REVIEW ARTICLES

The consumption and the stocks dynamics of antibiotics for systemic use in hospitals

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Abstract

The dynamics of the ratio between the consumption and stocks of antibiotics in a hospital pharmacy for the period of 2009-2012 is presented. The defined daily dose (DDD) based on the data by the National Science and Practice Centre of Emergency Medicine is determined. The resistance changes of pathogenic microbes causing nosocomial infections have been examined. The activities realized in the mentioned directions have brought out in the decrease of the consumption and stock ratio from 1:0.74 in 2009 to 1:2.03 in 2012, reducing the DDD consumption of antibiotics per 1000 occupied bed/days from 1118 to 840 grams or by 33.09%. The months/risk coefficient in the pharmaceutical supply has decreased from 4.41 to 2.12 or by 2.08 times. Despite the lack of the program for processing and analyzing the condition of the pathogenic antimicrobial resistance, the general analysis has showed that the average resistance of gram-negative and gram-positive pathogenic microorganisms in 2012 in comparison with 2010 and 2011 decreased by 16.8% and 13.58% respectively. Has been proposed the optimization of the ratio of drugs reserves and their monthly consumption in pharmacies, that is a new criterion for assessing the quality of current provision with drugs – the risk factor in pharmaceutical provision in the medical institutions, based on the ratio between the monthly consumption and the stocks. The measures based on the evaluation results to improve the planning, maintenance, insurance and the rational use of antibiotics and the quality of the study of the bacteriological tests database are proposed.

Key words: drug supplies, stocks, antibiotics, nosocomial infections, rational use, antibiotics resistance.

Динамика соотношения расхода и запаса антибиотиков в больницах

Е. Берназ

Реферат

Изучена динамика движения расхода и запасов антибиотиков, а также определена их средняя поддерживающая суточная доза (ПСД) в период 2009-2012 годов в Национальном Научно-Практическом Центре Ургентной Медицины. Определена средняя резистентность патогенных грамположительных и грамотрицательных микроорганизмов на антибиотики. Изучение состояния дел и своевременные действия в этом направлении понизили коэффициент соотношения между расходом и запасами антибиотоков с 1:0,74 в 2009 до 1:2,03 в 2012 году, уменьшив ПСД антибиотиков на одну тысячу койкодней с 1118 до 840 граммов или на 33,09%. Коэффициент риска фармацевтического обеспечения уменьшился с 4,41 до 2,12 месяцев риска. Несмотря на отсутствие специальной программы по обработке данных о состоянии резистентности патогенных микроорганизмов, проведенный общий анализ показал, что их резистентность уменьшилась в 2012 г. по сравнению с 2010-2011 гг. для грамположительных и грамотрицательных микроорганизмов на 16,8% и 13,58% соответственно. Представлена аргументация предложений по разработке нормативных актов для оптимизации соотношения между месячным расходом и наличием неснижаемых минимальных и максимальных запасов в больничных аптеках. Предложен еще один критерий определения качества бесперебойного обеспечения медикаментами – коэффициент риска фармацевтического обеспечения, являющийся соотношением между месячным расходом и наличием запасов. На основании полученных данных предложены меры по оптимизации планирования, обеспечения и рационального расхода антибиотиков, а также улучшению качества изучения базы данных бактериологических анализов.

Ключевые слова: обеспечение лекарствами, запасы, антибиотики, внутрибольничные инфекции, рациональное использование, устойчивость к антибиотикам.

Introduction

In providing permanent medications for the medical institutions the antibiotics present a particular permanent scientific and practical interest. Numerous textbooks, legislation and scientific research [1, 2, 3, 4] are dedicated to this subject. In many countries a special attention is drawn to the qualitative analysis of the rotation of antibiotics (both in hospitals and in outpatient medical institutions) used depending on the type of nosocomial infection, their consumption rate, the antibiotic subgroup used and the maximum limit of the systemic antimicrobial drug consumption [5, 6, 7].

Nevertheless, the ratio between the consumption and stocks, as an important indicator of optimal rational use of drug remedies generally, and antimicrobial ones, in particular, is not studied enough and highlighted by scientific research literature. This study is dedicated to the above theme and presents the analysis of gram-positive and gram-negative pathogenic microbial resistance to antibiotics as an important factor of qualitative treatment of the patients. The evaluation was based upon the drugs consumption data collected for four years (2009-2012) by the National Science and Practice Centre of Emergency Medicine (NSPCEM). The methods of

statistical, descriptive, mathematical, analytical and logical comparison were used.

