Original Article

Antibiotic consumption and healthcare-associated infections in a tertiary hospital in Belgrade, Serbia from 2011 to 2016

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Abstract

Introduction: Healthcare-associated infections (HAIs) and irrational use of antibiotics in healthcare settings are major global public health concerns. Surveillance of HAIs in intensive care units (ICU), surgical-site infections (SSIs), and *Clostridium difficile* infections (CDIs), together with implementation of antibiotic stewardship, are cornerstones of hospital infection prevention programs. The aim of this study was to evaluate antibiotic consumption, especially of broad spectrum antibiotics, in relation to HAI incidence density (ID).

Methodology: The study was conducted from 2011 to 2016 in a tertiary hospital, the Military Medical Academy (MMA), in Belgrade, Serbia. Through regular hospital surveillance we identified all patients with a new HAI. Data on consumption of antibacterials for systemic use were expressed as defined daily dose per 100 bed days (DDD/100 BD).

Results: The highest incidence density (ID) of HAI was observed among patients in surgical ICUs (47.2 per 1000 patient-days), while the highest incidence rate among SSI was 3.7%. Moreover, the highest ID of CDI in medical patients was 6.2 per 10,000 patient-days, while in surgical patients it was 4.3 per 10,000 patient-days. The most frequently used antibiotics were cephalosporins, aminoglycosides and carbapenems (16.0 ± 2.3, 4.8 ± 0.7, 4.3 ± 0.7 DDD/100 BD, respectively). There was no significant correlation between consumption of any groups of antibiotics and ID of CDI in medical and surgical patients.

Conclusion: The multidisciplinary healthcare team would have crucial importance in the implementation of the antibiotic stewardship program in order to decrease unnecessary exposures of patients treated in healthcare settings.

Key words: Clostridium infections; cephalosporins; carbapenems; surgical site infection.

Introduction

Healthcare-associated infections (HAIs) and irrational use of antibiotic in healthcare settings are major global public health concerns [1]. The intensive care unit (ICU) is often the epicenter of emerging problems of HAIs and antimicrobial resistance in a hospital. Patients admitted to ICU are at higher risk of HAI due to both intrinsic (age, underlying diseases, immunosuppression) and extrinsic (use of invasive devices such as mechanical ventilation, central vascular catheter,) risk factors (RFs) [2]. A systematic review and meta-analysis of the burden of endemic HAI in developing countries showed that pooled overall HAI infection density in adult ICU was at least three times higher than those reported from the US. Strikingly higher surgical-site infection (SSIs) rates, the most frequent HAI in surgical patients, were also observed in developing countries [3]. In contrast, a systematic review describing the epidemiology and management of *Clostridium difficile* infection (CDI) in developing countries suggested that the rate of community associated and healthcare-associated (HA) CDI appeared to be lower in developing countries than in developed countries, yet RFs appeared to be broadly similar between these two populations [4]. Antibiotic exposure represents a principal RF for CDI, in both developed and developing countries [5,6].

Antibiotics are among the most frequently used drugs in hospitalized patients. Each antibiotic has a different unit dose of daily administration; a specific standardized method should be used in the evaluation of in-hospital use. The World Health Organization

(WHO) recommends the use of the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) index as a method to express antibiotic consumption [7].

Appropriate antibiotic use in hospitals should ensure effective treatment but reduce unnecessary prescriptions [8]. Severe infections with multidrug-resistant pathogens present a medical challenge and a financial burden for hospitals. Critically ill patients are at very high risk of developing severe HAI in ICU, with incidence density (ID) 5-10- fold higher than in general medical wards [9,10]. The use of broad spectrum antibiotics is a particular problem. Characteristics such as the type of healthcare, knowledge of local common pathogens and resistance patterns as well as patient RFs for colonization or infection with multidrug-resistance pathogens should be used to select empirical broad spectrum antibiotics [11].

Surveillance of HAIs in ICU, of SSIs and CDIs together with implementation of antibiotic stewardship are cornerstones of infection prevention programs in modern hospitals.

The aim of this study was to evaluate the antibiotic consumption, especially the broad spectrum ones, and investigate its relation to HAI ID in a tertiary hospital in Serbia.

Methodology

This study of the antibiotic consumption and the ID of HAIs was conducted over a six-year period (2011-2016) in the Military Medical Academy (MMA), Belgrade, Serbia, a teaching hospital of the University of Defence. The MMA is a 1200-bed tertiary healthcare centre with 27 departments. The Ethics Committee of the MMA approved the research protocol (Project MF/VMA/02/17-19).

The Department of Healthcare-related Infection Control performs continuous active surveillance of MMA patients since 2006. Through regular hospital surveillance of MMA patients we prospectively identified all patients who had new HAI during the study period. The surveillance of HAI covered patients in four type of ICU (medical, surgical, toxicological and neurological). The case definitions were those specified by the European Centre for Diseases Control (ECDC) [2,12].

