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Original Scientific Paper

ETIOLOGY OF URINARY TRACT INFECTIONS IN NEONATES AND BACTERIAL RESISTANCE IN CROATIA

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SUMMARY – Urinary tract infection (UTI) occurs in approximately 15% of full-term neonates and 8% of those born before 37 weeks of gestation. Severe UTI can lead to sepsis or long-term complications such as renal scarring and hypertension. Given the rising concern of bacterial resistance to antibiotics, this research aimed to examine the epidemiology of neonatal UTI, most common antibiotic prescription patterns, as well as resistance of the causative agents in Croatia. This retrospective multicenter analysis was focused on neonates born in 2005 and 2015. Of the 103 bacterial UTI cases, 78.6% affected term neonates. Male neonates constituted 62.1% of the study population. Eutrophic neonates accounted for 87.4%, and hospital-acquired infections were prevalent in 47.6% of cases. The main causative pathogens were *Escherichia coli* (60.2%) and *Klebsiella pneumoniae* (28.2%). Most commonly prescribed empirical antibiotics included ceftriaxone (31.1%) and the ampicillin-gentamicin combination (10.7%). In 2005, 72.7% of isolates were sensitive to empirical therapy. In 2015, sensitivity to empirical antibiotic therapy was observed in 75.6% of cases. In this study, *Escherichia coli* frequently exhibited antibiotic resistance to ampicillin, amoxicillin, trimethoprim-sulfamethoxazole, and gentamicin. For UTIs attributed to *Klebsiella pneumoniae*, the prevailing bacterial resistance was observed against gentamicin, ceftibuten, ampicillin, cefazolin, and piperacillin. The predominance of *Escherichia coli* as the most common pathogen causing UTI was consistent with global trends. Founded on continuous differences in bacterial resistance, this study can serve as a basis for comprehending

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local resistance patterns of pathogens causing neonatal UTI, highlighting the need of additional prospective research.

Keywords: *Urinary tract infections; Neonates; Antibiotic resistance, escherichia coli; Klebsiella pneumoniae; Antibiotic therapy*

Introduction

Urinary tract infection (UTI) occurs in approximately 15% of full-term neonates, affecting approximately 8% of those born before 37 weeks of gestation[1,2]. Prematurity, male sex, uncircumcision and congenital anomalies of the kidney and urinary tract (CAKUT) are considered to be the main predisposing factors for development of UTI in neonates. Severe UTI can lead to sepsis, or result in long-term effects such as renal scarring and hypertension[3]. Gram-negative agents such as *Escherichia coli, Proteus, Klebsiella pneumoniae, Citrobacter,* and *Enterobacter* are predominant causative agents, while gram-positive organisms include coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*[1,4]. In recent times, there has been an increasing trend in bacterial resistance to antibiotics, particularly with a focus on multidrug-resistant gram-negative bacteria. Given the susceptibility of neonates to infections, the increasing trend of bacterial resistance, and the aforementioned adverse events, the selection of appropriate empirical antimicrobial therapy should include the knowledge about predominant causative agents of neonatal infections and local resistance patterns. As part of a national research, this study examined the epidemiology of UTI in neonates, the most common antibiotic prescription patterns for the treatment of neonatal UTI, as well as resistance of the causative agents in Croatia.

Material and Methods

This study was a multicenter retrospective analysis of the epidemiology, antibiotic prescription treatment trends, and bacterial resistance among pathogens causing neonatal UTIs in Croatia. Medical data were collected as part of a national survey entitled Etiology of Sepsis in Neonates Caused by Urinary Tract Infections and Current Bacterial Resistance in Maternity Wards and Intensive Care Units in Croatia: A National Survey.

The data analyzed comprised information on patients from the initial phase of the study, which specifically involved individuals with complete medical records receiving treatment in neonatal intensive care units at regional and subregional perinatal centers, pediatric nephrology departments, neonatal intensive care units across all Croatian pediatric departments, and pediatric departments specialized in infectious diseases. Second phase of the study will analyze additional data on patients for whom access to missing data is requested.

In order to depict differences in the epidemiology, empirically prescribed antibiotics, and antibiotic resistance of pathogens causing neonatal UTIs over a 10-year period, this study was focused on neonates diagnosed with UTI who were born in Croatia in 2005 and 2015. All medical records of neonates treated in maternity wards, neonatal units, and neonatal intensive care units were analyzed and only patients with complete medical data were considered eligible for analysis. Patients were included if they exhibited clinical signs of infection and had a significant number of the organism identified in urine, requiring antibiotic treatment. Patients with asymptomatic bacteriuria were not included in the study.

To minimize the potential bias between the two periods for statistical analysis, we focused on the two predominant species, *Escherichia coli* and *Klebsiella pneumoniae*. Furthermore, antibiotics that did not exhibit at least one instance of resistance across all samples in either 2005 or 2015 were removed from analysis. The following antibiotics were further analyzed: ampicillin, cefepime, ceftazidime, cefuroxime, ceftriaxone, gentamicin, cotrimoxazole, cephalexin, ampicillin-sulbactam, ceftibuten, cefixime, amoxicillin-clavulanate, amoxicillin, amikacin, and trimethoprim-sulfamethoxazole.

Resistance was visualized and statistically analyzed using the libraries[5,6]. Data on 2005 and 2015 were set as groups and % resistance tested using Mann-Whitney U test with alpha=0.05.

Results

Throughout the study period, 104 neonates with UTI were identified, among whom bacterial pathogens were identified in 103 patients. Positive finding of *Candida* spp. in one patient was not included in total analysis. Among the study patients with UTI caused by bacterial pathogens, 22 (21.36%) neonates were preterm. The mean age at the diagnosis of UTI for term neonates in 2005 and 2015 was 13.10 and 14.19 days, respectively, with a mean of 8.38 and 21.69 days for preterm neonates, respectively. The occurrence of UTI was more pronounced in male neonates, affecting 64 (62.14%) male patients. At the time of delivery, 90 (87.38%) neonates were eutrophic, 5 (4.85%) hypotrophic, and 8 (7.77%) hypertrophic, as defined by 10th and 90th percentiles used for singleton pregnancies. Prenatal ultrasound identified urinary tract anomalies in three patients, whereas seven patients presented with urinary tract anomalies at birth. The mean length of hospital stay was 20.11 days. Hospital-acquired UTIs were diagnosed in 49 (47.57%) patients, while community-acquired UTIs were diagnosed in 54 (52.43%) patients. Anthropometric and clinical data of analyzed neonates categorized by the year of birth are shown in Table 1.

Analyzing the prevalence of causative pathogens, *Escherichia coli* was identified in 62 (60.19%) cases, making it most prevalent among all UTIs, followed by *Klebsiella pneumoniae* in 29 (28.16%), *Enterococcus faecalis* in five (4.85%), *Enterobacter cloacae* in three (2.91%), group B streptococcus in two (1.94%) cases, and *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* in one case each (0.97% both). The prevalence of bacterial organisms causing neonatal UTI according to study years is illustrated in Figure 1.

Among all cases of neonatal UTIs treated with empirical therapy (n=50) analyzed in 2005, ceftriaxone was the most frequently administered antibiotic, used in 21 cases. Cefuroxime and meropenem were used in

Table 1. Anthropometric and clinical data on study group

	2005	2005 (%)	2015	2015 (%)
Preterm neonates	8	14.04	14	30.43
Mean age of UTI onset (days) in term neonates	13.10		14.19	
Mean age of UTI onset (days) in preterm neonates	8.38		21.69	
Male sex	32	56.14	32	69.57
Female sex	25	43.86	14	30.43
Mean birth weight (g)	3473.04		3253.75	
Mean birth length (cm)	50.26		49.55	
Mean Apgar score at 1 min	9.55		9.19	
Mean Apgar score at 5 min	9.64		9.57	
Community acquired infection	30	52.63	24	52.17
Hospital acquired infection	27	47.37	22	47.83
Rate of cesarean section	13	22.82	10	21.74
Need of resuscitation	0		4	
Need of mechanical ventilation	0		5	
Perinatal asphyxia	0		3	
Empiric antibiotic therapy initiated after birth	12	21.05	14	30.43

UTI = urinary tract infection

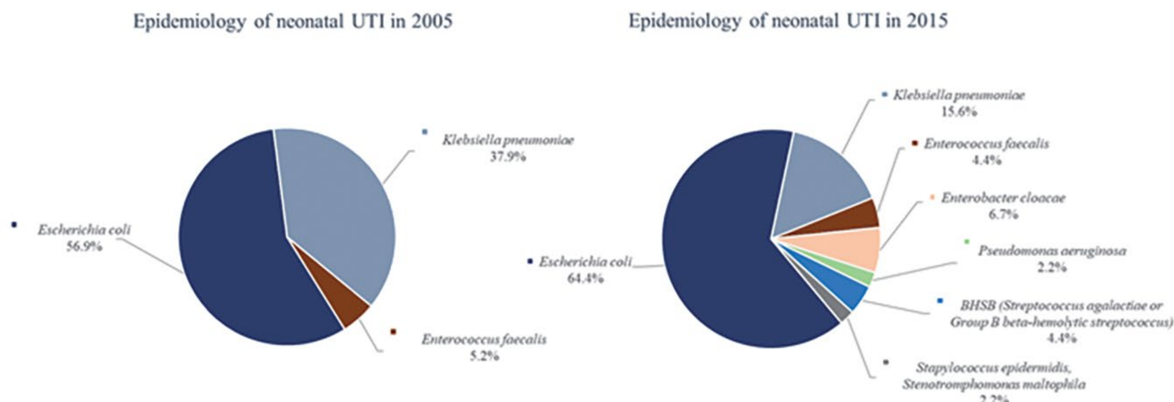

Fig. 1. Epidemiology of neonatal urinary tract infection (UTI).

3 cases each. Treatments involving combinations of antibiotics were less common, i.e., ampicillin + gentamicin was used in 6, meropenem + vancomycin in 2, and ceftazidime + cefuroxime in 2 cases. Several treatments were used only once, including ampicillin + cefuroxime + gentamicin, amikacin + gentamicin, ampicillin + netilmicin, ceftazidime + cloxacillin, cefuroxime + gentamicin, gentamicin, and netilmicin. Data were not available for 6 patients.

Concerning empirical therapy in 2015 (n=43), ceftriaxone was used in 11 cases, making it the most frequently administered antibiotic. Cefuroxime was used in 6 cases, while meropenem was used in 4 cases. Treatments involving combinations of antibiotics were also noted, i.e., ampicillin + gentamicin was used in 5 cases, and cefotaxime was used in 5 cases. Gentamicin alone was used in 2 cases. Several treatments were used only once, including amikacin, amikacin + meropenem, ampicillin + cloxacillin + meropenem, cephalexin, cefepime, ceftazidime + meropenem, ceftazidime + meropenem + vancomycin, and vancomycin. Data were missing for 2 patients.

The 2005 analysis of the appropriateness of empirical therapy (n=44) revealed that UTI bacterial isolates exhibited sensitivity to the ongoing empirical therapy in 32 (72.73%) cases. In two (4.55%) cases, the bacterial isolates initially sensitive to empirical therapy required subsequent therapy expansion. Empirical therapy was discontinued in two (4.55%) cases due to bacterial resistance, while in two (4.55%) cases, therapy persisted despite such resistance. Additionally, in six (13.64%) cases, bacterial isolates demonstrated partial resistance to dual empirical therapy, which was nonetheless continued.

In 2015, bacterial isolates exhibited sensitivity to the ongoing empirical therapy in 31 (75.6%) cases of UTI. In two (4.88%) cases, empirical therapy required subsequent expansion regardless of bacterial sensitivity. Empirical therapy was discontinued in four (9.76%) cases due to bacterial resistance, while in two (4.88%) cases, therapy persisted despite such resistance. In two (4.88%) cases, bacterial isolates demonstrated moderate sensitivity to dual empirical therapy. In 2005, no *Escherichia coli* specimens were found to produce extended spectrum beta-lactamases (ESBLs), whereas in 2015, they constituted 17.24% of total isolates. Of the cases of UTI attributed to *Klebsiella pneumoniae*, 2.1% of isolates were ESBL producers in 2005, rising to 100% in 2015.

In 2005, *Escherichia coli*, as the most prevalent pathogen, demonstrated resistance to ampicillin in 13 (39.39%), trimethoprim-sulfamethoxazole in 6 (18.18%), gentamicin in 5 (15.15%), tetracycline in 3 (9.09%), amoxicillin and amikacin in 2 (6.06%) cases, and to ampicillin-sulbactam, cephalexin, ceftriaxone, and piperacillin in one case each (3.03%). In 2015, the majority of *Escherichia coli* isolates exhibited resistance to ampicillin in 10 (34.48%), amoxicillin in 7 (24.13%), gentamicin in 5 (17.24%), ceftazidime, cefuroxime, and ceftriaxone in 4 (13.79%), cephalexin,

trimethoprim-sulfamethoxazole, and amikacin in 3 (10.34%), cefepime and cefixime in 2 (6.9%) cases, and to ceftibuten and amoxicillin-clavulanate in one case each (3.45%).

In 2005, *Klebsiella pneumoniae* most frequently demonstrated resistance to cefepime, ceftazidime, cefuroxime, and ceftriaxone, with 14 cases accounting for 63.64%. Resistance to gentamicin and ceftibuten was prevalent in 13 (59.09%) isolates, followed by ampicillin and cefazolin in 10 (45.45%), piperacillin in 6 (27.27%), cefotaxime and amikacin in 5 (22.73%), and cephalexin in 4 (18.18%) isolates. Resistance to cefoperazone and nitrofurantoin was observed in 3 (13.64%) isolates. Isolates also exhibited resistance to cefixime, tetracycline, amoxicillin-clavulanate, netilmicin, and amoxicillin in 2 (9.09%) cases, while resistance to ampicillin-sulbactam, tobramycin, and trimethoprim-sulfamethoxazole was seen in one case each (4.55%).

In 2015, *Klebsiella pneumoniae* demonstrated resistance to cefuroxime in 5 (71.43%), cefixime and amoxicillin-clavulanate in 4 (57.14%), gentamicin and trimethoprim-sulfamethoxazole in 3 (42.86%), and cephalexin, cefepime, ceftibuten, and ceftriaxone in 2 (28.57%) cases. Resistance to ampicillin-sulbactam, cefotaxime, ceftazidime, nitrofurantoin, and amoxicillin was present in one case each (14.29%). Individual resistance across the two species and for the selected antibiotics in 2005 and 2015 is illustrated in Figure 2.

Mann-Whitney U test was conducted to determine differences in antibiotic resistance of *Klebsiella pneumoniae* strains between 2005 and 2015. The test yielded a U-value of 110.5, with a two-sided p-value of 0.950157, indicating no significant difference in