The volume and spectrum of the antibiotics usage is dictated by the institution's specialization which is fully represented in antimicrobial treatment argumentation. The recent scientific research shows a direct relationship between the administered quantities of drugs and the resistance of pathogenic microorganisms depending, sometimes, on the seasonal temperature [8, 9].

The complete and dynamic analysis of the systemic antimicrobial remedies usage as well as the level of pathogenic microbes' resistance to great extent contributes to the rationalization and optimization of the consumption of antibiotics, and, ultimately, positively influences the quality of treatment of the patients.

The results of the evaluations

Let us remember that the total cost of the consumption of the supply resources in the NSPCEM in 2012 was 28447000 lei, of which 12130213 lei or 43% was spent on drugs generally, and the cost of the systemic antimicrobial remedies of the total amount of drugs was 1851036 lei or 15%.

The number of patients treated in the above institution was 20946 in 2009, 21341 in 2010, 19913 in 2011 and 20664 in 2013.

All the used antimicrobial remedies were divided into the subgroups: aminopenicillins, cephalosporins (I, II and III generations), carbapenems, aminoglycosides (II and III generations), chinolons, lincosamides, tetracyclines, amfenicols, antifungals, antivirals and antiprotozoy. After each year of 2009, 2010, 2011, 2012 the total amount of antibiotic consumption was calculated in grams and in lei according to the groups shown in the graphs below.

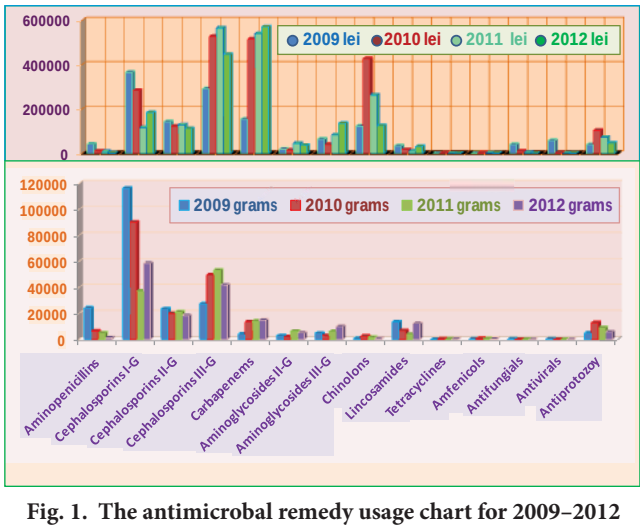

Fig. 1. The antimicrobal remedy usage chart for 2009–2012 in lei/grams.

Figure 1 is a chart of antimicrobial remedies systemic consumption in grams and lei indices in the period of 2009-2012. As we can see, the cost of the consumption of antibiotics from aminopenicillins group decreased from 42019 lei (24148.9 grams) in 2009 to 2136 lei (1374 grams) in 2012; for the first generations of cephalosporins – from 366194 lei (116307 grams) in 2009 to 162819 lei (58664 grams) in 2012; for antifungials – from 40538 lei (270.1 grams) in 2009 to 226 lei (26.7 grams) in 2012 etc. On the contrary, the cost of the third-generation cephalosporins consumption increased from 291530 lei (27382.7 grams) in 2009 to 401151 lei (41940 grams) in 2012, of carbapenems – from 155053 lei (4045.2 grams) in 2009 to 430808 lei (14895 grams) in 2012, of chinolons – from 123964 lei (717 grams) in 2009 to 263541 lei (1523 grams) in 2011. These sums were due to the broad spectrum of expensive and very expensive prices for antibiotics. In total to purchase the whole lot of systemic antimicrobial remedies only in 2009 1562575 lei (222878 grams) was spent and in 2012 – 1837614 lei (169800 grams), what amounts to 275039 more lei spent than in 2009 while for the total mass in grams a decrease in consumption of 53078 grams was registered. Some medical institutions with a wide consumption of antibiotics use some of them for surgery purposes as well [10].

