

INCREASE RESISTANT RATES AND ESBL PRODUCTION BETWEEN *E. COLI* ISOLATES CAUSING URINARY TRACT INFECTION IN YOUNG PATIENTS FROM IRAN

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ABSTRACT

Emerging antimicrobial resistance rates and Extended-spectrum beta-lactamase producing *Escherichia coli* recovered from urinary tract infections (UTI) is an increasing problem in specific regions, limiting therapeutic options. One hundred *E. coli* isolates causing UTI in patients with age from 2 months to 12 years admitted at CMC in the period of April 2009 to March 2010 were tested for antibiotic susceptibility using the disk diffusion method. Surprisingly high resistance rates were recorded for *E. coli* against TMP/SMX (84%), cefalotin (66%), cefuroxime (50%), cefixime (50%) and ceftriaxone (45%). Antimicrobial susceptibility of *E. coli* isolates was followed by meropenem (98%), amikacin (95%), nitrofurantoin (91%) and gentamicin (68%). Extended spectrum beta-lactamase production, was observed in 32% of community and 42% of nosocomial isolates. The results of this study and numerous observations regarding the increasing resistance to these antibiotics, in several countries, emphasize the need for local population-specific surveillance for guiding empirical therapy for UTI in children.

Key words: *E. coli*, Urinary Tract Infection, Antimicrobial susceptibility, ESBL

Urinary tract infection (UTI) is one of the most common bacterial diseases in children. Early diagnosis and quick antimicrobial treatment are required to minimize renal scarring and progressive kidney damage. In patients with suspected UTI, antibiotic treatment is usually started empirically, before urine culture results are available. Unfortunately, antibiotic resistance has become an increasingly critical problem in many countries like Iran (1,2).

A significant emerging problem is the Extended spectrum

beta-lactamase (ESBL) mechanism of resistance (3). ESBLs are beta-lactamases that hydrolyze extended spectrum cephalosporins with an oxyimino side chain (4). The present study was carried out with one hundred *E. coli* consecutive isolates (nonduplicate) originating from the urinary tract infections collected from April 2009 to March 2010.

The Children Medical Center (CMC) is a referral tertiary teaching hospital admitting patients from all regions of Iran.

The study population consisted of all patients (50 hospitalized

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and 50 community acquired) having positive urine cultures with a colony count of $\geq 10^5$ colony forming units per milliliter for midstream urine samples, $\geq 10^4$ for samples collected by catheter from infants and small children and growth of any count of bacteria for samples obtained as bladder punctures via suprapubic aspiration (5). Community acquired isolates were defined as a culture collection from a patient not admitted to the hospital whilst samples originating from patients hospitalised for 48 hrs or more on general or specialized wards were considered nosocomial. All *E. coli* isolates were microbiologically identified in the microbiology laboratory of CMC using standard biochemical identification methods (6). These samples had been processed on blood agar and MacConkey medium with a standard loop and were incubated at 37°C overnight.

The minimum inhibitory concentrations (MIC) of cefalotin, gentamicin, cefixime, cefuroxime, trimethoprim/sulfamethoxazole, meropenem, nitrofurantoin, ceftriaxone and amikacin were determined by using the E-test (AB bioMérieux, Solna, Sweden). Also ESBLs were detected by phenotypic confirmation with ceftazidime, ceftazidime-clavulanate and cefotaxime, cefotaxime-clavulanate disks, as recommended by the NCCLS (6). All statistical analysis was performed using SPSS software, version 11.5 and P-value <0.05 indicating significance.

The antimicrobial susceptibility for 9 selected antimicrobial agents of different classes against *E. coli* isolates were summarized in Table 1. Meropenem (98%), amikacin (95%) and nitrofurantoin (91%) showed highest percent susceptibility against *E. coli* in this study. The high resistance rates against trimethoprim-sulfamethoxazole (84%), cefalotin, cefuroxime, cefixime ($>50\%$) was also observed among these isolates.

This study and also the previous report of our center shows that there are some differences between the rate of antimicrobial resistance in Tehran and all other places in the world (7-9).

The spread of antimicrobial resistance among bacterial pathogens in Iran has emerged as an important challenge for the Iranian medical community. The increasing frequency of trimethoprim-sulfamethoxazole resistance is troublesome. The prevalence of resistance to this antibiotic has increased during the past decade (10-14). Aminzadeh, Kashef and their colleagues reported resistance rate of 50% and 62% to trimethoprim-sulfamethoxazole in Tehran (13, 14). The high resistance rate in our study seems to be result of widespread antibiotic usage of families even in the absence of prescription.

In this study the rate of resistance to amikacin was too low, therefore this agent can be a good choice for the empirical treatment of UTI in our population. Nitrofurantoin is considered as one of the oldest urinary anti-infective drugs in use, surprisingly, resistance to this drug remains minimal. As seen in Table 1, the overall resistance was 8%. The lack of resistance may be related to the fact that nitrofurantoin has multiple mechanisms of action, requiring organisms to develop more than a single mutation in order to develop resistance. In addition, in Iran limited usage of this drug for treating uncomplicated cystitis especially in children may also be a contributing factor to the lack of development of widespread resistance (15,16). Among bacterial isolates from children with UTI in our study resistance to meropenem was the least. This might be due to the limited usage of these antibiotics in our population.

Alarming high proportions of resistance to cephalosporins were found in our study. 64% and 68% to cefalotin, 36% and 64% to cefuroxime and cefixime, 34% and 56% to ceftriaxone for community and nosocomial isolates, respectively. The differences were statistically significant in both group to these antibiotics ($P<0.05$). In many countries such as our country, cephalosporins are the favorite antimicrobial agents for the empirical treatment of UTI and there is much evidence suggesting a relationship between prescribing habits and antibiotic resistance (17).

We found that 37% of isolates produced ESBL (32% for

community and 42% of nosocomial isolates).

Some surveys suggest that the overall rate of ESBL phenotypes is comparatively low. Distribution of ESBL-positive UTIs in Turkey was 3.6% in 2004, 3.9% in 2005, and 4.2% in 2006 (18). The ESBL rates are higher than some Middle East countries and other researchers from developed countries where ESBL production rates are less than 5% (18-22). The increasing frequency of ESBL phenotypes is an emerging problem and hospitalization, previous bacterial

infection, urinary abnormalities, previous antimicrobial treatment (especially third-generation cephalosporins), recurrent tract infections, and presence of high-level and multi-drug resistance have already been described as risk factors (23).

Our findings highlight the importance of access for clinicians especially in developing countries such as Iran to updated bacterial susceptibility data regarding commonly prescribed agents.

Table 1. Antimicrobial susceptibility testing results of *E. coli* isolates

Antibiotic	Nosocomial			Community			All			MIC50	MIC90
	R%	I%	S%	R%	I%	S%	R%	I%	S%		
Trimethoprim/sulfamethoxazole	78	-	22	90	-	10	84	-	16	32	32
Gentamicin	18	10	72	30	6	64	24	8	68	0.5	32
Cefalotin	52	12	36	64	4	32	58	8	34	256	256
Cefuroxime	36	-	64	62	2	36	49	1	50	15	256
Cefixime	34	2	64	58	6	36	46	4	50	1.25	256
Amikacin	4	-	96	4	2	94	4	1	95	2	8
Nitrofurantoin	10	-	90	6	2	92	8	1	91	8	32
Meropenem	2	2	96	-	-	100	1	1	98	0.023	0.226
Ceftriaxone	34	-	66	56	-	44	45	-	55	0.18	32

R= Resistant
I= Intermediate
S= Sensitive

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