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Original Article

The Emerging Resistance in Nosocomial Urinary Tract Infections: From the Pediatrics Perspective

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Abstract. ***Background.*** **Healthcare-associated infections results in increased health care costs and mortality. There are limited studies concerning the distribution of the etiologic agents and the resistance patterns of the microorganisms causing healthcare-associated urinary tract infections (HA-UTI) in pediatric settings.**
Objectives. **The aim of this study was to evaluate the distribution and antibiotic susceptibility patterns of pathogens causing HA-UTI in children.**
Material and Methods. **Isolates from 138 children with UTI who were hospitalized in pediatric, neonatal and pediatric surgery intensive care units were reviewed.**
Results. **Most common isolated organism was Klebsiella pneumoniae (34.1%) and Escherichia coli (26.8%). Among the Pseudomonas aeruginosa, Meropenem and imipenem resistance rates were 46.2% and 38.5%. Extended-spectrum beta-lactamase (ESBL) production was present in 48 Klebsiella species (82.8%). Among ESBL positive Klebsiella species, the rate of meropenem and imipenem resistance was 18.8%, and ertapenem resistance was 45.9%. Extended spectrum beta-lactamase production was present in 27 (72.9%) Escherichia coli species. Among ESBL positive E. coli, the rate of meropenem and imipenem resistance was 7.4%, and ertapenem resistance was 14.8%**
Conclusions. **Emerging meropenem resistance in P. aeruginosa, higher rates of ertapenem resistance in ESBL positive ones in E. coli and Klebsiella species in pediatric nosocomial UTI are important notifying signs for superbug infections.**

Keywords: Healthcare-associated urinary tract infections, Children, Antibiotic susceptibility.

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Introduction. Healthcare-associated infections (HAIs) are common and probably one of the most preventable complications during hospitalization resulting in increased health care costs and mortality.[1] According to CDC, healthcare-associated urinary tract infections (HA-UTIs) in the United States acute care hospitals are estimated to be about 93 300 annually in 2011.[2] Urinary tract infection was reported to be leading HAI among hospitalized adults and in critical care units[3,4] and the second or third most common type of nosocomial infection in intensive care units (ICUs).[5-7] The HA-UTI is frequently related to bladder catheterization,[3,4] and the risk of catheter-

associated urinary tract infection (CA-UTI) is reported to increase by 3% to 7% within each day of the indwelling urinary catheter remains.[8,9]

Most epidemiological data including the distribution of the etiologic agents and the resistance patterns of the microorganisms causing HA-UTI is mainly based on adult reports, and there are limited studies concerning the isolated HA-UTI in children.[4,10] In addition, most of the studies about nosocomial UTIs are mostly related to CA-UTI. Therefore the real epidemiology of symptomatic non-catheter-associated UTI (Non-CAUTI) has not been established in the pediatric settings. Thus, the objective of the study is to evaluate the distribution and also the antibiotic susceptibility patterns of pathogens causing HA-UTI, with especially focusing on whether it is catheter-associated or non-catheter-associated UTI in children hospitalized at ICUs.

Material and Methods. *Study subjects and methods.* This study included the symptomatic HA-UTI in children under 18 years old who were hospitalized in the ICUs of Dr. Behçet Uz Children's Hospital between the periods from January 2014 to December 2017. This hospital is a referral center for pediatric patients in the Aegean Region of Turkey with annual outpatient 600 000 patients and approximately 23 000 hospitalizations in 2016. The pediatric intensive care unit (PICU) has 24-bed capacity with 500 hospitalizations, the neonatal intensive care unit (NICU) has 60 bed-capacities with 1500 hospitalizations, and the pediatric surgery and the pediatric cardiovascular surgery ICUs have 6–bed capacities and 200 hospitalizations, annually.

Definitions. All children in ICUs who were diagnosed as symptomatic UTI with positive urinary culture results were included to study. The definitions of symptomatic UTI including symptomatic CA-UTI and non-CAUTI were defined according to the definitions of Centers for Disease Control and Prevention.[11]

Microbiological analysis. Each urinary culture was placed in the Bac T/ALERT 9240 95 automated system (bioM**é**rieux, Marcy l'Etoile, France) and incubated for seven days or until they were found to be positive.[12] The microorganisms were identified with the VITEK-2 compact system (bioM**é**rieux), and antibiotic susceptibility tests (including MIC levels, ESBL presence, and carbapenem resistance) were also performed with the same system for each isolate according to the manufacturer's instructions and the European Committee on Antimicrobial Susceptibility Testing. Identification and antibiotic susceptibility tests of gram-positive bacteria were performed using the automated VITEK-2 system with gram-positive identification card AST-P592, a supplementary E-test (bioMérieux, Durham, NC, USA), and a disk diffusion test according to the manufacturer's instructions. Vancomycin-resistant *Enterococcus spp*. (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) were also identified using the automated VITEK-2 system.[13] This system was also used for the identification and antibiotic susceptibility tests of gram-negative bacteria with Gram-negative identification card AST-N325, AST-N326, and AST-N327.[14]

This study was approved by the Local Ethical Committee of 120 Dr. Behçet Uz Children's Training and Research Hospital.

