Original Article

Causative agents of urinary tract infections and their antimicrobial susceptibility patterns at a referral center in Western India: An audit to help clinicians prevent antibiotic misuse

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Abstract

Background: Urinary tract infections (UTIs) remain one of the most common infections in community and susceptibility of uropathogens to commonly used antimicrobials has declined over years. It is important to periodically study susceptibility patterns of uropathogens, so that empiric treatment can be determined using recent data, helping improve patient outcomes. **Methods:** Urine samples received by the laboratory for culture and susceptibility testing over a period of 3 months were analyzed and included in this study. Antimicrobial susceptibility testing was done on cultured isolates. **Results:** Of total 3,151 urine samples received, 3,066 were processed, and organisms were isolated from 1,401 (45.69%) samples. Isolation rate from male and female urine samples was 45.29% and 46.32%, respectively. The most commonly isolated organism was *Escherichia coli* (36.11%), followed by *Candida* spp. (18.56%), and *Klebsiella* spp. (18.06%). *E. coli* was most susceptible to meropenem (91.89%) and imipenem (91.69%). *Klebsiella* spp. was most susceptible to imipenem(75.89%) and meropenem(75.49%). Susceptibility of *E. coli* and *Klebsiella* spp. to nitrofurantoin, cotrimoxazole, and ciprofloxacin was 72.33%, 32.02%, and 18.97%, and 51.77%, 27.27%, and 22.13%, respectively. *Candida* spp. was most susceptible to amphotericin B (97.30%). **Conclusion:** Treatment for UTIs should be determined based on current local antimicrobial susceptibility patterns of uropathogens to minimise therapeutic failures and prevent antibiotic misuse.

Keywords: Antimicrobial susceptibility, *Escherichia coli*, urinary tract infections, uropathogens

Introduction

Urinary tract infection (UTI) describes microbial colonization and infection of structures of the urinary tract. UTI is categorized by infection site as pyelonephritis (kidney), cystitis (urinary bladder), and urethritis (urethra), and can also be classified as uncomplicated or complicated.[1] UTIs are among the most prevailing infectious diseases in the community with substantial clinical and financial burden.[2] Almost 95% of all UTIs are caused by bacteria, most of them by *Escherichia coli* (30%–90%, depending on clinical setting).[1] *Klebsiella, Enterobacter, Proteus, Pseudomonas, Enterococcus, Staphylococcus,* and others can also cause UTI.[1,3]

Antibiotic resistance among bacteria causing common infections is increasing in all regions of the world.[4] It is interesting that pattern of resistance observed varies from hospital to community, large hospital to small hospital, state to state, and even vary from country to country.[5] Emergence of resistance to antibiotics illustrates importance of using evidence-based strategies for

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treatment.[6] In UTI cases, antibiotic treatment is often started empirically before the results of urine culture and susceptibility testing are available. Appropriate antibiotic use in patients with UTI seems to reduce length of hospital stay and therefore favors patient outcomes and healthcare costs.[7] Hence, it becomes important to regularly monitor the resistance or susceptibility patterns of uropathogens, so that the guidelines for empirical antibiotic therapy can be improved to include antibiotics with low resistance, aiding clinicians in proper management of UTIs with minimal therapeutic failures.[8,9]

Taking all these into consideration a need was felt for a study to know causative agents of UTI and their antimicrobial susceptibility patterns, in a referral hospital in Gujarat, Western India. This study can help us take a step towards evidence-based medicine and help us keep track of antimicrobial susceptibility trends.

Materials and Methods

Ethics

This study was approved by Institutional Ethics Committee.

Study area and population

A cross-sectional study was conducted in a teaching and public-sector referral hospital and its affiliated Bacteriology Laboratory, located in urban area of Ahmedabad, Gujarat. The hospital has around 2,000 beds and provides treatment to over 9 lac OPD (outdoor/ambulatory) patients and 1 lac IPD (indoor/hospitalized) patients annually. This hospital caters needs of patients from nearby urban and rural areas and also of patients referred from various districts of Gujarat as well as from Madhya Pradesh and Rajasthan. Patients whose urine samples were received by the Bacteriology Laboratory during 3-month period – July, August, and September of 2016 – were included in the study. Culture and susceptibility reports were obtained directly from the Bacteriology Laboratory.

