

## Antibiotics consumption evaluation in reanimation department

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### Abstract

**Background:** Unnecessary use of anti-infectives for systemic use is a major global issue and often results in too many problems such as: ineffective treatment and side effects in patients, increase of the risk of development of pathogen microbial resistance and treatment costs. Defined daily doses (DDD) is a method that integrated the evaluation of drugs consumption of worldwide hospitals, giving the possibility of comparison, improving the rational use, optimizing the possibility of coherent planning of antibiotics necessities.

**Material and methods:** The data of this study represents a six-year (2009-2014) period in Reanimation Department, which describes the consumption dynamics of anti-infectives for systemic use of drugs in natural and value indexes.

**Results:** The defined daily doses (DDD) per 1000 occupied-bed days (DDD/1000) of antibiotics in Reanimation Department has decreased from 3270.17 in 2009 to 1664.99 in 2014 and is by 22.76% higher than medium consumption of 1286.11 DDD/1000 in 1134 intensive care units from international hospitals. The value indexes per DDD/1000 declined from 87860 in 2009 to 54307 lei in 2014 or by 38.19%, when the cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei or by 21.40% in 2014. The pharmacoecconomy from 2010 to 2014 increased more than by 3 times.

**Conclusions:** The stated decrease in DDD/1000 OBD and the obtained pharmacoecconomy characterized the measures taken to improve the rational use of antibiotics. The increase of one DDD cost, shows the increase in the price of antibiotic medical remedies for the evaluated period.

**Key words:** antibiotics, defined daily dose, consumption, rational use, hospitals, occupied-bed days, indices.

### Introduction

The unnecessary use of antibiotics is a major global issue and often results in a great deal of problems, such as: ineffective treatment and side effects in patients, increased risk of development and dissemination of pathogen microbes resistance, triggered super infections and the increased treatment costs [1-6]. The data about morbidity and mortality, as well as unnecessary or inappropriate consumption of antibiotics in acute care hospitals of The United States, caused Centers for Disease Control and Prevention to recommend all acute care hospitals to implement Antibiotic Stewardship Programs [7].

It is known that in the Republic of Moldova drugs consumption analysis in defined daily doses (DDD) per 1000 occupied-bed days (DDD/1000), is an important objective indicator of drugs consumption evaluation, the result of which is serving as real database for optimizing the rational use and planning the medical necessities in health care institutions. This issue is not taken seriously enough and highlighted in the national scientific research literature.

The primary aim of this study is directed to determine the value of DDD/1000 in accordance with World Health Organization (WHO) requirements [8, 9] based on the evaluation of antibiotics consumption of the institutional representative data in Reanimation department for a six-year period (2009-2014). The obtained results from Reanimation department, in comparison with the published ones in intensive care units from worldwide hospitals, will permit to recommend measures to ensure the rational use and optimization of planning the annual necessities of anti-infectives for systemic use.

The Emergency Medicine Institute of the Republic of Moldova (EMI) was founded in 1959. The clinical services of EMI include: Orthopedic-Traumatology for 150 beds, Surgery for 140 beds, Neurosurgery for 80 beds, Neurology for 70 beds, Maxillofacial for 30 beds, Urology for 40 beds, Gynecology

for 30 beds, Microsurgery for 30 beds, Municipal center for hemodialysis with 8 seats and 9 beds, Clinical Intensive Care Unit for 30 beds and Reanimation department for 23 beds. The above-mentioned clinical services include 600 beds overall. In addition to the above-mentioned services, there are 4 more outpatient Departments of traumatology and orthopedics [10].

### Material and methods

The study uses data of a six-year period (2009-2014), from EMI Reanimation Department for 23 beds that shows the dynamics of consumption of anti-infectives for systemic use, in accordance with Anatomical Therapeutic Chemical (ATC) classifications system of World Health Organization, indicated in natural and value indexes. Statistical, analytical, mathematical, comparative, logical and descriptive methods were used in the study.

