The Impact of Antibiotic Consumption on Development of Acinetobacter Baumannii Resistance

Djana Granov1, Amela Dedeic Ljubovic1, Svjetlana Loga Zec2, Nermir Granov3, Mirsada Hukic4

1Clinical Microbiology, University Clinical Center Sarajevo, Bosnia and Herzegovina
2Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine University of Sarajevo, Bosnia and Herzegovina
3Clinic for Cardio Surgery, University Clinical Center Sarajevo, Bosnia and Herzegovina
4Institute for Biomedical Diagnostics and Research-Nalaz, Sarajevo, Bosnia and Herzegovina and International Burch University, Sarajevo, Bosnia and Herzegovina

Corresponding author: Prof Svjetlana Loga Zec, MD, PhD. Faculty of medicine, University of Sarajevo. Bosnia and Herzegovina. E-mail: svjetlana.loga@gmail.com

ABSTRACT
Aim: The aim of this study was to examine the impact of antibiotic consumption on development of antimicrobial resistance in Acinetobacter baumannii. Material and Methods: The study was conducted in University Clinical Center of Sarajevo. In our retrospective study Acinetobacter baumannii isolated in period from July 1st 2009 to December 31st 2012. Isolates were detected from different clinical samples including urine, wound swab, blood, bronchial aspirate and other samples which were collected from patients situated on various hospital wards. Clinical isolates belonged to one per patient in a given period of time. Results: Antimicrobial resistance was interpreted according to CLSI breakpoints. Consumption of antibiotics was analyzed according to recommendations of the ESAC-Net and current Acinetobacter baumannii classification. Pearson’s correlation showed a positive correlation between gentamicin consumption and emerging of resistance (p = 0.023). Conclusion: Increase in the antimicrobial use was followed with an increase in resistance of Acinetobacter baumannii isolates. Monitoring of antibiotic resistance and consumption is of a great importance in order to reduce the emergence and spread of antimicrobial resistant organisms in the health care settings.

Keywords: antimicrobials, surveillance, consumption.

1. INTRODUCTION
Acinetobacter baumannii is a non fermentative Gram-negative coccobacillus that is emerged as opportunistic nosocomial pathogen. A variety of human infections caused by Acinetobacter species have been reviewed including pneumonia (most often related to endotracheal tubes or tracheostomies), endocarditis, meningitis, skin and wound infections, peritonitis (in patients receiving peritoneal dialysis) and urinary tract infections (1).

Multidrug-resistant (MDR) A. baumannii is increasings held responsible for nosocomial infections (2) and plays a significant role in colonization and infection of hospitalized patients and can transmit from patient to patient with direct and indirect contact. The main risk factors of Acinetobacter baumannii bacteremia are invasive procedures such as central venous catheterization, mechanical ventilation and surgical procedures. Other risks include previous antimicrobial treatment, number of antimicrobial agents prescribed, treatment with carbapenems, cephalosporins or aminoglycosides, prolonged hospital stay, previous ICU stay, enteral nutrition (3).

A. baumannii can develop multiple antimicrobial resistance extremely quickly what is in contrast to other clinical bacteria, which require greater time to acquire resistance, usually in response to therapeutic strategies. General mechanisms of resistance are enzyme-mediated resistance, genetic adaptation, efflux pump and changes in the structure of the outer membrane (4). The ability to chronically colonize patients and cause outbreaks which are usually hard to eradicate poses significant challenges to infection control and increases healthcare costs (5). The selection and spread of resistant bacteria in hospitals is the biggest threat to patient safety.
The Impact of Antibiotic Consumption on Development of Acinetobacter Baumannii Resistance

The consequences of inappropriate antimicrobial treatment are increasing mortality and morbidity, adverse effects, prolonged hospital stay, secondary infection, the emergence of resistant microorganisms and increase of healthcare costs. Mortality, misuse of antimicrobials and microbial resistance are closely related (6).

Effective supervision is cornerstone of national and international efforts to control antimicrobial resistance. Monitoring the use of antibiotics, the occurrence and spread of resistant strains of bacteria provides the information and tools that are needed to promote appropriate use of antibiotics at all levels, from local to global.

In Bosnia and Herzegovina there is no established antimicrobial resistance surveillance system and there is no monitoring the influence of antibiotic consumption on development of bacterial resistance. The aim of this study was to examine the impact of antibiotic consumption on development of antimicrobial resistance in Acinetobacter baumannii.

