

Comparative Efficacy of Levofloxacin Versus Amoxicillin/Clavulanic Acid Combined with Azithromycin in Treatment of Community-Acquired Pneumonia

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Abstract

Background: Community-acquired pneumonia (CAP) is an important cause of mortality and morbidity worldwide. Early initiation of antibiotics is highly recommended. In most CAP cases, multiple drug options are increasingly becoming available, but there is often a lack of evidence that allows for a direct comparison of the efficacy of one drug versus another.

Aim: The main objective was to compare treatment outcomes using oral levofloxacin alone and combined azithromycin and amoxicillin/Clavulanic acid in outpatient treatment of Community-acquired pneumonia.

Methods: This study was a prospective longitudinal design. Patients diagnosed with CAP were randomly assigned to first and second treatment groups. Community-acquired pneumonia was diagnosed according to America Thoracic Society criteria. The sample size of 78 was arrived at by Yamane Taro (1967) formula. Every patient diagnosed and treated in the outpatient department who gave written consent to participate was enrolled in the study and randomly assigned to one of the treatment groups. Minors below 18 years were excluded from the study. Data were analysed using SPSS for Windows version 26. An independent t-test compared the effectiveness of the two treatment groups. Changes in white blood cell count during the follow-up visits were done using a chi-square test. A p-value of <0.05 was considered statistically significant.

Results. The majority, 33(50%) of the patients, were aged between 21 and 29 years, and over sixty percent, 42(63.6%) of participants were females. Of all the participants, 66(100%) had a cough and chest pain, 57(86.4%) had crackles, and about ten percent, 6(9.1%) had difficulty breathing at the time of admission into the study. About 29(43.9%) of patients had a fever at baseline, and 14(21.2%) had a respiratory rate between 16 and 29 breaths per minute at baseline. A combination of azithromycin and amoxicillin/clavulanic acid was associated with statistically significant faster resolution of chest pains and cough (mean 1.7 and 3.14 days, respectively) compared to levofloxacin group (mean 2.21 and 3.71 days, respectively) in patients who had community-acquired pneumonia ($p=0.009$). There was no difference in fever resolution, time to crackles subsidence, resolution of difficulty in breathing, and change in white blood cell count in participants in the two treatment groups.

Conclusions: Azithromycin combined with amoxicillin/clavulanic acid reduced chest pain in 1.70 days (SD=0.618) compared to levofloxacin alone (2.21 days, SD=1.204) ($p=0.009$). Azithromycin combined with amoxicillin/clavulanic acid reduced cough in 3.14 days (SD=0.789) versus levofloxacin alone (3.70 days, SD=0.588) ($p=0.014$). Hence, the azithromycin plus amoxicillin/clavulanic acid combination was found to be superior for managing CAP.

Keywords: community acquired pneumonia, CAP, Levofloxacin, Azithromycin, amoxicillin/clavulanic acid

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Introduction

Community-acquired pneumonia (CAP) is a type of pneumonia that is contracted outside of a hospital or other medical facility (1,2) characterised by inflammation of the lung parenchyma (3). Risk factors for CAP can be modifiable, such as smoking, or non-modifiable, such as inherited functional impairment of the lungs (4,5). Community-acquired pneumonia is a severe health issue that poses a significant threat to global healthcare systems as the primary cause of mortality among infectious illnesses (6,7).

Epidemiological studies in Kenya have demonstrated that viruses—particularly influenza viruses—were often detected in CAP patients and the underlying conditions, like HIV and cardiovascular diseases, among others, were comparable to those reported in high-resource areas, in contrast to other studies from sub-Saharan Africa (8). This suggests that the double burden of infectious and noncommunicable diseases is a growing cause for concern.

