Turkish Journal of Medical Sciences

Volume 41 | Number 1 Article 20

1-1-2011

Management of community-acquired acute bacterial cystitis in Turkey

ÖMER COŞKUN

HAKAN ERDEM

ALİ AVCI

TÜBİTAK

Original Article

Turk J Med Sci
2011; 41 (1): 149-157
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-0908-158

Management of community-acquired acute bacterial cystitis in Turkey

Ömer COŞKUN[1], Hakan ERDEM[2], Ali AVCI[3]

Aim: Community acquired acute bacterial cystitis (CA-ABC) is one of the most common infectious presentations in the community. This paper aims to provide a rational approach in the management of CA-ABC based on local Turkish data.

Materials and methods: The publications evaluating the microbiological data obtained from CA-ABC cases were searched in both Turkish and international databases.

Results: Fosfomycin and nitrofurantain appear to be baseline antibiotics while the empirical use of trimethoprim sulfamethoxazole, amoxicillin clavulanate, and first and second generation cephalosporins seems to be unreliable in Turkey. Moreover, quinolones seem to be at the edge with resistance rates up to 20%. On the other hand, aminoglicosides, third and fourth generation cephalosporins, and piperacillin-tazobactam look more trustworthy.

Conclusion: According to local Turkish data, caution is really indicated in rational antibiotic use in the community since the traditional drugs used in the management of CA-ABC are being lost steadily.

Key words: Community-acquired, urinary, infection, Turkey

Türkiye'de toplum kökenli akut baktriyel sistit tedavisi

Amaç: Toplum kökenli akut bakteriyel sistitle (TK-ABS) toplumda oldukça sık karşılaşılmaktadır. Bu çalışmanın amacı, Türkiye verileri temel alınarak TK-ABS tedavisinde en etkili tedavi yaklaşımını ortaya koymaktır.

Yöntem ve gereç: TK-ABS olguları ile ilgili mikrobiyolojik verilerin değerlendirildiği makaleler uluslararası ve Türkiye veritabanları taranarak araştırıldı.

Bulgular: Türkiye'de ampirik olarak kullanılan trimetoprim-sulfametaxazol, amoksisilin klavulanat, birinci ve ikinci kuşak sefalosporinler yeterince güvenilir değildir. Bunlar yerine fosfomisin ve nitrofurantain temel kullanımda olması gereken antibiyotikler gibi görünmektedir. Kinolonların direnç oranlarının %20'nin üzerine çıktığı tespit edilmiştir. Diğer yandan aminoglikozidler, üçüncü ve dördüncü kuşak sefalosporinler, piperasillin-tazobaktam bu açıdan daha güvenilir ilaçlar olduğu görülmektedir.

Sonuç: Türkiye verileri ele alındığında, TK-ABS tedavisinde potansiyel olarak kullanılan antibiyotikler giderek etkinliğini yitirmektedir. Toplum kökenli bu enfeksiyonlarda gerçek endikasyonlarda doğru antibiyotik kullanımı konusunda dikkatli olunmalıdır.

Anahtar sözcükler: Toplum-kökenli, üriner, enfeksiyon, Türkiye

Received: 05.08.2009 – Accepted: 28.06.2010

[1] Department of Infectious Diseases and Clinical Microbiology, Gülhane Medical Academy, Ankara - TURKEY
[2] Department of Infectious Diseases and Clinical Microbiology, Kasımpaşa Military Hospital, Ankara - TURKEY
[3] Department of Emergency Medicine, Urology Unit. Gülhane Medical Academy, Ankara - TURKEY
Correspondence: *Ömer COŞKUN, Department of Infectious Diseases and Clinical Microbiology, Gülhane Medical Academy, Ankara - TURKEY*
E-mail: coskunomer23@gmail.com

Introduction

Urinary tract infection (UTI) is one of the most common infectious presentations in the community and is defined as the presence of pyuria and clinical findings concordant with inflammation in the urinary system (1). Nonelderly patients with dysuria, frequency, or urgency without flank pain or fever, and who are otherwise healthy, are not pregnant, and have no known abnormalities of the urinary tract are considered to have community acquired acute bacterial cystitis (CA-ABC) (2).

According to the Turkish Statistical Institute (*Türkiye İstatistik Kurumu*), UTI was the third most common infection in Turkish medical practice following respiratory and gastrointestinal infections in 2004 (3). Moreover, the extensive use of antimicrobial agents has resulted in the development of antibiotic resistance, which has become a major problem worldwide (4). For this reason, therapeutic strategies should be updated due to changing epidemiology and the aim of this paper is to put forward a rationale based on Turkish data for antibiotic therapy in CA-ABC.

