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ORIGINAL ARTICLE

Pharmacoeconomic study of antibiotics used in the treatment of lower respiratory tract infections in ICU patients: A case study in an Egyptian hospital

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Abstract Community-acquired pneumonia (CAP) is a serious and widespread infection due to its high incidence, morbidity, mortality and increased healthcare costs. This study aimed at investigating antibiotic combination regimen containing fluoroquinolone (Group A) and antibiotic combination regimen not containing fluoroquinolone (Group B) in terms of effectiveness parameters and direct medical costs associated with treatment of CAP patients admitted to Intensive Care Unit (ICU). This study was designed as retrospective and prospective observational studies including CAP patients admitted to the Respiratory ICU. The patients' files were collected and the effectiveness parameters of outcomes were compared on admission and on discharge. Effectiveness and costs analyses between antibiotic regimens either containing or not containing fluoroquinolone were performed. A total of 16 patients were enrolled in our retrospective study; (Group A) included 7 patients, while (Group B) included 9 patients. The prospective study included 30 patients; (Group A) included 13 patients and (Group B) included 17 patients. There was non-significant difference in the number of days in ICU between the two groups with a trend to shorter length of stay in ICU in (Group B) compared to (Group A) in both retrospective and prospective studies. Cost analysis showed that there was non-significant difference with a trend to lower direct medical costs in (Group B) which resulted in cost savings of (L.E) 1277 and (L.E) 816 for retrospective study and prospective study respectively. In conclusion, regimens containing or not containing fluoroquinolone did not show a significant increase in either effectiveness or costs of CAP treatment in the ICU.

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1. Introduction

Community-acquired pneumonia (CAP) is a serious and widespread infection due to its high incidence, morbidity, mortality and increased healthcare costs. These factors make CAP associated with great implications for healthcare systems around

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the world especially in patients who are admitted to the intensive care unit (ICU). Mortality rates in ICU patients reached more than 50%.[1] CAP is the first common cause of death due to infectious diseases and generally the sixth leading cause of death in the United States.[1,2]

Due to the fact that causative pathogens responsible for CAP are not mostly identifiable by diagnostic tests, the empirical antibiotic treatment is applied in most cases and should target the most common typical pathogens of CAP such as (*Streptococcus pneumoniae* and *Haemophilus influenzae*) and atypical pathogens such as (*Chlamydia pneumoniae*, *Mycoplasma pneumonia*, and *Legionella pneumophila*) which account for 33% of CAP infection and are not sensitive in vitro to β-lactam.[1,3]

Recommendations for two common empirical approaches were identified: (1) β-lactam/β-lactamase inhibitor or (second- or third-generation) cephalosporin plus a macrolide; and (2) the oral respiratory fluoroquinolones.[4–6] Fluoroquinolones are an important option in the treatment of CAP due to the advantages of a wide spectrum property, high oral bioavailability, low resistance potential, efficacy and safety.[5,7] CAP patients who are treated with fluoroquinolones exhibited increased clinical response, faster resolution, greater improvement of signs and symptoms and shorter hospital stay compared to combination or nonstandardized therapies.[8]

Pharmacoeconomics is the description and analysis of the costs of drug therapy to health care systems and society. It identifies, measures, and compares the costs and consequences of pharmaceutical products and services. It measures if the added benefit of one intervention is worth the added cost of that intervention. Basic components of pharmacoeconomics are the drug product or service, costs and outcomes. If outcomes and costs are measured; but clinical outcomes are found to be equivalent (or assumed to be the same); and the costs of the alternatives are compared, then the study is cost-minimization analysis (CMA). Generally if costs are measured without regard for outcomes, it is a cost analysis (or partial economic analysis).[9]

Up-to-date there are no previous studies exploring antibiotic use and the pharmacoeconomics of CAP in ICU in Egypt. The objective of this study is to compare antibiotic combination regimen containing fluoroquinolone and antibiotic combination regimen not containing fluoroquinolone to investigate effectiveness parameters of patient outcomes to determine the efficacy or the equivalency of the two regimens and to evaluate direct medical costs associated with treatment of CAP patients in the ICU via cost analysis.

2. Subjects and methods

2.1. Study design

This study was designed as a prospective observational study. However, to ensure the possibility of conducting the study in the current hospital, we performed a similar study retrospectively using the patient records admitted to the ICU in the period from 2010 to 2011. The prospective study was conducted in the period from 2011 to 2012. All patients were admitted to the Respiratory Intensive Care Unit (RICU), Ain Shams University Hospital; Cairo; Egypt, for severe community-acquired pneumonia (CAP) and required initial intravenous therapy. Patients were divided into two groups; (Group A taking antibiotic regimen containing fluoroquinolone) and (Group B taking antibiotic regimen not containing fluoroquinolone). This study was approved by the Research Ethics Committee of Faculty of Pharmacy; Cairo University (CL 207). The attending physician was responsible for prescribing the antibiotic combination regimen in ICU and no intervention was applied because the observational nature of the study.

