ENGLISH VERSION: ESTIMATION OF USING MEDICATIONS OF DIFFERENT GROUPS FOR COMMUNITY-ACQUIRED PNEUMONIA TREATMENT OF PATIENTS WITH COMORBIDITIES*

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With purpose to assess the volume and rationality of prescription of medicines for the community-acquired pneumonia (CAP) treatment in patients with chronic comorbidities a prospective study of 438 in-patients (214 men (48.9%), average age - 56,1 ± 17,9) was conducted. Chronic comorbidities were in 359 (82.0%) patients. Controlled comorbidities were in 115 (26.3%), uncontrolled - 120 (27.4%), complicated chronic diseases - 124 (28.3%). Comorbidities were absent in 79 (18.0%) patients. There were significant polypharmacy of CAP patients, mean amount of medicines was 11,0 ± 4,0. Complicated chronic diseases in patients with CAP caused prescription of 13,7 ± 5,0 drugs. CAP in-patients with uncontrolled chronic diseases received 11,0 ± 2,9 medicines. CAP in-patients with controlled comorbidities used 9,7 ± 2,7 medicines and patients without comorbidity treated with 8,4 ± 2,5 drugs (p <0.001). All patients received antibiotics, as mandatory CAP treatment. Mucolytics were prescribed 92.7%, dextrans solutions - 36.0%, which was necessary due to features of CAP course. NSAIDs were administered 48.6% patients, but half of them did not need use these medications. Using sulfocamphocaine (39.0%), thiotriazoline (25.1%) and plasmol (13.2%) did not have any positive effect at the clinical course and outcome of CAP, it was mistaken.

Key words: the community-acquired pneumonia, treatment, chronic comorbidities.

Introduction

Diagnosis of community-acquired pneumonia (CAP) requires antibiotic treatment, which effectiveness is proven not only in large-scale studies, but almost half a century of clinical practice. After the beginning of the widespread use of antibiotics, mortality due to CAP declined rapidly and during past 50 years stabilized at 1% among outpatients, 5-15% among in-patients hospitalized to the therapeutic department, and 40% among ICU patients with severe CAP without any significant progress despite the introduction of new therapies [1].

Non-antimicrobial adjuvant therapy of CAP, which would contribute to improving the course and outcomes of the disease, is one of the actual problems of modern medicine. Appropriate evidence of the usefulness of mucolytic, analeptic, nonsteroidal anti-inflammatory, immunomodulatory drugs for treatment of CAP is absent, so they are not recommended by guidelines for the treatment of CAP [2].

However, in routine practice, basing oneself on their own experience and features of clinical presentation of CAP, doctors often prescribe antibiotics and other groups of medications to correct the symptoms, prevent complications that inevitably leads to polypharmacy, especially in patients with comorbidity.

Objective: to assess the volume and rationality of prescription of medicines for the CAP treatment in patients with chronic comorbidities

Materials and Methods

Prospective study of 438 in-patients with CAP who were treated in the pulmonology department of Vinnytsia City Clinical Hospital #1 from January till June 2012 was conducted. Males were 214 (48,9%), females – 224 (51,1%), average age of patients was 56,1±17,9 years.

Diagnosis of CAP and its severity was established on the basis of subjective, objective, laboratory, instrumental and radiological examinations in accordance with the national guidelines set out in order of Ministry of Health of Ukraine №128 from 19.03.2007 [3].

Most of patients had moderate severe CAP - 399 (91.1%) and only 39 (8.9%) patients had severe CAP.

CAP in-patients without chronic comorbidities were included in the comparison or “healthy” group (HG) - 79 (18.0%) ones.

Chronic comorbidities were observed in 359 (82.0%) patients. Almost half of the patients had chronic diseases with affection of two or more organ systems (Table 1).

Table 1

The structure of chronic diseases in patients with CAP (n=438)

Comorbidity	abs	%
Cardiovascular diseases	308	70,3
Respiratory diseases	143	32,6
Gastro-intestinal diseases	77	17,6
Diabetes mellitus	40	9,1
Obesity	116	26,5
Renal diseases	45	10,3
Nervous diseases	28	6,4
Malignancy	14	3,2
Alcohol and drug dependence	3	0,7
Total	359	82,0
Amount of comorbidity		
Disease of one system affection	143	32,6
Diseases of two and more systems affection	216	49,3

All chronic diseases in patients with CAP were evaluated according to control of them. Patients were divided into three groups: controlled group with well controlled comorbidity (CG) - 115 people, uncontrolled group (NG) - 120 people, and group of patients with complicated comorbidity and functional failure (FG) - 124 people.

