

Original Article

Increasing Antimicrobial Resistance in *Escherichia coli* Isolates from Community-Acquired Urinary Tract Infections during 1998-2003 in Manisa, Turkey

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SUMMARY: Urinary tract infections are among the most common infections with an increasing resistance to antimicrobials. The aim of this study was to determine the change in antimicrobial susceptibility of *Escherichia coli* isolates from patients with community-acquired urinary tract infection (UTI) for the years 1998 through 2003 and to suggest that the current empirical antibiotic therapy used for these patients is inappropriate. During the study period, 7,335 community urine samples of which 1,203 (16.4%) grew bacterial isolates were analyzed. Among the total of 1,203 isolates, 880 (73.2%) were *E. coli*. The range of resistance of *E. coli* to ampicillin was 47.8 to 64.6% and that to trimethoprim-sulfamethoxazole was 37.1 to 44.6% during the study period. The susceptibility pattern of *E. coli* to nitrofurantoin and cefuroxime did not vary significantly over the 6-year period. There was a significant increase in the susceptibility of *E. coli* to ciprofloxacin (11.3-26.7%), amoxicillin-clavulanate (18.4-29.2%) and gentamicin (7.0-25.6%) ($P < 0.05$). Empirical initial treatment with ampicillin and trimethoprim-sulfamethoxazole was thus inadequate in approximately half of UTI cases in our region.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common infectious diseases diagnosed in outpatients (1). *Escherichia coli* has been documented to be the most important pathogen associated with community-acquired UTIs (CA-UTIs) in many countries (2-4). Reporting of antimicrobial susceptibility testing of the urinary tract is usually achieved 48 h following sampling, and therefore, in the majority of CA-UTIs, the treatment decision is empirical, being influenced by available data reflecting antibiotic resistance (5). Since the initiation of antimicrobial therapy in CA-UTI is empirical, knowledge of the antimicrobial resistance patterns of common uropathogens is essential to provide clinically appropriate and cost effective therapy (6). Hence, there exists a great need for antimicrobial resistance surveillance at the local, national and international levels.

The aim of this study was to determine the susceptibility pattern to commonly used antibiotics of *E. coli* isolated from outpatients in Manisa in the western part of Turkey, from January 1998 to December 2003, and to evaluate the results so that the optimal empirical antibiotic therapy for such patients could be determined for our region.

MATERIALS AND METHODS

Study design: The retrospective study was carried out using non-duplicate bacteria isolated from patients with CA-UTI from January 1998 to December 2003 in Manisa in the western part of Turkey. Urine samples were collected from outpatients sent to Celal Bayar University Hospital in Manisa

for urine analysis.

Isolation and identification: Samples were cultured on blood and cystine lactose electrolyte-deficient (CLED) agar (Oxoid, N.Y., USA) and incubated for 24 h at 37°C aerobically. Organisms were included in our study when they occurred as a pure culture and at a concentration greater than 10^5 CFU/ml. Isolation and identification were performed by conventional biochemical tests as well as by BBL Crystal GN; N/F ID (Becton Dickinson, Paramus, N. J., USA).

Susceptibility testing: Antimicrobial susceptibility testing of the isolates was performed by the disk diffusion method according to the recommendations of the National Committee for Clinical Laboratory Standards (7). The sensitivity of *E. coli* isolates to eight per oral antibiotics except gentamicin, commonly used in the CA-UTIs, was determined. The antibiotics used were ampicillin (AMP), amoxicillin-clavulanic acid (AMC), cefazolin (KZ), trimethoprim-sulfamethoxazole (TMP-SXT), ciprofloxacin (CIP), cefuroxime (CXM), nitrofurantoin (F) and gentamicin (CN) (Oxoid). Multiple drug resistance (MDR) was defined as resistance to three or more of the antimicrobials agents tested. *E. coli* ATCC 25922 was used as a quality control strain.

