

Evaluation of Treatment Applications and Antibiotic Resistance Rates for Community Acquired Urinary Tract Infections in Turkey and a Review of the Literature

Türkiye’de Toplum Kaynaklı İdrar Yolu Enfeksiyonlarında Tedavi Uygulamalarının ve Antibiyotik Direnç Oranlarının Değerlendirilmesi ve Literatür Eşliğinde Gözden Geçirilmesi

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What’s known on the subject? and What does the study add?

In Türkiye, every day is used as empiric antibiotic resistance for urinary tract infection antibiotics urgently change our preferred and make more urine Culture.

Abstract

Objective: Increased extended-spectrum beta lactamase (ESBL) production is associated with higher rates of community-acquired strains in urinary tract infections (UTI) leading to an increase in the resistance rates, duration of treatment and costs. We aimed to investigate the resistance rates of ESBL-positive urine culture strains in our clinic, reviewed the literature and analysed antibiotics used in UTI treatment in outpatients in Türkiye.

Materials and Methods: 2913 patients who were admitted to the outpatient clinics of Maltepe University Faculty of Medicine and Başkent University Faculty of Medicine were evaluated retrospectively. Data on prescribed antibiotics in outpatients with the diagnosis of UTI from all cities of Türkiye were collected through the Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency.

Results: Out of 563 ESBL-positive (19.3%) urine culture isolates, 450 (79.9%) were *Escherichia coli* and 89 (15.8%) were *Klebsiella* sp. Resistance rates were as follows: 98.8% to cefuroxime, 67.6% to ciprofloxacin, 12.5% to fosfomycin, 8.7% to amikacin, 1.4% to meropenem and 15% to nitrofurantoin. The most commonly prescribed antibiotics were ciprofloxacin (22.25%), fosfomycin (21.10%) and nitrofurantoin (12.82%).

Conclusion: Our study suggests that the antibiotic resistance rates of most antibiotics prescribed for UTI in Türkiye are above the suggested rate of 10-20% to be used as empirical therapy. Updating and dissemination of guidelines for UTI in the light of antibiotic prescribing and resistance surveillance studies will contribute to the rational use of antibiotics in Türkiye.

Keywords: Community-acquired urinary tract infection, Empiric therapy, Extended spectrum beta lactamase

Öz

Amaç: Artan geniş spektrumlu beta laktamaz (ESBL) üretimi, idrar yolu enfeksiyonlarında (İYE) toplum kaynaklı suşların daha yüksek oranlarıyla ilişkilidir, bu da direnç oranlarında, tedavi süresinde ve maliyette bir artışa yol açar. Kliniğimizdeki ESBL pozitif idrar kültürü suşlarının direnç oranlarını araştırmayı, literatürü gözden geçirmeyi ve Türkiye’de ayaktan hastalarda İYE tedavisinde kullanılan antibiyotikleri analiz etmeyi amaçladık.

Gereç ve Yöntem: Maltepe Üniversitesi Tıp Fakültesi ve Başkent Üniversitesi Tıp Fakültesi poliklinikler’ine başvuran 2913 hasta retrospektif olarak incelendi. Türkiye’nin tüm illerinden idrar yolu enfeksiyonu tanısı alan ayaktan hastalarda reçete edilen antibiyotik verileri TC Sağlık Bakanlığı, Türkiye İlaç ve Tıbbi Cihaz Kurumu Reçeteleme Bilgileri ile toplandı.

Bulgular: Beş yüz altmış üç ESBL pozitif (%19,3) idrar kültürü izolatından 450 (%79,9) *Escherichia coli* ve 89 (%15,8) *Klebsiella* sp. Direnç oranları sefuroksime %98,8, siprofloksasine %67,6, fosfomisine %12,5, amikasine %8,7, meropeneme %1,4 ve nitrofurantoin %15 idi. En sık reçete edilen antibiyotikler siprofloksasin (%22,25), fosfomisin (%21,10) ve nitrofurantoin (%12,82).

