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Antibiotic therapy of adult inpatients with community-acquired pneumonia: a retrospective hospital-based study in Ukraine

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ABSTRACT

This study aimed to assess the antibiotic therapy of community-acquired pneumonia (CAP) in adults. A single-center, retrospective study was conducted in one of Lviv city hospitals, Ukraine. Adults with CAP (n=181) were enrolled. Fluoroquinolones (45.3%), cephalosporins (27.8%), and macrolides (16.1%) were the most common antibiotics. Antibiotic-associated drug-related problems (DRPs) were found in 87.3% (95%CI 81.5%:91.8%) of the participants. 4 items of antibiotic-associated DRPs were identified: potential drug-drug interactions (76.6%), inappropriate dosing (14.0%), inappropriate length of therapy (7.5%), and contraindicated usage (1.9%). Spiramycin, metronidazole, levofloxacin, azithromycin, and cefoperazone were associated with the highest risk of DRPs. Age of patients ($p<0.001$), number of antibiotics ($p<0.001$), length of antibiotic therapy ($p=0.036$), and the total number of antibiotic-associated DRPs ($p=0.005$) were defined as factors that statistically contribute to the patient's health status on discharge. Antibiotics should be the drug class most commonly involved in the interventions to improve the safety and quality of CAP therapy.

Keywords: Community-acquired infection, bacterial pneumonia, anti-bacterial agents, inappropriate prescribing, risk factors

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most common infectious diagnoses and a frequent cause of hospital admissions among adults[1,2]. The estimated worldwide incidence of CAP varies between 1.5 to 14 cases per 1000 per-

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son-years[3]. Bacterial pathogens are the most typical causative agents of CAP that require antimicrobial therapy[4]. Consequently, the CAP treatment can bring about numerous antibiotic-related adverse health and economic outcomes such as antimicrobial resistance, allergic reactions, *Clostridium difficile* infections, etc[5-7].

Problems associated with antibiotics treatment have a wide set of factors that can be considered as drug-related problems (DRPs)[8]. DRPs are known to be health and economic issues because they may affect treatment outcomes and incur considerable health costs[9-11]. For instance, in the United States the cost of negative outcomes of DRPs is estimating up to $672 billion US dollars per year[11].

According to the different studies, the incidence of antibiotic-associated DRPs is high[8,9,12,13]. Wrong dosage and frequency regimen, unnecessary treatment, inappropriate drug selection, duplicate therapy, drug interactions, contraindications are the most prevalent antibiotic-associated DRPs in hospitals[9,12-14]. The vast majority of DRPs can be attributed to the prescription of quinolones, macrolides and penicillins[8,9,12,14,15].

Different factors are associated with the occurrence of DRPs in inpatients with CAP[16]. Elder age, female gender, polypharmacy, comorbidity, and duration of hospitalization have been established as the significant determinants of DRPs[8,9,12]. Blix et al[12] developed a novel method with a drug risk ratio calculation for evaluation the risk of antibiotic-associated DRPs. This approach allows determining antibiotics that require heightened awareness and attention if they are going to be prescribed. Improving prescription of antibiotics has a positive influence the patients' health, treatment costs, and patients' quality of life[16].There are limited data in this area in Ukraine. Hence, this study aimed to (1) describe and characterize the prescription of antibiotics for inpatients with CAP, (2) identify the incidence and types of antibiotic-associated DRPs, (3) investigate the risk of occurrence of DRPs for the different antibiotics and (4) determine the factors (especially antibiotics-related) contributing to the patient's health condition on discharge.

METHODOLOGY

Definitions

A drug-related problem (DRP) is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"[17]. In addition, DRP is known to be any problem involving drug therapy that can affect desired health outcomes[9]. Drug risk ratio – the number of times the antibiotic was associated with DRPs in relation to the number of times it was used[12]. Potential drug-drug interaction (DDI) is considered to be a concomitant prescription of two interacting drugs, regardless of whether an adverse patient outcome occurs[18].

Study design and data collection

This retrospective study was conducted in one of Lviv city hospitals (Ukraine) that admits inpatients over 18 years. We do not give the name of the hospital owing to the ethical reasons. During the 12 months (from January 2019 to December 2019), 188 adult patients with CAP were hospitalized to the therapeutic department and recruited to the study, but 181 patients were included in the final analysis (Figure 1). The reason for exclusion (n=7) was the absence of antibiotic treatment for inpatients with CAP.

