Original Article

Which patient should start empirical antibiotic treatment in urinary tract infection in emergency departments?

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Abstract:

OBJECTIVES: This study aims to determine the factors that would lead the doctors in EDs to a more the accurate diagnosis of urinary tract infection (UTI) and the correct initiation of empirical antibiotherapy in the emergency room and reduce the use of unnecessary antibiotherapy.

METHODS: This study is a prospective observational study from a single-center, investigating patients with an age of 18 years and older who presented to the emergency department (ED) with the symptoms of UTI between January and May 2018. The guiding parameters to establish a UTI diagnosis and start an empirical antibiotherapy were investigated between the negative (Group 1) and positive ($>10^3$ colonies) (Group 2) groups, as a result of urine culture in terms of urine culture.

RESULTS: Our study included a total of 108 patients (59 women and 49 men). The average age was 47.11 ± 14.97. Age and gender were similar among the groups and not a discriminating factor in the diagnosis of UTI. High Charlson Comorbidity Index score, history of chronic kidney failure and cerebrovascular disease, leukocyte esterase, nitrite positivity, and leukocyte cluster presence were higher in Group 2. We suggest that these parameters might be predictive values to detect bacterial growth in urine culture. Empirical antibiotherapy was started in 48.4% of the patients in Group 1 and 95.7% of the patients in Group 2.

CONCLUSIONS: In EDs, admission complaints of the patients and physical examination findings do not always result in the diagnosis of UTI. Our study showed that UTI diagnosis could be made more accurately using leukocyte esterase, nitrite positivity, the presence of leukocyte clusters, and the Charlson Comorbidity Index score. We also suggest that regional antibiotic resistance should be considered before starting empirical antibiotherapy.

Keywords:
Emergency department, empirical antibiotherapy, urinary tract infection

Introduction

Besides being among the most common diseases across the world, urinary tract infections (UTIs) are also the second-most common with a frequency of 25% among all the infectious diseases.[1] UTIs are common health problems in primary health-care facilities and emergency departments (EDs), affecting men and women of all ages. UTI remains one of the top 15 diagnoses made annually in ED as well as being a reason for frequent admission to hospitals.[2] In the USA, there are 7 million admissions due to UTI, with at least 1 million to EDs, and 100,000 patients are hospitalized every year

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Box-ED

What is already known on the study topic?

Urinary tract infection treatment approach is well-known. We confirmed that the main diagnosis was made with urine culture, and the most common factor was *Escherichia coli*.

What is the conflict on the issue? Has it importance for readers?

Urinary tract infection is a frequent reason for application in the emergency room. Some known guiding parameters do not meet the need for correct initiation of empirical antibiotherapy or unnecessary antibiotic therapy.

How is this study structured?

This was a single-center, prospective observational study includes data from a total of 108 patients.

What does this study tell us?

We investigated the predictive values for starting empirical antibiotherapy in the treatment of urinary tract infection. In addition to the traditional knowledge on the management of urinary tract infection, we found that the patients with higher Charlson Comorbidity Index scores had higher positive urine cultures. Therefore, empirical antibiotherapy may be required for these patients, taking into account the regional susceptibility and resistance rates.

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due to the UTI.[3] Schappert and Rechtsteiner showed that 0.9% of nearly 10.5 million outpatient admissions in 2007 were due to UTIs, and 21.3% of these visits were made to hospital EDs.[4] Treatment costs of UTIs, which affect millions of people every year, have become a burden on health-care systems. Previous research showed that the annual treatment costs were 659 million dollars in 1995 and around 1.6 billion dollars in 1997.[3,5] In fighting against such a common and costly disease, physicians working in EDs need better and more accurate algorithms to predict and diagnose clinically significant disease and to prevent overuse of antibiotics.[6-8] In this study, we aimed to determine the factors that would lead the doctors in EDs to a more accurate diagnosis of UTI and the correct initiation of empirical antibiotherapy in the emergency room and reduce the use of unnecessary antibiotherapy.

Methods

Study type

This prospective, observational study was approved by Pamukkale University Ethical Committee for Clinical Investigations with the decision number 60116787-020/2646, date: 12/01/2016. In our study, STROBE (www.strobe-statement.org/) principles were followed.