Methods

The publications evaluating the microbiological data obtained from CA-ABC cases were searched through both Turkish (Pleksus) and international (Medline) databases. The search terms were agents, urinary-infection, community-acquired, Turkey, and their Turkish counterparts. Only the articles published after 2000 were included in this review. Data analysis was done according to the design below:

1. If the publications evaluated both hospital and community-acquired infections or isolates, the information related to nosocomial data was excluded.
2. The studies evaluating the results of the pediatric population were excluded.
3. The distribution of urinary pathogens was evaluated to delineate the potential uropathogenic bacteria in Turkey and the median rates were considered to provide a general understanding. The bacteria for which the median percentage exceeds 5% were accepted as significant uropathogens.
4. The median antibiotic resistance rate of a given antibiotic was used to provide general understanding.
5. If the study evaluated only a particular uropathogen, this was not included for the delineation of uropathogens, but it was only used for antibiotic resistance pool of the particular microorganism.

Limitations of the study

1. Local Turkish studies did not discriminate between complicated and uncomplicated CA-ABCs.
2. Turkish studies have almost always focused on laboratory data and the clinical correlations of in vitro data are lacking in the Turkish literature. For this reason, we combined the general knowledge with Turkish in-vitro data on antibiotic susceptibility.

Results

Overall 9 studies were included for pathogen distribution in CA-ABC and 29 studies were pooled for antibiotic susceptibility patterns. Two of the antibiotic susceptibility studies evaluated more than 5000 isolates. In 1 study 2687 isolates, in 7 trials 1000-2000 strains, in 9 studies 250-1000 bacteria, in 9 trials 100-250 isolates, and in 1 study 72 strains were assessed. *Escherichia coli* was the most common pathogen, followed by Klebsiella species in CA-ABC in Turkey. All other agents of urinary infection with shares of less than 5% were not interpreted as significant uropathogens. Local studies related to pathogen distribution in CA-ABC are presented in Table 1 and antibiotic susceptibility patterns of the isolates are shown in Table 2.

In this study, we detected exceedingly high resistance rates (over 20%) to ampicillin, amoxicillin-clavulanic acid, trimetoprin-sulfametaksazole (SXT), cefazolin and cefuroxime, which have been traditionally used in the management of CA-ABC. Fosfomycin and nitrofurantoine seem to have perfect in-vitro efficacies on *E. coli*, the most frequent agent in CA-ABC.

Table 1. Turkish studies evaluating the pathogen distribution of CA-ABC as percentages.

References	(41)	(42)	(43)	(44)	(45)	(46)	(47)	(48)	(49)	
Publication date	2001 (%)	2001 (%)	2003 (%)	2005 (%)	2006 (%)	2006 (%)	2006 (%)	2008 (%)	2008 (%)	Range (median)
E. coli	70.5	62	48.8	90	80.3	57	71.5	66	58	48.8-90 **(66)**
Klebsiella spp.	6.3	16	10.7	8	17	5	15.5	6.4	11	5-17 **(10.7)**
Proteus spp.	0	3	5.1	1	1.3	3	3.3	13	4	0-13 **(3)**
Enterobacter spp.	4.4	6	1.4	1	0	8	2.3	0	2	0-8 **(2)**
Serratia spp.	0.6	0	0	0	0	0	0	0	0	0-0.6 **(0)**
Pseudomonas spp.	6.3	7	4.1	0	0	0	3	2.1	3	0-7 **(3)**
Enterococci	2.5	0	5.6	0	0	4	3.5	9.1	7	0-9.1 **(3.5)**
CNS	6.3	0	5.2	0	1.3	12	0	0	3	0-12 **(1.3)**
S. aureus	2.5	4	5.8	0	0	4	0	3	1	0-5.8 **(2.5)**
Others	0.6	2	13.3	0	0	7	0	0.4	11	0-13.3 **(0.6)**

*CNS; Coagulase-negative *Staphylococcus.* **Bold numbers are the median values**

Table 2. Studies evaluating the resistance rates of CA-ABC isolates in Turkey.

References	(22,43-69)	(43,45,47,50,53,57)	(43,47,53,57,70)	43,47,49,50,53,57,70)	(43,49,50,53,70)
Pathogens	*E. coli* (%)	*Proteus* spp. (%)	*Enterobacter* spp. (%)	*Klebsiella* spp. (%)	*P. aeruginosa* (%)
Ampicillin	37-82.4 (55.2)	7.4-72.7 (47.8)	80-100 (80.6)	79-100 (91)	85
Amx-Clav	9.8-40 (26)	12.1-30 (21)	76	6.2-64 (41.5)	
Cephazolin	7-49 (28.8)			100	
Cefuroxime	5.4-34.2 (22)	16.7-29 (23)	28-62.5 (43)	20.3-54 (42)	46
Ceftriaxone	1.6-29.6 (7)	0-18 (0)	57	4.8-36 (27.5)	73
Ceftazidime	2-9.8 (6.2)	4-6 (5)	50	5-25 (25)	0-25 (20.5)
Cefepime	1.7-13 (9.7)	4	7.5-15 (11.2)	0-13 (7.8)	19 (19)
SXT	11.7-63.3 (40.2)	43-90.9 (48.5)	20-69.7 (48.9)	15.6-48 (35.3)	31-90.6 (88)
Gentamicin	3.1-47 (11)	13-20 (16.5)	5.8-43 (24.4)	11.7-30 (17.7)	33.3-67 (37.5)
Fosfomycin	0-3 (0.6)				
Amikacin	0.8-32 (4.5)	0-12 (4.4)	6.4-57 (31.7)	3.9-33 (19.5)	2.3-27 (20.5)
Nitrofurantoin	0.05-18 (5.3)	3.5-57 (36.3)	4.4-30 (17.2)	9.8-76 (11.6)	
Ciprofloxacin	6.2-39 (18.5)	0-17 (6.7)	7.9-43 (17.1)	5.8-30 (18)	8.1-52 (22)
Pip-tazo	3.1-17 (10)	1.6	22.7	15.3-35 (22.6)	19
Imipenem	0-3 (1)	0-10 (4)	0-7 (0)	0-5 (0)	7-17 (13)

