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Which Antibiotics Should be the First Choice for Empiric Therapy of Urinary Tract Infections ?

İdrar Yolu Enfeksiyonlarının Ampirik Tedavisinde İlk Seçenek Antibiyotikler Neler Olmalı ?

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Abstract

Objectives: The aims of the study were to investigate the distribution and the antibiotic resistance profiles of the microorganisms isolated from outpatients with lower urinary tract infection (UTI) during 2011-2012 period and to determine the most appropriate empirical therapy choices.

Materials and Methods: Culture and susceptibility test results of 14.096 urine samples sent from outpatient clinics with presumptive lower UTI diagnosis in the last year (2011-2012) were reviewed. Excluding the duplications, totally 2005 isolates were evaluated. Culture and identification tests were done by conventional/semi-automatic and automatic methods. Antibiotic susceptibility tests were performed by Kirby-Bauer disc diffusion method according to the recommendations of CLSI (Clinical Laboratory Standarts Institute).

Results: *Enterobacteriaceae* spp. were isolated from 82.3% of the urine samples; 1287 (64.2%) *Escherichia coli* and 238 (11.9%) *Klebsiella pneumoniae*.67 (3.3%) *Pseudomonas aeruginosa* was cultivated. Totally 12.9% of the samples yielded Gram-positive bacteria including 55 (2.8%) meticillin resistant coagulase negative *staphylococci*, 55 (2.8%) *Enterococcus faecalis* and 49 (2.4%) *Streptococcus agalactiae*. The extended spectrum beta-lactamase (ESBL) prevalence was 23.2% in *E.coli* and 25.4% in *K.pneumoniae*. Among oral antibiotics tested, nitrofurantoin (NF) had the lowest resistance rates for both Gram-positive and Gram-negative isolates with 2.7% and 12.1%, respectively. Ampicillin for Gram-positives and Cefuroxim for Gram-negatives were other oral drugs with the lowest resistance rates with 6.3% and 25.9%, respectively.

Conclusion: NF appears as the most effective oral drug for adult outpatients with UTI. Cefuroxim can be considered as the second effective choice because ampicillin-sensitive Gram-positive isolates (except *Enterococcus spp*) would also be sensitive to it. NF and trimethoprim-sulfamethoxazole (TMP-SMX) is suggested as first or second choice in UTI treatment in antimicrobial therapy guidelines like Sanford and IDSA. However, TMP-SMX resistance was found 35% in our population; consequently it is not a suitable option for our patients.

Key words: Urinary tract infection, antibiotic resistance, enterobactericeae, ESBL, empirical treatment

Öz

Amaç: Çalışmamızın amaçları, 2011-2012 tarihleri arasında, alt üriner sistem enfeksiyonu (ÜSE) tanılı poliklinik hastalarından izole edilen mikroorganizmaların dağılımı, antibiyotik direnç profillerinin araştırılması ve uygun ampirik tedavi seçeneklerinin belirlenmesidir.

Materyal ve Metot: 2011–2012 tarihleri arasında, hastanemiz polikliniklerinden alt ÜSE ön tanısı ile gönderilen 14096 idrar örneğinin kültür / antibiyogram sonuçları retrospektif olarak değerlendirildi. Tekrarlayan üremeler hariç tutularak toplam 2005 örnekteki üremeler değerlendirmeye alındı. Kültür ve identifikasyon testleri konvansiyonel/yarı otomatik ve otomatik yöntemlerle yapıldı. Antibiyotik duyarlılık testleri CLSI (Clinical Laboratory Standarts Institute) önerileri doğrultusunda Kirby-Bauer disk difüzyon yöntemiyle gerçekleştirildi.