Inclusion criteria were: (1) adult patients 20–65 years old; and (2) patients diagnosed with community-acquired pneumonia admitted to the ICU, meeting at least one major criterion or three minor criteria of the Infectious Disease Society of America/American Thoracic Society guidelines.[10]

Patients were excluded from the study if they had one of the following exclusion criteria: (1) children, pregnant women and elderly patients over 65 years old, (2) aspiration or hospital-acquired pneumonia, (3) discharge from hospital within the previous 14 days, (4) transferred from another hospital (unless transferred within 4 h of presentation at the original hospital), (5) immunosuppressed (HIV positive or immunosuppressant therapy or concurrent chemotherapy), (6) chronic chest disease; suspected or confirmed tuberculosis; aspiration or obstructive pneumonia; cystic fibrosis or bronchiectasis, (7) concomitant infections (e.g. sinusitis, urinary tract infections), (8) acute burn injury, (9) malignancy, and (10) major gastrointestinal bleeding within three months of the current hospitalization.

2.2. Data collection and assessment

Data were collected from the patient's files for the retrospective study and all prospective patients were assessed on hospital admission, during follow-up and on hospital discharge. The following parameters were monitored and evaluated for each patient: (1) demographical data (age, gender, date of admission, date of discharge from ICU); (2) clinical symptoms and features suggesting CAP on admission (cough, fever, chest pain, dyspnea, mental confusion and aspiration); (3) clinical signs (body temperature, blood pressure, respiratory rate and heart rate); (4) comorbidities; (5) diagnostic evaluation by chest X-ray at least on admission and at day 8; (6) routine laboratory screen including Complete Blood Count (CBC), coagulation profile, Blood Urea Nitrogen (BUN), creatinine, liver enzymes including Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) and serum bilirubin; (7) arterial Blood Gases (ABG) (pH, Pao_2, Pco_2) at least once daily to detect Pao_2:Fio_2; (8) culture and sensitivity of sputum, blood, urine or bronchoalveolar lavage to diagnose etiology of pneumonia and microbiological findings; (9) prescribed antibiotic regimen (empirical and after culture therapy); and (10) length of stay in ICU and death.

2.3. Antibiotic treatment regimen evaluation

The prescribed antibiotic regimen was recorded for each patient during stay in the ICU. The empirical antibiotic therapy was prescribed during the first 24 h of an admission to the ICU without waiting of an etiologic diagnosis due to the severity of illness. We compared prescribed antibiotic combination regimens to the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) antibiotic guidelines for CAP in ICU.

2.4. Calculation of the Sequential Organ Failure Assessment score (SOFA score) on admission and on discharge

SOFA scores were evaluated and calculated on admission and on discharge for each patient with CAP admitted to the ICU to predict their outcome.[11] The total SOFA score was calculated as the sum of SOFA scores on admission and on discharge during ICU stay for each patient.

2.5. Effectiveness parameters of patient outcomes

The following effectiveness parameters of outcomes were calculated for each patient during stay in the ICU: (1) number of days in the ICU; (2) number of days on mechanical ventilator; and (3) Sequential Organ Failure Assessment score (SOFA score) on admission and on discharge. The following effectiveness parameters of outcomes were calculated for each patient during stay in the ICU: (1) number of days in the ICU; (2) number of days on mechanical ventilator; and (3) Sequential Organ Failure Assessment score (SOFA score) on admission and on discharge.

2.6. Costs calculation

Different costs were calculated during the stay of patients in the ICU as follow:

1. Costs of antibiotics = [cost of antibiotic unit × (frequency ∗ No. of days)].
2. Costs of other medications = [cost of medication × (frequency ∗ No. of days)].
3. Costs of laboratory tests = [cost of Lab tests × (frequency ∗ No. of days)].
4. Costs of other diagnostic tests = [cost of other diagnostic tests × (frequency ∗ No. of days)].
5. Total ICU costs of antibiotics, other medications, laboratory tests & other diagnostic tests per hospital stay = (cost of antibiotics + cost of other medications + cost of Lab tests + costs of other diagnostic tests).

∗ All costs are in Egyptian Pound.
∗ Estimation of all direct medical costs was similar to that estimated by Dresser et al.[12] and Samsa et al.[13]

2.7. Costs analysis

After comparison of effectiveness parameters between the two groups in the ICU, the choice of appropriate pharmacoeconomic analysis was dependent on whether the two regimens compared in the two groups were equivalent or not. Data available for the primary cost analysis in this study included all direct medical costs used in the treatment of CAP patients in the ICU in addition to number of days in ICU. The primary outcome parameter in this cost analysis is the estimated direct medical costs per patient in the two comparable groups.

2.8. Statistical analysis

Statistical analysis was performed by statistical software (GraphPad Prism version 6.02; 1992–2013 GraphPad software, Inc.). Continuous data were presented as mean ± SD or median or number (%). Mann–Whitney *U* test was performed due to the small sample size in the two groups. Categorical variables were compared using Fisher's exact test. Level of significance of 5% (p-value < 0.05) was used and the exact p-values were recorded.