2. MATERIALS AND METHODS

The study was conducted in University Clinical Center of Sarajevo, isolates of Acinetobacter baumannii in period from July 1st 2009 to December 31st 2012. Isolates were detected from different clinical samples including urine, wound swab, blood, bronchial aspirate and other samples which were collected from patients situated on various hospital wards. Clinical isolates belonged to one per patient in a given period of time.

Identification of Acinetobacter baumannii isolates was done on the basis of morphological, cultural and biochemical characteristics. In addition, automated VITEK 2 Compact system (bioMérieux, Marcy l’Étoile, France) was used to aid in confirmation of the A. baumannii isolates (8).

Antimicrobial resistance profile was determined by automated VITEK 2 Compact system (bioMérieux, Marcy l’Étoile, France) for: ceftriaxone, cefazidime, cefotaxim, amikacin, gentamycin, imipenem, meropenem, ciprofloxacin, levofloxacin, trimetoprim-sulfametoksazol, cepefime, piperacillin/tazobactam, colistin, tobramycin. Results were interpreted according to CLSI breakpoints (9).

Consumption of above mentioned antibiotics was given in standard units (pill, capsule, or ampoule) and analyzed according to the recommendations of the ESAC-Net and current ATC classification. To better demonstrate the statistical data analysis, the research period is divided into 14 quarterly periods, respectively.

Descriptive statistics was applied. Results were given as total numbers, proportions, means±SD, and medians with ranges, where appropriate.

3. RESULTS

Over the study period, a total consumption of tested antimicrobials was 865,904 pieces, of which quinolones 285601 (33%), cephalosporin’s 3th and 4th generation with 285601 (33%), cephalosporin’s 3th and 4th generation with 285601 (33%), aminoglycosides 103227 (11,9%), carbapenems 107092 (12,36%). Consumption of particular antibiotics is shown in Table 1.

Between 2009 and 2012, consumption of all antimicrobials increased by 50% (from 65835 in 2009 to 98272 in 2012). The most commonly used antibiotic was ciprofloxacin – 275316 pieces (31,8%), then trimethoprim/sulfamethoxazol 155882 (18%), while the lowest consumption had colistin with 777 (0,08%) pieces, cefotaxime 2155 (0,24%) and piperacillin/tazobactam 4560 (0,52%) pieces, respectively. Highest consumption was during 11th quarter (Qtr), while the lowest

| Quarter | Amikacin | Cefepime | Ceftazidime | Cefotaxim | Ciprofloxacin | Gentamycin | Imipenem | Meropenem | Piperacillin/tazobactam | Colistin | Total |
|---------|----------|----------|-------------|-----------|---------------|------------|----------|-----------|------------------------|----------|-------|
| 1st     | 1665     | 1755     | 3500        | 172       | 9865          | 21398      | 7760     | 5529      | 3197                   | 372      | 10202 |
| 2nd     | 2341     | 2030     | 3472        | 44        | 10868         | 22728      | 6150     | 5693      | 3810                   | 459      | 10179 |
| 3rd     | 619      | 2006     | 3103        | 0         | 10450         | 20960      | 5940     | 8070      | 3443                   | 112      | 10893 |
| 4th     | 1538     | 554      | 3708        | 0         | 11274         | 20862      | 5550     | 5478      | 4433                   | 221      | 11395 |
| 5th     | 2037     | 4        | 4223        | 0         | 8310          | 20577      | 4580     | 3727      | 3396                   | 168      | 11495 |
| 6th     | 1965     | 0        | 6332        | 0         | 9883          | 19589      | 6400     | 3672      | 3519                   | 350      | 13636 |
| 7th     | 1695     | 0        | 4774        | 0         | 8976          | 17101      | 5690     | 3446      | 3855                   | 201      | 11919 |
| 8th     | 1576     | 168      | 5479        | 0         | 10840         | 21617      | 4810     | 3187      | 2728                   | 366      | 11301 |
| 9th     | 2295     | 627      | 10399       | 1034      | 12110         | 29742      | 10520    | 5224      | 6489                   | 393      | 17427 |
| 10th    | 1327     | 492      | 6369        | 904       | 6064          | 17965      | 5720     | 2414      | 3409                   | 550      | 6295  |
| 11th    | 1512     | 169      | 5048        | 1         | 6075          | 16618      | 5451     | 3677      | 3261                   | 536      | 10122 |
| 12th    | 1380     | 529      | 6628        | 0         | 8534          | 18536      | 5569     | 3223      | 3504                   | 470      | 12468 |
| 13th    | 2202     | 8334     | 70372       | 2155      | 127904        | 275316     | 81200    | 57486      | 49606                   | 4560     | 155882 |
| 14th    | 1573.36  | 595.29   | 5026.57     | 153.93    | 9136          | 19665.48   | 5800     | 4106.14   | 3439.29                 | 325.71   | 11134.48 |
| X       | 509.64   | 761.71   | 2104.21     | 243.93    | 2317.63       | 4841.34    | 1901.93  | 1744.03   | 1125.21                 | 147.48   | 3095.64 |
| SD      | 660      | 0        | 1689        | 0         | 4066          | 6939       | 1610     | 987       | 1115                   | 151      | 4208  |
| Min     | 619      | 0        | 1689        | 0         | 4066          | 6939       | 1610     | 987       | 1115                   | 151      | 4208  |
| Max     | 2341     | 2030     | 10399       | 1034      | 12110         | 29742      | 10520    | 8079      | 6489                   | 550      | 17427 |