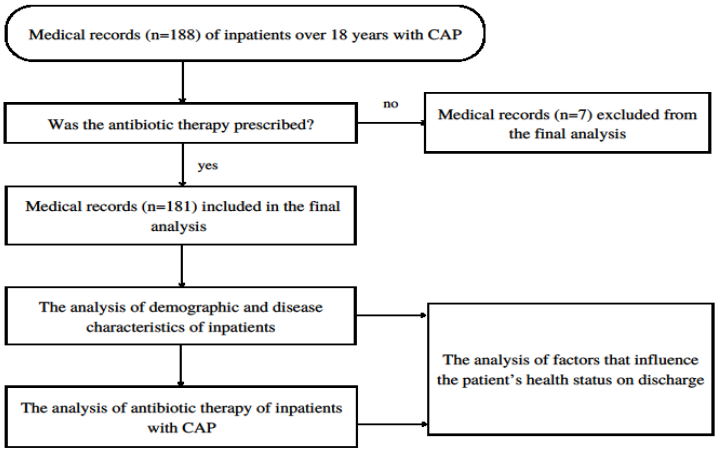

Figure 1. The Flowchart of the Study

Copies of medical records were acquired through an agreement with the hospital administration. Taking into consideration the retrospective design of this study, we did not (1) set a diagnosis, (2) evaluate the patient's health status on admission and discharge, (3) perform laboratory testing. All necessary data about patients (socio-demographic characteristics, medical history, comorbidities, health status on admission and discharge), diagnosis (type of CAP), and treatment (drugs, doses, frequency regimen, and length) was extracted from the medical records.

Antibiotic-related DRPs (inappropriate dosage and length of therapy, contraindications, potential DDIs) were identified by authors according to the Pharmaceutical Care Network Europe (PCNE) DRPs classification v5.01[17]. The appropriateness of antibiotic therapy was assessed by using Ukrainian guidelines for the management of CAP in adults[19], The State Register of Medicinal Products of Ukraine[20], and Medscape[21]. All types of potential DDIs according to the Med-

scape drug interaction checker (minor, significant, serious, and contraindicated)[21] were taken into account in this study.

Statistical analysis

Descriptive statistics were used to describe and summarize demographic and disease characteristics of patients. Qualitative variables were presented as frequencies and percentages. Quantitative variables were given as mean ± standard deviation (SD) and ranges.

The drug risk ratio was calculated for evaluation the risk of antibiotic-associated DRPs for antibiotics that had been prescribed at least 3 times.

Multiple logistic regression analysis was performed to figure out the factors that influence the patient's health status on discharge (patient fully recovered/ patient not fully recovered). Univariable analysis was conducted using simple logistic regression. Variables with a P value ≤0.25 were considered statistically significant and were included in the multiple logistic regression. A preliminary regression model was based on the results of backward and forward Wald methods. Multicollinearity and interaction among variables were checked. Hosmer-Lemeshow test, classification table and the area under the ROC-curve were applied to check the model fitness. Results were presented as adjusted odds ratio (OR), 95% confidence interval (CI) for OR, and P value for the variables included in the final model. A value of $P<0.05$ was considered statistically significant. The statistical analyses were performed with SPSS Trial.

RESULTS AND DISCUSSION

The distributions of demographic and clinical characteristics of the study population are summarized in Table 1.

Table 1. The Baseline Characteristics of the Patients

Characteristics	Frequency (%)	Mean (SD)
Gender		
male	94 (51.9)	
female	87 (48.1)	
Age, years		48.3 (18.1)
18-39	71 (39.2)	
40-64	67 (37.0)	
more than 65	43 (23.8)	
Co-morbidities		
yes	82 (45.3)	
no	99 (54.7)	
Previous drug allergy		
yes	16 (8.8)	
no	165 (91.2)	
Type of CAP		
right-sided	106 (58.6)	
left-sided	48 (26.5)	
bilateral	27 (14.9)	
Health status on admission		
moderate	143 (79.0)	
severe	38 (21.0)	
Number of prescribed medications		9.8 (3.5)
Length of stay at hospital, days		10.3 (2.7)
Health status on discharge		
patient fully recovered	54 (29.8)	
patient not fully recovered	127 (70.2)	

Note. CAP = community-acquired pneumonia; SD = standard deviation

The majority of inpatients were men (51.9%). The mean age was 48.3 ± 18.1 years (range 18-84 years). In 106 (58.6%) of medical records the right-sided CAP was noted, in 48 (26.5%) – left-sided and in 27 (14.9 %) – bilateral. The moderate health status on admission had 79.0% of patients, 21.0% – severe.

