Appropriateness of the Empirical Antibiotherapy Choices of Primary Care Physicians for the Treatment of Uncomplicated Cystitis

Komplike Olmayan Sistit Tedavisinde Birinci Basamak Hekimlerinin Ampirik Antibiyoterapi Seçimlerinin Uygunluğu

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ABSTRACT

Objective: In primary care, the frequency of inappropriate antibiotic prescriptions for urinary tract infections is very high. In this study, we aimed to evaluate the appropriateness of antibiotic choices of primary care physicians for treating uncomplicated cystitis in adult patients considering relevant guidelines.

Methods: The study was conducted with family physicians working in family health centers, general practitioners working as family physicians, and family medicine specialists and assistants working in secondary and tertiary care hospitals in İstanbul between December 2022 and January 2023. Google Forms was used to create a survey for data collection and was distributed to physicians online.

Results: The study included 421 physicians. Among the physicians, the rates of fosfomycin, nitrofurantoin, cephalosporin, sulfonamide, fluoroquinolone (FQ), and penicillin choices were determined to be 83.8% (n=353), 52.3% (n=220), 24% (n=101), 14.5% (n=61), 26.6% (n=112), and 10.7% (n=45). Accepting the use of FQ and aminopenicillin as inappropriate in the first-line treatment of uncomplicated cystitis, younger physicians with shorter tenure were more likely to prescribe appropriate empirical antibiotics (p=0.001). In addition, general practitioners working as family physicians applied inappropriate empirical treatment at a significantly higher rate than family medicine specialists and assistants (39.3% vs. 10% and 11.9%, respectively).

Conclusion: A significant portion of the primary care physicians who participated in this study were determined to prefer antibiotics not recommended in the relevant guidelines for the empirical treatment of uncomplicated cystitis. The higher rates of inappropriate treatment choices of general practitioners and senior physicians in empirical treatment indicate the need for in-service training in primary healthcare services.

Keywords: Primary health care, cystitis, urinary tract infection, anti-bacterial agents

ÖZ

Amaç: Birinci basamak sağlık hizmetlerinde idrar yolu enfeksiyonları (İYE) için uygunsuz antibiyotik reçete edilmesi prevalansı oldukça yüksektir. Bu çalışmada, birinci basamak sağlık hizmeti veren hekimlerin non-komplike sistit ile başvuran erişkinlerde antibiyotik seçiminin uygunluğunu kılavuzlar eşliğinde değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya Aralık 2022 ve Ocak 2023 tarihleri arasında İstanbul ilinde aile sağlığı merkezlerinde görev yapan aile hekimliği uzmanları, aile hekimi olarak görev yapan pratisyen hekimler, ikinci ve üçüncü basamak hastanelerde görev alan aile hekimliği uzmanı ve asistanları dahil edilmiştir. Veri toplama amacıyla Google Formu oluşturularak online olarak bu formlar hekimlere ulaştırılmıştır.

Bulgular: Çalışmaya 421 hekim dahil edilmiştir. Fosfomisin, nitofurantoin, sefalosporin, sulfonamid, florokinolonon (FQ) ve penisilin için kullanım oranları sırasıyla; %83,8 (n=353), %52,3 (n=220), %24 (n=101), %14,5 (n=61), %26,6'sı (n=112), %10,7 (n=45) bulunmuştur. FQ ve aminopenisilinlerin non-komplike sistitin birinci basamak tedavisinde kullanımlarının olmadığı kabul edildiğinde, yaşça daha küçük ve görev süresi kısa olan hekimlerde doğru ampirik antibiyotik reçete etme oranı daha yüksektir (p=0,001). Ayrıca aile hekimliği yapan pratisyen doktorlar, aile hekimliği uzmanı ve asistanlarına göre anlamlı olarak daha yüksek oranda yanlış ampirik tedavi uygulamışlardır (%39,3 vs. %10 ve %11,9).

