

Cross-resistance and associated resistance in *Escherichia coli* isolates from nosocomial urinary tract infections between 2004-2006 in a Turkish Hospital

Research Article

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Abstract: In this study, antimicrobial resistance profiles were determined for 748 isolates of *Escherichia coli* from patients with acute nosocomial urinary tract infections (UTIs) at a Turkish Training Hospital. Thirteen antibiotics were included. Resistance to ampicillin alone (45.1%) and ciprofloxacin alone (20.6%) were the most commonly identified 'single resistances'. Multiple resistance was found in 49.7% of the strains. The most common multiple antibiotic resistance profiles included ampicillin-sulbactam/amoxycilline-clavulonate (4.0%) and ampicillin-sulbactam/trimethoprim-sulfamethoxazole/amoxycilline-clavulonate (2.8%). From 2004 to 2006, ampicillin, trimethoprim-sulfamethoxazole and ciprofloxacin resistant strains increased to 76% from 57%, 53% from 43% and 55% from 41%, respectively. The percentage of extended-spectrum β -lactamase (ESBL) producing strains was 7.8% and imipenem resistance was seen in 5.2% of ESBL positive strains. We conclude that clinically important *E.coli* strains have now emerged with broader multidrug resistance. Periodical evaluation of laboratory results and clinical surveillance are crucially important for optimal antibiotic management of UTIs and infection control policies.

Keywords: *Escherichia coli* • Antibiotic resistance • Cross-resistance • Associated resistance

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1. Introduction

Urinary tract infections (UTIs), both nosocomial and community-acquired, remain a worldwide therapeutic problem. The most common pathogens include *Escherichia coli* (*E.coli*), other gram-negative bacilli and *Enterococcus* spp. [1]. Surveillance of the antimicrobial susceptibility of bacterial pathogens causing nosocomial urinary tract infection (UTI) is crucially important in

developing countries where UTIs are the most common nosocomial infection. National and international surveillance programmes are necessary to monitor the level of antimicrobial resistance [2]. According to the data obtained in a questionnaire from 228 hospitals in 29 European countries, the most frequent pathogen was identified as *E.coli* (35.6%), where 54.8% of isolates were resistant to ampicillin, 28% to co-trimoxazole and 9% to ciprofloxacin [3]. Alarming, significant ampicillin resistance (72.6%), cotrimoxazole resistance (77.9%)

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and norfloxacin resistance (78.4%) in *E. coli* strains were also reported [4]. Most susceptibility surveys report only overall percentage resistance/susceptibility rates and only a few surveys report information on cross-resistance or give details of associated resistance profiles. In this paper, detailed information on the resistance profiles of 748 *E. coli* isolates from a Turkish Training Hospital are given, including data on the changing profile of antibacterial resistance during the three year period from 2004-2006.

2. Materials and Methods

2.1. Study Population

This study was performed by focusing on nosocomial UTIs in which the causative pathogen was presumed to be *E. coli*. All patients who participated in the study gave informed consent under approval from local authorities. Patients between ages 16 and 75 with symptoms of nosocomial UTI who were hospitalized in Gulhane Military Medical Academy Haydarpasa Training Hospital were eligible to participate. Presumptive nosocomial UTI diagnosis was given according to CDC criteria [5]. Patients with community-acquired UTI diagnosed before the hospitalization, with abnormal urine analysis at the day of hospital admission, or who had undergone any surgical or urological procedure before the diagnosis of UTI were excluded. Patients who had received oral or systemic antibiotics, been hospitalized in a 2-week period before the onset of symptoms, had urinary tract abnormalities or other complicating factors or who were pregnant were not evaluated. Concomitant isolates from the same patient were excluded from the analysis. All *E. coli* strains isolated from patients who fulfilled the aforementioned criteria were investigated.