Sample collection and processing

Clean catch mid-stream urine samples or those obtained by aspiration from catheter tube or suprapubic aspirate collected in sterile, wide mouth universal container, from all the suspected UTI patients (outdoor/ambulatory patients and indoor/hospitalized patients) were received and processed by the Bacteriology Laboratory. Contaminated/non-sterile samples were discarded and not processed.

Culture and identification of isolates

Urine samples were inoculated on appropriate culture media by using semiquantitative methods and inoculated media was incubated for 48 hours aerobically at 37°C. Cultures were then examined for growth and colonies counted for determination of significant or insignificant bacteriuria. A growth of $\geq 10^5$ colony forming units/ml was considered as significant bacteriuria, suggestive of UTI.[10] Identification was done based on standard biochemical and other laboratory tests.[11]

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was done by Modified Kirby Bauer Disc Diffusion method on Muller Hinton Agar as per the CLSI Standards.[12] The antibiotics tested were amikacin (30 μg), ampicillin (10 μg), aztreonam (30 μg), cefepime (30 μg), ceftazidime (30 μg), cefuroxime (30 μg), cefotaxime (30 μg), cefoperazone (75 μg), co-trimoxazole (25 μg), chloramphenicol (30 μg), ciprofloxacin (5 μg), gentamicin (10 μg), imipenem(10μg),levofloxacin(5μg),linezolid(5μg),meropenem(10μg), nitrofurantoin (300 μg), piperacillin + tazobactam (100 + 10 μg), polymyxin B (300 μg), tetracycline (30 μg), ticarcillin + clavulanic acid (75 + 10 μg), and vancomycin (30 μg). For *Candida* spp., amphotericin B, clotrimazole, fluconazole, itraconazole, ketoconazole, miconazole and nystatin were used in antifungal susceptibility testing.

Statistical analysis

Calculations were done using Microsoft Excel. Results were presented as frequencies and percentages, and Z-test was applied where necessary and result considered significant at $P \leq 0.05$.

Definition of terms

1. Urinary tract infection: Infection and microbial colonization of urinary tract.[1,13]
2. Cystitis: Infection limited to urinary bladder/lower urinary tract. It often presents with dysuria, urinary urgency, frequency, and/or suprapubic pain.[13]
3. Pyelonephritis: Infection of the kidney/upper urinary tract. It often presents with fever, tachycardia, chills or rigors, costovertebral tenderness, and/or flank pain with or without symptoms of cystitis.[13]
4. Uncomplicated UTI: Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to nonpregnant, premenopausal women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.[13]
5. Complicated UTIs: UTIs in a patient with an increased chance of a complicated course, that is, all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases.[13]

Results

Of total 3,151 urine samples received, 1,901 from males and 1,250 from females, 85 contaminated/non-sterile samples were discarded. Of 3,066 samples processed, organisms were isolated from 1,401 samples yielding positive culture rate or isolation rate of 45.69%.

The isolation rate from samples received from OPD (30.23%) was lower than from samples received from IPD (51.62%) and the difference was statistically very significant (Z-value = 10.64, $P < 0.0001$) [Table 1]. Isolation rates in samples from males

Table 1: Frequency of positive culture or isolation, out of all urine samples received by the laboratory from OPD and IPD

	Total number of samples received	Number of samples processed	Number of samples that resulted in culture and isolation of organism	Positive culture rate or isolation rate (%)
OPD	909	850	257	30.23
IPD	2,242	2,216	1,144	51.62
Total	3,151	3,066	1,401	45.69

OPD: Out-Patient Department; IPD: In-Patient Department

and females were 45.29% and 46.32% respectively, without statistically significant difference (*Z*–value = 0.55, *P* = 0.58). Isolation rate from IPD + OPD (overall) and IPD samples was lower in males than in females. Isolation rate from OPD samples was higher in males than in females [Table 2].

The most common isolated organism was *E. coli* with 506 isolations (36.11%), followed by *Candida* spp.(18.56%), *Klebsiella* spp. (18.06%; *K. pneumoniae* = 17.15% and other *Klebsiella* spp. = 0.91%), *Pseudomonas* spp. (14.65%; *P. aeruginosa* = 13.19% and other *Pseudomonas* spp. = 1.46%), *Acinetobacter* spp. (5.06%; *A. baumannii* = 4.25% and other *Acinetobacter* spp.=0.81%), *Enterococcus* spp. (4.14% ; *E. feacalis* = 2.76% and *E. faecium* = 1.38%), *Proteus* spp. (1.78%; *P. mirabilis* = 1.07% and other *Proteus* spp. = 0.71%), *Staphylococcus* spp. (0.78%; *S. aureus* = 0.67% and coagulase-negative staphylococci = 0.11%), *Providencia* spp. (0.43%), and *Morganella morganii* (0.43%). Due to low number of *Providencia* and *Morganella* isolates, their antibiotic susceptibility results were excluded from the study. In males, followed by *E. coli* (33.29%), *Klebsiella* spp. (19.12%) was the second and *Candida* spp. (17.59%) was the third most isolated organism. In females, however, after *E. coli* (40.43%), *Candida* spp. (20.03%) was the second and *Klebsiella* spp. (16.42%) was the third most isolated organism [Table 3].