Bulgular: Örneklerin %83,7'sinde *Enterobacteriaceae* üyeleri üredi. Bunların 1287'si (%64,2) *E.coli*; 238'i (%11,9) *K.pneumoniae* idi. Toplam 67 (%3,3) örnekte *P.aeruginosa* üredi. Gram-pozitif üremelerin oranı; 55'i (%2,7) metisiline dirençli koagülaz negatif stafiolokok, 55'i (%2,7) *E.faecalis*, 49'u (%2,4) *S.agalactia* v.b. olmak üzere %12,86 idi. Genişlemiş spektrumlu beta laktamaz prevalansı *E.coli* izolatlarında %23,2; *K.pneumonia* izolatlarında %25,4 olarak belirlendi. Gerek Gram-pozitif, gerekse Gram-negatif izolatlarda, oral kullanımı olan antimikrobikler içinde nitrofurantoin (NF) en düşük direnç oranına sahipti (sırasıyla %2,7 ve %12,1). Öte yandan Gram-pozitif bakteriler için ampisilin (%6,3), Gram-negatif bakteriler için ise sefuroksim (%25,9) en düşük direnç oranlarına sahip diğer oral tedavi seçenekleri olarak belirlendi.

Sonuç: Yetişkin yaş grubundaki poliklinik hastalarımızın alt ÜSE enfeksiyonlarında NF en geniş

antibakteriyel etki spektrumuna sahip oral ilaç olarak öne çıkmaktadır. Ampisiline duyarlı Gram-pozitif izolatların (*Enterokokspp*. hariç) sefuroksime de duyarlı olacağı düşünülürse, ikinci en geniş spektrumlu oral ilacın sefuroksim olduğu söylenebilir. Sanford, IDSA v.b. tedavi kılavuzlarında NF, trimetoprim sulfametoksazol (TMP-SXT), ilk veya ikinci tedavi seçeneği olarak önerilmekle birlikte çalışmamızda bu oran %35 düzeyinde bulunduğu için TMP-SXT, hasta grubumuz için uygun bir tedavi seçeneği gibi görünmemektedir.
Anahtar kelimeler: Üriner system enfeksiyonu, antibiyotik direnci, enterobactericeae, ESBL, ampirik tedavi

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Introduction

Enterobacteriacea are responsible for the majority of symptomatic lower urinary tract infections (UTI). Escherichia coli is the most reported pathogen (80-95%) in both nosocomial and community-acquired UTI. In suspicion of UTI, clinicians start empirical antibiotic therapy before the antibiotic susceptibility test results. Antibiotics are prescribed for about five million patients with UTI per year in Turkey. The misuse and overuse of antibiotics for either therapy or prophylaxis speeds up the development of resistance.[1]

The aims of the study are to investigate the distribution and the antibiotic resistance profile of the microorganisms in our UTI outpatients during 2011-2012 period; to determine the most appropriate current empirical therapy choices.

Materials and Methods

Culture and susceptibility test results of 14096 urine samples sent from outpatient clinics with presumptive UTI diagnosis between April 2011 and March 2012 were reviewed. Pediatric age group (<15 years old) was excluded because of the limited number of the patient data. Culture and identification tests were done by conventional (IMVIC test)/ semi-automatic (API 20 E, bio Merioux, France) and automatic methods (VITEK 2, bio Merieux, France). Patients who had pyuria and UTI suspicion were selected for the study. Growth of one or two types of bacteria above 10^5cfu/mL detected in culture was considered as significant. Antibiotic susceptibility tests were performed by Kirby-Bauer disc diffusion method according to the recommendations of CLSI (Clinical Laboratory Standarts Institute).[2] The production of extended spectrum beta-lactamases (ESBL) was analyzed by double disc synergy method.[3] The intermediate resistant isolates were regarded as resistant.

Data were analyzed by frequency distribution, percentage values and Chi-square tests using SPSS (18.0, Windows) statistics program. A $p<0.05$ value was accepted as statistically significant.