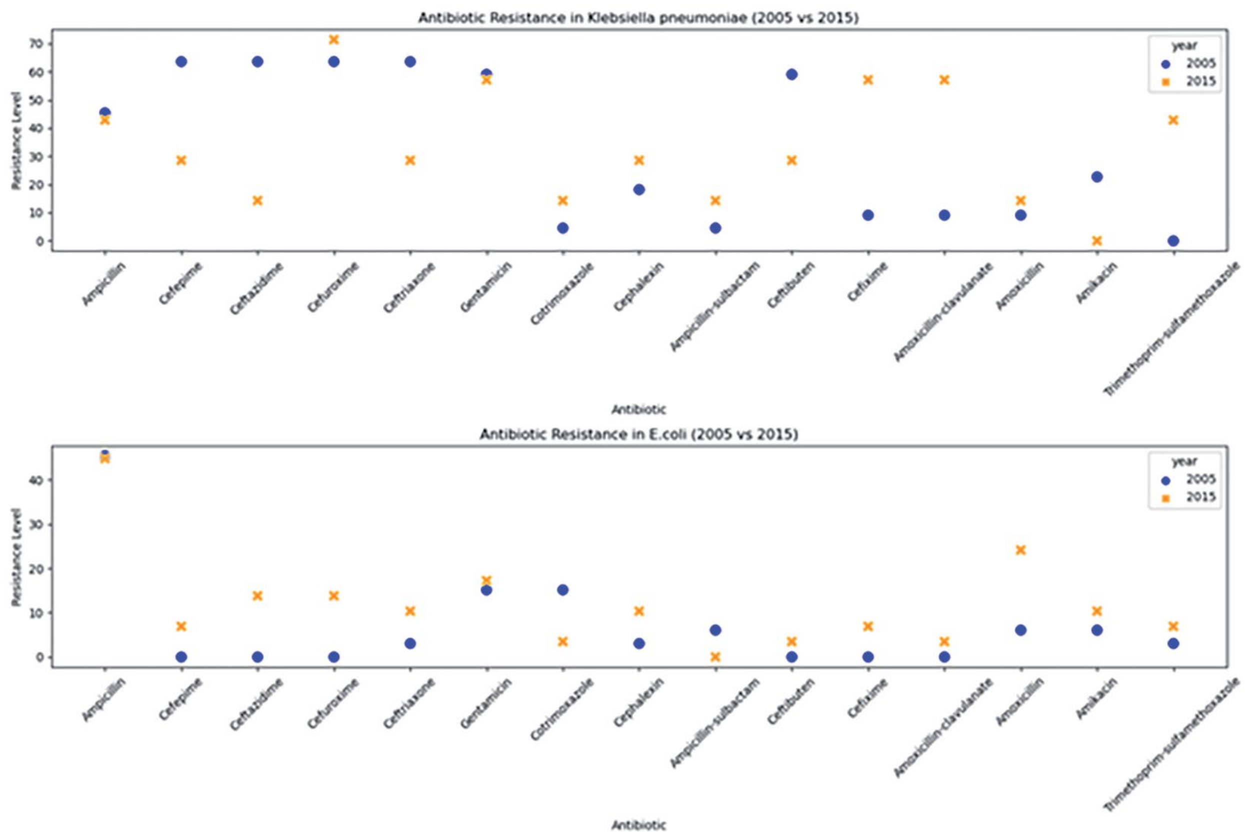

Fig. 2. Individual resistance across the two species and for the selected antibiotics in 2005 versus 2015.

resistance levels between the two years. For *Escherichia coli*, Mann-Whitney U test revealed a U-value of 57.0. The two-sided p-value was 0.021372, indicating a statistically significant difference in resistance between the two years.

Discussion

Along with continuous efforts in improving neonatal care, perinatal infections and their consequences remain among the leading causes of perinatal mortality. Within the first month of life, 10% of neonates acquire infections and infection related mortality is documented in 40% of neonates in the first week of life. In the group of surviving neonates undergoing treatment for perinatal infection, brain injury and related long-term neurodevelopmental disabilities remain a significant concern[7]. Reports on neonatal sepsis indicate substantial variations in its incidence due to differences in diagnostic criteria. Recent data report on the occurrence of 2824 cases *per* 100,000 live births, coupled with a mortality rate of 17.6%[8]. The reported prevalence of sepsis caused by UTI reaches 6%[1]. Due to the low incidence of UTI in early-onset sepsis (EOS) and a higher detection rate in late-onset sepsis (LOS), urine cultures are not routinely obtained during evaluation of neonates presenting with clinical signs of infection within the first 72 hours or 7 days after birth, depending on the definition criteria for EOS[9]. The reported data on the incidence of neonatal UTI vary between 0.1% and 25%, with a higher prevalence observed among preterm neonates, low birth weight neonates, and those necessitating central lines[9,10].

In this study, the projected occurrence of UTIs for each study year has been estimated to 0.1%, considering both the current number of UTI cases and number of live births in Croatia in 2005 (42,492 live births) and 2015 (37,503 live births)[11]. Nevertheless, it is crucial to interpret this significantly lower incidence cautiously, taking into account factors such as retrospective nature of the study, possibility of missed data, study sample size, and diagnostic criteria used for UTIs.

While the majority of study patients were males, the prevalence of other risk factors, including preterm birth, low birth weight, and congenital urinary tract anomalies was not evident in this study. The preponderance of male neonates was not accompanied by higher rates of CAKUT, as commonly explained, and CAKUT was equally prevalent in both genders. In accordance with published epidemiological data, *Escherichia coli* was the predominant pathogen causing UTI, followed by *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Enterobacter cloacae*. Similar to the research conducted by Foglia and Lorch[4], our research did not show a significant proportion, up to 42%, of neonatal UTIs caused by *Candida* sp., which could be explained by the higher prevalence of term and eutrophic newborns in this study.

Larger studies on the occurrence of ESBL-producing pathogens causing UTIs in the general pediatric population have revealed higher prevalence rates in Eastern countries, reaching up to 65% for *Escherichia coli*, compared to up to 17% in Western countries[12]. In contrast, this study, although smaller, demonstrated a total prevalence of 21.36% for ESBL producers. Similar to the study conducted by Degnan *et al.*[13], a higher prevalence of ESBL producers was observed for *Klebsiella pneumoniae* when compared to *Escherichia coli*. Furthermore, we did not find a previously reported significant association of ESBL-producing pathogens with the presence of CAKUT[14].