Table 1. Antibiotic consumption on Quarter (Qtr) level
The Impact of Antibiotic Consumption on Development of Acinetobacter Baumannii Resistance

Over the studied period a total of 1977 isolates of Acinetobacter baumannii were analyzed. Antibiotic resistance pattern was shown in Table 2 and Graph 1. The highest rate of resistance was to the 3rd generation of cephalosporin’s (~96%) and ciprofloxacin (91.87%), while there was no resistance to colistin. Resistance to imipenem and meropenem increased from 27% and 34% in 1st Qtr to 80% in 11th Qtr. For piperacillin/tazobactam the increase was from 33% in 1st to 88% in 11th Qtr. Resistance to ciprofloxacin increased from 80% to 100% in 14th quarter.

Pearson’s correlation test showed no significant correlation between the resistance of Acinetobacter baumannii and consumption of antimicrobials, except with gentamicin. The positive, statistically significant correlation was demonstrated between gentamicin consumption and emerging of resistance (p = 0.023) (Table 3).

4. DISCUSSION

Our results showed that Acinetobacter baumannii is among the most resistant bacteria and antimicrobial susceptibility testing pointed that it is a multidrug-resistant bacteria. This was confirmed and similar by results of authors from Italy (10), Slovakia (11), Greece (12).

Resistance to imipenem and meropenem increased from Quarter (Qtr) 1

| Quarter (Qtr) | AMIKACIN | CEFEPIME | CEFOTAXIME | CEFTAZIDIME | CEPHRAXON | CIPROFLOXACIN | COLISTIN | GENTAMICIN | IMIPENEM | MEROPENEM | PIPERACILLIN TAZOBACTAM | TOBRAMYCN | TRIMETHOPRIM – SULFAMETHOXAZOL |
|--------------|----------|----------|------------|-------------|-----------|---------------|---------|------------|---------|-----------|--------------------------|-----------|------------------------|
| 1st          | 58,18    | 58,90    | 95,08      | 83,93       | 91,48     | 80,24         | 0.00    | 73,99      | 27,17   | 37,14     | 33,53                    | 0.00      | 70,45                  |
| 2nd          | 56,82    | 71,01    | 100,00     | 94,35       | 99,22     | 85,25         | 0.00    | 83,20      | 26,28   | 34,75     | 57,78                    | 0.00      | 79,84                  |
| 3rd          | 48,53    | 75,76    | 97,67      | 93,44       | 98,13     | 86,72         | 0.00    | 85,94      | 33,56   | 39,44     | 69,18                    | 8,57      | 80,49                  |
| 4th          | 55,56    | 81,89    | 100,00     | 97,66       | 100,00    | 93,91         | 0.00    | 82,96      | 45,07   | 47,52     | 71,43                    | 3,13      | 81,34                  |
| 5th          | 43,37    | 81,61    | 98,63      | 94,35       | 98,63     | 93,25         | 0.00    | 80,56      | 62,30   | 64,29     | 72,13                    | 0.00      | 88,89                  |
| 6th          | 59,07    | 73,91    | 100,00     | 88,95       | 98,41     | 93,29         | 0.00    | 69,90      | 59,28   | 60,94     | 72,88                    | 6,25      | 89,89                  |
| 7th          | 69,90    | 66,67    | 100,00     | 95,92       | 98,41     | 95,65         | 0.00    | 83,51      | 64,15   | 66,67     | 66,35                    | 4,44      | 93,94                  |
| 8th          | 61,16    | 69,17    | 100,00     | 92,86       | 100,00    | 91,51         | 0.00    | 73,64      | 59,66   | 60,68     | 60,00                    | 10,34     | 94,39                  |
| 9th          | 68,00    | 78,63    | 95,00      | 93,48       | 96,55     | 93,85         | 0.00    | 65,81      | 61,27   | 66,19     | 65,18                    | 5,13      | 93,94                  |