Community-acquired pneumonia may arise from diverse pathogens, encompassing a broad spectrum of bacterial agents. The term "core respiratory pathogens" describes the bacteria and viruses that are believed to be the most likely cause of pneumonia acquired in the community in all cases (9). Individuals with dual bacterial and viral infection have double the risk of mortality compared to patients without dual infection, even though viral pneumonia is a self-limiting illness (10). Bacterial pathogens implicated in CAP vary with geographic distribution and host characteristics (7). The most often found pathogen is *Streptococcus pneumoniae* (8.2%), followed by *Pseudomonas aeruginosa* (4.1%) and *Klebsiella pneumoniae* (3.4%) (11). Due to insufficient etiological data and resources and the unavailability of microbiological tests, identifying causative agents in resource-scarce settings like those in primary care centres in Kenya remains challenging. Hence, empirical antibiotic therapy is frequently used to manage the condition. Moreover, empirical antibiotic therapy is often effective, and thus, microbiologic testing for bacterial aetiology is generally not indicated for the majority of patients receiving care in ambulatory settings (9,12).

The key factors of the antibiotic class and mode of administration include age, comorbidities, and disease severity (13). Adults who present with suspected CAP get empirical antimicrobial chemotherapy in compliance with relevant national guidelines (12,13). For previously healthy patients who have not taken any antibiotics in the three months before presentation, the 2019 American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) both advocate monotherapy with macrolides or doxycycline in outpatient settings. For individuals with CAP and recent antibiotic use or comorbidity, a combination of an anti-pneumococcal beta-lactam like amoxicillin and a macrolide like an azithromycin or a respiratory fluoroquinolone like levofloxacin is advised (14,15).

However, there are a growing number of pharmacological alternatives as many antibiotics are available. However, there is a lack of clinical data regarding the efficacy of different antibiotics in managing CAP in Kenya. However, decision-making in clinical practice requires knowledge of the relative efficacy of different antibiotics or drugs (14,16). The wrong choice of empirical antibiotic therapy not only poses health risks due to poor outcomes but may also contribute to rising antibiotic resistance in the region. Given the challenge posed by such multiple drugs available in the treatment of CAP, this study compared the effectiveness of oral levofloxacin when used alone and amoxicillin/clavulanic acid combined with azithromycin in the treatment of CAP in the outpatient setting for patients with comorbidities or who have been exposed to antibiotics within the last three months.

Objective

To compare the effectiveness of levofloxacin alone versus combined azithromycin and amoxicillin/clavulanic acid in the treatment of community-acquired pneumonia

Methods and Study Design

The study utilised a prospective longitudinal study design. Longitudinal designs involve repeated observation of the same participants to follow change over time. In the current study, patients diagnosed with community-acquired pneumonia were allocated to one of the usual treatment groups and observed for five days at intervals (Figure 1). The study was conducted between March 6, 2022, and December 18, 2022, at St Monica Hospital Kisumu, Kenya.