Despite the considerable decrease in the consumption of the generations of cephalosporins as it is showed in fig. 2 the wide administration of cephalosporins takes place. For the evaluated period the total consumption cost of cephalosporin antibiotics was 801078 lei or 51.3% (167140 grams or 75%) in 2009, 933844 lei or 40.2% (159792 grams or 77%) – in 2010, 811839 lei or 41.5% (111384 grams or 70.5%) – in 2011, 665 193 lei or 36.2% (105 950 grams or 62.4%) in 2012.

Generations of cephalosporins	Sensibility of microorganisms		Resistance to β-lactamases	
	Gram positive	*Gram negative*	staphylococci	Gram-negative bacteria
I	++++	+	++	-
II	+++	++	++	+/-
III	+	+++	+	+
IV	++	++++	++	++

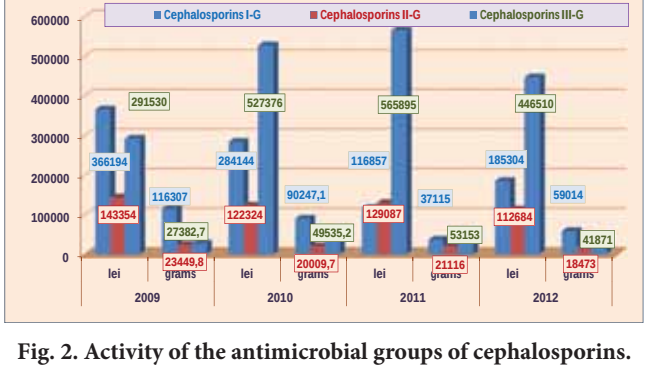

Fig. 2. Activity of the antimicrobial groups of cephalosporins.

According to the characteristics of the antimicrobial activity of cephalosporin generations [11] and the resistance of the pathogenic microbes (the data are gained from the institution's bacteriological laboratory) it is evident that the sudden switch to the cephalosporins III-G consumption in 2010 did not have a solid justification, especially keeping in mind that about 70-80% of nosocomial surgical infections are caused by the gram-positive pathogenic microbes [12, 13]. In comparison with 2011 in 2012 already the consumption cost of the first generation cephalosporins rose from 116857 lei (37115 grams) to 185304 lei (59014 grams), what amounts to 158.57%.

To determine and compare the consumption of antibiotics

for the period of 2009-2012 the statistics data concerning the number of treated patients, with the exception of those who paid for the treatment, the number of bed/days and total annual quantities of antibiotics were used. Taking the above as a base the defined daily dose (DDD) was calculated for one thousand days [1, 15]. The final data are presented in table 1.

As shown in table 1, the consumption of antibiotics in 2011 and 2012 decreased by 33.09% in comparison with 2009 and 2010 and this happened due to the several measures taken to use rationally this group of drug remedies. It is noteworthy that by the assessment of systemic antimicrobial remedies consumption in 530 hospitals in France, this ration is minimum 62.3 grams and maximum – 557.7 grams as a DDD/1000 daily occupied beds [17].

Table 2 shows the resistance in average percentage units of gram-negative and gram-positive microorganisms of bio-

Table 1

Defined Daily Dose for one thousand days (DDD/1000) in NSPCEM

Indicator	Year	2009	2010	2011	2012
Discharged patients	Number	20946	21341	19913	20664
Average duration of the treatment	Days	8.62	8.62	8.66	8.82
The number of occupied bed/days	Number	188762	191556	186246	199816
Antibiotics administration	Grams	222878	207880	157937	169800
Consumption of antibiotics – DDD	Grams	1.118	1.07	0.88	0.8
The average consumption of antibiotics – DDD/1000	Grams	1118	1080	840	840

Table 2

The average percent resistence of gram-negative and gram-positive microorganisms of biosubstrate in NSPCEM in 2010-2012

