

COMPARATIVE EFFICACY AND SAFETY OF CEFIXIME AND CIPROFLOXACIN IN THE MANAGEMENT OF ADULTS WITH COMMUNITY-ACQUIRED PNEUMONIA IN IBADAN, NIGERIA

O.M. Ige¹ and A.O. Okesola²

1. Department of Medicine, University College Hospital, Ibadan, Nigeria.
2. Dept. of Medical Micro. & Parasitology, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Correspondence:

Dr. O.M. Ige

Pulmonary Unit,

Department of Medicine,

University College Hospital,

Ibadan, Nigeria.

E-mail: olusojiige@yahoo.com

Mobile phone: +2348030658080

ABSTRACT

Background: Initial antibiotic therapy in upper and lower respiratory tract infections is usually empirical. However, the decreasing susceptibility of respiratory pathogens to antibacterials have raised concerns about the decreasing efficacy of currently available antibiotics.

Objective: This study was conducted to compare the efficacy and safety of cefixime and ciprofloxacin in the empirical treatment of community-acquired pneumonia among adult Nigerian patients in Ibadan.

Methods: This was an open-labelled, randomized, parallel-group study of seventy-three (73) radiologically and bacteriologically confirmed adult cases of community-acquired pneumonia, between July 1 and September 31, 2011 at two health care facilities in Ibadan, Nigeria. All of these patients had severity index (CURB 65) scores of either 1 or 2. They were treated with either Cefixime, 400mg twice daily or Ciprofloxacin 500mg twice daily for 14 days. They were evaluated four times during the course of their treatment for clinical responses, radiological and bacteriological clearances and safety of therapy.

Results: There were 39 (53.4%) patients in the Cefixime group and 34(46.6%) in Ciprofloxacin group. On day 7, patients on cefixime had a statistically significant lower temperature than patients on ciprofloxacin ($P < 0.01$). By day 14, only 10.3% of patients in cefixime group still had persistent residual radiological changes compared to 38.2% in the ciprofloxacin group ($P < 0.01$). Bacteria cure was obtained in 96% of the patients in the cefixime group and 83% in the ciprofloxacin group.

Conclusion: Cefixime was found to be superior to ciprofloxacin in terms of efficacy in the treatment of community-acquired pneumonia in adults in Nigeria. However, both antibiotics were well-tolerated by all the patients as there were no reports or documentation of adverse events.

Keywords: Cefixime, Efficacy, Safety, Community-acquired pneumonia

INTRODUCTION

Respiratory tract infections (RTIs) are amongst the most widespread and serious infections accounting for over 50 million deaths globally each year.¹ They are also the most common reason for physician's visit and antibiotic prescription.² The prevalence of pneumonia among adults with respiratory symptoms suggesting pneumonitis ranges from only 3% in a general outpatient setting to 28% in emergency department.^{3,4} Community-acquired pneumonia (CAP) is a common cause of hospital admission in Nigeria, and, in TB patients attending a TB clinic in South-Western Nigeria, 6.4% was found to have *Streptococcal pneumoniae*.⁵

Initial antibiotic therapy in upper and lower respiratory tract infections is usually empirical, focused towards the most common aetiologic agents, which include, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella*

pneumoniae and *Moraxella catarrhalis*.⁶ However, the decreasing susceptibility patterns of these pathogens, particularly *S.pneumoniae* and *H.influenzae*, to antibacterials have raised concerns about the decreasing efficacy of currently available antibiotics.^{7,8} In the United States, almost 100% of clinical *M. catarrhalis* and up to 50% of *H.influenzae* isolates produce beta-lactamase. Penicillin-resistant strains have been identified worldwide,⁹ and, resistance to other antibacterials such as cephalosporins, fluoroquinolones and macrolides is increasing among isolates of *S.pneumoniae*.¹⁰⁻¹²

Cefixime belongs to the third-generation cephalosporin antibiotics that exert their bactericidal effect by attaching to penicillin-binding proteins and inhibiting peptidoglycan synthesis, thus causing damage to the bacterial cell wall. The third-generation cephalosporins

are used all over the world because of their broad spectrum activity against all Gram-negative and positive pathogens and atypical organisms, e.g. Mycoplasma and Chlamydia.⁶