### Results and discussion

To evaluate the consumption of anti-infectives for systemic use, were taken 10 steps necessary to determine the DDD/1000 [11], the statistics data concerning the number of treated patients (only patients with health insurance and other free treated by the state categories of citizens) and occupied bed-days/per year: (2009 = 3990; 2010 = 6551; 2011 = 6985; 2012 = 9051; 2013 = 7384; 2014 = 7361), as well as the data related to the total annual consumption of antibiotics were used.

All in all, 50 antimicrobial remedies (both for parenteral and enteral use) for hospitalized patients' treatment in the evaluated period were used: 12 enteral forms; 18 parenteral forms and 10 names of both forms, which represent 40 active antimicrobial substances.

Rate of antibiotics subgroups consumption of parenteral forms evaluated in DDD/1000 during 2009-2014 period is shown in figure 1.

In figure 1 is demonstrated the average consumption annual rate of parenteral forms for the evaluated period for all antibiotic subgroups that recorded a decline from 3172 in 2009 to 1629 DDD/1000 in 2014 or by 48.64%. The main consumption of 2369.42 DDD/1000 or 74.70% from the total in 2009 to 1244.67 or 76.41% from the total in 2014, shows a decrease from the mentioned period of 47.47% for other beta-lactam antibacterials (Cefazolinum 3.0, Cefuroximum 3.0, Cefotaximum 4.0, Ceftazidimum 4.0, Ceftriaxonum 2.0, Cefoperazonum 4.0), aminoglycoside antibacterials (Streptomycinum 1.0, Gentamycinum 0.2, Kanamycinum 1.0, Amikacinum 1.0) and other antibacterials (Vancomycinum 2.0, Metronidazolium 1.5, Dioxydinum 0.7, Nitroxolinum 1.0). The mean consumption with a decrease in the mentioned period by 52.16%, from 770.43 DDD/1000 or 24.29% of the total in 2009 to 368.56 or 22.63% of the total in 2014 was recorded by beta-lactam antibacterials, penicillins, quinolone antibacterials and antimycotics for systemic use. Macrolides, lincosamides and streptogramins (Clarithromycinum 0.5, Azithromycinum 0.5, Lincomycinum 1.8) and amphenicols (Chloramphenicolum 0.3) showed a decline in consumption by 51.50%, from 32.08 DDD/1000 or 1.01% of the total in 2009 to 15.56 or 0.96% of the total in 2014, and were placed on the last third position.

In figure 2 is shown the consumption rate of enteral forms of antibacterials for systemic use subgroups in DDD/1000, during 2009-2014.

Figure 2 shows the average consumption annual rate of antibiotics for oral use that recorded an instable rate and is more appropriate to 80-100 DDD/1000 during four years: 2009, 2011, 2012 and 2013. The consumption of 80.45 DDD/1000 or 81.88% of the total in 2009 to 33.28 or 92.45% of the total in 2014 was registered by the antimycotics for systemic use (Ketoconazolium 0.2, Fluconazolium 0.2), they showed a decrease by 58.63%, when other subgroups registered only an episodic consumption for the same period. Figure 3 shows the total (parenteral and enteral forms) antibiotic subgroups usage rates.

Figure 3 states the average consumption annual rate of parenteral and enteral forms for all antibiotic subgroups that recorded a decline from 3270 in 2009 to 1665 DDD/1000 in 2014 or by 49.08%. The main consumption of 2369.42 DDD/1000 or 72.46% of the total in 2009 to 1244.67 or 74.76% of the total in 2014 with a decrease of 47.47% during the evaluated period, was registered for other beta-lactam antibacterials,

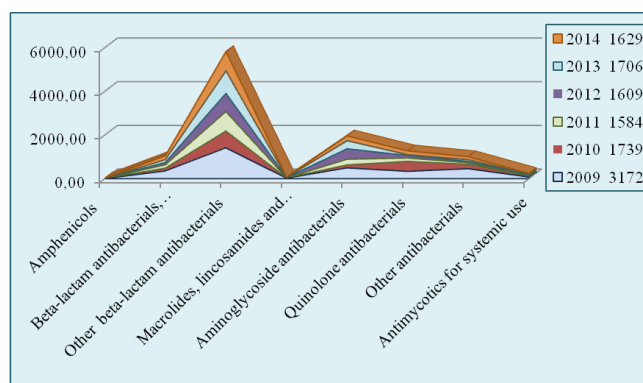


Fig. 1. Parenteral consumption forms of antibacterials for systemic use in DDD/1000.

