

Antibiotic Resistance of Uropathogens in Newborns and Young Children with Acute Pyelonephritis

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SUMMARY

Introduction Urinary tract infection is common in childhood. Depending on the localization of the infection, severity of its clinical presentation and possible acute and long-term complications, it may be described as either acute cystitis or acute pyelonephritis.

Objective The aim of this study was to assess the resistance patterns of uropathogens during the last 5 years in newborns and young children with acute pyelonephritis.

Methods Uropathogens resistance to commonly usable anti-microbial agents (ampicillin, a combination of sulphamethoxazole and trimethoprim, cephalexin, ceftriaxone, cefotaxime, ceftazidime, gentamycin, amikacin, ciprofloxacin, imipenem and nalidixic acid) was retrospectively studied in newborns and young children treated during early (2005–2007) and late (2008–2009) study periods. Anti-bacterial susceptibility testing of the urine isolates was performed by the standard disc diffusion method.

Results 117 newborns and 294 children aged 9.3 ± 0.7 months were treated during early ($n=136$) or late ($n=275$) study period due to the first episode of acute pyelonephritis. *Escherichia coli* was the most common bacterial pathogen (85.5%). Compared to children older than one month, newborns had higher degree of antibacterial resistance to 2nd and 3rd generation cephalosporins, aminoglycosides, and nalidixic acid during early, and to ceftazidime, aminoglycosides and nalidixic acid during late study period. Also, multidrug resistance was more common in newborns during the early study period.

Conclusion Newborns had higher rate of antibacterial resistance than young children. The progressive increase of anti-microbial resistance in children with acute pyelonephritis is of great concern.

Keywords: antimicrobial agents; urinary tract infection; *Escherichia coli*; bacterial resistance; children

INTRODUCTION

Urinary tract infection (UTI) is common in childhood, second only in frequency to that of the respiratory tract [1, 2, 3]. Depending on the localization of the infection, severity of its clinical presentation and possible acute and long-term complications, UTI may be described as either acute cystitis or as acute pyelonephritis [4-7]. Prompt treatment of childhood acute pyelonephritis is likely to reduce the risk of permanent renal scarring [7, 8]. However, increased anti-microbial resistance, especially the emergence of uropathogen strains producing extended spectrum β -lactamases (ESBLs) has threatened the antibiotic treatment of UTI in children [9, 10, 11].

OBJECTIVE

The aim of this study was to assess the changing trend of local resistance patterns of urinary pathogens to commonly usable anti-microbial agents during the last 5 years in newborns and young children with acute pyelonephritis.

METHODS

The medical records from January 2005 to December 2009 of all children aged less

than 18 years admitted at the Nephrology or Neonatology Department of the University Children's Hospital in Belgrade for their first UTI were reviewed. Two different periods, early (from January 2005 to December 2007) and late (from January 2008 to December 2009), were studied to evaluate the trend of anti-microbial resistance in children with clinically suspected acute pyelonephritis. Data were analyzed separately for two age groups: newborns (group I) and children older than one month (group II). Clinical parameters including age, gender, aetiology of UTI and bacterial resistance of uropathogens and urinary tract imaging were recorded for each patient. The patients who met the following criteria were included in the study: fever greater than 38.5°C with no other recognized cause, leukocytosis, C reactive protein (CRP) higher than 20 mg/l, positive dipstick for leukocyte esterase and/or pyuria (urine specimen with ≥ 10 white blood cells/hpf), and isolation of more than 10^5 colony-forming units (CFUs)/ml of a single species of bacteria in a urine sample obtained by midstream clean catch, or sterile bags. Those receiving antibiotics and immunosuppressed children as well as those with history of previous UTI were excluded from the study. Ultra-sonography performed within 72 hours after admission into hospital was required for all participants, while voiding cysto-urethrography and Tc-99m DMSA scin-

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tigraphy were optional at the treating physician's request and parents' decision.