Ciprofloxacin, also a broad-spectrum, early-generation fluoroquinolone, is one of the cheap and most commonly used antibiotics for most infections including RTI in this community, and, it exhibits bactericidal activity primarily by inhibiting bacterial DNA gyrase. These drugs were acceptable standard antibiotics for the treatment of community-acquired pneumonia during the study period. Even though there are many antibiotics that require less frequent administration, some studies indicate that older antibiotics that have fallen out of favour, are still effective for treatment of community-acquired pneumonia.¹³ This study was therefore conducted to evaluate the comparative efficacy and safety of Cefixime and Ciprofloxacin in the empirical treatment of CAP among adult Nigerian patients in Ibadan, Nigeria.

PATIENTS AND METHODS

Study population, enrolment and therapy

This was an open-labelled, randomized, parallel-group study conducted at the General Out Patient Department of the University College Hospital (UCH), Ibadan and Saint Mary's Catholic Hospital, Eleta, Ibadan, Nigeria, between July 1 and September 31, 2011.

The first 75 subjects who satisfied the inclusion criteria were randomised into Cefixime and Ciprofloxacin groups. However, 2 of these were lost to follow-up as they failed to turn up for subsequent visits to the clinic, leaving 73 to conclude the study.

The major inclusion criteria included: adult above 18 years of age, recent onset of fever ($>38.3^{\circ}\text{C}$), cough with purulent expectoration, bacteriologically positive sputum, presence of an infiltrate on chest radiography performed within 72 hours after the first clinical examination, pleuritic chest pain, crackles, new onset of dyspnea, or worsening dyspnea, female of child bearing potential with a negative urine pregnancy test prior to enrolment (including those who were practising birth control, those with tube ligation and those less than 1 year post-menopausal), willingness to partake in the study and provision of a signed informed or witnessed verbal informed consent.

The key exclusion criteria included: patients with bacteriologically negative sputum, negative chest radiograph, on antibiotics for any infective conditions within the preceding 30 days, hypersensitivity to

quinolones or cephalosporins or a severe allergic reaction to any other drug in the past, especially penicillin, patients with other chronic pulmonary diseases like active tuberculosis, bronchiectasis, or active pulmonary malignancies, patients with a life threatening or serious underlying disease, which is unstable, e.g. myocardial infarction, patients with known or suspected renal impairment and/or known creatinine clearance $<40\text{ml}/\text{min}$, patients with ALT, AST, or alkaline phosphatase levels 3 times greater than the upper limit of normal, patients who were immunocompromised including HIV positive patients, patients whose initial clinical status justified immediate hospitalization, and these were provided with hospital admission and excluded from the study.

A complete medical history was obtained and physical examination conducted on all the patients prior to entry into the study. Patients whose severity index (CURB 65) score were 1 or 2 were enrolled and those whose scores were higher than these were excluded from the study as many of these needed to be admitted. Enrolment was made after obtaining bacteriologically positive sputum and positive chest radiograph results from any of the patients apart from other inclusion criteria. Each eligible patient was assigned by a computer-generated sequence of random numbers to receive either Cefixime, 400mg twice daily or Ciprofloxacin, 500mg twice daily for 14 days.

Enrolled patients were followed up during treatment at the Medical Out-Patient Department of the respective study hospitals. Each study participant received the first dose of any of the 2 antibiotics on the first day of the study which corresponded to the time after positive radiological and bacteriological reports were obtained.

This was supervised by the study nurse and patients were then encouraged to take subsequent doses of the respective antimicrobial agent daily till the next follow up clinic visit. Compliance with drug regimen was crosschecked by direct questioning and pill count at every follow up clinic visit. Study participants were followed up on days 1, 3, 7, and 14.

Prior to enrolment, sputum samples were collected in sterile sputum cups and were transferred to the laboratory in a cold box the same day for laboratory evaluation. Pathogens were isolated and identified from sputa using standard bacteriological methods. Identified pathogens were then subjected to antibiotics susceptibility test to cefixime and ciprofloxacin using the Kirby-Bauer disc diffusion method.¹⁴ Sputum collection was repeated on days 3, 7 and 14 to check for bacteriological clearance.

