

Antibiotic resistance: a comparison between inpatient and outpatient uropathogens

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Abstract

Background: Urinary tract infection is one of the most common infections and its treatment is complicated by the emergence of antibiotic resistance. Resistance patterns of organisms differ between community-acquired and hospital-associated urinary tract infections.

Aims: The aim of this study was to determine the most effective antibiotics against uropathogens and if antibiotic resistance differed by setting (inpatient versus outpatient).

Methods: This 2016–2017 cross-sectional study examined 300 midstream clean-catch urine samples with positive culture (150 outpatient and 150 inpatient samples) for the uropathogens isolated and the resistance of these pathogens to different antibiotics. Samples were obtained from the laboratory of Baharloo hospital, Tehran. The differences in antibiotic resistance between inpatient and outpatient uropathogens were analysed using the chi-squared test.

Results: *Escherichia coli* (72.0% of the 300 samples) and *Klebsiella* spp (13.0%) were the most common uropathogens isolated. A greater proportion of inpatient samples showed resistance to ceftriaxone, cefixime, sulfamethoxazole–trimethoprim, ciprofloxacin and nalidixic acid than the outpatient samples ($P < 0.05$). The most effective antibiotics for Gram-negative uropathogens were imipenem (only 6.0% of these uropathogens overall were antibiotic-resistant), amikacin (6.3%) and nitrofurantoin (10.3%).

Conclusions: Uropathogen resistant rates in inpatients were higher than outpatient rates. The use of imipenem and amikacin instead of traditional first-line empirical therapy (fluoroquinolone and sulfamethoxazole–trimethoprim) is advised for hospitalized patients with urinary tract infections.

Keywords: antibacterial agents, urinary tract infections, inpatients, outpatients, Iran

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Introduction

Enterobacteriaceae are the organisms most commonly responsible for both community-acquired and health care associated urinary tract infections; they are found in 70–80% of such infections (1). The growing number of resistant pathogens is a concern for the empirical treatment of urinary tract infections. Regular monitoring of resistant organisms is essential and can reduce mortality, hospital admissions and the cost of health care for treatment of such infections (2–5).

Research conducted on uropathogens in inpatients and outpatients suggests that hospital-acquired uropathogens are more resistant to antibiotics than community-acquired uropathogens (5,6). It has also been suggested that the types of antibiotics that are ineffective against a particular uropathogens are increasing (7).

Urinary tract infection is one of the most prevalent infections. Uropathogens that are resistant to antibiotic therapy are a serious threat to the survival of hospitalized patients. It is vital to study the resistance patterns of organisms in community- and hospital-acquired urinary

tract infections so that physicians can find reliable alternative treatments for hospitalized patients with urinary tract infection.

We aimed to determine the most effective antibiotics against uropathogens in a hospital in the Islamic Republic of Iran and examine if antibiotic resistance differed by setting (inpatient versus outpatient) for different uropathogens.

Methods

Study design

This was a retrospective cross-sectional study of positive urine cultures obtained from urine samples taken in outpatient and inpatients settings between June 2016 and June 2017.

Sample selection and analysis

All samples were obtained from the laboratory of Baharloo hospital, a general hospital with 330 beds in Tehran. We randomly selected 150 samples from uropathogen-positive inpatient urine cultures and 150 from uropatho-

gen-positive outpatient urine cultures. The samples were analysed in the clinical laboratory of Baharloo Hospital.

Samples had been taken from adult patients presenting with a urinary tract infection. All samples had been collected as clean catch mid-stream samples in sterile containers. Samples were excluded if the patient had functional abnormalities of the genitourinary tract or had had catheterization. Samples with pyuria and bacteriuria were further processed for culture and antibiotic susceptibility testing by the disk diffusion method. Bacterial growth of more than 100 000 colony-forming units/mL was considered significant bacteriuria. Hence, the related samples were eligible for further study.

Statistical analysis

We calculated the sample size (150) based on a prevalence of uropathogen resistance to ceftriaxone of 24% for inpatients and 12% for outpatients (8), and an alpha error = 0.05, beta error = 20%.