Results

Excluding the duplications, totally 2005 isolates were evaluated. Of all isolates 1302 (64.9%) were from female patients and 703 (35.1%) were from males. Distribution of samples to the outpatient clinics was as follows: 44% urology, 16.4% internal medicine, 11.3% infectious diseases, 9.7% gynecology, 1.5% surgical units and 16.4% other various departments including oncology, institution physician unit, dermatology, family practice, pulmonary diseases, heamatology, geriatrics, home care and emergency services. *Enterobacteriaceae* spp. were isolated from 82.3% of the urine samples. The most frequently isolated two species were *E.coli* (1287, 64.2%) and *Klebsiella pneumoniae* 238, 11.9% (Table 1). A total of 67(3.3%) isolates were *Pseudomonas aeruginosa.* Gram-positive bacteria were isolated from 12.9% of the samples and species distribution was as follows; 55 (2.8%) meticillin resistant coagulase negative staphylococci (MRCNS), 55 (2.8%) *Enterococcus faecalis* and 49 (2.4%) *Streptococcus agalactiae*.

Table 1. The distribution of isolates

Bacteria	**Number**	**%**
Gram-negative bacteria		
Escherichia coli	1287	64.3
Klebsiella pneumoniae	238	12
Pseudomonas aeruginosa	67	3.3
Klebsiellaoxytoca	34	1.7
Enterobacter cloacae	30	1.5
Proteus mirabilis	27	1.3
Enterobacter aerogenes	12	0.6
Proteus vulgaris	11	0.5
Acinetobacter spp	11	0.5
Serratiaspp	6	0.3
Citrobacterfreundii	4	0.2
Other	20	1
Gram-positive bacteria		
MRCNS[1]	55	2.8
Enterococcus faecalis	55	2.8
Streptococcus agalactiae	49	2.4
MSCNS[2]	33	1.6
Enterococcus faecium	23	1.1
Enterococcus spp.	22	1.1
Staphylococcus saprophyticus	13	0.6
MSSA[3]	7	0.4
MRSA[4]	1	0
Total	2005	100.0

[1]*Methicillin resistant coagulase negative Staphylococcus,* [2]*Methicillin sensitive coagulase negative Staphylococcus,* [3]*Methicillin sensitive Staphylococcus aureus,* [4]*Methicillin resistant Staphylococcus aureus*

MRCNS isolates were 100% sensitive to vancomycin and linezolid. *Enterococcus spp*. were 100% sensitive to telithromycin and vancomycin. *Streptococcus spp*. were resistant only to erithromycin and clindamycin.

For *E.coli*, the highest resistance rates were against ampisilin and cephalothin among all tested oral drugs (62.5% and 44.8% respectively). Amikacin was determined as the second effective agent after imipenem for parenteral therapy. These results were rather similar to those of the other members of *Enterobacteriaceae*.

No *E.coli* isolate had resistance against imipenem or ertapenem. The extended spectrum beta-lactamase (ESBL) prevalence was 23.2% in *E.coli*, 25.4% in *K.pneumoniae* and 2.6% in *Proteus mirabilis*. The overall antibiotic resistance rates of ESBL-positive *E.coli* isolates were statistically higher than the ESBL-negative ones except for amikacin (p=0.69). Likewise, ESBL-positive *K.pneumoniae* isolates had higher resistance rates than the negative ones except for imipenem (p=0.267) and ertapenem (p=1.000) (Table 2).

Table 2. The distribution of antibiotic resistance of ESBL positive and negative isolates

Antibiotic	***E.coli* n(%)**			***K.pneumoniae* n(%)**		
	ESBL-positive n=298	**ESBL-negative n=989**	**p**	**ESBL-positive n=69**	**ESBL-negative n=203**	**p**
Imipenem	0	0	-	2 (2.9)	2 (1.0)	0.267
Ertapenem	0	0	-	1 (1.4)	3 (1.6)	1.000
AMC	229 (76.8)	97 (9.9)	0.001	54 (78.3)	33 (16.3)	0.001
Piperacillin	262 (98.5)	215 (24.4)	0.001	62 (93.9)	49 (26.6)	0.001
P/T	79 (26.6)	28 (2.8)	0.001	20 (29.9)	23 (11.3)	0.001
T/C	150 (70.8)	91 (12.5)	0.001	37 (68.5)	31 (20.1)	0.001
TMP-SMX	177 (60.0)	290 (29.4)	0.001	39 (5.5)	41 (20.6)	0.001
Nitrofurantoin	34 (11.6)	36 (3.7)	0.001	31 (44.9)	45 (22.2)	0.001
Gentamicin	135 (45.5)	85 (8.7)	0.001	26 (38.8)	8 (3.9)	0.001
Amikacin	1 (0.3)	7 (0.7)	0.069	4 (6.2)	0 (0)	0.003
Tobramycin	158 (61.0)	59 (6.9)	0.001	27 (41.5)	8 (4.6)	0.001
Ofloxacin	198 (75.6)	207 (23.7)	0.001	34 (50.7)	28 (15.4)	0.001
Ciprofloxacin	24 (82.8)	22 (19.5)	0.001	1 (50)	3 (16.7)	0.368

