Original Article

Antibiotic resistance in pathogens causing community-acquired urinary tract infections in India: a multicenter study

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Abstract

Background: Empiric treatment of community-acquired urinary tract infections (CA-UTI) is determined by the antibiotic sensitivity patterns of uropathogens in a population. This study was conducted to determine patterns of resistance amongst CA-uropathogens in India, to help establish local guidelines on treatment of CA-UTI.

Methodology: 531 consecutive positive urine cultures taken from adult non-pregnant females attending outpatient clinics of five hospitals in Delhi, India, were analysed. Sensitivity testing was done for ciprofloxacin, trimethoprim-sulphamethoxazole (SXT), amoxicillin, amoxicillin-clavulanate, amikacin, nitrofurantoin, piperacillin-tazobactam and meropenem in each isolate.

Results: *E. coli* comprised 68%; *Klebsiella* 16.9%; *Proteus* 5.5%; *Enterobacter* 5.3%; *Staphylococcus saprophyticus* 2.8%; and others 1.5% of the isolates. Furthermore, 26.9% of the gram negative isolates were ESBL producers. Antibiotic sensitivity of all the gram negative organisms showed that 35.8% were sensitive to ciprofloxacin; 30% to SXT; 17.7% to amoxicillin; 41.6% to amoxicillin/clavulanate; 75.6% to amikacin; 65.7% to nitrofurantoin; 90.2% to piperacillin-tazobactam; and 100% to meropenem.

Conclusion: High levels of ESBL producers among gram negative CA-uropathogens was seen in our country. This, along with the alarming rate of resistance to ciprofloxacin, SXT and amoxicillin, precludes the use of these commonly used antibiotics for empiric treatment of CA-UTI in India.

Key Words: CA-UTI; antibiotic susceptibility; India

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Introduction

Urinary tract infection (UTI) is the second most common infectious presentation in community medical practice. Worldwide, about 150 million people [1] are diagnosed with UTI each year, costing in excess of 6 billion dollars [2]. Among both outpatients and inpatients, *Escherichia coli* is the primary clinically relevant organism, accounting for 75% to 90% of uncomplicated UTI isolates [3,4]. *Staphylococcus saprophyticus*, *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp., and *Enterobacter* spp. are organisms less commonly isolated from outpatients.

In most Western countries, microbiological testing may be unnecessary in acute uncomplicated UTI, except for surveillance purposes [5], because in most cases urine culture and susceptibility testing cost more than the antibiotic treatment itself. The Infectious Diseases Society of America (IDSA) guidelines currently recommend empirically treating acute, uncomplicated bacterial cystitis in healthy adult, non-pregnant females with a 3-day course of double-strength trimethoprim-sulfamethoxazole (SXT) in settings where the prevalence of SXT resistance is <10-20% [6, 7]. Alternative therapy for uncomplicated UTI include a fluoroquinolone, nitrofurantoin or fosfomycin, wherever SXT resistance is >10-20% [7].

However, these guidelines may not be applicable in other countries such as India. The resistance pattern of community acquired uropathogens has not been extensively studied in the Indian subcontinent [8]. This study was planned to identify the most common pathogens associated with community acquired urinary tract infections (CA-UTI) in India and to determine their antibiotic sensitivities. This epidemiological data is essential to help formulate guidelines on empirical antibiotic treatment of uncomplicated CA-UTI in India.

Materials and Methods

Design & Setting

This was a multi-centric retrospective study done between June and December 2005. Samples were collected from outpatient departments of 5 different hospitals in Delhi and were submitted to the central clinical microbiology lab for analysis.

Clinical Isolates

Data was collected on 531 consecutive positive urine cultures. Only samples which had been submitted by adult, non-pregnant females in the outpatient department were considered. All patients had clinical evidence of a urinary tract infection, as determined by the treating physician. Only a single positive culture per patient was included in the analysis.

Microbiological Analysis

Semi quantitative urine culture was done using a calibrated loop. Samples were inoculated on blood and Mac Conkey agar and plates were read after overnight incubation at 37°C. For this study, significant bacteriuria was defined as culture of a single bacterial species from the urine sample at a concentration of 10^5 cfu/mL associated with microscopy findings of >10 WBC per high power field [9]. Identification of isolates was done up to species level using API ID 32E kits (bioMerieux SA, France).

