Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 138-142

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

The Potential of the Domestic Drug Ceftriaxone/Sulbactam in the Treatment of Moderate Severity Community-Acquired Pneumonia

Musayeva L.J., Yakubov A.V., Pulatova N.I., Zufarov P.S., Akbarova D.S., Abdusamatova D.Z.
Tashkent Medical Academy, Uzbekistan

ABSTRACT

Pneumonia in the 21st century remains a significant medical and social issue. This is primarily due to its widespread prevalence, relatively high mortality rate, and substantial economic losses. The foundation of community-acquired pneumonia therapy lies in the prescription of antibacterial agents. Enhancing the effectiveness of community-acquired pneumonia treatment is feasible only through timely diagnosis, adequate patient severity assessment determining indications for hospitalization, prompt initiation of treatment, and a rational selection of antibacterial therapy with consideration for the potential pathogen. The broad spectrum of antibacterial activity, favorable pharmacokinetic properties, good tolerability, and ease of administration of ceftriaxone/sulbactam has positioned it as one of the most widely employed agents for respiratory tract infection treatment. This article describes the clinical effectiveness of the ceftriaxone/sulbactam combination, which led to rapid resolution of intoxication and catarrhal syndromes, as well as a significant improvement in spirometry parameters and increased SpO2 levels.

Keywords: *community-acquired therapy, antibacterial therapy, third-generation cephalosporins, ceftriaxone/sulbactam.*

Received 28.03.2023 Revised 15.05.2023 Accepted 17.06.2023

INTRODUCTION

Community-acquired pneumonia (CAP) is a significant public health concern globally, accounting for a substantial burden of morbidity and mortality. The management of CAP is evolving due to changing microbial patterns and increasing antibiotic resistance. Ceftriaxone/sulbactam, a combination of a third-generation cephalosporin and a beta-lactamase inhibitor, has shown promising results in the treatment of various infections. This study aims to investigate the potential of ceftriaxone/sulbactam in the treatment of moderate-severity CAP. By evaluating its effectiveness, safety, and microbial coverage, we aim to provide valuable insights into the role of this antibiotic combination in combating CAP.

Community-acquired pneumonia (CAP) stands as one of the most pressing challenges in modern healthcare due to its high morbidity and mortality rates. As CAP continues to increase, owing to various factors, advancements in its diagnosis, prevention, and treatment have gained even greater interest and significance. The majority of CAP patients are treated empirically, making the selection of appropriate antibiotic therapy increasingly complex. This complexity arises from shifting CAP epidemiology, partly due to antimicrobial resistance, and the variability of CAP pathogens between countries and regions.

Furthermore, there is a noted increase in the prevalence of chronic comorbidities among CAP patients. Treating CAP has become an intricate endeavor due to these factors, as well as the varying safety and efficacy profiles of established antibiotics [9]. The incidence of community-acquired pneumonia in adults (≥18 years old) ranges from 1% to 11.6% in younger age groups, to 25% to 44% in older age groups (≥65 years old).

The incidence and mortality rates of CAP are high across all regions of the world, posing a threat not only to human health but also escalating the burden on national economies. According to WHO estimates, approximately 450 million pneumonia cases occur annually worldwide, with around 4 million resulting in death, constituting about 7% of the total annual mortality [8].

Timely and appropriate antibiotic therapy (ABT) plays a leading role in the treatment program for CAP. It has been established that systemic ABT, when administered promptly and with suitable drug selection, improves prognosis [7]. Initial ABT is recommended to be prescribed empirically, considering factors that determine the spectrum of potential pathogens and their susceptibility to antibiotics. When stratifying

patients, the risk of infection with uncommon pathogens (P. aeruginosa, MRSA, extended-spectrum beta-lactamase-producing enterobacteria) should be taken into account [2].

Currently, the physician's arsenal includes a vast array of diverse antibacterial agents that are highly effective against a wide range of pneumonia etiologies. The choice of treatment is also influenced by individual characteristics such as age, allergy history, liver and kidney function, and pregnancy. The severity of pneumonia also serves as a clinical guideline in the initial selection of an antibacterial agent and its administration route.

The inclusion of cephalosporins in the therapy of community-acquired pneumonia (CAP) is determined by the necessity to comprehensively cover the spectrum of the most likely pneumonia pathogens. This perspective is reflected in both domestic and international guidelines for treating this condition. Among third-generation cephalosporins, cefotaxime and ceftriaxone exhibit the highest activity against S. pneumoniae [3]. A significant advantage of ceftriaxone is the low resistance of infectious agents to this drug and its strong activity against multidrug-resistant strains of gram-negative bacteria.