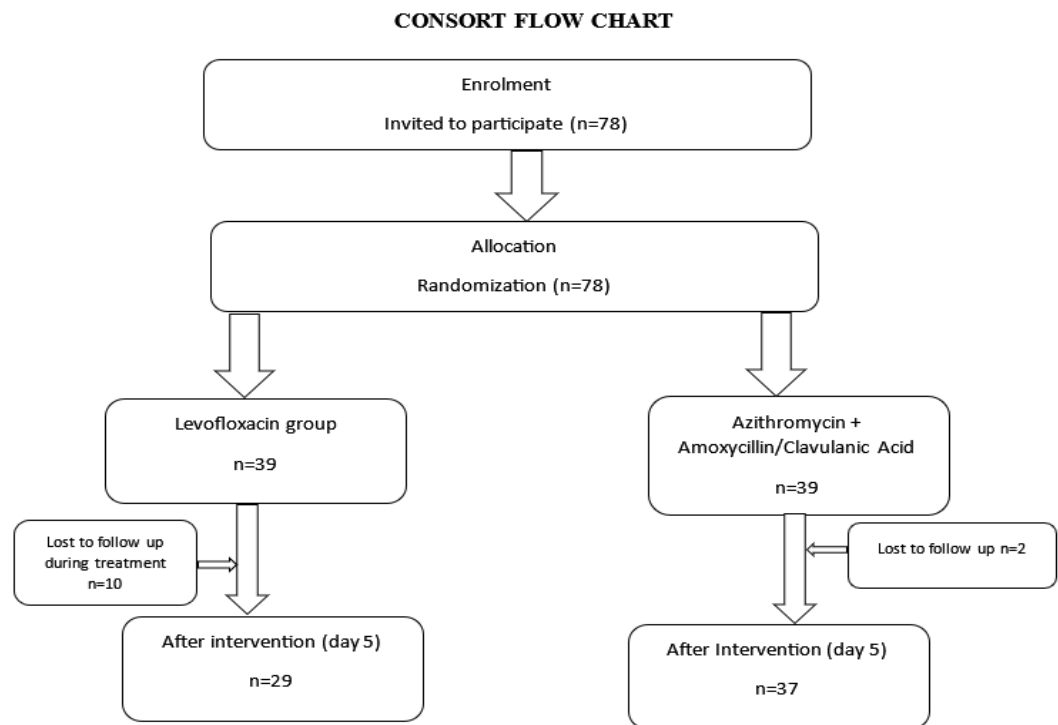


Figure 1: Consort flow chart. Seventy-eight participants were enrolled in the study and randomly allocated to the levofloxacin group or combined azithromycin and amoxicillin/clavulanic acid group, so each group had 38 participants. 10 participants in the levofloxacin group and 2 participants in the combined azithromycin and amoxicillin/clavulanic acid group were lost to follow-up, respectively.

This design was chosen to allow for a comparison of the efficacy of oral levofloxacin alone versus oral azithromycin and amoxicillin/clavulanic acid in the treatment of community-acquired pneumonia in patients who were observed at intervals during treatment. These drugs are already in use, and there is no new drug involved.

Participants were observed on days 1, 3, and 5. The patients' information on clinical parameters was gathered. The change in clinical parameters of patients during the observation was used to determine effectiveness. The clinical parameters in the study included fever, cough, chest pain, shortness of breath, physical findings of crackles, and white blood cell count. A drug was considered effective if taking it resulted in the resolution of clinical parameters at the end of the treatment period.

Participants

The participants consisted of patients diagnosed with community-acquired pneumonia at St Monica Hospital Kisumu, Kenya, between March 2022 and December 2022.

Community-acquired pneumonia was diagnosed according to **America Thoracic Society (ATS) criteria** in which signs and symptoms of pneumonia included at least two of the following:

- a) Fever (axillary temperature $> 37.5^{\circ}\text{C}$)
- b) Cough for less than 14 days
- c) Chest pain
- d) Shortness of breath
- e) Physical findings of consolidation
- f) White blood cell count $>15000/\mu\text{l}$ or $<5000/\mu\text{l}$
- g) Chest x-ray showing evidence of lung infection (pulmonary opacity).

Eligibility criteria

- a) Presentation to the Outpatient Department with probable community-acquired pneumonia.
- b) Age between 18yrs and above
- c) Smokes or used antibiotics for comorbidity within the last 3months
- d) Written consent has been obtained from the patient/guardian
- e) Parent or legal guardian is willing to allow the child to comply with the protocol and particularly to provide blood samples.

Interventions

The participants were put in one of the two intervention groups: Group 1: Levofloxacin group and Group 2: Azithromycin + Amoxicillin/Clavulanic acid group. In group 1, participants were given oral levofloxacin 500mg twice daily for five days. In group 2, participants were given azithromycin 500mg once daily for 3 days and amoxicillin/clavulanic acid 500mg/125mg twice daily for 5 days.

Outcomes

The main outcomes in the current study were the number of patients whose symptoms and clinical parameters (temperature, respiratory rate, white blood cell count) changed after the intervention. The primary outcomes included the resolution of cough, chest pain, and fever. The secondary outcomes included a change in white blood cell (WBC) count and a change in respiratory rate.

Sample size

A total of 78 participants were recruited for the study.

Randomisation

Every patient diagnosed and treated in the outpatient department who gave written consent to participate was enrolled in the study and randomly assigned to one of the treatment groups. Minors below 18 years were excluded from the study. With the help of research assistants, the researcher enrolled every eligible participant as they came until 78 participants were enrolled in the study. Patients were randomly assigned to each treatment group to get 39 patients in each group.