The surveillance of SSIs was conducted among general and orthopedic surgery patients, followed by surveillance of vascular and cardiac surgery, thoracic surgery, plastic surgery and burns, urology and maxillo-facial surgery patients. The wound class was assigned after operative procedure completion based on actual

occurrences as clean, clean/contaminated, contaminated, and dirty/infected [13]. For diagnosis of SSI, the CDC criteria were used [14].

Patients from all departments were included for the surveillance of CDI. A CDI case was defined as any hospitalized patient with laboratory confirmation of a positive toxin assay or *Clostridium difficile* nucleic acid amplification assay results together with diarrhea ($\geq$ 3 daily in a 24-hours' period with no other recognized cause) or visualization of pseudomembranes on sigmoidoscopy, colonoscopy, or histopathologic analysis [15,16]. Microbiological testing was performed at the Institute of Medical Microbiology at the MMA.

Only the first episode of HAIs, SSIs and CDIs was included for patients who had more than one infection during the study period.

The ID of HAIs in ICU was calculated as the number of HAI per 1000 patient-days. The IR of SSI was defined as the number of SSIs per 100 operative procedures. The ID of CDI was defined as the number of HAI CDI caused per 10,000 patient-days in medical and surgical patients.

Drug usage data for antibiotics were obtained from the hospital pharmacy records. The number of grams or international units of antibiotics were converted into a number of DDD using the 2017 version of the ATC/DDD index [7]. Data were expressed as DDD per 100 bed days (DDD/100 BD). DDD is the assumed average maintenance adult dose per day for the main indication of antibiotic, which refers to ATC code J01 (antibacterials for systemic use). Antibacterials are classified according to their mode of action and chemistry. The J01 antibacterials included in this study were the following: J01A tetracyclines (J01AA-tigecycline), J01C beta-lactam antibacterials, penicillins (J01CA-ampicillin, J01CG-ampicillin/sulbactam, J01CE-benzilpenicillin sodium/procainbenzilpenicillin, J01CR-amoxicillin/clavulanic acid, piperacillin/tazobactam), J01D other beta-lactam antibacterials (J01DB-cefazolin, J01DC-cefuroxime, J01DD-cefotaxime, ceftazidime, ceftriaxone, J01DE-cefepime; J01DH-carbapenems), J01E sulfonamides and trimethoprim (J01EE-sulfametoxazol and trimethoprim), J01F macrolides, lincosamides and streptogramines (J01FA-erythromicyn, azithromycin, J01FF-clindamycin), J01G aminoglycoside antibacterials (J01GB-gentamicin, amikacin), J01M quinolone antibacterials (J01MA-ciprofloxacin, levofloxacin), J01X other antibacterials (J01XA-vancomycin, teicoplanin, J01XB-colistin, J01XD-metronidazole). The

prescription of antifungal and antiviral drugs was excluded from the study [17].

According the patients' risk of developing CDI, antibiotics are grouped as: high risk-antibiotics (ATC codes: J01D, J01M and J01FF), medium-risk antibiotics (ATC codes: J01C, J01E, J01FA and J01G) and a low-risk antibiotics (ATC code: J01A) [5].

Relative numbers were expressed as percentages. In the case of continuous data, variables were presented as a mean value ± standard deviation (SD). Pearson correlation analysis was used to establish the relationship between different antibiotic groups and ID of CDI in medical and surgical patients. Statistical significance was set at a level of $p<0.05$. Complete statistical analysis of data was done using SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA).

Results

Healthcare-Associated Infections

The highest ID of HAI was observed in patients in surgical ICUs with a peak in 2015 (47.2 per 1000 patient-days). There was a trend of increasing ID of HAIs in the medical and toxicological ICU during the study period. The neurological ICU was founded in 2014; a peak of HAIs was registered in 2015 (23.4 per 1000 patient-days) (Figure 1).

From January 1st, 2011 to December 31st, 2016, a total of 35,995 different operative procedures were evaluated, with an overall cumulative IR of 2.9% (1.048) SSIs.

Among these cases, 22,035 (61.2%) were classified as clean, with an IR of 2.0%, 10,499 (29.2%) were

Figure 1. Incidence density (per 1000 patients-days) of Healthcare Associated Infections in surgical Intensive Care Units (ICU), medical ICU, toxicological ICU and neurological ICU in the Military Medical Academy, 2011-2016.
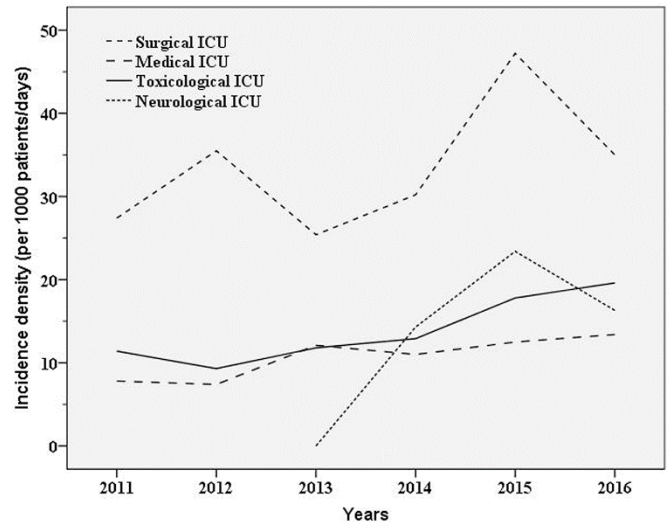
classified as clean/contaminated with an IR of 3.6%, 1,866 (5.2%) were classified as contaminated with an IR of 5.9%, and 1,595 (4.4%) were classified as dirty/infected with an IR of 8.2%. The highest IR was registered in 2016 (3.7%) and the lowest in 2011 (2.3%) (Figure 2).