3. Results

3.1. Population characteristics

3.1.1. Retrospective results

A total of 16 patients were enrolled in our retrospective study [11 males (68.75%) and 5 females (31.25%)]. Group A included 7 patients [5 males (71.4%) and 2 females (28.6%)], while Group B included 9 patients [6 males (66.7%) and 3 females (33.3%)]. The patients were admitted to the Ain Shams University hospital during the period between 2010 and 2011. The mean age ± SD was 47.71 ± 11.72 years in Group A compared to the mean age ± SD of 50.90 ± 10.87 years in (Group B). The median age of 49 years of Group A was compared statistically with the median age of 55 years of Group B. There was non-significant difference at (p-value < 0.05) in the median age between the two groups (p-value = 0.5892). Respiratory failure grade I was the most frequent comorbid condition in the two groups, with higher percentage in Group A, (71.4%) than in Group B, (66.7%).The epidemiological characteristics of the two groups are shown in (Table 1). No significant difference was found in any of the categories using the Fisher's exact test.

3.1.2. Prospective results

All patients admitted to the ICU during the study period due to CAP were screened for the study. Only 30 patients were eligible [17 males (56.7%) and 13 females (43.3%)]. Group A included 13 patients [9 males (69.2%) and 4 females (30.8%)] and Group B included 17 patients [8 males (47%) and 9 females (53%)]. The patients were admitted to the Ain Shams University hospital during the period between 2011 and 2012. The mean age ± SD was 54.61 ± 10.40 years in Group A compared to the mean age ± SD of 44.52 ± 15.90 years in Group B. The median age of 58 years in Group A was compared statistically with the median age of 51 years in Group B. Non-significant difference was obtained comparing the median age between the two groups (p-value = 0.0908). The most frequent comorbid illness in Group A was hypertension with a percentage of (53.8%) compared to Group B with pleural effusion (35.3%) as the highest comorbid illness. The epidemiological characteristics of the two groups are shown in (Table 2). Significantly more patients in the levofloxacin group were hypertensive than in the non-levofloxacin group. All other variables were not significantly different.

3.2. Microbiological diagnosis and causes of pneumonia

3.2.1. Retrospective results

Positive culture results (positive isolated pathogens) were reported in 4 (57.14%) of 7 patients in Group A. *Klebsiella pneumoniae* was the most frequently isolated etiologic agent (n = 4, 100%) in these 4 patients compared to *Pseudomonas*

Table 1 Epidemiological characteristics of retrospective patients with community-acquired pneumonia who have antibiotic combination regimens containing and not containing fluoroquinolone and admitted to the ICU.

Variable	(Group A) (regimen containing levofloxacin) ($n = 7$)	(Group B) (regimen not containing levofloxacin) ($n = 9$)	*P*-value
Age, mean years ± SD (median)	47.71 ± 11.72 (49)	50.90 ± 10.87 (55)	0.5892
Male gender	5 (71.4%)	6 (66.7%)	
Comorbidities			
Hypertension	1 (14.3%)	3 (33.3%)	0.5846
Diabetes	2 (28.6%)	2 (22.2%)	1.0000
Respiratory failure grade I	5 (71.4%)	6 (66.7%)	1.0000
Respiratory failure grade II	2 (28.6%)	1 (11.1%)	0.5500
Arterial embolism	0	2 (22.2%)	0.4750
Pleural effusion	0	1 (11.1%)	1.0000
Renal impairment	2 (28.6%)	2 (22.2%)	1.0000
Cardiac disease	1 (14.3%)	1 (11.1%)	1.0000
Subacute deep venous thrombosis (DVT)	1 (14.3%)	0	0.4375
Liver disease	1 (14.3%)	1 (11.1%)	1.0000
Rheumatoid arthritis	0	1 (11.1%)	1.0000

Note: Data are presented as mean ± SD or median or number (%) of patients, unless otherwise indicated.
Level of significance at p-value < 0.05 (Mann–Whitney test).
Fisher's exact test was done for comorbidities (data which presented as frequencies).

Table 2 Epidemiological characteristics of prospective patients with community-acquired pneumonia who have antibiotic combination regimens containing and not containing fluoroquinolone and admitted to the ICU.

Variable	(Group A) (regimen containing fluoroquinolone) ($n = 13$)	(Group B) (regimen not containing fluoroquinolone) ($n = 17$)	*P*-value
Age, mean years ± SD (median)	54.61 ± 10.40 (58)	44.52 ± 15.90 (51)	0.0908
Male gender	9 males (69.2%)	8 males (47%)	
Comorbidities			
Hypertension	7 (53.8%)	2 (11.8%)	0.0196*
Diabetes	4 (30.8%)	2 (11.8%)	0.3598
Respiratory failure grade I	4 (30.8%)	5 (29.4%)	1.0000
Respiratory failure grade II	5 (38.5%)	1 (5.9%)	0.0606
Pulmonary embolism	0	3 (17.6%)	0.2379
Arterial embolism	2 (15.4%)	0	0.1793
Pleural effusion	2 (15.4%)	6 (35.3%)	0.4069
Renal impairment	4 (30.8%)	2 (11.8%)	0.3598
Cardiac disease	4 (30.8%)	5 (29.4%)	1.0000
Liver disease	3 (23.1%)	2 (11.8%)	0.6278
Chronic calcular gallbladder stones	1 (7.7%)	0	0.4333
Prostate illness	1 (7.7%)	1 (5.9%)	1.0000
Neurological illness	0	1 (5.9%)	1.0000
Anemia	0	2 (11.8%)	0.4920

Note: Data are presented as mean ± SD or median or number (%) of patients, unless otherwise indicated.
Level of significance at p-value < 0.05 (Mann–Whitney test).
Fisher's exact test was done for comorbidities (data which presented as frequencies).
* Significant difference.

aeruginosa which was isolated only in one patient ($n = 1$, 25%). The expectorated sputum culture was done in all 4 patients who resulted in positive culture. One negative result by sputum culture was obtained in addition to three culture results in three patients that were not documented.

