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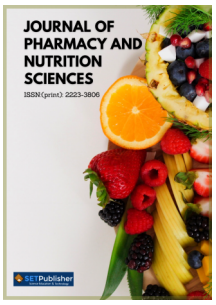

Therapeutic Effectiveness of Cefoperazone for Community-Acquired Pneumonia and Associated Factors in a Tertiary Care Hospital, Vietnam

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Abstract:

Purpose: This study aimed to (i) identify the pathogenic bacterial profile and Cefoperazone (CPZ) sensitivity; (ii) assess the therapeutic effectiveness of CPZ and (iii) determine factors associating with the treatment success.

Patients and methods: The retrospective study was conducted in Kien Giang hospital, Vietnam. Sample size was 210 medical records of community-acquired pneumonia (CAP) patients admitted to the hospital from January to December 2018. The Chi square and Fisher's exact test were used to determine factors associating with the treatment success such as age, gender, comorbidities, levels of CAP severity respiratory rate, PaO2, and laboratory findings of blood tests. Statistical significance was at level $\alpha = 0.05$.

Results: The main pathogenic bacteria were Klebsiella pneumoniae (29.1%), Streptococcus pneumoniae (26.7%) and Pseudomonas aeruginosa (14%), and were highly susceptible to CPZ. Mean duration of obtaining clinical stability was 3.01 days. The obtainment of clinical stability through CPZ monotherapy on the third, fifth and seventh day of treatment process accounted for 78.9%, 87.6% and 100% of total cases, respectively. CPZ achieved a highly successful rate in the monotherapy (79.07%) if the treatment was guided by antibiotic sensitivity testing results. The association between the treatment success and factors such as age, respiratory rate, and severity category of CAP were statistically significant ($p<0.05$).

Conclusion: Minimizing CPZ resistance, and CPZ overuse during CAP therapy is necessary. The factors associating with the success of therapy are useful in predicting the prognosis of CAP patients, planning the sequential therapy, and determining hospital discharge.

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common infectious disease and also one of the leading causes of death among the elderly with comorbid diseases [1]. In the United States, more than 5 million CAP cases occur annually, and the cost of treatment for CAP is estimated at greater than $12 billion annually [2]. One of the reasons for the increased cost of CAP treatment is the ineffective choice of antibiotic therapy, resulting from empirical therapy without detecting pathogens and determining the antibiotic susceptibility of bacteria [3]. Common CAP causative bacteria involve Gram-positive cocci and Gram-negative bacteria such as *Streptococcus pneumoniae, Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa* [4,5]. For treating CAP in Vietnam, public hospitals have been using antibiotics in the third generation Cephalosporin groups such as Ceftazidime and Ceftriaxone. Furthermore, Cefoperazone (CPZ) is also recommended in the treatment of CAP because this third-generation Cephalosporin antibiotic has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria[6,7]. In Taiwan, Jien WL *et al*. have assessed the clinical effect of the combination drug therapy of CPZ-Sulbactam to be active against commonly encountered multidrug-resistant pathogens for hospital-acquired pneumonia (HAP) and healthcare-associated pneumonia [6-8]. However, CPZ monotherapy recently has been used to treat HAP and CAP in Vietnam, but the therapeutic effect of CPZ monotherapy has not been published [9]. In 2018, nearly 1,000 patients diagnosed with CAP were hospitalized and treated with CPZ monotherapy in Kien Giang tertiary care hospital. A comprehensive analysis of available data is necessary and useful to explore the features of pathogens and evaluate the effectiveness of CPZ monotherapy. Therefore, this retrospective study aimed to (i) identify bacterial pathogens and their antibiotic susceptibility to CPZ, (ii) assess the therapeutic effectiveness of CPZ monotherapy, and (iii) determine factors related to the treatment success among hospitalized CAP patients at the Department of General Internal Medicine in Kien Giang tertiary care hospital, Vietnam

MATERIAL AND METHODS

A retrospective study was used to analyze medical records of patients diagnosed with CAP who were admitted to the Department of General Internal Medicine of Kien Giang Tertiary Hospital from January 2018 to December 2018. The total population sampling was applied.

Inclusion criteria: patient's medical records having ICD-10 diagnosis codes (International Classification of Diseases, Tenth Revision) from J12 to J18 (Diagnosis of CAP) and treatment with CPZ from hospital admission to discharge or death or referral. Age ≥ 18 years olds due to hospital admission only for adults.