Antimicrobial susceptibility testing and interpretation was performed using the disc diffusion method as described by the Clinical & Laboratory Standards Institute (CLSI)[10]. Sensitivity testing was done for amoxicillin (Am), trimethoprim-sulfamethoxazole (SXT), ciprofloxacin (Cf), amikacin (Amk), nitrofurantoin (Nf), amoxicillin-clavulanate (Aug), piperacillin-tazobactum (Taz) and meropenem (M) for each isolate.

Extended spectrum β-lactamase (ESBL) production was detected using ceftazidime and ceftazidime-clavulanic acid discs. A ≥5mm increase in the zone of diameter around ceftazidime-clavulanic acid, as compared to ceftazidime alone, was considered indicative of ESBL production [11, 12].

BBL™Sensi-Disc™ susceptibility test discs were obtained from Becton Dickenson India Pvt. Ltd. for susceptibility testing and ESBL detection. *E. coli* ATCC 25922, *S. aureus* ATCC 25923, *E. fecalis* ATCC 29212 and *P. aeruginosa* ATCC 27853 were used as quality control strains for antimicrobial discs. *E. coli* ATCC 25922 was used as ESBL negative and *K. pneumoniae* 700603 was used as ESBL positive reference strain to check ceftazidime and ceftazidime-clavulinic acid discs.

Results

The age distribution of the patients in the sample set was 18 to 72 years (mean 46.4 years, standard deviation 17.2 years).

The most common pathogen associated with CA-UTI was *E. coli*, with other organisms forming 32% of all the isolates (Table 1). Gram positive organisms formed only 4.3% of the isolates in our study.

Table 1. Causative microorganisms for CA-UTI.

Name	Number	Percentage
E. coli	361	68
Klebsiella spp.	90	16.9
Proteus spp.	29	5.5
Enterobacter spp.	28	5.3
S. saprophyticus	15	2.8
Enterococcus spp.	8	1.5

In all Gram negative isolates, which formed >95% of uropathogens, the routinely used antimicrobials showed susceptibilities of <50%, with only amikacin, piperacillin-tazobactum and meropenem showing susceptibilities of >75% (Table 2).

Table 2. Antibiotic susceptibilities for all Gram negative isolates (N=508).

Antimicrobial	Percentage Isolates Susceptible
Amikacin	75.6
Amoxycillin	17.7
Amoxycillin/Clavulanate	41.6
Ciprofloxacin	35.8
Cotrimoxazole	30
Nitrofurantoin	65.7
Piperacillin-Tazobactam	90.2
Meropenem	100

E. coli, which was the single most common cause of CA-UTI in women, also showed similar susceptibility results. Only nitrofurantoin, piperacillin-tazobactam and meropenem showed susceptibilities of >75% (Table 3).

Table 3. Antibiotic susceptibilities for *E. coli* isolates (N=361).

Antimicrobial	Percentage Isolates Susceptible
Amikacin	67
Amoxycillin	14.7
Amoxycillin/Clavulanate	40.8
Ciprofloxacin	28
Cotrimoxazole	26
Nitrofurantoin	75.6
Piperacillin-Tazobactum	90.3
Meropenem	100

Overall, 137 out of the 508 Gram negative isolates (26.9%) were presumptive ESBL producers, as detected by the combination disc method. Furthermore, 29.1% of *E. coli*, 25.6% of *Klebsiella* spp., 28.6% of *Enterobacter* spp. and 3.4% of *Proteus* spp. Isolates were ESBL producers.

Discussion

The most commonly isolated organism in CA-UTI among female outpatients in our study was *E. coli*. The proportion of bacterial species isolated was similar to those described in several previous studies [13,14].

The antimicrobial susceptibility pattern of uropathogens varies widely by region (Table 4). We demonstrated a high level of resistance to amoxicillin, ciprofloxacin, amoxicillin/clavulanate and cotrimoxazole. This is similar to previous community based studies in India (Table 4). In our study, 26.9% of all Gram negative isolates were ESBL producers. This number is less than that previously reported (36.5-48.3%) among urinary pathogens in India [8,27,28].

