Uropathogens Antimicrobial Sensitivity and Resistance Pattern From Outpatients in Balochistan, Pakistan

Taimoor Hussain [1] , Mehdi Moqadasi [2] , Sheza Malik [3] , Asjad Salman Zahid [4] , Kefayatullah Nazary [5] , Shafi M. Khosa [6] , Mohammad Mohsin Arshad [7] , John Joyce [8] , Rajeswari Khan [9] , Sneha Puvvada [10] , Khalida Walizada [11] , Abdul Rahim Khan [12]

1. Neurology/General Practitioner, Bolan Medical College, Quetta, PAK 2. Medical Laboratory Technology, Shafa Khana Sahib Zaman Hosptial, Quetta, PAK 3. Medicine, Army Medical College Rawalpindi, Rawalpindi, PAK 4. Internal Medicine, Allama Iqbal Memorial Teaching Hospital, Lahore, PAK 5. Internal Medicine, Kabul University of Medical Science, Kabul, AFG 6. Pathologist, Bolan Medical College, Quetta, PAK 7. Internal Medicine, Multan Medical and Dental College, Multan, PAK 8. Intern, M.S. Ramaiah Medical College, Bangalore, IND 9. Medicine and Surgery, College of Medicine & Sagore Dutta Hospital, Kolkata, IND 10. Medicine and Surgery, M.S. Ramaiah Medical College, Bangalore, IND 11. Neurological Surgery, Ali Abad Teaching Hospital, Kabul, AFG 12. Internal Medicine, Jinnah Medical and Dental College, Karachi, PAK

Corresponding author: Taimoor Hussain, taimoor_naran@yahoo.com

Abstract

Objective

To determine the pattern of microbes responsible for urinary tract infections and their susceptibility to different antibiotics.

Method

This is a cross-sectional study conducted at Quetta, Pakistan. The urine samples of 400 patients were collected and sent for culture and sensitivity analysis. The results were recorded on an excel datasheet. Descriptive statistics were used to describe the data.

Results

Out of 400 urine samples, 266 samples were culture positive for microorganisms. The most common organism on analysis was *Escherichia coli* 123/266 (46.24%) followed by *Staphylococcus saprophyticus* 59/266 (22.18%) and *Klebsiella pneumonia* 49/266 (18.42%). Gram-negative microorganisms were most susceptible to fosfomycin, cefoperazone/sulbactam, and meropenem. Gram-positive microorganisms were most susceptible to fosfomycin, cefoperazone/sulbactam, meropenem, and amoxicillin/clavulanate. High rates of resistance in *E. coli* were observed to most commonly prescribed broad-spectrum antibiotics; ceftriaxone (64.35%), cefotaxime (76.54%), ceftazidime (49.43%), cefepime (53.44%), levofloxacin (71.26%), and amoxicillin/clavulanate (70.31%). *E. coli* was the major multidrug-resistant organism.

Conclusion

High rates of antibiotic resistance and multi-drug resistance were revealed in this study due to the widespread and injudicious use of broad-spectrum antibiotics. Thus, it is highly recommended to regulate the pharmacies. Physicians should judiciously prescribe antibiotics and practice the culture and sensitivity of urine samples rather than blind prescription. Continued surveillance on uropathogens prevalence and resistance, new and next-generation antibiotics, and rapid diagnostic tests to differentiate viral from bacterial infections is the need of time.

Introduction

Urinary tract infections (UTIs) are among the most common types of infectious disease, accounting for approximately 150-250 million cases globally per year [1]. They are usually caused by gram-negative enteric rods, such as *Escherichia coli (E. coli), Klebsiella, Proteus,* etc. [2]. Approximately 50% of women acquire a UTI at least once in their lifetime [2]. The incidence of UTI among children is reported to be 30% all over the world [3]. 27% of women have a confirmed recurrence within the next six months, after the first episode of UTI [4]. UTIs can lead to renal scarring, ultimately leading to end-stage renal disease, therefore early diagnosis and treatment of UTI are necessary [5].