Exclusion Criteria

- Coexistence with the following diseases or condition could cause biased outcome evaluations such as
    - Acquired pulmonary tuberculosis, pulmonary cancer, pulmonary infarction, and HIV infection.
    - Undergoing chemotherapy.
- Pneumonia was diagnosed 48 hours after admission: hospital-acquired pneumonia or healthcare-acquired pneumonia.
- Loss of treatment follow-up information from admission to discharge: referrals from other departments or from other hospitals, and discharge without hospital permission

After the screening process, there were 210 medical records to satisfy the criteria. Access to data of medical records was allowed by the board of directors of Kien Giang Tertiary Hospital. The research tool for data collection was approved by the Research Ethics Council of the HCM City University of Medicine and Pharmacy (Number: 017 - 173 / DD-YD issued on December 22, 2017).

Evaluation of the Effectiveness of CPZ Monotherapy

The initial CPZ therapy depended on the result of CPZ susceptibility of causative bacteria [9].The effectiveness of CPZ was evaluated based on the therapeutic response on the 5th day of the treatment process as follows[10,11].

- Body temperature ≤ 37.8 ° C during 48 hours
- Only one sign showing clinical instability such as systolic blood pressure ≤ 90 mm Hg, respiratory rate > 24 breaths/min, heart rate > 100 beats/min, oxygen saturation pressure (SpO_2) < 90%, or arterial oxygen partial pressure (PaO_2) < 60 mm Hg.

Table 1: Elements of CURB-65 Score and Risk Stratification for Pneumonia

CURB-65	Clinical feature	Point
(C)	Confusion	1
(U)	BUN > 7 mmol/L or 20 mg/dL	1
(R)	Respiratory rate ≥ 30 breaths/min	1
(B)	Systolic BP< 90 mmHg Diastolic BP ≤ 60 mmHg	1
(65)	Age ≥ 65	1
Total CURB-65 score	**Risk group**	**Management**
0-1	1	Low risk, home treatment
2	2	Moderate risk, hospital admission
3-5	3	High risk, manage in hospital as severe pneumonia

Note: BUN (Blood Urea Nitrogen); BP (Blood Pressure).

The result of treatment that satisfies these criteria can conclude success or achieve therapeutic effectiveness.

Factors Associated with the Therapeutic Effectiveness of CPZ

According to Table **1**, CAP severity was determined by the British Thoracic Society's CURB-65 score, which consists of 5 risk factors: new onset of confusion, blood urea nitrogen (BUN) >7 mmol/L or 20 mg/dL, respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg or diastolic ≤ 60 mmHg, and age ≥ 65 years. Each risk factor scores one point, and the CURB-65 scores range from 0 to 5. The interpretation of CURB-65 scores is as follows: (i) 0-1 point: probably suitable for home treatment or outpatient care; low risk of death; (ii) 2 points: consider hospital supervised treatment or hospital admission; moderate risk of death. (iii) ≥ 3 points: manage in hospital as severe pneumonia; high risk of death; Intensive Care Unit (ICU) admission with a score from 4 to 5 [1,12]. Factors related to the therapeutic effectiveness of CPZ include the severity category of CAP based on CURB-65, comorbid chronic diseases, respiratory rate, PaO2, and laboratory findings of blood tests such as BUN, Creatinine, Albumin, and C- reactive protein (CRP).

Data Analysis

Data analysis was done with IBM SPSS statistical software 20. Results of descriptive statistics were frequencies and percentages to give the proportions of pathogens, CPZ susceptibility to pathogens, and therapeutic effectiveness. A Chi-square test was used to determine factors related to therapeutic effectiveness. The odds ratio (OR) and corresponding 95% confidence interval (CI) for each variable were calculated. A P-value less than 0.05 was considered statistically significant.

RESULTS

Patient's Characteristics

The study involved 210 inpatients' medical records that were diagnosed with CAP. Among them, 153 cases (72.9%) were ≥ 65 years old; 91 (43.3%) were men, and 119 (56.7%) were women. The mean age of the cases was 70.6 ± 15.1 years.

Bacterial Pathogens and Sensitivity to CPZ

The analysis of medical records revealed that 142/210 cases (67.6%) had the bacterial sputum culture for the identification of bacterial pathogens, and 86 cultured samples were positive. The result of antimicrobial susceptibilities of CPZ is shown in Table **2**. The rates of CAP cases caused by *Klebsiella pneumoniae* and *Streptococcus pneumoniae* were 29.1% and 26.7%, respectively. Next, *Pseudomonas aeruginosa* accounted for 14% of cases. Moreover, *K. pneumoniae, S. pneumoniae and P. aeruginosa* were highly susceptible to CPZ, and susceptibility rates accounted for 88%, 82.6%, and 83.3%, respectively.

