

Treatment of uncomplicated symptomatic urinary tract infections: Resistance patterns and misuse of antibiotics

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ABSTRACT

Introduction: Uncomplicated but symptomatic urinary tract infections (UTIs) are a common problem seen in practice. The study was undertaken to assess the most common pathogens responsible for uncomplicated symptomatic UTIs and the antimicrobial resistance pattern in a hospital in Bangalore. The study also explores the issue of antibiotic usage for these patients. **Materials and Methods:** The study was conducted in the Medicine department of a tertiary hospital in Bangalore. In all, 196 patients presented with symptoms of UTI. Bacterial growth was determined by standard microbiology techniques on freshly voided mid-stream urine samples collected from recruited patients. Patients' demographic data, urine culture results, resistance rates to antimicrobial agents and prescribed empiric antimicrobial therapy were analyzed. **Results:** The prevalence of UTI was 32.1%; majority (67.9%) of the symptomatic did not have UTI based on culture report. Gram-negative bacteria constituted the largest group with a prevalence of 84.1% (53/63), with *Escherichia coli* being the most common (70%) uropathogen. Gram-negative isolates showed high level of sensitivity to amikacin (90.6%) and nitrofurantoin (77.4%). Most of the gram-positive organisms were susceptible to nitrofurantoin (70%) and gentamicin (50%). Uropathogens isolated demonstrated high resistance to cotrimoxazole, fluoroquinolones, and beta-lactam antibiotics. It was found out that 30.1% of the patients were wrongly managed of which 14.7% were over treated. **Conclusion:** UTI can be over diagnosed and over treated on the basis of clinical signs, symptoms and urine microscopy. In the era of emerging anti-microbial resistance, effective counseling and delay in antibiotic initiation or empirical therapy with a short course of nitrofurantoin is highly recommended. Empirical therapy guidelines should be updated periodically to reflect changes in antimicrobial resistance of uropathogens.

Keywords: Anti microbial resistance, management, urinary tract infection

Introduction

Urinary tract infections (UTIs) are one of the most common types of bacterial infections occurring both in the community and hospital settings.^[1-4] Today it represents one of the most common diseases encountered in medical practices^[5] with the prevalence of UTI varying from 21.8% to 31.3% in various parts of India.^[6-8]

The current study was undertaken to assess the most common pathogens responsible for uncomplicated UTIs and the antimicrobial resistance pattern in a tertiary hospital in Bangalore. Additionally, the study throws light into the issues of overtreatment, under treatment and wrong treatment of UTI.

Materials and Methods

The study was conducted in Bangalore Baptist Hospital, Bangalore. Assuming a prevalence of 24%^[7] of UTI in symptomatic patients at 6% precision and 95% confidence level, the sample size calculated was 196.

Patients who came to the medicine OPD with symptoms (dysuria, frequency, urgency and suprapubic tenderness with or without fever) of UTI or any patients in whom the physician suspected uncomplicated UTI were recruited into the study. Patients with signs of pyelonephritis (a body temperature >38°C orally and flank pain or costovertebral angle tenderness), three or more episodes of UTI in the past year, symptoms of UTI in the last 3 months, previous upper UTI, other functional and structural

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urinary tract abnormalities, indwelling or recent use of a catheter, previous history of genitourinary system operation including urinary stones, current pregnancy, antibiotic use during the previous 2 weeks and patients who were hospitalized for any reason during past 3 months were excluded from the study.

The patients were interviewed using a semi-structured questionnaire which contained demographic information and symptomatology.

A freshly voided, midstream urine sample was collected in a sterile container from each patient enrolled for the study. All of them were given clear instructions on how to collect a midstream urine specimen.

The sample was inoculated for semi-quantitative culture on Cystine-Lactose-Electrolyte-Deficient (CLED) media using a calibrated loop. The culture plate was incubated at 37°C for 18-24 hours under aerobic conditions. Identification of bacterial growth was determined by Gram's staining and standard microbiology techniques.