Ten milliliters of blood was obtained by venepuncture for full blood count and blood chemistry evaluation which included aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), total bilirubin, electrolyte & urea and serum creatinine.

The laboratory investigations were conducted at the diagnostic medical microbiology, hematology and chemical pathology laboratories of University College Hospital Ibadan. Full blood count and differentials as well as biochemical parameters were again re-evaluated on day 14. Chest X-rays (posterior anterior & lateral views) were taken at the UCH or Saint Mary's Catholic Hospital, Eleta X-ray Departments prior to commencement of treatment and on day 14.

Efficacy and safety parameters

Patients were evaluated four times during the course of treatment. The primary efficacy was to evaluate the comparative clinical response at the two arms of treatment on days 3, 7 and 14. Secondary efficacy parameters included the comparative radiological response at the end of therapy and bacterial eradication rate on days 3,7 and 14. The bacterial sensitivity to Cefixime and Ciprofloxacin was determined for each isolated bacteria, irrespective of the treatment group assigned. The organisms were considered sensitive to Cefixime when the inhibition halo was equal to or greater than 19 mm and sensitive to Ciprofloxacin when the halo was equal or greater than 21 mm.¹⁵

The bacteriologic response was considered satisfactory if the causative organism had been eradicated with treatment. Radiologic response was considered satisfactory when the lobar consolidation noticed at the beginning of treatment has cleared completely on day 14 of antibiotics therapy as reported by the consultant radiologist.

The safety end point was to evaluate the incidence of adverse effects and laboratory parameters.

Statistical analysis

Data generated was entered using epidata program and the SPSS version 16 was used for further statistical analysis. Frequency tables, graphs and summary index were used for data presentation. The student t-test was used to investigate the statistical significance of the quantitative effects of the two drugs between the two groups.

Ethical considerations

All patients enrolled gave written informed consent and the trial was approved by the Joint Ethical Committee of the University College Hospital/ University of Ibadan, Nigeria.

RESULTS

Seventy-five patients that satisfied the inclusion criteria were recruited for this open-labelled, randomised, drug trial but two were lost to follow-up as they failed to turn up for subsequent visits to the clinics as scheduled. One was from each arm of the treatment leaving 39 in the cefixime group and 34 in the ciprofloxacin group. Table 1 shows the anthropometric characteristics of the patients from the two arms of treatment.

Primary efficacy parameter is the clinical response on follow up in each treatment group. Table 2 shows the clinical features of patients allocated to the 2 treatment groups while Table 3 shows the summary of statistics of patients' clinical characteristics on each day of follow-up in each treatment group.

The temperature pattern shows that the temperatures decreased slightly in both groups by day 3 but not statistically significant ($P>0.2$). However, on day 7, patients on cefixime had a statistically significant lower temperature than patients on ciprofloxacin ($P<0.01$). The same was observed with regards to the respiratory rate. This pattern was maintained on day 14 during the final clinical examination of the patients.

Table 1: Anthropometric characteristics of patients in the 2 arms of treatment.

| Anthropometric characteristics | Drug Group | Sample Size N | Mean | Standard Deviation | T-value | P-Value |
|--------------------------------|---------------|---------------|-------|--------------------|---------|---------|
| Age(yrs) | Cefixime | 39 | 44.6 | 18.59 | -0.50 | 0.62 |
| | Ciprofloxacin | 34 | 46.7 | 17.10 | | |
| Weight (kg) | Cefixime | 39 | 62.1 | 12.45 | -1.67 | 0.10 |
| | Ciprofloxacin | 34 | 67 | 14.61 | | |
| Height (cm) | Cefixime | 39 | 162.6 | 8.15 | 0.65 | 0.52 |
| | Ciprofloxacin | 34 | 161.5 | 5.97 | | |

Table 2: Summary Statistics of the duration of Symptoms in days of patients allocated to cefixime and ciprofloxacin treatment groups.