Antimicrobial resistance (AMR) is widespread across the globe, from the Americas to Australasia [6-16]. According to estimates by the Center for Disease Control (CDC), antibiotic-resistant bacteria cause at least 2.8 million illnesses and 35,000 deaths in the United States alone annually [17]. A study of trends of AMR in Europe observed that gram-negative uropathogens had high resistance to some of the most common antimicrobials. A north-to-south gradient in AMR exists in Europe, with higher resistance among southern European states like Greece, Cyprus, France, and Italy [18]. In a study of AMR in Asia pacific, "reduced sensitivity to commonly prescribed advanced-generation cephalosporin, piperacillin-tazobactam, and levofloxacin, among the studied gram-negative pathogens - *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp* (ESKAPE) were observed" [16]. One of the causes of antibiotic resistance is the empirical treatment of UTI [9-10]. In India, resistant bacterial infections resulted in 58,000 infants deaths in 2013 [19]. In the first and second years of life, infants and toddlers spend around 40 days on antibiotics, which clearly illustrates antibiotic overuse [20]. 85% of children with acute otitis media, below two years of age, are prescribed antibiotics [21]. Around 500 million courses of antibiotics are used to treat both bacterial and viral diarrhea each year across four middle-income countries India, Indonesia, Nigeria, and Brazil [10]. Nevertheless, antibiotic abuse for a diarrheal disease is a leading cause of increasing antibiotic resistance (ABR) [22]. Therefore, the regional antibiotic susceptibility patterns of the microorganisms should be used for treatment. World Health Organization's global plan of action on AMR has stressed AMR surveillance across nations as an important strategy for countering AMR [23]. This study is one of the few addressing antibiotic susceptibility and resistance patterns in Baluchistan, Pakistan. More extensive AMR surveillance data is the need of time.

Materials And Methods

This is a cross-sectional study conducted at Quetta, Pakistan over a period of nine months. The sampling technique was non-probability consecutive sampling. Informed consent was taken from all the participants. The study was conducted in the outpatient department of the hospital. The inclusion criterion was patients presenting with symptoms of uncomplicated urinary tract infection. The exclusion criteria of the study were patients who had refused to participate, immunocompromised, patients suffering from phimosis or paraphimosis, uncircumcised males, and patients who had taken antibiotics within the past 24 hours. The urine samples of the patients were then taken to confirm the diagnosis. Early morning mid-stream samples of urine were collected in sterile containers and immediately processed for further procedures. Urine samples with significant bacterial growth $\geq 10^5$ CFU/mL were considered positive. Colony study and biochemical tests were done to identify the microorganisms. MacConkey agar (Oxoid, England) was used to subculture the colonies to get pure growth of the microorganisms. Biochemical tests were done to identify the microorganisms. Tests performed for Gram-positive cocci include catalase, coagulase, and novobiocin test. Tests performed for gram-negative bacilli include Simmon's citrate agar, methyl red, urease, sulfur indole motility test, and triple sugar iron test. Kirby-Bauer disk diffusion method was used to determine the antibiotic susceptibility of the isolated colonies. Müller-Hinton agar plates were used to identify the sensitivity pattern. After this, the measurement of the zone of inhibition of bacterial growth was performed and a comparison was done with the guidelines of the Clinical and Laboratory Standards Institute (CLSI, 2018).

The organisms were subjected to various groups of antibiotics including penicillins, fluoroquinolones, aminoglycosides, cephalosporins, and tetracyclines. In addition, based on previous urine culture studies in Pakistan, due to high rates of resistance to recommended antibiotics, fosfomycin, meropenem, and vancomycin were also tested. The culture and sensitivity results for the specimens were recorded on a google form and an excel sheet was produced. The excel data sheet was analyzed for sensitivity and resistance patterns of microorganisms. Descriptive statistics were used to describe the data in terms of numbers and percentages

Results

Out of 400 urine samples, 266 samples were culture positive for microorganisms. 85 culture-positive samples were obtained from male participants and 181 culture-positive samples from female participants. *E. coli* was the most frequently observed microorganism followed by *Staphylococcus saprophyticus* and *Klebsiella pneumoniae*. The details of the frequency of uropathogens in urinary samples are shown in Table *1*.

Organism (n=266)	Frequency (%)
E. coli	123 (46.24)
Klebsiella pneumonia	49 (18.42)
Proteus mirabilis	13 (4.88)
Staphylococcus saprophyticus	59 (22.18)
Staphylococcus epidermidis	22 (8.27)

TABLE 1: Frequency of uropathogens in urinary samples.

E. coli was the most common organism in both genders. The second most common organisms were *Klebsiella pneumoniae* in males and *Staphylococcus saprophyticus* in females. The frequency distribution of bacteria based on gender is depicted in Table 2.

Uropathogens	*E. coli* (n=123)	*Klebsiella pneumonia* (n=49)	*Proteus mirabilis* (n=13)	*Staphylococcus saprophyticus* (n=59)	*Staphylococcus epidermidis* (n=22)
Male (85)	44 (51.76)	20 (25.88)	4 (4.7)	9 (10.58)	8 (9.41)
Female (181)	79 (43.64)	29 (16)	9 (4.97)	50 (27.62)	14 (7.73)

TABLE 2: Division of uropathogens according to gender.

Gram-negative bacteria were more common than gram-positive in males (78.82%) and females (64.64%). Table 3 depicts the microorganism's gram stain distribution pattern based on gender.