Sonuç: Birinci basamak sağlık hizmeti veren hekimlerimizin önemli bir kısmı halen rehberlerde önerilmeyen antibiyotikleri non-komplike sistitte ampirik tedavide reçete etmektedirler. Pratisyen hekimlerin ve yaşça büyük hekimlerin ampirik tedavide daha yüksek oranda yanlış tedavi seçimleri bize birinci basamak sağlık hizmetlerinde hizmet içi eğitim ihtiyacını göstermektedir.

Anahtar Kelimeler: Birinci basamak sağlık hizmetleri, sistit, idrar yolu enfeksiyonu, antibakteriyel ajanlar

INTRODUCTION

Uncomplicated cystitis is defined as acute, sporadic, or recurrent cystitis that is limited to non-pregnant women without comorbidities or known anatomical and functional abnormalities in the urinary tract (1). One in every three women experiences at least one episode of cystitis before the age of 24 (2). The most important cause of uncomplicated cystitis is *Escherichia coli* (*E. coli*). The presence of symptoms of the lower urinary system, such as dysuria, frequency, and urgency, together with supporting anamnesis, is sufficient for the diagnosis of this condition (1).

In primary healthcare services, the frequency of inappropriate antibiotic prescriptions for urinary tract infections (UTIs) is very high, with fluoroquinolone (FQ) being one of the leading inappropriate choices (3). The resistance of common UTI pathogens to FQ and trimethoprim-sulfamethoxazole (TMP-SMX) is increasing every year, and the prevalence of extended-spectrum beta-lactamase and other multidrug resistance is also increasing (4,5). It has been stated that the use of antibiotics only when needed should be a standard approach to reduce adverse drug effects and antibiotic resistance (6). Given the negative effects of inappropriate antibiotic use on individuals and societies, physicians should select appropriate antibiotic therapy for managing UTIs. In addition, healthcare professionals should be aware of local antibiotic resistance (6).

In this study, we aimed to evaluate the appropriateness of antibiotic choices of primary care physicians for treating adult patients with uncomplicated cystitis considering relevant international guidelines.

METHODS

Family physicians working in family health centers (FHCs), general practitioners working as family physicians, and family medicine specialists and assistants working in secondary and tertiary care hospitals in İstanbul between December 2022 and January 2023 were included in the study. A Google form was created for data collection and was distributed to physicians online. An invitation to participate in the study was sent to all participants via e-mail on December 1, 2022. Before completing the survey, all participants were directed to an informed consent page, and only those who agreed to participate in the study were able to access the form. The responses given until January 31, 2022 were recorded. Forms with missing responses were invalid and excluded.

The age, gender, title (general practitioner, assistant, or specialist), center, and professional experience of the participants were determined using the survey. Another question in the survey was related to which cases of UTIs the physicians would request a urinalysis for and whether this would be accompanied by urine culture. The patient profile, which was created to direct physicians to the preliminary diagnosis of uncomplicated cystitis, was planned as a healthy, non-pregnant female patient, and the empirical antibiotic choices of the participants were questioned by allowing more than one response. In accordance with the European Association of Urology (EAU) Urological Infections Guidelines (1) and the Infectious Diseases Society of America (IDSA) (7) guidelines, physicians who included FQ and/or aminopenicillin in their empirical antibiotic prescriptions had inappropriate treatment choices, and the rates of inappropriate antibiotic use were compared according to the demographic data of the physicians.

The methodology of the study and the survey were approved by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2023-01-18, date: 09.01.2023).

Statistical Analysis

Frequency and rates were used as descriptive statistics. The chi-square test was conducted to analyze qualitative, independent data. The SPSS v. 28.0 software package was used for statistical analysis.

RESULTS

A total of 421 physicians participated in the study. Demographic data on the participating physicians are given in Table 1. Accordingly, 37.8% (n=159) of the physicians were <30 years old, 35.6% (n=150) were 30-40 years old, 19% (n=80) were 40-50 years old, and 7.6% (n=32) were >50 years old. Of the entire physician group, 54.9% (n=231) were men and 45.1% (n=190) were women.