E. coli was most susceptible to meropenem (91.89%) closely followed by imipenem (91.69%). *E. coli* had least susceptibility to cefuroxime (18.18%) and ciprofloxacin (18.97%). *Klebsiella* was most susceptible to imipenem (75.89%) closely followed by meropenem (75.49%). *Klebsiella* spp. was least susceptible to ampicillin (2.37%). *Pseudomonas* spp. was most susceptible to polymyxin B (92.19%) followed by aztreonam (68.29%). *Pseudomonas* spp. was least susceptible to ciprofloxacin (25.85%). Gram-positive bacteria *Enterococcus* spp. and *Staphylococcus* spp. were most susceptible to linezolid at 96.55% and 100%, respectively followed by vancomycin at 87.93% and 100%, respectively [Table 4].

Susceptibility of *Candida* spp. was maximum to amphotericin B (97.30%), followed by nystatin (89.61%). *Candida* had minimal susceptibility to clotrimazole (50.38%) [Table 5].

Table 2: Isolation frequency of uropathogens based on gender and source of sample – OPD or IPD

	Males			Females		
	Processed	Isolated	Isolation rate (%)	Processed	Isolated	Isolation rate (%)
OPD	531	177	33.33	319	80	25.07
IPD	1339	670	50.03	877	474	54.05
Total	1870	847	45.29	1196	554	46.32

OPD: Out-Patient Department; IPD: In-Patient Department

Table 3: Sex based distribution of various uropathogens in culture positive samples

Organisms	Male, *n* (%)	Female, *n* (%)	Overall, *n* (%)
Escherichia coli	282 (33.29)	224 (40.43)	506 (36.11)
Klebsiella spp.	162 (19.12)	91 (16.42)	253 (18.06)
Pseudomonas spp.	138 (16.29)	67 (12.09)	205 (14.65)
Acinetobacter spp.	52 (6.13)	19 (3.43)	71 (5.06)
Enterococcus spp.	29 (3.42)	29 (5.23)	58 (4.14)
Proteus spp.	18 (2.12)	7 (1.26)	25 (1.78)
Staphylococcus spp.	8 (0.94)	3 (0.54)	11 (0.78)
Providencia spp.	5 (0.59)	1 (0.18)	6 (0.43)
Morganella spp.	4 (0.47)	1 (0.18)	6 (0.43)
Candida spp.	149 (17.59)	111 (20.03)	260 (18.56)
Total	847 (100)	554 (100)	1,401 (100)

Discussion

Positive culture rate or isolation rate of 45.69% obtained in this study was close to that obtained by similar studies conducted across India.[14-17] The data obtained from this study shows that spectrum of organisms causing UTI is also similar to that reported by other studies across India. However, isolation rates of various organisms varied from study to study.[14-17] Isolation rates in male and female samples were not statistically different which was in stark contrast to other studies conducted across India, in which the isolation rates were found to be higher in females.[14,15,17] This discrepancy could in part be because of higher number of complicated UTIs in males resulting in higher number of requests for culture and susceptibility reports and because treatment of most uncomplicated UTIs is usually done empirically without requesting culture and susceptibility reports.

E. coli was the most common isolated organism responsible for causing UTIs in our setup, in trend with other studies across India.[15-17] High *E. coli* isolation rate of 69.8% was seen in study conducted by George *et al*. in Karnataka compared to 36.11% seen in our study.[14] High susceptibility of *E. coli* to meropenem (91.89%) and imipenem (91.69%) was similar to that seen in other studies across India.[14-18] However, a study done in Lahore, Pakistan by Sabir *et al*. reported low *E. coli*