Amx-Clav= Amoxicillin-clavulanic acid; SXT= Trimetoprim-sulfametoxazol; Pip-tazo=Piperacillin-Tazobactam
Median ratio is presented in bold

Discussion

Trimethoprim sulfamethoxazole, quinolones, beta-lactams, nitrofurantoin, and fosfomycin have long been the recommended antibiotic choices in CA-ABCs (2). In almost all cases, antimicrobial therapy is initiated empirically before the results of urine culture are available. The most important factors that influence the selection of antimicrobial agents are the probable susceptibility of the organism, ease of administration, and the relative cost. The prevalence of antimicrobial resistance in both community and hospital patients with UTI are increasing and can vary according to region (5,6). For example, the 2005-2006 resistance rates of community acquired *E. coli* isolates in England were ampicillin 54%, amoxicillin/clavulanate 12%, ciprofloxacin 9%, nitrofurantoin 5%, and trimethoprim 39% (7), and in Spain fosfomycin 1.7%, nitrofurantoin 3.8%, amoxicillin-clavulanic 8.1%, cefuroxime 8.9%, and ciprofloxacin 23.9% were nonsusceptible (8). As the problem of antimicrobial resistance became more widespread, the use of narrow-spectrum antimicrobial agents turned out to be less feasible and in CA-ABCs, which have traditionally been readily treatable, therapeutic challenges began to appear (9). On the other hand, the costs of antibiotic resistance are generally ignored in economic evaluations of alternative strategies to manage infectious diseases. In a British study, there were significantly higher antibiotic costs for patients whose UTIs were resistant to at least one antibiotic compared with those with sensitive infections (10).

E. coli is by far the most frequent infecting organism in acute UTIs. In recurrent urinary tract infections, especially in the presence of structural abnormalities of the urinary tract, the relative frequency of infection caused by Proteus, Pseudomonas, Klebsiella, and Enterobacter species and by enterococci and staphylococci increases greatly. More than 95% of urinary tract infections are caused by a single bacterial strain in CA-ABC (11). According to our data *E. coli* and Klebsiella species were significant uropathogens in Turkey in CA-ABC and various gram-positives or negatives were seen infrequently with less than 5% ratios. Thus, the antibiotic susceptibility patterns of these 2 microorganisms, of *E. coli* in particular, should be taken into consideration in the management of CA-ABC.

In vitro resistance is expected to correlate with clinical and bacteriologic response to therapy in most infections. However, because most antimicrobial agents used to treat UTls can achieve high urinary concentrations, it may not translate into therapeutic failure (2). McCarty et al. found 50% bacterial eradication and 60% clinical cure rates among women infected with a SXT resistant uropathogen treated with the same drug (12). Evolving evidence suggests that SXT remains optimal first-line empiric therapy where resistance prevalence is lower than 20% (2,13) and this threshold is extrapolated to other antibiotics (14). It appears that half of uropathogens in Turkey are SXT resistant and if we interpret the Turkish data according to the results of McCarty as a model, which shows therapeutic failures in half of the patients when the infecting pathogen is SXT-resistant, then one fourth of Turkish patients would not be cured adequately. As a result, SXT should not remain the drug of choice for empiric therapy owing to the cumulative data in Turkey.

Fluoroquinolones are preferred as initial agents for empiric therapy of UTI in an area where resistance is likely to be of concern, particularly for SXT (15,16). They have been thought to show high bacteriological and clinical cure rates, as well as low rates of resistance, among most common uropathogens (17,18) Moreover, fluoroquinolones also have a significant postantibiotic effect against gram-negative organisms (19). However, it was shown that there are negative impacts of ciprofloxacin resistance to short-term outcomes of CA-ABC patients (20). In a local Turkish study, which evaluated the fluoroquinolone resistance trends, 2% nonsusceptibility in 1990 reached to 20% in 2001 (21). In another Turkish study, minimum inhibitory concentration (MIC) of fluoroquinolones in community acquired *E. coli* strains were assessed between 1999 and 2002 (22). Although MIC 50 of the isolates was not affected, MIC 90 values increased 4-fold for ciprofloxacin and 2-fold for both ofloxacin and levofloxacin in that 3-year period. Consequently, the extensive uses of fluoroquinolones in Turkey have led to obvious increases in resistance rates in the community. Today, the median rates of ciprofloxacin nonsusceptibilities

in *E. coli* and Klebsiella strains were 18% for both microorganisms, and alas these drugs are also at the edge of 20% nonsusceptibility threshold.

