Yatan hastaların idrar örneklerinden izole edilen Gram-negatif bakterilerin tür dağılımı ve antibiyotik duyarlılıkları

The distribution according to the species of Gram-negative bacteria isolated from hospitalized patients's urine specimens and their antimicrobial susceptibility

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ÖZET

Amaç: Bu retrospektif çalışmada; hastanemizde yatan hastalarda gelişen üriner sistem enfeksiyonlarının ampirik tedavi yaklaşımına katkıda bulunabilmek için üriner sistem enfeksiyonu gelişen yatan hastaların idrar kültürlerinden izole edilen Gram-negatif bakterilerin tür dağılımını ve antimikrobik duyarlılık paternlerini belirlemeyi amaçladık.

Yöntemler: Ocak 2006 ve Eylül 2011 tarihleri arasında, üriner sistem enfeksiyonu gelişen yatan hastaların idrar kültürlerinden elde edilen toplam 3.548 Gram-negatif izolatın identifikasyonu geleneksel yöntemler ve BD PhoenixTM 100 (Becton Dickinson, MD, ABD) tam otomatik mikrobiyoloji sistemi tarafından yapılmıştır. İzolatların antimikrobiyal duyarlılık testi Kirby-Bauer disk difüzyon yöntemi ile Clinical and Laboratory Standarts Institute (CLSI) kriterlerine göre çalışılmıştır. Ayrıca, baskın üropatojen bakterilerin genişlemiş spektrumlu beta-laktamaz (GSBL) üretimi çift-disk sinerji yöntemi ile araştırılmıştır.

Bulgular: Bu çalışmada, erkeklere göre kadınlarda önemli ölçüde daha yüksek üriner sistem enfeksiyonu insidansı gözlenmiştir, sırasıyla; 1.303 (%36,7) ve 2.245 (%63,3). *Escherichia coli*'nin baskın patojen bakteri olduğu belirlendi ve üriner sistem enfeksiyonu gelişen

ABSTRACT

Objective: In this retrospective study, we aimed to determine the distribution according to the species of Gram-negative bacteria in isolates obtained from urine cultures of hospitalized patients with urinary tract infections and to detect their antimicrobial susceptibility pattern for contribute to empirical treatment approach to urinary tract infections in our hospital.

Methods: Between the dates of January 2006 and September 2011, a total of 3,548 Gram-negative isolates obtained from urine cultures of hospitalized patients with urinary tract infection were identified by conventional methods and the BD PhoenixTM 100 (Becton Dickinson, MD, USA) fully automated microbiology system. Antimicrobial susceptibility testing of isolates was performed by Kirby-Bauer's disk diffusion method according to the Clinical and Laboratory Standarts Institute (CLSI) criteria. In addition, extended-spectrum beta-lactamase (ESBL) production of predominant urinary pathogenic bacteria was detected by the double-disk synergy method.

Results: In this study, a significantly higher incidence of urinary tract infection was observed in females compared with males; 2,245 (63.3%) and 1,303 (36.7%), respectively. *Escherichia coli* was the predominant pathogenic bacterium and accounted for

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toplam 3.548 yatan hastanın 2.341 (%65,8)'inde sorumlu etken olduğu bulundu. Ayrıca, 679 (%19,1)'unda *Klebsiella pneumoniae*, 177 (%5)'sinde *Acinetobacter* spp., 176 (%5)'sında *Enterobacter* spp., 142 (%4)'sinde *Pseudomonas aeruginosa* ve 38 (%1,1)'inde diğer Gram-negatif bakterilerin sorumlu etken olduğu saptandı. İdrar kültürlerinden izole edilen Gram-negatif bakterilerin antimikrobik duyarlılık oranları seftazidim, trimetoprim-sülfametoksazol, siprofloksasin, piperasilin-tazobaktam, sefoperazon-sülbaktam, amikasin, imipenem ve meropenem için sırasıyla; %34,5, %38, %42, %50, %70, %87, %90 ve %92 olarak tespit edilmiştir. Ayrıca, GSBL üreten *E. coli* ve *K. pneumoniae* oranları da sırasıyla; %38 ve %36 olarak bulunmuştur.

Sonuç: Bu çalışma ve diğer çalışmaların sonuçları yakın gelecekte, sefalosporinler, karbapenemler ve florokinolonlar gibi geniş spektrumlu antibiyotiklere karşı yüksek düzeyde direnç gelişiminin mümkün olduğunu ve tedavi seçeneklerimizin her zamankinden daha sınırlı hale gelebileceğini göstermektedir. Seftazidim, siprofloksasin ve trimetoprim-sülfametoksazole karşı gelişen yüksek düzey direnç nedeniyle, üriner sistem enfeksiyonlarının ampirik tedavisi için bu antibiyotiklerin kullanılmamasını öneririz.

