

# Antimicrobial Resistance of Uropathogens and Rationale for Empirical Therapy in Jordan

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## ABSTRACT

Urinary tract infection (UTI) is one of the most common infections in both outpatients and hospital patients. In the majority of the cases, antimicrobial treatment is usually started empirically before the laboratory results of the urine culture are available. Thus, antimicrobial resistance may increase in uropathogens due to frequent and improper use of antimicrobial agents. This study was conducted to identify the urinary pathogens of UTI, to determine the antimicrobial resistance pattern in UTI and to assess the choices available for empirical antimicrobial therapy in patients with UTI over a three-year period. This study was conducted at King Abdulla University Hospital, Irbid in the north of Jordan from 2003 to 2005. A retrospective analysis of data taken from all midstream urine samples (8,800 patients suspected of UTI) was analyzed and an antimicrobial susceptibility test for commonly usable antimicrobial agents was performed for the isolates using the standard disc diffusion method. Data was analyzed using SPSS software window version 12. The most frequent causative organisms isolated were *Escherichia coli* (48.2%), *Klebsiella pneumoniae* (14.5%), *Pseudomonas aeruginosa* (9.7%), *Enterococcus faecalis* (5.8%), and *Proteus mirabilis* (3.2%). Nitrofurantoin was found to be the most effective antimicrobial agent against *E. coli*, *Klebsiella pneumoniae* and *Enterococcus faecalis* isolates. Gentamycin and ciproflaxin were found to be the most effective antimicrobial agents against *Pseudomonas aeruginosa*. The progressive increase in antimicrobial resistance among patients with UTI is of great concern. Empirical antimicrobial selection should be based on knowledge of the local prevalence of bacterial organisms and antimicrobial sensitivities, because antimicrobial resistance patterns may vary in different regions. The findings of this study indicate that *E. coli* is the predominant pathogen of UTI. Moreover, nitrofurantoin should be considered for empirical therapy of lower tract UTI.

**Key words:** Antimicrobial agents; Urinary tract infection; Susceptibility; Uropathogens; *Escherichia coli*.

## INTRODUCTION

Antimicrobial agents have played an indispensable role in reducing the incidence of morbidity and mortality associated with infectious diseases in humans. However, the selective pressure on using antimicrobial agents was the main driving force behind the emergence and spread of antimicrobial resistance traits among bacterial pathogens (Farrell *et al.*, 2003; Huang *et al.*, 2014; Shaifali *et al.*, 2012; Wang *et al.*, 2014; Zhanet *et al.*, 2006).

Urinary tract infection (UTI) is one of the most common infectious diseases in community practice diagnosed in patients with high financial cost (Haller *et al.*, 2004; Kurutepe *et al.*, 2005). Early diagnosis and prompt antimicrobial treatment are required to decrease renal scarring and prevent progressive kidney damage (Filiatrault *et al.*, 2012). Indeed, antimicrobial therapy in patients with suspected UTI is usually started empirically before urine culture results are available. Unfortunately, antimicrobial resistance has become an increasingly pressing problem in many countries (Kiffer *et al.*, 2011; Sire *et al.*, 2007).

The antimicrobial susceptibility of urine pathogens, changing over the years, is influenced by such factors as the changing patient population, and the extensive use and misuse of antimicrobial agents, which contribute to alterations in the microbial profile of urine isolates (Karaca *et al.*, 2005). Therefore, the overuse of antimicrobial agents may increase the risks of antimicrobial resistant pathogens, side effects and the cost of medical care (Usluer *et al.*, 2005). Indeed, antimicrobial resistance is a growing problem that gives rise to major concerns (Wise *et al.*, 1998). Moreover, there are large geographical variations in the patterns of bacterial resistance properties depending on local practices of antimicrobial prescriptions. Thus, different centres consider the results of a urine culture previously obtained from the laboratory of microbiology in determining empirical antimicrobial treatment for UTI.