The overall ID of CDIs was highest in 2016 (4.7 per 10,000 patient-days). The highest ID of CDI among medical patients was observed in 2016 (6.2 per 10,000 patient-days), while in surgical patients it occurred in 2013 (4.3 per 10,000 patient-days) (Figure 3).

Figure 2. Incidence rate (%) of surgical site infection in the Military Medical Academy, 2011-2016.
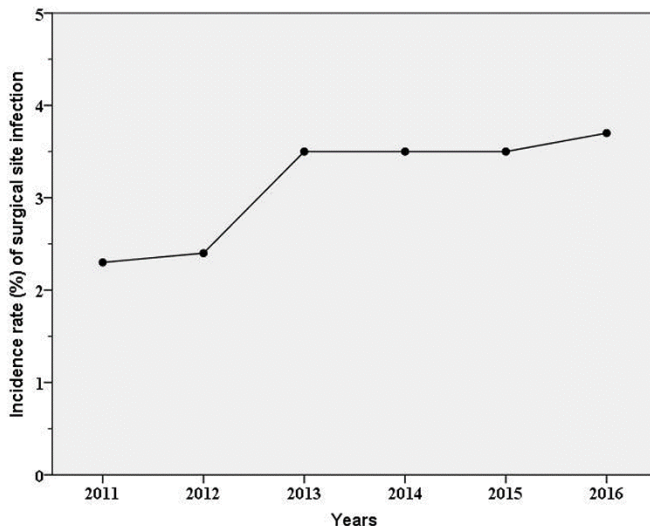

Figure 3. Incidence density (per 10,000 patient-days) of Clostridium difficile infection (CDI) in medical and surgical patients in Military Medical Academy, 2011-2016.
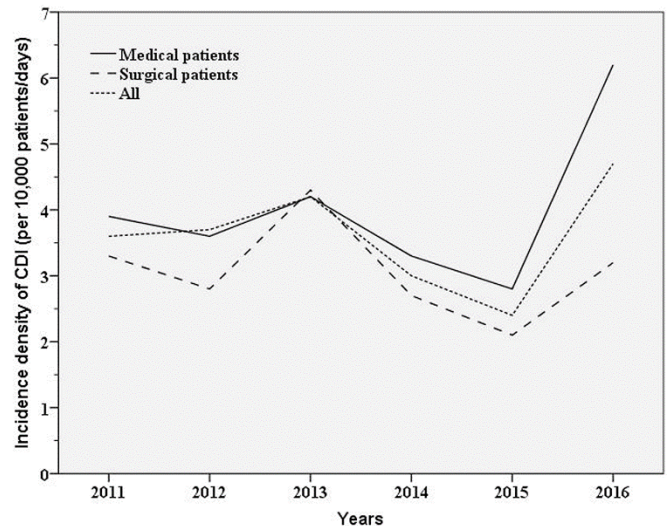
Table 1. Defined daily doses [DDDs] of antibiotics according to Anatomical Therapeutic Chemical classes per 100 bed days [BD] in the Military Medical Academy, 2011-2016.

Year	2011	2012	2013	2014	2015	2016
DDDs/100 BD	42.8	39.7	46.5	43.3	46.0	33.4

Antibiotic consumption

The highest consumption was detected in the years 2013 and 2015 (46.5 and 46.0 DDD/100 BD, respectively) and the lowest consumption in the year 2016 (33.4 DDD/100 BD). In 2016 there was a decrease in consumption of cephalosporins of 25% compared with 2015. Overall hospital consumption of antibiotics over a six-year period is shown in Table 1.

The most frequently used antibiotics from 2011 to 2016 were cephalosporins, followed by aminoglycosides and carbapenems (16.0 ± 2.3 DDD/100 BD, 4.8 ± 0.7 DDD/100 BD and 4.3 ± 0.7 DDD/100 BD, respectively). The highest consumption of cephalosporins was in 2011 (18.6 DDD/100 BD), with a rate of 43.5% of total consumption of antibiotics in that year, followed by a steady decrease in the following years. The lowest consumption was in the year 2016 (12.4 DDD/100 BD), at 37.1% of total consumption of antibiotics in that year. The trend in consumption of aminoglycosides was the same as for overall antibiotics consumption. It was highest in 2013 (5.6 DDD/100 BD), at 12.1% of total consumption of antibiotics and lowest in 2016 (4.1 DDD/100 BD) at 12.4%. Carbapenem consumption was different in comparison to the previous two groups. The highest consumption was recorded in 2015 (5.0 DDD/100 BD), at 11.0% of antibiotic consumption, while the lowest consumption was in 2011 (3.1 DDD/100 BD), at 7.3% (Figure 4). Meropenem was the mostly commonly used carbapenem (average consumption 2.1 ± 0.6 DDD/100 BD).