Anahtar Sözcükler: Üriner sistem enfeksiyonu, antimikrobik duyarlılık, Gram-negatif bakteriler, *Escherichia coli*, GSBL

2,341 (65.8%) of 3,548 hospitalized patients with urinary tract infections. In addition, *Klebsiella pneumoniae* accounted for 679 (19.1%), *Acinetobacter* spp. for 177 (5%), *Enterobacter* spp. for 176 (5%), *Pseudomonas aeruginosa* for 142 (4%), and other Gram-negative bacteria for 38 (1.1%). Antimicrobial susceptibility rates of Gram-negative bacteria isolated from urine cultures for ceftazidime, trimethoprim-sulfamethoxazole, ciprofloxacin, piperacillin-tazobactam, cefoperazone-sulbactam, amikacin, imipenem, meropenem were detected as 34.5%, 38%, 42%, 50%, 70%, 87%, 90%, and 92%, respectively. In addition, the rates of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* were detected as 38% and 36%, respectively.

Conclusion: The present study and the other studies show that in the near future it is possible our therapeutic options may become more limited than ever due to the development of high-level resistance against broad-spectrum antibiotics such as cephalosporins, carbapenems and fluoroquinolones. Due to the high-level resistance to ceftazidime, ciprofloxacin and trimethoprim-sulfamethoxazole, we recommend that these antibiotics should not be used for the empirical treatment of urinary tract infections.

Key Words: Urinary tract infection, antimicrobial susceptibility, Gram-negative bacteria, *Escherichia coli*, ESBL

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infections both community-acquired and hospital-acquired (nosocomial) in our country, as all over the world. UTIs are approximately 25-40% of nosocomial infections worldwide. However this rate varies according the region, hospital and clinic those microorganisms isolated from UTIs (1, 2). Most patients with nosocomial UTIs have either had genitourinary or urological manipulation or permanent urethral catheterization. Most catheter-associated UTIs derive from the patient's own colonic flora. The distribution according to the species of pathogenic bacterium that caused UTIs and their antimicrobial susceptibility pattern varies according to the regions. Gram-negative bacteria especially *Escherichia coli* and *Klebsiella pneumoniae* are the most frequent urinary pathogenic microorganisms isolated from UTIs in hospitalized patients (3-6).

Over the past years antimicrobial drug resistance of the causative urinary pathogenic bacteria have increased rapidly in nosocomial infections. Today, because of the rapidly increasing antimicrobial drug

resistance, we are encountering great difficulties in the treatment of UTIs developing in especially hospitalized patients. Therefore, it is essential to detect the distribution according to the species and antimicrobial susceptibility of gram-negative urinary pathogenic bacteria for optimizing the use of empirical antimicrobial treatment in UTIs (7, 8). The aim of this study was to determine the distribution according to the species of gram-negative bacteria among the UTIs isolates and to detect their antimicrobial susceptibility pattern in hospitalized patients in our hospital. In the light of our data, we want to contribute to the current treatment approach of UTIs in our hospital.

MATERIALS AND METHODS

The present study is a cross-sectional study of nosocomial and non-nosocomial infections in hospitalized patients diagnosed with UTI in our hospital between the dates of January 2006 and September 2011.

