, respiratory rate ≤24 breaths per minute, heart rate ≤ 100bpm, oxygen saturation ≥ 92%, temperature ≤ 37,2ºC, ability to tolerate oral intake, stable mental status [11]. Time to clinical stability was calculated by subtracting the admission date from the first date that the patient was determined to be clinically stable. The LOHS (in days) was calculated by subtracting the hospital admission date from the hospital discharge date.

Since the 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. In addition, these two outcome parameters were also compared in HIV-seropositive versus HIV-seronegative cases.

Statistical analysis

The time to clinical stability and length of hospital stay were compared in patients receiving guideline adherent versus guideline non-adherent therapy, in patients who were HIV-seropositive versus HIV-seronegative and in patients who were aged < 65 years versus those ≥ 65 years using the Wilcoxon Rank Sum test. The relationship between time to clinical stability and length of hospital stay and the CURB-65 score were evaluated using analysis of variance. Data analyses were done using the SAS JMP Windows version 8 statistical software.

Results

Cohort Description

A total of 181 patients met the inclusion criteria, of whom 101 were female and 80 male, and 109 were known to be HIV-seropositive (in 42 patients the HIV status was unknown) and 88.4% of the patients were younger than 65 years of age. Co-morbidities, mainly HIV infection, were found in 150/181 (82.9%) of patients. The demographic features of the patients are shown in Table 1. Microorganisms were isolated in 18.8% of the cases (Table 2). None of the patients were admitted to the intensive care unit.

Antibiotic regimens

The majority of patients (66%) were found to have received treatment that was adherent to the SATS guideline. Most of these 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. Of the 181 patients, 34% received treatment for CAP with drugs that were non-adherent to the SATS guideline.

Time to clinical stability

The time to clinical stability ranged from 1 – 8 days. There was a significantly ($p = 0.02$) longer time to clinical stability in patients whose therapy was adherent to the guideline (1.6 days) compared to the non-adherent group (1.3 days). There was also a tendency to

Table 1. Characteristics of patients with community-acquired pneumonia.

Characteristics	**Number (%)**
Demographics	
Gender (Male/Female)	80 (44%)/101(56%)
Age, median (range)(years)	38 (range 18-85)
≥65 years	21(12%)
<65 years	160(88%)
Co-Morbidities*	
HIV-seropositive	109(60%)
Chronic obstructive pulmonary disease	5(2.8%)
Neoplasia	2(1%)
Kidney disease	12(6.6%)
Hypertension	14(7.7%)
Diabetes mellitus	7(3.9%)
Hepatitis	1(0.6%)
CURB-65	
0	71(39.2%)
1	63(34.8%)
2	33(18.2%)
3	13(7.2%)
4	1(0.6%)

*Some patients had multiple co-morbidities

an increase in the time to clinical stability as the CURB-65 score increased; however, this was not statistically significant (p = 0.05).

Length of hospital stay (LOHS)

The length of hospital stay ranged from 1 – 29 days. There was a highly significant difference in the mean LOHS among the patients with the different CURB-65 scores (p = 0.0001). The higher the CURB-65 score, the longer was the LOHS (Table 3). This did not include the patient who had a CURB-65 score of 4 as statistical analysis could not be performed with only one patient. 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, which was not significantly different (p = 0.68)

Time to clinical stability and LOHS in HIV positive patients

The LOHS and time to clinical stability were 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 (p = 0.19). The mean time to clinical stability for HIV-positive patients (1.6) was also found to be not significantly different (p = 0.4) compared to HIV-negative patients, which was 1.5 days.

Time to clinical stability and LOHS related to age

There was no significant difference in time to clinical stability in patients < 65 years of age versus those ≥ 65years (p=0.56), although the LOHS was longer in the latter group of patients (p=0.01).

Mortality

Among the 181 patients, only one death occurred; that patient had 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.

Discussion

The main findings of this study were that most patients were treated with guideline-adherent antibiotic therapy (66%), the most widely used antibiotic

Table 2. Bacterial pathogens (36) isolated in 34 of the 181 patients (18.8%) with community acquired pneumonia.

