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Effectiveness of antimicrobial therapy for community-acquired pneumonia in real clinical practice

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ABSTRACT

Background. Community-acquired pneumonia (CAP) remains one of the most common infectious diseases, occupying an important place in the structure of mortality worldwide.

Aim. To evaluate the effectiveness of antimicrobial therapy for community-acquired pneumonia in hospitalized patients in real clinical practice.

Materials and methods. A retrospective, observational study was conducted, which included 236 patients hospitalized for community-acquired pneumonia at the Regional Clinical Hospital in Ryazan in 2019. Based on these case histories, an analysis of the effectiveness of the initial empiric antimicrobial therapy was performed.

Results. The initial empiric antimicrobial therapy in 73% of cases included administration of ceftriaxone, in 45% of cases – levofloxacin, in 14% of cases – azithromycin. It was found that initial antimicrobial therapy was effective in 58% of patients who did not require replacement for the antibiotic. A need for a change in the treatment regimen was significantly associated with an increase in the length of hospitalization ($p < 0.001$), heart rate upon admission ($p = 0.032$), myelocyte count in the complete blood count ($p < 0.001$), and urea and blood creatinine levels ($p = 0.004$ and $p = 0.044$, respectively). The selected antimicrobial therapy regimen was significantly associated with the expected treatment effectiveness ($p = 0.039$). The choice of levofloxacin in monotherapy or in combination with ceftriaxone was accompanied by a decrease in the relative risk of replacing the antimicrobial, compared with other treatment regimens (odds ratio (OR) = 0.86 (95% confidence interval (CI): 0.55–1.34) and OR = 0.57 (95% CI: 0.37–0.87), respectively).

Conclusion. Empiric antimicrobial therapy for community-acquired pneumonia in real clinical practice complies with current recommendations, however, at the same time, its ineffectiveness persists. Respiratory fluoroquinolones are most effective in treating pneumonia in hospitalized patients.

Key words: pneumonia, antibiotics, fluoroquinolones.

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Эффективность антибактериальной терапии внебольничной пневмонии в условиях реальной клинической практики

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РЕЗЮМЕ

Актуальность. Внебольничная пневмония остается одним из наиболее распространенных инфекционных заболеваний, занимающим важное место в структуре смертности населения во всем мире.

Цель – оценить эффективность антибактериальной терапии внебольничной пневмонии у госпитализированных пациентов в условиях реальной клинической практики.

Материалы и методы. Проведено ретроспективное наблюдательное исследование, в которое включены 236 больных, госпитализированных по поводу внебольничной пневмонии в ГБУ РО «Областная клиническая больница» (г. Рязань) в течение 2019 г. На основании данных историй болезни проведен анализ эффективности стартовой эмпирической антибактериальной терапии.

Результаты. Стартовая эмпирическая антимикробная терапия в 73% случаев включала назначение цефтриаксона, 45% – левофлоксацина, 14% – азитромицина. Установлено, что стартовая антибактериальная терапия была эффективной у 58% пациентов, которым не потребовалась замена антибиотика. Потребность в смене схемы терапии была значимо ассоциирована с увеличением сроков госпитализации ($p < 0,001$), частотой сердечных сокращений при поступлении ($p = 0,032$), уровнем миелоцитов в общем анализе крови ($p < 0,001$), уровнем мочевины и креатинина крови ($p = 0,004$ и $p = 0,044$ соответственно). Выбранная схема стартовой антибактериальной терапии значимо ассоциирована с ожидаемой эффективностью лечения ($p = 0,039$). Выбор левофлоксацина в монотерапии или в комбинации с цефтриаксоном сопровождался снижением относительного риска замены антибактериального препарата по сравнению с иными вариантами терапии (OR = 0,86 (95% CI: 0,55–1,34) и OR = 0,57 (95% CI: 0,37–0,87) соответственно).