Antibiotic sensitivity testing

Antibiotic susceptibility was performed by the Kirby-Bauer disc diffusion method on Mueller Hinton agar.^[9] The following antibiotics were tested at the concentrations given in brackets. Amoxiclav (20/10 mcg), ampicillin (10 mcg), amikacin (30 mcg), trimethoprim/sulphamethoxazole (cotrimoxazole) (1.25/23.75 mcg), norfloxacin (5 mcg), nalidixic acid (30 mcg), ciprofloxacin (5 mcg), nitrofurantoin (300 mcg), gentamicin (10 mcg), cefuroxime (30 mcg), ceftriaxone (30 mcg), ceftazidime (30 mcg), cephotaxime (30 mcg), netilmicin (30 mcg), piperacillin/tazobactam (100/10 mcg), cefoperazone/sulbactam (75/30 mcg), and vancomycin (30 mcg). Dehydrated media and antibiotic discs were procured from Himedia, India. The controls strains used were *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Staphylococcus aureus* 25922.

Definition of terms

Urinary tract infection: A quantitative count of more than 10^[5] Colony Forming Units of one bacterial species per ml from a properly collected midstream "clean catch" urine sample is considered as UTI.^[10]

Uncomplicated UTI: Uncomplicated UTI is defined as UTI in a person with a normal urinary tract and function.

Correct management:

- A person presented with symptoms of UTI, had a positive urine culture and treated with an antibiotic which was effective against the uropathogen isolated
or
- A person presented with symptoms of UTI, had a negative urine culture and not treated with an antibiotic
or

- A person who was started on empirical therapy with a resistant antibiotic, but was subsequently changed to an uropathogen sensitive antibiotic after culture report.

Wrong management:

- A person presented with symptoms of UTI, and a positive urine culture but treated with antibiotic which was not effective against the uropathogen isolated
or
- A person presented with symptoms of UTI, had a negative urine culture but treated with an antibiotic
or
- A person presented with symptoms of UTI, had a positive urine culture but not treated with an antibiotic
or
- A person who was started on empirical therapy with an antibiotic, but was not changed to an uropathogen sensitive antibiotic after culture report.

Ethics

The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. The study was approved by the Institution Review Board of Bangalore Baptist Hospital. Written informed consent was obtained from every recruited patients and confidentiality was maintained at every stage of the research.

Statistics

The data collected was first coded and then transferred to a master chart on Microsoft Excel which was programmed to minimize the error. The range of the continuous values was specified and codes were picked from drop down menu as a measure to reduce the error. Data was validated by double-checking by randomly picking different segments to look for incorrectly entered data. Descriptive analysis was done in SPSS to look for numbers that are out of range or errors in data entry.

Distribution as well as co-relation tables were prepared, analyzed and statistically evaluated by SPSS version 16.0. UTI prevalence was expressed in percentage. The Chi-square test was done to identify the variables associated with UTI (age, gender, presence of co morbidities). Frequencies and percentages were calculated for distribution of uropathogens in different age groups, gender and among diabetics.

Results

Among the 204 eligible patients approached, 196 people agreed to participate in the study, yielding a response rate of 96.1%. The mean age of the study population was 43.84 years. Majority (60.7%) were females. 17.8% of the patients had diabetes and 13.7% had hypertension. 71.4% had no co-morbid conditions.

Almost half (42.3%) of the studied population presented with dysuria alone and another 33.2% had a combination

of fever and dysuria. The prevalence of UTI was 32.1%. The prevalence of UTI was higher in females (39.5%) than males (20.8%) and this was statistically significant. The prevalence of UTI was more in diabetics (44.4%) than non-diabetics (29.4%); however this was not statistically significant ($P = 0.13$). Even though the prevalence of UTI is more in people above 80 years and those with co morbidities, the association was not statistically significant [Table 1]. Of the total 196 urine specimens collected, 63 (32.1%) showed significant bacterial growth. Eight strains of various bacteria were isolated from positive samples. Gram-negative bacteria constituted the largest group with a prevalence of 84.1% (53/63) while gram-positive bacteria constituted 15.9% (10/63) of the total isolates. The bacteria isolated were *E. coli* with a frequency rate of 69.8% followed by *Klebsiella pneumoniae* (7.9%), coagulase-negative Staphylococcus (CoNS) (4.8%), *Pseudomonas* sp. (4.8%), *Streptococcus viridans* (4.8%), *Enterococcus* (4.8%), MRSA (1.6%) and non-fermenting gram-negative bacilli (1.6%).