Drugs	Year 2010 %		Year 2011 %		Year 2012 %	
	Gram -	Gram +	Gram -	Gram +	Gram -	Gram +
Aminopenicillin						
Ampicillinum	84.1		84.1	52.7	84.7	82.8
Cephalosporins Generation I						
Cefazolinum	84		79.4	55.3	52.6	14.9
Cephalosporins Generation II						
Cefuroximum			93.9	48.7	56.6	15.7
Cefuroximum (Cefatoxim)	65.3	48.7	66.1	48.7	36.1	15.7
Cephalosporins Generation III						
Cefoperazonum	77.8		72.3	54.7	55	54.7
Ceftazidimum	89		70.9		47.6	
Ceftazidimum (Fortum)	89		70.9		47.6	
Ceftriaxonum	59.2	23.9	70.3	47.5	47.4	18.9
Generația IV						
Cefepimum	82.6		75.2		50.7	24.3
Combinations of b-lactams with inhibitors b-lactamases: inhibitors of beta-lactamases						
Amoxycillinum + Ac. Clavulanicum	85.4	19.8	75.6	23.1	41.3	9.2
Aminoglycosides Generation II						
Gentamicinum	47.4	11.6	58	20.4	48.6	17.1
Aminoglycosides Generation III						
Amikacinum (Amicil)	40	6.9	38.9	7.6	33.1	
Chinolons						
Ciprofloxacinum	45.1		63	44.3	48.1	29.9
Gatifloxacinum	42.6	10.3	43.8	10.3	55.5	
Lincosamides						
Lincomycinum		43.6		42.3		26.5

substrate in NSPCEM in 2010-2012. From this presentation we can see that the average resistance of pathogenic gram-negative microorganisms (*Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumonia, Enterobacter aerogenes* + *Enterobacter cloacae, Proteus vulgaris* + *Proteus mirabilis, Pseudomonas aeruginosa, Acinetobacter, Morganella* and *Rettgerella*) in 2012 compared to 2010 and 2011 decreased for the cephalosporins on average by 25.7%, combinations of beta-lactams and beta-lactamase inhibitors – by 32.2%, aminoglycosides – by 7.6% and chinolons – by 1.6%.

The average resistance of the gram-positive pathogenic microorganisms (*Streptococcus pyogenes*, *Enterococci, Staphylococcus aureus, Staphylococcus epidermidis*) in 2012 compared to 2010 and 2011 decreased for the cephalosporins by 33.7%, combinations of beta-lactams inhibitors of beta-lactamases – by 13.3%, aminoglycosides – by 3.3%, chinolons – by 14.4% and linconsamides – by 15.8%.

The above presented data have a general character. Unfortunately, the institution has not implemented a special program to set a database, containing the results of the analyses on microbial resistance got from organic substrates collected from the patients. In the absence of the above the margin of a possible error is still high. Thus, to discover the new classes of antibiotics is still difficult.

In the last 30 years only two genuinely new classes of antibiotics have come to the pharmaceutical market, and they are effective only for the treatment of the infections caused by gram-positive bacteria (oxazolidinones, cyclic lipopeptides) [18].

Figure 3 shows the antibiotics consumption data compared to the consumption data of the total amount of drugs in 2009, 2010, 2011, 2012.

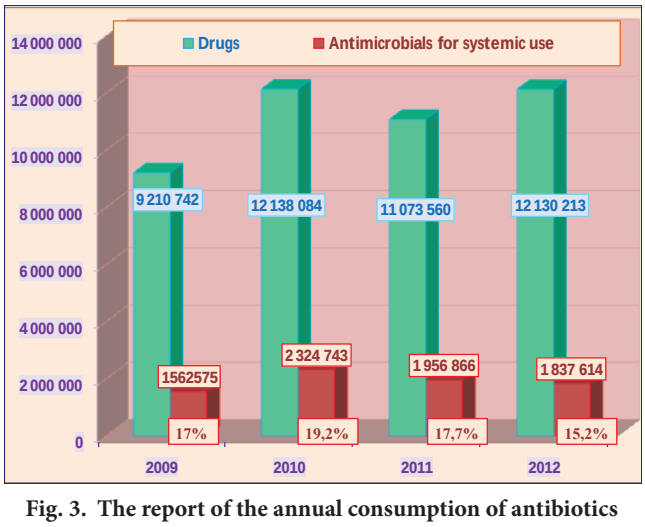

Fig. 3. The report of the annual consumption of antibiotics compared to the total annual amount of drugs.