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Received: 31.03.2020 **Accepted:** 03.04.2020



Cite this article as: Eroğlu A, Akduman Alaşehir E. Evaluation of Treatment Applications and Antibiotic Resistance Rates for Community Acquired Urinary Tract Infections in Turkey and a Review of the Literature. 2020;7(2):114-119.

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Sonuç: Çalışmamız, Türkiye'de İYE için reçete edilen çođu antibiyotiđin antibiyotik direnç oranlarının ampirik tedavi olarak kullanılmak üzere önerilen %10-20 oranının üzerinde olduđunu göstermektedir. Antibiyotik reçeteleme ve direnç sűrveyans çalışmalarını ışığında İYE kılavuzlarının güncellenmesi ve yaygınlaştırılması, Türkiye'de antibiyotiklerin akılcı kullanımına katkıda bulunacaktır.

Anahtar Kelimeler: Dirençli idrar yolu enfeksiyonu, Ampirik tedavi, Geniş spektrumlu beta laktamaz

Introduction

Urinary tract infections (UTIs), one of the most common infections in our country, are the reason of outpatient referral of more than 7 million patients with 2 million cases of cystitis in the United States, and 15% of antibiotics are prescribed for UTIs (1). UTIs account for an overall annual cost of more than 1 billion dollars in the US (2). It has been reported that the annual cost of treating UTIs was 150 billion dollars in the world (3). To our knowledge, there are no studies reporting the annual cost of UTI in Turkey.

The diagnosis and treatment of UTIs depend on a number of factors including patient-related risk factors, previous infections, previously isolated microorganisms and their resistance status (2). The most common cause of community-acquired UTIs is *Escherichia coli*, and the preferred antibiotics in empiric therapy are trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin monohydrate, fosfomycin trometamol, fluoroquinolones and beta lactam group antibiotics (4). Extended-spectrum beta lactamases (ESBLs) can hydrolyze third and fourth generation cephalosporins and monobactam, but they have no effect on cephamycin and carbapenems. ESBL is inhibited by clavulanic acid (sulbactam or tazobactam). The ESBL-encoding plasmids often lead to co-resistance against aminoglycosides and quinolones (5). It is noteworthy that ESBL production, which is important in terms of community health, is now highly prevalent in community-derived strains, and the increase in sulfonamide, aminoglycoside and fluoroquinolone resistance is also remarkable (6). Increased resistance rates lead to changes in the treatment regimen, prolongation of treatment time and increased cost.

Our aim in this study was to investigate the resistance patterns of ESBL-positive strains isolated in UTIs both in our laboratory and in different regions of Turkey and to evaluate antibiotics prescribed for UTI in outpatients in Turkey. The results of our study aimed at guiding the rational drug use in our country.

Materials and Methods

2913 patients, who were admitted to the outpatient clinics of Maltepe University Faculty of Medicine (Istanbul) and Bařkent University Training and Research Hospitals between 2010 and 2018 and had positive urine cultures, were evaluated retrospectively. Antibiotic susceptibility results of the same

strain were excluded from the study. Only the first sample was included in the study. All procedures received approval from the Ethics Committee of Samsun Research and Training Hospital. Institutional review board approved the study with the protocol number TUEK 112-2018 GOKAEK/1-8. All methods were carried out in accordance with relevant guidelines and regulations.

Urine samples of 10 μ L were inoculated onto sheep blood agar and eosin methylene blue agar plate. After 18-24 hours incubation at 37 °C, isolates with $\geq 10^5$ cfu/mL were evaluated as causative agents. The strains were identified by conventional methods, using the Api 20 E (Bio-Mérieux, France) and VITEK (Bio-Mérieux, France) systems and antibiotic susceptibility was investigated by the Kirby-Bauer disc-diffusion method according to the criteria of the Clinical and Laboratory Standards Institute. The presence of ESBL was investigated by combination disc test using cefotaxime, ceftazidime and clavulanic acid-added combination discs of the same cephalosporins and with VITEK 2.0 (7).

Data on the preferred antibiotics in the outpatients treated with the diagnosis of UTIs in all cities of Turkey (2016 calendar year) was collected through the Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency Prescription Information System and analyzed.