Statistical analysis: All data were analyzed with SPSS for Windows, version 10.0 (SPSS Inc., Chicago, Ill., USA). The trend χ^2 test was used for statistical comparisons between the groups and a P value <0.05 was considered as statistically significant.

RESULTS

A total of 7,335 urine samples, 5,647 (76.9%) from female outpatients and 1,688 (23.1%) from male outpatients, were received in our laboratory between 1998 and 2003. These samples grew 1,203 (16.4%) isolates. During the study period, *E. coli* isolates comprised 73.2% (880) of all isolates. The

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Table 1. Antimicrobial resistance of *E. coli* between 1998 and 2003

Antimicrobial agent	1998		1999		2000		2001		2002		2003		P ¹⁾
	n	%	n	%	n	%	n	%	n	%	n	%	
Ampicillin	88	47.8	102	64.6	66	53.2	69	61.0	84	59.1	78	49.1	>0.05
AMC	34	18.4	34	21.5	31	21.5	33	29.2	34	23.9	44	27.0	<0.05
Cefazolin	36	19.5	32	20.2	23	18.5	24	21.2	37	26.0	37	23.2	>0.05
Cefuroxime	11	5.9	11	6.9	9	7.2	7	6.2	16	11.2	12	7.5	>0.05
TMP-SXT	82	44.6	70	44.2	46	37.1	45	39.8	61	43.0	66	41.5	>0.05
Ciprofloxacin	27	14.7	18	11.3	23	18.5	29	25.6	38	26.7	39	24.5	<0.05
Gentamicin	13	7.0	22	13.9	19	15.3	29	25.6	28	19.7	22	13.8	<0.05
Nitrofurantoin	10	5.4	10	6.3	9	7.2	8	7.0	12	8.4	14	8.8	>0.05

¹⁾: trend χ^2 test

AMC, amoxicillin-clavulanic acid; TMP-SXT, trimethoprim-sulfamethoxazole; n, number of isolates tested.

total of 880 *E. coli* isolates comprised 184 (20.9%) isolates in 1998, 158 (18.0%) isolates in 1999, 124 (14.1%) isolates in 2000, 113 (12.8%) isolates in 2001, 142 (16.1%) isolates in 2002, and 159 (18.1%) isolates in 2003. These variations were not statistically significant ($P > 0.05$).

The range of resistance of *E. coli* to AMP is 47.8 to 64.6%, and that for TMP-SXT is 37.1 to 44.6%. Their susceptibility rates varied little over the 6-year period (Table 1). *E. coli* appeared to be about twice as resistant to AMP than to AMC (49.1 versus 27.0%) in 2003.

The resistance to KZ ranged from 18.5-26.0%. Between 1998 and 2003, there was an increase in resistance to AMC, CIP and CN ($P < 0.05$) (Table 1). No statistically significant differences were found over the time to CXM and F ($P > 0.05$), and these were antimicrobial agents with the highest levels of activity against *E. coli*.

MDR of *E. coli* was analyzed and 24.5% of isolates (216 of 880) were resistant to three or more antimicrobials and considered multidrug-resistant. Among the multidrug-resistant isolates, 100% were resistant to AMP and TMP-SXT, 97.2% were resistant to AMC, 87.5% were resistant to KZ, 80.6% were resistant to CIP, 74.1% were resistant to CN, 33.3% were resistant to F and 30.6% were resistant to CXM. MDR ratios were found to be 19.6% in 1998, 21.5% in 1999, 25.0% in 2000, 29.2% in 2001, 26.8% in 2002 and 27.7% in 2003.

DISCUSSION

This study showed the susceptibility patterns of *E. coli* isolates to the most commonly used oral antimicrobial agents causing CA-UTIs in Manisa, a part of Turkey, during 1998-2003. Worldwide, *E. coli* is the most important pathogen for uncomplicated and complicated UTI and has shown a slow but steady increase in resistance to several antibiotics over the past decade (4,8,9).

