

## A six-year evaluation of antibiotics consumption in the defined daily doses in the septic orthopedic-traumatology department

E. P. Bernaz

Business Administration Office, Emergency Medicine Institute, Chisinau, the Republic of Moldova

Corresponding author: bernaz\_e@yahoo.com. Received October 26, 2015; accepted December 12, 2015

### Abstract

**Background:** Septic orthopedic and traumatology treatment permanently required a great spectrum of antibiotics to be used. Evaluation of consumption in defined daily doses is one of principal methods for improving rational usage and good planning of hospitals' necessities of anti-infectives for systemic use. **Material and methods:** For this study we used data of a six-year (2009-2014) period, in septic orthopedic-traumatology department of the Emergency Medicine Institute, which show the consumption dynamics of anti-infectives for systemic use of drugs in grams and value indexes.

**Results:** The defined daily doses (DDD)/1000 occupied-bed days (OBD) of antibiotics in septic orthopedic-traumatology department from 578 in 2009 increased to 675 in 2014 or by 16.78% and is 14.05% lower than medium consumption of 769.83 in 152 international hospitals with the similar activity. The value of 5741 lei per DDD/1000 OBD in 2009 recorded a slow decline to 5447 lei or by 5.12%. The cost of one medium DDD from 9.94 lei in 2009 decreased to 8.07 lei in 2014 or 18.81%. The rate of anti-infectives for systemic use in 2014 presented 50169.00 lei or a share of 32% from the total departmental value of consumption; the same data in 2009 were 78054.84 lei or 34.75%. The share from the total antibiotics institutional consumption in 2014 was recorded 3.34% and 5.00% in 2009 respectively. The average antibiotics annual institution consumption constituting 464.1 in 2014 is higher by 1.06% comparatively with medium consumption of 459.20 registered in 1706 international hospitals, and by 35.31% in comparison with global consumption of 343 defined daily doses per 1000 patient-days.

**Conclusions:** The increase of DDD/1000 OBD took place as a result of worldwide increasing pathogenic microbes resistance to antibiotics. Nevertheless, decrease value indexes and cost of one DDD show in the best way the capacity of departmental management to cope with institutional budget deficiency and maintain qualitative antimicrobial treatment of hospitalized patients.

**Key words:** antibiotics, defined daily dose, consumption, rational use, hospitals.

### Introduction

"The doorstep to the temple of wisdom is knowledge of our own ignorance" – Benjamin Franklin. The battle against infection is as old as human civilization. During the last few centuries, great scholars such as Louis Pasteur, Ignaz Philipp Semmelweis, Alexander Fleming, and Joseph Lister have transformed the practice of medicine through their extraordinary discoveries. Despite the progress made and strides gained, our mission to prevent infection following surgery remains unaccomplished. It is not an exaggeration to claim that fear of infection lives in the heart of every surgeon who steps into the operating room daily [1]. Septic orthopedic and traumatology treatment permanently requires a great spectrum of antibiotics to be used. Evaluation of consumption in defined daily doses is one of principal methods for improving rational usage and good planning of hospitals necessities of anti-infectives for systemic use.

The World Health Organization "European strategic action plan on antibiotic resistance 2011–2016" mentioned that "Antimicrobial resistance is not a new phenomenon, but it is increasing and new resistant strains continue to emerge". One of the main aims of the plan includes to promote prudent use of antibiotics and other drugs [2]. An important source of information is "DRUG CONSUMPTION DATABASES IN EUROPE" published by a European Consortium in 2015 [3]. We must recognize that in the Republic of Moldova drugs consumption analysis in defined daily doses (DDD) per 1000 occupied-bed days (OBD), DDD/1000, as an important indicator for optimization of rational use of drug remedies in hospitals as all and the society are not addressed enough and highlighted by scientific research literature.

The primary aim of the study was to evaluate institutional representative data on antibiotics' utilization in accordance with World Health Organization (WHO) requirements, for six-year (2009-2014) period in septic orthopedic and traumatology institutional department, and to determine value of DDD/1000. Based on the obtained data, it aimed to make conclusions on the use of anti-infectives for systemic use in department and to propose recommendations for ensuring their optimization.

Emergency Medicine Institute of the Republic of Moldova (EMI) was founded in 1959. EMI consists of 9 clinical services with 600 beds overall including orthopedic-traumatology for 150 beds, municipal center with 8 seats of hemodialysis and 9 beds. There are 4 outpatient departments of traumatology and orthopedics as well [4].

