

The Analysis of Antibiotic Consumption and Bacterial Resistance in Tertiary Healthcare Centre Niš

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SUMMARY

Introduction: Antibiotics are the most frequently used drugs in hospitalized patients, but studies have shown that the prescribed antibiotics may be inappropriate and may contribute to bacterial resistance. The aim of this work is the evaluation of antibiotic consumption in Clinical Centre Nis, Serbia from 2011 to 2014, with the focus on the monitoring of the ceftriaxone (CTX) and ciprofloxacin (CIP) utilization. Secondly, we screened bacterial resistance towards monitored antibiotics used for intra-abdominal infection (IAI) and urinary tract infection (UTI) in tertiary healthcare institution.

Methods: Antibiotics consumption and antimicrobial resistance were monitored in the tertiary care university hospital- Clinical Centre Nis from 2011 to 2014. Data on the use of antibiotics in inpatients were obtained and expressed as defined daily doses per 100 bed days (DBD). Bacterial resistances were given as percentages of resistant isolates.

Results: During the investigation period the use of cephalosporins increased by 6.39 %, from 2011 to 2013, but in 2014 there was a reduction in its consumption by 16.46 %. Penicillins consumption had a decreasing trend, whereas quinolones consumption was variable during observation period. The resistance of *K. pneumoniae* to CTX and CIP for the isolates from IAI, and resistance of *E. coli* to analyze antibiotics for isolates from UTI showed increasing trend within observed period of time.

Conclusions: Our findings shows that cephalosporins were the most frequently used antibiotics in Clinical Centre Nis, and they were followed by penicillins and quinolones. Additionally, *K. pneumoniae* resistance to CTX and CIP increased markedly in IAI, while *E. coli* resistance showed an increasing trend to CTX and CIP in UTI over the study period.

Keywords: antibiotics, consumption, resistant bacteria, inpatients

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INTRODUCTION

Antibiotics are the most used drugs within hospitalized patients and represents 15 – 30 % of all prescribed drugs at the hospitals. Providing rationale antibiotic pharmacotherapy in the tertiary health care includes antibiotic procurement, prescribing, dispensing and administration [1,2]. Studies showed that in almost half of prescribed antibiotics, their usage were inadequate. The increasing rate of antibiotic resistance represents an increasing global public health problem in Europe and worldwide leading to less effective treatment of bacterial infections, growing costs and mortality [3,4]. Therefore, European countries try to implement actions to control antimicrobial resistance in the community and the hospitals as well, providing rational use of antimicrobials [5]. Additionally, intra- and inter-hospital spread of resistant microorganisms, community contribution to resistance, and infection control policies and practices, may also play a role in determining the burden of resistance in a hospitals [6]. The major pathogens in community-acquired intra-abdominal (IAI) and urinary tract infections (UTI) are coliforms, *Enterobacteriaceae*, especially *E. coli* and *Klebsiella sp.* [7,8]. Adequate empiric therapy of these bacterial infections appears to be crucial for reducing postoperative complications and mortality rates, but carries the risk of increased bacterial resistance [9].

The aim of this work is the evaluation of antibiotic consumption in Clinical Centre Nis, from 2011 to 2014, with the focus on the monitoring of the ceftriaxone (CTX) and ciprofloxacin (CIP) utilization. Secondly, we screened bacterial resistance towards monitored antibiotics used for IAI and UTI in tertiary healthcare institution.

METHODS

Antibiotics consumption and antimicrobial resistance were monitored in the Clinical Centre Nis, Serbia: a 1460- bed, tertiary care university hospital in Serbia, in the study period extended from 2011. to 2014. As this study did not have data on individual patients and surveillance was a part of quality assurance, approval by Ethical Committee was not considered necessary. This study has generally used the WHO classification system ATC and the volume unit defined daily dose (DDD). Utili-

zation of antibiotics in the Clinical Center Niš in the observed period was obtained from the computerized database of the Department of Clinical Pharmacology and expressed as DDD per 100 bed/days (DBD). Following implementation of a restriction policy in 2011, prescription of some antibiotics (carbapenems, piperacillin/ tazobactam, vancomycin, linezolid, tigecycline) was controlled. These agents could only be prescribed after consultation with a clinical pharmacologist / infectious disease specialist consultation or approval by the medical director.