Uropathogen distribution among females and males varied significantly ($P = 0.035$) [Table 2]. In females, *E. coli* was responsible for most (78.7%) of the cases whereas in males *E. coli* (43.8%), *Klebsiella* (12.5%) and *S. viridans* (12.5%) were the major causative agents. The prevalence of CoNS (12.5% vs. 2.1%) and *Pseudomonas* (18.8% vs. 0%) were higher in males than females. Among the culture-positive diabetic patients, *E. coli* (68.8%), *S. viridans* (18.8%), MRSA (6.3%) and *Klebsiella* (6.3%) were the common organisms [Table 2].

The antibiotic sensitivity pattern is shown in Table 3. Amikacin (90.6%), nitrofurantoin (77.4%) and cotrimoxazole (49.1%) were the most effective antibiotics against gram-negative organisms. Most of the gram-positive organisms were susceptible to nitrofurantoin (70%) followed by gentamicin (50%) and ampicillin (30%). Ciprofloxacin was effective against 20% of gram-positive and 37.7% gram-negative organisms.

E. coli was susceptible to nitrofurantoin in 71.4% males and 86.5% females. Almost half of females (48.6%) and males (42.9%) had trimethoprim-sulfamethoxazole-resistant *E. coli*. Only a few male patients (14.3%) had fluoroquinolone (ciprofloxacin and levofloxacin) sensitive *E. coli*.

Out of the 196 patients, 77 (39.3%) were prescribed an antibiotic. The criteria for prescribing antibiotic were different for different physicians. Urine routine examination report of pus cells more than five was considered as an indication for prescribing an antibiotic by 62.5% of the physicians. Fever and dysuria were considered as an indication to prescribe antibiotic by 41.5% of the physicians. Ciprofloxacin (27.3%) and cotrimoxazole (27.3%) were the most preferred antibiotics. Parenteral antibiotic was prescribed for 17/77 patients.

It was found out that 30.1% of the patients were wrongly managed in spite of urine culture [Table 4]. Wrong management

included not treating culture-positive patients, treating with the incorrect (resistant) antibiotics and prescribing an antibiotic when the culture is negative. 14.3% of the patients were overtreated (treatment not needed but treated) and under treatment (treatment needed but not treated) was in 7.1%. Among the people who needed treatment, only (32/63) 50.7% were treated with correct antibiotics. Almost one fifth of patients (28/133) who did not require treatment were treated with antibiotics. Overtreatment was not associated with age, gender and the presence of co-morbidities. The presence of 6-15 pus cells was associated with overtreatment [Table 5].

Discussion

The prevalence of UTI in our study was 32.1% and it was significantly higher in females (39.5%) compared to males (20.8%). Similar observations were also recorded by Astal et al.,^[11] Khalifa et al.,^[9] and Ahmed et al.^[12] Several reports have also indicated that females are more prone to having UTIs than males,^[13] as the urethra is shorter in females than males thus being more readily and easily prone to micro-organisms.^[14]

The bacteria isolated were *E. coli* with a frequency rate of 69.8% followed by *K. pneumoniae* (7.9%), CoNS (4.8%), *Pseudomonas* sp. (4.8%), *S. viridans* (4.8%), *Enterococcus* (4.8%), MRSA (1.6%) and non-fermenting gram-negative bacilli (1.6%). All the micro-organisms isolated in this study were of clinical significance and were similar to the data recorded by Manikandan et al.^[15] and Al-Sweih et al.^[16] The isolation frequency of the bacterial species reported in this study falls within the range of frequencies reported from other parts of India^[17] too.

