ISSN: 2588-4115; Infection Epidemiology and Microbiology. 2020;6(2):127-134 doi:10.29252/iem.6.2.127

The Effect of Antibiotic Resistance on Therapeutic Outcomes of Urinary Tract Infections in Hospitalized Patients with UTI

ARTICLEINFO

Article Type
Original Research

Authors
Tofigh Yaghubi Kalurazi, *MD*[1]
Lida Mahfoozi, *MD*[1*]
Yasaman Momeni, *MD*[1]

How to cite this article
Yaghubi Kalurazi, T., Mahfoozi L., Momeni Y. The Effect of Antibiotic Resistance on Therapeutic Outcomes of Urinary Tract Infections in Hospitalized Patients with UTI. Infection Epidemiology and Microbiology. 2020;6(2):127-134

[1] Department of Health, Nutrition, and Infectious Diseases, school of medicine, Guilan University of Medical Sciences, Rasht, Iran

**** Correspondence***
Address: Department of Health, Nutrition, and Infectious Diseases, school of medicine, Guilan University of Medical Sciences, Rasht, Irandrlidamahfoozi@yahoo.com

Article History
Received: April 15 ,2020
Accepted: June 01 ,2020
Published: June 10 ,2020

ABSTRACT

Aims: Numerous microbial agents have been identified as the causative agents of UTIs, such as *Escherichia coli*. The spread of antibiotic resistance is increasing among strains causing UTIs. The present study aimed to investigate the prevalence of etiological agents of UTIs and their antibiotic resistance patterns and to determine related risk factors and treatment outcomes of antibiotic resistance in Razi teaching hospital, Guilan, North of Iran.

Material & Methods: This retrospective cross-sectional study was performed from April 2017 to September 2018. All patients with clinical symptoms of UTI were included. The patients' complete medical records were assessed. Moreover, bacterial isolation and identification were performed by conventional bacteriological and standard biochemical tests. Antibiotic susceptibility testing was performed using the disk diffusion method based on the CLSI recommendation.

Findings: Gram-negative bacilli were identified as the most common causative agents of UTIs in all cases (140, 100%), of which *E. coli* had the highest isolation rate with 76 cases (54.3%), followed by *Klebsiella* spp. with 23 cases (16.4%). Antibacterial susceptibility tests revealed that 64.3% of the isolates were resistant to three antibiotics of different classes (MDR phenotype).

Conclusion: In conclusion, Gram-negative bacilli were the most common causative agents of UTIs, and *E. coli* had the highest isolation rate (54.3%). Regarding the high prevalence of antibiotic resistance and MDR phenotype, paying attention to drug resistance patterns of pathogens and proper and correct administration of antibiotics as well as proper and timely monitoring of treatment, could help physicians decrease the patients' mortality rate.

Keywords: Antibiotic resistance; *Escherichia coli*; Urinary tract infection; MDR.

CITATION LINKS

[1] Minardi D, d'Anzeo G, Cantoro D, Conti A, Muzzonigro G. Urinary tract infections in women: Etiology and ... [2] Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. Aging ... [3] Abbo LM, Hooton TM. Antimicrobial stewardship and urinary tract infections. Antibiotics ... [4] Halaji M, Shahidi S, Atapour A, Ataei B, Feizi A, Havaei SA. Characterization of extended-spectrum β-lactamase-producing uropathogenic Escherichia coli among Iranian kidney transplant patients. Infect ... [5] Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev... [6] Dadgostar P. Antimicrobial resistance: Implications and ... [7] Monack DM, Schwartz DJ, Conover MS, Hannan TJ, Hultgren SJ. Uropathogenic Escherichia coli superinfection enhances the severity of mouse bladder infection. PLoS... [8] Beahm NP, Nicolle LE, Bursey A, Smyth DJ, Tsuyuki RT. The assessment and management of urinary tract infections in adults: Guidelines for pharmacists. Can Pharm J ... [9] Oliva A, Giacobbe DR, Di Luca M, Miller NS. New insights into infections due to multidrug resistant Gram negative bacteria: The interplay between lab and clinic. Biomed Res ... [10] Ventola CL. The antibiotic resistance crisis: Part 1: causes and threats. Pharm ... [11] Fallah F, Parhiz S, Azimi L, Rashidan M. Distribution and antibiotic resistance pattern of bacteria isolated from patients with community-acquired urinary tract infections in Iran: A cross-sectional ... [12] Kornfält Isberg H, Melander E, Hedin K, Mölstad S, Beckman A. Uncomplicated urinary tract infections in Swedish primary care; etiology, resistance, and ... [13] Nicolle LE. Complicated urinary tract infection in adults. Can J Infect Dis ... [14] Bidell MR, Opraseuth MP, Yoon M, Mohr J, Lodise TP. Effect of prior receipt of antibiotics on the pathogen distribution and antibiotic resistance profile of key Gram-negative pathogens among patients with... [15] Mirzarazi M, Rezatofighi SE, Pourmahdi M, Mohajeri MR. Antibiotic resistance of isolated Gram negative bacteria from urinary tract... [16] Motamedifar M, Sedigh Ebrahim-Saraie H, Mansury D, Nikokar I, Hashemizadeh Z. Prevalence of etiological agents and antimicrobial resistance patterns of bacterial meningitis in ... [17] Sahoo KC, Tamhankar AJ, Johansson E, Lundborg CS. Antibiotic use, resistance development and environmental factors: A qualitative study among healthcare professionals in Orissa, India. BMC Public Health. 2010;10(1):629.