Ampicillin and amoxicillin had been active against the enteric gram-negative bacteria. These antibiotics have an identical spectrum of activity and are not stable to beta-lactamases. Amoxicillin is better absorbed from the intestine when administered orally and yields higher blood and urine levels. However, increased resistance to aminopenicillins in community acquired UTI isolates is seen in many parts of the world (7,23-26). Accordingly, more than half of the community-acquired *E. coli* strains were resistant to aminopenicillins in Turkey. On the other hand, Klebsiella strains usually show intrinsic resistance to aminopenicillins. Nevertheless, surveys of clinical strains revealed that some isolates of Klebsiella that carry bla_{SHV} remain susceptible to aminopenicillins (27). Consequently, these drugs can no longer be used empirically in CA-ABCs in Turkey.

The resistance profile of amoxicillin clavulanate seems to exceed the 20% threshold. The same is true to a degree for the first and the second generation cephalosporins. However, third and fourth generation cephalosporins seem to be more reliable with less than 10% resistance profiles in this part of the world. In gram-negative pathogens, beta-lactamases remain the most important contributing factor to beta-lactam resistance, and their increasing prevalence, as well as their alarming evolution, seems to be directly linked to the clinical use of novel sub-classes of beta-lactams. Extended-spectrum beta-lactamases (ESBL) are capable of hydrolyzing penicillins (e.g. ampicillin and piperacillin), cephalosporins and the monobactam aztreonam (28). In a study performed in Turkey by Yılmaz et al. on the risk factors for ESBL production in *E. coli* or *K. pneumoniae* isolates obtained from CA-ABC, the isolates that do not produce these enzymes were all susceptible to second, third, and fourth generation cephalosporins. Thus, ESBL production seems to be the main mechanism in CA-ABC agents for resistance to cephalosporins. Moreover, the resistance profiles of aminoglycosides, SXT, fluoroquinolones, and beta-lactams other than carbapenems in that study were significantly higher in ESBL producers, leading to the understanding that the extensive use of one of these antibiotics would decrease the efficacy of the other drugs too (29). In a multicentric study from Spain, cure rates were 93% in CA-ABC cystitis patients treated with amoxicillin-clavulanate when the infecting agent was susceptible. However, only 56% of the cases were cured when the uropathogens were intermediate or full resistant and the difference between the 2 groups was significant (30). On the other hand, recurrences are common in beta-lactam use in UTIs due to the fact that either beta-lactam agents are less effective in bacteriuria eradication or owing to increasing in vitro resistance (31). Therefore, they are not preferred agents in the treatment of UTIs. Beta-lactams can be preferred in certain settings such as pregnancy or both ampicillin and amoxicillin may still be appropriate choices when enterococci are suspected (2).

The major drawback that led to decreased use of aminoglycosides during the last decade was the adverse effects. Aminoglycoside antibiotics are equally effective as fluoroquinolones in achieving a clinical improvement in patients with UTIs and the discontinuation of therapy rates of these different classes of antibiotics are similar. The present data support the use of aminoglycosides in patients with UTI who are not immunosuppressed, without renal dysfunction and who are not pregnant (32), but the most important shortcoming was that these drugs have only parenteral formulations and this may cause problems during administration to outpatients. However, in certain circumstances as in therapeutic failures, gentamicin can be recommended as an empirical regimen in Turkey. Due to the evolving resistance burden, however, it would be more rational to reserve amikacin for more resistant and culture proven pathogens.

Nitrofurantoin has been in clinical use for several decades and is one of the oldest urinary anti-infective agents. It is used primarily for the treatment of cystitis since it does not attain appreciable serum levels. It is 90% renally excreted, and therefore the urine concentration is very high, making it an effective urinary anti-infective agent for most gram-positive and gram-negative uropathogens (33). The drug is well tolerated, and generally demonstrates a consistently low level of resistance among *E. coli*, gram-positive cocci, and many gram-negative species. Nevertheless, nitrofurantoin is less effective against

Proteus species, and some Enterobacter and Klebsiella strains. According to Turkish data the median resistance rate in *E. coli* is around 5% while one third of Klebsiella and Proteus species seem to confer resistance to nitrofurantoin. In one study, nitrofurantoin was less effective than SXT when both were given for 3 days (34), but, in a recent report, a 5-day course of nitrofurantoin was found to be equivalent to a 3-day course of SXT for clinical cure (35). Consequently, nitrofurantoin appears to be a safe and generally effective agent for the treatment of CA-ABC in Turkey, but it should be administered for a minimum of 5 days.

