Original Article

Susceptibility of hospital-acquired uropathogens to first-line antimicrobial agents at a tertiary health-care hospital, Saudi Arabia

Abdulaziz Alamri, Bahaeldin Hassan[1], Mohamed E. Hamid[2]

Departments of Surgery, [1]Obstetrics and Gynecology and [2]Clinical Microbiology and Parasitology, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia

Abstract

Context: Management of urinary tract infections (UTIs) is caused by antibiotic resistance uropathogens.

Aim: This study aimed to determine the important uropathogens and their resistance to first-line urinary tract antimicrobial agents.

Settings and Design: The region of Aseer, Southern Saudi Arabia, between 2013 and 2016.

Materials and Methods: A total of 1506 isolates were recovered from the urine samples of patients that were identified and tested against nine first-line UTI antimicrobial agents. Laboratory analysis was done as per the standard methods. Confirmation of bacterial identity and antimicrobial susceptibility assay was achieved by the VITEK 2 automated system.

Statistical Analysis Used: Statistical Package for the Social Sciences software version 21.0 was used for the statistical analysis.

Results: The dominant uropathogens were *Escherichia coli (E. coli)* 507 (33.7%); *Klebsiella pneumoniae* (*K. pneumoniae*), 229 (15.21%); *Pseudomonas aeruginosa*, 153 (10.2%); *Acinetobacter baumannii*, 80 (5.3%); *Enterococcus faecalis*, 71 (4.7%); and *Proteus mirabilis*, 61 (4.1%). Of all culture-positive uropathogens, 51.5% were resistant to the 39 agents, whereas 48.5% were sensitive ($P = 0.7969$). Regarding the susceptibility to the first-line agent, the most effective against the dominant *(in vitro)* agents against *E. coli* were fosfomycin and nitrofurantoin (93.5%) and (85.4%), respectively. Whereas those worked well against *K. pneumoniae* were cefoxitin (57.1).

Conclusions: The present study recommends the use of fosfomycin, cefoxitin, nitrofurantoin, and amoxicillin/clavulanate as the first choice UTIs treatment given their relatively high *in vitro* activity against major uropathogens. Knowledge of the bacterial species and their antimicrobial sensitivity patterns are always necessary to serve as a base for selecting the empirical treatment of UTIs as resistance rates vary geographically and with time.

Keywords: Antibiotic susceptibility, Aseer, drug resistance, Saudi Arabia, urinary tract infection

Address for correspondence: Dr. Abdulaziz Alamri, Department of Surgery, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia.
E-mail: aazizamri@gmail.com

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INTRODUCTION

Urinary tract infections (UTIs) are serious worldwide complaints affecting a large proportion of people, especially in women. UTIs represent the second most widespread infection and the main urological disease with a high overall economic burden.[1,2] UTIs continue to represent a challenge to the health-care setting, notably with the emergence of drug resistance to almost all known agents to varying degrees.[3,4] UTI causes a considerable economic load in the community and is related to substantial morbidity and mortality, especially among hospital-acquired infections.[5] *Escherichia coli* is still the main uropathogens responsible for acute pyelonephritis; however, routine antimicrobial sensitivity assay is needed to determine the empirical therapeutic choice. A good first-line choice for this pathogen remains to be amoxicillin-clavulanate.[6] Other studies advocate tigecycline to be an option that would reduce selection for ESBL-producing organisms including *E. coli*.[7]

It is imperative to try to use the first-hand antimicrobials sensibly for the treatment of UTIs caused by multidrug-resistant organism to prevent the development of resistance.[8] The first choice of antimicrobial agents for the empiric treatment of UTI is not well determined given the ever-changing resistance pattern among the uropathogens.[9] The misuse and overuse of antimicrobial medications is a worrying health problem that caused the spreading of bacterial resistance in many countries worldwide.[10] A study concluded that a single-dose fosfomycin trometamol was found an important choice for the first-line empirical treatment of uncomplicated lower UTIs.[11]

The prevalence of uropathogens and their resistance to antimicrobials showed a lot of variations.[12-14] *E. coli* and *Klebsiella pneumoniae* were shown to represent 78.8% and 75.3% resistance to three or more drugs, respectively. This study showed that cefotaxime revealed higher activity (87.1%) against mainstream uropathogens, which was followed by norfloxacin (83.3%).[15] Imipenem resistance was found low (14.3%), and the most resistance was found to be to ampicillin.[14]