Reporting the antimicrobial susceptibility testing of the urinary tract is usually achieved within 48 hours following the taking of a sample and, therefore, the treatment decision in the majority of UTIs is often empirical. The selection of antimicrobial agents is influenced by available data reflecting antibiotic resistance (Kurutepe *et al.*, 2005). Since the initiation of antimicrobial therapy in UTI is empirical, knowledge of the antimicrobial resistance patterns of common uropathogens is essential to provide clinically appropriate and cost effective therapy and achieve both a favourable clinical outcome and a reduction in antimicrobial resistance (Kurutepe *et al.*, 2005; Usluer *et al.*, 2005). As accurate information about prescribing patterns in hospitals is valuable in improving the quality of antimicrobial prescriptions (Usluer *et al.*, 2005), there will be a great need for antimicrobial resistance surveillance at the local, national and international levels (Kurutepe *et al.*, 2005).

For a better understanding of the emergence of resistance since the advent of the era of antimicrobial agents, leading to the baseline data in the first years of testing at King Abdulla University Hospital (KAUH), UTI collections were assayed from human sources obtained during 2003–2005 for antimicrobial agent susceptibility. This information will give a broader picture of the development of resistance and lay the foundation for understanding

the genetic mechanisms of resistance development.

The aim of this study was to determine the antimicrobial susceptibility patterns for most common strains of bacterial urine isolates taken from patients at KAUH in Irbid/the northern part of Jordan, from 2003 to 2005, and to evaluate the results. Therefore, the optimal empirical antimicrobial therapy for such patients could be determined in our region.

## Study design and methods

### Study design

A retrospective analysis was performed on all bacterial urine samples isolated from inpatients and outpatients sent to the bacteriology laboratory at KAUH for culture and sensitivity testing over three years, 2003, 2004 and 2005. Cultures with *Candida* growth were excluded from this analysis.

### Susceptibility testing

The sensitivity of bacterial urine isolates to commonly used antimicrobial agents from different groups was determined using the standard disc diffusion method. The antibiotics used were gentamycin, nitrofurantoin, cefuroxime, ampicillin, trimethoprim-sulfamethoxazole, ceftriaxone, ciprofloxacin, tetracycline, amoxicillin-clavulanic acid, imipenem, cefazolin and chloramphenicol.

### Statistical analysis

All data were analysed with SPSS for Windows, version 12.0, identified by percentage.

## RESULTS

A summary of the different urine bacterial microorganisms isolated from patients at KAUH in Irbid/the northern part of Jordan during the study period is shown in Table 1.

As expected, in 2004 *E. coli* (48.2%) was the leading uropathogen followed by *Klebsiella pneumonia* (14.5%), *Pseudomonas aeruginosa* (9.7%), *Enterococcus faecalis* (5.8%) and *Proteus mirabilis* (3.2%). Other bacteria were responsible in total for only 18.6% of positive urine cultures. For the other years (2003 and 2005), almost the same spectrum was found; *E. coli* (43.5 % and 43.9%, respectively) was the leading uropathogen

**Table 1: Prevalence (number and percentage) of bacterial urinary tract infections from patients at King Abdullah University Hospital in Irbid/the northern part of Jordan 2003-2005**