In figure 3 we can see that the share of antibiotics in the overall consumption of medications increased by 2.2% in 2010 compared to 2009, and during the periods of 2011 and 2012 it had a gradual decrease and amounted to the sum of 487129 lei or by 21% less than in 2010.

In accordance with the current regulations [19] the drugs providing quality must be optimal; the stock must be about twice as much as the consumption. We also pay attention to the fact that the annual stock of antibiotics is calculated as their amount left after the end of each month of the year.

Figure 4 presents the data on the relationship between the consumption and the stock of systemic antimicrobials for the years of 2009, 2010, 2011, 2012.

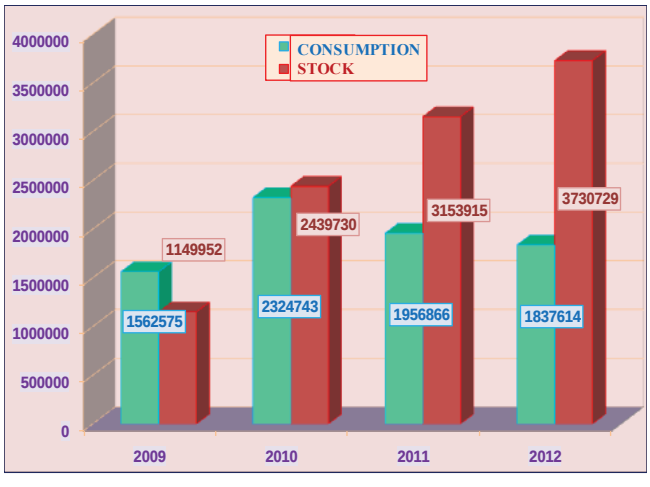

Fig. 4. The consumption/stock report of antibiotics for the period of 2009-2012 (in lei).

Figure 4 shows that the relationship between stock and consumption was of 0.74:1 in 2009, 1.05:1 in 2010, 1.61:1 in 2011 and 2.03:1 in 2012. Therefore, the optimal ratio between stock and consumption was obtained only in 2012. The consumption gradually decreased by 367.877 lei in 2011 and by 487.129 lei in 2012 in comparison with 2010.

The results of the monthly dynamic evaluation to maintain the ratio between the consumption and stock during the years 2009, 2010, 2011, 2012 is shown in the figure below.

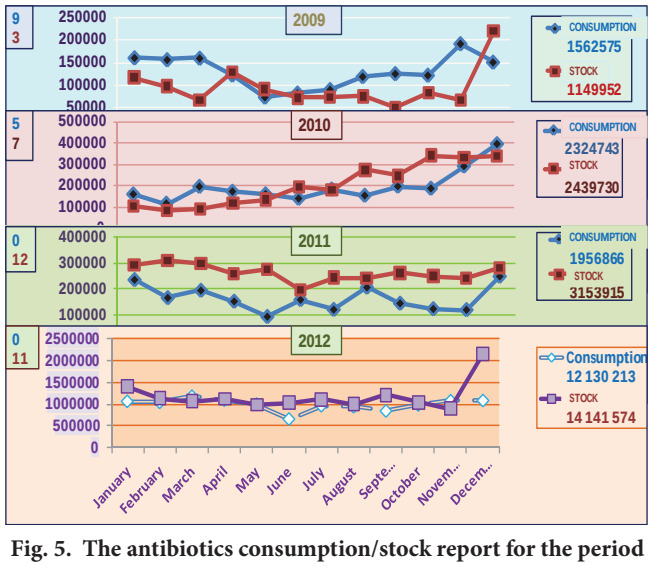

Fig. 5. The antibiotics consumption/stock report for the period of 2010-2012 (in lei).

The analysis of the monthly consumption of the systemic antimicrobials, shown in figure 5, demonstrates that during nine months in 2009 and during 5 months in 2010 the

consumption was higher than the stock, which involves the likelihood of deficit of some antibiotics. The situation was favourable in 2011 and 2012. During this period the monthly consumption curves were lying under the stocks curves. The analysis of the level of monthly consumption of antibiotics in comparison to their total annual stock (the amounts left after the end of each month of the year) shows that when the annual stock is 1.5 times higher than the consumption (fig. 4), all monthly stocks are higher than the monthly consumption as well.