Blinding

The current study was unblinded. All participants knew the drugs they were using for the treatment of community-acquired pneumonia.

Statistical analysis methods

Data were analysed using SPSS for Windows version 26. A comparison of effectiveness between the two treatment groups was done using an independent t-test. Changes in white blood cell count during the follow-up visits were done using a chi-square test. P value of <0.05 was considered statistically significant.

Ethical consideration

This study is a registered trial with trial number PACTR202308507206446 and was licensed by the National Commission for Science, Innovation, and Technology via license number NACOSTI/P/22/15077. Jaramogi Oginga Odinga University of Science and Technology Board of Postgraduate Studies approved this study vide approval letter reference number: 152/4071/2017. This study was approved by the Baraton University ethics committee with reference number B0734432021. Each patient was explained about the study, including benefits and risks. Those who accepted were given the consent form to sign written informed consent form. Minors (<18 years) were excluded from the study. The researcher kept All information from the study in a safe box. The participants were anonymised; thus, no patient identifiers were collected during and after the study. The researcher provided adverse events notification form in case a patient experienced allergies or reactions to the drugs in the study. No adverse event was documented at the end of the study.

Results

Demographic characteristics of respondents

The patients were categorised into two treatment groups, i.e., oral levofloxacin-based group, 29(43.9%) and dual Azithromycin and Amoxicillin/Clavulanic acid-based group, 37(56.1%) and compared during the study. In relation to participant age, the majority, 33(50%) of the patients, were aged between 21- 29 years, and over sixty percent, 42(63.6%) of participants, were females. Of all the participants, 66(100%) had a cough and chest pain, 57(86.4%) had crackles, and about ten percent, 6(9.1%) had difficulty breathing at the time of admission into the study. About 29(43.9%) of patients had a fever at baseline, and 14(21.2%) had a respiratory rate between 16 and 29 breaths per minute at baseline. **(Table 1)**

Table 1: Demographic detail and Baseline Characteristics of the patients

Variable	Total (N=66, %)	Groups	
		Oral Levofloxacin	Dual Azithromycin Plus Amoxicillin/Clavulanic acid
Age Category(years)			
<20	4(6.1%)	1(25%)	3(75%)
21-29	33(50%)	18(54.5%)	15(45.5%)
30-39	13(19.7%)	8(61.5%)	5(38.5%)
>40	16(24.2%)	10(62.5%)	6(37.5%)
Gender			
Male	24(36.4%)	14(58.3%)	10(41.7%)
Female	42(63.6%)	23(54.8%)	19(45.2%)
Fever (Axillary temperature)			

Yes	29(43.9%)	16(55.2%)	13(44.8%)
No	37(56.1%)	33(64.7%)	16(43.2%)
Difficulty in breathing			
Yes	6(9.1%)	3(50%)	3(50%)
No	60(90.9%)	34(56.7%)	26(43.3%)
Chest Pain			
Yes	66(100%)	37(66.1%)	29(43.9%)
Crackles			
Yes	57(86.4%)	34(59.6%)	23(40.4%)
No	9(13.6%)	3(33.3%)	6(66.7%)
Respiratory Rate(breaths/minute)			
16-20	52(78.8%)	30(57.7%)	22(42.3%)
21-29	14(21.2%)	7(50%)	7(50%)
WBC at first visit (x10⁹/μL)			
Visit 1	10.1±4.29	10.94± 2.93	9.03± 5.45
<6	7(10.6%)	6(85.7%)	1(14.3%)
6.1-14.9	51(77.3%)	20(39.2%)	31(60.8%)
>15	8(12.1%)	3(37.5%)	5(62.5%)
Cough at first visit			
Yes	66(100%)	29(43.9%)	37(56.1%)

Comparison of the effectiveness of Oral Levofloxacin and dual Oral Azithromycin and Amoxicillin/Clavulanic Acid in the treatment of CAP.