It has been noticed that almost all bacterial uropathogens apart from *Streptococcus* spp. have a multiple antibiotic resistance index >0.2. For this reason, in some parts of the world, for example, Nigeria, nitrofurantoin, ciprofloxacin, and ofloxacin are the first choice therapy.[16]

The current protocols for the empirical treatment of hospital-acquired UTI are mainly based on national and international recommendations. Information on the antimicrobial susceptibility patterns in any geographic territory is needed to update and strengthen national protocols.[17] The treatment of UTI in many countries is a problem due to a lack of information regarding the antibiotic resistance of uropathogens.[13] The objective of the present study is to analyze the uropathogens, and their susceptibility to the main antimicrobial agents to increase our standing toward the treatment of UTI in Aseer region, Saudi Arabia.

MATERIALS AND METHODS

Ethical approval

Approval of the research was obtained from the Institutional Review Board of Aseer Central Hospital (ACH) and the Ethics Committee of King Khalid University (REC#2016-07-07). Patient informed permission was not obligatory due to the anonymous nature of the collected data.

Data collection and patients

This was a noninterventional, retrospective study done between January 2013 and June 2016 in ACH, Abha, Saudi Arabia. Patient information was obtained from ACH electronic system.

Laboratory investigations

Laboratory investigations were accomplished following standard methods.[18] The culture of urine samples was done with (Cystine Lactose Electrolyte Deficient; Becton Dickinson GmbH). A positive culture is described as a clean-catch midstream urine specimen with a growth of 10^5 CFU/mL of a single microorganism or mixed flora with the main species. Negative urine culture was defined as no growth, insufficient growth, or a mixed microbial flora with no predominant organism.[18]

The 1506 strains were analyzed for antimicrobial susceptibility by the VITEK 2 system as per the company guidelines (BioMérieux, Paris, France). The antimicrobial agents tested were amoxicillin/clavulanate potassium, ampicillin, cefoxitin, cephalothin, ciprofloxacin, fosfomycin, levofloxacin, nitrofurantoin, and trimethoprim/sulfamethoxazole. Inoculum suspensions were prepared in sterile saline to turbidity equal to a 0.5 McFarland standard from a 24-h cultured bacterial isolate. Inoculum suspension for the VITEK 2 system.

Statistical analysis

Patients' demographical data, symptoms, physical examination results, urinalysis, urine culture results,

pathogen microorganisms, and resistance rates to antimicrobials and prescribed empiric antimicrobial therapy (agent and duration) were recorded and analyzed by the SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

RESULTS

A total of 1506 isolates were recovered from the urine samples of patients between 2013 and 2016. Distributed as follows: 2013, 383 (25.4%); 2014, 295 (19.6%); 2015, 294 (19.5%); and 2016, 535 (35.5%). Of these, the male sample was 903 (59.9%) and the female samples were 604 (40.1). The distribution of cases according to the age group is shown in Figure 1. More than half of the patients (53%) were between the age group of 60 and 90 years of age.

Bacterial species recovered from the urine samples of patients in Aseer region between 2013 and 2016 in Aseer region, Saudi Arabia, are shown in Table 1. The main species were *E. coli*, 507 (33.7%); *K. pneumoniae*, 229 (15.21%); *Pseudomonas aeruginosa*, 153 (10.2%); *Acinetobacter baumannii*, 80 (5.3%); *Enterococcus faecalis*, 71 (4.7%); and *Proteus mirabilis*, 61 (4.1%). The remaining uropathogens were 252 isolates (16.7%), which were not considered in detail in this study.

The remaining 192 (12.7%) species include *Staphylococcus epidermidis*, *Serratia marcescens*, *Streptococcus* sp., coagulase-negative *Staphylococcus* sp., *Staphylococcus haemolyticus*, *Pseudomonas* sp., *Proteus penneri*, Serratia fonticola, *Staphylococcus hominis*, *Enterobacter agglomerans* group, *Enterbacter* sp., *Citrobacter koseri*, *Staphylococcus* sp., and the most undersized uropathogens were having <4 isolates (not significant uropathogens).

The susceptibility of uropathogens to first-line option antimicrobial agents is shown in Table 1. These species were *E. coli*; *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *E. faecalis*, *P. mirabilis*, *Enterobacter cloacae*, *Enterococcus faecium*, *Providencia stuartii*, *Morganella morganii*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Klebsiella oxytoca*, *A. baumannii– Haemolyticus*, *Citrobacter freundii*, and others.