Statistics Analysis

Statistical analysis was performed using Google Sheets. Descriptive statistics are presented with mean, standard deviation, frequency and percentage values.

Results

In our study, a total of 563 ESBL-positive (19.3%) urine culture isolates were identified and the antibiotic susceptibility test results were evaluated. Of these isolates, 450 (79.9%) were *E. coli*, 89 (15.8%) were *K. pneumoniae/oxytoca*, 5 (0.9%) were *Proteus sp.* and 19 (3.4%) were identified as other members of the *Enterobacteriaceae* family.

The resistance rates of ESBL-positive isolates are shown in Table 1. The resistance rates were 100% for ampicillin, 98.8% for cefuroxime, 67.6% for ciprofloxacin, 12.5% for fosfomycin, 8.7% for amikacin, 1.4% for meropenem and 15% for nitrofurantoin.

The resistance rates of ESBL-positive *E. coli* strains are given in Table 2. The resistance rates were 100% for ampicillin, 98.8% for

cefuroxime, 69.9% for ciprofloxacin, 8.3% for amikacin, 14.3% for fosfomycin, 8.7% for nitrofurantoin, 0.6% for meropenem and 0.5% for imipenem.

The resistance rates of ESBL-positive *K. pneumoniae/oxytoca* strains against ampicillin are given in Table 3. The highest resistance was 100% for ampicillin, 100% for cefazolin, 98.4% for cefuroxime, 98.4% for ceftriaxone, 98.4% for cefotaxime, 12.1% for amikacin, 4.9% for meropenem, and 3.3% for imipenem.

Of the total of 3.517, 172 prescriptions were written with the diagnosis of UTI in Türkiye in 2016. 80.0% of these prescriptions were written by family medicine specialists. The most commonly prescribed antibiotics, prescription rates and our resistance rates for the respective antibiotics are shown in Table 4. The total cost of these antibiotics prescribed for outpatients was 51.859.247,82 Turkish Lira (TL) and the cost per prescription was calculated to be 14.74 TL. The provinces with the highest

number of prescriptions were İstanbul (14.0%), İzmir (4.8%), Ankara (4.2%), Balıkesir (4.1%) and Bursa (4.0%).

Discussion

Patients with UTIs constitute 17.8% of patients admitted to outpatient health services in Türkiye every year and account for significant health costs (8). In our study, the most commonly prescribed antibiotics for the diagnosis of UTI in Türkiye and their resistance rates of our clinic were examined and they were found to be 67.6% for ciprofloxacin, 12.5% for fosfomycin, 15% for nitrofurantoin, 100% for ampicillin and 98.8% for cefuroxime, respectively. The data we presented in our study showed that the treatment of UTI in Türkiye in 2016 incurred cost in excess of 50 million TL.

E. coli is the most common type in both the hospital- and community-acquired UTIs, and the incidence rate in all UTIs is reported to be 55-95% (9). In our study, *E. coli* constituted 79.9% of UTIs and this data was compatible with the literature.

ESBL-positive *E. coli* detection in uncomplicated UTIs indicates that these strains are no longer only in the hospital environment but are spreading and must be taken into account in the selection of treatment in primary care (10,11,12,13).

In our study, the ESBL rate was found to be 19.3%. This rate is consistent with the literature. A meta-analysis from Turkey that examined the results of 101 studies published between the years of 1996 and 2012 detected that in outpatients treated due to UTIs, the rates of strains producing ESBL was below 20% (14). In the same study, it was reported that ESBL rates increased in the period of 2008-2012 compared to the 2002-2007 period. In the SMART study presenting data on the prevalence of ESBL in Enterobacteriaceae isolates in UTI from 2009 to 2011, a high ESBL rate was reported in both Asia and the Middle East, and a significant increase in ESBL rate was reported over the years. The average prevalence of ESBL-positive pathogens causing