Gender	Frequency No. (%)	Gram-Positive	Gram-Negative
Male	85 (31.9)	18 (21.17)	67 (78.82)
Female	181 (68.04)	64 (35.35)	117 (64.64)

TABLE 3: Microorganisms gram stain distribution pattern based on gender.

High rates of resistance were observed to the most commonly prescribed antibiotics. *E. coli* were resistant to cephalosporins such as ceftriaxone (70.07%), cefepime (57.7%), and ceftazidime (48.7%). Cefepime resistance was more than 50 % in all organisms except *Staphylococcus saprophyticus* which showed comparatively lower resistance (27.77%). *E. coli* resistance pattern to fluoroquinolones was ciprofloxacin (67.4 %) and levofloxacin (71.5 %). *E. coli* showed high resistance to aminoglycoside gentamycin (58.5%) and lower resistance to amikacin (27.6%). Amoxicillin/Clavulanate also had high rates of resistance in all microorganisms except *Staphylococcus saprophyticus* which showed better sensitivity (70%). Vancomycin which is the therapy of choice for serious staphylococcal infections when penicillin and cephalosporin are resistant or cannot be used had high rates of resistance against *Staphylococcus saprophyticus* (86.2%) and *Staphylococcus epidermidis* (72.5%). *E. coli* showed good sensitivity to antibiotics such as cefoperazone/sulbactam (93.4%), fosfomycin (85.3 %), and meropenem (85.3 %). Sensitivity and resistance pattern to various groups of antibiotics was tested. The details of sensitivity and resistance patterns are depicted in Table 4.

Antibiotic	Bacteria/ Patterns	*E. coli* (n=123)	*Klebsiella pneumonia* (n=49)	*Proteus mirabilis* (n=13)	*Staphylococcus saprophyticus* (n=59)	*Staphylococcus epidermidis* (n=22)
Fosfomycin	Tested on	123	49	13	59	22
	S	105	39 (79.59%)	8 (61.53%)	35 (59.32%)	12 (54.54%)

		(85.3%)				
	R	12 (9.75%)	9 (18.36%)	5 (38.46%)	22 (37.28%)	8 (36.36%)
	I	6 (4.87%)	1 (2.04%)	-	2 (3.38%)	2 (9.09%)
Ceftriaxone	Tested on	101	40	12	53	21
	S	33 (32.67%)	17 (42.5%)	3 (25%)	20 (37.73%)	12 (57.14%)
	R	65 (64.35%)	19 (47.5%)	8 (66.66%)	25 (47.16%)	7 (33.33%)
	I	3 (2.97%)	4 (10%)	1 (8.33%)	8 (15.09%)	2 (9.52%)
Cefotaxime	Tested on	81	37	5	50	13
	S	19 (23.45%)	16 (43.24%)	3 (60%)	23 (46%)	1 (7.69$)
	R	62 (76.54%)	21 (56.75%)	2 (40%)	25 (50%)	11 (84.61%)
	I	-	-	-	2 (4%)	1 (7.69$)
Ceftazidime	Tested on	89	39	9	42	14
	S	42 (47.19%)	30 (76.92%)	5 (55.55%)	15 (35.71%)	5 (35.71%)
	R	44 (49.43%)	9 (23.07%)	4 (44.44%)	25 (59.52%)	9 (64.28%)
	I	3 (3.37%)	-	-	2 (4.76%)	-
Cefepime	Tested on	58.	21	6	18	11
	S	23 (39.65%)	11 (52.38%)	1 (16.66%)	12 (66.66%)	4 (36.36%)
	R	31 (53.44%)	10 (47.61%)	3 (50%)	5 (27.77%)	7 (63.63%)
	I	4 (6.89%)	-	2 (33.33%)	1 (5.55%)	-
Amoxicillin	Tested on	18	16	2	22	10
	S	1 (5.55%)	0 (0%)	-	7 (31.81%)	3 (30%)
	R	17 (94.44%)	16 (100%)	2 (100%)	15 (68.18%)	7 (70%)
	I	-	-	-	-	-
Amoxicilin/Clavulanate	Tested on	64	36	4	30	7
	S	17 (26.56%)	15 (41.66%)	-	21 (70%)	4 (57.14%)
	R	45 (70.31%)	20 (55.55%)	4 (100%)	9 (30%)	3 (42.85%)
	I	2 (3.12%)	1 (2.77%)	-	-	-
Ofloxacin	Tested on	67	37	4	35	8
		20				