Another oral drug, fosfomycin has been approved for use as single-dose therapy for the treatment of acute uncomplicated cystitis (2,36). Although the drug eliminates *E. coli* or *Enterococcus faecalis*, it is not approved for use in cystitis caused by *S. saprophyticus* or for treatment of pyelonephritis. It achieves very high concentrations in the urine and persists in the urine for more than 24 h (37). The efficacy of fosfomycin was also proved in a Turkish study, in which the drug was given as 3 g once daily for 3 days. In this study, the overall clinical and microbiological successes were 94.3% and 78.5%, respectively (38). In another Turkish study, 3 g of single dose fosfomycin was equal to 3 days of ciprofloxacin treatment, although side effects were more frequent in the ciprofloxacin arm (39). Nonetheless, it is generally accepted that single-dose therapy with fosfomycin was less effective in eradicating bacteriuria than was SXT for 10 days or ciprofloxacin for 7 days (2). Moreover, fosfomycin was effective on all ESBL producers of CA-ABC with a high cure rate (30,38). Although fosfomycin seems to be a suitable first-line medication according to Turkish epidemiology, therapeutic failures should be monitored.

Current management of CA-ABC is usually empirical, without the use of a urine culture or susceptibility testing to guide therapy. The rationale for this approach is based on the narrow and predictable spectrum of etiologic agents that cause acute cystitis and their susceptibility patterns (2,40). In vitro data show that significant uropathogens in Turkey are fosfomycin and nitrofurantoin susceptible and these 2 drugs may serve as baseline therapeutic options, but caution seems to be indicated for empirical fluoroquinolone use due to elevated resistance profiles. If the clinician is to prefer beta-lactams on an empirical basis in certain situations like pregnancy, third generation cephalosporins, or higher beta lactam choices appear to be rational. Similarly, aminoglycosides seem to be logical choices, although potential side effects or the absence of oral formulations of these drugs should be taken into consideration. Finally, the most widely used antibiotic, SXT, is no longer suitable in Turkey. Under the light of Turkish data, urine culture and susceptibility tests should be considered seriously when therapy fails.

References

1. Wilson WR, Henry NK. Urinary tract infectious. In: Wilson WR SM, ed. Current diagnosis and treatment in infectious diseases USA: McGraw- Hill: İstanbul: Nobel Tıp Kitabevi 2000: 220-30.
2. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis, 1999; 29: 745-58.
3. Türkiye İstatistik Kurumu. http://www.tuik.gov.tr/VeriBilgi.do?tb_id=6&ust_id=1. (in Turkish).
4. Kumar MS, Lakshmi V, Rajagopalan R. Occurrence of extended spectrum beta-lactamases among Enterobacteriaceae spp. isolated at a tertiary care institute. Indian J Med Microbiol, 2006; 24: 208-11.
5. Hooton TM. The current management strategies for community-acquired urinary tract infection. Infect Dis Clin North Am, 2003; 17: 303-32.
6. Kahlmeter G, Menday P, Cars O. Non-hospital antimicrobial usage and resistance in community-acquired Escherichia coli urinary tract infection. J Antimicrob Chemother, 2003; 52: 1005-10.
7. Bean DC, Krahe D, Wareham DW. Antimicrobial resistance in community and nosocomial Escherichia coli urinary tract isolates, London 2005-2006. Ann Clin Microbiol Antimicrob, 2008; 7: 13.
8. Andreu A, Planells I. Etiology of community-acquired lower urinary infections and antimicrobial resistance of Escherichia coli: a national surveillance study. Med Clin (Barc), 2008; 130: 481-6.

9. Gupta K, Hooton TM, Stamm WE Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. Ann Intern Med. 2001; 135: 41-50.

10. Alam MF, Cohen D, Butler C, Dunstan F, Roberts Z, Hillier S et al. The additional costs of antibiotics and re-consultations for antibiotic-resistant Escherichia coli urinary tract infections managed in general practice. Int J Antimicrob Agents, 2008; 15:(Epub ahead of print).

11. Sobel JD, Kaye D. Urinary Tract Infections. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6 ed: Churchill Livingstone 2005: 875-904.

12. McCarty JM, Richard G, Huck W, Tucker RM, Tosiello RL, Shan M et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Ciprofloxacin Urinary Tract Infection Group. The American Journal of Medicine, 1999; 106: 292-9.

13. Nicolle L, Anderson PA, Conly J, Mainprize TC, Meuser J, Nickel JC et al. Uncomplicated urinary tract infection in women. Current practice and the effect of antibiotic resistance on empiric treatment. Can Fam Physicia,. 2006; 52: 612-8.

14. McQuilkin M, Lund A, Palmer W. Antimicrobial resistance of uncomplicated urinary tract infections in northern Utah. Clin Lab Sci, 2008; 21: 99-101.

15. Schaeffer AJ. The expanding role of fluoroquinolones. Am J Med, 2002; 113: 45-54.

16. Biswas D, Gupta P, Prasad R, Singh V, Arya M, Kumar A. Choice of antibiotic for empirical therapy of acute cystitis in a setting of high antimicrobial resistance. Indian J Med Sci, 2006; 60: 53-8.

17. Goldstein FW. Antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections in France. Multicentre Study Group. Eur J Clin Microbiol Infect Dis, 2000; 19: 112-7.

18. Tankhiwale SS, Jalgaonkar SV, Ahamad S, Hassani U. Evaluation of extended spectrum beta lactamase in urinary isolates. Indian J Med Res, 2004; 120: 553-56.