| DRUG | FEVER | COUGH | COUGH WITH SPUTUM | CHILLS AND RIGORS | CATARRH | HEADACHE | CHEST PAIN |
|----------------------|-------|-------|-------------------|-------------------|---------|----------|------------|
| Cefixime | | | | | | | |
| Mean | 6.12 | 9.38 | 5.00 | 4.11 | 8.26 | 5.17 | 5.54 |
| Median | 7.00 | 10.00 | 7.0 | 3.00 | 7.00 | 7.00 | 7.00 |
| N | 33 | 39 | 18 | 9 | 19 | 12 | 26 |
| Ciprofloxacin | | | | | | | |
| Mean | 6.87 | 10.50 | 6.32 | 6.86 | 8.82 | 5.7 | 6.65 |
| Median | 7.00 | 10.00 | 7.00 | 7.00 | 10.00 | 7.0 | 7.0 |
| N | 30 | 32 | 19 | 7 | 17 | 13 | 26 |
| TOTAL | | | | | | | |
| Mean | 6.48 | 9.89 | 5.68 | 5.31 | 8.53 | 5.4 | 6.1 |
| Median | 7.00 | 10.00 | 7.00 | 6.00 | 8.00 | 25 | 7 |
| N | 63 | 71 | 37 | 16 | 36 | 7 | 52 |

Table 3: Summary of statistics of patients' clinical characteristics on each day of follow-up in each treatment group.

| Day of Exam. | Clinical Assessment | Cefixime Mean (SD) n = 39 | Ciprofloxacin Mean (SD) n = 34 | t-value | p-value |
|--------------|---------------------|---------------------------|--------------------------------|---------|---------|
| 1 | TEMP | 37.9 (0.7) | 37.8 (0.5) | 0.77 | 0.44 |
| | PR | 110.5 (162.0) | 93.0 (8.0) | 0.77 | 0.34 |
| | RR | 21.4 (2.5) | 22.1 (3.2) | -1.06 | 0.29 |
| 3 | TEMP | 37.2 (0.9) | 37.5 (0.5) | -1.21 | 0.23 |
| | PR | 103.9 (147.6) | 81.1 (18.6) | 0.89 | 0.38 |
| | RR | 21.5 (11.2) | 20.7 (2.6) | 0.38 | 0.69 |
| 7 | TEMP | 36.8 (0.8) | 37.2 (0.5) | -2.64 | 0.01* |
| | PR | 76.0 (6.4) | 79.8 (18.8) | -2.14 | 0.04* |
| | RR | 17.3 (1.4) | 18.7 (2.7) | -2.68 | 0.01* |
| 14 | TEMP | 36.8 (0.4) | 37.0 (0.5) | -2.36 | 0.02* |
| | PR | 75.1 (6.6) | 77.7 (8.0) | -1.42 | 0.16 |
| | RR | 16.5 (1.1) | 17.7 (2.5) | -2.58 | 0.01* |

* Statistically significant differences between the two treatment groups.

TEMP= Temperature

PR= Pulse rate

RR= Respiratory rate

Table 4: Percentage bacteria eradication rate and radiological clearance at follow-up of patients in Cefixime and Ciprofloxacin groups.

Patients with radiological consolidations and bacterial isolates

| Type of follow up | Days | Cefixime No (%) | Ciprofloxacin No (%) | χ ² -value | P – value |
|-------------------------------------------------|------|-----------------|----------------------|-----------------------|-----------|
| 1. Radiological clearance | 1 | 39(100.0) | 34(100.0) | - | |
| | 14 | 4(10.3) | 13(38.2) | 7.96 | 0.01* |
| 2. Microbiological (Bacterial eradication rate) | 1 | 39(100.0) | 34(100.0) | - | |
| | 3 | 30(76.9) | 29(85.3) | 0.82 | 0.37 |
| | 7 | 5(12.8) | 21(61.8) | 18.98 | 0.0001* |
| | 14 | 3(7.7) | 13(38.2) | 9.90 | 0.002* |

*Statistically significant differences between the 2 treatment groups.