Заключение. Эмпирическая антибактериальная терапия внебольничной пневмонии в целом соответствует действующим рекомендациям, однако при этом сохраняется крайне высокая частота ее неэффективности. Наибольшую эффективность в лечении пневмонии у госпитализированных пациентов имеют респираторные фторхинолоны.

Ключевые слова: пневмония, антибиотики, фторхинолоны.

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INTRODUCTION

Pneumonia is a group of acute infectious diseases (mainly bacterial ones) with different etiology, pathogenesis, and morphological characteristics. They are characterized by focal lesions in the lungs with the obligatory presence of intraalveolar exudate. Pneumonia is considered community-acquired, if it develops outside the hospital or is diagnosed in the first 48 hours of hospitalization.

Community-acquired pneumonia (CAP) remains one of the most common infectious diseases, occupying an important place in the structure of mortality worldwide. Among adults in Europe and North America, pneumonia occurs in 5–10 people per 1,000 population [1]. In the Russian Federation, where the population exceeds 140 million people, it can be stated that every year, more than 1.5 million people develop pneumonia among adult population [2]. In general, the Russian Federation demonstrates persistent

pneumonia morbidity, but in some regions, including the Ryazan region, a steady increase is registered [3]. Every year, about 400 thousand people with pneumonia are hospitalized in the Russian Federation, while the mortality rate for severe forms of the disease in the inpatient setting is approaching 10% [2].

High mortality rate from pneumonia is observed not only in the inpatient setting. Pneumonia is ranked 1st among the causes of mortality from infectious diseases and 6th among all causes in the overall structure of mortality [4, 5]. Despite advances in modern methods of diagnosis and treatment, CAP remains one of the topical problems in the Russian healthcare. In recent years, to improve the effectiveness of pneumonia patient management, international and national guidelines have been implemented, which help doctors choose the most rational treatment strategy in a specific clinical situation. However, in real clinical practice, the recommended approaches to the choice of empiric antimicrobial therapy are often neglected, which leads to an increase in the number of unfavorable outcomes in patients with pneumonia [6]. Therefore, the aim of the study was to evaluate the effectiveness of antimicrobial therapy for CAP in real clinical practice.

MATERIALS AND METHODS

A retrospective observational study was conducted to assess the comparative effectiveness of empiric antimicrobial therapy for CAP in real clinical practice. To carry out the study, a register of all CAP cases was formed that were registered at the Regional Clinical Hospital (Ryazan) from January to December of 2019. At the first stage of the study, an analysis of 236 case histories was carried out, including a clinical and demographic analysis of disease cases. At the second stage, two study groups were identified, depending on the need to change the empiric antimicrobial therapy prescribed at the time of hospitalization, in order to determine the most effective treatment regimens. When forming the study groups, the effectiveness of treatment was understood as achievement of the criteria for an effective response to antimicrobial therapy and absence of the need to revise the antimicrobial therapy regimen following the current guidelines [7]. At the second stage of the study, 3 case histories were excluded from further analysis due to the impossibility to definitely determine the applied initial antimicrobial therapy regimen.

Patient records were used as primary documentation for the study, from which the following information was obtained:

– demographic and medical and statistical information, including age, gender, date and duration of hospitalization, the outcome of hospitalization, information on concomitant diseases;

– information about the course of the disease, including the period from the onset of symptoms to the start of antimicrobial therapy, complaints upon admission, data of clinical examinations and additional research methods, including the severity of pneumonia, the presence of complications, the volume and localization of the lesion according to chest X-ray, findings of complete blood count and blood biochemistry test, results of sputum test.

Statistical analysis was performed using the StatSoft Statistica 10 software package. Normal distribution of variables was assessed using the Shapiro – Wilk test. The results obtained are presented as *Me [Q25; Q75*], where *Me* is the median, and *Q25* and *Q75* are lower and upper quartiles, respectively. The Kruskal – Wallis and Mann – Whitney tests were used to compare the groups by quantitative criteria. Relative parameters of qualitative variables (frequencies and proportions) were compared using Fisher's exact test with Yates' correction. The differences were considered statistically significant at $p < 0.05$.