Therapeutic Effectiveness of CPZ for CAP Patients

CPZ therapy of 210 CAP cases involved monotherapy for 161 cases (76.6%) and combination therapy for 49 cases (23.4 %). Temperature and signs of clinical

Table 2: Identified Bacterial Pathogens and Antimicrobial Susceptibilities of CPZ

Pathogens	N (%)	Susceptibilities of CPZ (%)
Klebsiella pneumoniae	25 (29.1)	22/25 (88)
Streptococcus pneumoniae	23 (26.7)	19/23 (82.6)
Pseudomonas aeruginosa	12 (14)	10/12 (83.3)
Staphylococcus spp	11 (12.8)	6/11 (54.5)
Escherichia coli	5 (5.8)	4/5 (80)
Enterobacter aerogenes	5 (5.8)	4/5 (80)
Acinetobacter baumannii	3 (3.5)	2/3 (66.7)
Citrobacter freundii	2 (2.3)	1/2 (50)
Total positive-cultured samples	86	

instability were recorded over the days of treatment and are shown in Table **3**.

The proportions of cases that showed clinical stability by CPZ monotherapy on the third, fifth and seventh day of treatment were 78.9%, 87.6%, and 100%, respectively. The mean duration of clinical stability was 3.01 days.

The CPZ therapy achieved a high success rate (72.1%). Compared with total CPZ susceptibility cases to CAP- causative bacteria, the success rate was higher with 56/68 = 82.3 % (Table **4**).

Factors Affecting the Therapeutic Effectiveness

Table **5** shows that age, respiratory rate, and severity category of CAP are significantly associated with the therapeutic effectiveness ($p < 0.05$).

In terms of age, patients under 65 were 4.4 times more likely to achieve treatment effectiveness than patients ≥ 65 years old ($p=0.034$). With respect to respiratory rate, patients with a normal rate were 91 times more likely to achieve therapeutic effectiveness than patients with an abnormal rate ($p = 0.0001$). For patients with varying levels of CAP severity, the odds of achieving therapeutic effectiveness between mild, moderate, and severe categories were statistically significantly different ($p = 0.001$).

DISCUSSION

Among 142 cultured - CAP samples, 86 samples were culture-positive. The prevalence of CAP due to gram-negative bacteria accounted for 60.5%, higher than the rate of CAP due to gram-positive bacteria with 39.5%. In our study, the elderly ≥ 65 years old accounted for

Table 3: Proportion of the Patient's Clinical Stability by CPZ Monotherapy

Signs	Day 2 n(%)	Day 3 n(%)	Day 5 n(%)	Day 7 n(%)
Body temperature ≤ 37.8^{0}C during 48 hours	120 (74,5)	155 (96,2)	161 (100)	161 (100)
Only one sign of clinical instability related to CAP	106 (65,8)	127 (78,9)	141 (87,6)	161 (100)
Clinical stability	106 (65,8)	127 (78,9)	141 (87,6)	161 (100)

Mean time achieving clinical stability= 3.01 days.

Table 4: Outcomes of CPZ in CAP Treatment Based on Antibiotic Sensitivity Testing Results

CPZ therapy based on CPZ's susceptibility to bacteria	Therapeutic results		Total n(%)
	Success n(%)	Failure n(%)	
Yes	56 (65.12)	12 (13.95)	68 (79.07)
No	6 (6.98)	12 (13.95)	18 (20.93)
Total	62 (72.10)	24 (27.90)	86 (100)