The clinical application of ceftriaxone/sulbactam is not distinct from ceftriaxone alone. The addition of sulbactam, a synthetic sulphone of penicillin, enhances the microbiological activity of the combination by binding to penicillin-binding proteins, which are unaffected by ceftriaxone, and broadens the spectrum of antibacterial activity against microorganisms producing cephalosporinases.

This study aimed to assess the impact of therapy with the combined drug ceftriaxone/sulbactam on the dynamics of clinical and functional indicators in patients with moderate-severity community-acquired pneumonia.

MATERIAL AND METHODS

An open, observational, prospective, non-interventional study was conducted on a group of hospitalized individuals from January to May 2023 at the pulmonology department of a multidisciplinary clinic affiliated with the Tashkent Medical Academy.

Patients with moderate-severity community-acquired pneumonia were enrolled in the protocol upon the treating physician's decision to prescribe ceftriaxone/sulbactam.

Criteria for therapy selection:

- Microbiological analysis of sputum;
- Ineffectiveness of prior penicillin-based antibiotic therapy;

Inclusion criteria for the study:

- Age of patients - ≥18 years;
- Diagnosis of community-acquired pneumonia confirmed radiologically or with CT scan data;
- Prescription of ceftriaxone/sulbactam for the treatment of community-acquired pneumonia in accordance with medical standards and clinical recommendations;
- Signed informed consent.

Exclusion criteria:

- Hypersensitivity to beta-lactam antibiotics;
- Positive sputum analysis for microorganisms naturally resistant to ceftriaxone/sulbactam.

The duration from the onset of illness ranged from 1 to 3 days. The age of patients ranged from 25 to 65 years. The ceftriaxone/sulbactam preparation (ATM SanitaPharma, Uzbekistan) was administered every 12 hours at a dose of 1.5 g twice a day intravenously, followed by a switch to intramuscular administration depending on the clinical situation. The duration of ceftriaxone/sulbactam intake ranged from 7 to 14 days. The average duration of treatment with the medication was 7.5 ± 13.4 days. Dosage adjustments were made for patients with impaired kidney function. One patient received levofloxacin as an additional antibacterial therapy. Antipyretic (paracetamol), mucolytic (acetylcysteine, ambroxol), and detoxification (reosorbilact) drugs were prescribed as indicated. Daily monitoring of clinical symptoms, body temperature, and blood oxygen saturation was conducted for all participants.

Upon admission, general patient information, medical history, clinical data, the severity of the condition, and indications for hospitalization were collected. Spirometry and microbiological examination of sputum with determination of antibiotic sensitivity were also conducted at this stage.

During the treatment (1st-3rd-5th-7th-10th-14th day), clinical data and severity criteria were assessed, cases of hospitalization in the Department of Intensive Care (ICU) were recorded, spirometry data were collected, microbiological analysis of sputum was performed, any changes in therapy and adverse events were noted.

Statistical data were processed using the Statistics Version 10 program. Mean values, standard deviation, and the t-test were used for evaluation. Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

The data of 30 hospitalized patients with moderate-severity CAP were analyzed: 13 (43.3%) were males, 17 (56.7%) were females; the mean age was 45.3 (25-65) years. The baseline characteristics of the patients are presented in Table 1.

Table 1. Baseline Characteristics of Patients (n = 30)

Indicator	Value
Male	13 (43,3)
Female	17 (56,7)
Age, years	36,7 ± 9,5 (25–65)
Bodyweight, kg	63,4 ± 9,8 (48–90)
Height, cm	168,2 ± 8,5 (152–188)
BMI, kg/m^2	23,3 ± 2,25 (16,7–25,8)

At admission to the hospital, all patients were prescribed antibiotic therapy (AT) which started within the first 24 hours of hospitalization and continued until discharge. The use of antibiotic therapy in the study group was accompanied by a positive clinical effect, which could be attributed to improvements in endothelial function as well as improvements in inflammation marker levels. According to the findings of the study conducted among 30 patients with moderate-severity community-acquired pneumonia, the effectiveness of antibiotic therapy was confirmed. The intoxication syndrome (fever, weakness, fatigue) regressed by the 5th day of therapy (Table 2).

Table 2. Dynamics of Reduction in Intoxication Syndrome in Patients with Community-Acquired Pneumonia.