Comparison of time to resolution of CAP as per WBC Count between the two treatment groups

At initial visit, about 8(12.1%) had elevated WBC count (>15x 10⁹/μL) and about ten percent, 7(10.6%) had low WBC count (<6x 10⁹/μL). At visits two and three, after the treatment change, the WBC count was significantly associated with the treatment group the patient belonged to (p<0.05). At visit 2, 3(75%) of patients had elevated WBCs in the oral Levofloxacin group compared to only 1(25%) in the dual azithromycin amoxicillin/clavulanic acid group. At visit 3, one patient had elevated WBCs in the oral levofloxacin group, whereas none had elevated WBCs in the dual Azithromycin and Amoxicillin/clavulanic acid group. (Table 2)

Table 2: WBC Count during the first visit and Subsequent visits.

Variable	Groups	P Value
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	Total (N=66, %)	Oral Levofloxacin	Dual Azithromycin and Amoxicillin/Clavulanic acid	
WBC at Visit 1(x10⁹/μL)				
<6	7(10.6%)	6(85.7%)	1(14.3%)	0.062
6.1-14.9	51(77.3%)	20(39.2%)	31(60.8%)	
>15	8(12.1%)	3(37.5%)	5(62.5%)	
WBC at Visit 2(x10⁹/μL)				
<6	12(18.2%)	10(83.3%)	2(16.7%)	0.002
6.1-14.9	50(75.8%)	16(32%)	34(75.8%)	
>15	4(6.1%)	3(75%)	1(25%)	
WBC at Visit 3(x10⁹/μL)				
<6	19(28.8%)	13(68.4%)	6(31.6%)	0.016
6.1-14.9	46(69.7%)	15(32.6%)	31(67.4%)	
>15	1(1.5%)	1(100%)	0%	

P Values yielded by chi-square test of association

Comparison of time to resolution of symptoms

There was a difference in the mean time to resolution of cough and chest pain between the two treatment groups. The mean time to resolution of chest pain was 1.7 days in the dual azithromycin and amoxicillin /clavulanic acid group as compared to 2.21 days in oral levofloxacin (p=0.009). The mean time to resolution of cough was 3.71 days in the oral Levofloxacin group as compared to 3.14 days in the dual Azithromycin and Amoxicillin/clavulanic acid(p=0.014). There was no difference in the meantime to fever resolution, time to crackles subsidence, time to resolution of difficulty in breathing, or change in WBC count at visits 2 and 3 in oral levofloxacin compared to dual Azithromycin and Amoxicillin/clavulanic acid (p>0.05). (Table 3)

Table 3: Comparison of effectiveness of oral Levofloxacin and the dual Azithromycin and Amoxicillin/Clavulanic acid based on time to resolution of symptoms

	Oral Levoflox- acin Group (Mean±SD)	Dual Azithromycin and Amoxicil- lin/Clavulanic acid Group (Mean±SD)	Mean Difference (95% CI)	P value
Time to Fever resolution(days)	0.88±1.204	1.0±1.815	-0.125(-1.216- 0.966)	0.817
Time to Chest pain resolu- tion(days)	2.21±0.902	1.70±0.618	0.504(0.130-0.878)	0.009

Time to Crackles subsidence(days)	1.00±0.853	1.11±0.583	-0.114(-0.491-0.263)	0.546
Time to difficulty in Breathing resolution(days)	0.10±0.310	0.11±0.393	-0.005(-0.183-0.173)	0.958
Time to Cough resolution by day 5	3.71±0.588	3.14±0.789	0.568(0.123-1.013)	0.014
Change in WBC count at visit 2	7.53±4.072	11.18±13.31	-3.654(-8.864-1.555)	0.166
Change in WBC count at visit 3	6.84±2.93	7.69±1.53	-0.855(-1.973-0.261)	0.131

P Value yielded by independent T-test

Discussions

In the current study, females made up the majority (42, 63.5%) of the participants who had community-acquired pneumonia. The results are contrary to other studies (17) which reported that males were affected more than females (36.5% versus 76%). It should be kept in mind that participants in such studies were both hospitalised and non-hospitalised, and studies have shown that males are more likely to be admitted than females (18). Participants aged 21 – 29 years were the majority (33, 50%). (**Table 1**). This finding was unexpected since, in the last decade, most studies (19,20) have indicated that old age (>65) is associated with an increased incidence of community-acquired pneumonia. One possibility could be the presence of underlying comorbidity among participants that predisposes the young age to community pneumonia, given that HIV infections are regarded as high in the setting of the study (21). Another possible explanation is that the study period (March to December) consisted of the winter season, which is often associated with sporadic respiratory infections (22). However, it should be kept in mind that this study did not delve into microbiological aspects of CAP diagnosis nor existing comorbidities among the participants.