Antibiotics were grouped according to their use for patients with different levels of risk of developing CDI:

high-risk antibiotics (cephalosporins, carbapenems, fluoroquinolones and clindamycin), medium-risk antibiotics (penicillins, aminoglycosides, macrolides and sulfametoxazol/trimethoprim) and low-risk antibiotics (tetracycline). The consumption of the three groups of antibiotics in DDDs per 100 BD in a six-year period is shown in Table 2.

The consumption of the 3rd generation cephalosporins (ceftriaxone and ceftazidime) was 66.8% of all cephalosporins used in a six-year period. Overall consumption of cephalosporins in defined daily doses (DDDs) according to Anatomical Therapeutical

Figure 4. Percentage of consumption of cephalosporins, carbapenems and aminoglycosides among overall antibiotic consumption in the Military Medical Academy, 2011-2016.
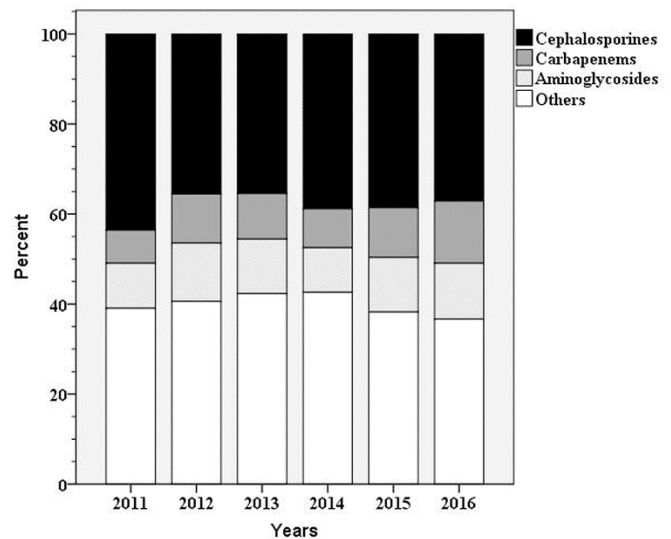

Table 2. The consumption of antibiotics according to the risk for patients to develop Clostridium difficile infection in defined daily doses [DDDs] per 100 bed days [BD] during 2011-2016.

Classification of different antibiotics according to the risk of developing CDI		Consumption in DDDs/100 BD during six years					
		2011	2012	2013	2014	2015	2016
High-risk antibiotics	Cephalosporins	18.6	14.1	16.5	16.8	17.8	12.4
	Carbapenems	3.1	4.3	4.7	3.7	5.0	4.6
	Fluoroquinolones	2.3	1.7	1.5	2.1	1.5	0.6
	Clindamycin	0.0	0.3	0.5	0.7	0.4	0.3
Medium-risk antibiotics	Penicillins	2.5	3.0	4.0	2.6	3.3	1.0
	Aminoglycosides	4.3	5.2	5.6	4.3	5.6	4.1
	Macrolides	0.0	0.1	0.2	0.4	0.3	0.1
	Sulfametoxazole and Trimethoprim	0.4	0.4	0.8	0.7	0.4	0.2
Low-risk antibiotics	Tigecycline	2.9	3.7	4.1	3.2	4.5	1.3

Chemical classes per 100 bed days (BD) is shown in Figure 5.

On the other hand, several broad spectrum antibiotics had a total consumption less than 5 DDD/100 BD during the six-year period. The consumption of glycopeptides (vancomycin and teicoplanin) was in the range of 1.3 DDD/100 BD in 2016 to 3.0 DDD/100 BD in 2015, while teicoplanin use was less than 1.00 DDD/100 BD.

Colistin consumption was at 0.1 DDD/100 BD from 2011 to 2014, but there was an increasing trend in the two following years and a total consumption of 0.2 DDD/100 BD.

Linezolid use was recorded only during three years (in 2014 and 2016 it was 0.1 DDD/100 BD and in 2015 twice that).

Correlations between consumption of antibiotics classified according to the risk for patients to develop *Clostridium difficile* infection (CDI) and incidence density (ID) of CDI in medical and surgical patients are shown in Table 3. There was no statistically significant correlation between any groups of antibiotics. However, the 3rd generation cephalosporins showed correlation with the highest value of total consumption increase ID CDI in surgical patients (Pearson correlation: 0.256).