### Material and methods

For this study we used the data of a six-year (2009-2014) period, in septic orthopedic-traumatology department of EMI for 40 beds, which show the dynamics of consumption of anti-infectives for systemic use drugs, as classified by Anatomical Therapeutic Chemical (ATC), classification system of World Health Organization indicated in grams and value indexes. Statistical, analytical, mathematical, comparative, logical and descriptive were used as the methods of study.

### Results and discussion

Total institutional antibiotic consumption in value indexes was 1562575 lei in 2009 and 1500888 lei in 2014 that represents respectively 17% and 14% from the whole amount of drugs [5].

In figure 1 it is shown the consumption rate of anti-infectives for systemic use in lei in comparison with other pharmacotherapeutic groups in orthopedic-traumatology department in 2014.

As can be observed the rate of anti-infectives for systemic use present 50169.00 lei or a share of 32% from the total value amount of 156821 lei drugs consumption in 2014. In 2009 the same data were 78054.84 lei or 34.75% from total of 224644 lei. The share of departmental from the total antibiotics institutional consumption in 2014 recorded 3.34% and 5.00% in 2009 respectively.

For evaluating the consumption of anti-infectives for systemic use drugs in the department during 2009-2014 were followed 10 steps of determining DDD/1000 [6, 7, 8] and the statistics data concerning the number of treated patients (for only patients with health insurance and other free treated by the state categories of citizens), the number of bed/days (2009 = 10664; 2010 = 10017; 2011 = 9540; 2012 = 10178; 2013 = 9701; 2014 = 9535) and data about total annual consumption of antibiotics were used.

All in all 48 antimicrobial remedies (both for parenteral and enteral use) for treating assistance of hospitalized patients in the evaluated period were used, from which with only enteral form 22 names, with only parenteral form 26 names and with both forms 10 names, which represents 37 active antimicrobial substances.

Parenteral forms consumption rate of antibiotic subgroups evaluated in DDD/1000 during 2009-2014 is shown in figure2.

As can be observed from figure 2 in the evaluated period the average consumption annual rate of all antibiotic subgroups records a decline from 543 in 2009 to 490 DDD/1000 in 2014 or by 9.76%. The main consumption of 461.65 DDD/1000 or 85.02% from the total in 2009 to 458.41 or 93.55% in 2014 with a slow decrease of 0.70% during mentioned years was registered for aminoglycoside antibacterials (Streptomycinum 1.0, Gentamycinum 0.2, Kanamycinum 1.0, Amikacinum 1.0), other beta-lactam antibacterials (Cefazolinum 3.0, Cefuroximum 3.0, Cefotaximum 4.0, Ceftazidimum 4.0, Ceftriaxonum 2.0, Cefoperazonum 4.0) and macrolides, lincosamides and streptogramins (Clarithromycinum 0.5, Azithromycinum 0.5, Lincomycinum 1.8).

In figure 3 consumption rate of enteral forms of antibacterials for systemic use subgroups in DDD/1000 during 2009-2014 is shown.

As it is seen from figure 2 the average consumption annual rate of antibiotics for oral usage increased from 35 in 2009 to 185 DDD/1000 OBD in 2014 or by 5.29 times. The highest consumption from 19.4 DDD/1000 or 55.43% of the total in 2009 to 169.9 or 91.84% of the total in 2014 and an increase by 8.76 times during the evaluated period was registered for quinolone antibacterials (Gatifloxacinum 0.4, Acidum pipe-midicum 0.8), other beta-lactam antibacterials (Cefalexinum 2.0, Cefuroximum 0.5, Cefaclorum 1.0 gram and Cefixim 0.4) and beta-lactam antibacterials, penicillins.

In figure 4 the total (parenteral and enteral forms) antibiotic subgroups used rates are demonstrated.

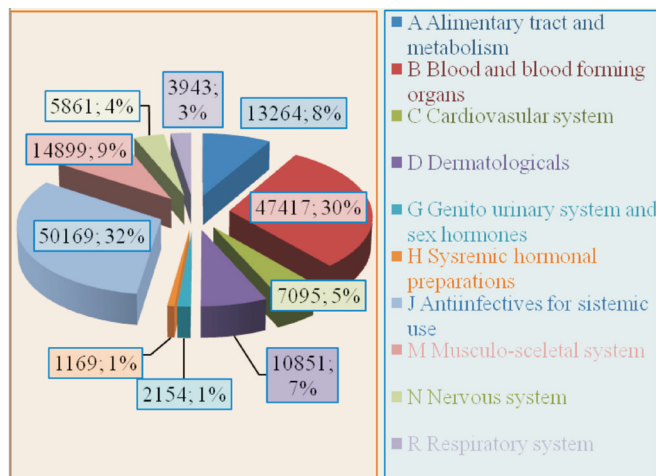


Fig. 1. Comparative share of anti-infectives for systemic use and other pharmacotherapeutic groups from total consumption.

