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A pooled analysis of the resistance patterns of *Escherichia coli* strains isolated from urine cultures in Turkey: a comparison of the periods 1997-2001 and 2002-2007

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Aim: To compare the resistance patterns of *Escherichia coli* strains reported to be isolated from urine cultures in published medical literature from Turkey in 1997-2001 and 2002-September 2007.

Materials and methods: To find the published series, 3 national databases (Ulakbim Turkish Medical Literature database, http://www.turkishmedline.com, http://medline.pleksus.com.tr), and 2 international databases (Pubmed and Science Citation Index (SCI)) were searched.

Results: Data for 25,577 *E. coli* strains were obtained from 53 articles (28 articles from 1997-2001, 25 from 2002-2007). Of these strains 18,106 were isolated from outpatients, whereas 7471 were from inpatients. When the strains isolated from outpatients were evaluated, there was a significant increase in the ciprofloxacin resistance, whereas there was a significant decrease in amikacin, netilmicin, and co-trimoxazole resistance ($P < 0.05$). When the data of hospitalized patients were analyzed, there was significant decrease in amikacin, gentamicin, netilmicin, co-trimoxazole, and amoxicillin/clavulanate resistance, whereas a significant increase was observed in nitrofurantoin resistance ($P < 0.05$). The ESBL rate increased in both the inpatients and outpatients ($P < 0.05$).

Conclusion: When looked at from Turkey's perspective, our data suggest that aminoglycosides and third-generation cephalosporins may be good choices in the treatment of inpatients. Fosfomycin/tromethamine, nitrofurantoin, and oral third-generation cephalosporins may be reasonable alternatives in the empirical treatment of uncomplicated outpatient cases. Policies to constrain resistance in both the community, and hospitals, such as antibiotic stewardship or restriction programs, should be implemented immediately.

Key words: *E. coli*, Turkey, urinary tract infections

Türkiye'de idrar kültürlerinden izole edilen *Escherichia coli* kökenlerinde direnç durumlarının havuz analizi: 1997-2001 ve 2002-2007 dönemlerinin karşılaştırılması

Amaç: Bu çalışmada; 1997-2001 ve 2002- Eylül 2007 dönemlerinde Türkiye'de yapılmış olan yayınlardaki üriner sistem enfeksiyonlarından izole edilen *Escherichia coli* kökenlerinin direnç durumlarının karşılaştırılması amaçlanmıştır.

Yöntem ve gereç: Yayımlanmış olan makaleler üç ulusal veri tabanı (Ulakbim Türk Medikal Literatür veritabanı, http://www.turkishmedline.com, http://medline.pleksus.com.tr) ve iki uluslar arası (Pubmed and Science Citation Index) veri tabanında taranmıştır.

Bulgular: Toplam 53 makalede (1997-2001 döneminden 28 makale, 2002-2007 döneminden 25 makale) 25577 *E. coli* kökenine ait veriye ulaşılmıştır. Bu kökenlerden 18.106'sı poliklinik hastalarından, 7471'i yatan hastalardan izole

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edilmiştir. Poliklinik hastalarından izole edilen kökenler değerlendirildiğinde siprofloksasin direncinde önemli bir artış görülürken amikasin, gentamisin, netilmisin ve kotrimoksazol direncinde anlamlı bir azalma görülmüştür. Hastanede yatan hastaların verileri analiz edildiğinde amikasin, netilmisin, kotrimoksazol ve amoksisilin/klavulonat direncinde anlamlı azalma izlenirken, nitrofurantoin direncinde anlamlı bir artış gözlenmiştir.

Sonuç: Türkiye perspektifinden bakıldığında verilerimiz aminoglikozit ve üçüncü kuşak sefalosporinler yatan hastalarda iyi seçenekler olabileceğini düşündürmektedir. Komplike olmayan hastaların ampirik tedavisinde fosfomisin/trometamin, nitrofurantoin ve oral üçüncü kuşak sefalosporinler uygun alternatifler olabilir. GSBL oranı yatan hastalarda ve poliklinik hastalarında artmaktadır. Toplumda ve hastanede direnç oranlarını sınırlamak için antibiyotik yönetim politikaları ya da kısıtlama programları acilen uygulamaya konulmalıdır.