Study population

The patients who were admitted to ED with UTI symptoms and agreed to participate in the study were included in this study. All of the patients in the study group accepted the informed consent form. This study was carried out at the Pamukkale University ED, which has an annual application of 80,000 patients aged 18 and over.

Subject selection and sample size estimation

Patients with an age of 18 years or older, presenting to the ED with the complaints of UTI between January and May 2018, were included in the study. The excluded individuals were those who did not fill the informed consent form, had other infection foci (vaginitis, diabetic foot, otitis, etc.) along with UTI, had a history and finding that reminded sexually transmitted diseases, suffered from urethritis or similar infections, and whose urine samples collected in the ED turned out to be contaminated [Figure 1]. A contaminated urine culture was defined as the presence of more than two isolates and Lactobacilli, Corynebacteria species, Gardnerella and aerobes, considered as urethral and vaginal contaminants.

Study protocol

All procedures from admission to discharge or hospitalization of the patients presenting with UTI complaints were followed by a single physician in the ED. The physical examination findings and the laboratory results, such as clinical and demographic data, Charlson Comorbidity Index (The Charlson comorbidity index predicts the 1-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer [a total of 22 conditions]), urinalysis, complete blood count, C-reactive protein (CRP), and urine culture, were recorded. Without interfering daily routine management protocols in the ED, the diagnoses and treatments, as well as the empirical antibiotherapy, were documented.

Assessment of urine culture

Culture results of the patients included in the study were followed. Urology outpatient control was recommended to the patients when a positive urine culture was
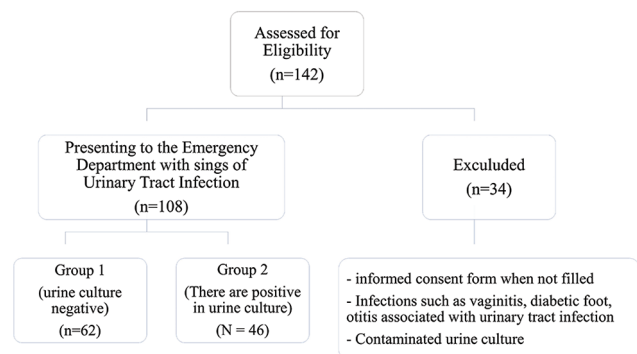

Figure 1: Flow diagram of eligible patients for the study

reported. Based on their culture results, the patients were divided into two groups according to the results of urine culture; negative (Group 1) and positive (>10³ colonies) (Group 2) groups. The patients' clinical and demographic data, Charlson Comorbidity Index scores, laboratory results, and physical examination findings were investigated between these two groups as a predictive factor of diagnosing UTI and starting empirical antibiotherapy.

Data analysis

The tests to compare the statistical evaluations were decided in line with the central limit theory. To evaluate the findings obtained in this study, IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) program was used. Conformity of the parameters to the normal distribution was evaluated by the Kolmogorov–Smirnov and Shapiro–Wilks test. Descriptive analyses were presented using median and minimum/maximum values for the non-normally distributed variables and n (%) for categorical variables. The Mann–Whitney U-test was used for the parameters with nonnormal distribution. Categorical variables were evaluated by the Chi-square test or Fisher exact test (when Chi-square test assumptions do not hold due to low expected cell counts). For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the logistic regression analysis to determine the independent predictors of patient outcome. Hosmer-Lemeshow goodness of fit statistics was used to assess the model fit. The significance value for the results was set as $P < 0.05$.

Results

In our study, a total of 108 patients were included (59 women and 49 men). Thirty-four patients were excluded from the study due to concomitant infections such as vaginitis, diabetic foot, otitis, and contamination of the culture [Figure 1]. The median age was 50 (minimum = 19, maximum = 66). Table 1 presents the clinical characteristics of the patients as well as the statistical analysis of the parameters affecting the urine culture results.

The findings revealed that the age and gender of the patients were similar in both groups, and these were not discriminating factors in the diagnosis of UTI. Further, the higher Charlson Comorbidity Index score in Group 2 was found to be statistically significant ($P = 0.002$). Similarly, there were significantly more patients who had chronic kidney failure and cerebrovascular disease history in Group 2 ($P = 0.012$ and $P = 0.014$).