2.2. Urine sampling procedures

Urine sampling was carried out for all the eligible patients. First, patients were required to provide a freshly voided midstream urine sample. Immediately after sampling, the urine was tested for leucocytes using a commercial system for urinalysis (Multistix 2™, Bayer Corporation, USA); results were recorded as “negative”, “trace”, +, ++ or +++, as instructed by the manufacturer. A Uricult™ dip-slide (Orion Diagnostica, Finland) was prepared according to the manufacturer's instructions and, without prior incubation, immediately forwarded by courier to the microbiology laboratory for incubation, quantification and identification. After identification, susceptibility tests of all isolates were carried out by the Kirby-Bauer disk diffusion method according to CLSI criteria, formerly known as NCCLS [6].

2.3. Quantitative assessment of urine cultures

All the urine samples were classified as negative or positive in accordance with the guidelines for testing issued by the Infectious Diseases Society of America (IDSA) [7]. A urine sample containing between $\geq 10^3$ and $< 10^5$ cfu/mL and positive for the presence of pyuria or a sample containing $\geq 10^5$ cfu/mL irrespective of the presence of pyuria was defined as positive. Pyuria was defined as ‘trace’ or more as determined with the Multistix 2 system (Bayer Corporation, Diagnostics Division, Elkhart, IN, USA). For the purposes of this report, all isolates with bacterial counts of $\geq 10^3$ cfu/mL were included irrespective of the presence of pyuria.

2.4. Identification of Bacteria

All bacteria detected in urine samples at $\geq 10^3$ cfu/mL were identified by their biochemical reaction profile using classical biochemical methods and APIU (spell out acronym) (Biomérieux, France) identification products [8]. In the case of mixed cultures, no more than two bacterial species (those with the two highest counts) were identified. Bacteria cultured at $< 10^3$ cfu/mL were excluded from this study. Identified bacteria were stored on microbeads at -70°C .

2.5. Antimicrobial susceptibility testing

The antimicrobial susceptibility of bacteria was determined using the disc diffusion method as described by the CLSI criteria, formerly known as NCCLS [6]. Isosensitest agar and antibiotic discs were obtained from Oxoid Limited (Basingstoke, UK). Inhibition zone diameters were measured to the nearest millimetre with a slide gauge. *E. coli* ATCC 25922 was used as a control strain. Test results were only accepted when inhibition zone diameters of the control strains were within performance ranges [6].

All bacteria were tested against the following antimicrobial agents: ampicillin, co-amoxiclav, cephazolin, ceftazidim, ceftriaxone, cefepim, ciprofloxacin, amikacin, gentamicin, imipenem, meropenem, nitrofurantoin, and trimethoprim-sulfamethoxazole. Disc strengths, zone diameter breakpoints and corresponding MIC breakpoints were published in the interim report [9]. In the case of mixed culture, only the major pathogen was tested.

2.6. Statistical analysis

The statistical significance tests of differences between antibacterial susceptibility and study year were carried out using analysis of variance. To adjust for multiple comparisons, the method of Tukey was used. Two-tailed χ^2 tests were also used for comparisons of antibacterial susceptibility results according to pathogens and years.

Table 1. Common cross-resistance and associated resistance of inpatient isolates.