Table 4: Susceptibility rates of isolated bacteria to various tested antibiotics

Antibiotic drugs	*Escherichia coli* (*N*=506), *n* (%)	*Klebsiella* spp. (*N*=253), *n* (%)	*Pseudomonas* spp. (*N*=205), *n* (%)	*Acinetobacter* spp. (*N*=71), *n* (%)	*Proteus* spp. (*N*=25), *n* (%)	*Enterococcus* spp. (*N*=58), *n* (%)	*Staphylococcus* spp. (*N*=11), *n* (%)
Amikacin	311 (61.46)	113 (44.66)	113 (55.12)	35 (49.29)	11 (44)		6 (54.54)
Ampicillin	137 (27.07)	6 (2.37)			4 (16)	12 (20.69)	6 (54.54)
Aztreonam	246 (48.61)	73 (28.85)	140 (68.29)	6 (8.45)	7 (28)		
Cefepime	173 (34.19)	65 (25.69)	82 (40.00)	25 (35.21)	14 (56)		
Cefoperazone	131 (25.89)	50 (19.76)	69 (28.78)	18 (25.35)	11 (44)		
Ceftazidime	131 (25.89)	50 (19.76)	83 (40.48)	20 (28.17)	9 (36)		
Cefuroxime	92 (18.18)	37 (14.62)			3 (12)		3 (27.27)
Ciprofloxacin	96 (18.97)	56 (22.13)	53 (25.85)	22 (30.98)	6 (24)	10 (17.24)	7 (63.63)
Cotrimoxazole	162 (32.02)	69 (27.27)			6 (24)		10 (90.90)
Gentamicin	269 (53.16)	97 (38.34)	96 (46.83)	26 (36.62)	8 (32)		10 (90.90)
Imipenem	464 (91.69)	192 (75.89)	138 (67.31)	45 (63.38)	23 (92)		
Levofloxacin	109 (21.54)	63 (24.90)	67 (32.68)	26 (36.62)	9 (36)	8 (13.79)	9 (81.81)
Linezolid						56 (96.55)	11 (100.00)
Meropenem	465 (91.89)	191 (75.49)	137 (66.83)	45 (63.38)	23 (92)	32 (55.17)	
Nitrofurantoin	366 (72.33)	131 (51.77)			4 (16)	48 (82.75)	
Piperacillin + tazobactam	262 (51.77)	89 (35.17)	111 (54.14)	27 (38.02)	17 (68)		
Polymyxin B			189 (92.19)	70 (98.59)			
Tetracycline	183 (36.16)	112 (44.27)			3 (12)	31 (53.45)	
Ticarcillin + clavulanic acid	223 (44.07)	103 (40.71)	121 (59.02)	28 (39.43)	18 (72)		
Vancomycin						51 (87.93)	11 (100.00)

Susceptibility rate %: *n*/*N*; where *n*: Susceptible isolates; N: Total isolates; Blank boxes: Test not done

Table 5: Susceptibility rates of isolated *Candida* spp. to various tested antifungals

Antifungal drugs	*Candida* spp. (*N*=260), *n* (%)
Amphotericin B	253 (97.30)
Clotrimazole	131 (50.38)
Fluconazole	169 (65.00)
Itraconazole	201 (77.30)
Ketoconazole	198 (76.15)
Miconazole	178 (68.46)
Nystatin	233 (89.61)

Susceptibility rate %: *n*/*N*, where *n*: Susceptible isolates; N: Total number of isolates

susceptibility rate of 39.5% to imipenem.[19] Susceptibility of *E. coli* to nitrofurantoin was found high at 72.33%, in trend with other studies across India.[14,15,17,18] Susceptibility of *E. coli* to cotrimoxazole was 32.02% in this study, while in other studies across India it varied from 15.15% to 52.3%.[14,15] Susceptibility of *E. coli* to ciprofloxacin was 18.97% which lower compared to susceptibility rates seen in other studies across India and Pakistan.[14-16,19] High susceptibility rates of *E. coli* to ciprofloxacin were reported in studies done in Iran (68.1%), Poland (65.8%) and Ethiopia (54.8%) showing geographical variations in antibiotic susceptibility trends[20-22] [Table 6].

Klebsiella spp. was the third most commonly isolated uropathogen at rate of 18.06%, similar to isolation rate of 18.71% reported in a study from Meerut, India.[15] *Klebsiella* spp. however, was the second most commonly isolated organism in various studies across India.[14-16] Susceptibility to nitrofurantoin, cotrimoxazole and ciprofloxacin was found to be 51.77%, 27.27% and 22.13% respectively. Susceptibility of *Klebsiella* isolates to nitrofurantoin varied from 38% to 67% in studies across India.[15,17] Susceptibility of *Pseudomonas* isolates to anti-pseudomonas cephalosporin ceftazidime was found to be 40.48%.

Candida spp. was the second most common isolated organism in this study at rate of 18. 56% which was higher compared to other studies across India, with isolation rate as low as 8% reported in a study in Kerala, India.[16] The isolation rate of *Candida* spp. in the current study could be influenced by various patient factors such as urinary catheterisation and stenting, diabetes, immunocompromised status, hospitalization and use of broad spectrum antibiotics. *Candida* isolates were most susceptible to amphotericin B (97.30%) which was close to susceptibility rate of 91% observed in a study done in Mangalore, India.[23]

Resistance to antibiotics is higher in India compared to nations like UK, USA, Australia and South Africa.[24] Decreased susceptibility of uropathogens to empiric antibiotics for UTI like cotrimoxazole and ciprofloxacin and even to broad spectrum antibiotics in India, as evident by this and other studies, could be because of rampant use of antibiotics predisposed by many factors. Tendency to self-medicate, noncompliance to treatment, financial constraints and lack of education on part of patient, sale of antibiotic drugs without proper prescription and failure to educate patient on part of pharmacists, negligible surveillance of susceptibility patterns, poor regulatory controls over antibiotics and lack of will to make change on part of health care system, and administering antibiotics before obtaining sample for culture, failure to educate patient and

Table 6: Comparison of susceptibility rates of *Escherichia coli* to various antibiotics, found in various studies across India and abroad

Studies	Country	Nitrofurantoin (%)	Ciprofloxacin (%)	Gentamicin (%)	Amikacin (%)	Imipenem (%)	Cotrimoxazole (%)
George *et al.*[14]	India	84.15	34.1	63.6	90.9	97.7	52.3
Prakash and Saxena[15]	India	74.24	30.3	30.3	90.91	98.48	15.5
Somashekara *et al.*[16]	India	-	28	-	84	92	31.2
Singhal *et al.*[17]	India	88.66	16.22	-	65	-	-
Kulkarni *et al.*[18]	India	92.41	34.18	59.24	90.89	96.71	-
Sabir *et al.*[19]	Pakistan	-	29.2	26.4	71.7	39.5	-
Kashef *et al.*[20]	Iran	71.3	68.1	49.3	-	-	38.2
Stefaniuk *et al.*[21]	Poland	64	65.8	92.7	98.9	100	65.1
Mamuye[22]	Ethiopia	20.8	54.8	22.6	-	-	22.6
Current study	India	72.73	18.97	53.16	61.46	91.69	32.02

poor prescribing practices on part of physicians are among many factors that lead to injudicious and inappropriate use of antibiotics in India, hence causing rapid development of resistance.[25-28]

Based on this study, it can be recommended that nitrofurantoin be preferred instead of cotrimoxazole and ciprofloxacin for use as empiric antibiotic for uncomplicated cystitis.[29,30] For uncomplicated and complicated pyelonephritis, aminoglycosides and carbapenems should be preferred over fluoroquinolones and cephalosporins.[29,30] In all cases, urine sample for culture and susceptibility testing should be collected before administration of antibiotics and then therapy should be modified to narrow spectrum agent as per urine culture and susceptibility report.[30] This study emphasizes the need for hospital or regional antibiograms in order to combat the problem of antibiotic resistance. Antibiograms help monitor antimicrobial resistance trends and help clinicians select appropriate antibiotic therapy.[31]

The major limitation of this study is that since direct laboratory data was used, it does not take into account risk factors that can cause drug resistant and complicated UTIs like diabetes, compromised immunity, cancer chemotherapy, HIV, prolonged urinary catheterisation, recent antibiotic use, incomplete treatment of prior UTIs, urinary tract malformations and old age.[32,33] This study is also limited by the fact that those patients who were treated on outpatient basis might have had uncomplicated UTIs and physicians treating them might not have requested urine culture and susceptibility reports.

Conclusion

This study provides important data to monitor and compare with other studies, the trend of antimicrobial susceptibility of uropathogens and helps us towards deciding empirical treatment of UTIs at this referral healthcare center. Similar studies should be done on a larger scale periodically in different regions, so that empiric antibiotic therapy guidelines can be framed according to local antimicrobial susceptibility trends improving patient outcomes and minimizing anitbiotic misuse.

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Conflicts of interest

There are no conflicts of interest.

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