19. Amsden GW. Tables of antimicroal agent pharmacology. In: Mandel GL BJDR, ed. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia: Churchill Livingstone, 2000: 551-603.

20. Gagliotti C, Buttazzi R, Sforza S, Moro ML. Resistance to fluoroquinolones and treatment failure/short-term relapse of community-acquired urinary tract infections caused by Escherichia coli, J Infect. 2008; 57: 179-84.

21. Baykan M, Kaya M, Arslan U, Baysal B. İdrar örneklerinden izole edilen E.coli suşlarının antimikrobiyallere duyarlılıklarının değerlendirilmesi (The evaluation of antibiotic susceptibility patterns of E.coli strains isolated from urine specimens). İnönü Üniv Tıp Fak Derg, 2001; 8: 15-7. (in Turkish).

22. Taşbakan MI, Pullukçu H, Yamazhan T, Arda B, Ulusoy S. Toplum kökenli üriner sistem infeksiyonlarından soyutlanan Escherichıa coli suşlarına fosfomisinin in-vitro etkinliğinin diğer antibiyotiklerle karşılaştırılması (The comparison of fosfomycin with other antimicrobials in Escherichia coli strains isolated from community acquired UTIs). ANKEM Derg, 2004; 18: 216-19. (in Turkish).

23. Rafal'skii VV, Rokhlikov IM, Strachunskii LS. Clinicomicrobiological characteristics of community-acquired infections of the urinary tracts in Moscow. Urologia, 2007; 18: 20-3.

24. Gobernado M, Valdes L, Alos JI, Garcia-Rey C, Dal-Re R, Garcia-de-Lomas J. Quinolone resistance in female outpatient urinary tract isolates of Escherichia coli: age-related differences. Rev Esp Quimioter, 2007; 20: 206-10.

25. Hima-Lerible H, Menard D, Talarmin A. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Bangui, Central African Republic. J Antimicrob Chemother, 2003; 51: 192-4.

26. Randrianirina F, Soares JL, Carod JF, Ratsima E, Thonnier V, Combe P, et al. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Antananarivo, Madagascar. J Antimicrob Chemother, 2007; 59: 309-12.

27. Fu Y, Zhang F, Zhang W, Chen X, Zhao Y, Ma J et al. Differential expression of bla(SHV) related to susceptibility to ampicillin in Klebsiella pneumoniae. International journal of antimicrobial agents, 2007; 29: 344-7.

28. Perez F, Endimiani A, Hujer KM, Bonomo RA. The continuing challenge of ESBLs. Curr Opin Pharmacol, 2007; 7: 459-69.

29. Yilmaz E, Akalin H, Ozbey S, Kordan Y, Sinirtas M, Gurcuoglu E et al. Risk factors in community-acquired/onset urinary tract infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. J Chemother, 2008; 20: 581-5.

30. Rodriguez-Bano J, Alcala JC, Cisneros JM, Grill F, Oliver A, Horcajada JP et al. Community infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Arch Intern Med, 2008; 168: 1897-902.

31. Gupta K, Stamm WE. Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. International journal of antimicrobial agents, 2002; 19: 554-6.

32. Vidal L, Gafter-Gvili A, Borok S, Fraser A, Leibovici L, Paul M. Efficacy and safety of aminoglycoside monotherapy: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother, 2007; 60: 247-57.

33. eckentdorf HK, Castringius RG, Spingler HK. Comparative pharmacodynamics, urinary excretion, and half-life determinations of nitrofurantoin sodium. Antimicrob Agents Chemother, 1962; 2: 531-37.

34. Hooton TM, Winter C, Tiu F, Stamm WE. Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. JAMA, 1995; 273: 41-5.

35. Fekete T. 5 days of nitrofurantoin was equivalent to 3 days of trimethoprim-sulfamethoxazole for women with non-complicated cystitis. Evid Based Med, 2008; 13: 80.

36. Knottnerus BJ, Nys S, Ter Riet G, Donker G, Geerlings SE, Stobberingh E. Fosfomycin tromethamine as second agent for the treatment of acute, uncomplicated urinary tract infections in adult female patients in The Netherlands? J Antimicrob Chemother, 2008; 62: 356-9.

37. Patel SS, Balfour JA, Bryson HM. Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. Drugs, 1997; 53: 637-56.

38. Pullukcu H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. Int J Antimicrob Agents, 2007; 29: 62-5.

39. Bozkurt ÖF, Kara C, Akarsu S, Çağlar M, Ünsal A. Semptomatik idrar yolu enfeksiyonu olan kadinlarin tedavisinde tek doz fosfomisin etkinliğinin siprofloksasin ile karşilaştirilması (The comparison of ciprofloxacin and single dose fosfomycin in the management of symptomatic urinary tract infections in women). Türk Urol Derg, 2008; 34: 360-62. (in Turkish).

40. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am, 1997; 11: 551-81.

41. Altoparlak Ü, Özek A, Aktaş F. Üriner sistem infeksiyonlarından izole edilen bakterilerin çeşitli antibiyotiklere duyarlılıkları (The antibiotic susceptibility patterns of bacteria isolated from urinary tract infections). Türk Mikrobiyol Cem Derg, 2001; 32: 167-73. (in Turkish).