Antibiotic						
	S	(29.85%)	16 (43.24%)	1 (25%)	16 (45.71%)	2 (25%)
	R	45 (67.16%)	21 (56.75%)	3 (75%)	19 (54.28%)	6 (75%)
	I	2 (2.98%)	-	-	-	-
Ciprofloxacin	Tested on	94	30	10	41	14
	S	21 (22.34%)	11 (36.66%)	2 (20%)	18 (43.90%)	4 (28.57%)
	R	64 (68.08%)	17 (56.66%)	8 (80%)	23 (56.09%)	9 (64.28%)
	I	9 (9.57%)	2 (6.66%)	-	-	1 (7.14%)
Levofloxacin	Tested on	87	40	10	36	17
	S	24 (27.58%)	16 (40%)	3 (30%)	18 (50%)	4 (23.52)
	R	62 (71.26%)	23 (57.5%)	6 (60%)	18 (50%)	13 (76.47%)
	I	1 (1.14%)	1 (2.5%)	1 (10%)	-	-
Norfloxacin	Tested on	83	37	12	40	13
	S	25 (30.12%)	12 (32.43%)	4 (33.33%)	9 (22.5%)	2 (15.38%)
	R	58 (69.87%)	25 (67.56%)	8 (66.66%)	30 (75%)	11 (84.61%)
	I	-	-	-	1 (2.5%)	-
Cefoperazone/Sulbactam	Tested on	60	38	4	24	9
	S	56 (93.33%)	35 (92.10%)	4 (100%)	22 (91.66%)	9 (100%)
	R	4 (6.66%)	3 (7.89%)	-	1 (4.16%)	-
	I	-	-	-	1 (4.16%)	-
Meropenem	Tested on	62	24	5	23	9
	S	52 (83.87%)	23 (95.83%)	2 (40%)	13 (56.52%)	7 (77.77%)
	R	5 (8.06%)	1 (4.16%)	-	6 (26.08%)	2 (22.22%)
	I	4 (6.45%)	-	3 (60%)	4 (117.39%)	-
Vancomycin	Tested on	Not tested	Not tested	Not tested	29	14
	S	-	-	-	2 (6.89%)	1 (7.14%)
	R	-	-	-	25 (86.20%)	11 (78.57%)
	I	-	-	-	2 (6.89%)	2 (14.28%)
Gentamycin	Tested on	54	13	6	25	14
	S	21 (38.88%)	5 (38.46%)	2 (33.33%)	11 (44%)	6 (42.85%)

	R	28 (51.85%)	7 (53.84%)	4 (66.66%)	11 (44%)	7 (50%)
	I	5 (9.25%)	1 (7.69%)	-	3 (12%)	1 (7.14%)
Amikacin	Tested on	58	17	8	28	16
	S	30 (51.74%)	9 (52.94%)	3 (37.5%)	20 (71.42%)	9 (56.25%)
	R	14 (24.13%)	7 (41.17%)	4 (50%)	7 (25%)	5 (31.25%)
	I	14 (24.13%)	1 (5.88%)	1 (12.5%)	1 (3.57%)	2 (12.5%)
Tetracycline	Tested on	67	37	3	36	15
	S	13 (19.40%)	18 (48.64%)	1 (33.33%)	12 (33.33%)	5 (33.33%)
	R	54 (80.59%)	19 (51.35%)	2 (66.66%)	24 (66.66%)	10 (66.66%)
	I	-	-	-	-	-
Doxycycline	Tested on	33	26	1	19	4
	S	13 (39.39%)	15 (57.69%)	-	15 (78.94%)	2 (50%)
	R	19 (57.57%)	11 (42.30%)	1 (100%)	4 (21.05%)	2(50%)
	I	1 (3.03%)	-	-	-	-

TABLE 4: Uropathogens antibiotic sensitivity and resistance patterns

S = Sensitive; R = Resistant; IS = Intermediate sensitive

The multidrug-resistant (MDR) pattern was also explored. Some of the samples were resistant to more than one antibiotic of the same or different groups. *E. coli* was the major multidrug-resistant organism, MDR in *E. coli* ranged from 1.6-17% while in *Staphylococcus saprophyticus* it ranged from 1.7-18.64%. Thirty-eight (14.28%) out of the 266 samples were multidrug-resistant to cefotaxime, ceftazidime, and ceftriaxone. 35 (13.15%) samples were multidrug-resistant to cefotaxime, ceftazidime, and ciprofloxacin. Twenty-six (9.77%) samples were multidrug-resistant to amoxicillin/clavulanate, ceftriaxone, and levofloxacin. Seventeen (6.3%) samples were multidrug-resistant to gentamycin, ciprofloxacin, and ceftriaxone. 15 (5.6%) samples were resistant to amoxicillin/clavulanate, ceftriaxone, and doxycycline. Eight (3%) samples were multidrug-resistant to four antibiotics, amoxicillin/clavulanate, levofloxacin, ceftriaxone, and doxycycline. Four (1.5%) of urine samples were resistant to amoxicillin/clavulanate, gentamycin, ciprofloxacin, ceftriaxone. Three (1.1%) urine samples were resistant to gentamycin, ceftriaxone, ciprofloxacin, and fosfomycin. Table 5 depicts the findings.