All urine samples were obtained in hospital by health care personnel. Contaminated specimens were discarded from the study. Standard methods for isolation and identification of the isolates were used. Anti-bacterial susceptibility testing of the isolates was performed by the standard disc diffusion method as recommended by the Clinical and Laboratory Standards Institute (CLSI) [12]. ESBL phenotypic confirmatory test with ceftazidime, ceftriaxone and cefotaxime was performed for all isolates by disc diffusion method on Mueller-Hinton agar plates. A ≥ 5 mm increase in a zone diameter for antimicrobial agent tested in combination with clavulanic acid versus its zone when tested alone was considered indicative of ESBL production. The methods used did not vary throughout the study period. No tests were performed to further characterize the clonal origin of isolates.

The following anti-microbial agents were tested: ampicillin (AMP), a combination of sulphamethoxazole and trimethoprim (TMP-SMZ), cephalexin (CEP), ceftriaxone (CX), cefotaxime (CTX), ceftazidime (CEF), gentamycin (GN), amikacin (AM), ciprofloxacin (CIP), imipenem (IMP) and nalidixic acid (N). Multi-drug resistance was defined when resistance to at least 3 different groups of antibiotics was apparent.

Statistical analysis

SPSS 13.0 for Microsoft Windows was used for all statistical analyses. Results for continuous variables were presented as mean (\pm SEM). Fisher's exact test was used to compare categorical variables. The Mann-Whitney U test was used for continuous variables. A P value <0.05 was considered to be statistical significant.

RESULTS

Clinical characteristics

A total of 598 children were hospitalized in the Nephrology and Neonatal departments of the University Children's Hospital in Belgrade due to the first UTI between the 1st of January 2005 and the 31st of December 2009. Of these, only 411 children (189 girls and 222 boys, median age of 4.0 months; range 0.1–112 months) fulfilled inclusion criteria of the study. Their clinical characteristics are shown in Table 1. The patients were divided in 2 groups based on age. Group I consisted of 117 newborns while group II consisted of 294 older children with a mean age of 9.3 ± 0.7 months. The patients were treated in early (2005–2007) or late (2008–2009) during the study period (136 and 275 patients, respectively). The early and late period of the research were comparable except for CRP and ESBL (+) UTI which were higher in early than in late period and renal ultrasound abnormalities which were more common in the early than in the later period. The percentage of urine specimen-obtaining methods for urine culture, midstream clean catch urine and sterile bags were 65 and 35% in the early and 67 and 33% in late study period, respectively.

Microbiology

Escherichia coli (*E. coli*) was the leading cause of UTI (85.5%), followed by *Klebsiella pneumoniae* (8.1%), *Enterococcus* spp. (3.6%), *Proteus mirabilis* (2.0%), *Enterobacter* (0.4%) and *Pseudomonas aeruginosa* (0.4%). The distribution of uropathogens did not vary significantly between the two study periods, but *E. coli* was more prevalent in group II while non-*E. coli* pathogens, *Klebsiella* and *Enterococcus*, were more common in group I (Table 2).

Table 1. Clinical characteristics

Parameter	Group I			Group II		
	2005–2007 (n=50)	2008–2009 (n=67)	P	2005–2007 (n=86)	2008–2009 (n=208)	P
Gender, male/female (%)	84/16	77.6/22.4	NS	32.6/67.4	48.1/51.9	<0.05
Age (months)	0.5 ± 0.2	0.5 ± 0.2	NS	11.4 ± 1.8	8.5 ± 0.7	NS
Temperature ($^{\circ}$ C)	38.5 ± 0.4	38.5 ± 0.4	NS	39.2 ± 0.7	39.1 ± 0.6	NS
White blood cells ($10^3/\text{mm}^3$)	18.2 ± 1.8	17.1 ± 1.1	NS	18.6 ± 0.8	18.9 ± 0.5	NS
C-reactive protein (mg/L)	45.4 ± 7.2	62.8 ± 8.0	NS	57.3 ± 3.6	87.8 ± 4.5	<0.01
Renal ultrasound abnormalities (%)	36.4	19.4	<0.05	38	29.1	NS
ESBL (+) UTI (%)	44	65.7	<0.05	11.6	63.0	<0.01

n – number of patients; ESBL (+) UTI – urinary tract infections caused by ESBL-producing microorganisms; NS – not statistically significant