42. Timurkaynak F, İnci KE, Arslan H. Toplum kökenli ve nozokomiyal üriner sistem infeksiyonlarından izole edilen etkenlerin dağılımı ve antibiyotik duyarlılığı (The distribution of agents and their antibiotic susceptibilities in community acquired and nosocomial UTIs). Ankara Üniv Tıp Fak Mec, 2001; 54: 287-92. (in Turkish).

43. Savaş L, Güvel S, Turunç T, Savaş N, Arslan H. Toplum kökenli ve nazokomiyal üriner sistem enfeksiyon etkenleri ve antibiyotik duyarlılıklarının karşılaştırılması (The causative agents isolated from community acquired and nosocomial UTIs and comparison of their antibiotic susceptibilities). Türk Üroloji Dergisi, 2003;29: 95-100. (in Turkish).

44. Arslan H, Azap ÖK, Ergönül Ö, Timurkaynak F Risk factors for ciprofloxacin resistance among Escherichia coli strains isolated from community-acquired urinary tract infections in Turkey. Journal of Antimicrobial Chemotherapy, 2005; 56: 914-18.

45. Akay H, Durunay M, Akay A. Üriner sistem enfeksiyonlarından izole edilen mikroorganizmaların dağılımı ve Escherichia coli suşlarında antibiyotik duyarlılığı (The distribution and susceptibility patterns of microorganisms isolated from urinary tract infections). J Ist Faculty Med, 2006; 69: 1-4. (in Turkish).

46. Çetin M, Ocak S, Görür S, Avunduk G. Semtomatik üriner sistem enfeksiyonlarında üropatojenler ve izole edilen Escherichia coli suşlarının antibiyotik duyarlılığı (The uropathogens in symptomatic UTIs and the antibiotic susceptibility of the Escherichia coli strains). ANKEM Derg, 2006; 20: 169-72. (in Turkish).

47. Pullukçu H, Taşbakan MI, Aydemir Ş, Sipahi OR, Turhan A, Özinel MA, Ulusoy S. İdrar kültürlerinde soyutlanan bakteriler ve çeşitli antibiyotiklere invitro duyarlılıklarının değerlendirilmesi (The bacteria isolated from urine cultures and investigation of their susceptibilities to various antibiotics). ANKEM Derg, 2006; 20: 26-30.

48. Akan ÖA. İbn-i Sina hastanesinde poliklinik idrar örneklerinden izole edilen Escherıchıa coli izolatlarının ilk seçenek antibiyotiklere direnç durumu (The resistance of E.coli strains isolated from outpatients in Ibn-i Sina Hospital). Ankara Üniv Tıp Fak Mecm, 2003; 56: 147-50. (in Turkish).

49. Dündar D, Topçu AW, Tamer GS. İdrar yolu infeksiyonu etkenleri ve antimikrobiyal duyarliliklari (The agents of UTIs and their antibiotic susceptibilities). Klimik Dergisi, 2008; 21: 7-11 (in Turkish).

50. Ay S, İşeri LA, Duman B. İdrar örneklerinden izole edilen gram olumsuz mikroorganizmaların antibiyotiklere duyarlılıkları (The antibiotic susceptibility of gram-negatives isolated from urine specimens). İnönü Üniversitesi Tıp Fakültesi Dergisi, 2003; 10: 59-62. (in Turkish).

51. Sümer Z, Coşkunkan F, Vahapoğlu H, Bakır M. The resistance of Escherichia coli strains isolated from community-acquired urinary tract infections. Advances in Therapy, 2005; 22 : 419-23.

52. Yuluğkural Z, Mutlu B. İdrar kültürlerinden izole edilen Escherichia coli suşlarının sık kullanılan antibakteriyellere karşı duyarlılıkları (The susceptibilities of Escherichia coli strains isolated from UTIs to commonly used antibiotics). Trakya Univ Tıp Fak Derg, 2007; 24: 6-11. (in Turkish).

53. Erdem H, Kilic S, Pahsa A, Besirbellioglu BA. Gram negative bacterial resistance to gram negative bacteria for cephalosporins in community acquired infections in Turkey. J Chemother, 2005; 17: 61-5.

54. Akçam ZF, Kaya O, Gönen İ, Yaylı G. İdrar Örneklerinden Izole Edilen Toplum ve Hastane Kaynaklı Escherichia coli suşlarında Antibiyotik Direnci (The antibiotic resistance of Escherichia coli strains isolated from nosocomial and community acquired infections). OMU Tıp Dergisi, 2004; 21: 23-7. (in Turkish).

55. Erdem H, Avcı A, Pahsa A. Toplum kaynaklı üropatojenik Escherichia coli suşlarında antibakteriyel direnç (The antibiotic resistance in community acquired uropathogenic Escherichia coli strains). ANKEM Derg, 2004; 18: 40-4. (in Turkish).