Anahtar sözcükler: *E. coli*, Türkiye, üriner sistem enfeksiyon

Introduction

Urinary tract infections (UTIs) are among the most common infectious diseases diagnosed in outpatients, and constitute the most common of nosocomial infections in many hospitals. *Escherichia coli* remains the principal causative pathogen of UTIs in both outpatients and inpatients (1). UTIs are also common indications for empirical antibiotic prescriptions. Trimethoprim/sulfamethoxazole, ciprofloxacin, semi-synthetic penicillins with or without inhibitors, nitrofurantoin, and fosfomycin tromethamine are the most commonly used antibacterial drugs in the treatment of community-acquired UTIs (2). Antimicrobial resistance is increasing in bacteria isolated from both nosocomial and community-acquired UTIs (3). Extended spectrum beta-lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae* are growing problems in many parts of the world (4,5).

The antimicrobial susceptibility of urinary pathogens has changed over the years and is influenced by such factors as the changing patient population and the extensive and inappropriate use of antimicrobial agents. Moreover, there are considerable geographic variations in bacterial patterns and resistance properties depending on local antimicrobial prescription practices. For these reasons, empirical antibiotic selection should be based on the knowledge of the local prevalence of bacterial organisms and antibiotic sensitivity patterns rather than on universal guidelines (6).

In this study, the aim was to analyze the resistance patterns of *E. coli* strains reported to be isolated from urine cultures in published medical literature between 1997 and September 2007 from Turkey.

Materials and methods

To find the published series, 3 national (Ulakbim Turkish Medical Literature database, http://www.turkishmedline.com, http://medline.pleksus.com.tr) and 2 international databases (Pubmed and Science Citation Index-Expanded (SCI-e)) were searched. Key words for the national databases were ["idrar yolu infeksiyonu", "idrar yolu enfeksiyonu", "üriner sistem infeksiyonu" ,"üriner sistem enfeksiyonu", or "urinary tract infection"]. Key words for Index Medicus and SCI were ["urınary tract infection" and "Turkey"]. In cases of presentations from a single study with intersecting periods, the one covering a longer period was chosen. Articles published before 1997 were excluded. In all studies, isolated bacteria were identified by standard laboratory techniques, and antibiotic susceptibility tests were performed by Kirby-Bauer disc diffusion method according to the National Committee for Clinical Laboratory Standards (NCCLS), and Clinical Laboratory Standards Institution (CLSI) criteria (7).

Resistance data of strains isolated from outpatients and hospitalized patients were evaluated separately. All data were analyzed with SPSS for Windows, version 13.00. Pooled resistance data of strains related to 1997-2001, and 2001-2007 were compared using the chi-square test. A P value less than 0.05 was considered significant.

Results

Our search yielded 53 articles (28 articles from 1997-2001, 25 from 2002-2007), which consisted of a total of 25,577 *E. coli* strains. Of these 25,577, 18,106

were isolated from outpatients, whereas 7471 were isolated from inpatients (1-3,8-57). A comparison of resistance rates of strains isolated from outpatients and inpatients is shown in Tables 1 and 2.

When the strains isolated from outpatients were evaluated, there was a significant increase in gentamicin and ciprofloxacin resistance, whereas there was a significant decrease in amikacin, netilmicin, and co-trimoxazole resistance. There was no significant difference for nitrofurantoin between the 2 periods. There was a decrease in amoxicillin/clavulanate and piperacillin/tazobactam resistances, and carbapenem resistance rates were low in both of the 2 periods (2.3% vs 1%).

When data of hospitalized patients were analyzed, there was significant decrease in amikacin, gentamicin, netilmicin, co-trimoxazole, and amoxicillin/clavulanate resistance, whereas a significant increase was observed in nitrofurantoin. Overall carbapenem resistance was low in the hospitalized cases as well (2.3% vs. 0.8%).

Discussion

E. coli is the most common aetiological agent in either community-acquired or hospital acquired UTI. The increasing prevalence of infections caused by antibiotic resistant *E. coli* makes empirical treatment of these infections more difficult (58). Hence, there exists a great need for antimicrobial resistance surveillance at the local, national, and international levels (59).

Our data suggest that aminoglycosides are still important in the empirical treatment of UTIs. Pooled data of 10 years in outpatients and inpatients yielded amikacin resistance rates of 6.1% and 6.8%, respectively. When 1997-2001 and 2002-2007 were compared, the resistant rates decreased significantly in both groups. While Puerto et al. (60) and Alhambra et al. (61) did not report amikacin resistant strains from Spain, Hernandez et al. (62) reported a resistance rate of 6.5% in ESBL-producing strains. Our results are similar to those of other Mediterranean countries**.** We may speculate that the decrease in aminoglycoside resistance may be because of probable low empirical therapy consumption rates, due to toxicity, obligatory use of parenteral route, and the narrow spectrum of this class.