In (Group B), positive culture results were reported in 5 (55.6%) of 9 patients. *K. pneumoniae* was the most frequently isolated etiologic agent ($n = 3$, 60%) in these 5 patients and *S. pneumoniae* ($n = 2$, 40%) was the second isolated etiologic agent. The expectorated sputum culture was done in all 5 patients who resulted in positive culture. One negative culture result by sputum was obtained in addition to four culture results in four patients that were not documented.

3.2.2. Prospective results

Positive culture results were reported in 8 patients (61.5%) of 13 patients in Group A. Gram-negative bacilli (*E. coli*) and *S. pneumoniae* ($n = 2$, 25%) were the most frequently isolated etiologic agents in these 8 patients. The expectorated sputum was cultured in 6 (75%) of 8 patients who resulted in positive

results. Five negative results by sputum culture were obtained in addition to three culture results in three patients that were not documented. Urine culture was made in 1 patient (12.5%) of 8 patients. There was one negative result by midstream urine.

Positive culture results were reported in 11 (64.7%) of 17 patients in Group B. Of 11 patients, three patients were associated with two culture results and two isolated microorganisms and one patient had two culture results with three isolated microorganisms. *S. pneumoniae* (n = 5, 45.5%) was isolated frequently in these 11 patients. In Group B, the etiologic diagnosis was made by expectorated sputum culture in 9 (81.8%) of 11 patients. Of 9 patients, two isolated microorganisms were identified by sputum culture. Urine culture was made in two patients (18.2%) and one of them had two isolated microorganisms. Blood culture and bronchoalveolar lavage culture were made in one (9.1%) of 11 patients. Two negative results by sputum culture and one negative result by bronchoalveolar lavage were reported and there were three not documented microbiological cultures.

3.3. Antibiotic treatment regimen

The empirical choice of antibiotic combination regimen was decided by the attending physician dependent on the clinical experience and the availability of antibiotics in the hospital because there was no antibiotic policy. These antibiotic regimens were changed by the attending physician according to the culture results of each patient.

3.3.1. Retrospective results

The most common antibiotic combination regimen used in Group A was [broad-spectrum fluoroquinolone (Levofloxacin) plus advanced generation macrolide (azithromycin) (n = 2)]. While in Group B, β-lactam third generation cephalosporin (ceftriaxone) plus advanced generation macrolide (azithromycin) (n = 4) was the most frequent combination regimen used in (Group B).

3.3.2. Prospective results

The most common antibiotic combination regimen used in Group A was broad-spectrum fluoroquinolone (levofloxacin) plus advanced generation macrolide (azithromycin) (n = 5).On the other hand, β-lactam third generation cephalosporin (ceftriaxone) plus advanced generation macrolide (azithromycin) (n = 4) was the most common combination regimen used in (Group B).

In the present study, empirical antibiotic regimens used for the treatment of hospitalized patients with CAP included mostly fluoroquinolones, macrolides and β-lactams; in accordance with ICU guidelines regarding choices. On the other hand, the antibiotic combination regimens used were mostly in disagreement with ATS and IDSA guidelines.

In the retrospective study, the majority of cases in (Group A) (5 out of 7 patients) did not follow the ATS/IDSA guidelines. Antibiotic monotherapy was prescribed for only one case given ciprofloxacin 0.2 g. According to the guidelines; monotherapy was not indicated for treatment of CAP patients in ICU. The greatest proportion of Group B patients (8 out of 9 patients) did not follow the ATS/IDSA guidelines. Antibiotic monotherapy was prescribed for some patients such as (imipenem-cilastatin sodium 0.5 g monotherapy and ampicillin 1 g/sulbactam 0.5 g monotherapy).

All cases of Group A in the prospective study did not follow the ATS/IDSA guidelines. Antibiotic monotherapy was prescribed for some cases such as (ceftriaxone 1 g monotherapy, imipenem-cilastatin sodium 0.5 g monotherapy, levofloxacin 0.5 g monotherapy, piperacillin 4 g/tazobactam 0.5 g monotherapy and ciprofloxacin 0.2 g monotherapy). All patients' antibiotic prescriptions in Group B did not follow the guidelines as well. Antibiotic monotherapy was prescribed for some cases such as (ceftriaxone 1 g monotherapy, cefepime 1 g monotherapy, imipenem-cilastatin sodium 0.5 g monotherapy and meropenem 0.5 g monotherapy).

3.4. Effectiveness parameters analysis

Long length of stay (LOS) in ICU, receipt of mechanical ventilation, development of complications such as septic shock and not improved SOFA scores on discharge are associated with severity of community-acquired pneumonia and correlated with mortality.