RESULTS

Cases of hospitalizations for CAP were recorded all year round, with peaks, according to the register, in the periods from April to May and from October to December. A significant decrease in the number of hospitalizations was noted only in summer months.

Among those included in the study, there were 122 (52%) men and 114 (48%) women, which indicates that there is no associated between gender and the development of pneumonia. The average age of those hospitalized for pneumonia was 61 years. The average hospital stay was 12 days. Most often, according to medical records, patients complained of cough, fever, shortness of breath, and generalized weakness. Less commonly, the complaints included sputum production, sweating, and chest pain (Figure).

Severe CAP was observed in 39 patients (17%). In 97 (41%) patients, the disease was complicated by the development of respiratory failure, in 7 (3%) patients – by exudative pleuritis. Other complications, including abscess, pleural empyema, and toxic shock syndrome, were isolated.

According to chest X-ray, the lesion volume in 55 (23%) cases corresponded to focal pneumonia, in 13 (6%) cases – to segmental pneumonia, in 130 (55%)

cases – to multilobar pneumonia, and in 36 (15%) cases – to lobar pneumonia. In 2 (1%) patients, chest X-ray revealed interstitial pneumonia. Most often, 104 (44%) patients had right-sided pneumonia, 74 (31%) patients had left-sided pneumonia, and 58 (25%) patients had bilateral pneumonia. The inflammatory process in 49% of cases was localized in the lower lobe, in 4% of cases – in the middle lobe, in 15% of cases – in the upper lobe; multiple localization was determined in 32% of patients.

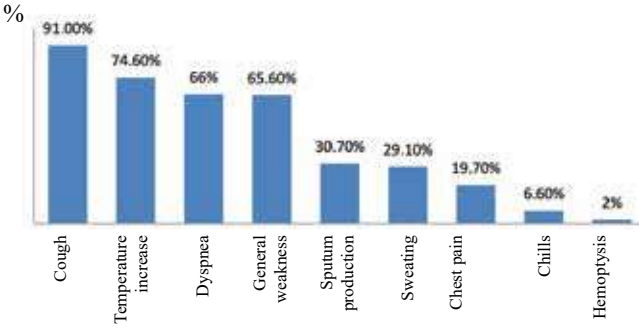

Figure. Complaints of patients hospitalized for pneumonia, %

The outcome of hospitalization in 92 (39%) patients was recovery, in 133 (56%) patients – improvement of the condition and discharge for outpatient treatment, in 11 (5%) cases – death of the patient. It was found that the outcome of hospitalization depended on the patient's age ($p = 0.0140$), respiratory rate ($p = 0.0012$), blood urea level ($p = 0.0118$), and blood oxygen saturation ($p = 0.0268$) and did not depend on the duration of the onset of the disease before hospitalization ($p = 0.8216$) and the level of systolic and diastolic blood pressure ($p = 0.6043$ and $p = 0.4468$, respectively). Analyzing the relationship between the complete blood count parameters and the outcome of hospitalization, it was found that the outcome of hospitalization was associated with the level of neutrophils ($p = 0.0248$), but did not depend on the level of erythrocytes, leukocytes, and hemoglobin ($p = 0.2428$, $p = 0.1083$, and $p = 0.9250$, respectively).

The results of the sputum culture test in the primary documentation were present only in 26 (11%) patients: of them, in 65% of cases the causative agent of pneumonia was *Streptococcus pneumoniae*, in 15% of cases – *Escherichia coli*, in 11% of cases – *Klebsiella pneumoniae*, and in 4% of cases – *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In 31% of cases, the sputum culture test detected fungi of the *Candida* genus.