Introduction

Urinary tract infection is the most common bacterial infection and the second leading cause of infection in women [1]. The infection often occurs between the ages of 16 to 35; and 10% of women experience it at least once a year and 60% at least once in their lifetime [2]. Recurrent UTIs (RUTI) are common, and nearly half of people become infected for the second time in a year [2-3]. Despite the fact that the infection could be found in all age groups and both sexes, UTIs are four times more common in women than in men [1, 3]. Numerous microbial agents have been identified as the causative agents of UTIs, such as *Escherichia coli*, *Klebsiella* spp, *Staphylococcus spp, Enterobacter* spp, *Pseudomonas spp*, *Proteus mirabilis*, *Enterococcus faecalis*, and *Candida* spp. *E. coli* is a common cause of UTIs, causing more than 59% of UTIs, especially in young and pregnant women [4-5]. On the other hand, increasing rates of antibiotic resistance and the widespread emergence of multidrug-resistant organisms have become an expanding public health threat. Therefore, owing to the emergence and prevalence of antibiotic resistance, treatment of UTIs, especially complicated UTI, have become increasingly difficult and challenging [5].

Previous studies have considered factors associated with a higher risk of resistance to commonly used antibiotics, such as age, sex, history of hospitalization, history of antibiotic use for the treatment or prophylaxis of UTIs, history of previous UTI, complicated-UTIs compared to uncomplicated-UTIs, community acquired-UTIs compared to hospital acquired-UTIs, history of self-medication, chronic underlying diseases, genital urinary tract disorders, hospital wards, consumption of immunosuppressive drugs, and history of recent surgery [6-7]. On the other hand, evaluating the risk factors of developing antibiotic resistance in bacterial UTIs could be helpful in designing antimicrobial stewardship programs as well as selecting appropriate treatment for patients at higher risk of resistant-UTIs [6-8]. However, the spread of antibiotic resistance is increasing among strains causing UTIs. On the other hand, antibacterial resistance varies from region to region, even from hospital to hospital [9]; hence, there is a knowledge gap about the antibiotic resistance pattern of this group of bacteria, which could be used as a guide in the final or experimental treatment of associated infections.

Objectives: The aim of the present study was to investigate the prevalence of etiological agents of UTIs and their resistance patterns and to determine related risk factors and treatment outcomes of antibiotic resistance in Razi teaching hospital, Guilan, North of Iran.

Materials and Methods

This retrospective cross-sectional study was performed during two years, from April 2017 to September 2018. All patients with clinical symptoms of UTI (according to clinical investigation and UTI criteria), who were referred to the Razi teaching hospital affiliated to the Guilan University of Medical Sciences, were included.

The exclusion criterion was incomplete medical records. In total, 140 urine samples were collected from patients with clinical symptoms of UTI. Urine samples were cultured on 5% blood agar and Eosin-Methylene blue (EMB) agar (Merck, Germany) using standard methods and incubated aerobically for 24 hours at 37 °C.

A urine sample was considered as positive for UTI, when there was at least a single organism in 10^5 colony forming unit (CFU) per milliliter of urine. The isolation and identification of the bacteria were performed by conventional bacteriological and standard

biochemical tests such as production of acid from different sugars, catalase, and oxidase. Information was collected from patients' medical records (such as co-morbidity, antibiotic resistance pattern, output of treatment, and history of disease) in order to better understand their treatment outcomes. The results of antibiotic susceptibility test were presented as resistance to one, two, and three antibiotics [12].