Resistance rate	Antibiotics and resistance rates
>80%	Ampicillin (100%), Cephazolin (98.9%), Cefuroxime (98.8%), Cefotaxime (98.8%), Ceftriaxone (98.3%), Cefepime (92.0%), Ceftazidime (83.0%), Ampicillin/Sulbactam (89.0%), Amoxicillin/Clavulanic Acid (86.2%)
60% -80%	Trimethoprim Sulfamethoxazole (73.1%), Ciprofloxacin (67.6%), Levofloxacin (64.1%), Cefoxitin (58.5%)
40% -60%	Gentamicin (42.0%)
20% -40%	Piperacillin/Tazobactam (30.4%)
<20%	Netilmicin (18.8%), Nitrofurantoin (15.0%), Amikacin (8.7%), Ertapenem (3.4%), Meropenem (1.4%), Imipenem (0.8%)

Resistance rate	Antibiotics and resistance rates
>80%	Ampicillin (100.0%), Cefuroxime (98.8%), Cefotaxime (98.9%), Cefazolin (98.5%), Ceftriaxone (98.3%), Cefepime (91.2%), Ampicillin/Sulbactam (89.2%), Ceftazidime (88.4%), Amoxicillin/Clavulanic Acid (86.4%)
60% -80%	Trimethoprim Sulfamethoxazole (70.7%), Ciprofloxacin (69.9%), Levofloxacin (69.3%), Cefoxitin (60.0%)
40% -60%	Gentamicin (41.8%)
20% -40%	Piperacillin/Tazobactam (27.2%)
<20 %	Netilmicin (19.2%), Fosfomycin (14.3%), Nitrofurantoin (8.7%), Amikacin (8.3%), Ertapenem (2.1%), Meropenem (0.6%), Imipenem (0.5%)

Resistance	Antibiotic and resistance rates
>80%	Cefazolin (100.0%), Ampicillin (100.0%), Cefuroxime (98.4%), Ceftriaxone (98.4%), Cefotaxime (98.4%), Cefepime (96.7%), Ceftazidime (96.8%), Ampicillin/Sulbactam (87.5), Trimethoprim -Sulfamethoxazole (88.5%), Amoxicillin/Clavulanic Acid (84.3%)
60% -80%	Nitrofurantoin (62.7%)
40% -60%	Piperacillin Tazobactam (48.4%), Ciprofloxacin (49.0%), Cefoxitin (46.6%), Gentamicin (41.3%)
20% -40%	Levofloxacin (31.7%)
<20%	Netilmicin (16.4%), Amikacin (12.1%), Ertapenem (9.5%), Meropenem (4.9%), Imipenem (3.3%)

Table 4. Antibiotics prescribed for outpatients for urinary tract infections in 2016 in Türkiye, the number and rate of prescriptions in Türkiye and our antibiotic resistance rates

Antibiotic	Prescription number and rate		Antibiotic resistance rates		
	n	Rate (%)	Total	<i>E. coli</i>	<i>Klebsiella sp.</i>
Ciprofloksasin	782.417	22.25%	67.6%	69.9%	49.0%
Fosfomycin	742.270	21.10%	12.5%	14.3%	-
Nitrofurantoin	450.950	12.82%	15.0%	8.7%	62.7%
Methenamin*	273.035	7.76%	-	-	-
Ampicillin	154.152	4.38%	100.0%	100.0%	100.0%
Cefuroxime	150.714	4.29%	98.8%	98.8%	98.4%
Amoxicillin/Clavulanic Acid	99.913	2.84%	86.2%	86.4%	84.3%
Trimethoprim sulfamethoxazole	85.040	2.42%	73.1%	70.7%	88.5%
Ceftriaxone	45.335	1.29%	98.3%	98.3%	98.4%
Gentamicin	28.634	0.81%	42.0%	41.8%	41.3%
Levofloxacin	9.455	0.27%	64.1%	69.3%	31.7%
Cefazolin	9.244	0.26%	98.9%	98.5%	100.0%
Amikacin	3.405	0.10%	8.7%	8.3%	12.1%
Cefepime	32	0.00%	92.0%	91.2%	96.7%
Ceftazidime	29	0.00%	89.6%	88.4%	96.8%
Ertapenem	22	0.00%	3.4%	2.1%	9.5%
Cefotaxime	20	0.00%	98.8%	98.8%	98.4%
Meropenem	9	0.00%	1.4%	0.6%	4.9%
Piperacillin tazobactam	8	0.00%	30.4%	27.2%	48.4%