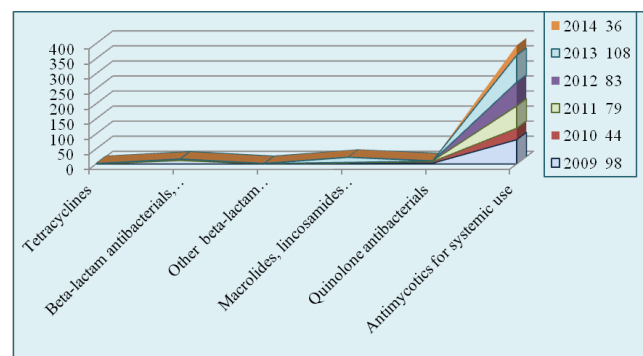


Fig. 2. Enteral consumption forms of antibacterials for systemic use in DDD/1000.

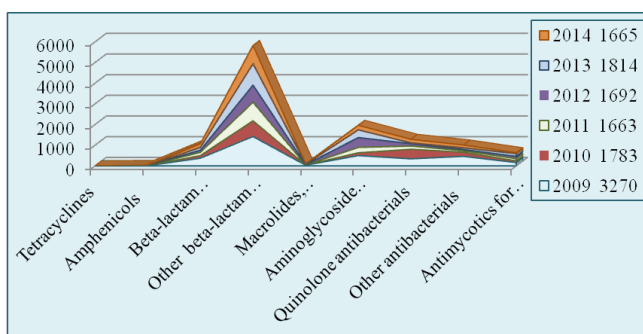


Fig. 3. The total consumption of antibacterials for systemic use in DDD/1000.

aminoglycoside antibacterials and other antibacterial. The mean consumption with a decrease by 53.55% from 865.17 DDD/1000 or 26.46% of the total in 2009 to 401.84 or 24.14% of the total in 2014 was recorded by beta-lactam antibacterials, penicillins, quinolone antibacterials and antimycotics for

Table 1

The ratio between DDD/1000 for parenteral to enteral antibiotics forms

Years		2009	2010	2011	2012	2013	2014
Parenteral		3171.9	1739.4	1583.5	1609	1706.4	1629
Enteral		98.25	43.51	79.36	83.31	107.67	36
The ratio of parenteral to oral		32.28	39.98	19.95	19.31	15.85	45.25
Total		3270.5	1782.1	1662.6	1692.1	1814.7	1665
Percentage forms from total	Parenteral	97.56	95.23	95.08	94.06	97.84	97.84
	Enteral	2.44	4.77	4.92	5.94	2.16	2.16

systemic use. Macrolides, lincosamides and streptogramins (Clarithromycinum 0.5, Azithromycinum 0.5, Lincomycinum 1.8) and amphenicols (Chloramphenicolium 0.3) were placed on the last position with a decline of 51.90% consumption from 35.59 DDD/1000 or 1.09% of the total in 2009 to 17.12 or 1.03% of the total in 2014. Table 1 demonstrates the ratio DDD/1000 of parenteral to enteral use forms and percentage from the total.

As stated in table 1 for the evaluated period, the ratio between antibiotics DDD/1000 parenteral to enteral forms recorded an instable report between 15 and 20 times during three years (2011-2013), as well as from 30 to 45 times during other three years (2009-2010; 2014). From the total DDD/1000, the percentage of parenteral forms of antibiotics, was more or less the same in the mentioned period with the annual average of 96%, as well as the enteral forms from 2% to 6%. Similar data of DDD/1000 for the entire institution can be found in recent publications [12].