The rate of family medicine assistants was 25.9% (n=109), and that of family medicine specialists was 14.3% (n=60).

The rate of general practitioners working as family physicians was found to be 59.9% (n=252). When the centers at which the participants worked were examined, it was determined that 62.2% (n=262) physicians worked in FHCs, while 37.8% (n=159) worked in secondary or tertiary hospitals.

Regarding the question, "In which cases would you request a urinalysis?", the physicians were able to select more than one option (Table 2). The 'yes' response was recorded at the following rates: presence of systemic symptoms, 96.9% (n=408); pregnancy, 92.2% (n=388); presence of a urinary tract catheter, 60.6% (n=255); presence of a concomitant chronic disease, 32.5% (n=137); and older age, 27.6% (n=116). In addition, 6.2% (n=26) of the physicians stated that they would request a urine culture in addition to urinalysis.

The physicians were presented with a patient profile that suggested uncomplicated cystitis and were asked which empiric antibiotic they would prefer for treating such a patient. They could select more than one option. For empirical treatment, most physicians chose fosfomycin (83.8%, n=353), followed by nitrofurantoin (52.3%, n=220), cephalosporins (24%, n=101), and sulfonamides (14.5%, n=61). In addition, 26.6% (n=112) of the physicians stated that they would use FQ, and 10.7% (n=45) stated that they would use penicillin in the empirical treatment of UTIs.

Quinolones and aminopenicillins should not be used in the first-line treatment of uncomplicated cystitis, and physicians who selected at least one of these antibiotics were considered to have inappropriate empirical treatment choices. When the rates of inappropriate responses were compared according to the age, gender, title, and tenure of the participants (Table 3), they did not significantly differ between male and female physicians (p=0.348); however, there were statistically significant differences according to age and tenure. Younger physicians and those with shorter tenure had statistically significantly higher rates of appropriate empirical treatment choices than older physicians and those with longer tenure, respectively (p=0.001). In addition, general practitioners working as family physicians had inappropriate empirical treatment choices at a significantly higher rate than family medicine specialists and assistants (39.3% vs. 10% and 11.9%, p=0.002).

DISCUSSION

Although the need for antibiotics for treating symptomatic UTIs is clear, the most important decision concerns antibiotic selection and optimization of treatment duration (3). Another question is whether urinalysis or urine culture should be requested in addition to the initiation of empirical antibiotherapy. In patients presenting with the typical symptoms of uncomplicated cystitis, urinalysis may lead to only a minimal increase in diagnostic accuracy (8).

Table 1. Demographic data of physicians

		n (%)
Age	<30 years	159 (37.8)
	30-40 years	150 (35.6)
	40-50 years	80 (19.0)
	>50 years	32 (7.6)
Gender	Male	231 (54.9)
	Female	190 (45.1)
Title	Specialist	60 (14.3)
	Assistant	109 (25.9)
	Practitioner	252 (59.9)
Center	Family health center	262 (62.2)
	Hospital	159 (37.8)
Tenure	<10 years	194 (46.1)
	10-20 years	142 (33.7)
	20-30 years	63 (15.0)
	>30 years	21 (5.0)
Empirical treatment choice	Appropriate	278 (66.0)
	Inappropriate	142 (33.7)

Table 2. Survey questions and distribution of physicians' responses

In which cases would you request urinalysis?	Systemic symptoms (sweating with fever, fatigue, nausea, and vomiting, etc.)	408 (96.9%)
	Pregnancy	388 (92.2%)
	Urinary catheter	255 (60.6%)
	Concomitant chronic disease	137 (32.5%)
	Older age	116 (27.6%)
Would you like to request urine culture with urinalysis?	Yes	26 (6.2%)
	No	395 (93.8%)
A healthy, non-pregnant female patient presented with a urinary tract infection. What would be your empirical antibiotic choice?	Fosfomycin	353 (83.8%)
	Nitrofurantoin	220 (52.3%)
	Quinolinone	112 (26.6%)
	Cephalosporin	101 (24%)
	Sulfonamide	61 (14.5%)
	Penicillin	45 (10.7%)
	Other	30 (7.1%)