The most effective agents *(in vitro)* and common uropathogens are illustrated in Figure 2. *E. coli* isolates were found sensitive to fosfomycin (93.5%) and nitrofurantoin (85.4%). Whereas that worked well against *K. pneumoniae* was cefoxitin (57.1) and fosfomycin (50%), *P. aeruginosa* was fosfomycin (70.3%) and ciprofloxacin (53%); *A. baumannii*, trimethoprim/sulfamethoxazole (61.2%); *E. faecalis*, amoxicillin/clavulanate potassium (100%) and nitrofurantoin (96.6%); *P. mirabilis* fosfomycin (92.7%) and cefoxitin (84%) [Table 1].

DISCUSSION

The most commonly isolated organisms were *E. coli, K. pneumoniae, P. aeruginosa, Proteus mirablis*, and *A. baumannii*. In a related study,[3] *E. coli* (70.4%), followed by *Klebsiella* (21.2%) were the most prevalent uropathogens. Other researches indicated a similar pattern of the etiological agents of UTI.[14,19] Although significant variation exists in some others, for instance, *E. coil* (44%), followed by *S. aureus* (20%), coagulase-negative *Staphylococci* (16%), and *K. pneumoniae* (8%) were the predominant uropathogens.[20]

Investigation of the bacterial types and their antibiotic resistance to a certain geographic variety of uropathogens is vital to help as a foundation for choosing the empirical treatment of UTIs. This has become essential because antibiotic resistance

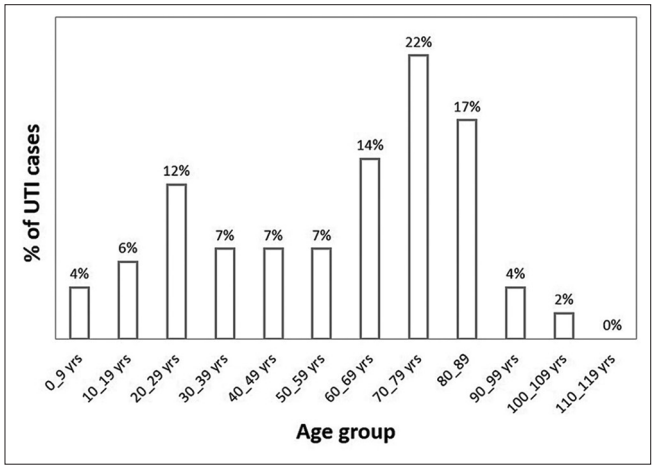

Figure 1: Distribution 1506 culture-positive uropathogens according to the age group

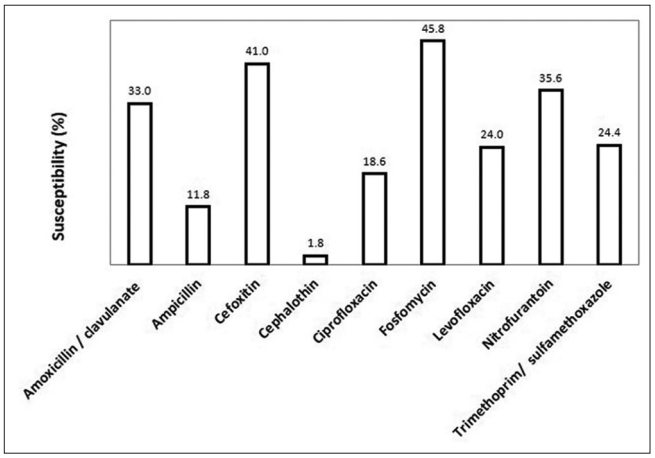

Figure 2: The sensitivity of common uropathogens some of the first-line antimicrobial agents for the treatment of urinary tract infections

Table 1: Percentage of sensitive strains of the dominant uropathogens* to first-line options antimicrobial agents