Table 5: Factors Associated with Therapeutic Effects on the 5th Day

Factors	Therapeutic effectiveness			OR	*p*
	Yes	No			
Age	N(%)	N(%)	Total n(%)	4.4 (1.0-20.0)	0.034
<65 years	43(95.6)	2 (4.4)	*45 (100)*		
≥ 65 years	96 (82.8)	20 (17.2)	*116 (100)*		
Gender				1.82 (0.70-4.76)	0.212
Male	64 (90.1)	7 (9.9)	*71(100)*		
Female	75 (83.3)	15 (16.70	*90(100)*		
Myocardial ischemia				9 (0.69-116.2)	0.053
Yes	27 (81.8)	6 (18.2)	*36(100)*		
No	1(33.3)	2 (66.7)	*3(100)*		
Hypertension				9.18 (1.17-71.7)	0.061
Yes	101 (88.8)	11 (11.2)	*112 (100)*		
No	2 (50)	2 (50)	*4(100)*		
Albumin (g/L)				1.12 (0.237-5.303)	0.622
Normal (35-50)	14 (87.5)	2 (12.5)	16 (100)		
Abnormal	125 (86.2)	20 (13.8)	145 (100)		
BUN (mmol/L)				1.065 (0.427-2.657)	1
Normal (2,7-7,5)	59 (86.8)	9 (13.2)	68 (100)		
Abnormal	80 (86)	13 (14)	93 (100)		
Creatinin (mmol/L)				2.58 (0.63-10.6)	0.173
Normal	131 (87.3)	19 (12.7)	150 (100)		
Abnormal	8 (72.7)	3 (27.3)	11 (100)		
CRP (mg/L)				0.21 (0.033-1.33)	0.129
Normal (<5mg/L)	3 (60)	2 (40)	5 (100)		
Abnormal	136 (87.7)	19 (12.3)	155 (100)		
PaO_2				2.48 (0.31-19.85)	0.698
Normal(80-100 mmHg)	14 (93.3)	1(6.7)	15 (100)		
Abnormal	124 (84.9)	22 (15.1)	146 (100)		
Respiratory rate(breaths/minute)				91.12 (23.89-347.4)	0.0001
Normal (18-20)	134 (96.4)	5(3.6)	139 (100)		
Abnormal	5 (22.7)	17 (77.3)	22 (100)		
Severity categories of CAP					0.001
Mild	36 (94.7)	2 (5.3)	38 (100)		
Moderate	96 (87.3)	14 (12.7)	110 (100)		
Severe	7 (53.8)	6 (46.2)	13 (100)		

Note: BUN (blood urea nitrogen); CRP (C-reactive protein).

72%. Therefore, the study on the elderly in Beijing, China, conducted by Ying Luan *et al*. and our study has similar results that Gram-negative bacteria are the main pathogenic bacteria in older patients acquiring CAP [13]. In terms of etiology, *K. pneumoniae* CAP in this study accounted for the highest prevalence rate of 29.1%, higher than the rate of 23% in Malaysia / Singapore, and the rate of 13% -18% in Thailand [13].

Over the past two decades, K. pneumoniae has become one rare cause of CAP in North America, Europe, and Australia. However, it remains an important cause of CAP in Asia [14]. An increase in the incidence of *K. pneumoniae* CAP in Asia could reflect the effect of different environmental conditions on transmission, or it could be an increase in the frequency of host factors such as abnormal nutritional status, comorbidities, or genetic background that can facilitate *K. pneumoniae* infection. In these regions, patients also have a classic risk factor of alcoholism because *K. pneumoniae* is traditionally associated with alcoholism [15]. After *K.pneumoniae*- CAP, the second-ranked prevalence rate was *S.pneumoniae* - CAP, accounting for 26.7%. This rate is consistent with prevalence rates in the United States, Hong Kong, and Thailand, with rates ranging from 26% - 41%, 22% - 30%, and 20% - 31%, respectively [14]. This study showed that the etiology of CAP has been changing. *S. pneumoniae* is not still the most frequently identified pathogenic bacteria in adults, similar to Malaysia / Singapore and Thailand [14]. Next, the third-ranked prevalence of *P.aeruginosa*-CAP accounted for 14% of culture-positive CAP. This rate is lower than a 19% prevalence of *P.aeruginosa* in hospitalized patients with CAP in the United States [16]. However, it is higher than a 2.2% prevalence among patients with positive cultures in Europe [17] and a 0.4% prevalence of adult patients with CAP in the United States [18]. Variations in the prevalence rates reported by different studies may be explained by differences in study design and different environments (i.e., single hospital, region, country, or continent) with specific differences in healthcare delivery, including antibiotic availability and policies for antimicrobial use [19].