		Gram-negative uropathogens			Gram-positive uropathogens	
Antibiotic Combinations	Total	*E. coli, n (%)*	*Klebsiella pneumonia, n (%)*	*Proteus mirabilis, n (%)*	*Staphylococcus Saprophyticus, n (%)*	*Staphylococcus epidermidis, n (%)*
AMC, GEN, FOS	2 (0.7)	0	0	2 (15.38)	0	0
AMC, GEN,CPR	6 (2.2)	3 (2.4)	1 (20.4)	1 (7.6)	1 (1.7)	0
	26	19				

AMC, CRO, LVO	(9.7)	(15.44)	5 (10.2)	0	1 (1.7)	1 (4.5)
AMC, CRO, LVO, MPM	2 (0.7)	2 (1.6)	0-	0-	0-	0-
AMC, CRO, DOX	15 (5.6)	6 (4.8)	5 (10.2)	1 (7.6)	2 (3.3)	1(4.5)
AMC, LVO, GEN	7 (2.6)	3 (2.4)	1 (20.4)	1 (7.6)	1 (1.7)	1 (4.5)
AMC, LVO, CRO, DOX	8 (3)	5 (4)	3 (6.2)	0-	0-	1 (4.5)
AMC,GEN,CPR,CTX	4 (1.5)	2 (1.6)	1 (20.4)	0	1 (1.7)	0
AMC, GEN, CPR, FOS	1 (0.3)	0	0	1 (7.6)	0	0
AMC, GEN,CPR,CTX,CPZ	4 (1.5)	2 (1.6)	1 (20.4)	0	1 (1.7)	0
AMC, GEN,CPR,CTX,CPZ,CRO	0	0	0	0	0	0
AMC,GEN,CPR,CTX,CPZ, CRO, LVO	0	0	0	0	0	0
GEN,CPR,CTX	17 (6.3)	12 (9.7)	1 (20.4)	0	4 (6.7)	0
GEN,CPR,CTX , FOS	3 (1.1)	1 (0.8)	0	0	2 (3.3)	0
GEN,CPR,CTX,CPZ	13 (4.8)	6 (4.8)	3 (6.2)	0	4 (6.7)	0
GEN,CPR,CTX,CPZ,CRO	8 (3.0)	4 (3.2)	1 (20.4)	0	3 (5)	0
GEN,CPR,CTX,CPZ,CRO, LVO	3 (1.1)	2 (1.6)	1 (20.4)	0	0	0
CPR,CTX,CPZ,CRO	27 (10.1)	17 (13.8)	3 (6.2)	1 (7.6)	6 (10)	0
CTX,CPZ,CRO	38 (14.3)	20 (16.26)	3 (6.2)	1 (7.6)	11 (18.64)	3 (13.63)
CPR,CTX,CPZ	35 (13.1)	21 (17.07)	5 (10.2)	1 (7.6)	8 (13.55)	0
CPR,CTX,CPZ, LVO	25 (9.3)	14 (11.38)	5 (10.2)	1 (7.6)	5 (8.4)	0
CRO,CTX,CPZ,CPE	13 (4.8)	7 (5.6)	2 (4)	0	1 (1.7)	3 (13.63)

TABLE 5: Multi drug resistance (MDR) patterns of uropathogens

The percentages are shown in parenthesis. The percentage of total MDR to a specific combination of antibiotics is calculated out of 266 culture-positive samples. The percentage MDR for a specified microorganism against a specified combination of antibiotics is calculated based on their relative frequencies

CTX = Cefotaxime; CPZ = Ceftazidime; CRO = Ceftriaxone; CPE = Cefepime; LVO = Levofloxacin; CPR = Ciprofloxacin; AMC = Amoxicillin/Clavulanate; GEN = Gentamycin; FOS = Fosfomycin; DOX = Doxycyline; MPM = Meropenem.