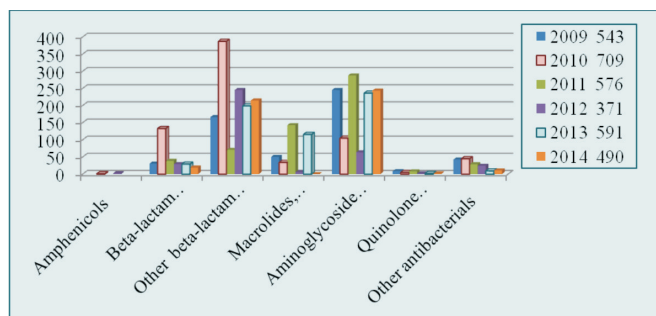


Fig. 2. Parenteral forms of consumption of antibacterials for systemic use in DDD/1000.

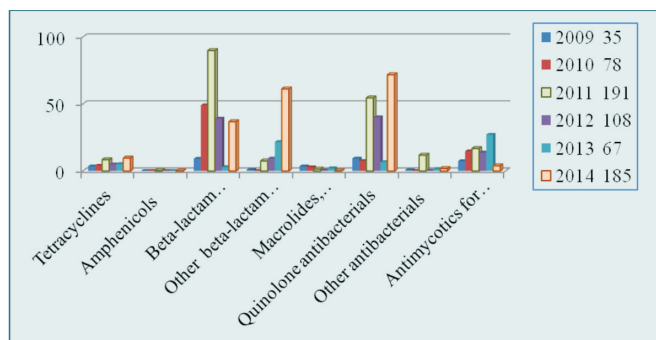


Fig.3. Enteral forms of consumption of antibacterials for systemic use in DDD/1000.

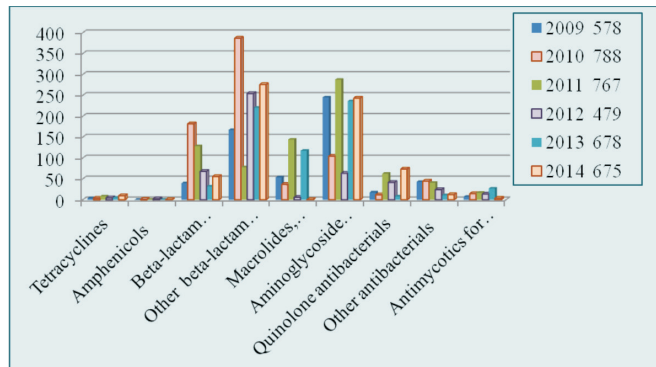


Fig. 4. The total consumption of antibacterials for systemic use in DDD/1000.

Table 1

The ratio between DDD/1000 for parenteral to enteral forms of antibiotics and percentage from the total

The ratio DDD/1000 of parenteral to enteral use and percentage from the total							
Years		2009	2 010	2011	2012	2013	2014
Parenteral		543	709	576	371	590	490
Enteral		35	78	191	108	67	185
The ratio of parenteral to oral		15.74	9.09	3.02	3.43	8.81	2.65
Total		578	788	767	479	657	675
Percentage from total	Parenteral	93.94%	89.97%	75.10%	77.45%	89.80%	72.59%
	Enteral	6.06%	9.90%	24.90%	22.55%	10.20%	27.41%

As it can be observed from figure 3 the average aggregated annual rate for total antibiotics consumption in the evaluated period increased from 578 in 2009 to 675 DDD/1000 in 2014 or by 16.78%.

The first 4 subgroups with the highest yearly consumption from 451,97 DDD/1000 or 78.20% of the total in 2009 to 575,42 DDD/1000 or 85.20% of the total in 2014 respectively and an increase of 27.31% during the evaluated period were registered for other beta-lactam antibacterials, aminoglycoside antibacterials, beta-lactam antibacterials, penicillins.

In table 1 the ratio DDD/1000 of parenteral to enteral use forms and percentage from the total is shown.

From table 1 it can be seen that in the evaluated period the ratio between antibiotics DDD/1000 parenteral to enteral forms decreased from 15.74 to 2.65 times. The percentage of parenteral forms from the total antibiotics DDD/1000 decreased from 93.94% in 2009 to 72.59% in 2014 and vice versa enteral forms increased the ratio from 6.06% to 27.41% respectively. Similar data for the entire institution were published early [9].

Comparison of total consumption data of anti-infectives for systemic use evaluated in DDD among 1576 European hospitals and surgeries, orthopedics and traumatology departments with the similar data of EMI and department is presented in figure 2.