Single agent susceptibility ^a	Antimicrobial resistance (%)												
	AMP	CFZ	GEN	AK	AMC	FEP	CIP	CAZ	CRO	MER	IMP	NIT	SXT
AMP -S (n=275)	0	10.9	14.2	4.0	12.0	2.2	22.9	3.6	3.6	0.7	0.7	3.6	18.9
AMP -R (n=473)	100	46.3	37.2	7.2	70.6	22.8	57.1	26.4	30.0	0.8	4.7	12.9	60.5
CFZ -S (n=499)	50.9	0	20.0	3.0	31.1	1.6	30.9	2.6	2.6	0.0	0.4	4.6	34.3
CFZ -R (n=249)	88.0	100	46.2	12.0	85.1	42.6	71.9	49.0	55.8	2.4	8.8	19.3	67.1
GEN - S (n=533)	55.7	25.1	0	2.6	40.3	9.2	34.0	10.7	12.9	0.7	1.3	6.0	36.6
GEN - R (n=215)	81.9	53.5	100	14.4	70.7	30.2	70.7	36.3	36.6	0.9	7.9	18.1	66.5
AK - S (n=703)	62.4	31.2	26.2	0	47.8	12.2	43.2	16.1	19.1	0.4	2.1	8.5	44.7
AK - R (n=45)	75.6	66.7	68.9	100	68.9	31.1	64.4	48.9	40.0	6.7	20.0	24.4	53.3
AMC -S (n=381)	36.5	9.7	16.5	3.7	0	2.6	26.0	3.4	3.8	0.5	1.3	4.7	26.5
AMC - R (n=367)	91.0	57.8	41.4	8.4	100	28.3	63.8	33.2	37.6	1.1	5.1	14.4	64.6
FEP - S (n=634)	57.6	22.6	23.7	4.9	41.5	0	37.1	5.8	7.4	0.5	2.1	9.0	40.9
FEP - R (n=114)	94.7	93.0	57.0	12.3	91.2	100	86.0	86.0	92.1	2.6	9.6	12.3	69.3
CIP - S (n=415)	6.7	6.5	3.9	0.7	6.0	3.1	0	4.3	5.1	0.7	1.7	2.0	6.0
CIP - R (n=333)	81.1	53.8	45.6	8.7	70.3	29.4	100	32.7	36.6	0.9	5.1	15.3	68.1
CAZ - S (n=613)	56.8	20.7	22.3	3.8	40.0	2.6	36.5	0	4.9	0.3	1.1	7.8	40.6
CAZ - R (n=135)	92.6	90.4	57.8	16.3	90.4	72.6	80.7	100	90.4	3.0	12.6	17.0	65.9
CRO - S (n=596)	55.5	18.5	22.1	4.5	38.4	1.5	35.4	2.1	0	0.3	1.1	7.9	39.0
CRO - R (n=152)	93.4	91.4	54.6	11.8	90.8	69.1	80.3	80.3	100	2.6	11.2	15.8	69.7
MER - S (n=742)	63.2	32.7	28.7	5.7	48.9	15.0	44.5	17.7	19.9	0	2.4	9.2	44.9
MER - R (n=6)	66.7	100	33.3	50.0	66.7	50.0	50.0	66.7	66.7	100	100	50.0	83.3
IMP - S (n=724)	62.3	31.4	27.3	5.0	48.1	14.2	43.6	16.3	18.6	0	0	8.8	43.8
IMP - R (n=24)	91.7	91.7	70.8	37.5	79.2	45.8	70.8	70.8	70.8	25.0	100	29.2	87.5
NIT - S (n=677)	60.9	29.7	26.0	5.0	46.4	14.8	41.7	16.5	18.9	0.4	2.5	0	42.2
NIT - R (n=71)	85.9	67.6	54.9	15.5	74.6	19.7	71.8	32.4	33.8	4.2	9.9	100	73.2
SXT - S (n=410)	45.6	20.0	17.6	5.1	31.7	8.5	25.9	11.2	11.2	0.2	0.7	4.6	0
SXT - R (n=338)	84.6	49.4	42.3	7.1	70.1	23.4	67.2	26.3	31.4	1.5	6.2	15.4	100

n, number of isolates; (AMP) Ampicillin; (AMC) Amoxicillin-clavulanic acid; (CFZ) Cefazolin; (CAZ) ,Ceftazidime; (CRO) Ceftriaxone; (FEP) Cefepime; (CIP) Ciprofloxacin; (AK) Amikacin; (GEN) Gentamicin; (MER) Meropenem; (IMP) Imipenem; (NIT) Nitrofurantoin, (SXT) Sulfamethoxazole/Trimethoprim. ^aFor each agent the first line gives antimicrobial resistance rates for *E.coli* susceptible (S) to the agent and the second line the rates for isolates resistant (R) to the agent. Cross-resistance (shown in italics) and associated resistance are defined in the text.

3. Results

From 01 January 2004 to 31 December 2006, a total of 748 *E. coli* isolates were recovered from UTI cases. Of all the patients, 463 (61.9%) were female (mean age 47), and 285 (38.1%) were male (mean age 42).

Of 748 *E. coli* isolates, only 150 (20.1%) were fully susceptible to the agents investigated. Overall, 102 (13.6%) isolates were resistant to only one agent, which was most commonly either ampicillin (45.1%) or ciprofloxacin (20.6%). Table 1 shows the data for cross-resistance and associated resistance.