Discussion

During the six-year period from 2011 to 2016, surveillance on HAIs was conducted in patients at the MMA hospital in Belgrade; antibiotic consumption was also measured. Like data obtained from the study

Figure 5. Overall consumption of cephalosporins in defined daily doses (DDDs) according to Anatomical Therapeutic Chemical classes per 100 bed days (BD)in the Military Medical Academy, 2011-2016.
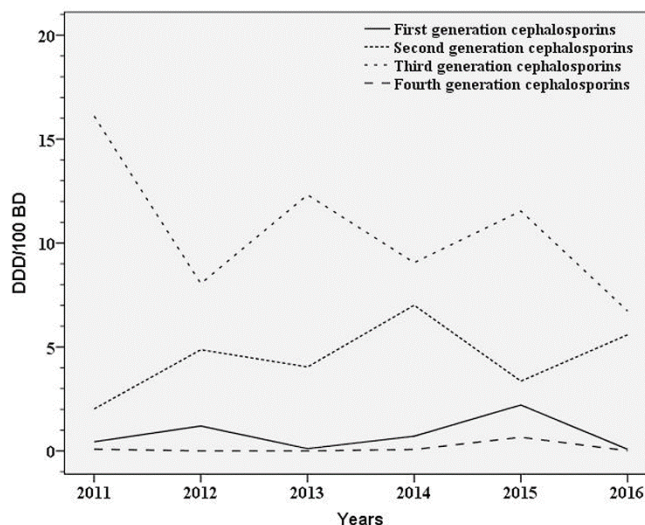
conducted in another tertiary hospital in Serbia [18], our investigation showed that cephalosporins were the most frequently prescribed antibiotics, followed by aminoglycosides and carbapenems.

Although we noticed a decrease in cephalosporin use in 2016, the use of the 3rd generation cephalosporins was constant over the study period. Our results are in accordance with studies from other countries, where cephalosporins were the most frequently used antibiotics in hospitals, ranging from 30% in Chinese tertiary hospitals to 57% in Turkish hospitals [19-21]. Reports of antibiotic consumption in

Table 3. Correlation between consumption of antibiotics classified according to the risk for patients to develop Clostridium difficile infection [CDI] and incidence density [ID] of CDI in medical and surgical patients.

Class of Antibiotics		MedicalIDCDI	Surgical IDCDI	TotalIDCDI
Cephalosporins	Pearson Correlation	-0.724	-0.092	-0.673
	Sig.[2-tailed]	0.104	0.862	0.143
Carbapenems	Pearson Correlation	0.083	-0.100	0.002
	Sig.[2-tailed]	0.876	0.850	0.996
Fluoroquinolones	Pearson Correlation	-0.736	-0.112	-0.558
	Sig.[2-tailed]	0.096	0.833	0.250
Clindamycin	Pearson Correlation	-0.472	0.008	-0.412
	Sig.[2-tailed]	0.344	0.989	0.417
Penicillins	Pearson Correlation	-0.707	0.193	-0.413
	Sig.[2-tailed]	0.116	0.715	-0.416
Aminoglycosides	Pearson Correlation	-0.475	0.067	-0.282
	Sig.[2-tailed]	0.341	0.900	0.589
Macrolides	Pearson Correlation	-0.867	-0.369	-0.825
	Sig.[2-tailed]	0.025	0.472	0.043
Sulfametoxazole and Trimethoprim	Pearson Correlation	-0.486	0.294	-0.095
	Sig.[2-tailed]	0.332	0.572	0.858
Tigecyclines	Pearson Correlation	-0.225	-0.150	-0.262
	Sig.[2-tailed]	0.668	0.777	0.616

European hospitals during 2011-2015 showed that consumption of cephalosporins and other beta-lactams included carbapenems ranged from 7% in the United Kingdom to 54% in Bulgaria [22]. National data on antibacterial consumption in Australia for the five-year period (2012-2016) revealed the greater usage of broad spectrum cephalosporins (ceftriaxone, ceftazidime, cefepime and cefotaxime) in larger hospitals might be explained by a more complex casemix [23].

During 2011, Ju *et al*. reported that rate of SSI was the highest among cases that were classified as dirty/infected (8.5%) and the lowest in the cases of the wounds that were clean (1.8%) [24], which is similar to our observations. Third generation cephalosporins, especially ceftriaxone, have generally not been recommended for surgical antimicrobial prophylaxis [25-27], but they have been widely accepted as the most common drugs in surgical antimicrobial prophylaxis in our hospital. Administration of surgical antimicrobial prophylaxis less than 30 minutes before incision has been routine practice at the MMA. The recommended duration of surgical antimicrobial prophylaxis is less than 24 hours for most procedures (except cardiothoracic procedures). However, in every day practice during clean/contaminated, contaminated and dirty/infected operative procedures, MMA surgeons extended surgical antimicrobial prophylaxis to more than 24 hours. The first EU-wide, ECDC-coordinated point prevalence survey of HAIs and antimicrobial use in acute care hospitals showed that surgical antimicrobial prophylaxis was prolonged for more than one day in 59.2% of cases [28]. However, the last CDC Guideline for the Prevention of SSI, published in 2017, pointed out that for clean and clean-contaminated procedures, additional prophylactic antimicrobial agent doses should not be administered after the surgical incision is closed in the operating room, even in the presence of a drain [29].