| 10th         | 86,46    | 77,78    | 100,00     | 97,03       | 100,00    | 96,34         | 0.00    | 72,73      | 72,22   | 73,83     | 79,69                    | 14,81     | 93,33                  |
| 11th         | 85,98    | 91,96    | 100,00     | 96,52       | 96,55     | 92,86         | 0.00    | 49,24      | 81,51   | 82,91     | 88,79                    | 13,16     | 94,17                  |
| 12th         | 77,04    | 85,93    | 100,00     | 97,06       | 99,03     | 95,24         | 0.00    | 62,09      | 77,46   | 83,21     | 84,44                    | 12,90     | 93,94                  |
| 13th         | 56,69    | 77,58    | 100,00     | 89,25       | 100,00    | 88,07         | 0.00    | 63,86      | 64,28   | 64,57     | 73,33                    | 16,12     | 89,56                  |
| 14th         | 51,72    | 82,89    | 100,00     | 97,30       | 100,00    | 100,00        | 0.00    | 75,95      | 69,62   | 70,51     | 78,67                    | 6,67      | 96,97                  |
| X            | 62,74    | 76,69    | 99,02      | 93,72       | 98,32     | 91,87         | 0.00    | 73,10      | 57,42   | 60,90     | 69,53                    | 7,25      | 88,65                  |
| MEDIAN        | 58,63    | 77,68    | 100,00     | 94,35       | 98,83     | 93,27         | 0.00    | 73,82      | 61,79   | 64,43     | 71,78                    | 6,46      | 91,61                  |
| MIN           | 43,37    | 58,90    | 95,00      | 83,93       | 91,48     | 80,24         | 0.00    | 49,24      | 26,28   | 34,75     | 33,53                    | 0.00      | 70,45                  |
| MAX           | 86,46    | 91,96    | 100,00     | 97,66       | 100,00    | 100,00        | 0.00    | 85,94      | 81,51   | 83,21     | 88,79                    | 14,81     | 96,97                  |

Table 2. An overall resistance of Acinetobacter baumannii to antimicrobials during the observed period

Figure 1. Percentage of A. baumannii isolates resistant to particular antibiotics in the observed period.

Table 3. Correlation between the incidence of resistant A. baumannii forms and consumption of certain antibiotics in the examined period

| Antibiotic | df | Pearson’s correlation | p    |
|------------|----|----------------------|------|
| Amikacin   | 14 | -0.267               | 0.355|
| Cefepime   | 14 | 0.116                | 0.694|
| Cefotaxim  | 14 | 0.014                | 0.963|
| Ceftazidime| 14 | 0.039                | 0.893|
| Ceftriakson| 14 | -0.252               | 0.384|
| Ciprofloxacin| 14 | -0.02               | 0.946|
| Colistin   | 14 | 0                    | 1    |
| Gentamicin | 14 | 0.601                | 0.023|
| Imipenem   | 14 | -0.296               | 0.304|
| Meropenem  | 14 | 0.189                | 0.517|
| Piperacillin/tazobactam | 14 | 0.204               | 0.484|
| Tobramycin | 14 | -0.388               | 0.17 |
| Trimethoprin – sulfame-toksazol | 14 | -0.228             | 0.433|
27% and 34% in 1st quarter to 80% in 11th Qtr. According to information from the Croatian Committee for Antibiotic Resistance Surveillance of the CAMS, resistance of clinical isolates of ABC to carbapenems in Croatia from 2006 to 2011 ranged from 2% for imipenem and 11% for meropenem in 2006, to 64% in 2011 (13), and in larger hospitals is 90% (13,14). The resistance of Acinetobacter baumannii to carbapenems, mostly to imipenem, has been the topic of various papers, and the published data on the resistance rates to imipenem have reported from 21% up to 100% of the tested isolates of A. baumannii (15, 16, 17). Among the European countries the resistance rates to carbapenems are highest in the countries in southern Europe, such as Greece and Croatia (14, 19).