Microbial resistance data

The bacteriological laboratory of the Institute for Public Health Nis routinely screens microbial resistance/sensitivity for all cases requiring antibiotic therapy, except for prophylactic use. Bacterial strains were isolated from clinical material from hospitalized patients and susceptibility to antibiotics was assessed by the diffusion and standard microdilution methods. The process of testing the susceptibility of bacteria to antibacterial medicines is conducted according to the recommendations of the American National Committee for Clinical and Laboratory Standards and the European Committee for Antimicrobial Susceptibility Testing. Bacterial resistance was reported as the percentage of total isolates showing resistance. The burden of resistance for each antibiotic was calculated as the percentage of all 'Resistant' + 'Intermediate Resistant' results among all tested isolates from all patient samples (fluid from intra-abdominal infections, incisions, abscesses, fistulas, blood, urine, etc) [10,11].

Statistics

All calculations were performed using SPSS software.

RESULTS

Trends of antibiotic consumption according to pharmacological groups from 2011. to 2014. are shown on Figure 1.

The most frequently used antibiotics were cephalosporins, followed by penicillins and quinolones. During the investigation period the use of cephalosporins increased by 6.39 %, from 2011. to 2013, but in 2014. there was a reduction in its consumption by 16.46 %. Penicillins consumption had a decreasing

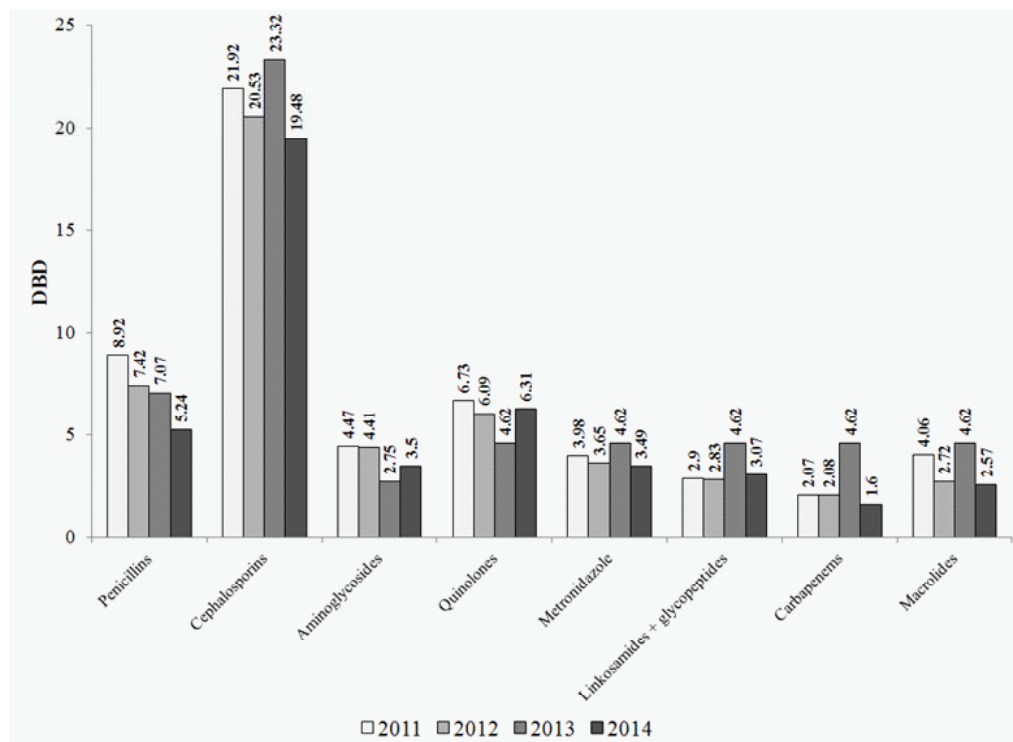


Figure 1. Trends of antibiotic consumption by pharmacological groups (in DBD) in the Clinical Center Niš from 2011 to 2014

trend, whereas quinolones consumption was variable during observation period.