Table 5: Distribution of the lung lesions and percentage clearance on days 1 and 14 in Cefixime and Ciprofloxacin drug groups.

| | | Cefixime | Ciprofloxacin | TOTAL |
|-----------------------|--------|-----------------|----------------------|---------------|
| | | No (%) | No (%) | No (%) |
| Left Lower Zone | Day 1 | 25 (64.1) | 25(73.5) | 50(68.5) |
| Left Lower Zone | Day 14 | 2(5.1) | 10(29.4) | 12(16.4) |
| Left Mid & Lower Zone | Day 1 | 3(7.7) | 0(0.0) | 3(4.1) |
| Right Lower Zone | Day 14 | - | - | - |
| Left Mid Zone | Day 1 | 0(0.0) | 1(2.9) | 1(1.4) |
| | Day 14 | - | - | - |
| Right Lower Zone | Day 1 | 10(25.6) | 7(20.6) | 17(23.3) |
| Right Lower Zone | Day 14 | 2(5.1) | 3(8.8) | 5(6.8) |
| Right Mid Zone | Day 1 | 0(0.0) | 1(2.9) | 1(1.4) |
| | Day 14 | - | - | - |
| Right Upper Zone | Day 1 | 1(2.6) | 0(0.0) | 1(1.4) |
| | Day 14 | - | - | - |

Left lower and right lower zones were the zones mostly affected by the consolidative changes on chest-x-ray accounting for 92.1%.

Table 4 shows the results of the secondary efficacy parameters of the two drugs in terms of their bacterial eradication rates and radiological clearance at follow-up of the patients. The distribution of lung lesions and percentage clearance on days 1 and 14 in the 2 treatment groups is demonstrated in Table 5. The predominant bacterial aetiology of community-acquired pneumonia in this study was *Staphylococcus aureus* 29 (39.7%), followed by *Streptococcus pneumoniae* 11(15.1%), *Klebsiella pneumoniae* 10(13.7%), *Escherichia coli* 17(23.3%) and *Proteus mirabilis* 6 (8.2%).

As regards the safety parameters considered for the two drugs, there were no adverse drug effects observed or reported by any of the patients in the two arms of treatment. The liver function tests, urea and creatinine, complete blood counts were essentially of normal values in all the patients at baseline and end of treatment.

DISCUSSION

Community-acquired pneumonia (CAP) is a cause of substantial morbidity, mortality, and resource utilization worldwide. Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death, and, there continues to be a major controversy concerning the antimicrobial management of this infection.¹⁶ The mixed aetiology and the changing susceptibility of pathogens causing CAP, in particular, that of *Streptococcus pneumoniae*, has created a challenge, in some circumstances, to clinicians in terms of optimal outcome.¹⁷

Initial antimicrobial therapy is normally given empirically before the bacterial cause of the infection

can be determined in the laboratory, and, in many cases, treatment is empirical throughout due to lack of reliable microbiological data. An understanding of the possible pathogens and resistant patterns is therefore helpful in guiding antibiotic choice. A detailed knowledge of the local susceptibility of the potential pathogens would ensure a more appropriate selection of the antimicrobial agent to be used.^{18,19} In this environment, ciprofloxacin is the most commonly used antibiotics for management of infections including RTIs, being the most readily available and very cheap, which leads to the comparison of its efficacy and safety with cefixime in this study.

The choice of these empirical antibiotics for CAP in this study was in conformity with the guidelines of IDSA (Infectious Disease Society of America)/ATS (American thoracic society)/Canadian guidelines (CIDS,CTS).²⁰⁻²³ The major criterion that guided the management decision of the CAP patients revolved around the initial assessment of the severity since the oral route can only be recommended in these non-severe (mild to moderate) pneumonia which was the case in this study.^{22,23}

The finding of persistent residual radiological changes in this study is in keeping with the observation of earlier researchers that radiographic response to treatment usually lags behind clinical improvement and pneumococcal pneumonia may take 6 weeks to clear on the chest film.^{24,25} This delay of the radiographic clearing that contrasts with the rapid clinical response seen on the third day of antibiotic treatment was one of the striking findings in this study.

The results of our study show that cefixime administered at the dose of 400mg twice daily is an effective oral antibiotic treatment in the management of community-acquired pneumonia in adults. This is in keeping with most previous clinical studies that found it very effective for lower respiratory tract infections.²⁶⁻³² The efficacy of cefixime in acute exacerbation of chronic bronchitis (AECB) has also been well documented in both comparative and non-comparative clinical studies.^{33,34}

In this study, the predominant cause of community-acquired pneumonia was *Staphylococcus aureus* 29 (39.7%), followed by *Streptococcus pneumoniae* 11 (15.1%), *Klebsiella pneumoniae* 10 (13.7%), *Escherichia coli* 17 (23.3%) and *Proteus mirabilis* 6 (8.2%).