3.4.1. Retrospective results

There was statistically non-significant difference at p-value < 0.05 between both groups in the number of days in ICU (p-value = 0.0580), in SOFA score on admission (p-value = 0.1779) and in SOFA score on discharge (p-value = 0.3881) (Fig. 1). One patient in (Group B) received mechanical ventilation and died. In contrast, there were no ventilated patients and no deaths in (Group A) (Table 3). The difference was not statistically significantly different.

3.4.2. Prospective results

The results in (Table 4) revealed that there was statistically non-significant difference between both groups in number of days in ICU (p-value = 0.1712) and in SOFA score on discharge (p-value = 0.2444), but there was significant difference in SOFA score on admission (p-value = 0.0193) (Fig. 2). There was one patient who received mechanical ventilation in Group A compared to 6 patients who were mechanically ventilated in Group B. There was higher mortality in Group

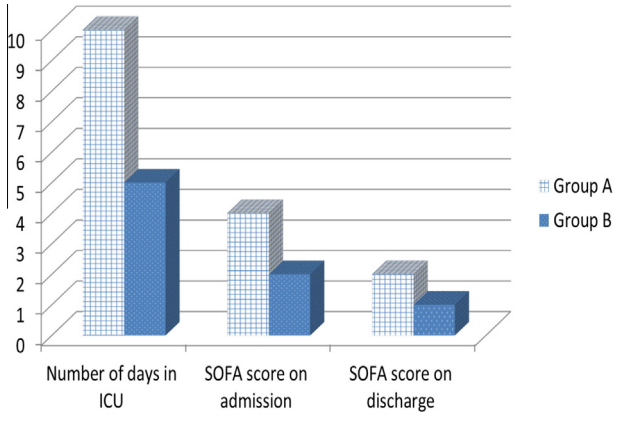

Figure 1 The difference of medians of effectiveness parameters between (Group A) and (Group B) retrospective patients. Non-significant difference at p < 0.05 (Mann–Whitney test).

Table 3 Medians of effectiveness parameters and factors associated with severity of community-acquired pneumonia for (Group A) and (Group B) retrospective patients.

Parameter	(Group A) (regimen containing fluoroquinolone) (n = 7)	(Group B) (regimen not containing fluoroquinolone) (n = 9)	P-value
Number of days in ICU	10	5	0.0580
SOFA scores on admission	4	2	0.1779
SOFA scores on discharge	2	1	0.3881
Number of patients who received mechanical ventilation	0	1 (11.1%)	1.0000
Number of deaths in ICU (arrest)	0	1 (11.1%)	1.0000
Other complications			
Septic shock (need for vasopressor)	0	1 (11.1%)	
Post arrest	0	1 (11.1%)	

Level of significance at p-value < 0.05 (Mann–Whitney test). Fisher's exact test was done for data which presented as frequencies.

Table 4 Medians of effectiveness parameters and factors associated with severity of community-acquired pneumonia for (Group A) and (Group B) prospective patients.

Parameter	(Group A) (regimen containing fluoroquinolone) (n = 13)	(Group B) (regimen not containing fluoroquinolone) (n = 17)	P-value
Number of days in ICU	15	11	0.1712
SOFA scores on admission	3	2	0.0193*
SOFA scores on discharge	2	1	0.2444
Number of patients who received mechanical ventilation	1 (7.7%)	6 (35.3%)	0.1038
Number of deaths in ICU (arrest)	0	4 (23.5%)	0.1129
Other complications			
Septic shock (need for vasopressor)	0	4 (23.5%)	
Post arrest	0	4 (23.5%)	

Level of significance at p-value < 0.05 (Mann–Whitney test). Fisher's exact test was done for data which presented as frequencies.
* Significant difference.

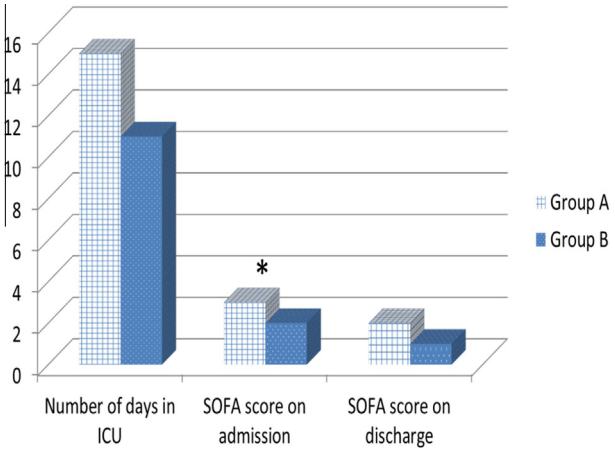

Figure 2 The difference of medians of effectiveness parameters between (Group A) and (Group B) prospective patients. Non-significant difference at p < 0.05 in number of days in ICU and SOFA score on discharge; * significant difference at p < 0.05 in SOFA score on admission (Mann–Whitney test).

B (4 deaths) compared to none in Group A. This difference was not statistically significantly different.