Figure 2 shows resistance of *E. coli* and *Klebsiella sp.* to CTX and CIP in the observed period from all patient samples.

There was no significant difference in *E. coli* and *Klebsiella sp.* resistance to CIP and CTX, during investigation period, whereas the CTX consumption (11.21-12.89 DBD) was very high and CIP consumption (6.08-5.39DBD) seemed to be moderate.

The distribution of pathogens in IAI and UTI (2011-2014) is shown on Figure 3.

E. coli was the most frequently iso-

lated *Enterobacteriaceae* (61.51%) in IAI, followed by *P. aeruginosa* (10.19%), *K. pneumoniae* (6.42%) and *P. mirabilis* (6.42%). Considering UTI, the most frequently isolated bacterial strains were *K. pneumoniae* (35.75%), followed by *E. coli* (32.96%).

Table 1. shows resistance to CTX and CIP of *E. coli* and *K. pneumoniae* isolated from IAI and UTI samples between 2011 and 2014.

The resistance of *K. pneumoniae* to CTX and CIP for the isolates from IAI, and resistance of *E. coli* to analyze antibiotics for isolates from UTI showed increasing trend within observed period of time.

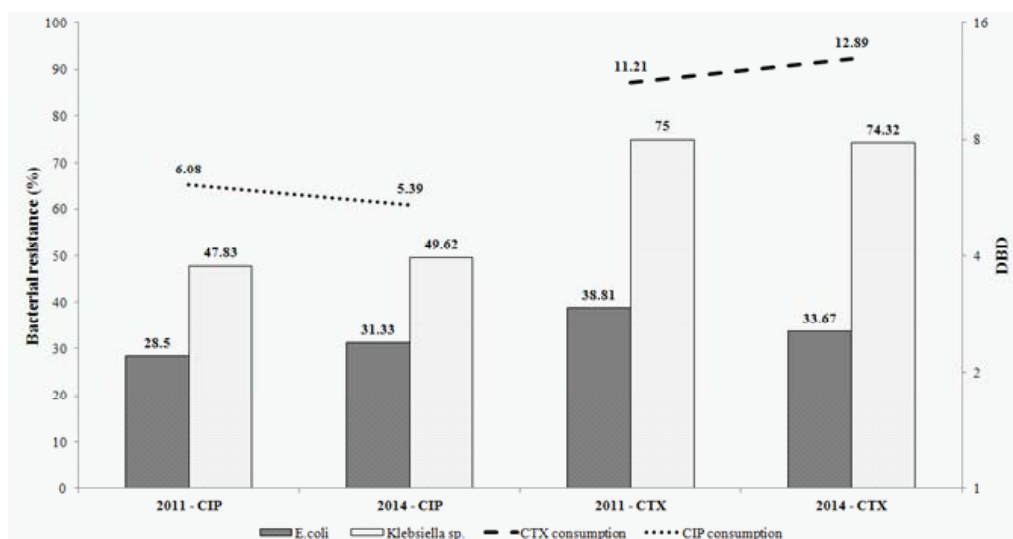


Figure 2. Resistance of *E. coli* and *Klebsiella sp.* to CTX and CIP in the observed period from all patient samples

Figure 3. The distribution of the major pathogens in IAI and UTI (2011-2014)