Discussion

UTIs are caused by several microorganisms. *E. coli* (46.2%) followed by *coagulase-negative staphylococci (CONS)* (30.6%) and *Klebsiella pneumoniae* (18.4 %) were the most common uropathogens in our study. A

brief review of the most common uropathogens isolated from urine culture studies in Pakistan is as follows. Various urine culture studies in Pakistan have reported *E. coli* as the most common uropathogen ranging from 52%-77.4 % [24-29]. Another common organism was *Klebsiella pneumoniae* ranging from 1.9%-18.69% [24-29]. Few of the other uropathogens reported were *Pseudomonas aeruginosa, Enterobacter, and Proteus mirabilis* [24-29]

After the discovery of penicillin, antibiotics have revolutionized healthcare. No doubt, it has played a significant role in decreasing the mortality rate of various infections. Unfortunately, its widespread and indiscriminate use has led to antibiotic resistance especially in countries with poor regulation of the health sector. As per our study, the rate of resistance of *E. coli* to the most commonly prescribed antibiotics was as follows; ceftriaxone (64.35%), cefotaxime (76.54%), ceftazidime (49.43%), cefepime (53.44%), levofloxacin (71.26%), and amoxicillin/clavulanate (70.31%). A similarly high rate of resistance is observed in *CONS, Klebsiella pneumonia, and Proteus mirabilis* species, to most commonly prescribed antibiotics, as presented in Table *4*. As per our study, *E. coli* showed the highest sensitivity to cefoperazone/sulbactam (93.3%), followed by fosfomycin (85.36 %), and meropenem (83.87%). Klebsiella Pneumonia showed the highest sensitivity to meropenem (95.83%), followed by cefoperazone/sulbactam (92.10%), fosfomycin (79.59%), and ceftazidime (76.92%). *Staphylococcus saprophyticus* showed the highest sensitivity to cefoperazone/sulbactam (91.66 %), followed by doxycycline (78.94%), amikacin (71.42%), and amoxicillin/clavulanate (70%). *Staphylococcus epidermidis* showed the highest sensitivity to cefoperazone/sulbactam (100%) followed by meropenem (77.77%), amoxicillin/clavulanate, and ceftriaxone (57.14%) each.

Alarming rates of antibiotic resistance have been observed by other researchers in Pakistan. A brief description of such studies is reviewed here. Farooqi et al. observed that in the seven years study period from 1990-1997, the microorganisms were observed to have a low rate of resistance to cefotaxime, ceftriaxone, aztreonam, ofloxacin, amikacin, gentamicin, and nitrofurantoin, despite an increase in antibiotic resistance [24]. However, antibiotic resistance has increased now to the most commonly prescribed antibiotics as observed by more recent studies. According to a study by Muzamil et al., "almost more than 60% of the total sample were resistant to co-amoxiclav, cefotaxime, and ceftriaxone, piperacillin/tazobactam, cefoperazone/sulbactam, and ciprofloxacin. All 100% cultures were resistant to amoxicillin" [25]. Their findings are similar to our study except for cefoperazone/sulbactam which showed better sensitivity in our study. Malik et al. concluded that "the rates of resistance of amoxicillin/clavulanate, ciprofloxacin, ceftriaxone, ceftazidime were almost 70 %. The cultures were more than 90% sensitive to amikacin, fosfomycin, and nitrofurantoin. Imipenem showed a sensitivity of 85%" [26]. The rates of resistance and sensitivities in their study are similar to ours except for nitrofurantoin which was not tested in our study . In their study Rizvi et al. observed that "more than 75% of the strains were resistant to fluoroquinolones. 63% of *E. coli* samples were found resistant to ceftriaxone and cefepime. However, the resistance profile towards nitrofurantoin, fosfomycin, and carbapenem was less than 10.7%." [27]. In their study, Inam Ullah Khan et al. reported "The susceptibility pattern of *E. coli* showed that approximately more than 80% of the bacterial isolates were sensitive to imipenem, amikacin, tazobactam/piperacillin, and 69% to nitrofurantoin. Sensitivity to commonly used oral antibiotics was very low" [28]. Basharat Ali Khan et al. observed that "Out of 246 patients (20.43%) with nosocomial urinary tract infections, almost more than 60% of the samples were resistant to cefotaxime, ciprofloxacin, and gentamycin [29].

All the aforementioned studies indicate rising antibiotic resistance to some of the most commonly prescribed and broad-spectrum antibiotics. The high level of resistance is alarming when compared to developed countries like America. The prevalence of extended-spectrum beta-lactamase producers among the Enterobacteriaceae was less than 10% in North America, much lower as compared to Asia and the Middle East countries (>40%), according to "Study for Monitoring Antimicrobial Resistance Trends (SMART)" [30]. Health authorities, physicians, and pharmacies should work together to tackle this problem, regulate the healthcare industry especially prescription and purchase of antibiotics. Anyone in Pakistan can self-prescribe antibiotics and pharmacies dispense them without any prescription. Self-medication's overall prevalence was reported to be 39% in a review of 34 studies from low-middle-income countries with 31,340 participants, [31]. The short duration of treatment, insufficient doses, taking the wrong medicine and inappropriate sharing of medicines were some of the most common malpractices [31]. On the other hand, doctors also overprescribe antibiotics, without following standard treatment algorithms. America's national strategy to combat antibiotic resistance is an exemplary initiative for other countries. It recommends that "Improved detection can be achieved through appropriate data sharing, expansion, and coordination of existing surveillance systems, and establishment of a standardized platform for resistance testing and genetic characterization of bacteria. Development of Rapid "point-of-need" tests to distinguish between viral and bacterial infections and identifying bacterial drug sensitivities, new and next-generation antibiotics, diagnostics, and vaccines is the need of time. Rapid detection and control of outbreaks is another strategy to combat AMR. Global collaboration and capacities should be enhanced" [32].