Mean and standard deviations (SD) were used for continuous variables and frequency and percentage for categorical variables. The chi-squared was used to assess differences in antibiotic resistance between inpatient and outpatient resistance. We used SPSS, version 23 for all statistical analyses. A *P*-value < 0.05 was considered statistically significant.

Ethical considerations

Ethical approval for this study was granted by the institutional review board of Tehran University of Medical Sciences.

Results

We included 300 midstream urine catches (150 outpatient samples and 150 inpatient samples) in our study. Most samples came from patients aged 18–65 years: 6 (2.0%) were < 18 years; 192 (64.0%) were 18–65 years and

102 (34.0%) were > 65 years. Mean age of the patients was 54.88 (SD 23.54) years. Most patients were women (225 (75.0%)) and 75 (25.0%) were men. Resistance to cefixime, ceftriaxone, ciprofloxacin, nalidixic acid, nitrofurantoin and sulfamethoxazole–trimethoprim was considerably higher in the age group > 65 years than the age group 18–65 years (Table 1).

The pathogens isolated from the 300 samples were: *Escherichia coli* (72.0%), followed by *Klebsiella* spp (13.0%), *Enterobacter* spp (6.8%), *Pseudomonas* spp (5.7%), *Proteus* spp (1.8%), *Acinetobacter* spp (0.36%) and *Citrobacter* spp (0.36%).

The least effective antibiotic for Gram-negative bacteria was ampicillin–sulbactam (51.3% of the samples were resistant), followed by piperacillin–tazobactam (50.7%) and ampicillin (50.3%; Table 2). A significantly greater proportion of inpatient samples than outpatient samples with Gram-negative pathogens were resistant to: cefepime (*P* = 0.024), ceftriaxone (*P* < 0.001), cefixime (*P* = 0.001), sulfamethoxazole–trimethoprim (*P* = 0.047), ciprofloxacin (*P* < 0.001) and nalidixic acid (*P* < 0.001; Table 2).

As shown in Table 3, the most effective antibiotics for *E. coli* were nitrofurantoin, imipenem and amikacin with resistance rates of 4.7%, 5.1% and 5.1%, respectively. Cefepime and ceftazidime were the second most effective antibiotics against *E. coli*. These five antibiotics had a resistance rate of 30.8% or less against all the uropathogens except for nitrofurantoin to which *Pseudomonas* spp. was highly resistant (66.7%). Ciprofloxacin and levofloxacin were the third most effective antibiotics with less than 41.2% resistance against all the organisms (Table 3). *E. coli* resistance to widely used antibiotics such as ciprofloxacin, sulfamethoxazole–trimethoprim, amoxicillin–clavulanic acid and nitrofurantoin was 38.1%, 51.4%, 42.4% and 4.7% respectively (Table 3).

Uropathogens that were resistant to oral ciprofloxacin were also resistant to at least one other oral antibiotic (e.g.

Table 1 Antibiotic resistance according to demographic characteristic of the patients from whom samples were taken

Antibiotic	Resistant samples, no. (%)				
	Sex		Age (years)		
	Female (n = 225)	Male (n = 75)	< 18 (n = 6)	18–65 (n = 192)	> 65 (n = 102)
Amoxicillin–clavulanic acid (n = 62)	53 (23.6)	9 (12.0)	2 (33.3)	50 (26.0)	10 (9.8)
Ampicillin (n = 152)	116 (51.6)	36 (48.0)	6 (100.0)	90 (46.9)	56 (54.9)
Cefepime (n = 35)	27 (12.0)	8 (10.7)	3 (50.0)	22 (11.5)	10 (9.8)
Cefixime (n = 131)	93 (41.3)	38 (50.7)	6 (100.0)	59 (30.7)	66 (64.7)
Ceftazidime (n = 82)	59 (26.2)	23 (30.7)	2 (33.3)	46 (24.0)	34 (33.3)
Ceftriaxone (n = 108)	77 (34.2)	31 (41.3)	5 (83.3)	43 (22.4)	60 (58.8)
Ciprofloxacin (n = 110)	76 (33.8)	34 (45.3)	0 (0.0)	48 (25.0)	62 (60.8)
Imipenem (n = 9)	7 (3.1)	2 (2.7)	0 (0.0)	6 (3.1)	3 (2.9)
Nalidixic acid (n = 148)	110 (48.9)	38 (50.7)	5 (83.3)	71 (37.0)	72 (70.6)
Nitrofurantoin (n = 31)	19 (8.4)	12 (16.0)	3 (50.0)	12 (6.3)	16 (15.7)
Piperacillin–tazobactam (n = 76)	66 (29.3)	10 (13.3)	4 (66.7)	61 (31.8)	11 (10.8)
Sulfamethoxazole–trimethoprim (n = 137)	100 (44.4)	37 (49.3)	5 (83.3)	77 (40.1)	55 (53.9)