The average for a hospital stay was 10.3 ± 2.7 days (range 5-25). Each patient during hospitalization took at least 3 medicines (a mean of 9.8 ± 3.5 medicines per patient, range 3-22).

Antibiotics were prescribed in a total number of 353 items. The mean number of antibiotics received by the patients was 2.0 ± 0.7 ranging from 1 to 5 (Table 2).

Table 2. Characteristics of Antibiotic Therapy

Characteristics	Frequency (%)	Mean (SD)
Number of prescribed antibiotics in medical records, items 1 2 3 4 5	 43 (23.7) 114 (63.0) 15 (8.3) 8 (4.4) 1 (0.6)	2.0 (0.7)
Groups of antibiotics Fluoroquinolones Cephalosporins Macrolides Penicillins with a beta-lactamase inhibitor Nitroimidazoles Others*	 160 (45.3) 98 (27.8) 57 (16.1) 20 (5.7) 10 (2.8) 8 (2.3)	
The route of administration Injections Both injections and oral	 108 (59.7) 73 (40.3)	
Length of antibiotic therapy, days 5-10 more then 10	 124 (68.5) 57 (31.5)	10.0 (2.6)

The most frequent antibiotics prescribed were fluoroquinolones, followed by cephalosporins and macrolides, accounting for 45.3%, 27.8%, and 16.1% of prescriptions, respectively. Levofloxacin (n=157; 44.5%), cefepime (n=79; 22.4%) and azithromycin (n=42; 11.9%) were the most common antibiotics in this study.

Most of the patients received antibiotics in injections 5 to 10 days (a mean length of antibiotic therapy 10.0 ± 2.6 days; range 5-25).

Antibiotic therapy of CAP was associated with numerous DRPs, which were found in 158 (87.3%; 95%CI 81.5%:91.8%) medical records out of 181 enrolled. Totally 321 DRPs (on average 1.8 ± 1.4 DRPs, range 0-8 DRPs) of 4 items were identified in this study: (1) potential DDIs (76.6%), (2) inappropriate dosing (14.0%), (3) inappropriate length of antibiotic therapy (7.5%) and (4) contraindicated usage of antibiotics (1.9%) (Table 3).

Table 3. Identified Antibiotic-Associated DRPs (n=321)

Items of DRPs	Frequency	%
Potential DDIs	246	76.6
Dose-related DRPs	45*	14.0*
insufficient daily dose of antibiotics	32	10.0
exceeded daily dose of antibiotics	7	2.2
insufficient dose of solvent	1	0.3
exceeded dose of solvent	5	1.5
Length of antibiotic therapy	24*	7.5*
insufficient	20	6.2
exceeded	4	1.3
Contraindicated usage	6	1.9

The drug risk ratio was high for spiramycin (1.000), metronidazole (1.000), levofloxacin (0.828), azithromycin (0.714) and cefoperazone (0.600). Ceftriaxone, amoxicillin with a beta-lactamase inhibitor and cefepime were associated with a lower risk of DRPs, 0.533, 0.450 and 0.300 respectively.

Univariable analysis was done using simple logistic regression to identify the variables associated with the patient's health status on discharge (patient fully recovered/not fully recovered) (Table 4).

Table 4. Univariable Analysis of Factors Associated with the Patient's Health Status on Discharge