Despite all efforts, certain limitations exist in the study. First, the urine culture and sensitivity data are from a single institution with smaller sample size, and can not be generalized to all UTI patients. Secondly, the data is primarily focused on urine culture findings, therefore, epidemiologic and demographic characteristics and comorbid conditions of patients are not extensively described.

Conclusions

High rates of antibiotic resistance and multi-drug resistance were revealed in this study due to the widespread and injudicious use of broad-spectrum antibiotics. Thus, it is highly recommended to regulate the pharmacies. Physicians should judiciously prescribe antibiotics and practice culture and sensitivity of urine samples rather than blind prescription. Efforts to increase the global AMR surveillance research should be increased. New generation antibiotics, advanced "point-of-need" diagnostics to differentiate bacterial and viral infections, and vaccines should be developed.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Shafa Khana Sahib Zaman Hospital Quetta, Pakistan issued approval MiscNo206. The research with the title " Uropathogens Antimicrobial Sensitivity and Resistance Pattern from Outpatients in Baluchistan, Pakistan" conducted by Dr.Taimoor Hussain is approved at Shafa Khana Sahib Zaman Hospital Quetta, Pakistan. . **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

References

1. Zowawi HM, Harris PN, Roberts MJ, et al.: The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol. 2015, 12:570-84. 10.1038/nrurol.2015.199
2. Schaeffer, AJ.: Infections of the urinary tract . Campbell-Walsh Urology, Tenth Edition. AJ Wein, LR Kavoussi, AC Novick, AW Partin, CA Peters (ed): Elsevier Saunders, Philadelphia, PA, USA; 2012. pp.:258-260.
3. Yolbaş I, Tekin R, Kelekci S, et al.: Community-acquired urinary tract infections in children: pathogens, antibiotic susceptibility and seasonal changes. Eur Rev Med Pharmacol Sci. 2013, 17:971-976.
4. Alós JI: Epidemiology and etiology of urinary tract infections in the community. Antimicrobial susceptibility of the main pathogens and clinical significance of resistance (Article in Spanish). Enferm Infecc Microbiol Clin. 2005, 23 Suppl 4:3-8. 10.1157/13091442
5. Pennesi M, L'erario I, Travan L, Ventura A: Managing children under 36 months of age with febrile urinary tract infection: a new approach. Pediatr Nephrol. 2012, 27:611-5. 10.1007/s00467-011-2087-3
6. Hamid F, Islam MR, Paul N, Nusrat N, Parveen R: Urinary tract infection in children: a review . Delta Med. 2013, 1:51-57. 10.3329/dmcj.v1i2.15919
7. Bonkat G, Müller G, Braissant O, et al.: Increasing prevalence of ciprofloxacin resistance in extended-spectrum-β-lactamase-producing Escherichia coli urinary isolates. World J Urol. 2013, 31:1427-32. 10.1007/s00345-013-1031-5
8. Iacchini S, Sabbatucci M, Gagliotti C, et al.: Bloodstream infections due to carbapenemase-producing Enterobacteriaceae in Italy: results from nationwide surveillance, 2014 to 2017. Euro Surveill. 2019, 24:10.2807/1560-7917.ES.2019.24.5.1800159
9. Cullen IM, Manecksha RP, McCullagh E, et al.: The changing pattern of antimicrobial resistance within 42,033 Escherichia coli isolates from nosocomial, community and urology patient-specific urinary tract infections, Dublin, 1999-2009. BJU Int. 2012, 109:1198-206. 10.1111/j.1464-410X.2011.10528.x
10. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF: Susceptibility patterns and ESBL rates of Escherichia coli from urinary tract infections in Canada and the United States, SMART 2010-2014. Diagn Microbiol Infect Dis. 2016, 85:459-65. 10.1016/j.diagmicrobio.2016.04.022
11. Guyomard-Rabenirina S, Malespine J, Ducat C, et al.: Temporal trends and risks factors for antimicrobial resistant Enterobacteriaceae urinary isolates from outpatients in Guadeloupe. BMC Microbiol. 2016, 16:121. 10.1186/s12866-016-0749-9
12. Sierra-Díaz E, Hernández-Ríos CJ, Bravo-Cuellar A: Antibiotic resistance: Microbiological profile of urinary tract infections in Mexico. Cir Cir. 2019, 87:176-82. 10.24875/CIRU.18000494
13. Okeke IN, Laxminarayan R, Bhutta ZA, et al.: Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis. 2005, 5:481-493. 10.1016/S1473-3099(05)70189-4
14. Fasugba O, Mitchell BG, Mnatzaganian G, Das A, Collignon P, Gardner A: Five-year antimicrobial resistance patterns of urinary escherichia coli at an australian tertiary hospital: time series analyses of prevalence data. PLoS One. 2016, 11:e0164306. 10.1371/journal.pone.0164306
15. Hyun M, Noh CI, Ryu SY, Kim HA: Changing trends in clinical characteristics and antibiotic susceptibility of Klebsiella pneumoniae bacteremia. Korean J Intern Med. 2018, 33:595-603. 10.3904/kjim.2015.257
16. Karlowsky JA, Hoban DJ, Hackel MA, Lob SH, Sahm DF: Antimicrobial susceptibility of Gram-negative ESKAPE pathogens isolated from hospitalized patients with intra-abdominal and urinary tract infections in Asia-Pacific countries: SMART 2013-2015. J Med Microbiol. 2017, 66:61-9. 10.1099/jmm.0.000421