56. Karaca Y, Coplu N, Gozalan A, Oncul O, Citil BE, Esen B Co-trimoxazole and quinolone resistance in Escherichia coli isolated from urinary tract infections over the last 10 years. Int J Antimicrob Agents, 2005; 26: 75-7.

57. Eroğlu M, Koçoğlu E, Karabay O, Semercioöz A. Toplum kaynaklı erişkin üriner sistem enfeksiyonlarından izole edilen Enterobacteriacea türlerinin bazı antibiyotiklere duyarlılıkları (The susceptibility of Enterobacteriacea species isolated from community acquired adult UTIs to various antibiotics). Türk Üroloji Dergisi, 2007; 33: 100-3. (in Turkish).

58. Ertuğrul MB, Çolak N İdrardan izole edilen toplum kökenli Escherichia coli suşlarının antibiyotik duyarlılıkları (The antibiotic susceptibilities of community-acquired urinary E. coli isolates). ANKEM Derg, 2004 ;18: 161-5. (in Turkish).

59. Ertuğrul MB, Güleç LA, Akal D, Çağatay AA, Özsüt H, Eraksoy H. Üropatojen Escherichia coli suşlarının tedavide sık kullanılan antibiyotiklere duyarlılıkları (The susceptibilities of uropathogenic E. coli strains to frequently used antibiotics). Klimik Derg. 2004; 17: 132-6. (in Turkish).

60. Kurutepe S, Surucuoglu S, Sezgin C, Gazi H, Gulay M, Ozbakkaloglu B. Increasing antimicrobial resistance in Escherichia coli isolates from community-acquired urinary tract infections during 1998-2003 in Manisa, Turkey. Jpn J Infect Dis, 2005; 58: 159-6.

61. Sucu N, Boz GA, Bayraktar Ö, Çaylan R, Aydın K, Köksal İ. Üropatojen Escherichia coli suşlarının antibiyotik duyarlılıklarının yıllar içerisindeki değişimi (The changes in antibiotic susceptibilities in uropathogen Escherichia coli strains). Klimik Derg. 2004; 17: 128-31. (in Turkish).

62. Şencan İ, Sevinç ME. Toplum Kökenli Üropatojen Escherichia coli izolatlarında antimikrobiyal direncin izlemi (The follow up of antibiotic resistance in community acquired Escherichia coli isolates). Klimik Derg, 2002; 15: 85-8. (in Turkish).

63. Bayraktar B, Özcan N, Borahan S, Başarı F, Bulut E. Yatan ve ayaktan hastalardan izole edilen üriner sistem enfeksiyonu etkeni gram negatif çomaklarda antibiyotiklere direnç (The antibiotic resistance of gram negatives obtained from urinary tract infections in inpatients and outpatients). ANKEM Derg, 2004; 18: 137-40. (in Turkish).

64. Otağ F, Yıldız Ç, Delialioğlu N. İdrardan soyutlanan Escherichia coli suşlarında antibiyotik direnci (The antibiotic resistance in Escherichia coli strains isolated from urine). ANKEM Derg, 2003; 17: 284-7. (in Turkish).

65. Ozyurt M, Haznedaroglu T, Sahiner F, Oncul O, Ceylan S, Ardic N et al. Antimicrobial resistance profiles of community-acquired uropathogenic Escherichia coli isolates during 2004-2006 in a training hospital in Istanbul. Mikrobiyol Bul. 2008; 42: 231-43.

66. Köken G, Aşık G, Çifçi İH, Çetinkaya Z, Aktepe OC, Yılmazer M. Toplum kökenli üriner sistem infeksiyonu etkeni E.coli suşlarında fosfomisin trometamol etkinliği (The efficacy of fosfomycin trometamol in community acquired E.coli strains. ANKEM Derg, 2008; 22: 23-7. (in Turkish).

67. Afşar İ, Gönül B, Şener AG, Türker M. In-vitro susceptibility of clinical isolates of Escherichia coli to fosfamycin trometamol and other antibiotics. ANKEM Derg. 2005; 19: 77-9. (in Turkish).

68. Okaygün E, Kipritçi Ö, Akman A, Aydın D. Toplum ve hastane kaynaklı üriner sistem enfeksiyonlarında etken mikroorganizmalar ve antibiyotik direnci (The causative pathogens and their antibiotic susceptibilities in community acquired and nosocomial UTIs). ANKEM kongresi Antalya, 2006. (in Turkish).

69. Koçoğlu E, Karabay O, İnce NK, Özkardeş F, Yıldırım R. Toplum kaynaklı üriner sistem enfeksiyonlarından izole edilen E. coli izolatlarından genişletilmiş spektrumlu beta laktamaz ve bazı antibiyotiklere direnç sıklığının araştırılması (The investigation of ESBL production and resistance profiles to various antibiotics in E.coli strains isolated form community acquired UTIs). ANKEM Derg, 2007; 21: 5-9. (in Turkish).

70. Bayraktar B, Özcan N, Borahan S, Başarı F, Bulut E. Yatan ve ayaktan hastalardan izole edilen üriner sistem enfeksiyonu etkeni gram negatif çomaklarda antibiyotiklere direnç. ANKEM Derg, 2004; 18: 137-40.