Variables	Crude OR (95%CI)	Wald Statistics (df)	P value[a]
Gender			
male	1.00		
female	0.74 (0.38-1.39)	0.921 (1)	0.337
Age, years	0.97 (0.94-0.98)	14.346 (1)	<0.001
Co-morbidities			
no	1.00		
yes	0.34 (0.17-0.69)	9.169 (1)	0.002
Previous drug allergy			
no	1.00		
yes	1.08 (0.36-3.26)	0.017 (1)	0.897
Type of CAP			
bilateral	1.00		
right-sided	1.67 (0.81-3.40)	1.922 (1)	0.166
left-sided	0.58 (0.20-1.66)	1.044 (1)	0.307
Health status on admission			
severe	1.00		
moderate	1.06 (0.48-2.32)	0.018 (1)	0.893
Length of stay at hospital, days	0.97 (0.85-1.09)	0.383 (1)	0.536
Number of prescribed medications	0.91 (0.82-1.00)	4.078 (1)	0.043
Number of prescribed antibiotics	1.38 (0.90-2.09)	2.120 (1)	0.145
Length of antibiotic therapy, days	0.91 (0.80-1.04)	1.954 (1)	0.162
The route of antibiotic administration			
both injections and oral	1.00		
injections	0.57 (0.30-1.08)	2.960 (1)	0.085
Number of antibiotic-related DRPs	0.79 (0.61-1.02)	3.224 (1)	0.073

Eight variables (age, co-morbidities, type of CAP, number of prescribed medications, number of prescribed antibiotics, length of antibiotic therapy, the route of antibiotic administration, and number of antibiotic-related DRPs) were found to have a P value ≤0.25 and included in the multiple regression model. Age of patients ($p<0.001$), number of antibiotics ($p<0.001$), length of antibiotic therapy ($p=0.036$), and total number of antibiotic-associated DRPs ($p=0.005$) were defined as factors that influence the patient's health status on discharge (Table 5).

Table 5. Factors Associated with the Patient's Health Status on Discharge, Final Model

Variables	Adjusted OR (95% CI)	Wald Statistic (df)	P value[a]
Age	0.96 (0.94-0.98)	13.237 (1)	<0.001
Number of prescribed antibiotics	3.10 (1.65-5.84)	12.333 (1)	<0.001
Length of antibiotic therapy	0.84 (0.71- 0.99)	4.379 (1)	0.036
Number of antibiotic-related DRPs	0.60 (0.42-0.86)	7.900 (1)	0.005

Note. OR = odds ratio; CI = confidence interval; DRPs = drug-related problems. Multicollinearity and interaction term were checked and were not found. Hosmer-Lemeshow test (P=0.686), classification table (70.2% of subjects are correctly classified by the model) and the area under the ROC-curve (74.7%; 95% CI 66.9%-82.5%) were applied to check the model fitness and reported to be fit. [a] – multiple logistic regression (Wald test), significant at P<0.05

This study aimed to characterize the antibiotic treatment for adult inpatients with CAP in Ukraine, describe the incidence and types of antibiotic-associated DRPs, investigate the risk of occurrence of DRPs for the different antibiotics and determine the factors contributing to the patient's health condition on discharge.

CAP is a common problem in adults[1,22,23]. The average age of hospitalized patients with CAP in the USA is 57 years[24], in France – 63 years[25], in Spain – 66 years[26], in Germany – 70 years[27]. Compared with these data, the mean age of inpatients in Ukraine is much less (48.3 years). In addition, we found that the incidence of CAP decreased with increasing age. This result is opposite to data in the other studies[1,2,24,28]. It could be, possibly, related to the high prevalence of self-treatment of respiratory tract infections among working-age adults in Ukraine, underestimating threats associated with ignoring the doctor's consultation, delaying medical care appointments, and, therefore, deterioration requiring hospitalization[29].

In our study, CAP was slightly more common among men (51.9%). This distribution confirms the results of previous studies in France[25], Spain[26], Germany[27], the Netherlands[28]. However, in numerous other studies the slight predominance of women has been established[1,30-32].

In 79.0% of medical records, the patient's health status on admission was noticed as moderate, in 21.0% as severe. Comorbidity had 45.3% of patients. The most common comorbidities were coronary heart disease, hypertension, cardio sclerosis and heart failure. As reported by Torres et al[33], the presence of comorbid conditions, especially chronic respiratory and cardiovascular diseases, increases the risk of CAP significantly. Furthermore, comorbidity and the severity of CAP influence the duration of hospitalization that varies considerably in

different countries (5 to 15 days)[23,25,28,32]. According to the results of this study, the mean length of stay at the hospital was 10.3 days.