An important direction in the achieving big progress in antimicrobial treatment is the study of the dependence of pathogenic microbes' resistance on the seasonal temperature throughout the year. The thorough analysis performed by American scientists in more than 300 hospitals in the US in the period of 1999-2007 showed that antibiotics are more used in cold seasons. It can be noticed that in the colder months of the year (November, December, January, February, March and a part of April) the antibiotic consumption is, in most of the cases, more than in the other time of the year.

At the same time a thorough analysis, performed in over 300 hospitals in the United States, in the period of 1999-2007,

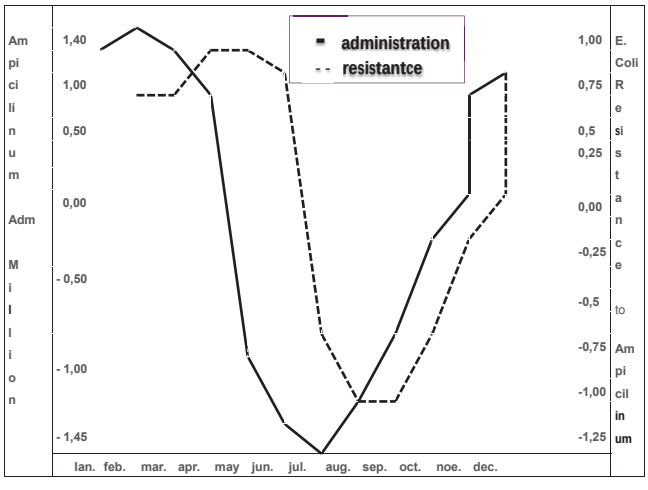

Fig. 6. Seasonal pattern - the antibiotic use depending on the strength of *E. coli*.

showed that antibiotics have a higher use in the cold season. Fig. 6 shows that the resistance of pathogenic microbes in the case of *E. coli* is much higher to aminopenicillins during cold and not hot period of the year [20]. Promoting the results of such important achievements and performing the research

Table 3

Consumption/stock monthly report by pharmacotherapeutical groups

Monthly report consumption / stock	2009		2010		2011		2012	
Pharmacotherapeutic group / month	Months consumption	Months stock	Months consumption	Months stock	Months consumption	Months stock	Months consumption	Months stock
Aminopenicillins	1	11	2	10	1	11	1	11
Cephalosporins I-G	10	2	10	2	8	4	8	4
Cephalosporins II-G	10	2	2	10	3	9	2	10
Cephalosporins III-G	4	8	5	7	3	9	3	9
Carbapenems	2	10	1	11	2	10	0	12
Aminoglycosides II-G	6	6	8	4	5	7	7	5
Aminoglycosides III-G	2	10	1	11	0	12	0	12
Chinolons	10	2	1	11	0	12	2	10
Lincosamides	2	10	3	9	0	12	0	12
Antiprotozoy	6	6	10	2	9	3	3	9
Total group / month	53	67	43	77	31	89	26	94

Year	Months consumption > months stock		Year months		Coefficient months/risk
2009	53	:	12	=	4.41
2010	43	:	12	=	3.58
2011	31	:	12	=	2.58
2012	26	:	12	=	2.12

in this direction will help improve the treatment, saving the remedies of systemic use antimicrobials, and make the organization of the use of antibiotics more efficient.

The analysis of the relationship between the consumption and stock subgroups and not the general group of antibiotics demonstrates that the monthly consumption of these subgroups needs to be considered a definitive qualitative indicator.

Table 3 gives the recent data of the consumption/stock monthly report, according to pharmacotherapeutic subgroups of antibiotics. The need for such an assessment is dictated by qualitative provision with medications, as well as by the fact that, according to the valid normative acts, the overall acquisition process of the drugs takes 35-45 days. As shown in the table, we can see that the yearly medication consumption varied from one month to another, depending on the quality of the antibiotic subgroups supply.

During the evaluated period for 4 sub groups of antibiotics the monthly consumption was higher than the stocks during 10 months: for 1 sub group – within 9 months, in two sub-groups-within 8 months and so on. The months/risk ratio is determined by the number of months where a higher consumption than the stock was registered for all subgroups, divided by the number (12) of months of the year. For the period of 2009-2012 this coefficient decreased from 4.41 in 2009 to 2.12 in 2012 or was 2.08 times as little (4.41:2.12). It can be noticed that the lack of one or another medical remedy in the period of risk months is more likely, but not necessarily takes place, and is related to several factors, the main of which is the organization of the effective dynamics of providing supplies of drugs followed by the permanent analysis of the existing stock, according to the pharmacotherapeutical groups in the medical institution pharmacy.