This is contrary to a study conducted in the United States in 2006, where, in approximately 4.2 million ambulatory care visits for CAP, *Streptococcus pneumoniae* was the most commonly identified pathogen.³⁵⁻³⁷

None of the patients experienced vital signs of potential clinical concern or reported any adverse events during the course of study in the two arms of treatment. Cefixime was found to be safe and well tolerated in all the patients which contrasts the previous documentation of mild or moderate diarrhea and epigastric discomfort.³¹⁻³³ Thus, cefixime was shown to be superior to ciprofloxacin in the treatment of bacterial pneumonia among adults who have been properly assessed not to need hospitalization in Nigeria.

Limitation of the study

The clinical efficacy of Cefixime should also be compared with the new-generation fluoroquinolones (clonifloxacin, gemifloxacin, levofloxacin or moxifloxacin) and with another potent third-generation cephalosporins (cefepodoximeproxetil).

The on-going research will address this and help the clinicians with the right choice of empiric antibiotic treatment of CAP in Nigeria.

ACKNOWLEDGEMENTS

The trial was supported by Swipha Pharmaceutical Limited which provided clinical trial materials and other logistic support and for this, we are grateful.

REFERENCES

- 1 World Health Organization. Burden of Disease Project. Geneva: World Health Organization;2005 Thomas Neumark Lars Brudin, Sven Engstro, Sigvard MO.
- 2 **Neumark et al.** Trends in number of consultations and antibiotic prescriptions for

- respiratory tract infections between 1999 and 2005 in primary healthcare in Kalmar County, Southern Sweden. *Scand J Pri Health Care*, 2009; 27: 18-24.
- 3 **Heckerling PS**, Tape TG, Wigton RS, et al. Clinical prediction rule for pulmonary infiltrates. *Ann. Intern Med* 1990; 113:664-700
- 4 **Diehr P**, Wood RW, Bushyhead J, et al. Prediction of pneumonia in outpatients with acute cough: a statistical approach. *J Chr Dis* 1984; 37:215-225
- 5 **Agwu E**, Ohihion AA, Agba MI. Incidence of *Streptococcus pneumoniae* among patients attending tuberculosis clinics in Ekpoma, Nigeria. *Shiraz E-Medicine* 2006; 1-7
- 6 **Mandell LA**, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44:S27-72
- 7 **Tleyjeh IM**, Tlaygeh HM, Hejal R, et al. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: A systematic review and meta-analysis. *Clin Infect Dis* 2006; 42:788-797
- 8 **Jan Verhoefa A** Gillissen. Resistant *Haemophilus influenzae* in community-acquired respiratory tract infections: a role for cefixime. *J Antimicrob Agent* 2003, 21; 6501-6509
- 9 **Allen KD**. Penicillin-resistant pneumococci. *J Hosp Infect* 1991,17:3-13
- 10 **Falco V**, Almirante B, Jordano Q, et al. Influence of penicillin resistance on outcome in adult patients with invasive pneumococcal pneumonia: Is penicillin useful against intermediately resistant strains? *J Antimicrob Chemother* 2004;54:481-488.
- 11 **Appelbaum PC**. World-wide development of antibiotic resistance in pneumococci. *Eur J Clin Microbiol* 1987;6:367-377.
- 12 **Wierzbowski AK**, Nichol K, Laing N, et al. Macrolide resistance mechanisms among *Streptococcus pneumoniae* isolated over 6 years of Canadian Respiratory Organism Susceptibility study (CROSS) (1998-2004). *J Antimicrob Chemother* 2007; 60:733-740.
- 13 **Gleason PP**, Kapoor WN, Stone RA et al. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *J Am Med Assoc* 1997; 278: 32-39
- 14 **Kirby VM**, Bauer AW. Antibiotic susceptibility testing by a Standard Disc Method, *AMJ Clin Path* 1996; 36: 493-496.
15. Clinical and Laboratory Standards Institute. Performance standard for antimicrobial disk susceptibility testing. Approved Standard 2006.
16. **Pagarin F**, Lilienthal F, Bourdin A, et al. Community-acquired pneumonia: Assessment of