Decreased use of fluoroquinolones was noticed in 2016. The most frequently used was ciprofloxacin, while moxifloxacin has not been used yet due to the limited number of standard indications. A report from Australia showed that fluoroquinolone use had a downward trend over the period 2012-2016 [23], while in MMA the decrease of 37% was recorded in 2016 in comparison to 2015. Data from nine regional tertiary hospitals in Ireland for 2011-2012 showed that fluoroquinolone use was 5.8 DDD/100 BD in 2011 and 5.9 DDD/100 BD in the 2012 [30]. In the same period, the consumption of the same group in MMA was lower (2.3 DDD/100 BD in 2011 and 1.7 DDD/100 BD in 2012). Consumption of fluoroquinolones in different European hospitals during 2011-2015 ranged from 4% in United Kingdom to 19% in Malta [22]. Consumption of fluoroquinolones in MMA during 2011-2016 varied from 1.7% to 5.4%. The administration of fluoroquinolones emerged as the most important RF for CDI in Quebec during one of the first described epidemics caused by a hypervirulent strain of *Clostridum difficile* [31]. Recently, authors from England reported that national fluoroquinolone and cephalosporin prescribing practice correlated highly with the incidence of CDI, in contrast to total antibiotic prescribing. They also concluded that restriction of fluoroquinolone prescribing should be a cornerstone in the control of epidemic CDI in the UK and worldwide [32].

We did not find a correlation between fluoroquinolone consumption (nor any other group of antibiotics) and ID of CDIs. The only association established between ID of CDI and an individual group of antibiotics was with the 3rd generation cephalosporin in surgical patients. The overall ID of CDI was highest in 2016 at 4.7 per 10,000 patient-days in our hospital, which is lower than the mean ID of 7.0 of HA CDI (country range 0.7–28.7) in a European, multicentre, prospective, biannual point prevalence study of CDI in hospitalized patients with diarrhea (EUCLID) [33]. We also observed the differences in ID of CDI between medical and surgical patients. Silva-Velazco *et al*. reported that although surgical patients tended to have more difficult clinical presentation of CDI, overall they did better than medical patients. However, future studies focusing on modifiable RFs for each group are needed [34].

In order to improve the quality of especially broad spectrum antibiotic use, a multidisciplinary healthcare team (infectious disease specialist, epidemiologist, clinical pharmacologist, hospital pharmacist, clinical microbiologist) was formed in our hospital in 2008. The main goal of this team is to monitor the use of antibiotics and to make that more appropriate. The team determined the list of restricted antimicrobial agents as well as the criteria for their use combined with an approval system. In comparison to analysis of antibiotic consumption in the previous ten-year period (2001-2010) in MMA, when the average consumption was 56.6 ± 3.01 DDD/100 BD, we have noticed a 25% decrease in consumption of antibiotics, due to the efforts of the multidisciplinary team to reduce irrational use of antibiotics in our hospitals, especially the restricted ones [35].

The highest consumption of carbapenems was recorded in 2015, with a total rate of 11.0%. It is not

surprising that in the same year the highest ID of HAI was observed in patients in surgical ICU and neurological ICU. The most frequently used was meropenem, which has become a key restricted-line antibacterial because of its superior activity against *Pseudomonas* species and lower incidence of neurotoxicity.

The median consumption rate of tygecycline in our hospital was similar to that reported from Ireland (3.3 DDD/100 BD in Ireland *vs.* 2.9 DDD/100 BD in MMA in the year 2011; 3.5 DDD/100 BD in Ireland *vs.* 3.7 DDD/100 BD in MMA in the year 2012) [30]. Its current position in the context of rational antibiotic prescribing policy in our hospital is not yet defined.

In MMA, colistin is an important antibacterial in the treatment of HAIs caused by carbapenemase-producing multidrug-resistant gram-negative microorganisms, where meropenem is ineffective. Since it was registered for the Serbian market in 2013, it was not often used up to 2014, with a slight increase in the following two years. This result reflects the fears of MMA doctors about its serious adverse effects.

Linezolid is reserved for complex infections caused by multidrug resistant gram-positive organism including vancomycin-resistant *Enteroccoci* (VRE).

Parenteral colistin, teicoplanin and linezolid usage remained low, but showed a possible trend upwards that requires ongoing monitoring. The very low usage teicoplanin may be due to its higher cost in comparison to vancomycin in Serbia.