Table 2 Antibiotic resistance of isolated Gram-negative uropathogens in inpatient and outpatient samples

Antibiotic	Inpatient resistance (n = 150)	Outpatient resistance (n = 150)	P-value	Total antibiotic resistance
	No. (%)	No. (%)		No. (%)
Amikacin	13 (8.7)	6 (4.0)	0.088	19 (6.3)
Amoxicillin–clavulanic acid	–	62 (41.3)	NA	62 (41.3) ^a
Ampicillin	65 (43.3)	87 (58.0)	0.319	152 (50.7)
Ampicillin–sulbactam	–	77 (51.3)	NA	77 (51.3) ^a
Cefazolin	–	17 (11.3)	NA	17 (11.3) ^a
Cefepime	6 (4.0)	29 (19.3)	0.024	35 (11.7)
Cefixime	76 (50.7)	55 (36.7)	0.001	131 (43.7)
Ceftazidime	45 (30.0)	37 (24.7)	0.158	82 (27.3)
Ceftriaxone	73 (48.7)	35 (23.3)	< 0.001	108 (36.0)
Ciprofloxacin	69 (46.0)	41 (27.3)	< 0.001	110 (36.7)
Imipenem	–	9 (6.0)	NA	9 (6.0) ^a
Levofloxacin	–	44 (29.3)	NA	44 (29.3) ^a
Nalidixic acid	86 (57.3)	62 (41.3)	< 0.001	148 (49.3)
Nitrofurantoin	14 (9.3)	17 (11.3)	0.832	31 (10.3)
Piperacillin–tazobactam	–	76 (50.7)	NA	76 (50.7) ^a
Sulfamethoxazole–trimethoprim	68 (45.3)	69 (46.0)	0.047	137 (45.7)

NA= not applicable.

^an = 150.

– = Antibiotic was not used.

amoxicillin–clavulanic, sulfamethoxazole–trimethoprim and nitrofurantoin) (Table 4).

Discussion

Urinary tract infection affects 150 million people annually (9). Both community-acquired and hospital-acquired urinary tract infections are associated with increasing morbidity and mortality of patients and economic burden

(9). Antibiotics are recommended treatment for urinary tract infections. However, administering unnecessary and inappropriate antibiotics leads to antibiotic-resistant pathogens (6,10). The increasing rate of antibiotic-resistant organisms is a global concern. High resistance patterns have been identified worldwide (5–7). These resistant microorganisms often do not respond to standard antimicrobial therapy, causing prolonged disease.