Differences in clinical practices of UTI screening in neonates impact the studies on its bacterial resistance patterns. Lutter *et al.* conducted a study on antibiotic resistance among pathogens causing UTI in the general pediatric population and found the highest antibiotic resistance to cefotaxime in children receiving prophylactic antibiotics[15]. In children with UTIs who presented as outpatients, testing of the six most common antibiotics showed resistance to ampicillin (44.3% in females and 44.6% in males), followed by sulfamethoxazole/trimethoprim (24.5% in females and 36.7% in males), amoxicillin/clavulanic acid (12.4% in females and 27.5% in males), cefazolin (10.9% in females and 27.1% in males), ciprofloxacin (0.9% in females and 2.4% in males), and nitrofurantoin (4.4% in females and 11.0% in males)[16]. Larger prospective studies on antibiotic resistance of pathogens causing neonatal UTI are lacking. A heightened occurrence of resistant bacterial pathogens in neonates is affected by prior antibiotic treatment, prophylactic antibiotics, or urinary tract anomalies[15]. The observed relation was not present in this study, as

previous antibiotic therapy was primarily short-term, and CAKUT was identified in a minority of cases. Considering that a small percentage of children in this study fell into this category, data on the resistance of causative factors are important.

Conclusion

The predominance of *Escherichia coli* as the most common pathogen causing UTI is consistent with global trends, and antibiotic resistance remains a significant concern. Founded on continuous differences in bacterial resistance, this study can serve as a basis for comprehending local resistance patterns of pathogens causing neonatal UTI, highlighting the need of additional prospective research.

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Sažetak

ETIOLOGIJA INFEKCIJA MOKRAĆNOG SUSTAVA U NOVOROĐENČADI I BAKTERIJSKA REZISTENCIJA U HRVATSKOJ

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Infekcije mokraćnog sustava (IMS) prisutne su u približno 15% donesene i 8% novorođenčadi rođene prije 37. tjedna gestacije. Teški oblici novorođenačkih IMS-a mogu dovesti do razvoja sepse, ali i dugoročnih posljedica poput ožiljčenja bubrega i hipertenzije. U vremenu porasta bakterijske rezistencije na antibiotike predmetno istraživanje provedeno je s ciljem utvrđivanja najčešćih uzročnika IMS-a u novorođenčadi rođene 2005. i 2015. godine u Hrvatskoj. Ispitani su najčešći obrasci propisivanja antibiotika i osjetljivost uzročnika na antibiotike. Ukupno su analizirana 103 bolesnika s IMS-om uzrokovanog bakterijama, pri čemu je udio terminske novorođenčadi iznosio 78,6%. Udio muške novorođenčadi iznosio je 62,1%, a eutrofične novorođenčadi 87,4%. Retrospektivnom analizom utvrđeno je da su bolničke IMS bile prisutne u 47,6% slučajeva, a vodeći uzročnici bili su *Escherichia coli* (60,2%) i *Klebsiella pneumoniae* (28,2%). Posebno je ispitana osjetljivost uzročnika na empirijski propisanu antibiotsku terapiju. Ceftriakson (31,1%) i kombinacija ampicilina i gentamicina (10,7%) bili su najčešće empirijski propisani antibiotici. Godine 2005. osjetljivost na empirijsku terapiju je iznosila 72,7%, a 2015. godine udio osjetljivih izolata iznosio je 75,6%. *Escherichia coli* kao vodeći uzročnik najčešće je bila rezistentna na ampicilin, amoksicilin, trimetoprim-sulfametoksazol i gentamicin. U slučajevima IMS-a uzrokovanih *Klebsiellom pneumoniae* uočena je značajna rezistencija na gentamicin, ceftibuten, ampicilin, cefazolin i piperacilin. Zastupljenost *Escherichia coli* kao uzročnika IMS-a odgovara globalnim trendovima uz značajan udio rezistentnih sojeva. Ovo istraživanje temelji se na analizi dugoročnih promjena u bakterijskoj rezistenciji na antibiotike, a provedeno je s ciljem uvida u moguće obrasce rezistencije bakterija uzročnika IMS-a na antibiotike. Dobiveni rezultati ističu potrebu daljnjih prospektivnih istraživanja na većem broju ispitanika.

Ključne riječi: *Infekcije mokraćnog sustava; Novorođenčad; Rezistencija na antibiotike; Escherichia coli; Klebsiella pneumoniae; Liječenje antibioticima*