Pathogens	Patient No. (%)*	Source
Gram-positive		
S. pneumoniae	21(61.8%)	Blood
S. aureus	1 (2.9%)	Blood
A. neuii	1(2.9%)	Blood
Gram-negative		
H. influenzae†,‡	5(14.7%)	4 blood and 1 sputum
K. pneumoniae	2 (5.9%)	Sputum
S. marcescens†,‡	2(5.9%)	Blood and sputum
Mixed pathogens		
S. pneumoniae† and *H. parainfluenzae*‡	1(2.9%)	Blood and Sputum
S. pneumoniae† and *K. pneumoniae*‡	1(2.9%)	Blood and sputum

*Since in two patients there were two pathogens isolated, percentages do not add up to 100%; †Blood source of microorganisms; ‡Sputum source of microorganisms.

Table 3. The outcomes and the relationship to the CURB-65, HIV status, age group comparison.

Variables	LOHS (days)	P value	Time to clinical stability (mean days)	P value
CURB-65 score comparison				
CURB-65 score =0	5	0.0001	1.4	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	

treatment regimen being a beta-lactam agent alone or together with a macrolide; however, there was no significant difference in LOHS among those receiving adherent versus non-adherent therapy, but the time to clinical stability was significantly longer in the guideline-adherent group (p=0.02).

This study is the second to analyse the impact that the South African CAP guidelines have had on physician practice and patient outcomes. The previous study evaluated these parameters in relationship to the older guideline (1996) [7], while the current study evaluated the impact of the revised guideline of 2007 [2]. The patient demographics in the current study were different from that described in studies of patients with CAP in the developed world [12] in that the current cases were younger, with much fewer of our cases being ≥ 65 years of age, and there was a higher ratio of female patients (Table 1). Demographics of patients with CAP in a number of studies through Europe tend to show an older patient population, with underlying co-morbid conditions other than HIV infection and with a male predominance, at least among hospitalized cases [12] These difference are almost certainly related to the significant association of CAP with HIV-seropositivity in South Africa and in the current study, among those patients tested, 78% were HIV-seropositive. The clinical findings of the current study were similar to that documented in the previous study conducted in South Africa, in which 84% of patients were documented to be HIV-positive [7].

Table 1 indicates the CURB-65 score of the patient admitted to hospital. Overall, 74% of the patient had a score of 0-1, which according to the CURB-65 scoring system would have indicated that these patients may be suitable for outpatient care. The decision to admit these patients to hospital had been made by the emergency room physicians. We did not determine the reason(s) in the current study that these patients had been admitted by emergency department doctors. However, it is well documented in both South Africa and internationally that CAP patients with low severity of illness scores are frequently admitted to hospital [13,14]. As described previously the South African Thoracic Society guideline does indicate additional criteria over and above the CURB-65 score that may require patients to be admitted to hospital, including their socio-economic status and home circumstances, as well as the presence of co-morbidities such as HIV infection. This may be the reason, at least in some of the cases, that patients with low CURB-65 scores had been admitted to hospital.

Table 2 documents the microbiological findings in the patients. Overall 36 microorganisms were identified in 34 of the 181 patients (18.8% of the patients). Of these microorganisms the most common isolate was *Streptococcus pneumoniae* (representing 58.3% of the isolates, and being documented in 61.8% of the patients). The previous study from South Africa identified 113 isolates in their 182 study patients and of these 50% were *S. pneumoniae* [7] The findings of both these studies that the pneumococcus was the most common isolate is compatible with what has been documented in most studies throughout the world, even among HIV-seropositive individuals [15]. There are a number of reasons for the significant differences in the frequency with which microorganisms were isolated in the two South African studies. The earlier study was a prospective study in which a concerted effort was made to document the microbial aetiology, whereas the current study was retrospective, relied purely on patient records for isolate documentation, and the extent of the microbial workup had been decided upon by the treating clinician rather than the study investigators. Furthermore, the earlier study was restricted to severely ill cases in whom microorganisms are more commonly isolated than among general CAP patients, and particularly less severely ill cases, such as was the case in the current study [2,7,15].