Table 3 Antibiotic resistance of Gram-negative uropathogens

Antibiotic	Escherichia coli	Enterobacter spp	Klebsiella spp	Proteus spp	Pseudomonas spp
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Amikacin	10/197 (5.1)	0	4/37 (10.8)	1/5 (20.0)	0
Amoxicillin–clavulanic acid	42/99 (42.4)	10/17 (55.8)	7/19 (36.8)	0	0
Ampicillin	99/191 (51.8)	14/18 (77.8)	23/37 (62.2)	3/5 (60.0)	3/4 (75.0)
Ampicillin–sulbactam	50/99 (50.5)	11/17 (64.7)	11/19 (57.9)	0	0
Cefepime	23/105 (21.9)	2/17 (11.8)	4/19 (21.1)	0	2/7 (28.6)
Cefixime	86/195 (44.1)	7/18 (38.9)	12/37 (32.4)	2/5 (40.0)	9/11 (81.8)
Ceftazidime	50/200 (25.0)	4/18 (22.2)	11/36 (30.6)	2/4 (50.0)	4/13 (30.8)
Ceftriaxone	74/196 (37.8)	5/18 (27.8)	12/37 (32.4)	2/5 (40.0)	9/15 (60.0)
Ciprofloxacin	75/197 (38.1)	7/18 (38.9)	14/37 (37.8)	2/5 (40.0)	3/8 (37.5)
Imipenem	5/99 (5.1)	0	2/19 (10.5)	0	0
Levofloxacin	28/99 (28.3)	7/17 (41.2)	5/19 (26.3)	0	0
Nalidixic acid	103/198 (52.0)	6/18 (33.3)	15/37 (40.5)	0	4/11 (36.4)
Nitrofurantoin	9/191 (4.7)	2/18 (11.1)	12/36 (33.3)	1/5 (20.0)	4/6 (66.7)
Piperacillin–tazobactam	44/99 (44.4)	13/17 (76.5)	10/19 (52.6)	0	0
Sulfamethoxazole–trimethoprim	93/181 (51.4)	8/17 (47.1)	16/33 (48.5)	2/4 (50.0)	9/13 (69.2)

The number of samples analysed for the different organisms was different.

In our samples, *E. coli* (72.0%) was the most common organism found. The prevalence of *E. coli* in urinary tract infections in different parts of the Islamic Republic of Iran has been reported to range from 50.5% to 78.1% (11). Other studies have also reported *E. coli* to be the most prevalent uropathogen in both inpatient and outpatient groups, even in children (2,5–10).

In our study, samples from older the patients showed higher resistance to cephalosporin, ciprofloxacin and nitrofurantoin. Older patients are more likely exposed to more health care settings, multiple comorbidities and different antibiotics. Together, these factors might have led to the development of pathogens resistant to fluoroquinolones and other oral antibiotics, e.g. amoxicillin–clavulanic acid, nitrofurantoin and sulfamethoxazole–trimethoprim (12–14). The low effectiveness of oral antibiotics to treat urinary tract infections in older patients may result in hospitalization and parenteral therapy, which in turn may lead to further complications.

Resistance to most of the antibiotics was slightly higher in samples from male patients than female patients (Table 1). Other studies also found that uropathogens in male patients were more resistant to antibiotics (e.g. fluoroquinolone, nitrofurantoin and gentamicin) than in female patients (12,13). Men were prone to complicated urinary tract infections so they needed more potent antibiotics and longer hospitalization (14). Both long-term antibiotic use and hospital stay have been shown to lead to the development of antibiotic-resistant pathogens (12–15).

Coresistant organisms are resistant to two or more than two commonly used antibiotics (7). We found coresistance to ciprofloxacin and other antibiotics. Other studies have reported that ciprofloxacin resistance was in conjunction with other oral antibiotics and did not develop on its own (16–18). Coresistance to oral antibiotics reduces the options for outpatient treatment, so patients need to be treated in hospital or with parenteral antibiotics in outpatient clinics (1).

The antibiotic resistance reported for children with urinary tract infections in the Islamic Republic of Iran (imipenem 3.8% and amikacin 23.7%) are different from the overall resistance rates we found (imipenem 6.0% and amikacin 6.3%) (11). Low resistance rates for these two antibiotics suggest that they are the best for inpatient empirical therapy.

The most effective antibiotics against *E. coli* were imipenem and amikacin (5.1% resistance rate for both). A multicentre study showed that *E. coli* resistance to antibiotics was as follow: aminoglycosides 19.3%, fluoroquinolones 39.5% and third-generation cephalosporins 24.2% (19). We found a significantly lower resistant rate for amikacin (5.1%) but similar resistant rates for fluoroquinolone (38.1%) and third-generation of cephalosporins (22–44%).