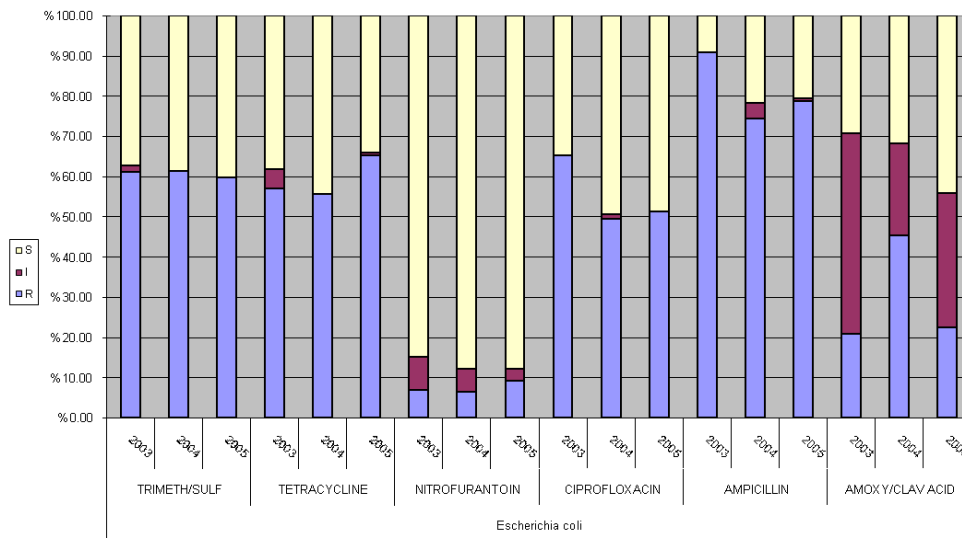
Isolates	2003		2004		2005	
	Percent	Frequency	Percent	Frequency	Percent	Frequency
<i>Escherichia coli</i>	43.5	594	48.2	1903	43.9	1530
<i>Klebsiella pneumoniae</i>	18.4	252	14.5	572	13.7	476
<i>Pseudomonas aeruginosa</i>	11.3	154	9.7	385	9.2	321
<i>Proteus mirabilis</i>	5.1	70	3.2	126	5.3	186
<i>Enterococcus faecalis</i>	4.5	62	5.8	230	3.4	120
Others	17.1	234	18.6	734	24.4	851
Total	100	1366	100	3950	100	3484

followed by *Klebsiella pneumoniae* (18.5% and 13.7%, respectively), *Pseudomonas aeruginosa* (11.3% and 9.2%, respectively), then followed here by *Proteus mirabilis* (5.1% and 5.3%, respectively) and *Enterococcus faecalis* (4.5% and 3.4%, respectively). Other bacteria were responsible in total for only 17.1% and 24.4% of positive urine cultures respectively (Table 1).

Antimicrobial resistance profiles of bacterial urinary isolates, at KAUH in Irbid/the northern part of Jordan from 2003 to 2005, were summarized in Table 2. Antimicrobial resistance patterns from different groups for *E. coli* isolates, from patients at KAUH in

Irbid/the northern part of Jordan from 2003 to 2005, were also presented in Figure 1.

Generally, the most effective antibiotic for the *E. coli* isolates observed was nitrofurantoin followed by amoxicillin/clavulanate and cephalosporins. Regarding *E. coli*, trimethoprim/sulfamethoxazole susceptibility (yearly range, 60 to 61%), nitrofurantoin susceptibility (yearly range, 6 to 9%) and gentamicin (yearly range, 35 to 41%) were generally unchanged over the 3 years studied. Tetracycline was the only agent studied that demonstrated a consistent stepwise increase in resistance from 2003 (57%) to 2005 (65%). Resistance rates to ampicillin (yearly



**Fig. 1. Antimicrobial resistance patterns in *E. coli* isolates from patients at KAUH in Irbid/the northern part of Jordan from 2003 to 2005**

Table 2: Percentage of resistance to the antimicrobial agents of bacterial urine isolates from patients at KAUH in Irbid/the northern part of Jordan, from 2003 to 2005 (ND=Not Determined)(R=resistance)

Antibiotic	Isolates																		
	<i>Escherichia coli</i>			<i>Klebsiella pneumoniae</i>			<i>P. aeruginosa</i>			<i>P. mirabilis</i>			<i>Enterococcus faecalis</i>						
	R%	2003	2004	2005	R%	2003	2004	2005	R%	2003	2004	2005	R%	2003	2004	2005			
Amoxicillin/ Clavulanate	21	45	23	36	48	38	100	100	100	100	100	100	0	27	7	7	ND	0	ND
Ampicillin	91	75	79	100	87	94	100	83	88	67	75	64	30	75	64	30	17	5	5
Cefazolin	52	45	38	31	20	31	100	100	89	50	0	14	100	0	14	100	100	100	100
Ceftriaxone	25	35	34	33	40	28	73	31	50	22	10	6	Nd	10	6	Nd	75	75	100
Cefuroxime	23	35	40	43	47	39	100	100	95	38	8	12	0	8	12	0	44	44	33
Chloramphenicol	24	67	44	33	Nd	16	100	Nd	100	60	Nd	33	100	Nd	33	100	43	43	25
Ciprofloxacin	65	50	51	17	38	21	50	32	44	0	0	27	67	0	27	67	44	44	56
Gentamycin	41	40	35	36	35	35	54	33	29	22	25	17	80	25	17	80	49	49	50
Nitrofurantoin	7	6	9	23	26	17	100	100	91	89	15	67	9	15	67	9	6	6	10
Tetracycline	57	59	65	50	10	50	100	81	86	83	Nd	94	80	Nd	94	80	76	76	85
Trimethoprim/ Sulfamethoxazole	61	61	60	61	50	47	90	89	97	78	70	57	ND	70	57	ND	100	100	ND