Over the study period we observed increased consumption of carbapenem antibiotics what resulted in increasing resistance on carbapenems in Acinetobacter baumannii. Highest consumption of imipenem and meropenem was in 11th quarter and in the same period the highest resistance to carbapenems was observed, but there was no correlation between resistance and consumption by Pearson correlation test. Carbapenem justified use in ESBL isolates (Eng. Extended spectrum β-lactamase; ESBL) reflected to the resistance of nonfermentative bacteria primarily A. baumannii (18). If we compare the resistance of imipenem and meropenem we can find that through all 14 quarters greater resistance was to meropenem. This is similar to the data of Committee for Antibiotic Resistance Surveillance in the Republic of Croatia for the period 2002 - 2008, where the difference in sensitivity within the carbapenem antibiotics group was observed and almost all microbiological laboratories had a higher percentage of resistant isolates of A. baumannii to meropenem over imipenem (13).

Average resistance to the 3rd generation of cephalosporins is ~ 95%, 97% to ciprofloxacin and to cefepime 76%. Medic et al. found that the resistance to cephalosporins third and fourth generations as well as ciprofloxacin was greater than 93% (19). Acinetobacter baumannii isolates are often susceptible only to colistin or tigecycline. Over the study period there was no resistance to colistin. SENTRY Antimicrobial Surveillance from 2001 to 2011, which includes different centers in USA, Europe, South America and Asia, showed that colistin resistance was on low level (0.9%–3.3%) (20, 21). According to data collected by the European Regional Branch of study monitoring resistance in 2011, followed by the antimicrobial resistance in 21 countries of Europe including Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, etc, Acinetobacter was less susceptible to all antibiotics except colistin. In the European component of the Regional Resistance Surveillance study for 2011, a total of 21 countries were monitored for antimicrobial resistance patterns including Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Russia, Slovenia, Spain, Sweden, United Kingdom etc. Acinetobacter was generally less susceptible, except against COL (99.2–99.6% S) and TIG (95.0% inhibited at ≤2 μg/mL) (22).

Application of Pearson's correlation to the resistance of Acinetobacter baumannii compared to consumption of certain antibiotics not found a significant correlation between these two variables in all tested antibiotics, except with to gentamicin where a positive, statistically significant correlation (p = 0.023) was proven. Pearson's-correlation test showed no significant correlation between the resistance of Acinetobacter baumannii and consumption of antimicrobials, except with gentamicin. The positive, statistically significant correlation was demonstrated between gentamicin consumption and emerging of resistance (p = 0.023). There are a lot of studies about relationship between consumption of antimicrobial agents and developing of resistance. Sédlákova et al. found a positive correlation between amnoglycoside consumption and resistance to gentamicin in Escherichia coli and Klebsiella pneumonia (23). H Jin et al. found that gentamicin usage was significantly correlated with resistance in Acinetobacter baumannii to this drug (24).

5. CONCLUSION

Increase in the antimicrobial use in University Clinical Center of Sarajevo was followed with an increase in resistance of Acinetobacter baumannii isolates. The fastest development of resistance has been to carbapenems, while there was no resistance to colistin. There was a positive correlation between the development of resistance and consumption of gentamicin. Monitoring of antibiotic resistance and consumption is of a great importance in order to reduce the emergence and spread of antimicrobial resistant organisms in the health care settings.

REFERENCES

1. Winn WC, Allen SD, Janda WM, Koneman EW, Schreckenberger PC. Koneman’s Color Atlas and Textbook of Diagnostic Microbiology. 6th ed. Lippincott Williams & Wilkins, 2005.
2. Navon-Venezia S, Ben-Ami R, Carmeli Y. Update on Pseudomonas aeruginosa and Acinetobacter baumannii infections in the healthcare setting. Curr Opin Infect Dis. 2005; 18: 306-13.
3. Cisneros JM, Rodriguez-Bano J, Fernandez-Cuenca F, Ribera A, Vila J, Pascual A, Martinez-Martinez L, Bou G, Pachon J. Risk-factors for acquisition of imipenem-resistant Acinetobacter baumannii in Spain: a nationwide study. Clin Microbiol Infect. 2005; 11: 874-79.
4. Maragakis LL, Perl TM. Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis. 2008; 46: 1254-63.
5. Dijkshoorn, L, Nemec A, Seifert H. An increasing threat in hospitals: Multidrug-resistant Acinetobacter baumannii. Nat. Rev. Microbiol. 2007; 5: 939-51.
6. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M.. Early goal directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345: 1368-77.
7. Cheesborough, M. Medical laboratory manual for tropical countries Volume II: microbiology, ELBS. 1984; 35: 40-6.
8. Dedecic-Ljubovic, A, Granov D, Hukic M. Emergence of extensive drug-resistant (XDR) Acinetobacter bauman-
The Impact of Antibiotic Consumption on Development of Acinetobacter Baumannii Resistance