The comparison of total consumption data of the anti-infectives for systemic use, evaluated in DDD in 1576 international hospitals and their intensive care units with

the similar data in the EMI and Reanimation department, is presented in table 2.

Table 2 states the average annual rate for total-hospital antibiotics utilization period in EMI that decreased from 662.4 in 2009 to 464.1 DDD/1000 in 2014 or by 30%. The overall medium consumption in 1706 international hospitals, constituting 459.20 DDD/1000, was lower than the consumption of 464.1 DDD/1000 in EMI in 2014 by 4.90 DDD/1000, and, lower by 121.1 comparatively to medium global annual hospital antibiotics consumption of 343 DDD/1000 or by 20.09% [13].

The Reanimation department registered a decrease of antibiotics consumption from 3270.17 in 2009 to 1664.99 DDD/1000 in 2014 or by 49.09% respectively. An approximate calculation of DDD/1000 was conducted for 1134 intensive care units of international hospitals that resulted in an average consumption of 1286.11 DDD/1000  $\{[(10 \times 1013.1 + 2 \times 1762.3 + 1 \times 982 + 38 \times 1016 + 38 \times 1143 + 35 \times 1254 + 1 \times 1761 + 1 \times 683 + 43 \times 1156 + 34 \times 1110 + 58 \times 1400 + 38 \times 1335 + 8 \times 1223 + 744 \times 1332 + 1 \times 1260 + 40 \times 1169 + 40 \times 1127 + 1 \times 1109 + 1 \times 1052) = 1458445 : 1134] = 1286.11 \text{ DDD/1000}\}$ , which was 1984.06 in 2009 or by 60.67% and 378.88 DDD/1000 in 2014 or by

Table 2

**Surveillance studies of antibiotics use in international hospitals, comparing with the similar data in Emergency Medicine Institute and Reanimation department**

Setting	Surveillance time-period	Data source	Frequency of data collection	Use of antibiotics in DDD/1000
Emergency Medicine Institute	6 years (2009– 2014)	Pharmacy dispensing records (PDR)	Annual	662.4 in 2009; 464.1 in 2014.
Reanimation department of EMI	6 years (2009–2014)	(PDR)	Annual	3270.17 in 2009; 1664.99 in 2014.
10 primary and 2 secondary acute care hospitals in the Canton of Zurich in Switzerland [14]	in 2006	(PDR)	Annual	1013.1 to 1762.3
1 university hospital in Greece [15]	5 years (1998-2002)	(PDR)	Annual	982.0
54% of the national acute care hospitals in Switzerland [16]	5 years (2004- 2008)	(PDR)	Annual	1016.0 to 1143.0
38 ICUs providing services to a population of approximately 6 million in Sweden [17]	in 1999	(PDR)	Annual	1257.0
35 European Intensive Care Units [18]	in 2005	(PDR)	Annual	1254.0
Spanish general hospital [19]	5 years (1996–2000)	(PDR)	Annual	1761.6
Geneva University Hospital and its adult ICUs [20]	5 years (1996–2000)	(PDR)	Annual	683.0
43 intensive care units in Germany [21]	in 2005	(PDR)	Annual	1156.0
2 cohorts of intensive care units (ICUs) in Germany (N=34), (N=58) [22]	in the 2005	(PDR)	Annual	1110.0 and 1400.0
38 German general, surgical, and interdisciplinary ICUs in [23]	4 years (2000- 2003)	(PDR)	Annual	1335.0
8 German University Hospitals [24]	3 years (1998-2000)	(PDR)	Annual	1223.0
744 reported ICU in Germany [25]	3 years (2000-2002)	(PDR)	Annual	1332.0
The main university clinic for medical emergencies from Bucharest municipality [26]	in 2008	(PDR)	Annual	1260.0
40 non–university regional general hospitals in southwestern Germany [27]	2 years (2001- 2002)	(PDR)	Annual	1169.0 and 112.7
Military Medical Academy hospital of Bulgaria [28]	in 2011	(PDR)	Annual	1109.0 and 1052.0