As we can see from table 2 the average annual rate for total-hospital antibiotics utilization period in EMI decreased from 662.4 in 2009 to 464.1 DDD/1000 in 2014 or by 30%. That result was higher by 67.65 DDD/1000 or by 14.58% than the medium consumption of 396.45 DDD/1000 registered in case of 1256 international hospitals [(1115x393 + 34x395 + 43x422 + 55x448 + 1x400 + 1x403 + 7x390):1256] and lower by 112.66 DDD/1000 or by 36.68%

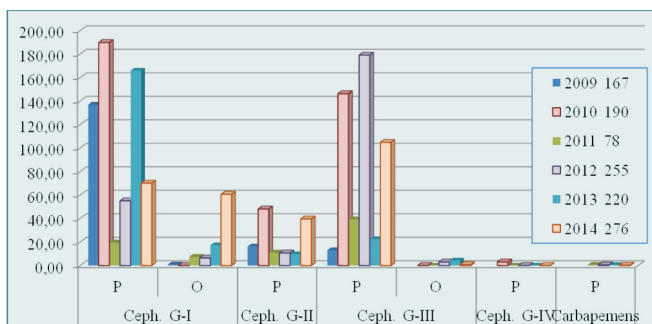


Fig. 5. Total consumption of J01D other beta-lactam antibacterials for parenteral and enteral use in DDD/1000.

in case of 450 international hospitals where the mentioned medium was 634.34 DDD/1000 [(8x601 + 54x547 + 1x595 + 40x499 + 195x583 + 7x570 + 7x1610 + 8x724 + 776x130) : 450] respectively.

Other all medium consumption in 1706 (1256+450) international hospitals constituting 459.20 DDD/1000 was lower than consumption of 464.1 DDD/1000 in EMI in 2014 by 4.90 DDD/1000 or by 1.06% and lower by 121.1 comparatively to global antibiotic consumption of 343 defined daily doses per 1000 patient-days or by 20.09%.

In septic orthopedic-traumatology department of EMI in the evaluated period was registered an increase from 578 in 2009 to 675 DDD/1000 in 2014 respectively or by 16.78%. In case of 152 international hospitals with similar surgery and orthopedic-traumatology activities medium consumption was (8x793 + 7x570 + 8x724 + 776x130) : 152= 769.83 DDD/1000, that was by 94.83 DDD/1000 more than results recorded in EMI in 2014 or by 14.05%.

In figure 5 the total consumption of other beta-lactam antibacterials for parenteral and enteral use in DDD/1000 is demonstrated.

From this chart as one can see in the evaluated period the total consumption of parenteral and enteral forms of cephalosporin's G-I (Cefalexinum and Cefazolinum) decreased slowly from 137.83 to 130.68 or by 5.20%, cephalosporin's G-II (Cefuroxim, Cefaclorum) and G-III (Cefotaximum, Cefprozidimum, Ceftriaxonum, Cefixim, Cefoperazonum, Cefoperazonum + Sulbactamum) demonstrate a considerable increment of consumption from 29.29 (16.25+13.04) in 2009 to 145.15 DDD/1000(39.64+105.5) or by 4.85 times, cephalosporins G-IV and carbapenems (Meropenemum, Imipenemum+Cilastatinum) had a low consumption only during 2010 to 2014. The total consumption of other beta-lactam antibacterials shows a considerable increment from 167 to 276 DDD/1000 or by 65.27%. It can be mentioned a visible decrement of consumption of cephalosporin's G-I with parenteral forms from 136.92 DDD/1000 in 2009 to 70.56 in 2014 or by 48.47% and vice versa a considerable growth of consumption of cephalosporin's G-I with enteral use forms from 0.93 in 2009 to 70.1 in 2014 or by 75.38 times. Similar data for the entire institution were published early [23].

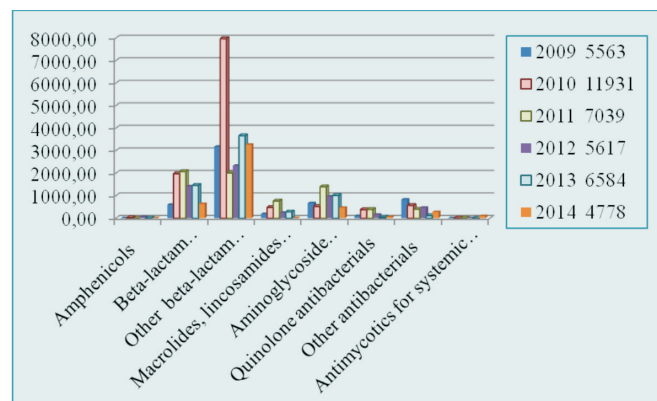
The cost of DDD/1000 in lei for parenteral forms of antibacterials for systemic use during 2009-2014 is shown in figure 6.