Ciprofloxacin is among the most widely used agents in outpatient urinary tract cases due to its high bioavailability, concentration in the urinary system, and antibacterial spectrum (66). It is also a widely used agent in diarrhea and intra-abdominal infections. Resistance to ciprofloxacin was found to be 20.1% in outpatients and 31.7% in inpatients. When compared with 1997-2001, ciprofloxacin resistance increased significantly in both inpatients and outpatients in 2002-2007. This may be associated with the following: i) oral ciprofloxacin is widely used without any restriction, or ii) increasing ESBL rates, since ESBLs are often located on plasmids, which also carry QNR determinants (67). In studies carried out in Turkey, the quinolone resistance was found to be between 2.1% and 44.2% in community acquired UTIs (24,51). In studies reported from various countries, there were variable resistance rates. Marchese et al. reported a 12% ciprofloxacin resistance in *E. coli* strains isolated as UTI pathogens (68). Puerto et al., in a region experiencing a resistance problem from Spain, reported high resistance rates similar to our results (60). In a Brazilian multicenter study, ciprofloxacin resistance was reported to be 21.6% (64). Ciprofloxacin is one of the most important agents in the treatment of UTIs, but regional resistance rates should be kept in mind when using this agent in empirical therapy.

Nitrofurantoin resistance rates were similar in outpatients in 1997-2001 and 2002-2007. However, in inpatients there was a significant increase in 2002-2007. Resistance rates of nitrofurantoin reported from developing countries range between 6.9% and 31.6% (63-65,69). Rates such as 6.2% from Spain (70) and 3.7% from the UK (71) are also reported. Nitrofurantoin has been used for a very long time for the treatment of UTIs; however, the introduction of ciprofloxacin to the market has limited its consumption. The fact that nitrofurantoin is effective in both in vitro and clinical studies against ESBL and *E. coli* suggests that it may be an important and economical treatment option in the near future (44,72,73). Although non-significant, the decrease in nitrofuratoin resistance among strains isolated from outpatients strengthens this hypothesis, and suggests that it may be a reasonable choice in the empirical treatment of UTIs.

Table 1. The resistance rates of *E. coli* strains isolated from outpatients.

	1997-2001 % (Resistant/n)	2002-2007 % (Resistant/n)	Total % (Resistant/n)	P
Gentamicin	11.6 (822/7073)	16.6 (774/4671)	13.6 (1596/11744)	0.0001
Amikacin	8.2 (387/4736)	3 (96/3224)	6.1 (483/7960)	0.0001
Netilmicin	7.2 (127/1743)	3.8 (128/3296)	5 (255/5039)	0.0001
Ciprofloxacin	16.6 (1353/8149)	24.1 (1705/7072)	20.1 (3058/15221)	0.0001
Nitrofurantoin	20 (558/2785)	18.4 (624/3397)	19.1 (1182/6182)	0.097
Co-trimoxazole	48.5 (4631/9543)	45.4 (3626/7990)	47.1 (8257/17533)	0.0001
Ceftriaxone	9.3 (588/6325)	8.3 (279/3366)	8.9 (867/9691)	0.098
Cefuroxime	16.3 (757/4636)	20.6 (999/4843)	18.5 (1756/9479)	0.0001
Amoxicillin/clavulanate	37.7 (1192/3159)	24.4 (1321/4812)	31.5 (2513/7971)	0.0001
Piperacillin/tazobactam	12.5 (54/430)	8.2 (171/2077)	9 (225/2507)	0.004
Imipenem	2.3 (65/2822)	0.07 (3/4182)	1 (68/7004)	0.0001
ESBL	8 (36/450)	13.1 (333/2534)	12.4 (369/2984)	0.002

Trimethoprim-sulfamethoxazole is an agent that has been used in the treatment of UTIs for a very long period, even before quinolones entered the market (5). In our study, resistance to co-trimoxazole was found to be 47.1% in outpatients, and 52.4% in inpatients. The resistance rates to this agent decreased significantly in 2002-2007. The probable reason for decreased usage was the high resistance rates, which might have contributed to this situation. However, the rates being still very high, co-trimoxazole cannot be recommended in the empirical therapy of UTIs. Co-trimoxazole resistance is high in almost every part of the world (74,75). Ungheri et al. reported co-trimoxazole resistance in strains resistant to quinolones as 48.1% (76). In the study by Puerto et al., there was a co-trimoxazole resistance rate of 49.3%, which is similar to our rates (60).