Statistical analysis

Data were analyzed using SPSS™ software Version 16 (IBM Corp., USA). The Chi-square or Fisher's exact test was performed to investigate the significance of the differences. A *p*-value of less than 0.05 was considered as statistically significant.

Findings

The frequency of male and female patients was 57.1 and 42.9%, respectively. There was no statistically significant gender difference. The median age was 65 years. Gram-negative bacilli were identified as the most common causative agents of UTIs in all cases (140, 100%), of which *E. coli* had the highest isolation rate with 76 cases (54.3%), followed by *Klebsiella* spp. with 23 cases (16.4%). Gram negative isolates were the predominant pathogens isolated from all male and patients up to 64 years old. Antibacterial susceptibility tests revealed that 64.3% of the isolates were resistant against three antibiotics from different groups, 15.7% were resistant to one antibiotic, and none of the isolates were completely susceptible to antibiotics tested. Moreover, according to the patients' medical records, 50.7, 45, and 25% had a history of hospitalization, use of antibiotic, and UTIs, respectively. Also, 33.6% of the patients with UTI had a comorbidity such as diabetes, history of kidney transplant, and use of immunosuppressive drugs, while 55% of the patients had no comorbidity. The frequency distribution of the organisms and patients' characteristics are presented in Table 1. According to the results presented in Table 2, there was no significant relationship between different variables and antibiotic resistance, except the treatment outcome and age. Accordingly, 90% of the patients who died, were resistant to at least one antimicrobial agent. Furthermore, based on the antibiotic resistance pattern, 64.3% of the isolates were MDR, while there was no significant relationship between MDR isolates and different variables, except the treatment outcome and sex. Accordingly, the mortality rate in patients who didn't show MDR phenotype was higher than in the discharged patients.

Discussion

Antibiotic resistance incidence is dramatically increasing around the world. New mechanisms of antibiotic resistance have warned physicians about infectious diseases[10]. UTI, afflicting many people every year, is an infectious disease caused by bacteria that have different antibiotic resistance patterns [7]. Antibiotic resistance in turn leads to higher treatment costs, longer hospitalization, and higher mortality [6]. Given that few studies have been conducted to assess treatment outcomes of antibiotic resistance in pathogens in our region; thus, the present study aimed to investigate the clinical effects and outcomes of antibiotic resistance in urinary pathogens in patients with UTI [6]. This study examined 140 patients diagnosed with urinary tract infection and positive urine culture, admitted to Razi hospital in Rasht, Iran during 2017-2018. The results showed that 60% of the patients had at least one of the underlying diseases related to the urinary tract system, including kidney stone, urinary obstruction, continuous urinary catheter,

Table 1) Characterization of patients with UTIs

Co-Morbidity	
One	47 (33.6)
Two	14 (10)
Three	2 (1.4)
Number of Urinary Tract Disorders	
One	43 (30.7)
Two	27 (19.3)
Three	14 (10)
Frequency of Organism	
Escherichia coli	76 (54.3)
Klebsiella spp	23 (16.4)
Pseudomonas spp	8 (5.7)
Enterobacter spp	13 (9.3)
Citrobacter spp	20 (14.3)
Number of Antibiotic Resistance	
One antibiotic	22 (15.7)
Two antibiotics	17 (12.1)
Three antibiotics	90 (64.3)
History of antibiotic use	63 (45)
History of hospitalization	71 (50.7)
History of UTIs	35 (25)
Output of Treatment	
Discharge	130 (92.9)
Death	10 (7.1)

Table 2) Relationship between characterization of patients and antibiotic resistance pattern