Table 2

**Surveillance studies of antibiotic use in international hospitals  
in comparison with the similar data in Emergency Medicine Institute and department**

Setting	Surveillance time-period	Data source	Frequency of data collection	Use of antibiotics in DDD/1000 bed-days over the study period
Emergency Medicine Institute	6 years (2009–2014)	Pharmacy dispensing records (PDR)	Annual	662.4, hospital-wide in 2009; 464.1, hospital-wide in 2014
Septic orthopedic-traumatology department of EMI	6 years (2009–2014)	(PDR)	Annual	578, department-wide in 2009; 675, department-wide in 2014.
1115 hospitals in France [10]	3 years (2008–2010)	(PDR)	Annual	370.0, hospital-wide in 2008; 393.0, hospital-wide in 2010.
34 public hospitals and 43 private hospitals located in south-western France [11]	2005	(PDR)	Annual	395, hospital-wide; 422, hospital-wide.
49–59 hospitals in the Netherlands [12] medium 54 hospitals	5 years (1997–2001)	(PDR)	Annual	472.0, hospital-wide in 1997; 547.0, hospital-wide in 2001.
55 public hospitals in Denmark [13]	5 years (1997–2001)	Danish Medicines Agency	Annual	380.0, hospital-wide in 1997; 448.0, hospital-wide in 2001.
1 university hospital in Switzerland [14]	5 years (1996–2000)	(PDR)	Not specified	400.0, hospital-wide;
Military Medical Academy, Sofia, Bulgaria [15]	1 year (2011)	(PDR)	Annual	403.0, hospital-wide.
1 general hospital in Spain [16]	5 years (1996–2000)	(PDR)	Annual	595.0, hospital-wide.
8 university hospitals in Germany [17]	3 years (1998–2000)	(PDR)	Annual	601.0, medical wards; 793.0, surgical wards.
40 non-university regional acute care general hospitals in south-western Germany, 2001–2002 [18]	2 years (2001–2002)	(PDR)	Annual	499.0, with a mean in internal medicine; 434.0, with a mean in surgery.
530 French hospitals in 2007 from which 195 in general hospitals and 357 for hospitals detailed clinical surgery activity [19]	1 year (2007)	(PDR)	Annual	557.0, in medicine; 553.0, in surgery.
7 hospitals in Stockholm [20]	1 year (2000)	(PDR)	Annual	390 to 570 internal medicine; 1020 to 1610 infectious disease.
8 Norwegian hospitals serving 36% of the nation's population [21]	from 2002 to 2007	(PDR)	Annual	increased from 617 to 724 DDDs/1000 bed-days.
130 US hospitals [22]	August 2002 1–31 July 2003	(PDR)	Annual	792 776
The global antibiotic consumption [23]	varied little between 2006 and 2008	(PDR)	Annual	343 defined daily doses (DDD) per 1000 patient-days (PD).



**Fig. 6. The cost of parenteral forms of antibacterials for systemic use per DDD/1000 in lei.**

As we can see from figure 5 the average consumption annual rate per DDD/1000 in value indexes (lei) of all parenteral antibiotic subgroups records a decline from 5563 in 2009 to 4778 lei in 2014 or by 14.11%. The medium yearly consump-

tion for the evaluated period with more than 1000 lei per DDD/1000 was registered for other beta-lactam antibacterials (3735.62 leis) and for beta-lactam antibacterials (1358.73 lei), more than 500 lei recorded aminoglycoside antibacterials (838.3 lei). Other subgroups as other antibacterials, macrolides, lincosamides and streptogramins, quinolone antibacterials, antimycotics for systemic use registered less than 500 leis per DDD/1000.

Consumption rate in value indexes in lei for enteral forms of antibiotics subgroups per DDD/1000 during 2009–2014 is shown in figure 7.

From figure 7 it can be found that the average consumption annual rate in value indexes of all antibiotic subgroups records an increase from 177 in 2009 to 669 lei per DDD/1000 in 2014 or by 3.78 times. The medium yearly consumption for the evaluated period with more than 100 lei per DDD/1000 was registered for beta-lactam antibacterials, penicillins, other beta-lactam antibacterials

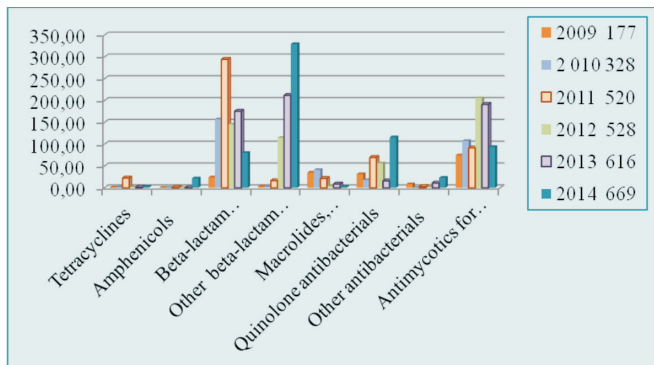


Fig. 7. The cost in lei for enteral forms of antibacterials for systemic use per DDD/1000.