The microbiological and antibiotic sensitivity pattern observed in our study is similar to findings of Banerjee et al.,^[18] and Sharma et al.^[19] The alarming finding was AMP, AMC and most of the Cephalosporins were resistant to most of the strains. The possible explanation may be because these antibiotics have been in use for a long period and more often due to the misuse of antimicrobial drugs, which has today led to a general rise in the emergence of resistant bacteria.^[20,21]

Table 1: UTI and associated factors

Parameter	Categories	UTI present		95% confidence interval	P value
		Number	%		
Gender	Male	16	20.8	±5.68	0.01
	Female	47	39.5	±6.84	
Age	20-30	3	42.9	±6.93	0.07
	31-40	15	28.3	±6.31	
	41-50	9	25.7	±6.12	
	51-60	9	32.1	±6.54	
	61-70	13	40.6	±6.88	
	71-80	5	18.5	±5.44	
	>80	9	64.3	±6.71	
Co-morbidity	Present	21	37.5	±6.78	0.397
	Absent	42	30	±6.42	

UTI: Urinary tract infections

Table 2: Distribution of organism among culture-positive samples

Organisms	Overall		Males (N=16)		Females (N=47)		Patients with diabetes (N=16)		Hypertensive patients (N=12)	
	No.	%	No.	%	No.	%	No.	%	No.	%
<i>E. coli</i>	44	69.8	7	43.8	37	78.7	11	68.8	9	75.0
Klebsiella	5	7.9	2	12.5	3	6.4	1	6.3	1	8.3
Enterococcus	3	4.8	1	6.3	2	4.3	0	0.0	0	0.0
Coagulase –Ve Staphylococcus	3	4.8	2	12.5	1	2.1	0	0.0	1	8.3
Viridans Streptococci	3	4.8	1	6.3	2	4.3	3	18.8	1	8.3
Pseudomonas	3	4.8	3	18.8		0.0	0	0.0	0	0.0
MRSA	1	1.6	0	0.0	1	2.1	1	6.3	0	0.0
Non-fermenting gram-negative bacilli	1	1.6	0	0.0	1	2.1	0	0.0	0	0.0
Total (culture positive)	63	100.0	16	100.0	47	100.0	16	100.0	12	100.0
P value				0.035				0.033		0.9

MRSA: Methicillin-resistant Staphylococcus aureus

Table 3: Antibiotic susceptibility percentage of the uropathogens isolated from culture-positive samples

	N	AMP	AMC	CEF	CEFT	TAX	CTX	CEFP	CEFS	ERT	IE	MER	PITA	GEN	AK	CIP	LEV	COT	NIT	VA	COL
<i>E. coli</i>	44	18.2	27.3	25.0	6.8	2.3	20.5	45.5	79.5	59.1	97.7	93.2	70.5	63.6	90.9	34.1	38.6	52.3	84.1	0.0	2.3
Klebsiella	5	0.0	0.0	20	0.0	0.0	20	60	80	60	80.0	60.0	80.0	60.0	80.0	40.0	40.0	40.0	40.0	0.0	20.0
Pseudomonas	3	0.0	0.0	0.0	100	0.0	0.0	66.7	100	0.0	100	66.7	100	66.7	100	66.7	33.3	0.0	33.3	0.0	0.0
<i>Streptococcus viridans</i>	3	0.0	33.3	0.0	0.0	0.0	0.0	33.3	0.0	0.0	33.3	0.0	0.0	0.0	0.0	0.0	33.3	33.3	0.0	0.0	0.0
CNSA	3	0.0	33.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100	0.0	66.7	66.7	0.0	100	0.0	0.0
Enterococcus	3	100	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	66.7	0.0	0.0	66.7	0.0	0.0	0.0	33.3	100	66.7	0.0
MRSA	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100	0.0	0.0
NFGNB	1	100	0.0	100	100	0.0	0.0	100	100	0.0	100	100	100	100	100	100	100	100	100	0.0	0.0

AMP: Ampicillin; AMC: Amoxicillin Clavulanic acid; CEF: Cefazolin; CEFT: Ceftazidime; TAX: Cefotaxim; CTX: Ceftriaxone; CEFP: Cefipime; CEFS: Cefoperazone Sulbactam; ERT: Ertapenam; IE: Imipenam; MER: Meropenam; PITA: Piperacillin Tazobactam; GEN: Gentamicin; AK: Amikacin; CIP: Ciprofloxacin; LEV: Levofloxacin; COT: Cotrimoxazole; NIT: Nitrofurantoin; VA: Vancomycin; COL: Colistin