AMC: Ampicilin - clavulanic acid, P/T: Piperacillin - tazobactam, TMP-SMX: Trimethoprime – sulfamethoxazole, T/C: Ticarcillin clavulanic acid

To obtain a more general consideration, the isolates were also grouped into three categories as Gram-positives, Gram-negatives and *P.aeruginosa*, and antibiotic resistance rates were calculated for each group (Table 3). As seen in table 3; the highest resistance rates were against to ampicillin (69.6%) and cephalothin (45.7%) for gram-negatives. Gram-positives were resistant at the most against quinupristin-dalfopristin (68.3%), oxacillin (62.7%) and tetracycline (%58.2) respectively. Nitrofurantoin had the lowest resistance rate among oral antibiotics tested for both gram-positive and

negative isolates; 2.7% and 12.1%, respectively. On the other hand, ampicillin for gram-positives (except MRSA and MRCNS) and cephalothin for gram-negatives were the other oral treatment choices with lower resistance rates (6.3% and 25.9% respectively).

Table 3. The antibiotic resistance list of the urine sample isolates resistance list of the urine sample isolates

Antibiotics	**Number/n**	**%**
Gram-negative bacteria		
İmipenem	51/1626	0.3
Ertapenem	6/1536	0.4
Amikacin	14/1602	0.9
Cefoxitin	81/1596	5.1
P/T	156/1629	9.6
Nitrofurantoin	196/1620	12.1
Gentamicin	260/1628	16
Tobramycin	262/1424	18.4
Cefepime	339/1468	23.1
Cefotaxime	356/1474	24.2
Cefuroxime	420/1623	25.9
T/C	333/1218	27.3
AMC	468/1632	28.6
Ofloxacin	479/1459	32.8
TMP-SMX	572/1629	35.1
Cephazolin	523/1479	35.4
Piperacillin	60/1472	40.8
Cephalothin	676/1480	45.7
Ampicillin	1141/1639	69.6
Gram-positive bacteria		
Vancomycin	0	0
Linezolid	1/202	0.5
Nitrofurantoin	5/188	2.7
Ampicillin	6/96	6.3
Rifampin	12/105	11.4
Telithromycin	13/108	12
TMP-SMX	16/108	14.8
Gentamycin 120µg	16/100	16
Clindamycin	36/154	23.4
Norfloxacin	30/82	36.6
Erythromycin	70/153	45.8
Penicillin	108/229	47.2

Levofloxacin	50/98	51
Tetracycline	121/208	58.2
Oxacillin	69/110	62.7
Q/D	58/85	68.3
P. aeruginosa		
İmipenem	3/67	4.5
Ceftazidime	3/67	4.5
P/T	3/63	4.8
Piperacillin	4/66	6.1
Cefepime	4/63	6.3
Aztreonam	6/62	9.7
Amikacin	8/66	12.1
Tobramycin	11/67	16.4
Meropenem	11/66	16.7
Ticarcillin	11/62	17.7
Gentamicin	13/67	19.4
Ciprofloxacin	13/63	20.6

AMC: Ampicilin - clavulanic acid, P/T: Piperacillin - tazobactam, TMP-SMX*: Trimethoprime sulfamethoxazole, T/C: Ticarcillin - clavulanic acid, Q/D: Quinupristin-dalfopristin*