As documented by previous reports (10-12), *E. coli*, representing 73.2% of the strains isolated, was the principal uropathogen responsible for UTIs among our outpatients.

The range of resistance of *E. coli* to AMP is 47.8 to 64.6% and that for TMP-SXT is 37.1 to 44.6% in this region. The resistance rates in our results were higher than those in studies from developed countries; in the US (13) the rates are 39.1 and 18.6%, and in the EU (4) they are 29.8 and 14.1%, respectively. On the other hand, similar rates have been found in other countries, such as Senegal (14) (77%, 55%), Spain (15) (65%, 33%), Taiwan (16) (80%, 56%), and Israel (17) (66%, 26%). Therefore, these drugs should no longer be

prescribed as initial empirical therapy in our region.

It is worth noting that considerable reductions in the efficiency of AMC and quinolones (CIP) to *E. coli* were observed over the 6-year period. There was a statistically significant linear increase in the prevalence of resistance from 1998 to 2003 among *E. coli* isolates to CIP ($P < 0.000$) and to AMC ($P < 0.01$). Resistance of *E. coli* to TMP-SXT is a significant problem in our region and has also been reported from a number of institutions in Turkey. Of even greater concern is that increasing resistance is eroding the usefulness of second line agents such as CIP as reliable alternatives for the management of UTI. In our region, resistance to CIP has increased significantly by as much as 24% in the past 6 years.

The sensitivity of *E. coli* to KZ remained stable over the 6 years, and resistance rates showed no significant changes. Empirical treatment of CA-UTI with this drug may be reasonable.

Although CN is not a per oral antibiotic, it was frequently used as a second line agent in CA-UTI in Turkey. Between 1998 and 2003, these resistance rates were higher than in European countries and there was a statistically significant linear increase in the prevalence of resistance among *E. coli* isolates to CN ($P < 0.000$) (3,4,15).

F still exhibited low resistance rates in all countries investigated (0-5.4%), despite its being used for many years (5-7). In this study, *E. coli* isolates were found to be sensitive to F (5.4-8.8% resistant). This may have been due to the fact that this antibiotic has not been widely used in treating CA-UTI over the past decade in this region.

The resistance rate of *E. coli* to CXM was lower than 12%, which is consistent with other CA-UTI studies in Europe, Israel and the US (11,17,18). Since *E. coli* isolates were more sensitive to F and CXM compared to the other antibiotics tested, these drugs may be considered a good choice for the empirical treatment of CA-UTI in our region.

Higher resistance rates to all antibiotics tested with the exception of F and CXM may be explained by high and uncontrolled consumption of these antibiotics during the past decade in our region. These antibiotics were prescribed not only for UTI, but also for infections in other body sites. All antimicrobials are available in the pharmacies without prescriptions in our country.

Among the 880 isolates that were tested against all eight antimicrobials, the majority (47.7%) were susceptible to all the agents studied. MDR isolates accounted for 216 of the 880 isolates (24.5%). MDR ratios were found to range between 19.6-29.2%, indicating a statistically significant elevation in the past 6 years ($P < 0.05$, trend χ^2 test). Resist-

ance to AMP and TMP-SXT were component of 100% of the MDR isolates. Similarly, 97.2, 87.5, 80.6, 74.1, 33.3, 30.6% of MDR isolates were resistant to AMC, KZ, CIP, CN, F and CXM, respectively. The evaluation of antimicrobial resistance among MDR isolates indicated a high resistance against all antimicrobials agents tested, except F and CXM.

In conclusion, the main findings of this study are that there are high resistance rates to both AMP and TMP-SXT, and alarmingly high resistance rates to AMC and fluoroquinolones in Turkey. This necessitates a reevaluation of the first and second line therapies for the treatment of CA-UTI in our region, and regular monitoring of the usage of antimicrobials in order to make reliable information available for optimal empirical therapy for outpatients with UTIs.

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