range, 75 to 91%), ciprofloxacin (yearly range, 50 to 65%), amoxicillin/calvulinic acid (yearly range, 21 to 45%), and chloramphenicol (yearly range, 24 to 67%) varied over this 3-year period.

Although almost 91% of the *E. coli* isolates in 2003 were resistant to ampicillin, only 7% in 2004 were resistant to nitrofurantoin. From 2003 to 2005, more than 50%, 60% and 57% of the *E. coli* isolates were resistant to ciprofloxacin, trimethoprim/sulfamethoxazole and tetracycline, respectively. Also, a wide range of resistance patterns to cephalosporins (*Cefazolin*, *Ceftriaxone*, *Cefuroxime*) was observed.

A wide range of antimicrobial resistance patterns was observed for *Proteus mirabilis* and *Klebsiella pneumoniae*. From 2003 to 2005, more than 64% and 47% of these bacterial urinary isolates were resistant to ampicillin and trimethoprim/sulfamethoxazole, respectively. Relatively, lower resistance of ciprofloxacin, nitrofurantoin and cefazolin was observed for *Klebsiella pneumoniae* while lower resistance of ciprofloxacin, ceftriaxone, cefuroxime and amoxicillin-clavulanic acid was observed for *Proteus mirabilis*.

As shown in Table 2, almost all antimicrobial agents were highly resistant to *Pseudomonas aeruginosa*, and the relatively susceptible antimicrobial agents were ciprofloxacin, ceftriaxone, gentamycin for these bacteria.

As shown in Table 2 for *Enterococcus faecalis*, relatively lower resistance to nitrofurantoin and ampicillin was observed while other antimicrobial agents had relatively higher resistance for these bacteria.

## DISCUSSION

This study showed the distribution of microbial species causing UTIs in the north of Jordan 2003-2005 and their patterns of susceptibility to the most commonly used antimicrobial agents. To help characterise the evolution of antimicrobial resistance in bacterial urine isolates since antimicrobial agents were first widely used at KAUH, existing strain collections of bacterial urine isolates were

tested for their susceptibility to a common panel of antimicrobial agents during 2003 to 2005.

As expected, the most common pathogen was *E. coli*, followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Proteus mirabilis*. Generally, this study data is in line with many previous studies (Huang *et al.*, 2014; Sharan *et al.*, 2013; Wang *et al.*, 2014), including the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study. In the NAUTICA study, forty-one medical centres (30 from the USA and 11 from Canada) participated, the most common organisms found were *Escherichia coli* (57.5%), *Klebsiella pneumoniae* (12.4%), *Enterococcus* spp. (6.6%), *Proteus mirabilis* (5.4%), and *Pseudomonas aeruginosa* (2.9%) (Zhanel *et al.*, 2006). Indeed, the NAUTICA study has shown a similarity to the Jordanian bacterial urinary isolates in the most common organisms causing UTI.