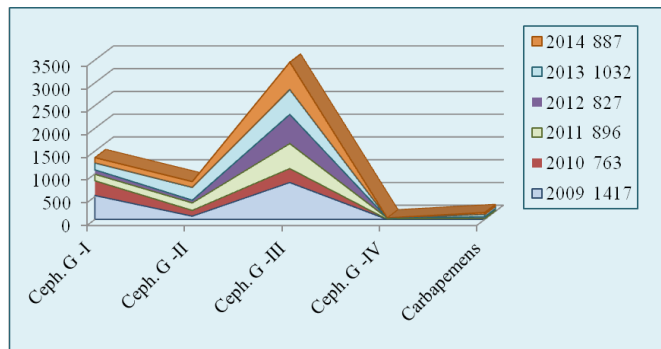


Fig. 4. Total consumption of other beta-lactam antibacterials for parenteral use in DDD/1000.

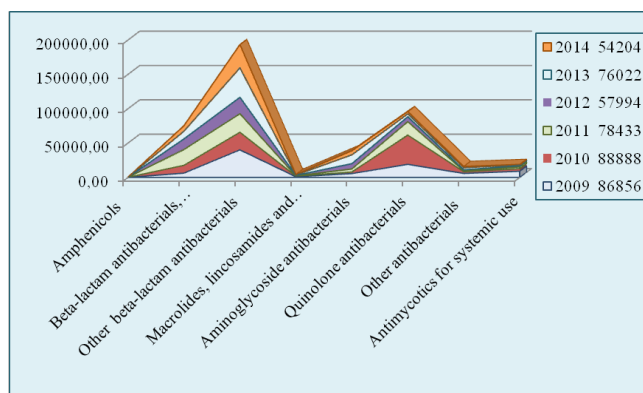


Fig. 5. Value cost of parenteral forms of antibacterials for systemic use per DDD/1000 in lei.

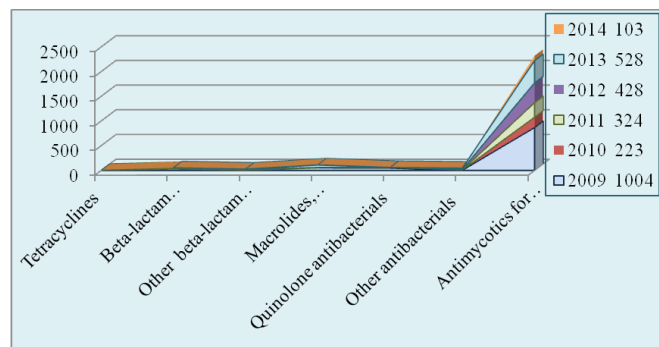


Fig. 6. Value cost for enteral forms of antibacterials for systemic use per DDD/1000 in lei.

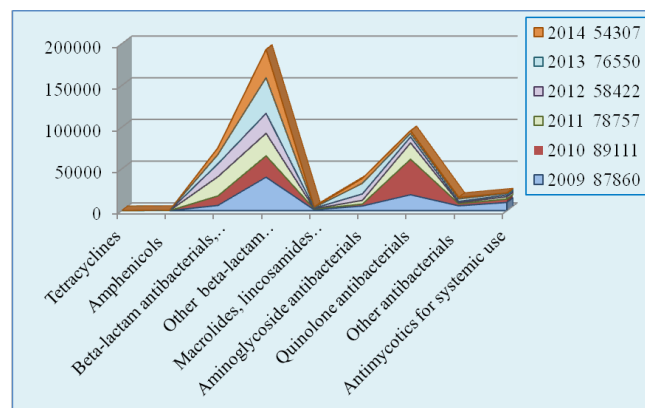


Fig. 7. Total value cost of antibacterials for systemic use per DDD/1000 in lei.