Table 2. Frequency of urinary pathogens

Urinary pathogens	Group I			Group II			p (Group I vs Group II)	
	2005–2007 (n=50)	2008–2009 (n=67)	P	2005–2007 (n=86)	2008–2009 (n=208)	p	2005–2007	2008–2009
<i>Escherichia coli</i>	72.0	73.1	NS	88.4	92.8	NS	<0.05	<0.01
<i>Klebsiella</i>	20.0	19.4	NS	3.5	3.4	NS	<0.01	<0.01
<i>Enterococcus</i>	6.0	7.5	NS	2.3	1.0	NS	NS	<0.01
Other	2.0	0	NS	5.8	2.9	NS	NS	NS
Total	100.0	100.0		100.0	100.0			

Resistance patterns

Resistance to anti-microbial agents for overall pathogens both in the early and late study periods is presented in Table 3. When early and late study periods were compared increasing trends in bacterial resistance patterns were observed towards TMP-SMX, 2nd and 3rd generation cephalosporins and gentamicin as well as in multidrug resistance, while a decreasing trend was seen towards AM and unchanged towards CIP, IMP and to N (Table 3). Compared to children older than 1 month, newborns had similar (AMP; TMP-SMZ, CIP, IMP and N) or higher degree of antibacterial resistance (CEP, CX, CTX and multidrug resistance during early, and CEF, GN and AM during whole study period) (Table 3). ESBL (+) was more common in the late than in early period (Table 1).

DISCUSSION

The prevalence of the resistance to specific antibiotics is highly variable in different populations and in different countries [13-28]. In general, in poor and undeveloped countries overall prevalence of antimicrobial resistance is notably high, reflecting irrational and inordinate use of anti-microbial agents [29, 30]. Bacterial resistance of uropathogens in the paediatric population in Serbia has been regularly monitored [31, 32, 33]. Herein, we compared the trend of the bacterial resistance prevalence over a recent 5-year period in newborns compared to that in young children with the first acute pyelonephritis. The increased number of young children with acute pyelonephritis during the later study period may be explained by its better diagnosis due to the improved education of paediatricians [32], as well as by an enlarged bed capacity of nephrology service from 2008.

The predominance of *E. coli* among uropathogens in our study is in agreement with many other paediatric studies [28-31, 33-38]. Also, a high resistance to ampicillin (>80%) is not surprising based on epidemiological studies from elsewhere [10, 15, 31-34]. According to these results, ampicillin should not be used alone for the empirical treat-

ment of paediatric UTIs. The resistance towards TMP/SMX (about 50%) is similar to that in Turkey [37], Greece [26], England [38], Belgium [36] and Taiwan [30], but less common than in Cambodia [33], Central African Republic [34] and Pakistan [39]. Thus, the use of TMP-SMZ as a single agent for empiric treatment of paediatric UTI would not cover half of the uropathogens. The resistance to gentamicin and amikacin was higher in newborns than in young children to whom amikacin remained suitable for empiric treatment of acute pyelonephritis. None of the isolates was found to be resistant to imipenem. However, this drug should be reserved only in the most severe forms of illness caused by multi-drug resistant uropathogens.

In general, we observed a strikingly increasing trend for ESBL (+) and for multi-drug-resistant uropathogens during the late study period compared to the early period. These findings were even worse in the newborns than in older children. Multi-drug-resistance was most common among ESBL (+) uropathogens. This can be explained by the fact that the resistance towards beta-lactam drugs usually extends to other classes of antibiotics through resistance genes carried on the same plasmids.

The increased resistance rate found in our study cannot be attributed to either more sensitive methods of detection of resistant strains (as identification methods remained the same throughout the study period), to incidental spread of hospital-resistant organisms at a certain time (as UTI in our patients was mainly community acquired) or to a greater frequency of urinary tract anomalies reported by other authors [13, 15]. The increased uropathogen resistance trend demonstrated by our current study could be linked to non-restricted use of antibiotics in Serbia by physicians as well as to high degree of self medication in population.