Strengths and limitations

Our study has several limitations. First, it was a single-center study. The consumption of antibiotics may not be representative for other hospitals in the country. Second, we did not calculate the resistance ratio of microorganisms which were the cause of HAI during the study period. One of the limitations was the DDD methodology for calculating use of antibiotics in our research. The use of prescribed daily doses (PDDs) is nowadays widely used for measuring antibiotic consumption in hospitals because it will give the amount of a drug that has actually been prescribed. Some authors think that there are discrepancies between the two methods [17,36]. Obviously, additional research is needed to determine which method should be used for calculation of antibiotic usage. Finally, we have not taken into account the oral formulations of antimicrobial drugs, which will be considered in future investigations.

The strength of this study is the large material covering the consumption of all antibiotics used in the

MMA and the emergence of HAI in ICU, SSI and CDI during six years. This long surveillance period gives good insight into the rate of HAIs and the consumption of antibiotics in a tertiary care hospital in a small, poor, developing country with the problems resulting from economic transition in the healthcare system.

Conclusions

Our analysis showed that cephalosporins were the most frequently prescribed antibiotics, followed by aminoglycosides and carbapenems in a tertiary hospital in Belgrade, Serbia. Surgical antimicrobial prophylaxis is one reason for the high consumption of cephalosporins in MMA. The multidisciplinary healthcare team had very important role in monitoring of the use of antibiotics and would have crucial importance in the implementation of the antibiotic stewardship program in order to decrease unnecessary exposures of patients treated in MMA.

References
1. World Health Organization (WHO) (2011) Report of the Burden of Endemic Health Care-Associated Infection Worldwide. A systematic review of the literature. Available: http://apps.who.int/iris/handle/10665/80135. Accessed: 29 October 2018.
2. European Centre for Disease Prevention and Control (ECDC) (2010) European Surveillance of Healthcare-Associated Infections in Intensive Care Units-HAI-Net ICU protocol, version 1.01. Available: http://ecdc.europa.eu/sites/portal/files/documents/HAI-Net-ICU-protocol-v1.01.pdf.Accessed: 6 May 2017.
3. Allegranzi B, Bagheri Nejad S, Combescure C, Attar H, Donaldson L, Pittet D (2011) Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. The Lancet 377: 228-241.
4. Forrester JD, Cai LZ, Mbanje C, Wren SM (2017) Clostridium difficile infection in low and middle human development index countries: a systematic review. Trop Med Int Health 22: 1223-1232.
5. Brown K, Valenta K, Fisman D, Simor A, Daneman N (2015) Hospital ward antibiotic prescribing and the risks of *Clostridium difficile* infection. JAMA Intern Med 175: 626-633.
6. Šuljagić V, Miljković I, Starčević S, Kostić Z, Jovanović D, Brusić-Renaud J, Mijović B, Šipetić-Grujičić S (2017) Risk factors for *Clostridium difficile* infection in surgical patients hospitalized in tertiary hospital in Belgrade, Serbia: a case-control study. Antimicrob Resist Infect Contro 6: 31.

7. World Health Organisation (WHO) Collaborating Centre for Drug Statistics and Methodology (2016). Guidelines for the ATC classification and DDD assignment, 2017. Available: http://www.whocc.no/atcddd/. Accessed 10 November 2017.

8. Davey P, Brown E, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S (2017) Interventions to improve antibiotic prescribing practices for hospital inpatients (Review).Cohrane Database Syst Rev 2: CD003543.

9. Vincent JL (2003) Nosocomial infections in adult intensive-care units. Lancet 361: 2068–2077.

10. Pea F, Viale P, Furlanut M (2005) Antimicrobial therapy in critically ill patients. A review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 44: 1009-1034.

11. Kollef MH (2008) Broad-spectrum antimicrobials and the treatment of serious bacterial infections: getting it right up front. Clin Infect Dis 47 Suppl 1: 3-13.

12. European Centre for Disease Prevention and Control (ECDC) (2015) European Surveillance of Healthcare-Associated Infections in Intensive Care Units– HAI-Net ICU protocol, version 1.02. Available: http://ecdc.europa.eu/sites/portal/files/documents/HAI-Net-ICU-protocol-v1.01.pdf. Accessed: 6 May 2017.

13. Liu Y, Cohen ME, Hall BL,Ko CY, Bilimoria KY (2016) Evaluation and enhancement of calibration in the American College of Surgeons NSQIP Surgical Risk Calculator. J Am Coll Surg 223:231-239.

14. Centers for Disease Control and Prevention (2011) Acute care hospital surveillance for surgical site infections. Available: http://www.cdc.gov/nhsn/acute-care-hospital/ssi/index.html.Accessed 3 December 2011.

15. McDonald LC, Coignard B, Dubberke Ehoran T, Kutty PK, *ad hoc Clostridium difficile* Surveillance Working Group (2007) Recommendations for surveillance of *Clostridium difficile*–associated disease. Infect Control Hosp Epidemiol 28: 140-145.

16. Kuijper EJ, Coignard B, Tüll P; ESMID Study Group for Clostridium difficile EU Member states; European Centre for Disease Prevention and Control (2006) Emergence of *Clostridium difficile*-associated disease in North America and Europe. Clin Microbiol Infect 12 Suppl 6: 2-18.