3.5. Cost calculation and analysis

ICU costs of feeding (food and fluids) were reported by the hospital to be 37.67 L.E/day while staff wages in the ICU were 2816.7 L.E/day. Because of costs of feeding and wages were similar in all patients in both groups, ICU costs of feeding and wages per hospital stay can be calculated dependent on number of days in ICU for each patient.

Since comparison of effectiveness parameters between the two groups in ICU showed no significant differences, cost-minimization analysis (CMA) was chosen to analyze cost data dependent on the equivalency of the two regimens containing and not containing fluoroquinolone. The data available for the primary economic analysis (cost-minimization analysis) in this study included all direct medical costs which were used in the treatment of CAP patients in the ICU in addition to number of days in ICU.

3.5.1. Retrospective results

There was no statistically significant difference between the two groups at p-value < 0.05 in the median total ICU costs per hospital stay (p-value = 0.1413) and in medians of costs of antibiotics (p-value = 0.2509), costs of medications other than antibiotics (p-value = 0.2096), costs of feeding (p-value = 0.0580) and costs of wages (staff) (p-value = 0.0580).

Table 5 The median total and treatment costs of CAP patients in ICU for (Group A) and (Group B) retrospective patients.

Cost parameter	Group A	Group B	*P*-value
Total ICU costs per hospital stay	2688	1411	0.1413
Costs of antibiotics	1098	575.1	0.2509
Costs of medications other than antibiotics	913.8	174.7	0.2096
Costs of Lab and diagnostic tests	616	426	0.0392*
Costs of feeding	376.7	188.4	0.0580
Costs of wages (staff)	28,167	14,084	0.0580

Level of significance at p-value < 0.05 (Mann–Whitney test).
Total ICU costs per hospital stay excluding costs of wages (staff) and feeding.
* Significant difference.

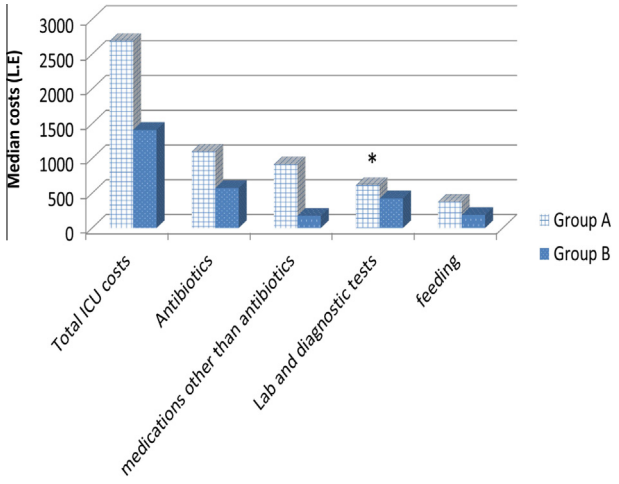

Figure 3 The difference of median total and treatment costs of CAP patients in ICU between (Group A) and (Group B) retrospective patients. Non-significant difference at $p < 0.05$ in the median of total ICU costs and median costs of antibiotics, medications other than antibiotics, feeding and wages; * significant difference at $p < 0.05$ in median costs of Lab and diagnostic tests (Mann–Whitney test).

Table 6 The median total and treatment costs of CAP patients in ICU for (Group A) and (Group B) prospective patients.

Cost parameter	Group A	Group B	*P*-value
Total ICU costs per hospital stay	4408	3592	0.4535
Costs of antibiotics	2857	1980	0.3571
Costs of medications other than antibiotics	573.5	431.1	0.8937
Costs of Lab and diagnostic tests	1067	866	0.6577
Costs of feeding	565.1	414.4	0.1712
Costs of wages (staff)	42,251	30,984	0.1712

Level of significance at p-value < 0.05; (Mann–Whitney test).
Total ICU costs per hospital stay excluding costs of wages (staff) and feeding.

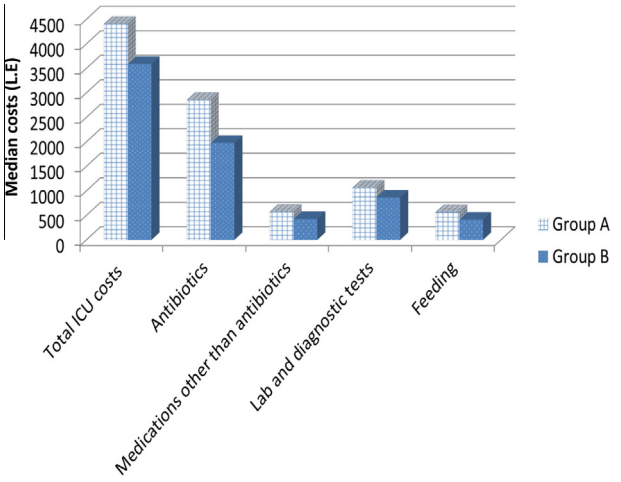

Figure 4 The difference of median total and treatment costs of CAP patients in ICU between (Group A) and (Group B) prospective patients. Non-significant difference at $p < 0.05$ (Mann–Whitney test).