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The analysis of treatment included a determination of volume of antibiotic and adjuvant therapy. All medications that the patient received due to CAP were recorded indicating the dose, frequency and duration of use. Compliance of prescribed therapy with the guidelines, its efficacy and safety, drug interactions, risks of bad outcome of CAP was evaluated.

Therapy was considered ineffective if the patient died or had complications of CAP, requiring surgical treatment.

The therapy was not enough effective, if the patient had rest symptoms of the CAP after discharge and needed additional treatment of the disease in the outpatient setting.

Treatment in a hospital was considered effective when the patient was discharged with recovery.

Statistical analysis was conducted using statistical software package SPSS for Windows version 11. The level of significance was $p < 0.05$.

Variables related to nominal scale were analyzed by constructing cross-tables and chi-square statistics.

Descriptive statistics were determined for each interval variable and presented as the mean ± standard error. Comparison of variables was performed using the definition of Student's t-test or univariate analysis of variance in the case of normal distribution and nonparametric methods of comparison in the event of abnormal distribution.

Results and discussion

The average number of prescribed medicines was 11.0 ± 4.0 (4 to 34 drugs). Patients with moderate severe CAP received 10.4 ± 3.1 medicines and patients with severe CAP – 16.9 ± 6.5 drugs ($p < 0.001$).

Average number of medicines was 8,4 ± 2.5 in CAP patients without comorbidity. If patient had one concomitant disease, this figure statistically significantly increased to 9.7 ± 2.9, while in case of multiple concomitant chronic diseases - to 12.3 ± 4.3 drugs ($p<0.001$).

Assessment of prescribed medications according to the level of control of chronic diseases found that patients from FG received significantly most drugs – 13.7 ± 5.0, against 11.0 ± 2.9 drugs in NG, 9.7 ± 2.7 drugs in CG and 8.4 ± 2.5 drugs in HG ($p < 0.001$).

Comparing the number of medications in patients with CAP and the presence of the most common chronic diseases of the cardiovascular system (coronary heart disease, hypertension, heart failure, arrhythmia), respiratory (COPD, asthma), digestive (chronic cholecystitis, peptic ulcer, chronic hepatitis and cirrhosis), diabetes mellitus and obesity revealed that patients with respiratory diseases (13.2 ± 4.8 drugs) and diabetes mellitus (13.0 ± 4.6 drugs) used significantly the most number of medications than CAP patients without these diseases (Table 2).

Table 2

The average number of prescribed medications for CAP patients with and without comorbidity

Comorbidity	Average number of medications in patients with comorbidity	Average number of medications in patients without comorbidity	p
Cardiovascular diseases (n=307)	11,8±4,2	8,9±2,5	<0,001
Respiratory diseases (n=143)	13,2±4,8	9,9±3,0	<0,001
Digestive diseases (n=77)	11,4±4,7	10,9±3,8	0,266
Diabetes mellitus (n=40)	13,0±4,6	10,8±3,9	0,001
Obesity (n=116)	11,3±3,9	10,8±4,0	0,314

Patients with CAP and cardiovascular comorbidity received significantly more than the 3 drugs than those without affection of heart and vessels.

The presence of concomitant diseases of the gastrointestinal tract and obesity did not lead to an additional use of medications in CAP patients compared to other without this comorbidity.

Treatment of in-patients with CAP is characterized with polypharmacy or using 5 or more drugs at the same time and has been shown to be associated with several important adverse events in older adults [4].

For assess rationality of polypharmacy in patients with CAP and comorbidity spectrum of prescribed medications according to ATC classification (Anatomical Therapeutic Chemical classification) was analyzed (Table 3).