Analyzing the prescribed treatment, we obtained data that the initial empiric antimicrobial therapy in 73% of cases included prescription of ceftriaxone, in 45% of cases – levofloxacin, in 14% of cases – azithromycin; in some cases the therapy regimen included the use of amikacin, amoxicillin, vancomycin, gentamicin, josamycin, clarithromycin, co-trimoxazole, meropenem, metronidazole, cefotaxime, and ertapenem. It was found that initial antimicrobial therapy was effective only in 136 (58%) patients who did not require replacement of the antibacterial drug. The need to change the therapy regimen was significantly associated with an increase in hospitalization time ($p < 0.001$), heart rate upon admission ($p = 0.032$), the level of myelocytes in the complete blood count ($p < 0.001$), and the level of urea and blood creatinine ($p = 0.004$ and $p = 0.044$, respectively) and was not associated with other clinical and laboratory parameters (Table 1).

Table 1

Clinical and demographic analysis of disease cases, *Me* [Q_{25}; Q_{75}]

Parameter	Total, $n = 236$	Replacement of antibacterial treatment was not required, $n = 136$	Replacement of antibacterial treatment was required, $n = 100$	p
Age, years	61 [41.5; 75.5]	65.5 [51; 79]	56 [37; 69]	< 0.001
Gender, male/female	122/114	64/72	58/42	$\chi 2 = 2.95$; $p = 0.085$
Length of hospitalization (days)	12 [9; 16]	10 [8; 14]	15 [11; 17]	<0.001
Time from the onset of symptoms to hospitalization (days)	6 [4; 10]	7 [4; 8,5]	6 [4; 11]	0.719
Respiratory rate (per minute)	20 [18; 22]	20 [18; 22]	20 [18; 21]	0.359
Systolic blood pressure (mmHg)	130 [120; 140]	130 [116; 140]	125 [120; 140]	0.760
Diastolic blood pressure (mmHg)	80 [70; 80]	80 [70; 80]	80 [70; 80]	0.442
Heart rate (beats per minute)	84 [78; 92]	82 [74; 92]	84,5 [80; 97]	0.032
Blood oxygen saturation (%)	95 [92; 97]	95 [91; 97]	95 [92; 97]	0.766
Time from the onset of symptoms to the start of antimicrobial therapy, days	6 [4; 9]	7 [4; 9]	6 [4; 11]	0.654
Duration of initial antimicrobial therapy, days	7 [5; 8]	7 [6; 8]	6 [3; 7]	<0.001
Duration of prescribed antimicrobial therapy, days	9 [7; 12]	7 [6; 8]	12 [10; 15.5]	<0.001

Table 1 (continued)

Parameter	Total, $n = 236$	Replacement of antibacterial treatment was not required, $n = 136$	Replacement of antibacterial treatment was required, $n = 100$	p
Complete blood count				
Erythrocytes, $\times 10^{12}$	4.6 [4.2; 4.9]	4.6 [4.2; 4.9]	4.6 [4.2; 5]	0.456
Hemoglobin, g/l	132 [119; 143]	130 [116; 141]	133 [122; 146]	0.082
Platelets, $\times 10^9$	229 [169; 329]	233 [178; 349]	211.5 [129; 294]	0.398
Leukocytes, $\times 10^9$	9.6 [7.3; 13.9]	9.7 [7.5; 14.1]	9.6 [6.5; 13.9]	0.381
Basophils, %	1 [1; 1]	1 [1; 1]	1 [1; 1]	1.000
Eosinophils, %	2 [1; 4]	2 [1; 4]	2 [1; 3]	0.907
Myelocytes, %	8 [5; 11]	8 [5; 11]	0 [0; 0]	<0.001
Immature neutrophils, %	2 [1; 2]	2 [1; 4]	1.5 [1; 2]	0.648
Band neutrophils, %	2 [1; 4]	2 [1; 4.5]	2 [1; 4.5]	0.837
Segmented neutrophils, %	65 [54; 74]	65 [54; 74]	65 [57; 75]	0.778
Lymphocytes, %	21 [11.55; 29]	21 [14.6; 29]	20 [10; 28]	0.348
Monocytes, %	7 [6; 10]	8 [6; 10]	7 [5.5; 10]	0.384
Blood biochemistry test				
Urea, mmol / l	5.7 [4.4; 8.8]	6.35 [4.8; 10.35]	5.4 [4; 7.4]	0.004
Creatinine, mmol / l	0.102 [0.081; 0.121]	0.107 [0.086; 0.135]	0.099 [0.08; 0.116]	0.044