When the admission complaints and physical examination findings of the patients were investigated,

we observed that 35 patients (55.5%) in Group 1 and 35 patients (76.1%) in Group 2 had dysuria ($P = 0.035$) and 8 patients (12.9%) in Group 1 and 11 patients (23.9%) in Group 2 had suprapubic pain ($P = 0.137$). Therefore, the presence of dysuria was significantly higher in Group 2. We found a relationship with positive urine culture with a sensitivity of 76% and a specificity of 43.5% in patients with dysuria. We determined positive and negative predictive values for dysuria as 58.9% and 90.5%. The percentage of the patients without and physical examination findings were 50% in Group 1 and 23.9% in Group 2. The most common physical examination finding was suprapubic sensitivity, which was found in 25.8% of the patients in Group 1 and 45.6% of the patients in Group 2. The costovertebral angle sensitivity was present 24.2% in Group 1 and 21.7% in Group 2, whereas the presence of fever was identified only in Group 2, in 8.7% of the patients.

As a result of laboratory, sensitivity and specificity values were calculated for leukocyte esterase and nitrite positivity. As shown in Table 1, a significant difference was found for leukocyte esterase and nitrite between the groups, and the sensitivity was calculated as 91.3% and specificity as 62.2% for leukocyte esterase. For nitrite positivity, we measured sensitivity as 21.7% and specificity as 100%. In addition, we found a relationship positive urine culture 73.9% sensitivity and 97.7% specificity in patients with leukocyte cluster in urine.

The results of logistic regression analysis showed that Charlson comorbidity index score ($P = 0.001$), urinalysis leukocyte count ($P = 0.008$), urine microscopy leukocyte cluster number ($P < 0.001$), cerebrovascular disease ($P = 0.014$), and urinalysis leukocyte esterase [+1 ($P = 0.006$), +2 ($P = 0.004$), +3 ($P < 0.001$)] were the variables that could predict urine culture positivity outcomes [Table 2].

According to the urine culture reports, *Escherichia coli* was the most frequently (65.2%) causative microorganism in our study group. The antibiogram results indicated that *E. coli* resistance rates for the tested antibiotics were 40% for amoxicillin clavulanate, 33.3% for ampillicine, 26.7% for trimethoprim-sulfamethoxazol, 10% for cefepime, 6.6% for ceftazidime, 26.7% for ceftriaxone, 26.7% for ciprofloxacin, and 6.6% for gentamycine. Any resistance to fosfomycin, meropenem, and imipenem was not detected in either group.

When the study groups were analyzed for the initiation of empirical antibiotherapy, we observed that 95.7% of the patients in Group 2 were started that protocol in ED. In this group, when the patients who had not received the antibiotherapy in the ED, they were referred to the

Table 1. Clinical characteristics of the patient groups

		GROUP 1 *n*=62	GROUP 2 *n*=46	*P*
Age (year) [Median (IQR)]		48.50 (40.50-56)	54.00 (28-63.25)	0.216▲
Charlson Comorbidity Index score [Median (IQR)]		1 (0-3)	2 (1-6.50)	0.002▲
Urinalysis pH [Median (IQR)]		5.00 (5.00-5.50)	5.00 (5.00-6.50)	0.660▲
Urinalysis Leukocyte count (P/HPF) [Median (IQR)]		2 (1 - 13.75)	125 (26.25 - 857)	<0.001▲
Urinalysis Erythrocyte Count (P/HPF) [Median (IQR)]		3 (1-5)	67 (17.75-796)	<0.001▲
Serum CRP level (mg/L) [Median (IQR)]		0.11 (0.03 - 1.04)	2.20 (0.20 - 12.70)	<0.001▲
Gender	Female (*n*)	33 (53.2)	26 (56.5)	0.734♦
	Male (*n*)	29 (46.8)	20 (43.5)	
Diabetes Mellitus	No (*n*)	49 (79)	30 (65.2)	0.109♦
	Yes (*n*)	13 (21)	16 (34.8)	
Chronic Kidney Failure	No (*n*)	62 (100)	41 (89.1)	0.012◊
	Yes (*n*)	0 (0)	5 (10.9)	
COPD/Asthma	No (*n*)	56 (90.3)	38 (82.6)	0.238♦
	Yes (*n*)	6 (9.7)	8 (17.4)	
Cerebrovascular Disease	No (*n*)	59 (95.2)	36 (78.3)	0.014◊
	Yes (*n*)	3 (4.8)	10 (21.7)	
Hypertension	No (*n*)	53 (85.5)	37 (80.4)	0.486♦
	Yes (*n*)	9 (14.5)	9 (19.6)	
Urine Microscopy Leukocyte Cluster Number (P/HPF)	No (*n*)	60 (96.8)	15 (32.6)	<0.001◊
	Yes (*n*)	2 (3.2)	31 (67.4)	
Urinalysis Leukocyte Esterase	No (*n*)	38 (61.3)	4 (8.7)	<0.001♦
	+1 (*n*)	13 (21)	9 (19.6)	
	+2 (*n*)	6 (9.7)	6 (13)	
	+3 (*n*)	5 (8)	27 (58.7)	
Urinalysis Nitrite Positivity	No (*n*)	62 (100)	36 (78.3)	<0.001◊
	Yes (*n*)	0 (0)	10 (21.7)	