Group of Patients	Number of Patients, %	Days of Treatment			
		3rd	5th	7th	10th
Traditional Therapy Ceftriaxone + /Sulbactam	n=30 (100%)	21 (70%)	7 (23,3%)	2 (6,7%)-	-

As seen from the table, the administration of the ceftriaxone/sulbactam medication led to the successful alleviation of the intoxication syndrome in the majority of patients by the 3rd day of therapy. If on the 3rd day of therapy, signs of intoxication persisted in 8 (38.1%) patients, on the 5th day in 2 (9.5%) patients, by the 7th day a complete disappearance of intoxication symptoms was observed. The results of the study on the reduction of clinical symptoms of pneumonia are presented in Table 3.

Table 3. Dynamics of Disappearance of Main Symptoms in Patients with Community-Acquired Pneumonia

Group of Patients	Symptoms / number of patients and %	Days of Treatment			
		3rd	5th	7th	10th
Traditional Therapy + Ceftriaxone/Sulbactam	headache / n= 21 (70%)	17 (80,9%)	4 (19,1%)	-	-
	chestpain / n= 18 (60%)	5(27,8%)	12 (66,7%)	1 (5,5%)	-
	cough / n=30 (100%)	15 (50%)	13(43,3%)	2 (6,7%)	-
	Sputum production n=25 (83.3%)	11 (44%)	13 (52%)	1 (4%)	-
	Shortness of breath / n=17 (56.7%)	11 (64,7)	6 (35,3%)	-	-

As evident from the presented data, the therapy led to a more rapid resolution of all symptoms, particularly noticeable within the first 5 days of treatment. The number of patients showing a reduction in headache, chest pain, coughs, and shortness of breath by the 5th day of therapy was 28 (93.3%) patients. On average, the disappearance of headache took 2.92±0.75 days, and chest pain decreased within 4.5±1.37 days. A more pronounced reduction in cough symptoms was also observed on the 5th day of treatment. Only 2 patients had their cough symptoms disappear on the 7th day of therapy. By the 5th day of treatment, nearly all patients reported the absence of sputum. The use of the ceftriaxone/sulbactam combination in our study alleviated the severity of the disease in patients with community-acquired pneumonia, reducing the intensity of catarrhal and intoxication syndromes within 3-5 days from the beginning of treatment.

The analysis of spirometry revealed an improvement in the external respiratory function on the background of ceftriaxone/sulbactam therapy. When compared to the baseline values, on the 14th day,

the forced expiratory volume in 1 second (FEV1) increased by 0.257 (11.9%) liters, the forced vital capacity (FVC) increased by 0.349 (11.5%) liters, and the arterial blood hemoglobin oxygen saturation level (SpO2) increased by 3.8% (for all parameters $p < 0.001$). Changes in spirometry parameters are presented in Table 4.

Table4. Spirometry parameters (n = 30).

Indicator	Initial	14th day	p
FEV1, L	1,325 ± 0,589 (0,53–2,75)	1,582 ± 0,796 (0,59–3,64)	< 0,001
FEV1, %predicted	49,12 ± 17,87 (18,3–71,5)	54,32 ± 21,20 (21,3–82,6)	< 0,001
FVC, L	2,537 ± 1,091 (1,35–5,82)	2,886 ± 1,121 (1,42–5,89)	< 0,001
FVC, %predicted	59,18 ± 23,68 (37,7–112,9)	72,59 ± 22,64 (45,6–114,8)	< 0,001
FEV1 / FVC, %predicted	51,7 ± 11,8 (36–83)	55,3 ± 12,3 (35–81)	0,4
FEF 25-75, %predicted	29,77 ± 15,13 (9,9–57,3)	35,28 ± 25,90 (14,7–82,9)	0,4

Note: FEV1 - forced expiratory volume in 1 second; FVC - forced vital capacity; FEV1/FVC - ratio of FEV1 to FVC; FEF 25-75 - forced expiratory flow between 25% and 75% of FVC.

During the microbiological examination of sputum, S. pneumoniae was isolated in 25 (83.3%) patients. S. aureus was detected in 5 (16.7%) patients, and P. aeruginosa was identified in 3 (10%) of those surveyed. There was high resistance of S. pneumoniae to antibacterial drugs. Low sensitivity of this microorganism to amoxicillin was observed in 3 (10%) patients, to ceftriaxone in 4 (13.3%), to azithromycin in 5 (16.7%), and to levofloxacin in 7 (42.8%). A higher sensitivity was determined for amikacin in 15 (50%) cases and for meropenem in 19 (63.3%) cases. In comparison with the listed medications, ceftriaxone/sulbactam demonstrated a better profile: sensitivity to it was recorded in 25 (83.3%) patients (Table 5).