It was found that the chosen regime of initial antimicrobial therapy was significantly associated with the expected effects of treatment and the need to replace the antibacterial drugs ($p = 0.039$). At the same time, only the regimens with levofloxacin were accompanied by a decrease in the relative risk of antibiotic replacement compared with any other treatment options. Monotherapy with levofloxacin reduced the relative risk of antibiotic replacement in etiotropic therapy by 14% compared with other treatment options. The most effective combination of ceftriaxone and levofloxacin reduced the risk of antibiotic replacement by 43%. Any other treatment options that did not include respiratory fluoroquinolones demonstrated an increased relative risk of antibiotic replacement.

Table 2

Effect of initial antimicrobial therapy on the need for further change of the antibacterial drug

Antimacrobial therapy regimen	Replacement of the antibiotic was required	Replacement of the antibiotic was not required	Relative risk of replacing the antibiotic
Ceftriaxone	42	42	OR = 1.28 (95% CI: 0.96–1.72)
Azithromycin	7	6	OR = 1.27 (95% CI: 0.75–2.16)
Levofloxacin	14	23	OR = 0.86 (95% CI: 0.55–1.34)
Azithromycin + ceftriaxone	9	10	OR = 1.11 (95% CI: 0.68–1.83)
Ceftriaxone + levofloxacin	17	45	OR = 0.57 (95% CI: 0.37–0.87)
Other options for antimicrobial therapy	11	7	OR = 1.48 (95% CI: 0.99–2.21)

Note: OR – odds ratio, CI – confidence interval.

DISCUSSION

Many studies are devoted to assessing the effectiveness and safety of antimicrobial drugs in pneumonia. The most commonly prescribed antibiotic in the treatment of pneumonia in the inpatient setting in the Russian Federation is ceftriaxone. According to the pharmacoeconomic analysis carried out in Nizhny Novgorod, the drug load of 1 CAD patient with ceftriaxone per day is 3.2 g, which exceeds the load with ampicillin / sulbactam by 2.3 times, levofloxacin and azithromycin – by 5 times, moxifloxacin – by 19 times [8]. Our results also confirm high frequency of ceftriaxone use for initial antimicrobial therapy for pneumonia, but the effectiveness of this prescription is doubtful.

According to the study conducted by Professor A.I. Sinopalnikov in 2012 in real clinical practice, in hospitalized patients, initial antimicrobial therapy was effective and did not require replacement of the antibacterial drug in only 45% of patients, which is consistent with our data [6]. In this case, a single antibiotic replacement was sufficient to obtain the necessary clinical effect only in 39% of cases, in 16% of cases,

a two- or three-time change of etiotropic therapy was required. In 2012, the main reason for the ineffectiveness of the initial therapy, according to data obtained by Professor A.I. Sinopalnikov, was low adherence to recommendations for CAP treatment, including widespread use of drugs with insufficient antimicrobial activity against the key pathogens (primarily cefazolin and ciprofloxacin). However, in our work, similar treatment failure was noted with the use of antibiotics included in the current clinical guidelines, which may indicate other mechanisms, for example, an increase in the drug resistance of typical pathogens causing pneumonia observed in recent years [7].

It has now been shown that monotherapy with β-lactam antibiotics is often insufficiently effective due to an increase in the number of CAP cases associated with atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. The study by K. Eljaaly, conducted in the USA, showed that inclusion of drugs fighting atypical pathogens in empiric antimicrobial therapy for CAP can significantly reduce the risk of clinical treatment failure (RR = 0.851; 95% CI, 0.732–0.99; $p = 0.037$), while not affecting the overall mortality and development of adverse drug reactions requiring antibiotic withdrawal (RR = 0.549; 95% CI, 0.259–1.165, $p = 0.118$ and RR = 0.83; 95% CI, 0.542–1.270, $p = 0.39$, respectively) [9].