According to recent studies around the world, many antimicrobial resistances have been reported in *E. coli* urinary isolates (Adam *et al.*, 2013; Sharan *et al.*, 2013). Since *E. coli* is the main uropathogen, the resistance of many antimicrobial agents to *E. coli* is an important indicator in whether these antimicrobial agents should still be used empirically. Higher rates of susceptibility to many antimicrobial agents have been reported in the general population with UTI worldwide (Barrett *et al.*, 1999; Beunders, 1994; Gruneberg, 1994; Gupta *et al.*, 1999; Huang *et al.*, 2014; Sharan *et al.*, 2013; Wang *et al.*, 2014; Weber *et al.*, 1997; Winstanley *et al.*, 1997)

The present study of bacterial urine isolates for *E. coli* confirms that high resistance to trimethoprim/sulfamethoxazole was approaching 60%, but also that this rate (yearly range, 60 to 61%) was unchanged during the 3 years studied, from 2003 to 2005 (Table 2). Indeed, previous documented studies conducted in the United States showed a significant increase in trimethoprim/sulfamethoxazole resistance over the decade preceding 1995, from rates of 10% to levels of approximately 16% to 20% (Tadesse *et al.*, 2012).

It has been suggested that fluoroquinolones are a logical choice for empirical therapy of UTIs

(Hwang *et al.*, 2014). The data presented in this study appear to validate this assumption; however, the widespread subsequent overuse of fluoroquinolones for such a common infection raises concerns regarding the possibility for the rapid development of resistance (Hwang *et al.*, 2014). This study also noted ciprofloxacin, trimethoprim/sulfamethoxazole, tetracycline and ampicillin demonstrated more than 50% resistance to *E. coli* from 2003 to 2005 (Table 1). However, the rate of resistance in this study for *E. coli* to nitrofurantoin (yearly range, 6 to 9%) remained remarkably low from 2003 to 2005. This data regarding the nitrofurantoin is in line with rates of resistance similar to those published in earlier studies (Schaeffer, 2003). Nitrofurantoin has multiple mechanisms of action (McOsker *et al.*, 1994). This appears to have enabled it to maintain a strong activity against *E. coli*, despite its use for around 50 years. The *in vitro* activities of nitrofurantoin found in the present study suggest that they would provide appropriate alternative treatment where trimethoprim/sulfamethoxazole and ciprofloxacin use is no longer wise because of high (more than 50%) rates of resistance.

Generally, all strains were resistant to ampicillin (Table 2). Thus, the use of ampicillin as an empirical treatment for a suspected UTI would not cover the majority of pathogens. Moreover, there were also high rates of resistance to alternative agents such as trimethoprim-sulfamethoxazole which is frequently used in Jordan.

In the literature, there is a general similarity with the rates of resistance to nitrofurantoin, trimethoprim/sulfamethoxazole and ampicillin (Prakash *et al.*, 2013; Sharan *et al.*, 2013). However, there are high rates of resistance to amoxicillin/clavulanic acid and ciprofloxacin and gentamicin compared to other studies such as the ECO-SENS study and Canadian National Surveillance Study (Kahlmeter, 2003). The trend of increasing urinary pathogens resistance during the past few years is

similar to our findings (Prakash *et al.*, 2013; Sharan *et al.*, 2013). However, the overall resistance of uropathogens was higher in this study. This disparity may be attributed to differences in the study samples. In addition, laboratory studies may include specimens from asymptomatic patients or patients with external contamination. Local monitoring of resistance, performing of surveillance studies, wise prescribing, and the establishment and use of infection control guidelines are vital to monitor and reduce the possibility of resistance development.

The expected antimicrobial resistance patterns must be considered when selecting empirical antimicrobial treatment strategies for UTI. Consequently, antimicrobial policy should be formulated according to local surveillance data. In our region, the spectrum and antimicrobial resistance patterns of uropathogens were analysed and there was an increase in the rates of resistance to commonly used antimicrobial agents.

## CONCLUSION

The results presented in this study indicate that it is time to reconsider the empirical use of quinolones and to develop clear strategies to counteract the development of further resistance. Since antimicrobial resistance patterns may vary in different regions, it is mandatory that hospitals formulate their antimicrobial policy according to their local resistance pattern, which must be assessed in hospital and laboratory-based surveillance studies. In summary, the data in this study provide much needed information on the prevalence of antimicrobial resistance among pathogens that caused UTI in Jordan. Generally, *E. coli* is the main bacterial pathogen for UTI and nitrofurantoin demonstrated *in vitro* the most sensitive antimicrobial agents tested, hence highlighting its great usefulness as a choice for empirical therapy of lower UTI in Jordan.

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