Discussion

E.coli has always been the most common pathogen among UTI pathogens (60-90%) for both sexes and for all ages. Especially in spring, CNS is the second isolate responsible for UTIs of sexually active young women. *E.coli* is still the dominant agent although the percentage of *P.aeruginosa* and other gram-negative bacilli and *enterococci* has begun to increase in complicated infections.[1] *E.coli* was the most frequent agent (64.2%) isolated from outpatients above 15 years old in this study. This is consistent with the results of several studies from Turkey and the other countries. The other isolates ensuing *E.coli* were CNS (5.2%), *enterococci* (4.9%) and *Pseudomonas spp.* (3.3%). In several domestic studies, isolation frequencies of these species in UTI were reported as 1-10%, 2.5-6% and 0.3-7.8% respectively.[4-9] For all of the three species, our results are parallel to those of both domestic and international studies. [6-9]

Most of the present literature of UTI are about *E.coli*, the most frequent UTI agent. The resistance rates of *E.coli* are continuously rising because of the misuse of the antibiotics both in Turkey and in the world. As there was no significant difference between *E.coli* and *Enterobacteriaceae spp. in* resistance rates, we preferred to give the total resistance percentage of *Enterobacteriaceaespp* in this study. According to our results, the most effective antibiotics were carbapenems especially imipenem for *Enterobacteriaceae spp.* and *Pseudomonas spp*. Consistently, rare or no *Pseudomonas* or *Enterobacteriaceae* isolates were reported as resistant against carbapenems in other domestic studies.[15]

Amikacin (0.9% resistance) was the most and tobramycin was the least (18% resistance) effective agent among the tested aminoglycosides (amikacin, gentamicin, tobramycin) for enteric bacteria. In some other Turkish reports, amikacin resistance ranges between 0.6 and 10.3% for *E.coli* and this drug happens to be the second effective antibiotic following carbapenems.[1-6] The reason of the low amikacin resistance in both *Enterobacteriaceae spp.* and *Pseudomonas spp* is thought to be the restricted reporting of antibiogram results .

The resistance rates of enteric bacteria against cephalosporins varied between 5.1% (cefoxitin) and 45.7% (cephalothin) in our study. Despite its relatively high resistance rate determined as 25.9%, cefuroxime came up as the second effective oral drug. Sağlam et al. found a similar resistance rate for cefuroxime, while, several other studies reported quite different rates ranged between 17.8% and 54.1% .[13,14]

Ceftazidime and cefepime are the selected cephalosporins tested for *Pseudomonas spp*. According to our results, ceftazidime was one of the most effective antibiotics which had an equal susceptibility with imipenem (4.5%). Cefepime had a resistance rate of (6.3%). The second and third effective agents were Piperacillin-tazobactam (P/T) and piperacilline for *Pseudomonas spp*. However, the relevant literature is not enough to make a comment for this situation.

We found the resistance rates of ampicilline and AMC as 69.6% and 28.6 respectively. In a metaanalysis by Aykan et al. these rates were determined as 62% and 34%.[15] The usage of different prescribed antibiotics in studied populations might be the reason of the different rates especially for AMC resistance. According to our results AMC can be considered as an alternative for cefuroxime among orally administered drugs.

The usage of beta-lactam antibiotics and extended spectrum cephalosporins have been increased during the last 20 years. This made easier the raising of ESBL-positive microorganisms, especially resistant *E.coli* and *K.pneumoniae* strains. Beta lactamases, especially ESBL are responsible for the majority of resistance against beta-lactams.[16]

The percentage of *ESBL-positive E.coli* in UTI was reported as 5-26% by several studies from Turkey.[14] In our study, ESBL positivity rates (23.2% of *E.coli* and 25.4% of *K.pneumonia* isolates) were a little higher than those of domestic and outsider reports.[6,12,14,16] This might be partially due to the admission of some inadequately treated patients with resistant strains to our hospital which is a tertiary care institute.