22.76% that was more than the results recorded in Reanimation department of EMI. In figure 4 the total consumption of other beta-lactam antibacterials for parenteral and enteral use in DDD/1000 is demonstrated.

The chart states a registration of a total stable consumption of parenteral forms during the years of 2010, 2011, 2012 and 2014 from 763 to 887 DDD/1000, which is more characteristic for all the evaluated period, with high records of 1417 in 2009 and 1032 DDD/1000 in 2013. The cephalosporin's G-I (Cefalexinum and Cefazolinum) consumption has visibly decreased from 525.06 DDD/1000 in 2009 to 116.56 in 2014 or by 77.8%. The cephalosporin's G-II (Cefuroximium, Cefaclorum) and G-III (Cefotaximum, Cefazidimum, Ceftriaxonum, Cefixim, Cefoperazonum, Cefoperazonum + Sulbactamum) consumptions show a slow decrease from 880.2 (70.68+809.52) in 2009 to 730.20 DDD/1000 (127.56+602.64) or by 17.04%. The carbapemems (Meropenemum, Imipenemum+Cilastatinum) recorded an increment from 11.28 DDD/1000 in 2010 to 39.94 in 2011 that was by 3.54 times more. The cephalosporins G-IV registered the only consumption in 2011. Figure 5 shows the value cost of DDD/1000 in lei for parenteral forms of antibacterials for systemic use during 2009 - 2014.

Figure 5 demonstrates that the cost of DDD/1000 in value indexes (lei) of subgroups with antibiotics for parenteral use, recorded a decline from 86856 in 2009 to 54204 lei in 2014 or by 37.59%. The increment in cost per DDD/1000 of 2146.52 from 11865.96 lei (6246.62 + 5587.22 + 32.12) in 2009 to 14012.48 lei (8041.70 + 5879.70 + 91.08) in 2014 or by 18.09% was recorded by 3 subgroups: beta-lactam antibacterials, penicillins, aminoglycoside antibacterials and amphenicols. The following subgroups: other beta-lactam antibacterials, quinolone antibacterials, antimycotics for systemic use, other antibacterials, macrolides, lincosamides and streptogramins recorded a decline of cost per DDD/1000 from 74990 (40122.89 + 19035.30 + 8977.57 + 5826.32 + 1027.92) in 2009 to 40191 lei (33981.3 + 3366.60 + 458.56 + 1793.70 + 591.22) in 2014 or by 46.41%. Figure 6 shows the consumption rate in value indexes in lei, for subgroups with antibiotics for enteral forms per DDD/1000, during 2009-2014.

Figure 6 shows an unstable amount of lei spent per DDD/1000 during 2009 to 2014, recording the highest in 2009 and abrupt decline in 2014, that amounted to 103 lei per DDD/1000 or by 9.70 times. The main annual consumption rate per DDD/1000 in value indexes of all antibiotic subgroups recorded antimycotics for systemic use with a decline from 866.05 or 86.29% of the total in 2009 to 98.42 lei or 95.71% of the total in 2014 or by 8.80 times.

The total institutional antibiotics consumption in value indexes varied from 1562575 in 2009 to 1500888 lei in 2014, which represents respectively 17% and 14% from whole amount of drugs [29]. The same data for Reanimation department was 341581 in 2009 and 399754 lei in 2014 or 22.34% and 20.03% respectively from the whole amount of drugs, and 21.88% and 26.63% from the total institutional antibiotics consumption. Figure 7 states the consumption rate in value indexes (lei) of subgroups with antibiotics for parenteral and enteral forms in DDD/1000 during 2009-2014.

In chart 7 the presented data demonstrates that in the evaluated period total annual antibiotics consumption in value indexes per DDD/1000, recorded a decline from 87860 in 2009 to 54307 lei in 2014 or by 38.19%. In figure 8 is presented the total value cost of other beta-lactam antibacterials for parenteral use of DDD/1000 in lei.

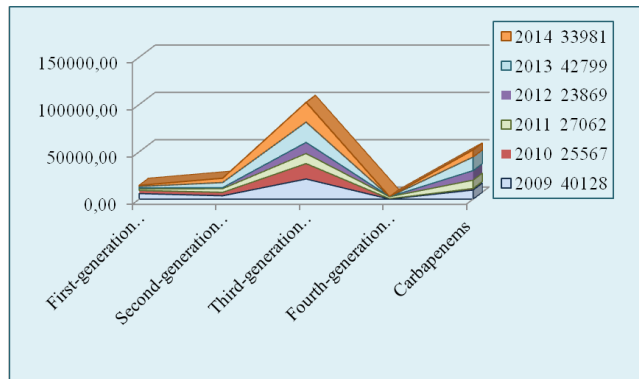


Fig. 8. Total value cost of other beta-lactam antibacterials for parenteral use of DDD/1000 in lei.

Figure 5 shows that the cost of DDD/1000 in value indexes (lei) of subgroups with antibiotics for parenteral use recorded a decline from 40128 in 2009 to 33981 lei in 2014 or by 15.32%. An exceptional decline was in 2013 year with the higher consumption of 42799 lei per DDD/1000. The increment in cost per DDD/1000 was recorded by the second generation of cephalosporin from 3481.95 in 2009 to 4528.20 lei in 2014 or by 30.05%. First and third cephalosporin generations and carbapenems, recorded a decline from 36646.19 (5856.39

+ 21224.8 + 9565) in 2009 to 29453.10 lei (1124.1 + 20913 + 7416) in 2014 or by 19.63%.

To determine the cost of one medium DDD of antibacterials for systemic use separately for parenteral and enteral forms, the value cost of DDD/1000 to DDD/1000 was divided respectively. The medium cost of one antibiotic DDD in lei for parenteral and enteral forms is shown in tables 3 and 4

Table 3 states that in the evaluated period the total cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei in 2014 or by 21.40% and of parenteral forms from 27.38 to 33.27 lei or by 21.51%. For enteral forms this cost registered a significant decrease from 10.22 to 2.86 lei or by 3.57 times. The ratio between the cost of one medium DDD of parenteral and enteral forms was respectively 2.68:1; 9.96:1; 12.14:1; 7.01:1; 9.09:1 and 11.63:1 for the evaluated years.

The calculation of one medium DDD costs in lei of parenteral forms of other beta-lactam antibacterials is shown in table 4. As stated in the table for the evaluated period, the cost of one medium DDD of parenteral forms increased from 12.65 to 20.86 lei or by 35.10%.

The periodical evaluation and presentations of antibiotic consumption in DDD led to making practical decisions on rational use of this group of drugs. In table 5 are presented the results of pharmacoconomy in the Reanimation Department of intensive care.

As stated in table 5, starting from 2009 and taking into consideration the exchange rate, the pharmacoconomy increased from 14046 in 2010 to 45407 lei in 2014 per DDD/1000 that amounted to 3.32 times, corresponding to the annual savings from 92015,3 to 334241 lei. In case of not taking into

Table 3

Cost of 1 (one) DDD antibiotics in lei for parenteral and enteral forms

Reanimation department intensive care unite						
	2009	2010	2011	2012	2013	2014
Parenteral cost in lei DDD/1000	86856	88888.10	78432.60	57993.60	76022.00	54204.00
Enteral cost in lei DDD/1000	1003.66	223.05	323.93	428.13	527.47	102.83
Parenteral and enteral cost of DDD/1000 in lei	87859.66	89111.15	78756.53	58421.73	76549.47	54306.83
Parenteral DDD/1000	3171.90	1739.40	1583.50	1609.00	1706.40	1629.00
Enteral DDD/1000	98.25	43.51	79.36	83.31	107.67	36.00
Parenteral and enteral DDD/1000	3270.15	1782.91	1662.86	1692.31	1814.07	1665.00
Total cost of one DDD in lei	26.87	49.98	47.36	34.52	42.20	32.62
Parenteral cost of one DDD in lei	27.38	51.10	49.53	36.04	44.55	33.27
Enteral cost of one DDD in lei	10.22	5.13	4.08	5.14	4.90	2.86

Table 4

Cost of one DDD other beta-lactam antibacterials in lei of parenteral and enteral forms

Reanimation department						
	2009	2010	2011	2012	2013	2014
Parenteral cost in lei DDD/1000	40122.89	25566.49	27043.07	23869.4	42798.9	33981.3
Parenteral DDD/1000	3171.90	1739.40	1583.50	1609.00	1706.40	1629.00
Parenteral cost of one DDD in lei	12.65	14.70	17.08	14.84	25.08	20.86

Table 5

## Departmental pharmacoecconomy in the period of 2009 - 2014

Years and DDD/1000	2009 3270	2010 1783	2011 1663	2012 1692	2013 1814	2014 1665
Cost of DDD/1000 (lei)	87859,6	89111,2	78756,5	58421,7	76549,7	54307
National Bank of RM exchange rate, of February 20th (\$US)	10,5672	12,7572	12,0338	11,8977	12,1176	13,5178
Pharmacoecconomy to DDD/1000 exchange rate, starting from 2009	0	14046	18701	35971	21104	45407
Annual pharmacoecconomy taken into consideration, according to 2009 exchange rate	0	92015,3	130626	325574	155832	334241
Pharmacoecconomy to DDD/1000, 2009 as the reference point, without exchange rate	0	-1251,6	9103,1	29437,9	11309,9	33552,6
The annual number of thousands occupied beds	3,99	6,551	6,985	9,051	7,384	7,361
Annual pharmacoecconomy not taken into consideration 2009 exchange rate	0	-8199,2	63585,2	266442	83512,3	246981

consideration the exchange rate, the amount was from 63585.2 to 246981 lei.

### Conclusions

1. The DDD/1000 OBD of antibiotics in Reanimation department decreased by 49.09% or from 3270.17 in 2009 to 1664.99 in 2014 and was by 22.76% higher than the medium consumption of 1286.11 in 1134 intensive care units of international hospitals.

2. The value indexes per DDD/1000 declined from 87860 in 2009 to 54307 lei in 2014 or by 38.19%. The cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei in 2014 or by 21.40%. The pharmacoecconomy increased yearly and in 2014 was more than 3 times, comparatively with 2009.

3. The average annual institutional rate for the total antibiotics consumption for the stated period decreased from 662.4 in 2009 to 464.1 DDD/1000 OBD in 2014 or by 30%. The overall medium consumption in 1547 international hospitals constituting 425.81 DDD/1000 was less than 38.29 DDD/1000 or by 8.25% than the consumption in 2014 in EMI.

4. The parenteral use forms recorded a decline from 3172 in 2009 to 1629 DDD/1000 in 2014 or by 48.64% and with an unstable consumption for the ones with enteral use forms, varying from 38 to 108 DDD/1000 in different years.

5. The total institutional antibiotics consumption in value indexes varied from 1562575 in 2009 to 1500888 lei in 2014 that represents 17% and 14% from the whole amount of drugs. The same data for Reanimation department was 341581 in 2009 and 399754 lei in 2014 or 22.34% and 20.03% from the whole amount of drugs, and 21.88% and 26.63% from the total institutional antibiotics consumption.

6. The cost of DDD/1000 declined from 87860 in 2009 to 54307 lei in 2014 or by 38.19%, and vice versa the cost of one medium DDD increased from 26.87 in 2009 to 32.62 lei in 2014 or by 21.40%, when the cost of one medium DDD of parenteral forms of other beta-lactam antibacterials increased from 12.65 to 20.86 lei or by 35.10%.

7. The ratio between costs of one medium DDD of parenteral and enteral forms were respectively 2.68:1; 9.96:1; 12.14:1; 7.01:1; 9.09:1 and 11.63:1 for the years under consideration.

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