We found that the least effective antibiotics for Gram-negative uropathogens were ampicillin-sulbactam,

Table 4 Coresistance of Gram-negative uropathogens to oral antibiotics

Pathogens resistant to:	No. (%)
Amoxicillin–clavulanic acid and ciprofloxacin	30/219 (13.7)
Amoxicillin–clavulanic acid and ciprofloxacin and sulfamethoxazole–trimethoprim	24/237 (10.1)
Amoxicillin–clavulanic acid and sulfamethoxazole–trimethoprim	40/198 (20.2)
Ciprofloxacin and nitrofurantoin	11/285 (3.9)
Ciprofloxacin and nitrofurantoin and sulfamethoxazole–trimethoprim	8/298 (2.7)
Ciprofloxacin and sulfamethoxazole–trimethoprim	62/275 (22.5)
Nitrofurantoin and sulfamethoxazole–trimethoprim	14/290 (4.8)

piperacillin–tazobactam and ampicillin with 51.3%, 50.7% and 50.3% resistance rates, respectively. The ampicillin resistance rate in our study is higher than in developed countries (23%–43%) but lower than in Ethiopia (78.3%) and Saudi Arabia (88.3%) (2,10). In Saudi Arabia, the most effective antibiotics for Gram-negative uropathogens were meropenem (6.5% resistance), amikacin (20.8%) and cefepime (28.6%). Only the figure for meropenem is similar to ours; the resistance rates for amikacin, cefepime and amoxicillin–clavulanic acid (66.2%) are higher than our rates (10).

Our findings on resistance rates of cefepime, cefixime, ceftriaxone, ciprofloxacin and sulfamethoxazole–trimethoprim are similar to the other studies (1,6–8). The development pathogens resistant to third-generation cephalosporins in our study is the most critical issue, because this is the first choice of treatment in some cases, such as pregnant women and children (1).

The inpatient antibiotic resistance rates for cefixime, ceftriaxone, ciprofloxacin and nalidixic acid were significantly higher than the resistance rate in community-acquired Gram-negative pathogens in our study. Previous studies support this finding (2,5,7,9). The Saudi Arabian study reported higher uropathogen resistance rates in outpatients than our rates: ampicillin 88.3% versus 58.0% and sulfamethoxazole–trimethoprim 49.4% versus 46.0% (10).

The findings of our study suggest that the most effective antibiotics for outpatient urinary tract infections in our country are amikacin (4.0% resistance) and nitrofurantoin (11.3%). However, in North America, the resistance rate of outpatient uropathogens for ciprofloxacin was lower than our study (25% in the United States of America and 12% in Canada versus 27.3% in our study) (20,21). The use of imipenem and amikacin instead of traditional first-line empirical therapy (fluoroquinolone and sulfamethoxazole–trimethoprim) is advised for hospitalized patients with urinary tract infections.

Our study has some limitations. It was conducted in only one centre and its findings cannot be generalized

to other settings. Due to the retrospective nature of the study, we had no access to the medical records of the patients. Consequently, it was not possible to differentiate contaminated cultures (from patients with, for example, urethritis and vaginitis) from true urinary

tract infections. Similarly, it was not possible to establish the correlation between existence of risk factors and underlying diseases.

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Résistance aux antibiotiques : comparaison entre les agents uropathogènes associés aux soins hospitaliers et ambulatoires

Résumé

Contexte : L'infection urinaire est l'une des infections les plus fréquentes et son traitement est compliqué à cause de l'apparition d'une résistance aux antibiotiques. Les schémas de résistance des organismes diffèrent entre les infections des voies urinaires acquises dans la communauté et les infections hospitalières.

Objectifs : Le but de la présente étude était de déterminer les antibiotiques les plus efficaces contre les agents uropathogènes et si la résistance aux antibiotiques différait selon le contexte (patient hospitalisé ou ambulatoire).

Méthodes : La présente étude transversale réalisée en 2016-2017 a examiné 300 échantillons d'urine de capture propre à mi-jet avec culture positive (150 échantillons pour les patients ambulatoires et 150 échantillons pour les patients hospitalisés) pour détecter les uropathogènes isolés et la résistance de ces agents pathogènes à différents antibiotiques. Les échantillons ont été obtenus au laboratoire de l'hôpital Baharloo, à Téhéran. Les différences en matière de résistance aux antibiotiques entre les agents uropathogènes associés aux soins hospitaliers et ambulatoires ont été analysées à l'aide du test du khi carré.