Traditionally, nitrofurantoin, fluoroquinolons, TMP-SMX, phosphomycine and beta-lactams (except ampicillin and amoxicillin) are the recommended antibiotics for adult UTIs. These agents are preferred because of their pharmacokinetic properties and broad antimicrobial spectrums covering most of the gram-positive and negatives.[4]

TMP-SMX has been recommended as the first choice for treatment of UTI for a long time, however it is placed in lower ranges of effectiveness alignment with its really high resistance rate (35.1%) in our study. Several studies from Turkey also reported very high resistance rates (39-47%) against TMP-SMX.[1,4,14,16] Similarly, TMP-SMX resistance rates vary a lot in other regions of the world. Karlowsky et al. reported it as 66.5% in USA and Canada;[17] while European countries have relatively lower rates ranging between 17.1% and 40% .[13]

Following the appearance of high resistance rates against TMP-SMX, floroquinolons substituted it as an effective treatment alternative. According to the data of the 2009-2010 SMART programme, the regional resistance of quinolons were 23.5% in North America, 29.4% in Europe, 33.2% in Asia, and 38.7% in Latin America. In the same study, the range of resistance varied a lot; from 6% (Estonia) to 75% (India), with Turkey being the fifth country having a rate of 45%.[18] The quinolon resistance was 32.8% in our study. Lower and higher rates ranging between 23.6% and 70% were reported from several studies in Turkey.[4,15,17] Ciprofloxacin was found to be the less effective member of the group to *Pseudomonas spp*. in our study. The quinolon resistance was very high both for gram-positives and negatives with a close percentage to the resistance of TMP-SMX. It is a clear indicator of irrational antibiotic usage that, the quinolons had begun to be used in treatment long time after TMP-SMX but got the same resistance rates in a shorter time than it.

NF has had a limited usage in recent years, and is not included into the antibiogram list of many care centers. Whereas, it has been used in USA since 1953, in spite of its rarely seen serious side effects.[19] It is still very effective against the uropathogens.[20] Considering the increase of the resistance to the other agents, NF is on the agenda again. Notably, it was the most effective antimicrobial for all isolates in our study. The resistance of NF was reported 3.6-8.4% for outpatients.[4,7] Expectedly, resistance of ESBL-positive isolates to it was found higher. Gözel et al. reported a slope down in NF resistance (from 4% to 0%) of ESBL-positive *E.coli* isolates in 2006-2010 period.[16] NF is preferred in the primary health care facilities for its high effectiveness, low cost and low resistance especially in the regions which have high resistance rates of quinolons and TMP-SMX.[19,20]

E.faecalis and *E.faecium* not only have chromosomal resistance to many antibiotics but also have tendency to gain resistance easily to the other antimicrobial agents. Being quite similar to our results, Rudy et al. reported resistance rates of *E.faecalis* isolates from urine samples to glycopeptides and NF as 0% and to penicilin as 4%. In that study, the less effective antibiotic to *Enterococcus spp*. was found as ciprofloxacin.[21] There are several studies from Turkey including parallel results.[6,22] We found no resistance to cefotaxime and vancomycin in gram-positive isolates and the most effective oral antimicrobials to these microrganisms were NF and ampicilline, in our study.

According to our one year data of culture and antibiogram, NF appears as the most effective oral drug for outpatients with UTI in adults for empiric therapy. Cefuroxim can be considered as the second effective oral choice because ampicillin-sensitive gram-positive isolates (except *Enterococcus spp*) would also be sensitive to it. If the regional resistance is below 20%, NF and TMP-SMX, is suggested as first or second choice in UTI treatment in antimicrobial therapy guidelines like Sanford and IDSA.[23,24] However, TMP-SMX resistance was found 35% in our population; consequently it is not a suitable option for us.

According to the data of Turkish Ministry of Health, 20% of the sold drugs are antibiotics in Turkey. Rational drug use is an important concern for all drug groups but it has a special importance for antimicrobials.[25] Culture and antibiogram tests are generally not recommended for community-acquired UTI because of the cost-effectivity reason. However, as the resistance of TMP-SMX, ampicillin and quinolones

are over 20% for especially *E.coli* isolates widely in Turkey, it seems as the safer and more effective option to do culture and antibiogram tests before antimicrobial treatment of UTI whichever care facility the patient admits.

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