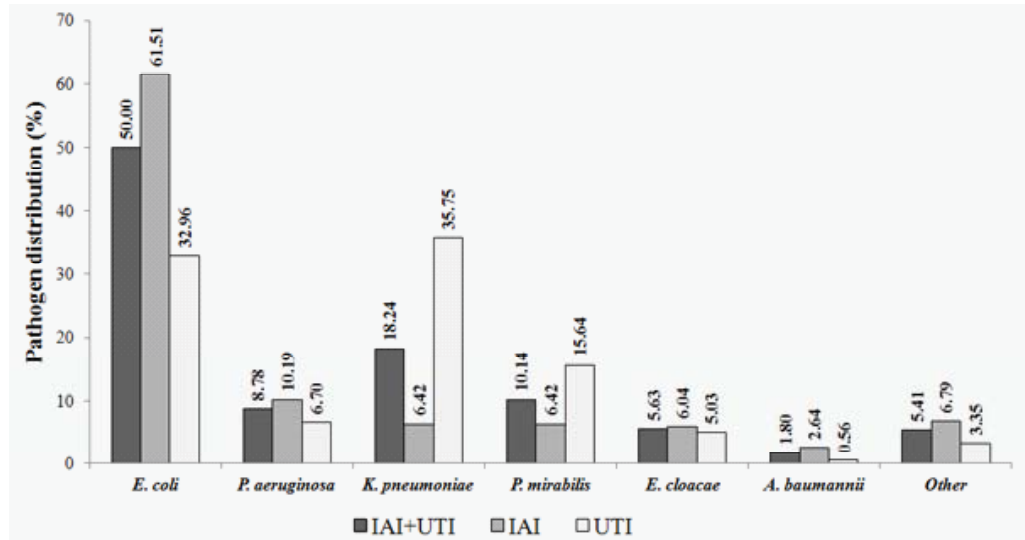


Table 1. Resistance to CTX and CIP of bacterial strains isolated from IAI and UTI

Antibiotics	Resistance of bacterial strains (%)							
	IAI				UTI			
	<i>E. coli</i>		<i>K. pneumoniae</i>		<i>E. coli</i>		<i>K. pneumoniae</i>	
	2011	2014	2011	2014	2011	2014	2011	2014
CTX	10	11	1	71	12	38	91	99
CIP	1	8	1	61	16	38	82	99

DISCUSSION

Antibiotics are the background of the treatment of infectious diseases, but still one third have been prescribed inappropriately [12]. Our analysis showed that cephalosporins were the most frequently prescribed antibiotics, followed by penicillins and quinolones (Figure 1). Versporten et al., report showed that Serbia took fifth place in antibiotic consumption among non-EU countries [13]. It is assumed that demographic, cultural, and economic factors as well as supply-side factors such as the density of doctors and their prescribing policies may underlie differences in antibiotic use across geographical areas [14]. In accordance to our results, Keuleyan et al., demonstrated an increase of third-generation cephalosporins consumption, but no change in penicillin and quinolones consumption on the territory of Bulgaria [15]. Conversely, in the study conducted in Romania, the most prescribed antibiotics were penicillins plus beta-lactamase inhibitors, second-generation cephalosporins and fluoroquinolones, but not third-generation cephalosporins [16].

An 11-year follow-up of antibiotics consumption at emergency department adults

unit of an academic hospital showed increase in third-generation cephalosporins use from 9.7% of total antibiotic use to 22.6% (estimate per year, 1.2%), whereas use of fluoroquinolones decreased from 19.5 to 12.3% (estimate per year, -0.7%) [17]. Although, we noticed an decrease in third-generation cephalosporins use between 2011 and 2014, there was an increase in CTX consumption, which was the most prescribed antibiotic at our clinical centre (estimate per year, 3.7%). Conversely, we have decrease in CIP consumption within observed period (estimate per year, -2.8%). Given their ability to select bacterial resistance, especially extended-spectrum β -lactamases, particular attention should be paid to increasing use of third-generation cephalosporins in the hospital environment. Monitoring of antibiotic consumption is of crucial importance due to the increasing trend in antibiotic resistance globally. Among the rest, fluoroquinolones and third-generation cephalosporins are particularly prone to select bacterial resistance to antibiotics [17,18,19]. Our results show that high consumption of CTX from 2011 to 2014 corresponded to higher rate of *E. coli* and *Klebsiella sp.* resistance (Figure 2). Although, CIP consumption expressed in DBD, was approxi-