Our results revealed that the resistance to any agent was associated with increased resistance to the other agents tested. This was naturally more pronounced for related drugs (complete or partial cross-resistance) but was also clearly evident among drugs totally unrelated

to each other. As an example, amikacin resistance was 8.7% in *E. coli* resistant to ciprofloxacin but only 0.7% in susceptible *E. coli*. Similarly, imipenem resistance was 5.1% in *E. coli* resistant to ciprofloxacin compared with 1.7% in susceptible organisms (Table 1).

Ampicillin and ciprofloxacin resistance were more common in male patients whereas ampicillin and trimethoprim-sulfamethoxazole resistance were more frequent in the female patients. Ampicillin, ciprofloxacin and trimethoprim-sulfamethoxazole resistance were the most common phenotypes in male population regardless of age. Amoxycilline-clavulonate resistance was more frequent in patients over 40 in both sexes. For females under the age of 41, ampicillin and trimethoprim-sulfamethoxazole resistance were common whereas ampicillin and amoxycilline-clavulonate resistance were more frequent in older women (Table 2).

Table 2. The distribution of antimicrobial resistance in nosocomial *E.coli* isolates according to age and gender.

RESISTANCE (%)														
GENDER AND AGE	n	AMP	CFZ	GEN	AK	AMC	FEP	CIP	CAZ	CRO	MER	IMP	NIT	SXT
MALE (16-40)	114	37	11	11	1,8	2,6	2,6	27	2,6	4,4	0	0	7	23
MALE (41-75)	171	82	52	40	7	83	26	61	33	36	1,2	6,4	12	63
FEMALE (16-40)	134	41	25	26	3,7	38	11	30	12	11	0,7	3	9,7	54
FEMALE(41-75)	329	72	35	30	7,9	52	16	48	18	21	0,9	2,7	9,1	40

n, number of isolates; (AMP), ampicillin; (AMC), amoxicillin-clavulonic acid; (CFZ), cefazolin; (CAZ), ceftazidime; (CRO), ceftriaxone; (FEP), cefepim; (CIP), ciprofloxacin; (AK), amikacin; (GEN), gentamicin; (MER), meropenem; (IMP), imipenem; (NIT), nitrofurantoin, (SXT) trimethoprim-sulfamethoxazole.

Table 3. The most common co-resistant phenotypes of *E.coli* urinary isolates.

Co-resistant phenotype	Co-resistant isolates (n)	Co-resistant isolates according to age and gender				Co-resistant isolates (%)	All isolates (%)
		MALE	MALE	FEMALE	FEMALE		
		(16-40)	(41-75)	(16-40)	(41-75)		
		(n)	(n)	(n)	(n)		
AMP, AMC	30	1	13	0	16	6,4	4,0
AMP, SXT	21	4	3	10	4	4,2	2,8
AMP, CIP	9	2	0	0	7	1,8	1,2
AMP, AMC, SXT	21	0	5	7	9	4,2	2,8
AMP, CIP, SXT	14	4	0	0	10	2,8	1,9
AMP, AMC, CFZ	10	1	2	0	7	2,0	1,3
AMP, AMC, SXT, CIP	20	0	10	2	8	4,0	2,7
AMP, GEN, CIP, SXT	10	4	1	1	4	2,0	1,3
AMP, AMC, CFZ, SXT	7	0	4	1	2	1,4	0,9
AMP, AMC, CIP, SXT, GEN	20	0	8	1	11	4,0	2,7
AMP, AMC, CFZ, CIP, SXT	8	0	6	0	2	1,6	1,0
AMP, AMC, CIP, CFZ, GEN	3	0	0	0	3	0,6	0,4
AMP, AMC, CFZ, GEN, CIP, SXT	9	0	1	3	5	1,8	1,2

n, number of isolates; (AMP) Ampicillin; (AMC) Amoxicillin-clavulanic acid; (CFZ) Cefazolin; (CAZ) Cefepime; (CIP) Ciprofloxacin; (GEN) Gentamicin; (SXT) Sulfamethoxazole/Trimethoprim.