In contrast, significant difference was obtained between the two groups at (p-value < 0.05) in the median costs of laboratory and diagnostic tests (p-value = 0.0392) (Table 5) and (Fig. 3).

3.5.2. Prospective results

Statistically non-significant difference was obtained between the two groups in the median total ICU costs per hospital stay (p-value = 0.4535) and in medians of costs of antibiotics (p-value = 0.3571), costs of medications other than antibiotics (p-value = 0.8937), costs of laboratory and diagnostic tests (p-value = 0.6577), costs of feeding (p-value = 0.1712) and costs of wages (staff) (p-value = 0.1712) (Table 6) and (Fig. 4).

4. Discussion

In the current study, we compared antibiotic combination regimen containing fluoroquinolone (Group A) to antibiotic combination regimen not containing fluoroquinolone (Group B) in terms of effectiveness parameters and cost analysis since this has never been documented before in any Egyptian hospital. The two groups were not statistically significantly different in efficacy and direct medical costs associated with treatment of CAP patients in ICU.

This study focused on fluoroquinolones for the following reasons: (1) fluoroquinolones are included as an important treatment option in the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) guidelines for treatment of CAP patients in ICU[10,14]; (2) they have a number of advantageous pharmacokinetic properties, including high penetration into the lung and high oral bioavailability, and a good safety profile.[7] In addition to these advantages of fluoroquinolones, there was lower resistance potential than other β-lactams and especially macrolides. For this reason, the Centers for Disease Control and Prevention recommend reserving fluoroquinolones in CAP for patients at risk for resistant pneumococcal infections.[7,15] Fluoroquinolones (for example, levofloxacin) have been also associated

with increased clinical response, faster resolution, greater improvement of signs and symptoms and shorter hospital length of stay compared to non-standardized treatment.[8]

Patients hospitalized with CAP especially those admitted to the ICU with multidrug resistant (MDR) pathogens require empiric intravenous broad-spectrum antibiotic therapy to provide appropriate initial atypical coverage.[16] Empirical antibiotic therapy including macrolides (in combination with a cephalosporin) or fluoroquinolones (levofloxacin) provide an increased importance in reducing hospital length of stay (LOS) and mortality.[12,13,17] Respiratory fluoroquinolones (such as levofloxacin) should be regarded as appropriate first-line antimicrobials for the monotherapeutic treatment of CAP in outpatients and hospitalized patients, as well as in combination with β-lactam antibiotics in those patients requiring ICU admission. Respiratory fluoroquinolones are considered the only antimicrobials that are highly active against *S. pneumoniae*, including macrolide-resistant and penicillin-resistant strains, *H. influenzae*, *Legionella* spp., and atypical pathogens.[7]

It is clear that the hospital did not follow the ATS/IDSA guidelines and this may be associated with negative impact on length of stay in ICU, microbial resistance and costs of hotel and antibiotics.

Effectiveness parameters and direct medical costs used to compare treatments in both retrospective and prospective phases of the study did not differ significantly. The sample size included in the two groups is too small to derive a statistically significant difference. This small number is due to the fact that in one hospital the number of patients with severe CAP requiring ICU admission is usually low. This was evident from the retrospective screening study and in other international studies.[18]

Data from the retrospective study showed that the median number of days in ICU between both groups was non-significantly different with a 5-day reduction in the median length of stay in the non-fluoroquinolone group (Group B) compared to the fluoroquinolone group (Group A). In addition, there was non-significant difference between the two groups in SOFA score on admission and on discharge indicating that the two regimens compared in the two groups were clinically equally efficacious. Due to the small sample size, occurrence of mechanical ventilation and death was not statistically comparable and we could not judge if this difference is due to fluoroquinolones or not. Total median ICU costs per hospital stay between the two groups were statistically insignificantly different as well with cost difference of (L.E) 1277 with a trend to lower costs in the non-fluoroquinolone group (Group B).

In the prospective study, the median number of days in ICU did not differ significantly between the two groups with a 4-day reduction in the median length of stay in the non-fluoroquinolone group (Group B). There was significant difference in SOFA score on admission but non-significant difference in SOFA score on discharge. However, the median scores for both groups were 3 and 2 which are not clinically significantly different, since all patients in all groups did not exceed a score of 9 on admission.[11] Even though there was one patient who received mechanical ventilation with no deaths in (Group A), there were 6 patients who were mechanically ventilated with 4 deaths in (Group B). Total median ICU costs per hospital stay between the two groups were statistically non-significantly different with cost difference of (L.E) 816 with a trend to lower costs in the non-fluoroquinolone group (Group B).

Overall there was no death in patients receiving levofloxacin and only one patient received mechanical ventilation but due to the small sample number the difference was not found to be statistically significantly different.

The major findings of the present costs analysis are: (1) the major contributors to the medical direct costs were treatment costs, hotel and medical staff costs; (2) the major determinant of direct medical costs included in the treatment of CAP hospitalized patients was length of stay (LOS) in ICU. Hospital (LOS) considered a significant cost factor in treating CAP hospitalized patients and may contribute to higher costs especially in the ICU.[19] Consistent with our analysis, Bauer et al.[18] identified the length of stay and ICU admission as the two most important single predictors of resource utilization in the treatment of CAP hospitalized patients.