Characterization	Antibiotic Resistance Pattern				*P*-Value
	Without Resistant No. (%)	One Resistant No. (%)	Two Resistant No. (%)	Three Resistant No. (%)	
Gender					
Female	9 (15)	8 (13.3)	9 (15)	34 (56.7)	.032
Male	2 (2.5)	14 (17.6)	8 (10)	56 (70)	
Number of Prescribed Antibiotics					
One	6 (16.7)	6 (16.7)	4 (11.1)	20 (55.6)	.403
Two	3 (4.7)	12 (18.8)	8 (12.5)	41 (64.1)	
Three	2 (5)	4 (10)	5 (12.5)	29 (72.5)	
Total	11 (7.9)	22 (15.7)	17 (12.1)	90 (64.3)	
Co-Morbidity					
None	4 (5.2)	10 (13)	11 (14.3)	52 (67.5)	.786
One	5 (10.6)	9 (19.1)	5 (10.6)	25 (59.6)	
Two	2 (14.3)	3 (21.4)	1 (7.1)	8 (57.1)	
Three	0 (0)	0 (0)	0 (0)	2 (100)	
Total	11 (7.9)	22 (15.7)	17 (12.1)	90 (64.3)	
History of Antibiotic Resistance					
Yes	4 (6.3)	9 (14.3)	6 (9.5)	44 (69.8)	.68
No	7 (9.1)	13 (16.9)	11 (14.3)	46 (59.7)	
History of UTIs					
Yes	4 (6.3)	9 (14.3)	6 (9.5)	44 (69.8)	.68
No	7 (9.1)	13 (16.9)	11 (14.3)	46 (59.7)	
Total	11 (7.9)	22 (15.7)	17 (12.1)	90 (64.3)	
Output of Treatment					
Discharge	10 (10)	19 (30)	14 (30)	87 (30)	.046
Death	1 (7.7)	3 (14.6)	3 (10.8)	3 (66.9)	
Total	11 (7.9)	22 (15.7)	17 (12.1)	90(64.3)	
Disorders of the Urinary System					
None	8 (14.3)	10 (17.9)	8 (14.3)	30 (53.6)	.209
One	2 (3.7)	7 (3.7)	4 (11.1)	30 (69.8)	
Two	1 (3.7)	1 (3.7)	3 (11.1)	22 (81.5)	
Tree	0 (0)	4 (28.6)	2 (14.3)	8 (57.1)	
Total	11 (7.9)	22 (15.7)	17 (12.1)	90 (64.3)	
Duration of Hospitalized					
>12 day	3 (12.5)	1 (14.1)	4 (16.6)	16 (66.6)	.505
<12 day	8 (6.8)	21 (18.1)	13 (11.2)	74 (63.7)	

and urinary system surgery, indicating that the presence of underlying urinary tract diseases in patients with UTI is very common and makes the treatment of this infection more problematic or delayed [11-12]. In addition, 45% of the patients had at least one underlying disease, such as diabetes, a history of using immunosuppressive drugs, or a kidney transplant. According to the previous studies results, comorbidities and underlying diseases in patients with UTI make the disease treatment more complicated [13].

The present study results also indicated that *E. coli* and generally Enterobacteriaceae were the most common etiological agents of UTI, which is consistent with the findings of previous studies [14]. In a study conducted by Mirzarazi et al. (2013), the most prevalent isolated bacteria were *E. coli* 138 (68%) and *Klebsiella* spp. (13%) [15]. Moreover, Motamedifar et al. (2015) reported that E. coli (50.6%) was the most frequent Gram-negative isolated strain, followed by Klebsiella spp., and Enterobacter spp. [16]. Isberg et al. (2019) in Sweden reported that *E. coli* strains were isolated from 72% of the positive urine samples, which is in agreement with this study results [12].

Comparing the results of various studies on antibiotic resistance in Iran and other countries, it was determined that multi-drug resistance in urinary pathogens in Iran and other countries is a serious threat to the treatment of UTI patients as well as social health system [11]. In this regard, the current study results indicated that 25.7% of the patients received only one antibiotic, while 28.6% received three and more antibiotics during their hospitalization [4]. Based on the statistical analysis results, there was no relationship between the number of courses of antibiotic treatment and antibiotic resistance. Underlying diseases of the urinary system and other underlying diseases were also shown to be among possible risk factors of increasing antibiotic resistance [17]. In addition, 45% of the patients had a history of antibiotic use three months prior to the hospitalization. However, there was no significant relationship between the history of antibiotic use and antibiotic resistance. Therefore, various studies should be conducted to investigate the causes of antibiotic resistance. The results of a study conducted by Isberg et al. (2019) in Sweden revealed that the history of antibiotic use in the past year was independently associated with antibiotic-resistant *E. coli* in the urine sample [12], which is not in agreement with the present study results. It was also indicated that 45% of the patients had a history of UTI; however, there was no significant relationship between the antibiotic resistance and history of UTI. The present study investigated the outcomes of patient's treatment. The results revealed that 90% of the patients with antibiotic resistance to more than one antibiotic died, and a significant relationship was reported. In this study, there was a high antibiotic resistance, especially a high frequency of multidrug-resistant isolates from patients; there was also a significant relationship between MDR phenotype and patients' death.