High resistance rates to the oral antibiotics in our study may be due to the uncontrolled consumption of these antibiotics in the community in the past decade in our region [29,30]. On the other hand, resistance to amikacin, piperacillin-tazobactum and meropenem are low, likely reflecting lower usage of these drugs.

Our study demonstrates extremely low susceptibility to the first-line agents (amoxicillin, amoxicillin/clavulanate, ciprofloxacin, cotrimoxazole) in uropathogens in our population. As these oral agents usually achieve high urinary concentrations, it was thought that *in vitro* resistance may not result in treatment failure. However, recent studies have demonstrated therapeutic failure in more than 50% of patients infected with cotrimoxazole resistant urinary pathogens [5,31].

The IDSA guidelines consider cotrimoxazole as the current standard therapy for uncomplicated CA-UTI in women [7]. The guidelines, however, have a caveat that local antimicrobial susceptibility patterns must be taken into account before choosing an agent. As demonstrated in this study, and corroborated by previous studies [8,25,26], aminopenicillins, ciprofloxacin and cotrimoxazole cannot be used as antimicrobial agents for empirical treatment of CA-UTI in our setting.

While nitrofurantoin has poor activity against *Proteus* spp. and our study showed 24.4% resistance in *E. coli*, previous Indian studies have shown lower resistance rates [25,26]. Nitrofurantoin may, therefore, be an appropriate agent as first-line treatment of CA-UTI in the Indian setting. β-lactam agents are less effective in bacteriuria eradication, leading to increased rates of recurrence [32] and therefore are not preferred agents for treatment of UTI. Fosfomycin is another oral antibiotic which is commonly used for treatment of CA-UTI in Europe with low resistance rates [18,19,21]; however it is not marketed in India.

Table 4. Regional antibiotic susceptibilities of *E. coli* isolated from CA-UTI: review of literature.

				Percentage Resistance			
Author	**Country**	**Year**	**Setting**	**Aminopenicillin**	**Ciprofloxacin**	**Cotrimoxazole**	**Nitrofurantoin**
North America							
Zhanel *et al.*[13]	USA & Canada	2005	Outpatients	37.7	5.5	21.3	1.1
Karlowsky *et al.*[15]	USA	2002	Outpatients	36-37.4	0.7-2.5	14.8-17.0	0.4-0.8
Zhanel *et al.*[16]	Canada	2000	Outpatients	41.1	1.2	18.9	0.1
Andrade *et al.*[14]	Latin America	2006	Outpatients	53.6	21.6	40.4	6.9
Europe							
Lobel et al[17]	France	2008	Outpatients	39.2	3.7	14.1	-
Garcia *et al.*[18]	Spain	2007	Outpatients	58.7	22.7	33.8	5.7
Gobernado *et al.*[19]	Spain	2007	Outpatients	52.1	18	26	-
Stratchounski *et al.*[20]	Russia	2006	Outpatients	37.1	4.5	21	4.3
Kahlmeter[21]	Europe	2003	Outpatients	30	2.3	14	1.2
Farrell *et al.*[22]	UK	2003	Outpatients+ Inpatients	48.7	2.3	-	3.7
Colodner *et al.*[23]	Israel	2001	Outpatients	66	6	26	1
Vromen *et al.*[24]	Netherlands	1999	Nursing Home	59	29*	38	9
India							
Akram *et al.*[8]	India	2007	Outpatients	-	69	76	80
Biswas *et al.*[25]	India	2006	Outpatients	63.6	35.1	40.3	9.3
Gupta *et al.*[26]	India	2002	Outpatients	74	38	70	12

*= Norfloxacin Resistance.

The worldwide trend of empirically treating CA-UTI may not apply for specific geographical regions such as India, where decreased susceptibility rates are documented for common urinary pathogens. In the Indian setting, routine urine cultures may be necessary, since treatment failure with empirical therapy is likely to occur. International guidelines are no longer applicable for treating CA-UTI in India, and development of specific guidelines based on local susceptibility patterns are necessary. Development of regional surveillance programs is necessary to provide information which would then enable the development of Indian CA-UTI guidelines.

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