Table 5. Microbiological Examination of Sputum.

Sensitivity of Streptococcus pneumoniae to antibiotics, baseline (n = 30); n (%)	
Amoxicillin	3 (10)
Azithromycin	5 (16,7)
Ceftriaxone/Sulbactam	25 (83,3)
Cefotazidime	4(13,3)
Cefoperazone	8 (26,6)
Meropenem	19 (63,3)
Amikacin	15 (50)
Levofloxacin	7 (23,3)

Safety assessment included monitoring and recording of adverse reactions throughout the study by evaluating clinical and physical data, results of blood biochemical analysis, complete blood count, urine analysis, and instrumental examination results before and after antibiotic therapy administration. Adverse reactions were identified in 6 cases. Antibiotic-associated diarrhea occurred in 3 (10%) patients, oral candidiasis in 1 (3.3%) patient, and leukopenia in 2 (6.6%) patients.

Our study findings also align with the results of other research. For instance, MostovoyYu.M. et al. [6] investigated the effectiveness of the SulbaktoMax (ceftriaxone/sulbactam) preparation in treating community-acquired pneumonia in 32 adult patients. Patients were administered SulbaktoMax at a daily dose of 1.5-3 g in 2 intravenous injections with a subsequent transition to intramuscular administration. The duration of treatment ranged from 6 to 15 days. The study results demonstrated that out of the 32 enrolled patients, 31 (96.9%) completed the study, and all of them experienced a favorable clinical effect. Positive dynamics of clinical and laboratory indicators were observed in all patients receiving SulbaktoMax, starting as early as 3-5 days of treatment. Within 3-5 days after completing the treatment, almost complete regression of dyspnea, chest pain, wheezing, normalization of body temperature, significant improvement in blood indicators, and normalization of the lung X-ray image were noted. No signs of drug toxicity or other side effects were detected.

In the work by V.G. Maidannik and colleagues [5], the comparative effectiveness of therapy with beta-lactam antibiotics and the combination of ceftriaxone/sulbactam (SulbaktoMax) was reported in 63 children with moderate and severe pneumonia. The authors concluded that as early as the 3rd day of treatment in the group of children receiving the comprehensive therapy regimen of SulbaktoMax, a significant acceleration of positive dynamics was observed compared to patients receiving other beta-lactam antibiotics. Further treatment revealed regression of pneumonia symptoms and a decrease in the severity index to 42.8 ± 1.6 on the 10th-14th day of treatment, which was significantly lower than in the control group (76.7 ± 2.1, $P < 0.05$). The authors also reported a much faster reversal of signs of

respiratory failure in patients taking SulbaktoMax compared to those using other beta-lactam antibiotics (39.4% versus 13.3%).

In the work by Abdulhakova V.R. [1], the effectiveness of initial empirical therapy with ceftriaxone/sulbactam in treating pneumonia in children (n=66) was also determined. According to clinical and laboratory data, an effective response to treatment was observed in the group receiving ceftriaxone/sulbactam in 68.7% of cases. Additionally, the average duration of hospitalization in the control group was 6.59 days, while in the placebo group, it was 8.55 days ($p<0.001$).

CONCLUSION

According to both domestic and international clinical guidelines for the treatment of community-acquired pneumonia (CAP), beta-lactam antibiotics continue to be the drug of choice for empirical therapy, regardless of the severity of the disease [3]. Among the key antibiotics for treating hospitalized patients with CAP, third-generation cephalosporins, particularly ceftriaxone/sulbactam, play a significant role.

In our study, antibacterial therapy with ceftriaxone/sulbactam led to a rapid resolution of intoxication and catarrhal symptoms, as well as a significant improvement in spirometric parameters and increased SpO2 levels. Throughout antibacterial treatment, no lethal outcomes, cases of intensive care unit (ICU) admissions, or serious adverse drug reactions were recorded. According to the results of our study, the administration of ceftriaxone/sulbactam is justified and effective in the management of moderate-severity pneumonia.

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CITATION OF THIS ARTICLE

Musayeva L.J., Yakubov A.V., Pulatova N.I., Zufarov P.S., Akbarova D.S., Abdusamatova D.Z.. The Potential of the Domestic Drug Ceftriaxone/Sulbactam in the Treatment of Moderate Severity Community-Acquired Pneumonia. Bull. Env. Pharmacol. Life Sci., Vol 12[6] June 2023: 138-142.