*: Methenamine is a bacteriostatic agent used in the prophylaxis of urinary tract infection and in the maintenance therapy and resistance to this agent is not routinely measured

UTI in Europe has been reported to be 20% (15). Forming a part of the SMART study, uncomplicated UTI data belonging to Türkiye (2011-2012); the most prevalent Gram-negative bacteria associated with uncomplicated UTI were *E. coli* (73.9%). The rate of ESBL-positive *E. coli* was 38.2% and ESBL-positive *K. pneumoniae* was 42% and it was stated that these rates were higher than in the other participating regions. Decrease in susceptibility to fluoroquinolone, ampicillin-sulbactam and cephalosporins was also remarkable in terms of limiting the choice of empiric treatment (16). Similarly, high rates of resistance to ampicillin, amoxicillin/clavulanic acid (AMC) and cephalosporins were found in our study. The high rate of prescription of these antibiotics for UTI indicates improper use of these drugs.

In a multicenter study from Belgium, Germany and Spain, *E. coli* strains isolated from community-acquired UTIs were generally resistant to AMC, fluoroquinolones and TMP-SMX, but the resistance to fosfomycin and nitrofurantoin was rare. Oral cephalosporins were found to be effective except for ESBL-positive strains. Lower resistance rates were found in Belgium compared to Germany and Spain (17). Thus, the resistance epidemiology differs between patient groups and countries due to the use of antimicrobials and/or the spread of resistant clones (18,19).

Antimicrobial resistance rates play an important role in the selection of an antimicrobial agent to be used empirically for treatment. For this reason, it is important to conduct studies based on country, region and even hospital. It is recommended

that the rate of resistance to the empiric agent should not exceed 10-20% (9). The Infectious Diseases Society of America recommends the use of nitrofurantoin, fosfomycin or TMP-SMX for uncomplicated cystitis in women, and fluoroquinolone or beta-lactam in acute pyelonephritis if local resistance rates do not exceed 20% (4). When we look at the resistance rates of these antibiotics in our current series, we can see that the rates of resistance to nitrofurantoin and TMP-SMX for *E. coli* are below 20% and they are the second and third most common antibiotics. On the other hand, the rate of resistance to the most prescribed antibiotic ciprofloxacin in Turkey was found to be 67.6% (only 69.9% for *E. coli*). Aktar et al. (20) found that the rate of resistance to ciprofloxacin was 23.9% for ESBL-negative *E. coli* and 61.5% for ESBL-positive strains and in addition, in different studies from Türkiye, the rate of ESBL-positive *E. coli* resistance to ciprofloxacin has been reported to be 55.6%-96%. In 2012, Mollahaliloğlu et al. (21) analyzed antibiotics prescribed in Turkey's 10 provinces (Eskişehir, Denizli, Niğde, Nevşehir, Bartın, Karabük, Gümüşhane, Bayburt, Çankırı ve Kırşehir) and found that one of the fifth most common diagnoses subject to antibiotic prescription was UTI. In the same study, it was reported that the most frequently prescribed antibiotics for UTI were ciprofloxacin (23.3%) and levofloxacin (20.3%). Considering our data, the fact that ciprofloxacin is still the most commonly prescribed antibiotic may be associated with a high rate of resistance.