Species	*n* (%)	Percentage susceptibility							
		Amoxicillin/clavulanate	Ampicillin	Cefoxitin	Cephalothin	Ciprofloxacin	Fosfomycin	Levofloxacin	Nitrofurantoin	Trimethoprim/sulfamethoxazole
E. coli	507 (33.7)	58.2	11.7	72.0	7.8	23.8	93.5	22.9	85.4	39.1
K. pneumoniae	229 (15.2)	32.3	6.7	57.1	0.0	10.0	50.0	27.8	37.9	24.0
P. aeruginosa	153 (10.2)	2.1	1.1	8.8	1.3	53.0	70.3	44.1	8.0	4.5
A. baumannii	80 (5.3)	3.0	2.1	10.0	0.0	9.1	0.0	14.3	8.3	61.2
E. faecalis	71 (4.7)	100.0	79.9	0.0	0.0	21.7	0.0	30.6	96.6	0.0
P. mirabilis	61 (4.1)	74.4	5.3	84.8	10.4	12.8	92.7	25.5	7.7	11.8
E. faecium	37 (2.5)	50.0	10.7	0.0	0.0	9.8	0.0	9.0	42.9	0.0
P. stuartii	29 (1.9)	21.3	18.8	67.7	4.0	19.1	42.9	24.3	9.5	25.0
M. morganii	22 (1.5)	43.1	4.1	85.0	0.0	10.1	52.0	13.1	6.0	10.6
E. aerogenes	20 (1.3)	12.2	6.5	53.3	0.0	11.1	68.8	20.5	33.3	40.0
K. oxytoca	16 (1.1)	32.3	6.7	57.1	0.0	10.0	50.0	27.8	37.9	24.0
A. baumannii-haemolyticus	15 (1.0)	0.0	0.0	0.0	0.0	15.0	0.0	13.8	0.0	54.8
C. freundii	14 (0.9)	0.0	0.0	37.5	0.0	35.7	75.0	37.9	89.7	22.2
Average susceptibility rate	1254 (83.3)	33.0	11.8	41.0	1.8	18.6	45.8	24.0	35.6	24.4

*Of the 1506 uropathogens, 1254 (83.3%) are listed above, the remaining uropathogens were 252 isolates (16.7%), which were not considered in detail in this study. *E. coli: Escherichia coli, K. pneumoniae: Klebsiella pneumonia, P. aeruginosa: Pseudomonas aeruginosa, A. baumannii: Acinetobacter baumannii, E. faecalis: Enterococcus faecalis, P. mirabilis: Proteus mirabilis, E. faecium: Enterococcus faecium, P. stuartii: Providencia stuartii, M. morganii: Morganella morganii, E. aerogenes: Enterobacter aerogenes, K. oxytoca: Klebsiella oxytoca, A. baumannii: Acinetobacter baumannii, C. freundii: Citrobacter freundii*

rates are variable geographically and with time.[21] Antimicrobial agents that are regularly used for empiric UTI treatment such as fluoroquinolones (ciprofloxacin and levofloxacin) co-trimoxazole, levofloxacin, fosfomycin, or nitrofurantoin[22] were compared with the results from the present study. An outstandingly elevated resistant rate was developed with these empirically used agents. Particularly, a high resistance rate (>80%) was observed in, for example, ampicillin for the major four uropathogens as follows *E. coli* (88.3%), *K. pneumoniae* (93.7%), *P. aeruginosa* (98.9%), and *A. baumannii* (97.9%).

The most suitable antibiotic chosen for the outpatient's empirical treatment in all age groups in Turkey was oral nitrofurantoin and parenteral amikacin. The appropriate parenteral antibiotics that should be selected for the empirical treatment of inpatient UTI in all age groups are cefoperazone/sulbactam, amikacin, and carbapenems.[4] Comparable to our finding, previously *E. coli* and *S. aureus* were found the main pathogens in and many of them were resistant to regularly approved antibiotics. This leaves the clinicians with only limited alternative drugs for UTIs treatment.[23] Routine surveillance and monitoring educations are needed to bring up-to-date clinicians on the predominant pathogens and the antibiogram suitable to tackle such spread.[23] Moreover, forceful and constant health education using feasible media is suggested to prevent the threat of drug resistance largely caused by inappropriate antibiotic usage.

We would suggest fosfomycin which showed an overall inhibitory activity of 45.8%, then cefoxitin (41%), nitrofurantoin (35.6%), and amoxicillin/clavulanate (33.0%) [Table 1] taking into consideration their *in vitro* antimicrobial actions. This conclusion from our present analysis agreed with another investigation who decided that a single-dose fosfomycin trometamol as a valuable first-line empirical treatment of uncomplicated lower UTIs.[11] Many of the prescribed antibiotic treatments were shown to have high resistance rates.

CONCLUSION

The empirical use of these agents should be discouraged because of increased antimicrobial resistance rates. The present study concludes and recommends the use of fosfomycin followed by cefoxitin, nitrofurantoin, and amoxicillin/clavulanate as the first choice UTIs treatment because of their better in vitro inhibitory activity against most of the uropathogens. Knowledge of the local antimicrobial sensitivity pattern is periodically required to plan an updated treatment regimen.

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Conflicts of interest

There are no conflicts of interest.

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