17. Antibiotic resistance threats in USA . (2019). Accessed: 29 June, 2021: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

18. Hrbacek J, Cermak P, Zachoval R: Current antibiotic resistance trends of uropathogens in central Europe: survey from a tertiary hospital urology department 2011-2019. Antibiotics (Basel). 2020, 9:630. 10.3390/antibiotics9090630

19. Rather IA, Kim BC, Bajpai VK, Park YH: Self-medication and antibiotic resistance: crisis, current challenges, and prevention. Saudi J Biol Sci. 2017, 24:808-12. 10.1016/j.sjbs.2017.01.004

20. Vergison A, Dagan R, Arguedas A, et al.: Otitis media and its consequences: beyond the earache . Lancet Infect Dis. 2010, 10:195-203. 10.1016/S1473-3099(10)70012-8

21. Levy C, Pereira M, Guedj R, et al.: Impact of 2011 French guidelines on antibiotic prescription for acute otitis media in infants. Med Mal Infect. 2014, 44:102-6. 10.1016/j.medmal.2014.01.005

22. Richardson LA: Understanding and overcoming antibiotic resistance. PLoS Biol. 2017, 15:e2003775. 10.1371/journal.pbio.2003775

23. Global action plan of antimicrobial resistance . (2020). Accessed: 20 December 2020: https://apps.who.int/iris/handle/10665/193736.

24. Farooqi BJ, Shareeq F, Qureshi HS, Ashfaq MK, Rizvi QK: Changing pattern of antimicrobial susceptibility of organisms causing community acquired urinary tract infections. . . J Pak Med Assoc.. 2000, 50(11):369-373.

25. Muzammil M, Adnan M, Sikandar SM, Waheed MU, Javed N, Ur Rehman MF: Study of culture and sensitivity patterns of urinary tract infections in patients presenting with urinary symptoms in a tertiary care hospital. Cureus. 2020, 12:e7013. 10.7759/cureus.7013

26. Malik J, Javed N, Malik F, Ishaq U, Ahmed Z: Microbial resistance in urinary tract infections . Cureus. 2020, 12:e8110. 10.7759/cureus.8110

27. Rizvi ZA, Jamal AM, Malik AH, Zaidi SM, Abdul Rahim NU, Arshad D: Exploring antimicrobial resistance in agents causing urinary tract infections at a tertiary care hospital in a developing country. Cureus. 2020, 12:e9735. 10.7759/cureus.9735

28. Khan IU, Mirza IA, Ikram A, et al.: Antimicrobial susceptibility pattern of bacteria isolated from patients with urinary tract infection. J Coll Physicians Surg Pak. 2014, 24:840-844.

29. Khan BA, Saeed S, Akram A, Khan FB, Nasimet A: Nosocomial uropathogens and their antibiotic sensitivity patterns in a tertiary referral teaching hospital in Rawalpindi, Pakistan. J Ayub Med Coll Abbottabad. 2010, 22:11-12.

30. Morrissey I, Hackel M, Badal R, Bouchillon S, Hawser S, Biedenbach D: A review of ten years of the study for monitoring antimicrobial resistance trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel). 2013, 6:1335-46. 10.3390/ph6111335

31. Ocan M, Obuku EA, Bwanga F, Akena D, Richard S, Ogwal-Okeng J, Obua C: Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. BMC Public Health. 2015, 15:742. 10.1186/s12889-015-2109-3

32. U.S. National strategy for combating antibiotic-resistant bacteria . (2014). Accessed: 29 June, 2021: https://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf.