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Original Article

FISHBURNE's METHOD AND THE CLASSICAL METHOD OF PHARMACOECONOMIC ANALYSIS IN THE EVALUATION OF ANTIBIOTIC TREATMENT OF ACUTE AND RECURRENT BRONCHITIS IN CHILDREN

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ABSTRACT

Objective: This study was performed in order to estimate clinical effectiveness of antibiotic therapy in acute and recurrent obstructive bronchitis. For estimation the following was used: the Fishbern method of antibiotics distribution according to clinical effectiveness levels with the help of weighted coefficients and classical "cost–efficiency" pharmacoeconomic analysis of the given antibiotic therapy. Then, for the first time ever, the obtained results of both methods were combined.

Methods: Materials were presented by the data on antibiotic therapy, given for patients who were hospitalized to the in-patient medical facilities due to acute or recurrent obstructive bronchitis. Medical records of 2 259 patients were included in the study. The patients were 0 to 18 y old. In order to determine the weighed coefficients of each used antibiotic with subsequent distribution according to the levels of clinical effectiveness the Fishbern method was applied. Three levels of clinical effectiveness were used in this study, i.e. high, medium and low. The "cost–efficiency" pharmacoeconomic analysis was applied to combine costs and efficiency of the compared therapy courses in acute and recurrent obstructive bronchitis.

Results: Finally we found out that the highest probability of positive effect of cephalosporins group agents was associated with the use of Cefotaximum. *(Biosynthesis)*. From the pharmacoeconomic point of view the most effective in treating acute and recurrent obstructive bronchitis in children in the in-patient facilities was Ceftriaxonum (*Synthesis).* Out of protected penicillins group, we used Amoxicillin/clavulanic acid–original drug Augmentin (*Smithkline Beecham Pharmaceuticals)* and generic drug Amoxiclav *(Lek d. d)*. Augmentin effectiveness was 0.591, and Amoxiclav effectiveness–0.530. Cost of Augmentin treatment course was 106.26 rub. (1.68 US$), cost of Amoxiclav treatment course–103.50 rub.(1.63 US$). Augmentin use turned out to be the most reasonable. Augmentin treatment course was characterized by lower ICER coefficient versus Amoxiclav. We found out that from the pharmacoeconomic point of view Azitromicin (*Vertex Ltd*.) treatment turned out to be the most reasonable of the whole macrolides antibiotics for treatment of acute and recurrent obstructive bronchitis. However, according to the Fishbern clinical effectiveness classification this antibiotic belonged to the group with medium effectiveness level. The group with high effectiveness level included Sumamed, Azitral, Hemomicin, Clacid, Zitrocin and Clabax. Clacid and Clabax were excluded during the pharmacoeconomic analysis. The highest value of ICER coefficient was obtained for Sumamed and made up 39,367.50 rub. (621.53 US$). The highest level of clinical effectiveness was characteristic for Sumamed as well. Besides Sumamed was an original drug of azitromicin. According to the obtained data Azitral and Hemomicin had the lowest values of ICER coefficient (1151.67 rub. (18.18 US$) and 1812.22 rub. (28.61 US$) respectively). Therefore based on the clinical economic analysis these medical agents turned out to be the most suitable.

Conclusion: The results of the pharmacoeconomic analysis showed that the most effective drugs in treatment of acute and recurrent obstructive bronchitis in children in in-patient facilities appeared to be the following: out of cephalosporins-Ceftriaxonum (*Synthesis)*, out of protected penicillins-Augmentin (*Smithkline Beecham Pharmaceuticals)*, out of macrolides-Azitromicin (*Vertex Ltd*.). According to the Fishbern classification, these drugs belonged to the group with medium level of effectiveness.

Keywords: Fishburne' method, Acute obstructive bronchitis, Recurrent obstructive bronchitis, Analysis of "cost-effectiveness", Antibiotic.

INTRODUCTION

Acute obstructive bronchitis (AOB)-a widespread disease that affects 10-15% of the child population and is characterized by the growing incidence worldwide. A considerable number of young children (over 50%) due to acute respiratory infections (ARI) may be repeated episodes of obstructive bronchitis [1]. In cases of repeated (2-3 times or more during the year) of cases of bronchitis with a bronchoostructive syndrome (BOS) is formed by recurrent obstructive bronchitis (ROB). In many cases, bronchial asthma (BA) is the cause of a recurrence of obstructive bronchitis (OB).

Currently, there is a constant increase in the incidence of BA and the growing severity of the disease. Often, asthma in children is formed in early childhood. This problem is actualized [2]. It is now established, that the microbe-viral association, where in one of the infectious agents are intracellular pathogens, such as, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella spp. *et al.*, play an important role in the formation of bronchial obstructive diseases and can cause exacerbation of their [3]. Therefore, the problem of the treatment of bacterial infections in patients with obstructive syndrome is important. Among these patients, concomitant diseases are often observed, such as, rhinitis, sinusitis, tonsillitis and otitis.

An important objective in therapy is to determine the clinical effectiveness of drugs and schemes of treatment. The problem is of particular importance due to the wide range of drugs, as well as a significant number of generic drugs. Comparison of the clinical effectiveness of original and generic drugs is possible by distribution of drugs over the so-called levels of clinical effectiveness. Fishburne's method can be used for this purpose. It is mathematics method.

Also, currently a pharmacoeconomic analysis (PEA) of drug therapy is a fundamental and determinant direction of the planning and definition of medical measures. Using the results of PEA can streamline the system of prescribing of drugs, to eliminate appointment of unnecessary drugs. Comparative evaluation of the quality of two or more methods of prevention, diagnostics, drug and non-drug treatment is a major technique of PEA.

The aim of the study was to evaluate the clinical effectiveness of antibiotic treatment of AOB and ROB, namely the distribution of antibiotics in levels of clinical efficiency with the help of weighting coefficients by method of Fishburne, and classic PEA of conducted antibiotic therapy, as well as a comparison of the results obtained by both methods, which was conducted for the first time.

MATERIALS AND METHODS

Materials for the study were data on antibiotic therapy of patients admitted to hospitals of medical organizations with AOB or ROB. The study included 2 259 patients. The age of patients ranged from 0 to 18 y old.

In order to determine the weighting factors of each of the used antibiotics with their subsequent distribution on levels of clinical efficiency was used Fishburne' method. In this study three levels of clinical efficiency used-namely high, medium and low.

The analysis of "cost-effectiveness" was applied for compare the cost and effectiveness courses of therapy of OB. For each alternative scheme of treatment CER (cost-effectiveness ratio) was calculated of the formula:

CER= DC/E, where

CER — ratio of «cost/effectiveness»;

DC — direct medical costs;

E — effectiveness of treatment

Further, incremental cost for using more expensive methods of treatment was estimated, if more effective schemes of treatment corresponded larger direct medical costs. Incremental costs (the cost of the additional effect of using alternative methods of treatment "B" instead of the method «A») are calculated as:

ICER= $(C_2-C_1)/(E_2-E_1)$, where

ICER-incremental cost-effectiveness ratio,

C_2–cost for method of treatment «B»,

C_1.cost for method of treatment «A»,

E_2–effectiveness of method of treatment «B»,

E_1-effectiveness of method of treatment «A».

RESULTS

Three groups of antibiotics: cephalosporins, penicillins and macrolides were used for the treatment of AOB and ROB in the analyzed period. The largest number of appointments accounted for injectable cephalosporins-57.8%.

Cefotaxim (56.9%), ceftriaxon (23%), cefuroxim (13.8%), cefazolin (6.3%) were used from the cephalosporin antibiotics (table 1).

Table 1: The structure of the cephalosporin antibiotic prescriptions

Cefotaxim 56.9%		**Ceftriaxon 23%**		**Cefazolin 6.3%**	**Cefuroxim 13.8%**
Cefotaxim	Claforan	Ceftriaxon	Lendacin	Cefazolin	Axetin
92.1%	7.9%	86.7%	13.3%	100%	100 %

Amoxicillin/clavulanic acid (Augmentin, Amoxiclav) was used in 16.3% of appointments of the group of protected penicillins. Macrolides were used in 25.9%. Antibiotics-macrolides were used such as azithromycin (65.6%), clarithromycin (9.5%), spiramycin (18,9%), midecamycin (6%) (table 2).

Table 2: Assignment's structure of macrolides

Azithromycin 65.6%					**Clarithromycin 9.5%**			**Spiramycin 18.9%**	**Midecamycin 6%**
Azithromycin	Azithral	Zithrocin	Sumamed	Hemomycin	Clacid	Fromilid	Clabax	Rovamycin	Macropen
17.8%	15.2%	7.0%	37.8%	22.2%	15.4%	41.0%	43.6%	100%	100%

The largest numbers of cases of highly effective antibiotic therapy of AOB, ROB (the clinical effect of "recovery") were observed with use of macrolides. Clinical effects, such as "significant improvement" and "recovery" were noted for the cephalosporins and protected penicillins in the presence of co-morbidities in patients with AOB, ROB, such as otitis, sinusitis, tonsillitis, often accompanied by fever, intoxication.

Table 3: The clinical efficacy of antibiotic therapy * of AOB/ROB

INN (International Nonproprietary Name)	**Antibiotic**	**Clinical effectiveness**
Cefotaxim	Cefotaxim	0.630
	Claforan	0.537
Ceftriaxon	Ceftriaxon	0.546
	Lendacin	0.214
Cefazolin	Cefazolin	0.140
Cefuroxim	Axetin	0.512
Amoxicillin/Clavulanic acid	Augmentin	0.591
	Amoxiclav	0.530
Azithromycin	Azithromycin	0.947
	Sumamed	0.980
	Azithral	0.976
	Zithrocin	0.957
	Hemomycin	0.970
Clarithromycin	Clacid	0.969
	Clabax	0.951
	Fromilid	0.948
Spiramycin	Rovamycin	0.920
Midecamycin	Macropen	0.850

* represented as a fraction of a unit

Low efficiency of cephalosporins and protected penicillins in the treatment of AOB and ROB in the absence of concomitant diseases may indicate an allergic, viral or atypical nature of the AOB and ROB, since AOB and ROB are often developed in patients with ARI (table 3)

Each antibiotic x_i (i=1,n) is associated with an assessment of its significance to determine the level of clinical effectiveness. Then system of weights was build observing the following conditions

$$\begin{cases} \sum_{i=1}^{n} a_i = 1, \\ a_i \geq 0, i = 1, n \end{cases}$$

Where; a_i–is the weight of i-th antibiotic, i-number of antibiotic, n-quantity of antibiotics.

All antibiotics were placed by rank of factor (table 4), i.e. in order of decreasing their significance (in our case-clinical effectiveness)

$$x_1 \succ x_2 \succ \ldots \succ x_i \succ \ldots \succ x_n. \quad \ldots\ldots (1)$$

After ranking of antibiotics by clinical effectiveness weights were determined by Fishburne's scale (table 5).

$$a_i = \frac{2 \cdot (n - i + 1)}{n \cdot (n + 1)} \quad \ldots\ldots\ldots (2)$$

Fishburne's rule reflects the fact that about the level of significance of indicators do not know anything except (1). Then the estimate by the formula (2) corresponds to the maximum entropy cash information uncertainty about the object of research.

Table 4: Ranking of antibiotics by the clinical effectiveness

Antibiotic	Clinical effectiveness	Rank of factor, a_i
Sumamed	0.980	1
Azithral	0.976	2
Hemomycin	0.970	3
Clacid	0.969	4
Zithrocin	0.957	5
Clabax	0.951	6
Fromilid	0.948	7
Azithromycin	0.947	8
Rovamycin	0.920	9
Macropen	0.850	10
Cefotaxim	0.630	11
Augmentin	0.591	12
Ceftriaxon	0.546	13
Claforan	0.537	14
Amoxiclav	0.530	15
Axetin	0.512	16
Lendacin	0.214	17
Cefazolin	0.140	18

Table 5: Weight coefficients of antibiotics calculated by the Fishburne method

Antibiotic	Rank of factor, ai	Weight coefficients of antibiotics calculated by the Fishburne method
Sumamed	1	0.105
Azithral	2	0.099
Hemomycin	3	0.094
Clacid	4	0.088
Zithrocin	5	0.082
Clabax	6	0.076
Fromilid	7	0.070
Azithromycin	8	0.064
Rovamycin	9	0.058
Macropen	10	0.053
Cefotaxime	11	0.047
Augmentin	12	0.041
Ceftriaxone	13	0.035
Claforan	14	0.029
Amoxiclav	15	0.023
Axetin	16	0.018
Lendacin	17	0.012
Cefazolin	18	0.006

Then all the antibiotics were distributed by levels of clinical effectiveness (high, medium and low).

The largest weight coefficient, calculated on the criteria of Fishburne, was put at the highest level. For low level a maximum weight coefficient, divided by three, is assigned (the number of levels). After that, the value of d-step formula, which is calculated as the difference between the high level and low level, divided in half, was defined. The index of the average level is equal to the lower level, increased on step by the formula (3).

$$d = (\text{value of high level} - \text{value of low level})/2 \quad (3)$$

Thus, in the calculations the boundaries of levels of clinical effectiveness of antibiotics in the treatment of AOB/ROB were defined:

high-0,071-0,105; medium-0,036-0,070; low-≤0,035.

Antibiotics, possessing a high level of clinical effectiveness**,** are macrolides, such as Sumamed, Azithral, Hemomycin, Clacid, Zithrocin, Clabax (table 6).

Table 6: Classification of antibiotics by levels of clinical efficiency

Levels of clinical effectiveness	Antibiotic
high 0.071-0.105	Sumamed
	Azithral
	Hemomycin
	Clacid
	Zithrocin
	Clabax
medium 0.036-0.070	Fromilid
	Azithromycin
	Rovamycin
	Macropen
	Cefotaxim
	Augmentin
low-≤0,035	Ceftriaxon
	Claforan
	Amoxiclav
	Axetin
	Lendacin
	Cefazolin

After the distribution of antibiotics on levels of clinical effectiveness by the method of Fishburne PEA was held for used antibiotics.

As a basic pharmacoeconomic indicator was calculated coefficient "cost-effectiveness", showing which costs are necessary to achieve unit of efficiency (in this case, one cured patient) with treatment by compare antibiotics (table 7).

Table 7: CER coefficient for the antibiotic of cephalosporin series, used in the treatment of AOB and ROB

Antibiotic (trade name, manufacturer)	The cost of the course, rub. (US$)	The effectiveness of treatment	CER, rub. (US$)
Cefotaxim, *Biosynthesis*	190.94 (3.01)	0.630	303.08 (4.78)
Claforan, *Sotex*	1 427.80 (22.50)	0.537	2 658.85 (41.98)
Ceftriaxon, *Synthesis*	114.97 (1.82)	0.546	210.57 (3.32)
Lendacin, *Sandoz GmbH*	1 399.72 (22.10)	0.214	6 540.75 (103.26)
Cefazolin, *Sandoz GmbH*	1 954.88 (30.86)	0.140	13 963.43 (220.45)
Axetin, *Medochemie, Ltd*	811.75 (12.82)	0.512	1 585.45 (25.03)

Calculation of the CER was performed by finding the ratio between the average cost of a course of antibiotic treatment to its effectiveness (the probability of a positive clinical effect)

CER=DC/Ef

Where, DC-direct medical costs,

Ef–the effectiveness of the treatment (relative amount of cured patients).

The most expensive of the cephalosporin antibiotics is Cefazolin (*Sandoz GmbH)*. The effectiveness of its is 0.140. The course of Ceftriaxone *(Synthesis*) is the least expensive. It costs 114.97 rub. (1.82 US$) with an effectiveness of 0.546.

Cefotaxim (*Biosynthesis)* has the most probability to offensive the positive clinical effect. In this case we used the coefficient ICER for determining cost (C) required to achieve one unit of efficiency (E). A compared course of antibiotics divide by the effectiveness and calculates the ICER for each pair of alternatives (table 8).

Table 8: Calculation of the ratio of ICER

Antibiotic	E	C, rub. (US$)	ΔE	ΔC	ICER, rub. (US$)
0	**0**	**0**			
Cefazolin, *Sandoz GmbH*	0.140	1 954.88 (30.86)	0.140	1 954.88	13 963.43 (220.45)
Lendacin, *Sandoz GmbH*	0.214	1 399.72 (22.10)	0.074	-556.16	-7 515.68 (118.66)
Axetin, *Medochemie, Ltd*	0.512	811.75 (12.82)	0.298	-587.97	-1 973.05 (31.15)
Claforan, Sotex	0.537	1 427.80 (22.54)	0.025	616.05	24 642.00 (389.04)
Ceftriaxon, *Synthesis*	0.546	114.97 (1.82)	0.009	-1 312.83	-145 870.00 (2 302.97)
Cefotaxim, Biosynthesis	0.630	190.94 (3.01)	0.084	75.97	904.40 (14.28)

For first variant of treatment comparison is carried out with the absence of antibiotic, for which the values of the cost and effectiveness will be zero.

The negative value of the coefficient of ICER (such as, for Ceftriaxon) shows that the use in the treatment of AOB or ROB this antibiotic instead of the reference Claforan will achieve the best effect while reducing costs, and cost savings will amount to 145 870.00 rub. (2 302.97 US$) for unit of effectiveness.

At this step we excluded the courses of antibiotic therapy with low efficiency (Cefazolin, whose the effectiveness is 0.14 and Lendacin, the effectiveness of which is 0.214); courses of antibiotic therapy with the highest values of the coefficient of increments (Claforan, for which ICER is 24 642.00 rub. (389.04 US$)), as well as courses of antibiotic therapy, when the coefficients of increment of costs for following them courses have negative values (Cefazolin, Lendacin, Claforan).

After excluding we re-calculated the coefficient of increment (table 9).

Table 9: Calculation of the ratio of ICER for cephalosporin antibiotics after exclusion

Antibiotic	E	C, rub. (US$)	ΔE	ΔC	ICER, rub. (US$)
	0	**0**			
Axetin, *Medochemie, Ltd*	0.512	811.75 (12.82)	0.512	811.75	1 585.45 (25.03)
Ceftriaxon, *Synthesis*	0.546	114.97 (1.82)	0.034	-696.78	-20 493.53 (323.55)
Cefotaxim, *Biosynthesis*	0.630	190.94 (3.01)	0.084	75.97	904.40 (14.28)

Table 10: CER coefficient for the protected penicillin antibiotics used in the treatment of AOB and ROB

Antibiotic (trade name, manufacturer)	The cost of the course, rub. (US$)	The effectiveness of treatment	CER, rub. (US$)
Augmentin (*Smithkline Beecham Pharmaceuticals)*	106.26 (1.68)	0.591	179.80 (2.84)
Amoxiclav (*Lek d. d)*	103.50 (1.63)	0.530	195.28 (3.08)

Thus, as a result of the analysis obtained, that with a pharmacoeconomic standpoint Ceftriaxon *(Synthesis)* is the most effective in the treatment of AOB and ROB in children in hospital.

Amoxicillin/clavulanic acid (the original drug is Augmentin *(Smithkline Beecham Pharmaceuticals)* and generic drug is Amoxiclav *(Lek d. d))* were used from the group of protected penicillins. The effectiveness of Augmentin is 0.591, and the effectiveness of Amoxiclav-0.53. Price of Augmentin'course is 106.26 rub. (1.68 US$), Amoxiclav's course price-103.50 rub. (1.63 US$) (table 10).

The most expedient is the use of Augmentin. Therapy of Augmentin is characterized by a lower value of the coefficient CER of relative Amoxiclav.

Course of Clacid is the most expensive of the group of macrolides (clarithromycin, *Abbott Laboratories*)–896.00 rub. (14.15 US$). The least expensive is the course of Azithromycin, (*Vertex Ltd.*)-49.41 rub. (0.78 US$).

Sumamed (*Pliva*) has the highest probability of the positive clinical effect. In this case we use the coefficient ICER for determining cost (C) required to achieve one unit of effectiveness (E). Compared courses of antibiotics rank by effectiveness and calculates the ICER to each pair of alternatives (table 11).

For first variant of treatment comparison is carried out with the absence of antibiotic, for which the values of the cost and effectiveness will be zero.

Then, we excluded courses of antibiotic therapy with low effectiveness (Macropen, for which the efficiency is 0.850); courses of antibiotic therapy with the highest values of the coefficient of increments (From lid, for which ICER is 297 090.00 rub. (4 690.40 US$) and Clacid-63 121.67 rub. (996.55 US$)), as well as courses of antibiotic therapy when the coefficients of increment costs following them rates are negative (Rovamycin, Fromilid, Clabax, Clacid).

We re-calculated the coefficient of increment after excluding factors (table 12).

Table 11: Calculation of the ratio of ICER for antibiotics-macrolides

Antibiotic	E	C, rub. (US$)	ΔE	ΔC	ICER, rub. (US$)
0	0	0			
Macropen, *KRKA*	0.850	77.77 (1.23)	0.850	77.77	91.49 (1.44)
Rovamycin, *Famar France*	0.920	212.29 (3.35)	0.070	134.52	1 921.71 (30.34)
Azithromycin, *Vertex Ltd*.	0.947	49.41 (0.78)	0.027	-162.88	-6 032.59 (95.24)
Fromilid, *KRKA*	0.948	346.50 (5.47)	0.001	297.09	297 090.00 (4 690.40)
Clabax, *Ranbaxy*	0.951	291.24 (4.60)	0.003	-55.26	-18 420.00 (290.81)
Zithrocin, *Unique Pharma*	0.957	138.54 (2.19)	0.006	-152.70	-25 450.00 (401.80)
Clacid, *Abbott Laboratories*	0.969	896.00 (14.15)	0.012	757.46	63 121.67 (996.55)
Hemomycin, *Hemofarm Koncern A. D.*	0.970	187.47 (2.96)	0.001	-708.53	-708 530.00 (11 186.14)
Azithral, *Shreya Life Sciences Pvt. Ltd*	0.976	194.38 (3.07)	0.006	6.91	1 151.67 (18.18)
Sumamed, *Pliva*	0.980	351.85 (5.55)	0.004	157.47	39 367.50 (621.53)

Table 12: Calculation of ICER for microcline antibiotics, after exclusion

Antibiotic	E	C, rub. (US$)	ΔE	ΔC	ICER, rub. (US$)
0	**0**	**0**			
Azithromycin, *Vertex Ltd*.	0.947	49.41 (0.78)	0.947	49.41	52.18 (0.82)
Zithrocin, *Unique Pharma*	0.957	138.54 (2.19)	0.010	89.13	8 913.00 (140.72)
Hemomycin, *Hemofarm Koncern A. D.*	0.970	187.47 (2.96)	0.027	48.93	1 812.22 (28.61)
Azithral, *Shreya Life Sciences Pvt. Ltd*	0.976	194.38 (3.07)	0.006	6.91	1 151.67 (18.18)
Sumamed, *Pliva*	0.980	351.85 (5.55)	0.004	157.47	39 367.50 (621.53)

Thus, we find, that the course of Azithromycin (*Vertex Ltd*.) from the pharmacoeconomic point of view, is the most appropriate of the antibiotics-macrolides in the treatment of AOB and ROB. However, the antibiotic according to the classification of the clinical effectiveness of Fishburne refers to the average level. Sumamed, Azitral, Hemomycin, Clacid, Zithrocin and Clabax belong to the high level of effectiveness. Clacid and Clabax were excluded from the PEA. The highest value ICER ratio was obtained for Sumamed and was 39 367.50 rub. (621.53 US$). Sumamed is characterized of the highest value of clinical effectiveness. Besides Sumamed is original drug of azithromycin. Azitral and Hemomycin have the lowest values of ICER (1151,67 rub. (18.18 US$) and 1812.22 rub. (28.61 US$), respectively) after Azithromycin. Thus, these drugs are most suitable according to the results of clinical and economic analysis.

DISCUSSION

Currently bronchitis treatment is often presented by the use of penicillins (amoxicillin, inhibitor-protected penicillins), II-III generation cephalosporins and macrolides [4, 5]. Today we observe the increase of infections, caused by β-lactamase-producing microorganisms, which destroy the β-lactam ring of penicillins and cephalosporins [6-8].

Nowadays the compounds, which inactivate the bacteria β-lactamases, i.e. clavulanic acid (clavunat), sulbactam and tazobactam, are used in clinical practice. These compounds are called β-lactamase inhibitors [9, 10]. Very often due to their efficiency and low toxicity the cephalosporins are used in clinical practice. For example, cefotaxim and ceftriaxonum (III generation cephalosporins) are used in treatment of severe bronchitis forms. The ceftriaxonum pharmacokinetics, which allows taking the drug once daily, is the apparent advantage (half-life period of this antibiotic in children is 5-7 h) [11].

Today it is difficult both from the point of view of diagnostics and therapy to treat patients with recurrent broncho-obstructive diseases associated with "atypical" respiratory infections causative microorganisms (*Chlamydia pneumoniae, Mycoplasma pneumoniae,* etc.). Recently the atypical" causative microorganisms (*Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella spp.*) are often the etiology reasons of bacterial respiratory infections [12, 13]. Chlamydia and mycoplasmas contribute to broncho-obstruction development. Quite often in patients suffering from obstructive bronchitis and asthma a mixed infection is found (chlamydial and mycoplasmal) [14].

The etiological meaning of the "atypical" infections associated with asthma development is confirmed by the presence of specific *IgE*-antibodies to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* [15-18].

The "atypical" infections contribute to the bronchi hyperactivity development and respiratory tract clearance mechanism deceleration. In its turn it leads to increase of micro-organisms capability to penetrate and distribute in the tissues, and to form a prolonged and chronic infection processes. For "atypical" infections treatment macrolides, tetracyclines and fluoroquinolones are used. The use of medical agents in pediatric practice should be combined with their maximal safety. In treatment of "atypical" infections in children only macrolides antibiotics are used. Today the most frequently used are 10-14 d courses of macrolides therapy [19, 20]. Only azitromicin is an exception: due to its pharmacokinetics this drug should be given for 3-5 d. In case of persistent "atypical" infection with concomitant recurrent broncho obstructive syndrome the most justified is the use of prolonged macrolides courses, "overlapping" 6-8 development cycles of the "atypical" micro-organisms, such as Chlamydia [21, 22].

Currently the macrolides are considered the first-line agents for treatment of bronchitis in children, especially in case of β-lactam intolerance [23].

It is for the first time proposed to use in this study the Fishbern method for distribution of antibiotics, used in the in-patient treatment of acute and recurrent obstructive bronchitis forms in children, according to the clinical effectiveness levels as well as the classical "cost–efficiency" pharmacoeconomic method, which results in determination of the most suitable drugs for treatment from both clinical and economical points of view. The study results demostrate that the macrolide antibiotics possess high efficiency level according to Fishbern. Among them Sumamed *(Pliva)* has the highest value of clinical effectiveness (0.980). Besides Sumamed (*Pliva)* is an original azitromicin drug. Based on the PEA the most appropriate choice of the macrolide antibiotics is Azithromycin (*Vertex Ltd*.). This antibiotic possesses the medium efficiency level according to Fishbern. Azitral (*Shreya Life Sciences Pvt. Ltd*) and Hemomycin (*Hemofarm Koncern A. D.)* possess the lowest ICER coefficient values (1151, 67 rub. (18.18 US$) and 1812.22 rub. (28.61 US$), respectively) among the macrolides next to Azithromycin (*Vertex Ltd.)*. Clinical effectiveness value of Azitral (*Shreya Life Sciences Pvt. Ltd*) is 0.976, and clinical effectiveness value of Hemomycin (*Hemofarm Koncern A. D.)*–0.970. These antibiotics follow after Sumamed *(Pliva)* in the list of clinical effectiveness according to Fishbern. Therefore these drugs are the most suitable for treatment of AOB and ROB in children.

CONCLUSION

As a result of PEA it was found that Ceftriaxon (*Synthesis*) is the the most effective cephalosporin in treatment of AOB and ROB in children in the hospital; from the group of protected penicillins–Augmentin (*Smithkline Beecham Pharmaceuticals*), from the group of macrolide-Azithromycin (*Vertex Ltd*.). These drugs belong to the medium level of clinical efficiency determined using the Fishburne's method.

CONFLICT OF INTERESTS

The authors have no conflict of interests to disclose

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