Conclusions

1. The utilization spectrum of antibiotics for systemic use in NSPCEM includes 10 subgroups of antibiotics. The total consumption cost in 2009 was 1562575 lei (222878 grams) and in 2012 it amounted to 1837614 lei (169800 grams). In the period of 2009-2012 the consumption of antibiotics increased by 17.6%, which amounts to 275039 lei, and it decreased in mass by 23.81%, what makes up 53078 grams.

2. The DDD per one thousand occupied bed/days in the period of years 2009-2012 decreased from 1118 grams to 840 grams or by 33.09%.

3. The most widely used antimicrobials are cephalosporins, which were registered as having the highest consumption corresponding to 801078 lei or 51.3% (167140 grams or 75%) in 2009 with a gradual decrease to 665193 lei or 36.2% (105950 grams or 62.4%) in 2012.

4. The consumption/stock ratio was reduced from 1:0.74 in 2009, to 1:1.05 in 2010 and from 1:1.61 in 2011 to 1:2.03 in 2012. It can be noted that when the annual stock is 1.5 times as much as the consumption, the monthly stocks being less than the consumption were not registered.

5. We propose a new criterion, so-called months/risk coefficient to assess the quality of medical remedies availability in the medical institutions, where a higher consumption than the stock for the antibiotic subgroups drugs, divided to 12 (number of months of the year) was registered. For the period of 2009-2012, according to the assessment, the coefficient decreased from 4.41 to 2.12 or by 2.08 times (4.41:2.12).

6. The evaluation results of the analysis of biomaterial in institutional bacteriological laboratory demonstrated that, in comparison with 2012, the average resistance of gram-negative and gram-positive microorganisms decreased by 16.8% in 2010 and by 13.58% – in 2011. Therefore the margin of error remains high in the absence of a modern database and analysis program to evaluate the collected biomaterial analyses results.

7. The absence of analysis or a superficially made analysis of the dynamic ratio between the consumption and stock leads to the difficulties of the optimization of the current medications availability. This situation allows us to assume that the months/risk coefficient of the pharmaceutical supply in other medical institutions in Moldova at present is the same as one recorded in NSPCEM for 2009-2010, that means that it is not less than for the period of 4 months.

8. A rational usage of antibiotics directly correlated with the resistance of pathogenic microbes, which, in turn, depends on the change of seasonal temperature during the year, does not have any scientific or practical base, as there are no any researches carried out in the medical institutions in the Republic of Moldova.

Suggestions

1. To ensure the presence and the continuous improvement of the results referred to in points 1, 2, 3 and 6 of the conclusions, the author proposes to develop the project "On norms of the availability of stocks of antibiotics in medical institutions not less than 1.5 times as much and not more than twice as much in quantity in comparison with the average monthly consumption correlated with the DDD/1000 and submit it for the approval by the order of MSRM.

2. To introduce the pharmaceutical supply coefficient of months/risk as one of the basic criteria in assessing the quality of availability of drugs in the medical institutions.

3. To continue the evaluation of the origin of gram positive and gram negative pathogenic microbes resistance in order to ensure the quality of antimicrobial treatment and the organization of the rational use of antibiotics in medical institutions:

a) to specify the data according to the medical departments,
b) to adopt the measures aimed to develop a statistic program for database and analysis of the collected biosubstances showing the type of pathogenic microbes and the level of their resistance to antibiotics.

4. To organize the investigation regarding the rational consumption of antibiotics, based on the presented important scientific results about the sharp changes of the pathogenic microbes resistance, depending on the seasonal temperature, what implies the following starting points:

a) to study the scientific and practical achievements, concerning the correlation between pathogenic microbes'

resistance and the seasonal temperature in the countries having more scientific centers in this field,

b) to plan and realize several scientific studies in the NSPCEM that will demonstrate the dependence of the microbial resistance on the climatic conditions of the Republic of Moldova.

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