Statistical analysis. Statistical analysis was performed using SPSS, version 15.0 1 (IBM SPSS, Chicago, IL). Quantitative data are expressed as a mean and standard deviation or median with interquartile range (IQR) if data followed a non-normal distribution. Qualitative variables were expressed as absolute and relative frequencies. Chi-square, with Fisher's exact correction where required for discrete variables, and Student's t-test for parametric and Wilcoxon rank sum test for non-parametric continuous variables were used. Probabilities (p values) less than 0.05 were considered significant for all tests.

Results. During the study period, a total of 152 nosocomial symptomatic UTI episodes were recorded. Fourteen of these were excluded due to absent data. A total of 138 UTI episodes which had complete medical files and susceptibility patterns were included in the final analysis. Among the 138 UTI episodes, 74 (53.6%) episodes were in NICU, 55 (39.9%) episodes were in PICU, 7 (5.1%) episodes were in pediatric surgery ICU, and 2 (1.4%) episodes were in pediatric cardiovascular surgery ICU. Of all analyzed UTIs, 26 (18.8%) were symptomatic CA-UTI and 112 (81.2%) were symptomatic non-CAUTI.

Table-1. Isolated microorganisms in the study.

Microorganisms	Symptomatic CA-UTI n	Symptomatic non-CAUTI n	Number / Ratio n (%)
Klebsiella pneumonia	2	45	47 (34.1)
Escherichia coli	7	30	37 (26.8)
Pseudomonas aeruginosa	3	10	13 (9.4)
Enterococcus faecalis	9	4	13 (9.4)
Klebsiella spp.	-	8	8 (5.6)
Enterobacter cloacae	-	7	7 (5.1)
Candida species	4	2	6 (4.3)
Klebsiella oxytoca	-	3	3 (2.2)
Proteus mirabilis	1	1	2 (1.4)
Stenotrophomonas maltophilia	-	2	2 (1.4)
Total	**26**	**112**	**138 (100)**

CA-UTI: catheter-associated urinary tract infection; non-CAUTI: non-catheter-associated urinary tract infection

Gram-negative microorganisms were the most common isolated organisms (119 isolations, 86.2%) followed by Gram-positive bacteria (13 isolations, 9.4%) and *Candida* spp. (4.3%). The distribution of the isolated microorganisms was reviewed in **Table 1**. The most common isolated organism was *K. pneumoniae* (34.1%) and *E. coli* (26.8%) followed by other microorganisms reviewed in **Table 1**.

Resistance patterns. Among the *P. aeruginosa*, in vitro susceptibility was highest to amikacin, followed by colistin, gentamicin, tobramycin, levofloxacin, and ciprofloxacin. Meropenem and imipenem resistance rates were 46.2% and 38.5%, consecutively (**Table 2**). Nearly 53.8% of the *P. aeruginosa* were resistant to ceftazidime showing the highest resistance rate.

Extended-spectrum beta-lactamase (ESBL) production was present in 48 *Klebsiella* species (82.8%). Among ESBL positive *Klebsiella* species, the rate of meropenem and imipenem resistance was 18.8%, and ertapenem resistance was 45.9% (**Table 2**). Aminoglycoside resistance ranges from 8.3 to 43.8% in *Klebsiella* species, and ciprofloxacin resistance were present in 39.6% of the isolates. Colistin resistance was observed in 12.5% of the *Klebsiella* species isolate (**Table 2**).

Extended spectrum beta-lactamase production was present in 27 (72.9%) of *E. coli* species. Among ESBL positive *E. coli*, the rate of meropenem and imipenem resistance was 7.4%, and ertapenem resistance was 14.8% (**Table 2**). Aminoglycoside resistance ranged from 25.9% to 66.7% (amikacin, tobramycin, and gentamicin resistance were 25.9%, 66.7%, 66.7%, respectively) and ciprofloxacin resistance was present in 33.3% in ESBL positive *E. coli* species. Resistance to colistin was not observed in *E. coli* isolates.

Among 7 *Enterobacter cloaca* strains, only 1(14.3%) was ESBL positive, and this isolate was resistant to meropenem, imipenem, aminoglycosides, and other antimicrobial agents.

Among the 13 *Enterococcus fecalis* strains, vancomycin resistance was present in 2 isolates

Table-2: Prevalence and antibacterial resistance of Gram negative pathogens in the study.