In a prospective study including 429 patients conducted by Aypak et al. (22) in 2009, it was reported that the most frequently

prescribed antibiotics were fluoroquinolones (77%), TMP-SMX (10.7%), fosfomycin (9.2%) and nitrofurantoin (2.1%). In our country, when we look at the first 10 antimicrobials prescribed for UTI in the outpatient clinics (ciprofloxacin, fosfomycin, nitrofurantoin, methenamine, ampicillin, cefuroxime, AMC, TMP-SMX, ceftriaxone and gentamicin), these agents account for almost 80% of the prescriptions and just the rate of resistance to fosfomycin and nitrofurantoin was less than 20%. The rate of resistance to less prescribed antibiotics, such as amikacin, meropenem, piperacillin-tazobactam and chloramphenicol, is below 20% but these agents do not have enteral form.

Güneysel et al. (23) found high rates of resistance to cefpodoxime, AMC and ciprofloxacin for *E.coli*, especially in patients over 50 years of age and suggested that TMP-SMX should be excluded from empiric treatment for uncomplicated UTI due to high resistance rate. In addition, it was emphasized that fosfomycin was a good option in all age groups.

Klebsiella sp. pathogens other than *E. coli* are more resistant to many antibiotics such as AMC, cephalosporin, nitrofurantoin and amikacin (24). The high rate of resistance to nitrofurantoin in *Klebsiella sp.* isolates found in our study is also consistent with this information. This shows that it is not always appropriate for empiric treatment in non-*E.coli* strains. Urine culture and antibiotic susceptibility tests are very important in the treatment of these patients (24).

The data we presented in our study revealed that 80.0% of the prescriptions for the outpatient treatment of UTI was written by family physicians in Türkiye. When this data is taken into account, the need for a training program can be seen obviously and we assume that the first step should be family physicians. TMP-SMX has been recommended as the first choice empiric treatment for uncomplicated UTI in Türkiye (25,26). However, the rate of prescribing of this antibiotic was only 2.42%. The rate of TMP-SMX resistance was found to be 73.1% for all strains and 70.7% for *E. coli*, and it is not appropriate to use for empiric therapy and the empiric treatment suggestions in our country should be changed.

Our study has some limitations. No distinction was made between child and adult patients in the calculation of antibiotic resistance rates and costs. In addition, it is not known whether antibiotics were prescribed for empiric treatment or according to culture-antibiogram test results. However, high resistance rates suggested that they were used for empiric treatment. The fact that the data on antibiotic resistance rates presented in this study was from two provinces and two centers can be considered as another limitation. However, although we have not statistically tested these rates, the results can be generalized as these two provinces are the largest in Turkey also where the most prescriptions for UTI are written.

Conclusion

Our study suggests that the antibiotic resistance rates of most prescribed antibiotics to be used as empiric therapy for UTI in Türkiye are 10-20% higher than estimated. In the light of this data, one can say that there is an improper use of commonly prescribed antibiotics for UTI. It is also recommended that the resistance rates of each region or even every hospital should be analysed and ESBL-positive rates should be calculated in order to choose the antibiotic to be used in empiric treatment. High rates of resistance to quinolones, cephalosporins, AMC and TMP-SXT indicate the importance of drug selection according to the results of antibiotic susceptibility test, especially in ESBL-positive isolates (27).

As a result; such pharmacoepidemiological studies have led to the emergence of increased antibiotic resistance rates due to irrational use of antibiotics. Pre-treatment culture, agent-specific treatment planning, and good evaluation of region-specific resistance profiles in the selection of empiric treatment are the basis of rational antibiotic use. Antibiotic prescribing and resistance surveillance studies will lead to updating of guidelines for UTI treatment and expanding their use will contribute to the rational use of antibiotics in Türkiye.

Acknowledgments

We would like to thank due to her contribution to the collection of the data which constitute the source of this article, industrial engineer Esma Kadi, Rational DrugUse Department for Monitoring and Evaluation, and Assoc. Dr. David T. Thomas for evaluation of the data.

Ethics

Ethics Committee Approval: The study were approved by the Samsun Research Hospital of Local Ethics Committee (Protocol number: TUEK 112-2018 GOKAEK/1-8).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.E., Concept: A.E., E.A.A., Design: A.E., Data Collection or Processing: A.E., E.A.A., Analysis or Interpretation: A.E., E.A.A., Literature Search: A.E., E.A.A., Writing: A.E., E.A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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