Conclusion

In conclusion, Gram-negative bacilli were the most common causative agents of UTIs, and *E. coli* had the highest isolation rate (54.3%). A significant relationship was found between the antibiotic resistance of pathogens involved in complicated UTI and patients' death. Moreover, antibiotic resistance in female patients was lower than in male patients. Therefore, regarding the high prevalence of antibiotic resistance and MDR phenotype, paying attention to drug resistance patterns of pathogens and proper and correct administration of antibiotics

as well as proper and timely monitoring of treatment, could help physicians decrease the patients' mortality rate.

Acknowledgments: Not applicable.
Ethical Permissions: This study was supported by Guilan University of Medical Sciences (Grant No: 1919710021).
Conflict of Interests: The authors declare that they have no conflicts of interest.
Author Contributions: Conceptualization: YM; Data curation and formal analysis: LM and YM; Investigation: LM, TYK and YM; Methodology and project administration: TYK and LM; Supervision: LA; Validation: TYK and LM; Writing of original draft: TYK and YM; Writing, reviewing, and editing: TYK and YM.
Fundings: Not applicable.
Consent to participate: Not applicable.

References

1. Minardi D, d'Anzeo G, Cantoro D, Conti A, Muzzonigro G. Urinary tract infections in women: Etiology and treatment options. Int J Gen Med. 2011; 4:333-43.
2. Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. Aging Health. 2013; 9(5):519-28.
3. Abbo LM, Hooton TM. Antimicrobial stewardship and urinary tract infections. Antibiotics (Basel). 2014; 3(2):174-92.
4. Halaji M, Shahidi S, Atapour A, Ataei B, Feizi A, Havaei SA. Characterization of extended-spectrum β-lactamase-producing uropathogenic Escherichia coli among Iranian kidney transplant patients. Infect Drug Resist. 2020; 13:1429-37.
5. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015; 13(5):269-84.
6. Dadgostar P. Antimicrobial resistance: Implications and costs. Infect Drug Resist. 2019; 12:3903-10.
7. Monack DM, Schwartz DJ, Conover MS, Hannan TJ, Hultgren SJ. Uropathogenic Escherichia coli superinfection enhances the severity of mouse bladder infection. PLoS Pathog. 2015; 11(1):e1004599.
8. Beahm NP, Nicolle LE, Bursey A, Smyth DJ, Tsuyuki RT. The assessment and management of urinary tract infections in adults: Guidelines for pharmacists. Can Pharm J (Ott). 2017; 150(5):298-305.
9. Oliva A, Giacobbe DR, Di Luca M, Miller NS. New insights into infections due to multidrug resistant Gram negative bacteria: The interplay between lab and clinic. Biomed Res Int. 2018; 2018:8905874.
10. Ventola CL. The antibiotic resistance crisis: Part 1: causes and threats. Pharm Ther. 2015; 40(4):277-83.
11. Fallah F, Parhiz S, Azimi L, Rashidan M. Distribution and antibiotic resistance pattern of bacteria isolated from patients with community-acquired urinary tract infections in Iran: A cross-sectional study. 2019; 4(2).
12. Kornfält Isberg H, Melander E, Hedin K, Mölstad S, Beckman A. Uncomplicated urinary tract infections in Swedish primary care; etiology, resistance, and treatment. BMC Infect Dis. 2019; 19(1):1-8.
13. Nicolle LE. Complicated urinary tract infection in adults. Can J Infect Dis Med Microbiol. 2005; 16(6):349-60.
14. Bidell MR, Opraseuth MP, Yoon M, Mohr J, Lodise TP. Effect of prior receipt of antibiotics on the pathogen distribution and antibiotic resistance profile of key Gram-negative pathogens among patients with hospital-onset urinary tract infections. BMC Infect Dis. 2017; 17(1):176.
15. Mirzarazi M, Rezatofighi SE, Pourmahdi

M, Mohajeri MR. Antibiotic resistance of isolated Gram negative bacteria from urinary tract infections (UTIs) in Isfahan. Jundishapur J Microbiol. 2013; 6(8):e6883.
16. Motamedifar M, Sedigh Ebrahim-Saraie H, Mansury D, Nikokar I, Hashemizadeh Z. Prevalence of etiological agents and antimicrobial resistance patterns of bacterial meningitis in Nemazee hospital, Shiraz, Iran. Arch Clin Infect Dis. 2015;10(2):e22703.
17. Sahoo KC, Tamhankar AJ, Johansson E, Lundborg CS. Antibiotic use, resistance development and environmental factors: A qualitative study among healthcare professionals in Orissa, India. BMC Public Health. 2010;10(1):629.