Table 3. Comparative analysis of appropriate response rates according to physicians' demographic data

n (%)		Appropriate antibiotic choice	Inappropriate antibiotic choice	p-value
		n (%)	n (%)	
Age	<30 years	122 (76.7)	37 (23.3)	0.001$^{x^2}$
	30-40 years	86 (57.3)	64 (42.7)	
	40-50 years	53 (66.3)	27 (33.8)	
	>50 years	17 (53.1)	15 (46.9)	
Gender	Male	148 (64.1)	83 (35.9)	0.348$^{x^2}$
	Female	130 (68.4)	60 (31.6)	
Title	Specialist	54 (90)	6 (10)	0.002$^{x^2}$
	Assistant	96 (88.1)	13 (11.9)	
	Practitioner	153 (60.7)	99 (39.3)	
Center	Family health center	180 (68.7)	82 (31.3)	0.138$^{x^2}$
	Hospital	98 (61.6)	61 (38.4)	
Tenure	<10 years	144 (74.2)	50 (25.8)	0.001$^{x^2}$
	10-20 years	93 (65.5)	49 (34.5)	
	20-30 years	35 (55.6)	28 (44.4)	
	>30 years	6 (28.6)	15 (71.4)	

$^{x^2}$Chi-square test

The EUA guidelines indicate the use of the urine dipstick test at a 'weak' recommendation level in the diagnosis of uncomplicated cystitis and state that urine culture should only be used in the presence of suspected pyelonephritis, symptoms that persist despite the completion of treatment or recur within four weeks, atypical symptoms, or pregnancy (1). In a study conducted to increase diagnostic accuracy and reduce unnecessary antibiotic use in women with suspected cystitis, the factors associated with a positive urine culture were dysuria, positivity in urinalysis, and the presence of more than trace amounts of leukocytes (9). Almost all the physicians who participated in our study stated that they would request a urinalysis in the presence of systemic symptoms, such as fever, sweating, fatigue, nausea, vomiting (96.9%), and pregnancy (92.2%). Although there is no guideline recommendation related to older age, the presence of a urinary catheter, or comorbidities, we determined that a urinalysis would be requested in these cases by 60.6%, 32.5%, and 27.6% of the physicians, respectively. Lastly, the rate of those who requested a urine culture with a urinalysis was determined to be only 6.2%.

In the empirical treatment of uncomplicated cystitis, the EAU guidelines recommend a single 3 g dose of fosfomycin, 3x400 mg of pivmecillinam for three to five days (not available in Türkiye), or 2x100 mg of nitrofurantoin for five days. As an alternative, cephalosporins or TMP-SMX can be administered if the resistance pattern is suitable (1). Similarly, in the IDSA guidelines, single-dose fosfomycin, five-day nitrofurantoin, and TMP-SMX are recommended as appropriate antibiotherapy options for uncomplicated cystitis in adults, whereas ciprofloxacin, levofloxacin, and TMP-SMX are presented as the first-line treatment options for pyelonephritis (6,7,10).

Nitrofurantoin is an old antibiotic that specifically targets the urinary tract and has bacteriostatic effects at low concentrations and bactericidal effects at high concentrations (11). In a study conducted by Grigoryan et al. (12) in the USA, nitrofurantoin was found to be the second most frequently used antibiotic for treating uncomplicated cystitis in primary healthcare services. In the same study, other mostly prescribed antibiotics were determined to be FQ and TMP-SMX, and it was reported that the treatment durations were longer than recommended by the guidelines. Older age and the presence of diabetes were found to be the most important predictors of a treatment duration longer than necessary (12). Although nitrofurantoin is recommended as the first-line treatment option by the EAU and IDSA guidelines, which were used as reference standards in our study, we determined a rate of 52.3% for nitrofurantoin preference among physicians in the empirical treatment of uncomplicated cystitis.