The urine cultures were performed from mid-stream specimens of urine sent to a clinical microbiology laboratory. The mid-stream specimens of urine were obtained from hospitalized patients with a preliminary diagnosis of UTI. The urine specimens were inoculated quantitatively onto 5% sheep blood agar and Eosin-Methylen Blue agar (EMB) (Merck KGaA, Darmstadt, Germany) media plates. Then, these media plates were aerobically incubated at 35 ± 2°C for 18-24 hours. We included a total of 3.548 urinary pathogenic Gram-negative isolates with urine cultures yielding growth of pathogenic bacteria ≥ 10^5 colony forming units/mL (CFU/mL) from mid-stream specimens of urine in this study. Identification of urinary pathogenic isolates was performed by conventional methods and the BD PhoenixTM 100 (Becton Dickinson, MD, USA) fully automated microbiology system. Antimicrobial susceptibility testing of isolates was determined by measuring the diameter of inhibition zone around the antibiotic discs with using the Kirby-Bauer's disc diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) susceptibility interpretive breakpoints (9). A pure culture of the pathogenic Gram-negative bacteria which had been grown onto 5% sheep blood agar and EMB agar plates was suspended in normal sterile saline to form direct colony suspension equivalent to 0.5 McFarland opacity standards. The bacterial suspension was then inoculated onto Mueller-Hinton agar (Merck KGaA, Darmstadt, Germany) plates. Antibiotic impregnated discs (Oxoid, Basingstoke, UK) were placed 20 mm apart onto Mueller-Hinton agar plates in a straight line, with the amoxicillin-clavulanic acid disc in the center. Then, Mueller-Hinton agar plates were aerobically incubated at 35 ± 2°C for 16-18 hours. Inhibition zone diameters were measured and interpreted for susceptibility according to the CLSI breakpoint criteria (9). In addition, extended-spectrum beta-lactamase (ESBL) activity was investigated by double-disc synergy method with using amoxicillin-clavulanic acid (20/10 µg), cefotaxime (30 µg), and ceftazidime (30 µg) (Oxoid, Basingstoke, UK) impregnated disks (10). *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218 (for ESBL-producing strains), *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853 reference strains were used for the quality control of fully automated microbiology system, antimicrobial susceptibility test and double-disc synergy method.

RESULTS

Gender and age groups distribution of patients

In this study, the most hospitalized patients of UTIs were recorded among young and middle age (among 20-59 years, 2.176 patients, 61.3%). Pediatric patients (0-19 years) comprised 857 (24.2%) and elderly (> 60) constituted 515 (14.5%) of the total number of UTIs. Urinary tract infections were observed more frequently in females compared with males, 2.245 (63.3%) and 1.303 (36.7%), respectively (figure 1).

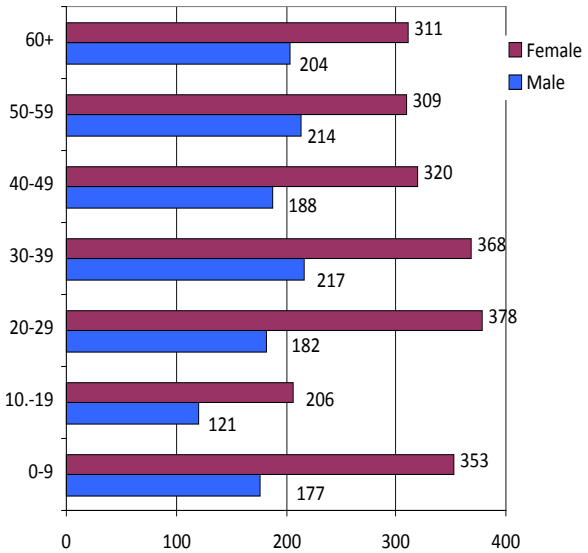

Figure 1. Distribution according to the gender and age groups of hospitalized patients with UTIs.

Species distribution of isolates

E. coli was the predominant urinary pathogenic bacterium and accounted for 2.336 (65.8%) of a total of 3.548 hospitalized patients with UTIs. *K. pneumoniae* was accounted for 679 (19.1%), *Acinetobacter spp.* for 177 (5%), *Enterobacter spp.* for 176 (5%), and *P. aeruginosa* for 142 (4%). The other Gram-negative bacteria were accounted for 38 (1.1%) of a total of 3.548 hospitalized patients with UTIs. The detailed analysis of the etiological pathogens is shown in Figure 2.

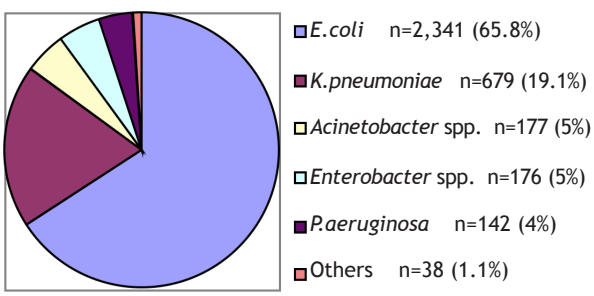

Figure 2. Distribution according to the species of Gram-negative bacteria.