All patients who presented had chest pains and coughs. (**Table 1**). Similar findings have been reported by (23,24). At the time of reporting to the hospital for treatment, most participants (37, 56%) did not have fever, 60 (96.9%) did not have difficulty breathing. Fever has been reported by other authors (24) to have a positive predictive value in 57% of viral infections. The results of the current study raise the possibility of mixed microbial infections among the participants. Although cough is common in CAP, studies such as(24) have reported that the viral aetiologies of CAP are less likely to cause productive cough. The current study did not emphasise productive versus nonproductive cough, and neither was a COVID-19 test required.

When examined, the majority (57, 86.4%) of the participants had crackles (24,25), and 52 (78.8%) had a normal respiratory rate (16 – 20). The study also found that most (51, 77.3%) had a normal white blood cell count at baseline versus 8, 12.1% who presented with white blood cell count $>15 \times 10^9/\mu\text{L}$. Similar findings have been reported by other authors (23,24). The implication of this finding is that white blood count should not be relied upon as a marker in making a diagnosis of community-acquired pneumonia. Similar recommendations have been made in other studies (25).

There was a statistically significant difference between the two groups in days taken to resolve chest pain and cough. Chest pain resolved on average 1.70 days, SD=0.618 in azithromycin plus amoxicillin/clavulanic acid group versus levofloxacin group in which chest pain resolved in 2.21 days, SD=1.204 (p=0.009). Cough resolved on average 3.14 days, SD=0.709 for azithromycin plus amoxycillin/clavulanic acid group versus 3.71 days, SD=0.588 for levofloxacin group (p=0.014). There was no statistical difference between the combined azithromycin and amoxycillin/clavulanic acid versus levofloxacin group in relation to changes

in fever, crackles, difficulty in breathing and white blood cell count among the participants ($p>0.05$). (**Table 3**). Combining a beta-lactam/lactamase and a macrolide demonstrated better outcomes in the treatment of community-acquired pneumonia and appears to result in improved survival and, possibly, shorter hospital length of stay in the hospital (15,26). A possible explanation would be that combination therapy provided a broader spectrum of antimicrobial activity and offered multiple mechanisms of action for better antimicrobial coverage (27). Given that all of the participants reported chest pains and cough when they presented to the hospital at the initial visit, the implication of the current findings is that a drug(s) that can resolve the most common symptoms fastest may be appropriate in the current setting.

Conclusions

Azithromycin combined with amoxicillin/clavulanic acid reduced chest pain in 1.70 days (SD=0.618) compared to levofloxacin alone (2.21 days, SD=1.204) ($p=0.009$). Azithromycin combined with amoxicillin/clavulanic acid reduced cough in 3.14 days (SD=0.789) versus levofloxacin alone (3.70 days, SD=0.588) ($p=0.014$). There was no statistical difference between combined azithromycin and amoxicillin/clavulanic acid versus levofloxacin group in relation to change in fever, crackles, difficulty in breathing and white blood cell count among the participants with community-acquired pneumonia ($p>0.05$).

Recommendations for clinical practice

Based on these conclusions, the practitioners and policymakers should;

- I. Prioritise the use of amoxicillin/clavulanic acid combined with azithromycin in treating community-acquired pneumonia in patients who have had previous antibiotic exposure within the last three months.
- II. Not restrict the use of levofloxacin in patients who may benefit from treatment of community-acquired pneumonia, provided the possibility of tuberculosis has been ruled out.

To better understand the implications of the results in this study, future studies could address the optimal dosage for patients using the drugs in the current study.

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