In terms of antimicrobial properties, CPZ has a broad spectrum of activity against gram-negative bacteria and gram-positive cocci. Our results showed that CPZ alone showed good activity against most species of *K.pneumoniae, E.coli,* and *P.aeruginosa* with antimicrobial susceptibility rates of 88%, 80 %, and 83.3, respectively. In our study, the antimicrobial susceptibility rate of CPZ is higher than the rates of CPZ against *K.pneumoniae* (64.9%) and *P.aeruginosa* (75.8%) in Taiwan [20]. In China, drug susceptibilities of major gram-negative bacteria to CPZ were also lower such as *K.pneumoniae* with 56.3%, *E.coli* (42.9%), and *P.aeruginosa* (71.4%) [13]. This means that CPZ is highly susceptible to the main pathogenic bacteria (Gram-negative bacteria) among older CAP cases in Vietnam. This can be explained by not abusing CPZ in the treatment of CAP.

Regarding the therapeutic effectiveness of CPZ monotherapy, the success rate of treatment based on the antibiotic sensitivity testing results accounts for 65.12% (56/86 cases), higher than the rates of 50% and 35.5% of 2 studies conducted in Vietnam [21, 22]. The reason can be explained that the isolates are still very sensitive to CPZ due to the less common use in primary care settings and the high prevalence of CPZ-sensitive Gram-negative bacteria in the study samples. The mean time to achieve clinical stability is 3.01 days. Compared with a study on nursing home-acquired pneumonia in the USA, the mean time of therapy effectiveness is 10.75 days [23]. The difference in the mean time of effective treatment may originate from the different proportions of older adults over 65 years of age, common isolates from samples, and rates of comorbidities. The proportion of patients achieving clinical stability on day 3 of treatment was 78.9%, on day 5: 87.6%, and on day 7: 100% of total cases were treated with the CPZ monotherapy. Our result is slightly higher than the results of the study conducted by Halm *et al*. (3rd day: 77%, 4th day: 86%) [24], clearly higher than the study by Rosario *et al*. (58.2% on day 4) [25].The significant difference could be explained due to reasons: (1) Rosario chose ≤ 37.2 C instead of ≤ 37.8 C as a determining factor of clinical stability, (2) their patients were older and more severely ill than our patients. This indicates that the patient responded well to the CPZ monotherapy in our study. Regarding factors affecting the therapeutic effectiveness, the Chi-square test showed that three factors associated with the effectiveness of CPZ monotherapy, including the age of patients, respiratory rate, and severity categories of CAP classified by the British Thoracic Society's CURB-65 score. Increasing age is a predictor of a poor prognosis in CAP patients as well as influences the treatment [26]. Age is included as a prognostic factor in the PSI [27], CURB-65 [28], and A-DROP scoring system [29]. Therefore, increasing age is also a poor prognostic factor for CAP. Next, respiratory status is considered a poor prognostic factor of CAP and affects therapeutic effectiveness [26]. It is included in all pneumonia severity scores, and respiratory rate is adopted in CURB-65 [28]. Finally, the CAP severity based on CURB-65 scores not only affects the therapeutic effectiveness but is also considered a predictor of mortality [30].The finding of our study highlights the most attention on the severe category of pneumonia due to the lowest rates of treatment success.

This study has some limitations. Firstly, it was a retrospective study, so the outcome depends on the

availability of secondary data in medical records. For instance, data related to the identification of pathogens and their susceptibility to CPZ were available in 86 medical records, accounting for 41% of total cases. Therefore, we were not able to evaluate the effect of causative pathogens and their resistance to CPZ on the treatment outcomes in the full study population. Next, we only mentioned bacterial pathogens, not including pneumonia-causing viruses, since serological tests were not routinely performed in hospitals.

CONCLUSION

The prevalence of pneumonia caused by *K. pneumoniae* in the community is the highest among the elderly hospitalized at tertiary care hospitals in Vietnam. Research on the virulence of *K. pneumoniae* to produce vaccines for the elderly in the coming time is necessary. CPZ is still sensitive to Gram-negative bacteria and Gram-positive cocci as there is proven effectiveness of CPZ monotherapy on day 3, with nearly 80% of patients achieving clinical stability. Although CPZ seemed to be a good choice of therapy, it is important to minimize CPZ resistance and CPZ overuse leading to the influence on the therapeutic effectiveness in the future. During hospitalization, the factors associated with the success of achieving clinical stability are age below 65 years old, normal respiratory rate (18-20 breaths/min), and mild or moderate categories of CAP severity based on CURB-65 scores. These identified factors are useful for clinicians in predicting the prognosis of CAP patients, planning the sequential therapy, and determining hospital discharge.

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DISCLOSURE

The author reports no conflicts of interest in this work.

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