Antimicrobial susceptibility pattern

In this study, the antimicrobial susceptibility rates of Gram-negative bacteria were 34.5% (1.224) for ceftazidime, 38% (1.348) for trimethoprim-sulfamethoxazole, 42% (1.490) for ciprofloxacin, 50% (1.774) for piperacillin-tazobactam, 70% (2.484) for cefoperazone-sulbactam, 87% (3.087) for amikacin, 90% (3.193) for imipenem, and 92% (3.264) for meropenem, respectively. Antimicrobial susceptibility rates (%) according to the species of Gram-negative bacteria were shown in Table 1. In addition, the rates of extended-spectrum beta-lactamase producing *E. coli* and *K. pneumoniae* were determined as 38% and 36%, respectively.

DISCUSSION

UTIs are one of the most common infections in hospitalized patients. The majority of UTIs in hospitalized patients associated with urinary catheter (11). The bacterial spectrum of UTIs in hospitalized patients is very extensive, including *Enterobacteriaceae* family, non-fermenters and Gram-positive bacteria. Among these causative agents, the most frequently encountered microorganisms are Gram-negative bacilli, especially *E. coli* and *K. pneumoniae*.

In this study, *E. coli* was the most common (65.8%) Gram-negative urinary pathogenic bacterium isolated from urine cultures of hospitalized patients with UTI and it is followed by *K. pneumoniae* (19.1%). The first finding is in keeping with the big majority of studies from the data where *E. coli* was the predominant urinary pathogenic bacteria. However, distribution of Gram-negative bacteria obtained from UTIs may vary according to the gender, age groups, underlying risk factors, regions, and hospitals.

According to a study carried out by SENTRY Participant Group the order of isolation the remaining Gram-negative bacteria were: *E. coli* (46.9%), *Klebsiella spp.* (11%), *P. aeruginosa* (7.5%), *Proteus mirabilis* (5%), *Enterobacter spp.* (3%),

Table 1. Distribution according to the species of antimicrobial susceptibility rates of Gram-negative bacteria

Name of microorganisms	Ceftazidime (%)	Trimethoprim-sulfamethoxazole (%)	Ciprofloxacin (%)	Piperacillin-tazobactam (%)	Cefoperazone-sulbactam (%)	Amikacin (%)	Imipenem (%)	Meropenem (%)
Escherichia coli	34	38	38	55	78	98	99	99
Klebsiella pneumonia	42	48	64	39	67	95	98	98
Acinetobacter spp.	13	29	15	14	54	40	44	44
Enterobacter spp.	42	42	49	36	62	91	94	96
Pseudomonas aeruginosa	34	3	40	73	50	68	74	75
Other gram-negatives	35	39	41	55	68	80	90	93

Citrobacter spp. (2%) (12). SENTRY group was also detected the distribution of Gram-negative bacteria as the order of *E. coli*, *Klebsiella spp.*, *P. aeruginosa*, and *P. mirabilis* in UTIs in another study (13).

In a study from Korea it was investigated the results of urine cultures according to the voiding method over 10 years in patients with spinal cord injury and it was detected causative microorganisms were mostly Gram-negative bacteria (84%), including *P.aeruginosa* (22.9%), *E. coli* (21.1%), *Klebsiella spp.* (6.7%), and *Citrobacter* spp. (6.3%) (14).

In another study from Nigeria distribution of bacterial pathogens in UTIs in pregnant women was accounted for 38.1% for *K. oxytoca*, (31.3%) for *E. coli*, 9.3% for *P. aeruginosa*, and 6.8% for *P. mirabilis* (15).

In a retrospective study from Istanbul, causative agents of 3.739 patients with UTIs between January 2005 and April 2008 were investigated. *E. coli* was accounted for 49.6%, *P. aeruginosa* for 10.5%, *K. pneumoniae* for 5.3% and *P. mirabilis* for 4.3% (16).

In a study from Diyarbakir, the most frequently isolated Gram-negative agents from UTIs specimens were *E. coli*, *Klebsiella species*, *Enterobacter species*, *P. aeruginosa*, respectively (17).

In our study, we determined that the number of patients with UTI in 10-19 age groups had been lower according to the number of patients in other age groups. Because, most of the patients with UTI in 10-19 age groups are sent to other hospitals. The patients with UTI admitted to our hospital are usually complicated.

In current study, for the culture positive urine specimens, 63.3% were from females and 36.7% from males, which is a finding similar to studies from the different regions of the world (13, 18). These findings are to be expected as women are more prone to UTIs than men. In present study, the common Gram-negative isolates had a very high-level resistance to ceftazidime, ciprofloxacin and trimethoprim-sulfamethoxazole. In addition the rates of ESBL-producing *E. coli* and *K. pneumoniae* were

determined as > 30%. In addition, these common Gram-negative bacteria displayed much lower resistance to amikacin, imipenem and meropenem. Amikacin and carbapenems were also found the most effective agents against Gram-negative bacteria in a surveillance study of Geyik et al. in Dicle University Hospital in 2008 (19).