mately 50% less than CTX, the resistance of analyzed bacterial strains was also high to CIP. Ceftriaxone, along with other third-generation of cephalosporins, cefotaxime and ceftazidime, have been used in the treatment of IAI. Our findings suggest an increase of *K. pneumoniae* resistance to CTX and CIP during study period for the IAI isolates (Table 1). This of the utmost importance due to acquired resistance to cephalosporins by the *enterobacteriaceae* may limit the use of those agents in high risk IAI [20]. At the same observed period, *E. coli* resistance to CTX and CIP showed increasing trend for isolates from UTI (Table 1). Broad spectrum agents, such as fluoroquinolones in 35%, cephalosporins in 27% and penicillins in 16% are the most commonly-used antibiotics for UTI [21]. Routine antibiotic prophylaxis of all urological procedures was highest in Asia, Africa and Latin America with 86%, 85% and 84%, followed by Europe with 67%. Antibiotic prophylaxis was not always consistent with recommended guidelines [22]. Tandogdu et al., showed that resistance to almost all pathogens isolated during UTI was lowest in North Europe, with no single year where an outbreak of resistance has been detected [23]. Still, it was reported that resistance to CIP in *E. coli* from UTI in Denmark was increasing parallel to increased use of fluoroquinolones, which also shown for another European countries [24]. Resistance to CIP, which are the preferred empiric treatment for UTI, prolongs hospitalization and increases the cost of antibiotic treatment [25].

CONCLUSION

In conclusion, cephalosporins were the most frequently used antibiotics in Clinical Centre Nis, and they were followed by penicillins and quinolones. CTX was reported to have increased consumption, while CIP utilization seemed to be slightly reduced in 2011-2014 period. The prevalence of antibiotic resistance among *E. coli* and *K. pneumoniae* has increasing trend in recent years. Our findings showed that *K. pneumoniae* resistance to CTX and CIP increased markedly in IAI, while *E. coli* resistance had increasing trend to CTX and CIP in UTI over the study period. This study provide additional basis for guidelines on the use of antimicrobial agents for treating *Enterobacteriaceae* infections, especially those caused by *E. coli* and *K. pneumoniae*.

ACKNOWLEDGMENTS

This study was supported by grant of Ministry of Science and Technological Development – project number 41018

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Analiza potrošnje antibiotika i bakterijske rezistencije u tercijernom Zdravstvenom centru Niš

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KRATAK SADRŽAJ

Uvod: Antibiotici su među najčešće korišćenim lekovima kod hospitalizovanih pacijenata. Istraživanja su pokazala da se antibiotici često neracionalno primenjuju što značajno doprinosi razvoju bakterijske otpornosti. Cilj ovog rada je evaluacija potrošnje antibiotika u Kliničkom centru Niš, sa akcentom na monitoring potrošnje ceftriaksona (CTX) i ciprofloxacina (CIP). Uporedo sa potrošnjom antibiotika prikazana je bakterijska otpornost prema antibioticima koji se koristi za terapiju intraabdominalnih (IAI) i urinarnih infekcija (UTI).

Metode: Potrošnja antibiotika i antimikrobna otpornost praćene su u tercijarnoj zdravstvenoj ustanovi - Kliničkom centru Niš od 2011. do 2014. Korišćenjem *Anatomical Therapeutic Chemical/Defined Daily Dose* metodologije ukupna potrošnja antibiotika izražavana je brojem definisanih dnevnih doza na 100 bolesničkih dana (DBD). Ispitivanje i praćenje osetljivostibakterija vršeno je u Institutu za zaštitu zdravlja u Nišu. Bakterijska rezistencija izražavana je procentom rezistentnih sojeva bakterija.

Rezultati: U toku ispitivanog perioda upotreba cefalosporina je povećana za 6,39%, od 2011. do 2013. godine, dok je 2014. godine utvrđeno smanjenje potrošnje za 16.46%. Potrošnja penicilina je smanjena, dok je potrošnja hinolona bila promenljivo toku perioda praćenja. Registrovan je rastući trend otpornosti *K. pneumoniae* prema CTX i CIP u lečenju IAI i *E. coli* u terapiji UTI u navedenom periodu.

Zaključci: Naši rezultati pokazuju da su cefalosporini najčešće korišćeni antibiotici u Kliničkom centru Niš, nakon čega slede penicilini i hinoloni. Povećana je otpornost *K. pneumoniae* prema CTX i CIP u lečenju IAI i *E. coli* prema CTX i CIP u terapiji UTI, tokom ispitivanog perioda.

Ključne reči: antibiotici, upotreba, bakterijska rezistencija, bolnički pacijenti

Received: March 23, 2016

Accepted: April 04, 2016