IQR=Indianquartile range, CRP=Creactive protein, COPD=Chronic obstructive pulmonary disease, HPF=Highpower field
▲ Mann-Whitney U test, ♦ Chi-square test, ◊ Fisher exact test

Table 2: Logistic regression analysis for urine culture positivity

	OR	95% CI	*P*
Charlson Comorbidity Index score	1.505	1.180-1.921	0.001
Serum CRP level (mg/L)	1.051	0.968-1.141	0.236
Urinalysis leukocyte count (P/HPF)	1.016	1.004-1.028	0.008
Urinalysis erythrocyte count (P/HPF)	1.001	0.999-1.003	0.314
Urine microscopy leukocyte cluster number (P/HPF)	0.016	0.003-0.075	<0.001
Urinalysis leukocyte esterase			
+1	6.577	1.730-25.007	0.006
+2	9.5	2.056-43.888	0.004
+3	51.3	12.596-208.926	<0.001
Cerebrovascular disease	5.463	1.409-21.182	0.014

OR=Odds ratio, CI=Confidence interval, CRP=C-reactive protein, HPF=High-power field

inpatient services, and the antibiotherapy was started by the physician in charge there. On the other hand, 48.4% of the patients received empirical antibiotherapy in Group 1. The most common antibiotics started empirically were ciprofloxacin (30.7%), fosfomycin (10.7%), ceftriaxion (9.3%), the combination of cefdinir + clavulanic acid, and fosfomycin (13.3%). The rate of starting single medication as empirical antibiotherapy was 56%, while that of combined (dual) medication was 44%.

Discussion

UTI can be diagnosed effectively through admission complaints, medical history, physical examination, and laboratory tests. Although the symptoms play a crucial role in diagnosing UTI, there may also be patients who have symptoms without any UTI diagnosis. Therefore, clinical findings should be supported with laboratory findings, including pyuria, bacteriuria, leukocyte esterase positivity, nitritepositivity, and urine culture for the precise diagnosis. In outpatient conditions, there is usually time to perform and wait for the urine culture results. However, since EDs are not convenient to wait for these results, admission complaints, medical history, physical examination, and laboratory tests are required to achieve an accurate diagnosis. In this study,

we showed that having dysuria as the initial complaint, having a high Charlson Comorbidity Index score, history of chronic kidney failure, or cerebrovascular disease were significant determinant factors fort he diagnosis of UTI, in addition to pyuria, hematuria, and high urine leucocyte esterase, nitrite, and serum CRP levels. Symptoms prompting UTI diagnosis, such as dysuria, increased urinary frequency, odor in the urine and suprapubic pain typically indicate cystitis, whereas additional fever, vomiting, and side or back pain symptoms that develop a few days after the onset of symptoms indicate pyelonephritis.[9] Dysuria may be associated with increased urinary frequency, odor in the urine, or suprapubic pain in sexually transmitted diseases, vaginitis, exposure to chemical or allergic irritants, yet UTI is not typically related to vaginal discharge.[6,10,11] Leman reported a relationship with positive urine culture with a sensitivity of 90.9% and a specificity of 57.6% in patients with dysuria.[12] In our study, we established the sensitivity for dysuria as 76% and the specificity as 43.5%, which were lower. While the researchers specified the positive and negative predictive values for dysuria as 58.9% and 90.5%, respectively, in the same study, these values were found as 50% and 71.0%, respectively, in our study.[12] We can conclude that the absence of dysuria could be a significant indicator of positive urine culture although we did not encounter a similar situation in the patients who had described suprapubic pain during their admission.