Table 3

Structure of prescribed drugs from different pharmacological groups for treatment of CAP patients

Anatomical therapeutic chemical class	Total (n=438)	
	абс	%
Respiratory system		
Mucolitics	406	92,7
MDI bronchodilator	64	14,6
Bronchodilator for nebulization	118	26,9
MDI inhaled corticosteroids	44	10,0
Inhaled corticosteroids for nebulization	74	16,9
Theophyllines	53	12,1
Cardiovascular system		
Renin-angiotensin system agents	160	36,5
Beta-blockers	70	16,0
Calcium-channel blockers	29	6,6
Diuretics	192	43,8
Aldosterone antagonists	58	13,2
Cardiac glycosides	50	11,4
Amiodarone	6	1,4
Nitrates	14	3,2
Meldonium	135	30,8
Quercetine	28	6,4

Lipid-lowering agents	10	2,3
Sulfocamphocaine	171	39,0
Alimentary tract and metabolism		
Microbial antidiarrheal drugs (probiotics)	229	52,3
Thiotriazoline	110	25,1
Other hepatoprotectors	10	2,3
Proton-pump inhibitors	8	1,8
Spasmolytics	6	1,4
Oral diabetes agents	27	6,2
Vitamins	21	4,8
Plasmol	58	13,2
Blood and blood-forming organs		
Antithrombotic agents (heparin and warfarin)	45	10,3
Antiagreganty (aspirin, clopidogrel)	105	24,0
Antihemorrhagic means (aminocaproic acid, etamsylate)	16	3,7
Dextran (reopolyglukine)	158	36,0
Electrolyte solutions	83	18,9
Solutions aminoacids (arginine)	56	12,8
Systemic corticosteroids	75	17,1
Nonsteroid anti-inflammatory drugs	213	48,6
Other	81	18,5

All patients received antibacterial medicines for systemic use. The choice of antibiotic in most cases corresponded to recommended drugs for the treatment of patients with moderate severe or severe CAP (table 4).

Table 4

Spectrum of antibiotics used for hospital treatment of patients with community acquired pneumonia (n=438)

Corresponded to recommendation drugs			Corresponded to recommendation antipseudomonas drugs		
antibiotic	abs	%	antibiotic	abs	%
Ceftriaxone	295	67,4	Amikacin	37	8,4
Levofloxacin	274	62,6	Cefoperazone	33	7,5
Clarithromycin	100	22,8	Cefepim	18	4,1
Azithromycin	14	3,2	Ceftazidime	18	4,1
Amoxicillin/clavulanate	16	3,7	Meropenem	3	0,7
Gatifloxacin	14	3,2	Ciprofloxacin	1	0,2
Moxifloxacin	4	0,9	Gentamycin	1	0,2
Cefotaxime	3	0,7			
Non-Corresponded to recommendation drugs					
Ceftriaxone/sulbactam	21	4,8	Vancomycin	1	0,2
Ofloxacin	1	0,2	Amoxicillin	1	0,2
Doxicycline	1	0,2	Cefuroxime	2	0,4

Rational antibiotic therapy is not only selection of effective drug against the possible pathogen, but it involves matching severity of CAP. Analysis of the correspondence of antibiotic therapy to national guidelines found significant differences with recommendations (table 5).

The combination of respiratory fluoroquinolones (levofloxacin) and 3rd generation cephalosporin (ceftriaxone) was the most frequently prescribed combination, regardless of the severity of the CAP. This combination is alternative antibiotic treatment for severe CAP, so it can be considered rational. Using this combination of antibiotics in patients with moderate severe CAP is inappropriate, excessive. It provoked adverse event - development of Candida infection of the oral cavity and respiratory tract in 47 (10.7%), diarrhea in 23 (5.3 %).

Table 5

Compliance with the recommendations of antibiotic therapy of in-patients with CAP

Corresponded antibiotic therapy	abs	%	Non-corresponded antibiotic therapy	abs	%
Patient with moderate severe CAP (n=399)					
3rd generations of cephalosporin + macrolide	109	27,3	Beta-lactam + Respiratory fluoroquinolone	182	45,6
Respiratory fluoroquinolone	30	7,5	Antypseudomonas beta-lactam + macrolide / fluoroquinolones	37	9,3
Protected aminopenicillins + macrolide	11	2,8	Three antibiotics	21	5,3
			Incorrect antibiotic monotherapy	9	2,3
Total	150	37,6	Total	249	62,4
Patient with severe CAP (n=39)					
Beta-lactam + macrolide	2	5,1	Incorrect three antibiotics	5	12,8
Beta-lactam + Respiratory fluoroquinolone	13	33,3	Incorrect antibiotic monotherapy	6	15,4
Antypseudomonas beta-lactam +ciprofloxacin (levofloxacin)/aminoglycoside	13	33,3			
Total	28	71,8	Total	11	28,2

The respiratory system medicines were leader among other groups of drugs.