When compared with other European countries, cephalosporin resistance in *E. coli* may be considered high (61,63). Especially resistance to cefuroxime was found to have increased significantly in outpatients. Ceftriaxone may be preferred in cases of failure with first line drugs, or infections with resistant strains. Resistance to β-lactam-β lactamase inhibitors is high, except piperacillin/tazobactam. Hence, empirical usage cannot be recommended without antibiotic susceptibility results.

Table 2. The resistance rates of *E. coli* strains isolated from hospitalized patients.

	1997-2001 % (Resistant/n)	2002-2007 % (Resistant/n)	TOTAL % (Resistant/n)	P
Gentamicin	24.5 (533/2177)	18.3 (432/2358)	21.3 (965/4535)	0.0001
Amikacin	10.7 (222/2072)	2.7 (52/1953)	6.8 (274/4025)	0.0001
Netilmicin	11.8 (39/330)	5.7 (120/2107)	6.5 (159/2437)	0.0001
Ciprofloxacin	30.9 (989/3199)	32.4 (1312/4051)	31.7 (2301/7250)	0.52
Nitrofurantoin	15.5 (153/989)	19.8 (297/1497)	18.1 (450/2486)	0.006
Co-trimoxazole	56 (1845/3295)	48.7 (1973/4051)	52.4 (3848/7346)	0.0001
Ceftriaxone	15.7 (503/3210)	15 (316/2104)	15.4 (819/5314)	0.521
Cefuroxime	28.4 (440/1551)	27.1 (695/2565)	27.6 (1135/4116)	0.376
Amoxicillin/clavulanate	52.8 (716/1355)	31.5 (827/2628)	38.7 (1543/3983)	0.0001
Piperacillin/tazobactam	8.3 (8/96)	12.2 (155/1272)	11.9 (163/1368)	0.261
Imipenem	2.3 (65/2787)	0.8 (24/3077)	1.5 (89/5864)	0.0001
ESBL	13.7 (19/139)	20 (376/1880)	19.6 (395/2019)	0.069

Reports from Turkey suggest that ESBL-producing *E. coli* is increasing. The treatment of cases infected with these bacteria is challenging. Sparing carbapenems for the treatment of these cases may be a rational approach (73).

This study comprised pooled resistance data of 25,577 urinary tract infection related *E. coli* strains published between 1997 and 2007. The main limitations of our study were: i) resistance data of all antibiotics were not provided in all studies and so data were not homogeneous, ii) analyzed studies comprised retrospectively retracted data, iii) we cannot exclude some of the strains that were not reported from more than one center, iv) patient groups were mostly classified as inpatients and outpatients in the articles. There was no classification as to healthcare associated infections. Hence, some of the inpatients or outpatients might be healthcare-associated infections.

Despite these disadvantages, this study provides the largest available data regarding the issue and enlightens future studies.

The Infectious Diseases Society of America guidelines suggest being cautious when using an antibiotic in empirical therapy, when resistance to it exceeds 20% (59). In light of our data, which give a global Turkish perspective, it is not rational to

offer quinolones, co-trimoxasole, and beta-lactams (except third-generation cephalosporins) in the empirical treatment of UTIs. Aminoglycosides and third-generation cephalosporins may be good choices in the treatment of inpatients. Fosfomycin, nitrofurantoin, and oral third-generation cephalosporins may be reasonable alternatives in the empirical treatment of uncomplicated cases. Quinolones and co-trimoxazole should be used only in cases with culture results showing specific sensitivity. Carbapenems should be conserved for extended-spectrum beta lactamase producing strains. Our data suggest that the ESBL-producer *E. coli* rate in the outpatient strains is alarming. Policies to constrain resistance in both the community and hospital, such as antibiotic stewardship or restriction programs, should be implemented immediately. Finally, we may recommend making a discrimination of healthcare-associated infections in strains isolated from inpatients and outpatients in future studies. This will help us to accumulate more accurate data about the issue.

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