The present study reports that 14.3% of the studied population was over treated. Overtreatment in elderly patients presenting with symptoms of UTI has been reported in other studies.^[22,23] Literature also rates UTI as the second most common reason for empirical antibiotic therapy in secondary care.^[22] However, in this study old age and gender was not associated with overtreatment. Urine routine report of 6-15 pus cells in a symptomatic patient was associated with overtreatment. Predictive value of 6-15 pus cells is low and therefore treating with antibiotic without consulting the culture report might have resulted in overtreatment.

8.7% were treated with resistant drugs which could have been avoided if the physician waited for the culture report. The patient could have been managed by other symptom relieving drugs or by empirical therapy with nitrofurantoin. Among these 17 patients who were treated with a resistant drug, 11 (64.7%) were sensitive to nitrofurantoin. The chance of treating with resistant antibiotic was higher when the physician started on cephalosporins (cefixime, ceftriaxone and cefoperazone sulbactam). This was because most of the organisms were resistant to cephalosporins. This implies the importance of checking the culture report before starting on antibiotics.

There are no country specific guidelines for treating UTI; the Indian Society of Nephrology states that knowledge of local resistance pattern is needed to guide empirical therapy in the light of rising resistance to amoxicillin, sulfa drugs,

Table 4: Empirical treatment of UTI and its consequences

Correct management			
Treatment needed and correctly treated	32	16.3	137 69.9
Not needed and not treated	105	53.6	
Wrong management			
Treatment needed but not treated	14	7.1	59 30.1
Treatment needed but treated with resistant drugs	17	8.7	
Treatment not needed but treated	28	14.3	
Total	196	100	196 100

UTI: Urinary tract infections

cotrimoxazole and fluoroquinolones.^[24] According to an update by the Infectious Diseases Society of America (IDSA) guidelines, a short-course therapy (3 day) with either nitrofurantoin or trimethoprim-sulfamethoxazole (if the local resistance prevalence less than 20%) is recommended.^[25] However, trimethoprim-sulfamethoxazole is not a good option for empirical therapy as there are many studies including the present study which reports a resistance of more than 20%.

Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommends a 7 day course of fluoroquinolones for cystitis in men, however a more detailed evaluation is recommended in men.^[26] Fluoroquinolones may not be appropriate for empirical drug therapy as 85.7% of men with *E. coli* demonstrated resistance to fluoroquinolones in the present study. Though

Table 5: Factors associated with overtreatment

Parameter	Overtreatment present		Overtreatment absent		Total		P value
	No.	%	No.	%	No.	%	
	Age						
<60	21		130		151	100	0.782
>60	7		38		45	100	
Gender							
Male	9	11.7	68	88.3	77	100	0.0403
Female	19	16	100	84	119	100	
Co-morbidities							
Present	10	17.9	46	82.1	56	100	0.373
Absent	18	12.9	122	87.1	140	100	
Pus cells							
≤5	0	100	91	100	91	100	0.000
6-15	18	32.7	37	67.3	55	100	
>15	10	20	40	80	50	100	

empirical antibiotic treatment can be cost effective in primary and secondary care settings, it can promote antimicrobial resistance, hence should be cautiously initiated in tertiary care settings. Consequently, evolving practice seeks to achieve good symptom control for uncomplicated acute cystitis while reducing antibiotic use. For example, European practice increasingly includes the option of offering a 48-hour delayed antibiotic prescription to be used at the patient's discretion.^[27]

Conclusion

Almost one third of the patients were managed inappropriately in spite of the availability of a culture report. Ciprofloxacin and Cotrimoxazole were preferred by most of the physicians, with one fifth of patients being started on parenteral antibiotics with no apparent rationale.

Periodic surveillance of antimicrobial resistance of uropathogens, re-evaluation of empirical therapy, pre-therapy counseling for delayed antibiotic initiation and short-course antibiotic therapy with sensitive antibiotics are vital in an era of emerging antimicrobial resistance.

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