The vast majority of patients received mucolytics and expectorants (406 (92.7%) patients), the main effect of which is aimed at creating adequate drainage of trachea-

bronchial secretions to facilitate the recovery of the patient. Their using can be considered partially appropriate.

More than half of patients treated with antidiarrhoeal microbial products - probiotics containing bifidobacteria and lactobacilli required for normal functioning of the intestine (Table 3).

Rationality of probiotic using with antibiotics is discussed. According microbiology research lactobacilli and bifidobacteria are suppressed with antibiotics as well as pathogens, so rational combination questionable [5]. However, analysis of numerous randomized clinical trials showed that the use of probiotics with antibiotic therapy reduced the risk of antibiotic-associated diarrhea by 60% and more [6-8]. According to Swedish researchers use drugs with lactobacilli in patients receiving antibiotic therapy, reduced the incidence of diarrhea and nausea [9].

These drugs are not included in the protocol of care for patients with CAP, which makes their use is not relevant recommendations.

Despite the fact that NSAIDs are not recommended for the treatment of patients with CAP, nearly half of them treated with NSAIDs (Table. 3). They are usually prescribed for reduction of symptomatic pleural pain, headache, and fever. But patients with these symptoms were significantly less than who received NSAIDs: high fever was determined in 35 (8.0%), pleural pain in 54 (12.3%), and the administration of the drugs was observed in 213 (48.6%) patients.

Excessive use of NSAIDs can mask the effectiveness of antibiotic therapy, leading to erroneous assessments of the patient condiotion, in addition to loads liver enzyme system, creating the risk of gastropathy [10].

The combination of NSAIDs with aminoglycosides increased nephrotoxicity, with fluoroquinolones - stimulates the nervous system and increases the risk of seizures [11].

More than a third of patients received sulfocamphocaine, which effectiveness for CAP treatment is not proven. Comparison of dynamics of CAP symptoms in patients treated with this drug, found positive changes on the 3rd day of treatment observed significantly less frequently than in patients who did not take the sulfocamphocaine (table 6).

Table 6

Comparison of the dynamics of CAPsymptoms in patients who received or did not receive sulfocamphocaine

	Dynamics of CAPsymptoms on the 3-rd day					Dynamics of CAPsymptoms on the 7-th day				
	Patients received sulfocampho-caine (n=171)		Patients not receive sulfocampho-caine (n=267)		P	Patients received sulfocampho-caine (n=171)		Patients not receive sulfocampho-caine (n=267)		P
	abs.	%	abs.	%		abs.	%	abs.	%	
Positive	100	58,5	178	66,7	0,001	128	74,9	185	69,3	0,114
Negative	30	17,5	17	6,4		4	2,3	2	0,7	
Without dynamics	41	24,0	72	27,0		39	22,8	80	30,0	

Analysis of CAP outcome showed that the use sulfocamphocaine was often associated with treatment failure of CAP - development of complications or death of the patient (table 7). Perhaps, it was due to the more severe patient condition, whom was administered analeptic. But the data suggested use of the sulfocamphocaine in patients with CAP was unnecessary.

Table 7

Comparison of the CAP outcome in patients received and not received sulfocamphocaine

CAP outcome	Patients received sulfocamphocaine (n=171)		Patients not receive sulfocamphocaine (n=267)		P
	abs.	%	abs.	%	
Recovery	104	60,8	159	59,6	<0,001
Outpatient treatment	52	30,4	101	37,8	
Surgical treatment	10	5,8	7	2,6	
Death	5	2,9	0	0	

Prescription of electrolyte solutions, like rheosorbilact, observed in 158 (36.0%) patients with CAP, who showed signs of dehydration and hypovolemia, so its use was rational. The drug was administered during the first three days of hospital stay in most patients.