The standard treatment of CAP includes antibiotics[19,34,35]. The vast majority of inpatients (63.0%) during the study period received two antibiotics, 13.3% – at least 3. As described in scientific literature, the administration of 3 or more antibiotics, increases the risk of prescribing medication errors[36]. In this study, fluoroquinolones (in particular levofloxacin) were the most common antibiotics (45.3%), followed by cephalosporins (27.8%) and macrolides (16.1%). Similar results have been found in Germany[27] and Denmark[30]. But in contrast to our study, moxifloxacin and ciprofloxacin were the most frequently administrated for inpatients with CAP[27,30]. Prescribing of other antibiotics (mainly nitroimidazoles, penicillins/cephalosporins with beta-lactamase inhibitors) was low. The choice of antibiotics influences the risk of CAP treatment failure with the following switching to another antimicrobial therapy[27]. Ott et al[27] established that moxifloxacin or a combination of β-lactam and macrolide are possible strategies to prevent the treatment failure.

The proper duration of antibiotic therapy is a serious controversial issue in the management of CAP[37-39]. The majority of guidelines do not have specific recommendations regarding the proper length of antibiotic treatment of inpatients with CAP[40]. It is generally accepted that the traditional antibiotic regimens are 7 to 14 days long[39]. Our findings are consistent with it because the mean length of antibiotic therapy was 10.0 days. However, in different countries, the duration of antibiotic treatment of CAP differs significantly[32,37]. The longer duration is associated with numerous antibiotics-related adverse health and economic outcomes such as antimicrobial resistance, allergic reactions, *Clostridium difficile* infections, etc[5,6,39,41]. Therefore, the efficacy of short versus traditional antibiotic courses has been investigated in recent studies. According to some of them, there is no difference in efficacy between antibiotic therapy of CAP throughout 3-5 days and 7-14 days, respectively[38,39,42]. Moreover, some guidelines have been updated and now suggest a 5-day course of antibiotic treatment[35].

For 59.7% of inpatients, antibiotics were prescribed in injections, for 40.3% in both injections and oral forms. Overall, the choice of the route of antibiotic administration depends on the severity of CAP, patient's health condition and risk factors for methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* infections[35]. Sæterdal et al[43] found that there is little or no difference between the effectiveness of oral and intravenous antibiotic treatment in patients with CAP.

A lot of studies have described the inappropriateness of antibiotic prescription

so far[9,10,12,36]. The presence of antibiotic-related DRPs is associated with (1) the patient's duration of hospital stay, (2) polypharmacy, and (3) comorbidity[9]. In our study, antibiotic-related DRPs were found in 87.3% of medical records. This result is much higher compared to other studies (up to 72%)[9,12,14,15].

According to the scientific literature, beta-lactamase-resistant penicillins, quinolones, and macrolides provoke the highest risk of antibiotic-related DRPs[12]. Our results agree with these findings up to a point because the highest levels of drug risk ratio were defined for spiramycin, metronidazole, levofloxacin, azithromycin, and cefoperazone. Consequently, the abovementioned antibiotics are at the biggest risk of occurrence of DRPs. Ceftriaxone, amoxicillin with a beta-lactamase inhibitor, and cefepime were associated with a lower risk of DRPs.

In the present study, the most frequent antibiotic-associated DRPs were potential DDIs (76.6%). This is consistent with previous studies where DDIs were highly prevalent in patients with CAP[44]. DDIs can lead to (1) different adverse drug reactions, (2) decreasing clinical effectiveness, (3) toxicity etc[44]. For instance, we identified 7 contraindicated potential DDIs between ceftriaxone and calcium chloride/gluconate. This combination is associated with the risk of potentially fatal particulate precipitation in the lungs and kidneys[20,21].

Antibiotic dose-related DRPs were frequent (14.0%). This subset of DRPs involved both the wrong dosage of antibiotics and the wrong dosage of solvents. Amoxicillin with clavulanic acid, metronidazole and cefepime were the most frequently associated with DRPs «Insufficient daily dose of antibiotics». For example, amoxicillin/clavulanic acid 1000 mg/200 mg for injection/infusion should be used every 8 hours[20]. But it was prescribed every 12 or 24 hours. Metronidazole was administrated only once a day instead of 3 times per day[20]. The injection regimen of cefepime is every 8 to 12 hours[20]. However, our patients received it every 24 hours.

DRPs of item «Exceeded daily dosage of antibiotics» were less common and entirely related to azithromycin. According to the recommendations, the dose regimen of azithromycin for CAP treatment is 500 mg orally as a single dose on day 1, followed by 250 mg orally once a day on days 2 to 5[21]. Nevertheless, inpatients took 500 mg of azithromycin throughout therapy.