Although fosfomycin has been used for many years in Türkiye, its resistance rates are very low. Fosfomycin is a phosphoenolpyruvate analog and a fermentation product of *Streptomyces viridochromogenes*, *Streptomyces fradiae*, and *Streptomyces wedmorensis* (11). Grigoryan et al. (12) reported that fosfomycin was not preferred by primary care physicians. We observed that 83.8% of the physicians preferred fosfomycin in the empirical treatment of uncomplicated cystitis, as recommended by both the EAU and IDSA guidelines.

The EAU guidelines do not indicate the use of FQ or aminopenicillins at a 'strong' recommendation level in uncomplicated cystitis (1). In addition to FQ being known to cause serious adverse effects, their use in cystitis increases antibiotic resistance and paves the way for *Clostridium difficile* infections (6,13). The aminopenicillin resistance of *E. coli* is very common, and the probability of treatment failure with this agent is very high (1,7). Similarly, the IDSA guidelines exclude beta-lactams as a suitable option for

the treatment of UTIs because of their low efficacy and the availability of many other antibiotic options for adults with appropriate local sensitivities (6,7). In our study, 26.6% of the physicians preferred FQ and 10.7% preferred penicillin in the empirical treatment of uncomplicated cystitis.

In 2019, the European Medicine Agency took a decision that would be valid in all European Union countries, introducing limitations based on the rational use of FQ to minimize its potential side effects (14). In uncomplicated cystitis, FQ should be used only if other common agents are not appropriate. In a recent study conducted in the USA, it was observed that the most commonly prescribed antibiotic in uncomplicated UTIs was FQ, which is recommended to be used not in first-line treatment but in more serious infections, and that it constituted half of all prescriptions (12,15). FQ is still highly preferred in primary care medicine, despite the resistance of *E. coli* to this agent being 20% in the USA, and this rate is almost ten times that reported for fosfomycin (1-2%) (4).

In a recent study, Chardavoyne and Kasmire (6) examined the antibiotics prescribed for the treatment of UTIs in emergency departments. Similar to our study, they used the IDSA guidelines and UpToDate as a reference for appropriate antibiotic therapy in adult women (6,10). They determined that amoxicillin and beta-lactams constituted 79% of inappropriate antibiotics prescribed for UTIs. In addition, FQ prescribed for cystitis constituted 6% of inappropriate prescriptions, and nitrofurantoin administered for pyelonephritis constituted 12% of inappropriate antibiotic use (6). In the same study, it was also emphasized that the use of antibiotics for longer than recommended contributed to antibiotic resistance, and the rate of antibiotic prescription at the correct dose and duration in adults with uncomplicated cystitis was only 34%.

In the literature, studies of European origin examining compliance with the relevant UTI guidelines have yielded different results. In a study conducted in France, it was observed that only 20% of outpatients presenting with UTIs were treated with the agent, dose, and duration recommended by the guidelines (16). While the rate of use of first-line antibiotics in the empirical treatment of uncomplicated UTI was reported to be 18% in Spain (17), compliance with the guidelines in antibiotic selection was very high in Norway, with the rate of FQ preference being only 6% (18). In a 2014 study covering six European countries, TMP-SMX was the most preferred antibiotic for lower UTIs, whereas the rate of complete treatment compliance was reported to be 72.7% in the Netherlands, 40% in Denmark, 38.3% in Norway, and 22.2% in Slovenia (19). In the current study, sulfonamides were preferred at a rate of 14.5% as the first-line treatment.