Résultats : *Escherichia coli* (72,0 % des 300 échantillons) et *Klebsiella* spp (13,0 %) étaient les uropathogènes les plus fréquemment isolés. Une plus grande proportion d'échantillons ambulatoires que d'échantillons hospitaliers ont montré une résistance à la ceftriaxone, à la céfixime, au sulfaméthoxazole-triméthoprime, à la ciprofloxacine et à l'acide nalidixique ($p < 0,05$). Les antibiotiques les plus efficaces pour les agents uropathogènes à Gram négatif étaient l'imipénem (seulement 6,0 % de ces uropathogènes étaient résistants aux antibiotiques), l'amikacine (6,3 %) et la nitrofurantoïne (10,3 %).

Conclusions : Les taux de résistance des uropathogènes étaient plus élevés chez les patients hospitalisés que chez les patients ambulatoires. L'utilisation de l'imipénem et de l'amikacine au lieu d'un traitement empirique de première intention traditionnel (fluoroquinolone et sulfaméthoxazole-triméthoprime) est recommandée pour les patients hospitalisés souffrant d'infections des voies urinaires.

مقاومة المضادات الحيوية: مقارنة بين مُمرضات الجهاز البولي التي تصيب المرضى الداخليين والمرضى الخارجيين، جمهورية إيران الإسلامية

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الخلاصة

الخلفية: تُعدُّ عدوى الجهاز البولي من أكثر أنواع العدوى شيوعاً، ويتعدّد علاجها بسبب ظهور مقاومة المضادات الحيوية. وتختلف أنماط مقاومة الكائنات الحية فيما بين عدوى الجهاز البولي المكتسبة مجتمعياً والعدوى المرتبطة بالمستشفيات.

الأهداف: هدفت هذه الدراسة إلى تحديد أكثر المضادات الحيوية فعالية ضد مُمرضات الجهاز البولي في أحد مستشفيات جمهورية إيران الإسلامية، وما إذا كانت مقاومة المضادات الحيوية تختلف باختلاف المكان (المرضى الداخليين في مقابل المرضى الخارجيين).

طرق البحث: فحصت هذه الدراسة المقطعية التي أُجريت خلال الفترة 2016 - 2017 عينة نظيفة من وسط جريان البول جاءت نتائج زرعها إيجابية (150 عينة من المرضى الخارجيين و150 عينة من المرضى الداخليين) للكشف عن مُمرضات الجهاز البولي وعزلها والكشف عن مقاومتها للمضادات الحيوية المختلفة. وتم الحصول على عينات من مختبر مستشفى بهارلو في طهران. وحُللت الاختلافات في مقاومة المضادات الحيوية بين مُمرضات الجهاز البولي صفوف المرضى الداخليين والمرضى الخارجيين باستخدام اختبار مربع كاي.

النتائج: كانت الإشريكية القولونية (72.0% من العينات البالغ عددها 300 عينة) والكلبيسيلا بأنواعها (13.0%) أكثر مُمرضات الجهاز البولي المعزولة شيوعاً. وأظهرت نسبة أكبر من عينات المرضى الداخليين مقاومة لسيفترياكسون، وسيفكسيم، وسلفاميثوكسازول - تريميثوبريم، وسيبروفلوكساسين، وحمض ناليديكسيك، مقارنة بعينات المرضى الخارجيين ($P < 0.05$) وكانت المضادات الحيوية الأكثر فعالية مع مُمرضات

الجهاز البولي سالبة الجرام هي الإيميبينيم (6.0%) وحسب من مُمرضات الجهاز البولي إجمالاً كانت مقاومة للمضادات الحيوية)، والأميكاسين (6.3%)، والنيتروفورانتين (10.3%).

الاستنتاجات: كانت معدلات مقاومة مُمرضات الجهاز البولي في صفوف المرضى الداخليين أعلى من نظيرتها في صفوف المرضى الخارجيين. ويُصح باستخدام الإيميبينيم والأميكاسين بدلاً من علاج الخط الأول التجريبي التقليدي (الفلوروكوينولون وسلفاميثوكسازول – تريمتوبريم) للمرضى الذين يدخلون المستشفى لوجود عدوى بالجهاز البولي.

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