Regardless of the presence of chronic diseases a quarter of patients treated with thiotriazoline (table 3). According to the instructions thiotriazoline is recommended for the comprehensive treatment of coronary artery disease, arrhythmia, chronic hepatitis, cirrhosis of the liver. We compared outcome of CAP in patients who suffered from these comotbidities and received or did not received thiotriazoline.

It was found using this drug did not influence the outcome of CAP in patients with coronary artery disease and arrhythmias (Fig. 1).

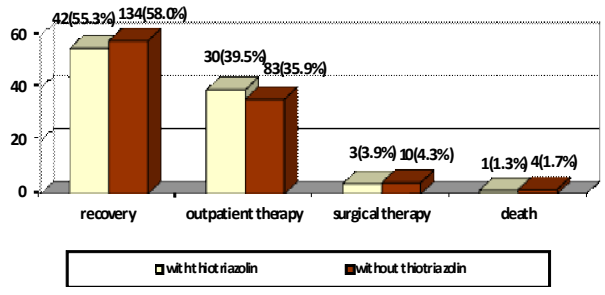

Fig. 1. Influence of thiotriazoline use on the CAP outcome of patient with cardiovascular diseases (p=0,950)

In CAP patients without chronic cardiovascular diseases receiving thiotriazoline, recovery in hospital was not achieved more than half of patients, 18 (52.9%) patients needed outpatient follow-up care, while the group without thiotriazoline outpatient follow-up care

needed only 22 (22.7%), and 71 (73.2%) patients recovered (Table 8).

Table 8

Influence of thiotriazoline use on the CAP outcome of patient without cardiovascular diseases

Outcome	Thiotriazolin use				P
	Yes (n=34)		No (n=97)		
	abs	%	abs	%	
Recovery	16	47,1	71	73,2	0,003
Outpatient therapy	18	52,9	22	22,7	
Surgical therapy	0	0	4	4,1	
Death	0	0	0	0	

Similar effects are observed in patients with chronic diseases of the digestive system, which also had statistical significance (table 9).

Patients with thiotriazolin therapy recovered only 9 (45.0%), other were needed outpatient follow-up care. But more than two-thirds of CAP patients without thiotriazolin taking recovered. It indicates the unreasonableness use of thiotriazolin in treatment of CAP as in patients with chronic cardiovascular, digestive systems and those who do not have this comorbidity.

Table 9

Influence of thiotriazolin use on the CAP outcome of patient with chronic digestive disease

Outcome	Thiotriazolin use				P
	Yes (n=20)		No (n=57)		
	abs	%	abs	%	
Recovery	9	45,0	39	68,4	0,031
Outpatient therapy	11	55,0	14	24,6	
Surgical therapy	0	0	4	7,0	
Death	0	0	0	0	

Our data differ from the results of I. A. Ilyuk (2014), who reported that thiotriazolin use at the patients with moderate severe CAP significantly reduced rates of endogenous intoxication, improved adaptive reactions, positive dynamics of radiological emergency signs, increased the rate of recovery from CAP till 72.0% against 60.0% in patients was not received thiotriazolin. Duration of hospital stay significantly reduced 29.3% [12].

Taking into account the drug is not recommended by national guidelines for treatment of CAP patients, data on its beneficial effect on the treatment of CAP controversial prescription of thiotriazoline is considered irrational.

Among the drugs are not recommended for the treatment of CAP, but traditionally used for a long time one of the most popular is Plasmol. This drug received 58 (13.2%) patients. The main indication for Plasmol using is a comprehensive treatment of neuralgia, sciatica, neuritis, chronic inflammatory processes that have not been observed in studied patients. The prescription of this drug for CAP patients is false.

Conclusions

Pharmacotherapy in-patients with CAP characterized with significant polypharmacy. Its volume increases according to number of comorbidities and their control. Analysis of the influence of prescribed medications use at course and outcome of the CAP shows inadequate use of sulfocamphocain, tiotriazolin, and Plasmol. Using mucolitics and expectorans, plasma substituting drug was necessary, despite the clinical course of CAP. NSAIDs use was not always rational, but in half of patients it was unnecessary.

Evaluation of the use of drugs found deficiencies in patients with CAP and comorbidities that needs additional educational activities among doctors, supervisory monitoring studies the use of drugs to improve management of these patients.

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