In addition to the guideline recommendations on the management of uncomplicated cystitis, knowing the antibiotic resistance profile in Türkiye has an important place in treatment planning. In a large-scale study on this subject, the resistance rates of TMP-SMX, amoxicillin-clavulanate, and FQ among outpatients were found to be 47.1%, 31.5%, and 20.1%, respectively (20). In another study conducted in the pediatric patient group, the antibiotics with the highest resistance in all Gram-negative microorganisms obtained from the urinary tract were as follows: ampicillin (75.1%), cefazolin (59%), ampicillin-subactam (49.7%), ceftriaxone (31.4%), cefixime (33.1%), and TMP-SMX (45.2%). The lowest resistance was found in meropenem (3.2%), whereas other antibiotics with low resistance rates were ertapenem (3.4%), colistin (7.2%), amikacin (16.2%), and ciprofloxacin (21.1%) (21). The authors stated that they found ciprofloxacin resistance to be higher than previously reported. In a more recent study, isolates were examined in urine culture, and the resistance rates were determined to be 81% for ampicillin, 42% for amoxicillin-clavulanic acid, 42% for cefixime, 41% for ciprofloxacin, 40% for TMP-SMX, 18% for gentamicin, 5% for amikacin, 4% for nitrofurantoin, 4% for fosfomycin, and 2% for imipenem (2%) (22). Here, TMP-SMX, which is recommended by the guidelines for first-line treatment, shows a very high resistance pattern in Türkiye. However, it was observed that nitrofurantoin and fosfomycin still have high efficacy.

Our results show that, in primary care, compliance with the relevant guidelines is low in antibiotherapy agent selection for treating uncomplicated cystitis, and there is a need to develop focused strategies to increase this compliance. The ideal antibiotic therapy plan should be determined based on the current local prevalence of resistance to common uropathogens, not merely on drug tolerability. The higher rate of appropriate treatment preferences among younger physicians with shorter tenure and the higher preference for inappropriate antibiotic regimens among general practitioners indicate the need for in-service training in terms of rational antibiotic use. The most important shortcoming of our study is that the participants were limited to family physicians in İstanbul, and therefore, the results cannot be generalized to the whole of Türkiye, considering the sample size. In addition, because the data collection tool used in the study was a survey, the physicians' responses may not reflect their actual preferences in clinical practice or the real situation in the field.

CONCLUSION

A significant portion of the primary care physicians who participated in this study were found to prefer antibiotics that are not recommended in the relevant guidelines and are even considered objectionable due to their side-effect profile and resistance patterns in the empirical treatment of uncomplicated cystitis. The higher rates of inappropriate empirical treatment choices by general practitioners and senior physicians indicate that the approach to uncomplicated cystitis in primary healthcare services should be improved with in-service training.

ETHICS

Ethics Committee Approval: The methodology of the study and the survey were approved by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2023-01-18, date: 09.01.2023).

Informed Consent: Before completing the survey, all participants were directed to an informed consent page, and only those who agreed to participate in the study were able to access the form.

Authorship Contributions

Surgical and Medical Practices: H.P., Concept: H.P., Design: H.P., D.N.Ö., Data Collection or Processing: H.P., Analysis or Interpretation: D.N.Ö., Literature Search: H.P., D.N.Ö., Writing: H.P., D.N.Ö.