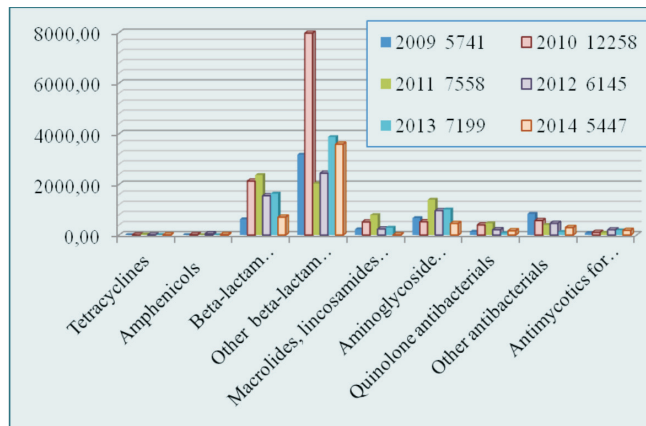


Fig. 8. Total cost of antibacterials for systemic use per DDD/1000 in lei.

and antimycotics for systemic use. All other subgroups recorded a consumption from 3 to 51 DDD/1000.

Consumption rate in value indexes (lei) of parenteral and enteral forms of antibiotics subgroups in DDD/1000 during 2009-2014 is shown in figure 8.

In this chart the presented data demonstrate that the average consumption annual rate in value indexes (lei) of total antibiotics record a decline from 5741 in 2009 to 5447 lei per DDD/1000 in 2014 or by 5.12%. The medium yearly cost of

DDD/1000 was registered more than: 3000 lei for other beta-lactam antibacterials, 1500 lei for beta-lactam antibacterials, penicillins, 500 lei for aminoglycoside antibacterials, between 100 – 500 lei for macrolides, lincosamides and streptogramins, quinolone antibacterials, other antibacterials and antimycotics for systemic use, and between 2 – 20 lei for tetracyclines and amphenicols.

Table 3

Cost of one medium DDD antibacterial for systemic use of parenteral, enteral forms and total in lei

Septic orthopedic-traumatology department						
Data for determining and cost of 1(one) DDD	2009	2010	2011	2012	2013	2014
Parenteral cost (lei) DDD/1000	5563.38	11930.48	7039.12	5616.86	6583.6	4778
Enteral cost (lei) DDD/1000	177.27	327.53	519.6	528.1	615.67	669.24
Total (Parenteral and enteral cost (lei) DDD/1000)	5741	12258	7558	6145	7199	5447
Parenteral DDD/1000	543.12	709.39	576.33	371.17	590.46	490.06
Enteral DDD/1000	34.5	78.07	190.67	108.17	67	185.21
Total (Parenteral and enteral DDD/1000)	577.62	787.46	767	479.34	657.46	675.27
Total (Parenteral and enteral cost (lei) 1 (one) DDD)	9.94	15.57	9.85	12.82	10.95	8.07
Parenteral cost (lei) 1 (one) DDD	10.24	16.82	12.21	15.13	11.15	9.75
Enteral cost (lei) 1(one) DDD	5.14	4.20	2.73	4.88	9.19	3.61

Table 4

The medium cost per one DDD in lei of other beta-lactamantibacterials for parenteral and enteral forms and total

Septic orthopedic-traumatology department						
Data for determining and cost of 1(one) DDD	2009	2010	2011	2012	2013	2014
Parenteral cost (lei) DDD/1000	3174.22	7974.98	2012.62	2328.99	3662.1	3260.84
Enteral cost (lei) DDD/1000	3.02	2.88	16.52	114.6	211.81	329.52
Parenteral and enteral cost (lei) DDD/1000	3177.24	7977.86	2029.14	2443.59	3873.9	3590.4
Parenteral DDD/1000	166.21	387.24	70.55	245.24	198.74	214.89
Enteral DDD/1000	0.93	0	7.44	19.73	21.65	61.25
Parenteral and enteral DDD/1000	167.14	387.24	77.99	254.57	220.39	276.14
Total (Parenteral and enteral cost (lei) 1 (one) DDD)	19.01	20.60	26.02	9.60	17.58	13.00
Parenteral cost (lei) 1 (one) DDD	19.10	20.59	28.53	9.50	18.43	15.17
Enteral cost (lei) 1 (one) DDD	3.25	0.00	2.22	5.81	9.78	5.38

To determine the cost of one medium DDD of antibacterials for systemic use separately for parenteral and enteral pharmaceutical forms were divided by the cost of DDD/1000 to DDD/1000 respectively. The cost of one medium DDD antibiotics in lei for parenteral and enteral forms and total is shown in table 3 and 4.

As we can see from table 3 in the evaluated period the cost of one medium DDD decreased from 10.24 lei in 2009 to 9.75 lei in 2014 or by 4.79% for parenteral forms, from 5.14 to 3.61 lei or by 29.77% for enteral forms and from 9.94 to 8.07 lei or by 18.81% for one total DDD.

In chronological way for the evaluated years the ratio between the cost of one medium DDD of parenteral and enteral forms was respectively 1.99:1; 4:1; 4.47:1; 3.1:1; 1.2:1 and 2.7:1.

Calculation of the cost in lei per one medium DDD for parenteral, enteral forms and total for other beta-lactam antibacterials is shown in table 4. As we can see from this table in the evaluated period total cost of one medium DDD decreased from 19.01 in 2009 to 13.00 leis in 2014 or by 31.94%, for parenteral from 19.10 to 15.17 lei or by 20.58% and for enteral use increased from 3.32 to 5.38 lei or by 59.64%.

The ratio between the cost of parenteral and enteral forms per one medium DDD in the evaluated years was respectively 5.88:1; 20:1; 12.87:1; 1.64:1; 1.88:1 and 2:82:1.

### Conclusions

1. DDD/1000 OBD in the septic orthopedic-traumatology department from 578 in 2009 increased to 675 in 2014 or by 16.78% of which other beta-lactam antibacterials from 167 or 28.89% and 276 or 40.89% respectively. The consumption of parenteral forms constituting 543 DDD/1000 or 93.95% from the total in 2009 decreased to 490 DDD/1000 OBD or by 9.76% in 2014 and vice versa use of enteral forms constituting 35 or 6.06% from the total in 2009, increased to 185 DDD/1000 OBD in 2014 or by 5.29 times respectively.

2. The cost of 5741 lei per DDD/1000 OBD in 2009 recorded a slow decline to 5447 lei or by 5.12%. The cost of one medium DDD from 9.94 lei in 2009 decreased to 8.07 lei in 2014 or by 18.81%. The rate of anti-infectives for systemic use in 2014 presented 50169.00 lei or a share of 32% from the total departmental value consumption; the same data in 2009 were 78054.84 lei or 34.75%. The share from the total antibiotics institutional consumption in 2014 recorded 3.34% and 5.00% in 2009 respectively.

3. The average annual rate for total-institution antibiotics utilization period in EMI decreased from 662.4 in 2009 to 464.1 DDD/1000 OBD in 2014 or by 30%. Obtained record is higher by 6.69% comparatively with medium consumption of 433.06 DDD/1000 registered in 1576 international hospitals, and by 35.31% than global antibiotic consumption of 343 defined daily doses per 1000 patient-days.

4. There were evaluated 48 antimicrobial remedies (both for parenteral and enteral use) for hospitalized patients, from which with only enteral form 22 names, with only parenteral form 26 names and with both forms 10 names, which represent 37 active antimicrobial substances.

5. The ratio between the cost of one medium DDD of parenteral and enteral forms of antibacterials for systemic use was 1.99:1; 4:1; 4.47:1; 3.1:1; 1.2:1 and 2.7:1 for the evaluated years. For other beta-lactam antibacterials this ratio was 5.88:1; 20:1; 12.87:1; 1.64:1; 1.88:1 and 2:82:1 respectively.

6. The increase of DDD/1000 OBD during the evaluated period took place as a result of worldwide increasing pathogenic microbes' resistance to antibiotics. Nevertheless, decrease value indexes and cost of one DDD show in the best way the capacity of departmental management to cope with institutional budget deficiency and maintain qualitative antimicrobial treatment of hospitalized patients.