Many studies were devoted to comparing regimens of etiotropic therapy for pneumonia. In the work by Wei Nie et al. [10], 2,946 publications on this topic were analyzed, of which 16 articles were included in a further meta-analysis devoted to comparing the effectiveness of monotherapy with β-lactam antibiotics and their combination with macrolides. The meta-analysis showed that two-component therapy was associated with higher treatment effectiveness and a reduced risk of death due to pneumonia. Similarly, our results indicate that the combination of ceftriaxone and azithromycin is associated with a lower relative risk of failure compared with both ceftriaxone monotherapy and azithromycin monotherapy (Table 2). At the same time, even the combination ceftriaxone + azithromycin is less effective in comparison with monotherapy with levofloxacin and especially in comparison with the combination ceftriaxone + levofloxacin.

The advantages of monotherapy with respiratory fluoroquinolones in patients with CAP are shown in a meta-analysis by A. Raz-Pasteur et al., including the results of inpatient treatment of 4,809 patients. It was found that monotherapy with fluoroquinolones reduced the relative risk of treatment ineffectiveness and antibiotic withdrawal (RR = 0.72 (0.57–0.91) and RR = 0.65 (0.54–0.78), respectively). Additionally, it was accompanied by a smaller number of diarrhea cases compared with the combination macrolide + β-lactam antibiotic (RR = 0.13 (0.05–0.34)) [11].

Similar results were obtained by K. Skalsky et al. in a systematic review on the comparative effectiveness of macrolides and fluoroquinolones in patients with pneumonia [12]. The study involved 83 publications, of which 16 randomized controlled trials conducted from 1993 to 2005 were included in a further analysis. According to the meta-analysis results, it was found that mortality from pneumonia did not differ in the groups of fluoroquinolones and macrolides, however, the use of fluoroquinolones was accompanied by a lower risk of clinical and microbiological treatment failure (RR 0.63 (95% CI 0.49–0.81)). The authors of the meta-analysis indicated that in therapy with fluoroquinolones, the clinical effect occurred faster and the cure time was shorter. However, not all results on the benefits of respiratory fluoroquinolones are so clear-cut.

In a prospective, randomized clinical study conducted by M. Izadi from December 2016 to June 2017 in Iran, it was shown that the effectiveness of monotherapy with oral levofloxacin at a dose of 750 mg per day did not differ from that of the combination of ceftriaxone at a dose of 1,000 mg per day and oral azithromycin at a dose of 250 mg per day. Although it is worth noting that the doses of drugs used in the study are lower than those traditionally used in Russian clinical practice [13]. The benefits of respiratory fluoroquinolones were shown in a systematic review by J.H. Lee, comparing the combinations fluoroquinolone + β-lactam antibiotic versus macrolide + β-lactam antibiotic in patients with severe CAP. According to the review, the combination macrolide + β-lactam antibiotic resulted in a lower percentage of deaths than the combination fluoroquinolone + β-lactam antibiotic (19.4% versus 26.8%) and was accompanied by a decrease in the duration of hospital stay by 3.05 days [14]. Therefore, the issue of recommending monotherapy with fluoroquinolones as the first line therapy in patients hospitalized for CAP requires further study, at the same time, their high effectiveness in combination therapy is beyond doubt.

CONCLUSION

Our analysis of CAP in hospitalized patients showed that the applied empiric antimicrobial therapy

for CAP generally complies with the current guidelines. However, extremely high frequency of its ineffective outcome remains. Among the groups of drugs used in clinical practice, respiratory fluoroquinolones have the greatest effectiveness in the treatment of pneumonia in hospitalized patients, which can be recommended as one of the key drugs in the treatment of this cohort of patients.

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