Average LOS of 12.59 days in the present study was longer than average LOS of less than 1–5 days reported in the literature.[8,18] The longer LOS may be attributed to the non-adherence to the ATS/IDSA guidelines. If the hospital follows these guidelines or its own guidelines, possibly there will be faster improvement of signs and symptoms, lower microbial resistance; consequently lower length of stay in ICU and lower costs of hotel and antibiotics.

Comparing the results of the present study to the literature showed that our results were in accordance with Samsa et al.[13], Bauer et al.[18] and Drummond et al.[8] who showed that there was non-significant difference in both efficacy and direct medical costs associated with treatment of hospitalized CAP patients; while Dresser et al.[12] and Torres et al.[20] agreed with our effectiveness parameter results and revealed that there was non-significant difference in the efficacy between the two groups.

Samsa et al.[13] showed that there was a longer hospital stay in levofloxacin group patients compared to azithromycin group patients who experienced a shorter hospitalization with a 1.8-day reduction in the average length of stay than the levofloxacin group and revealed that there was non-significant difference in clinical success rates (i.e. similar clinical success rates defined as cured and improved). They also concluded that there was a trend to lower direct medical costs associated with the azithromycin group than the corresponding costs in the levofloxacin group and this non-significant difference in costs resulting from the 1.8-day reduction in the average length of stay.

In addition, Bauer et al.[18] concluded that there was a little tendency to high clinical efficacy with initial antibiotic therapy with moxifloxacin compared to non-standardized therapy but did not differ significantly. Also, there was non-significant difference but a trend to lower direct medical costs in the moxifloxacin cohort compared to the non-standardized treatment group. A trend to lower costs in the moxifloxacin cohort may be also because of the lower number of patients in addition to monotherapy treatment. They also reported that mortality was significantly higher in the non-standardized antibiotics cohort compared to the moxifloxacin cohort and this higher mortality may be due to the fact that there were more severe cases enrolled in the non-standardized antibiotics cohort. However, mechanical ventilation and mortality could not be statistically compared in the present study.

Drummond et al.[8] also reported that effectiveness parameters (clinical cure rate) although in favor of moxifloxacin were not statistically significantly different between both groups. They also demonstrated that empirical treatment with sequential IV/oral moxifloxacin monotherapy is less costly relative to IV/oral co-amoxiclav with or without clarithromycin and the treatment with moxifloxacin is likely to result in cost savings per additional patient cured to health care payers which is mainly due to the shorter length of stay; but they showed that cost savings associated with moxifloxacin also did not reach statistically significance levels due to the higher variability of cost data. Dresser et al.[12] concluded that clinical outcomes analysis in terms of (clinical cure rate, microbiological eradication rate and treatment failure) were not powered to demonstrate a statistically significant difference, but did show a trend toward improved clinical outcomes with fluoroquinolone (gatifloxacin) monotherapy. Torres et al.[20] also concluded that sequential intravenous and oral moxifloxacin monotherapy was non-inferior to a combination of intravenous ceftriaxone plus sequential intravenous and oral levofloxacin for the treatment of hospitalized patients with CAP III–V. There was a good correlation between clinical cure and bacteriological success, and both regimens were safe and well tolerated.

On the other hand, Finch et al.[21] and File et al.[22] disagreed with our effectiveness parameter results and showed that there was significant difference in the efficacy between both groups; while Dresser et al.[12] disagreed with our cost analysis results and concluded that there was significant difference in the costs between the two comparable groups.

Finch et al.[21] concluded that monotherapy with moxifloxacin is superior (statistically significant higher clinical success rates, significantly faster resolution of fever, lower duration of hospital admission, fewer deaths and fewer serious adverse events) to that with a standard combination regimen of a β-lactam and a β-lactamase inhibitor, co-amoxiclav, with or without a macrolide, clarithromycin, in the treatment of hospitalized CAP patients. File et al.[22] who compared IV and/or oral levofloxacin monotherapy versus IV ceftriaxone and/or oral cefuroxime axetil with or without erythromycin or doxycycline in hospitalized CAP patients also showed that there was a statistically significant difference in the clinical success rate in favor of levofloxacin. In addition, Dresser et al.[12] cost analysis offers further evidence that fluoroquinolone (gatifloxacin) monotherapy is a cost-effective alternative with lower medical costs including drug costs and non-drug costs over the standard regimen of IV ceftriaxone with or without an IV macrolide.

5. Conclusion

In conclusion, despite the fact that there was non-significant difference in the number of days in ICU and the overall costs between the two groups, there was a trend toward shorter length of stay in ICU and lower medical costs in the non-fluoroquinolone group in both retrospective and prospective studies. The length of stay in ICU in this Egyptian hospital for CAP patients was on average longer than previous international studies. The hospital did not adopt any antibiotic policies which could be partly the cause of the longer length of stay. Further future multicenter clinical trials on a larger sample size are required to investigate the effectiveness and costs analysis of antibiotics used for the treatment of CAP in the ICU in Egypt. Proper antibiotic policies should be adopted and implemented to be able to provide a higher level of healthcare.

6. Conflict of interest

We have no conflict of interest to declare.

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