When the medical history of patient groups was investigated, the presence of diabetes, hypertension, chronic obstructive pulmonary disease, and asthma were similar between the groups, whereas the history of cerebrovascular disease and chronic kidney failure were reported more in Group 2. On the other hand, Carlsen *et al*. reported a higher frequency of diabetes in their retrospective, cross-sectional study.[13] In a retrospective case–control study, Lee *et al*. found that diabetes and cerebrovascular disease were more frequent than other comorbid conditions in 150 patients with positive urine cultures.[14]

Medical history, complaints, and physical examination do not always yield the diagnosis of UTI accurately, so additional procedures are required to support the diagnosis and the decision for starting an empirical antibiotherapy in EDs, where urine culture results cannot be waited for. In patients presenting with typical symptoms of uncomplicated cystitis, urine analysis is useful but has a limited value and provides only a minimal increase in diagnosis.[15] To rule-out acute pyelonephritis, the presence of leukocyte and erythrocytes in addition to urinalysis, including the evaluation of nitrite, is recommended for routine diagnosis.[15] Moreover, certain findings might help

to detect bacteria in the urine. For instance, leukocyte esterase has a sensitivity of 62% to 98% and a specificity of 55% to 96%; however, the results may vary with high glucose or protein concentration, glucocorticoid use, and the presence of a viral disease.[10] Furthermore, nitrite positivity is rather sensitive between 95% to 98%.[16] Some studies report nitrite tests with a sensitivity rate of 35% to 85% and a specificity rate of 95% to diagnose UTI.[17,18] Nitrite positivity may not exist in some bacterial infections, such as S. saprophyticus and Pseudomonas, which are unable to convert nitrate to nitrite. The most specific investigation would be a sample that is positive for both leukocyte esterase and nitrite which increases specificity to 98%–100%, but sensitivity decreases to 35%–84%.[16] Devillé *et al*. reported a sensitivity of 75% to 90% and a specificity rate close to 100% for the combined use.[18] In our study, a significant difference was found for leukocyte esterase and nitrite between the groups, and the sensitivity was calculated as 91.3% and specificity as 62.2% for leukocyte esterase, both of which were parallel to the rates reported in literature. For nitrite positivity, we measured sensitivity as 21.7%, which was lower than the rates previously reported, and specificity as 100%, which was higher than the rates in the literature. Even when the leukocyte esterase and nitrite tests were negative, treatment can be initiated if there is a strong suspicion for UTI.[6,17] Contrary to the previous research, we found that increasing the Charlson Comorbidity Index score by 1 unit increases the positive urine culture detection by 1.505 times in patients admitted to the ED with UTI findings. In addition, we suggest that it would be beneficial to use leukocyte cluster in urine with 73.9% sensitivity and 97.7% specificity.

Antibiotics are the primary treatment in the patients with UTI. The causative agent and its susceptibility for certain antibiotics can be determined by urine culture and antibiogram. Empirical antibiotic therapy is usually initiated earlier as it takes some time to obtain urine culture and antibiogram results. The empirically chosen antibiotic should be determined carefully because of the risk for the development of antibiotic resistance. Previous research has shown that the sensitivity results of hospitals and their surrounding regions should be monitored at certain intervals in selecting the most appropriate empirical antibiotic. Gozukucuk *et al*. reported that positive urine culture was detected in 348 of 1493 patients visiting the outpatient clinic due to UTI and *E. coli* was the main causative agent in 54.8% of the cases.[19] According to the urine culture and antibiogram reports, they detected sensitivity rates as; 36.3% for ampicillin, 80.2% for ciprofloxacin, and 87.6% for nitrofurantoin.[19] In a retrospective study, Pekdemir *et al*. detected positive urine culture in 90 of 257 patients admitted to the ED, and they identified *E. coli* as the most common agent (57.8%), and antibiotic susceptibility to