The high levels of resistance obtained from our study against ceftazidime, ciprofloxacin and trimethoprim-sulfamethoxazole may be associated with the frequent use of these antibiotics for treatment and prophylaxis in our hospital. However, antimicrobial susceptibility testing findings vary according to the regions and hospitals and increase over the years.

In a SENTRY Antimicrobial Surveillance Program's study between 1997 and 2000, antimicrobial susceptibility rates of piperacillin-tazobactam, aztreonam, extended-spectrum cephalosporins, carbapenems, nitrofurantoin and amikacin were reported as > 87.0%. In addition, antimicrobial resistance rates to fluoroquinolones and trimethoprim-sulfamethoxazole were observed as 17.5-18.9% and > 45.0%, respectively. In the same study, due to the high number of ESBL-producing isolates (> 30%), the carbapenems were detected the only effective therapeutic option against *Klebsiella* spp. infections. Fluoroquinolones showed limited activity against *Klebsiella spp.* (72.1-88.6% susceptible) and the *P. aeruginosa* isolates showed high resistance rates to most antimicrobial agents tested in this study (13).

In another large-scale study from 1993 to 2004 of SENTRY group, antibiotic resistance/intermediate resistance rates of *E. coli* to ceftazidime, imipenem, amikacin, ciprofloxacin were detected as 0.9/1.1%, 0.2/0.3%, 0.4/0.4%, 0.2/16.3%, respectively in UTIs. These rates were 1.4/2.9%, 0.5/0.2%, 3.4/2.3%, 1.1/16.1% for *K. pneumoniae*, 10.5/22.8%, 1.8/8.8%, 5.3/31.6%, 0/74.5% for *A. baumannii*, 4.1/3.1%, 3.1/13.4%, 7.8/4.7%, 2.1/41.9% for *P. aeruginosa*, respectively (20).

The Study for Monitoring Antimicrobial Resistance Trend (SMART) program detected the rate of ESBL as 17.9% of *E. coli* in UTIs of hospitalized patients and the highest ESBL rate was from the Asia/Pacific region between countries worldwide (27.7%). According to the data of this study from 2009 to 2010, ertapenem and imipenem were the most active agents tested, inhibiting > 98% of all *E. coli* phenotypes. Overall, amikacin and piperacillin-tazobactam achieved 90% inhibition levels only for ESBL-negative isolates. Ciprofloxacin and levofloxacin were not effective for ESBL-positive isolates, with only 14.6% and 15.9% susceptible, respectively (21). In a comprehensive study from Turkey, the rate of ampicillin-resistant *E. coli* accounted for 73.8% of all *E. coli* isolated from UTIs. According to this study, 8.2% and 24.6% of *E. coli* were resistant to quinolones and ceftriaxone, respectively. There was no resistance to carbapenems in *E. coli* but 6.3%, 40.6%, 59.4% of *Klebsiella spp.* was resistant to carbapenems, quinolones and ceftriaxone, respectively (22).

In our hospital *Acinetobacter spp.* isolates have lower susceptibility to all tested antibiotics similar to the other studies from the world. In a Surveillance Network (TSN) study in the USA a large number of *Acinetobacter spp.* isolates were tested between 2002 and 2008 and the rates of resistance to ceftazidime, ciprofloxacin, amikacin, imipenem were determined as 70%, 66%, 57%, 36%, respectively (23). In the studies from Korea between 2002 and 2009, similar results to USA study were detected (24, 25).

As a conclusion, we aimed to have an opinion about distribution according to the species and antimicrobial susceptibility of Gram-negative urinary pathogenic bacteria and contribute to the current therapeutic approach in our hospital. The present study and the other studies show that in the near future it is possible the development of high-level resistance against broad-spectrum antibiotics such as cephalosporins, carbapenems are fluoroquinolones will limit our therapeutic options more than ever.

Due to the high-level resistance to ceftazidime, ciprofloxacin and trimethoprim-sulfamethoxazole, we recommend that these antibiotics should not be used for the empirical treatment of UTIs. Fosfomycin and nitrofurantoin should be considered as an option in empirical treatment.

Our study clearly demonstrates once again that culture and antimicrobial susceptibility testing should be prompt to the patients with suspected urinary tract infection.

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