- microbial aetiology as mortality factor. *Eur Respir J* 2004; 24:779-785
17. **Oncu S**, Erdem H, Pahsa A. Therapeutic options for pneumococcal pneumonia in Turkey. *Clin Ther* 2005; 27:674-683
 18. **Okesola, AO**, Ige OM. Trends in bacterial pathogens of lower respiratory tract infections. *The Ind J Chest Dis & All Sci* 2007; 50: 269-273
 19. **Okesola AO**, Ige OM. Occurrence of antibiotic resistance and extended-spectrum B-lactamase production among bacterial respiratory pathogens in Nigeria. *Int J Pharm Biomed Sci* 2012; 3(3): 85-88
 20. **Bartlett JG**, Dowell SF, Mandell LA, *et al*. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis* 2000; 31:347-382
 21. **Mandell LA**, Marrie TJ, Grosman RF, *et al*. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. *Clin Infect Dis* 2000; 31:383-421
 22. **File TM Jr**, Garau J, Blasi F, *et al*. Guidelines for empiric antimicrobial prescribing in community-acquired pneumonia. *Chest* 2004; 125:1888-1901
 23. **Niederman MS**, Mandell LA, Anzueto A, *et al*. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163:1730-1754
 24. **Jay SJ**, Johnson WG, Pierce AK. The radiographic resolution of Streptococcus pneumoniae. *N Engl J Med* 1975; 293:798-802
 25. **Ort S**, Ryan JL, Barden G, D'Esopo N, Pneumococcal pneumonia: Clinical and radiological presentations. *JAMA* 1983; 249: 214-217.
 26. **Markham A**, Brogden RN. Cefixime: a review of its therapeutic efficacy in lower respiratory tract infections. *Drugs* 1995; 49: 1007-1022
 27. **Kiani R**, Johnson D, Nelson B. Comparative, multicenter studies of cefixime and amoxicillin in the treatment of respiratory tract infection. *Am J Med* 1988; 85:6-13
 28. **Modal J**. Efficacy and tolerability of cefixime in lower respiratory tract infections in adults: French multicenter study. *Press Med* 1989; 18:1605-1607
 29. **Quintiliani R**. Cefixime in the treatment of patients with lower respiratory tract infections: results of US clinical trials. *Clin Ther* 1996; 18:373-390
 30. **Verghese A**, Roberson D, Kailbfleisch JH, *et al*. Randomized comparative study of cefixime versus cephalexin in acute bacterial exacerbations of chronic bronchitis. *Antimicrob Agent Chemother* 1990; 34:1041-1044
 31. **Hamilton-Miller**. Overview of cefixime use in community-acquired pneumonia. *Clin. Micro Infect* 2000; 6 Suppl 3:81-97
 32. **Dreshai SH**, Doda-Ejupi-Ti, Tolai I Q, *et al*. Clinical role of cefixime in community-acquired infections. *Prilozi*. 2011; 32(2): 143-155
 33. **Cazzola M**, Vinciguerra A, Beghi GF, *et al*. Comparative evaluation of the clinical and microbiological efficacy of co-amoxiclav vs cefixime or ciprofloxacin in bacteria exacerbation of chronic bronchitis. *J Chemother* 1995; 7:432-441
 34. **Cogo R**, Monzani GP, Caiazzo G. Safety and efficacy of cefixime vs ceftriaxone in the treatment of infectious exacerbations of chronic bronchitis. *J Drug Dev* 1993; Suppl, 1: 55-56
 35. **File TM Jr**, Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgrad Med*. 2010; 122(2):130-141.
 36. **Marrie TJ**, Poulin-Costello M, Beecroft MD, Herman-Gnjidic Z. Etiology of community-acquired pneumonia treated in an ambulatory setting. *Respir Med*. 2005; 99(1):60-65.
 37. **D Wootton**. The review of diagnosis, aetiology and severity of community-acquired pneumonia in adults. *Afri J of Respir Med. March* 2010; 4:55-58