E. coli was reported as; 51.9% for ciprofloxacin, 34.6% for ampicillin, and 85.3% for nitrofurantoin.[1] In a similar study by Kurutepe *et al*., *E. coli* was detected in 73.2% of urine culture samples and the resistance to ampicillin was between 47.8% and 64.6%.[20] Almulhim *et al*. reported the resistance of *E. coli* to ciprofloxacin as 5.2%, and trimethoprim-sulfamethoxazol as 28.5%.[21] In their study, also investigating the population under 18-year-old, Alanazi found that *E. coli* was highly sensitive to nitrofurantoin (92%), followed by ciprofloxacin (81.8%), amoxicillin–clavulanic acid (81.1%), and cefazolin (77.5%).[2] Moreover, they found a decreasing level of sensitivity of *E. coli* to co-trimoxazole (55.6%), followed by ampicillin (33.1%).[2] Rosa *et al*. showed that *E. coli* isolates were sensitive to trimethoprim-sulfamethoxazol (54%) and to Fluoroquinolones (60%).[22] In our study, we also identified *E. coli* as the most common microorganism with a rate of 65.2%. We detected that the rates of *E. coli* resistance to commonly used antibiotics in our region were higher than the rates in the published studies. On the other hand, no *E. coli* resistance was detected for fosfomycin, meropenem, and imipenem.

Knowing the antibiotic susceptibilities of microorganisms can facilitate the initiation of empirical treatment and saves time fort he physician and the patients, especially in EDs. Today, the increase in antibiotic-resistance is what makes empirical treatments even more important. The literature cites *E. coli* as the most common factor in UTIs, and its sensitivity to the most frequently resorted antibiotics decreases day by day. In Alanazi's study, the most commonly prescribed antibiotics in adults were cefuroxime (35.4%), norfloxacin (17.9%), and amoxicillin-clavulanic acid (16.6%), followed by amoxicillin (9.8%), nitrofurantoin (6.9%), co-trimoxazole (4.4%), and ciprofloxacin (4.1%).[2] Almulhim *et al*. stated that ciprofloxacin was most frequently prescribed at the rate of 36%–45% in their studies.[21] Similarly, Kobayashi *et al*. indicated that ciprofloxacin was the most commonly prescribed antibiotic, with 45% among the cases they investigated.[23] In our study, the rate of ciprofloxacin prescription (30.7%) was between the reported rates in these studies. In a study on combined antibiotherapy prescription, Martínez *et al*. stated that Spanish emergency doctors prescribe too many second-line antibiotics for UTI treatment. In our study, the rate of combined drug onset was found to be similar with a rate of 44%.[24]

Limitations

We are aware that our study has some limitations. One of these was the limited number of patients which was the consequence of being a single-center prospective study and the short period of time available to recruit patients. Only patients presenting with UTI symptoms were included and this was apparently narrowly defined by dysuria, as there was no mention of urgency, frequency, hesitancy, hematuria, etc., and also, patients with "contaminated urine samples" were excluded from the study. Although all the procedures of the patients were performed by a single physician in the ED, the difference of interpretation concerning the findings was possible. Since our study was a prospective observational study, treatment preferences of emergency doctors were also observed. Therefore, it not specified a protocol for deciding on a particular antibiotic regimen. In this case, the difference in interpretation about the findings such as the decision to start antibiotics and the choice of antibiotics started may have been possible. Therefore, though the findings are compatible with the literature and shed light on starting an empirical antibiotherapy, further research conducted with larger series is needed.

Conclusions

We believe that our study will be a guide for handling patients admitted to EDs with UTI findings. Patients' admission complaints and physical examination findings may not always make emergency physicians diagnose UTI. Instead, the diagnosis of UTI can be made more accurately with leukocyte esterase, nitrite positivity, presence of leukocyte cluster, and Charlson Comorbidity Index score. The rates of regional antibiotic resistance should also be considered before an empirical antibiotherapy is started.

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