The choice of empiric antibiotic treatment in the current study was adherent with the SATS 2007 CAP guideline [2] in a significant percentage of patients (66% of cases). This is in contrast with the previous study from South African [7], which documented poor adherence to the earlier SATS CAP guideline. In keeping with the global trend, most patients received either amoxicillin/clavulanic acid monotherapy (54%), or amoxicillin/clavulanic acid in combination with other antibiotics (40%). Interestingly, in both the current and previous South African studies, among the patients receiving antibiotic therapy that was non-adherent to the SATS guidelines, rather than the patients being undertreated, they had mostly received treatment that was in excess of what was recommended (i.e. broader antibiotic cover). The latter therapies included the use in non-ICU cases, in patients younger than 65 years of age with no comorbidity, amoxycillin/clavulanic acid plus gentamycin and a macrolide, or ceftriaxone, and lastly, in those patients older than 65 years with comorbidity, the use of piperacillin/tazobactam [2].

With regard to the patient outcomes, there was a significantly longer time to clinical stability in patients whose antibiotic therapy was adherent to the guideline

(1.6 days) compared to those whose treatment was non-adherent to the guideline (1.3 days) (p = 0.02). The reasons for this are uncertain, and are in sharp contrast with other studies which have shown that clinical stability is reached earlier when antibiotic treatment is adherent with guideline recommendations but also is administered early [5]. Unfortunately, in our study, because of the retrospective nature of the investigation, we were unable to determine how soon antibiotics were administered to the patients after the diagnosis of pneumonia was made, which may account for this difference.

The length of hospital stay in the current study was no different whether the antibiotic treatment was adherent or non-adherent to the guideline, a finding similar to that from other studies [4]. Interestingly, in the current study the LOHS was shorter than in the previous South African study [7]. Part of the reason may be related to the findings in some studies that the LOHS is independently associated with the admitting hospital rather than the choice of antibiotic therapy [4] while an additional consideration is that the previous study only recruited severely ill cases [7].

Furthermore, in the current study there was no significant association between the CURB-65 score, HIV status and age (cut-off of 65 years) and time to clinical stability, whereas higher CURB-65 and older age, but not HIV status, were associated with a longer LOHS (Table 3).

In the current study only one patient was documented to have died and therefore the impact of adherent versus non-adherent antibiotic therapy on mortality could not be determined. The previous South African study documented an overall mortality of 20%, this being 28.5% in those given guideline-adherent therapy, and 19% in those given guideline-non-adherent therapy, which was not significantly different; p = 0.71) [7]. The reasons for the differences in mortality between these two studies is uncertain but may relate to the fact that the earlier study was restricted to the investigation only of severely ill cases with CAP, and also that microorganisms were isolated in a significantly greater number of the cases (although the site of isolation was not reported) and CAP cases that are more severe [9], as well as those that have documented bacteraemia are known to have a poorer prognosis [16]. An additional reason that non-adherent therapy was not associated with a higher mortality in either of the studies may relate to the fact that in both studies, those patients that received non-adherent therapy, had not received, in most cases, inadequate therapy, but had received antibiotic therapy in excess of what was recommended [7].

There are potential limitations of the current study. It was conducted in a single institution and therefore the findings may not be generalizable. Being a retrospective record review, some data was unavailable for analysis. Because of the very low mortality the impact of guideline adherence of mortality could not be evaluated. Furthermore, this also limited our ability to undertake multivariate analysis to look for independent predictors of outcome.

Nevertheless, the study is the first to investigate adherence to the 2007 SATS guideline and did show reasonably good adherence to 2007 CAP guideline, and a low mortality rate among the patients. However, a much larger, national, multicenter, prospective study is required to truly validate the current guideline recommendations and to assess the impact of adherence on various outcome and economic variables

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