### References

- Gehrke Thorsten, Javad Parvizi. Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection. [https://www.efort.org/wp-content/uploads/2013/10/Philadelphia\\_Consensus.pdf](https://www.efort.org/wp-content/uploads/2013/10/Philadelphia_Consensus.pdf).
- The world medicines situation - 2011. Centre for Drug Statistics in Oslo, Norway. [www.who.int/.../WMS\\_ch14\\_wRational.pdf](http://www.who.int/.../WMS_ch14_wRational.pdf): <http://www.whocc.no/>.
- Surveillance of antimicrobial consumption in Europe 2010. <http://ecdc.europa.eu/en/publications/Publications/antimicrobial-antibiotic-consumption-ESAC-report-2010-data.pdf>. 2010; 3-59.
- Medical and public health institution Emergency Medicine Institute. <http://urgenta.md/Index.aspx>.
- Bernaz EP. The consumption and the stocks dynamics of systemic antibiotics for systemic use in hospitals. *Curierul medical*. 2013;4:49-55.
- How to Calculate Antimicrobial Defined Daily Doses (DDDs) and DDDs per 1000 Patients Days. [www.antimicrobialstewardship.com/.../how-to-calculate-ddds-final.pdf](http://www.antimicrobialstewardship.com/.../how-to-calculate-ddds-final.pdf).
- Guidelines for ATC classification and DDD assignment WHO, 16th edition. WHO Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. Oslo, 2013;284.
- Bernaz E. Evaluation of the antimicrobials used in defined daily doses in hospitals of the Republic of Moldova. *Buletinul Academiei de Științe a Moldovei. Științe Medicale [Bulletin of the Moldovan Academy of Sciences. Medical Sciences]*. 2014;3(44):189-200.
- Bernaz EP. Evaluation of consumption in defined daily doses of antimicrobials for systemic use in hospitals. *Curierul medical*. 2015;5:6-10.
- Dumartin CA, Rogues M., L'Heriteau F, et al. Trends in antibiotic use and antimicrobial resistance in French hospitals, 2008-2010. Data from the nationwide network "ATB-RAISIN". 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). London, Sunday, April 01, 2012.
- Amadeo B. Easily available adjustment criteria for the comparison of antibiotic consumption in a hospital setting: experience in France. *Clinical microbiology and infection. Clinical Microbiology and Infect*. 2010;16(6):735-41.
- Filius PM, Liem TB, Van Der Linden PD, et al. An additional measure for quantifying antibiotic use in hospitals. *J Antimicrob Chemother*. 2005;55: 805-808.
- Muller-Pebody B, Muscat M, Pelle B, et al. Increase and change in pattern of hospital antimicrobial use, Denmark, 1997-2001. *J Antimicrob Chemother*. 2004;54:1122-1126.
- Loeffler JM, Garbino J, Lew, et al. Antibiotic consumption, bacterial resistance and their correlation in a Swiss university hospital and its adult intensive care units. *Scand J Infect Dis*. 2003;35:843-850.
- Savov E, Gergova I, Borisova M, et al. Consumption of antimicrobial drugs and antibiotic resistance in problematic for hospital infectious pathology bacteria. *Trakia Journal of Sciences*. 2013;11(4):338-342.
- Hermosilla Najera L, Canut Blasco A, Ulibarrena Sanz, et al. Trends in antimicrobial utilization at a Spanish general hospital during a 5-year period. *Pharmacoepidemiol Drug Safety*. 2003;12:243-247.
- De With K, Bergner J, Buhner J, et al. Antibiotic use in German university hospitals 1998-2000 (project INTERUNI-II). *Int J Antimicrob Agents*. 2004;24:15-20.

18. Kern WV, de With K, Steib-Bauert M, et al. Antibiotic use in non-university regional acute care general hospitals in south-western Germany, 2001-2002. *Infection*. 2005;33(5-6):333-9.
19. Dumartin Catherine, L'Heriteau Francois, Pefau Muriel, et al. Antibiotic use in 530 French hospitals: results from a surveillance network at hospital and ward levels in 2007. *J Antimicrob Chemother*. 2010;65:2028-2036.
20. Bergman U, Risinggard H, Vlahović-Palcevski V, Ericsson O. Use of antibiotics at hospitals in Stockholm: a benchmarking project using internet. *Pharmacoepidemiol Drug Saf*. 2004;13(7):465-71.
21. Haug JB, Berild D, Walberg M, Reikvam A. Increased antibiotic use in Norwegian hospitals despite a low antibiotic resistance rate. *J Antimicrob Chemother*. 2011;66(11):2643-6.
22. Polk Ronald E., Fox Christina, Mahoney Anne, et al. Measurement of Adult Antibacterial Drug Use in 130 US Hospitals: Comparison of Defined Daily Dose and Days of Therapy. *Clinical Infectious Diseases*. 2007;44(5):664-670.
23. Henard S, Rahib D, Léon L, et al. Consommation des antibiotiques rapportée via les bilans standardisés de lutte contre les infections nosocomiales et relation avec l'ICATB. *Medecine et Maladies Infectieuses*. 2010;41(4):197-205.