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REFERENCES

1. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam, the Netherlands [internet] 2022. Accessed on: 05/03/2023 Available from https://uroweb.org/guidelines/urological-infections/chapter/the-guideline.
2. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002;113:5-13.
3. Grigoryan L, Zoorob R, Germanos G, Sidani M, Horsfield M, Khan F, et al. Case-based audit and feedback around a decision aid improved antibiotic choice and duration for uncomplicated cystitis in primary care clinics. Fam Med Community Health 2021;9:e000834.
4. Sanchez GV, Babiker A, Master RN, Luu T, Mathur A, Bordon J. Antibiotic Resistance among Urinary Isolates from Female Outpatients in the United States in 2003 and 2012. Antimicrob Agents Chemother 2016;60:2680-3.
5. Bidell MR, Palchak M, Mohr J, Lodise TP. Fluoroquinolone and Third-Generation-Cephalosporin Resistance among Hospitalized Patients with Urinary Tract Infections Due to Escherichia coli: Do Rates Vary by Hospital Characteristics and Geographic Region? Antimicrob Agents Chemother 2016;60:3170-3.
6. Chardavoyne PC, Kasmire KE. Appropriateness of Antibiotic Prescriptions for Urinary Tract Infections. West J Emerg Med 2020;21:633-9.
7. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.
8. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002;287:2701-10.
9. McIsaac WJ, Moineddin R, Ross S. Validation of a decision aid to assist physicians in reducing unnecessary antibiotic drug use for acute cystitis. Arch Intern Med 2007;167:2201-6.
10. Hooton TM, Gupta K. Acute simple cystitis in women. Post TW, editor. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com.
11. Taşbakan MI. Urinary tract infections and rational use of antibiotics. Ankem Derg 2014;28:178-81.
12. Grigoryan L, Zoorob R, Wang H, Trautner BW. Low Concordance With Guidelines for Treatment of Acute Cystitis in Primary Care. Open Forum Infect Dis 2015;2:ofv159.
13. Food and Drug Administration. Fluoroquinolone antimicrobial drugs information. [internet] Available from https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass.htm..
14. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. Quinolone and fluoroquinolone Article-31 referral, [internet] 2019. Available from https://www.ema.europa.eu/en/ documents/referral/quinolone-fluoroquinolone-article-31-referraldisabling- potentially-permanent-side-effects-lead_en.pdf
15. Kobayashi M, Shapiro DJ, Hersh AL, Sanchez GV, Hicks LA. Outpatient Antibiotic Prescribing Practices for Uncomplicated Urinary Tract Infection in Women in the United States, 2002-2011. Open Forum Infect Dis 2016;3:ofw159.
16. Denes E, Prouzergue J, Ducroix-Roubertou S, Aupetit C, Weinbreck P. Antibiotic prescription by general practitioners for urinary tract infections in outpatients. Eur J Clin Microbiol Infect Dis 2012;31:3079-83.
17. Llor C, Rabanaque G, López A, Cots JM. The adherence of GPs to guidelines for the diagnosis and treatment of lower urinary tract infections in women is poor. Fam Pract 2011;28:294-9.
18. Agdestein B, Lindbæk M, Gjelstad S. Do general practitioners follow the national guidelines for treating urinary tract infections with antibiotics?. Tidsskr Nor Laegeforen 2011;131:1641-4.
19. Philips H, Huibers L, Holm Hansen E, Bondo Christensen M, Leutgeb R, Klemenc-Ketis Z, et al. Guidelines adherence to lower urinary tract infection treatment in out-of-hours primary care in European countries. Qual Prim Care 2014;22:221-31.
20. Aykan SB, Ciftci IH. Türkiye'de İdrar Kültürlerinden İzole Edilen Escherichia coli Suşlarının Antibiyotiklere Direnç Durumu: Bir Meta-Analiz [Antibiotic resistance patterns of Escherichia coli strains isolated from urine cultures in Turkey: a meta-analysis]. Mikrobiyol Bul 2013;47:603-18.
21. Kömürlüoğlu A, Aykaç K, Özsürekçi Y, Başaranoğlu ST, Bıçakçıgil A, Liste Ü, et al. [Antibiotic Resistance Distribution of Gram-Negative Urinary Tract Infection Factors: A Single Center Experience.] Türkiye Çocuk Hast Derg 2018;12:10-7.
22. Avcıoğlu F, Behçet M. [Evaluation of Resistance Rates of Escherichia coli Isolates of Urinary Tract Infection to Various Antibiotics] Turk Mikrobiyol Cemiy Derg 2020;50:172-7.