In addition, 6 DRPs regarding the wrong dosage of solvents were identified. The volume of sodium chloride was at least twice much or less as necessary. This subset of DRPs is rather significant because the inappropriate amount of solvent influences the rate of drug administration and, therefore, effectiveness and safety of therapy[45].

Although the duration of antibiotic therapy has recently become a controversial question, we identified 24 DRPs related to this issue. The necessary length of CAP pharmacotherapy should be at least 7 days for levofloxacin, cefepime and metronidazole, 6 days – for clarithromycin, 5 days – for amoxicillin and azithromycin[20]. However, the duration of treatment was insufficient in 20 medical records. At the same time, in 4 medical records, the length of antibiotic treatment was exceeded. All DRPs of this subset were associated with azithromycin prescription 7 to 11 days.

In this study, all cases of contraindicated usage of antibiotics have its origins from the allergy. Almost all DRPs of this item were related to cross allergy between cephalosporins and penicillins. Additionally, we identified one DRP of contraindicated levofloxacin prescribing due to the ofloxacin allergy.

The next step of this study was to identify the factors contributing to the patient's health condition on discharge. It is known that the awareness of the risk factors can improve the therapy and clinical outcomes[46,47]. Despite publishing numerous studies in scientific literature dedicated to determinants of DRPs[9,13], predictors of CAP antibiotic treatment failure, early deterioration or so[46-50], the information about factors that influence the patient's health condition on discharge is limited. According to our results, these factors include the age of patients ($p<0.001$), number of prescribed antibiotics ($p<0.001$), length of antibiotic therapy ($p=0.036$), and the total number of antibiotic-associated DRPs ($p=0.005$). Thus, interventions to reduce antibiotic-related factors may have a significant positive impact on CAP therapy.

Limitations

Limitations of this study include its retrospective design. Identifying of DPRs was based only on the information available from the medical records. Therefore, we were able to check potential DDIs, contraindications, appropriateness of doses, frequency and length of antibiotic therapy. We did not monitor the patient's condition throughout the therapy. Hence, DDIs could be considered only as potential.

Only 4 subsets of DRPs were included in the regression analysis. Adverse drug reactions, treatment failure, long-term clinical outcomes were not taken into consideration because the medical records did not include such kind of information or it was missed. Future studies are needed to explore the impact of other types of DRPs (not only antibiotic-associated) on a patient's health condition on discharge. Moreover, other factors that influence a patient's health condition on discharge cannot be excluded.

In this study, we had only 2 options of patient's health status on discharge: (1) patient fully recovered, (2) patient not fully recovered and was discharged under the care of primary care physicians. Further investigations are required to define factors contributing to the other options of patient's health status on discharge (died, discharged with deterioration, etc.).

In addition, the analysis of medical records only from one hospital limits the generalizability of our results.

In conclusion, CAP is a common problem in adults that requires antibiotic therapy. The prevalence of antibiotic-related DRPs in hospitalized patients with CAP was found to be high. Potential DDIs were defined as the most common antibiotic-associated DRPs. Spiramycin, metronidazole, levofloxacin, azithromycin and cefoperazone were identified as antibiotics with the highest drug risk ratio level and the biggest risk of occurrence of DRPs. Age of patients, number of prescribed antibiotics, length of antibiotic therapy, and the total number of antibiotic-associated DRPs were defined as the factors that significantly contribute to the patient's health status on discharge. Thus, antibiotics should be the drug class most commonly involved in the interventions to improve the safety and quality of CAP therapy.

STATEMENT OF ETHICS

The study received ethical approval from the Human Research Ethics Committee of Danylo Halytsky Lviv National Medical University (Protocol No.10 of 16.12.2019).

Due to the retrospective design of this study, we did not have written patient's consent for being included in the study. An agreement with the hospital administration was obtained.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

Concept – Oksana Horodnycha, Andriy Zimenkovsky (authors contributed equally); Design – Oksana Horodnycha, Andriy Zimenkovsky (authors contributed equally); Data Collection and Processing – Oksana Horodnycha; Statistical Analysis and Interpretation – Oksana Horodnycha; Literature Search – Oksana Horodnycha; Drafting of the manuscript – Oksana Horodnycha; Critical revision of the manuscript – Andriy Zimenkovsky.

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