9. Wayne, P A. Clinical and Laboratory Standards Institute. M100-S17. Performance standards for antimicrobial susceptibility testing; 16th informational supplement, 2007

10. Bassetti, M, Righi E, Esposito S, Petrosillo N, Nicolini L. Drug treatment for multidrug-resistant Acinetobacter baumannii infections. Future Microbiol. 2008; 3(6): 649-60.

11. Babik J, Bodnarova L, Sopko K. Acinetobacter: serious danger for burn patients. Acta Chir Plast. 2008; 50: 27-32.

12. Giamarellou H, Antoniadou A, Kanellakopoulou K. Acinetobacter baumannii: a universal threat to public health? Int J Antimicrob Agents. 2008; 32: 106-19.

13. Goić-Barišić, I. Multidrug-resistant Acinetobacter baumannii (MRAB) – ten years after the onset of these isolates in Croatia. Croatian Journal of Infection. 2012; 32: 67-70.

14. Croatian Committee for Antibiotic Resistance Surveillance. Antibiotic resistance in Croatia in 2012. Zagreb: Croatian Academy of Medical Sciences (CAMs), 2013

15. Goić- Barišić I, Bedenic B, Tonkić M, Novak A, Katić S, Kalenic S, Punda-Polić V, Towner K. Occurrence of OXA-107 and ISAba1 in carbapenem-resistant isolates of Acinetobacter baumannii from Croatia. J Clin Microbiol. 2009;47: 3348–9.

16. Srinivasa Rao R, Karthika RU, Singh SP, Shashikala P, Kanungo R, Jayachandran S, Prashanth K. Correlation between biofilm production and multiple drug resistance in imipenem resistant clinical isolates of Acinetobacter baumannii. Indian J Med Microbiol. 2008; 26: 33-7.

17. Gogou, V, Pournaras, S, Giannouli M, Voulgarí E, Pippakis ET, Zarrilli R, Tsakis A. Evolution of multidrug-resistant Acinetobacter baumannii clonal lineages: a 10 year study in Greece (2000-09). J Antimicrob Chemother. 2011; 66: 2767-72.

18. Goić-Barišić I, Bedenic B, Tonkić M, Katić S, Kalenić S, Punda-Polić V. First report of molecular characterization of carbapenem resistant Acinetobacter baumannii in different intensive care units in University Hospital Split. Croatia. J Chemother. 2007; 19: 416-8.

19. Medić D, Mihajlović-Ukropina M, Gusman V, Jelesić Z, Milošavljević B. Carbapenems resistance of Acinetobacter spp strains isolated from wound swabs during 2009-2010. Med Pregl. 2010; 64: 583-7.

20. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). J Antimicrob Chemother. 66: 2070-74.

21. Gales AC, Reis AO, Jones RN. Contemporary assessment of antimicrobial susceptibility testing methods for polymyxin B and colistin: review of available interpretative criteria and quality control guidelines. J Clin Microbiol. 2001; 39: 183-90.

22. Jones RN, Flonta M, Gurler N, Cepparulo M, Mendes RE, Castanheira M. Resistance surveillance program report for selected European Nations(2011). Diagn Microbiol Infect Dis. 2014; 78: 429-36.

23. Sedláková MH, Urbánek K, Vojtová V, Suchánková H, Imwensi P, Kolář M. Antibiotic consumption and its influence on the resistance in Enterobacteriaceae. BMC Research Notes. 2014. 7: 454.

24. Jin H, Qiu F, Jian Ji H, Lu Q. Analysis of drug resistance in 1,861 strains of Acinetobacter baumannii. Biomedical Reports 2016; 4: 463-6.