Our analysis has some limitations. The first one is the retrospective design of the study. Also, sterile bags or mid-stream clean catch urine is not the method of choice to obtain sterile urine in infants and children. Nevertheless, urine samples were obtained in hospital by health care personnel and the collections of data as well as the laboratory methods were consistent through the study period. Therefore, the increasing evolution of the antibacterial resistance over this five-year period should represent the

Table 3. Antibiotic *in vitro* resistance

Antibacterial drugs	2005–2007 (n=136)			2008–2009 (n=275)			2005–2007 (n=136)	2008–2009 (n=275)	p (2005–2007 vs 2008–2009)
	Group I (n=50)	Group II (n=86)	p	Group I (n=67)	Group II (n=208)	p			
Ampicillin	83.3	87.2	NS	86.6	89.8	NS	85.8	98.0	NS
TMP-SMZ	37.8	38.9	NS	57.1	59.7	NS	38.5	59.2	<0.001
Cephalexin	46.8	22.1	<0.05	71.0	68.8	NS	30.8	69.3	<0.001
Cephtriaxone	46.8	21.3	<0.05	71.0	65.8	NS	34.0	67.0	<0.001
Cefotaxime	46.8	12.1	<0.001	71.0	62.9	NS	26.5	65.0	<0.001
Ceftazidime	43.5	20.5	<0.05	70.5	40.9	<0.05	42.6	62.7	<0.05
Gentamicin	61.7	17.4	<0.001	72.6	51.5	<0.005	33.1	56.3	<0.001
Amikacin	36.2	4.6	<0.001	21.0	4.0	<0.001	17.9	8.5	<0.05
Ciprofloxacin	0	1.5	NS	0	1.2	NS	0.9	0.9	NS
Imipenem	0	0	NS	0	1.0	NS	0	0	NS
Nalidixic acid	11.4	0	<0.01	11.3	2.9	<0.05	4.4	5.2	NS
Multidrug resistance	32.0	8.1	<0.001	44.8	44.7	NS	16.9	44.7	<0.01

general trend among urinary tract pathogens in children with first UTI treated at a key paediatric centre in Serbia.

CONCLUSION

Our study has demonstrated the progressive increase in anti-microbial resistance in children with first UTI in Serbia during the period 2005-2009. High prevalence rate of ESBL (+) uropathogens and multi-drug-resistance in

children, especially in the newborns is of great concern. Further studies are needed to follow regional and time trends as well as to develop effective methods to limit increasing multi-drug resistance.

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Антибактеријска резистенција уринарних бактерија код новорођенчади и мале деце оболеле од акутног пијелонефритиса

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КРАТАК САДРЖАЈ

Увод Инфекција уринарног тракта је честа у детињству. У зависности од места инфекције, јачине њене клиничке слике и могућих акутних и дугорочних компликација, она се описује као акутни циститис или акутни пијелонефритис.

Циљ рада Циљ рада био је да испита резистенција уринарних бактерија током пет година код новорођенчади и мале деце оболеле од акутног пијелонефритиса.

Методe рада Ретроспективно је анализирана резистенција уропатогених бактерија на антибактеријске лекове (ампицилин, комбинацију сулфометоксазола и триметоприма, цефалексина, цефтриаксона, цефотаксима, цефтазидима, гентамицина, амикацина, ципрофлоксацина, имипенема и налидиксичне киселине) код новорођенчади и мале деце током раног (2005–2007) и каснијег (2008–2009) студијског периода. За одређивање антибактеријске сензитивности у урину коришћена је стандардна диск-дифузиона метода.

Резултати Укупно 117 новорођенчади и 294 мала детета уз-

раста $9,3 \pm 0,7$ месеци лечено је током раног (136 болесника) и касног (275 болесника) студијског периода. *Escherichia coli* је била најчешћи узрочник инфекције у оба периода (85,5%). У односу на децу старију од месец дана, код новорођенчади је утврђен већи степен антибактеријске резистенције на цефалоспорине друге и треће генерације, аминогликозиде и налидиксичну киселину за време раног студијског периода, а на цефтазидим, аминогликозиде и налидиксичну киселину током каснијег периода испитивања. Резистенција на неколико лекова била је такође чешћа код новорођенчади у раном студијском периоду.

Закључак Код новорођенчади је већи степен антибактеријске резистенције него код деце старије од месец дана. Забрињава, међутим, повећање учесталости антибактеријске резистенције код деце с првим акутним пијелонефритисом.

Кључне речи: антимиљробни лекови; инфекција уринарног тракта; *Escherichia coli*; бактеријска резистенција; деца

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