The most common and pronounced multiple resistance profiles in this study are shown in Table 3. Ampicillin/amoxycilline-clavulonate resistance was the most common phenotype, which was present in 6.4% of co-resistant and 4.0% of all isolates. The second most common were ampicillin/trimethoprim-sulfamethoxazole and ampicillin/amoxycilline-clavulonate/trimethoprim-sulfamethoxazole, which was present in 4.2% of co-resistant and 2.8% of all isolates. The least frequent profile was ampicillin/amoxycilline-clavulonate/ciprofloxacin/cefazolin/gentamicin, which was present in 0.6% of co-resistant and 0.4% of all isolates. Multiple resistance was found in 49.7% of the strains. The most common co-resistance pattern was observed in ampicillin and amoxycilline-clavulonate phenotypes in older males and females. In contrast, ampicillin and trimethoprim-sulfamethoxazole phenotypes were the most frequent co-resistance pattern in young males and

females. Ampicillin and ciprofloxacin co-resistance was more common in older females than in other populations (Table 3).

From 2004 to 2006, increased resistance was found against 9 of 13 tested agents. The highest increase in resistance was seen for amoxycilline-clavulonate (39% and 63%) and ceftazidim (12% and 30%). Antibacterial resistance decreased in amikacin, gentamicin, imipenem and meropenem during this three-year period. With the exception of imipenem and meropenem, the observed variations in resistance were statistically significant. Resistance to cephalosporins cefazolin, ceftazidim, ceftriaxone and cefepim was seen in 33%, 18%, 20% and 15% of isolates, respectively (Table 4).

Extended-spectrum β -lactamase activity was found 7.75% of the strains. Three (5.2%) of the ESBL producing strains were resistant to imipenem.

Table 4. Comparison of antimicrobial resistance in nosocomial *E. coli* between 2004 – 2006.

YEARS (n)	RESISTANCE (%)												
	AMP	AMC	CFZ	CAZ	CRO	FEP	CIP	AK	GEN	IMP	MER	NIT	SXT
2004 (252)	57	39	34	12	17	9	41	10	33	8	1	8	43
2005 (236)	56	44	24	11	15	9	37	4	21	2	1	12	39
2006 (260)	76	63	41	30	29	27	55	3	31	1	0	9	53
TOTAL (748)	63	49	33	18	20	15	45	6	29	3	1	9	45
P	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.007	0.001	0.199	0.183	0.007

P, p value; n, number of isolates; (AMP), ampicillin; (AMC), amoxicillin-clavulonic acid; (CFZ), cefazolin; (CAZ), ceftazidime; (CRO), ceftriaxone; (FEP), cefepim; (CIP), ciprofloxacin; (AK), amikacin; (GEN), gentamicin; (MER), meropenem; (IMP), imipenem; (NIT), nitrofurantoin; (SXT) trimethoprim-sulfamethoxazole.

4. Discussion

This study has confirmed the suspected increased resistance to ampicillin, amoxicillin-clavulanic acid, ciprofloxacin and trimethoprim-sulfamethoxazole in *E. coli* causing nosocomial UTIs in our hospital. Resistance against these antibiotics was seen in over 40% of isolates. Ampicillin and amoxycilline-clavulonate resistance were the most common resistances, both as single resistances (63% and 49%) and as part of a phenotype with two or more resistances. The most common associated resistance involved ampicillin with amoxycilline-clavulonate, alone and linked with resistance to trimethoprim-sulfamethoxazole. The association of ampicillin with trimethoprim resistance has been present for many years and is known to be plasmid-linked [9]. However, the most common associated resistance was seen for ciprofloxacin and ampicillin, alone and linked with resistance to amoxycilline-clavulonate and trimethoprim-sulfamethoxazole. This resistance profile is more common in our hospital than ampicillin and ciprofloxacin resistance. These results indicated that multiple resistance in our intensive care unit (ICU) appears to be based on the association of ampicillin, amoxycilline-clavulonate, trimethoprim-sulfamethoxazole and ciprofloxacin resistance profiles. Furthermore, ciprofloxacin resistant *E. coli* strains have the potential for multiple resistance. It would thus seem logical that increased use of ampicillin in community-acquired uncomplicated UTIs, any sulphonamide, trimethoprim or the combination of sulphonamide and trimethoprim selects for resistance to any and all of these drugs. The fact that high consumers of ampicillin or trimethoprim-sulfamethoxazole have the highest rates of ciprofloxacin resistance could indicate that this drug,

by the partial cross-resistance that is easily observed, selects for the multiple resistant pattern.