	No.	P/T	CAZ	M	IMP	ETP	CP	GM	TO	AMK	CO	SXT
Pseudomonas aeruginosa	13	30.8	53.8	46.2	38.5	0	30.8	23.0	23.0	0	15.4	0
ESBL(-) Klebsiella spp.	10	40.0	20.0	0	0	0	10.0	30.0	0	12.5	0	20.0
ESBL(+) Klebsiella spp.	48	70.8	95.8	18.8	18.8	45.9	39.6	68.8	8.3	33.3	12.5	77.1
ESBL (-) Escherichia coli	10	0	30	0	0	0	10.0	20.0	10	0	0	40.0
ESBL (+) Escherichia coli	27	55.5	88.9	7.4	7.4	14.8	33.3	66.7	66.7	25.9	0	77.8

ESBL: extended spectrum beta lactamase; P/T: piperacillin tazobactam; CAZ: ceftazidime; M: meropenem; IMP: imipenem; ETP: ertapenem; CP: ciprofloxacin; GM: gentamicin; TO: tobramycin; AMK: amikacin; CO: colistin; SXT: sulphamethoxazole-trimetoprim.

(15.4%), while all isolates were susceptible to linezolid.

Discussion. In this cross-sectional study, the pathogens causing symptomatic HA-UTIs and their resistance patterns are evaluated. The most common isolated species were *Klebsiella* spp. followed by *E. coli* and *P. aeruginosa* isolates. Extended spectrum beta-lactamase production was present in 82.8% of the 48 *Klebsiella* species and 72.9% of the *E. coli* species. Among ESBL positive *E. coli* and *Klebsiella* species, the rate of meropenem (imipenem) resistance was 18.8% and 7.4% while ertapenem resistance was found to be higher and 45.9% in *Klebsiella* species and 14.8 in *E. coli* species.

Although the dominant pathogen in children was reported to be *E. coli*[15-20] in previous studies, *Klebsiella* species were the most common isolated organisms as HA-UTI pathogen in the current study. In a study of European Study Group on Nosocomial infections group including 298 patients, *E. coli* (35.3%) was the most commonly isolated organism, and *Klebsiella* spp. were reported as 9.8% of the pathogens.[20]

Emerging of resistance among uropathogens is increasingly reported within a variety of resistant patterns.[21,22] In this study, the rate of ESBL positive *Klebsiella* species was 82.8%, and meropenem resistance was 18.8%, while ertapenem resistance was reported to be 45.9%. In one study from our center which had focused on 335 ESBL-producing *Enterobacteriaceae* including 193 urinary tract pathogens, meropenem resistance was not reported, and ertapenem resistance was reported to be as low as 8.5% in 2009.[23] Although this was a cross-sectional comparison, a remarkable increase in resistance patterns for *Klebsiella* species was observed. As well as in other studies worldwide,[24-26] there is an undesirable trend toward the emergence of carbapenemase resistance. Since its first detection in 1996, carbapenemase-producing *Klebsiella pneumoniae* (KPC) had been an important medical problem, and the rate of KPC production was high enough to have serious concern.[24]

Although ESBL production was observed in 72.9% of the *E. coli* isolates in this study, the rate of carbapenem resistance was much lower compared to *Klebsiella* species. In one study from India reported a dramatic increase over the 5-year study period.[21] İlker et al. reported that 99% of the ESBL-producing *E. coli* isolates in their center during the period of 2009, was found to be susceptible to ertapenem and 100% to meropenem, however the ertapenem resistance increased to 14.8% and meropenem to 7.4% suggesting the emerging resistance during the last five years.[23]

The rates of resistance to aminoglycoside have a wide spectrum ranging from 8.3% to 43.8% in *Klebsiella* species and from 6% to 66.7% in ESBL positive *E. coli* isolates. Resistance to colistin in *E. coli* isolates was not observed. The use of amikacin monotherapy for UTI with ESBL-producing bacteria in children is limited, and Polat et al. reported that this treatment regimen might be a reasonable alternative.[27] In our study, the resistance patterns suggested that the selection of the type of aminoglycoside is also important due to different resistance patterns.

This study has some limitations due to its retrospective design. The study included resistance patterns of the common pathogens of nosocomial UTI and did not focus on mortality and treatment response. Secondly, the timeline trends of resistance patterns for specific bacteria were not compared due to the cross-section pattern, while the data including current study was compared to the previous study from our center in 2009.

Most epidemiological data on nosocomial resistance patterns are limited to adult studies and generally focused on studies about nosocomial CA-UTI. In our study emerging meropenem resistance in *P. aeruginosa*, ESBL production and higher rates of ertapenem resistance in ESBL positive ones in *E. coli* and *Klebsiella* species, in nosocomial UTI are important notifying signs for the development of superbug infections also in children in the future.

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