17. Laine N, Hoppu K, Airaksinen M, Saxen H (2016) Antimicrobial consumption in a tertiary children's hospital in Finland (2003-2013). Eur J Hosp Pharm 23:266-271.

18. Veličković-Radovanović R, Stefanović N, Damnjanović I, Petrović J, Mitić R, Kocić B, Antić S, Dinić M, Catić-Đorđević A (2016) The analysis of antibiotic consumption and bacterial resistance in tertiary healthcare Centre Niš. Hospital Pharmacology 3: 341-347.

19. Wushouer H, Tian Y, Guan XD, Han S, Shi LW (2017) Trend and patterns of antibiotic consumption in China´s tertiary hospitals: Based on 5-year surveillance with sales records, 2011-2015. Plos ONE 12: e0190314.

20. Baditoiu L,Axente C, Lungeanu D, Muntean D, Horhat F, Moldovan R, Hogea E, Bedreag O, Sandesa D, Licker M (2017) Intensive care antibiotic consumption and resistance patterns: a cross-correlation analysis. Ann Clin Microbiol Antimicrob 16: 71.

21. Bitterman R, Hussen K, Leibovici L, Carmelli Y, Paul M (2016) Systematic review of antibiotic consumption in acute care hospitals. Clin Microbiol Infect 22: 561.e7-561.e19.

22. European Centre for Disease Prevention and Control (ESAC) (2016) Surveillance of antimicrobial consumption in Europe. Available: http://ecde.europa.eu/en/activities/surveillance/ESAC-Net/publications/Pages/documents.aspx. Accessed: 10 November 2017.

23. National Antimicrobial Utilisation Surveillance Program Government of South Australia: SA Health (NAUSP) (2016) Antimicrobial utilisation surveillance statistics. Available: http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/about+us/health+statistics/healthcare+infection+statistic/antimicrobial+utilisation+surveillance+statistic. Accessed 13 December 2017.

24. Ju MH, Cohen ME, Bilimoria KY, Latus MS, Scholl LM, Schwab BJ, Byrd CM, Ko CY, Dellinger EP, Hall BL (2014) Effect of wound classification on risk adjustment in American College of Surgeons NSQIP. J Am Coll 219: 371-381.

25. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, Fish DN, Napolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA (2013) Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 70:195-283.

26. Geroulanos S, Marathias K, Kriaras J, Kadas B (2001) Cephalosporins in surgical prophylaxis. J Chemother 13 Suppl 4:23-26.

27. Liu W, Neidert MC, Groen RJ, Woernle CM, Grundmann H(2014) Third-generation cephalosporins as antibiotic prophylaxis in neurosurgery: What's the evidence? Clin Neurol Neurosurg 116: 13-19.

28. European Centre for Disease Prevention and Control (ECDC) Stockholm (2013) Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals. Available: http://ecde.europe.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf. Accessed: 5 December 2017.

29. Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, StoneEC, Kelz RR, Reinke CE, Morgan S, Solomkin JS, Mazuski JE, Dellinger EP, Itani KMF, Berbari EF, Segreti J, Parvizi J, Blanchard J, Allen G, Kluytmans JAJW, Donlan R, Schecter WP (2017) Centers for disease control and prevention guideline for the prevention of surgical site infection. JAMA Surgery 152: 784-791.

30. Health Protection Surveillance Center (HPSC) Ireland (2016) Hospital antimicrobial consumption surveillance. Available: http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/EuropeanSurveillanceofAntimicrobialConsumption/ESAC/SurveillanceReports/HospitalAntibioticReports/Accessed: 13 December 2017.

31. Pépin J, Saheb N, Coulombe MA, Corriveau MP, Authier S, Leblanc M, Rivard G, Bettez M, Primeau V, Nguyen M, Jacob CE, Lanthier L (2005) Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*–associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 419: 1254-1260.

32. Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, Harding RM, Wilson DJ, Griffiths D, Vaughan A, Finney JM (2017) Effects of control interventions on *Clostridium difficile* infection in England: an observational study. Lancet Infect Dis 17: 411-421.

33. Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, Delmée M, Fitzzpatrick F, Ivanova K, Kuijper E, Macovei IS (2014) Under diagnosis of *Clostridium difficile*

across Europe: the European, multicentre, prospective, biannual, point-prevalence study of *Clostridium difficile*infection in hospitalised patients with diarrhea (EUCLID) Lancet Infect Dis 14: 1208-1219.

34. Silva-Velazco J, Hull TL, Messick C, Church JM (2016) Medical *versus* Surgical Patients with *Clostridium difficile* Infection: Is There Any Difference?Am Surg82:1155-1159.

35. Brusić-Renaud J, Šuljagić V, Antunović M (2016) The analysis of antimicrobial consumption within the tertiary healthcare institution in Serbia during 10-year period (2001-2010) Int J Pharm Pharm Sci 5: 401-403.

36. Muller A, Monnet D, Talon D, Hénon T, Bertrand X (2006) Discrepancies between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital. Br J Clin Pharmacol 61:585-591.

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