Fluoroquinolone resistance is an increasing problem in ICUs of some European countries [10,11], where it has been reported that resistance to this agent could be fostered by the use of ampicillin/amoxicillin, sulfamethoxazole and trimethoprim-sulfamethoxazole [12]. Our results also indicate that a multiple-resistant phenotype including fluoroquinolone resistance is now present in hospital flora.

The role of the unit of hospitalization has rarely been studied. Sotto *et al.* [13] showed that sulfamethoxazole resistance was higher in isolates from the ICU. Nosocomial acquisition was not found to be a risk factor for resistance in the study. In a comparative study of nosocomial and community-acquired bacteremias due to *E. coli*, Olesen *et al.* [14] did not find major differences. However, according to Perrin *et al.* [15], the rates of resistance to amoxicillin clavulonate, floxacillin, and sulfamethoxazole for *E. coli* strains responsible for nosocomial UTIs were higher than those for strains responsible for community-acquired UTIs. Antimicrobial resistance reports of nosocomial UTIs from Turkey indicate an ampicillin resistance frequency of 50.3% – 82% and trimethoprim-sulfamethoxazole resistance frequency of 36.7%-61% according to various authors [16-21]. Although ciprofloxacin resistance generally has been reported in the range of 13-35.5% [16-18,20,21], a higher rate of 47% was reported in 2006 [19]. Our results also reveal an increasing level of amoxycilline-clavulonate resistance when compared to these previous studies (14.6 - 52%) [16,18-20]. The studies cited and our results indicate that significant resistance against ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole and amoxycilline-clavulonate exists for *E. coli* related nosocomial UTI.

Increasing resistance was also noted for ceftriaxone, ceftazidim and cefepim. This is probably due to the increase of ESBL producing isolates. Especially in recent years, cephalosporins such as cefuroxime and cefixime have become preferred antibiotics for the empirical treatment of not only UTI but also community-acquired respiratory infections. The emergence and spread of ESBL activity in *E.coli* strains are complicating the treatment of serious nosocomial infections and certain species have become resistant to most currently available agents. The resistance in *E.coli* is typically caused by the acquisition of plasmids containing genes that encode for ESBL and these plasmids often carry other resistance genes as well. For this reason, quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole are generally not appropriate initial therapeutic choices for serious infection caused by ESBL-producing *E.coli* strains [22]. Our results also demonstrate the real risk that treatment of infections caused by ESBL-producing *E.coli* strains may be compromised due to multidrug resistance.

Carbapenems are currently considered to be the preferred agents for treatment of serious infections caused by ESBL-producing *E.coli* strains. Carbapenem

resistance is currently rare among these, but expression of AmpC or class A (TEM or SHV-type) ESBLs plus loss of outer-membrane proteins have been observed in recent years [22]. Resistance to carbapenem has also been reported in *E.coli*-producing class B-beta lactamases (metallo-beta-lactamase) in various countries, including the USA and Greece [23,24]. In our study, 5.2% of the ESBL-producing strains were resistant to imipenem. Furthermore, all of those were isolated in 2006. This finding shows that ESBL-producing *E.coli* strains are emerging and spreading in our hospital settings.

In conclusion, our study indicates that treatment of nosocomial UTIs in the Turkish population should be revised, and ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole and amoxycilline-clavulonate should not be preferred as an empirical treatment of choice. It is also evident that clinically important *E.coli* strains have now emerged with broader multidrug resistance than has ever before been observed. For this reason, stricter infection control policies should be implemented, and the therapeutic strategies for infection treatment should be carefully formulated.

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