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RESEARCH ARTICLE

EMPIRICAL TREATMENT OF COMMUNITY ACQUIRED URINARY TRACT INFECTIONS: IS THERE A NEED TO UPDATE THE CURRENT POLICIES?

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ABSTRACT

Introduction: The empirical use and abuse of antibiotics is quite common in community acquired urinary tract infection, leading to increase in antimicrobial resistance. Patients presenting to the outpatient department of a hospital are a heterogenous set of population, including all age groups and socioeconomic strata. Monthly and annual review of the antibiotic prescribing pattern and the trends in antimicrobial resistance is needed to curb the menace of antimicrobial resistance. **Objectives:** To study the etiology and trends in antimicrobial resistance of community acquired urinary tract infections and to update the antibiotic policy for the treatment of community acquired urinary tract infections at our institution. **Methods:** The study was performed at a tertiary care super speciality hospital in North India. This was an observational study including urine samples from patients presenting to the outpatient department of the hospital, with symptoms suggestive of urinary tract infection. The samples were cultured on routine culture media and identified according to standard guidelines. Antimicrobial susceptibility testing was done on Mueller Hinton agar plates by Kirby Bauer disc diffusion method as per the Clinical and Laboratory Standards Institute (CLSI) guidelines. Extended spectrum beta lactamase (ESBL) testing was also performed as per CLSI guidelines. **Results:** A total of 3758 urine specimens from outpatient department were received, out of which 452 samples were culture positive, of which 414 (91.6%) were Gram negative and 38 (8.4%) were Gram positive. *Escherichia coli*(67.0%),*Klebsiella pneumonia* (12.4%) and *Pseudomonas aeruginosa* (3.0%) were the predominant Gram negative isolates. Of the 414 Gram negative isolates, 271 (65.5%) were found to be multidrug resistant (MDR) strains. By combined disc test, 182 (44.0%) Gram negative isolates were found to be ESBL producers. **Conclusion:** The present study emphasizes on the need to develop and regularly update the antibiotic policy in each hospital, as the antimicrobial resistance trends are changing rapidly and the trends vary in each region.

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INTRODUCTION

Urinary tract infections (UTI) are one of the most common causes of outpatient department (OPD) visits with an annual incidence of nearly 150 million cases worldwide [1]. UTI is also a common cause of bacteraemia and may lead to hospitalization. However, despite the huge impact of UTIs on the social and health status of an individual, there are very few studies focused on the etiology and the rising antimicrobial resistance in this population [2-4]. *Escherichia coli* is the commonest uropathogen among both outpatients and inpatients. Around 80-90% of the urinary tract infections are caused by E.coli. [5] Deciding the line of treatment for outpatients is difficult, as the microbiological testing is still awaited. Moreover, the continuous struggle to balance between the overuse of antibiotics and the development of antimicrobial resistance is a major challenge for the clinicians. The development of antibiograms based on the pattern of antimicrobial sensitivity in the local population can help in managing this problem by aiding in the selection of appropriate empirical antibiotic therapy. The aim of the present study was to study the antimicrobial resistance pattern and develop an antibiotic policy for community acquired urinary tract infection.

MATERIAL AND METHODS

This was a cross sectional study conducted at a super specialty hospital in Northern India.

Sample collection: Patients were instructed to provide a clean-catch midstream urine sample in their local language. A total of 3758 urine samples received for culture in the microbiology laboratory between January 2018 to December 2018 were included in the study. Relevant demographic and laboratory data was collected from the electronic laboratory information system. Urine culture was performed for all the urine samples as requested by the treating physician.

Urine culture: Urine samples were inoculated on Cystiene Lactose Electrolyte Deficient agar (CLED) by semi-quantitative method using a calibrated loop (0.01 ml volume). The plates were incubated at 37°C for 18-24 hours and were observed the next day. In accordance to the Kass criteria for significant bacteruria, a colony count of $\geq 10^5$ CFU/ml of a uropathogen was taken as significant. [6] Urine cultures showing the presence of three or more organisms were reported as mixed microbial flora, and further antibiotic sensitivity tests were not performed for such patients. Urine cultures with a colony count of $\leq 10^2$ CFU/ml were reported as insignificant colony count, whereas cultures with a colony count of 10^3 to 10^4 CFU/ml were reported as positive and further testing was performed in case of a clinical indication, like the prior intake of antibiotics or at the request of the treating physician. The isolates were identified by the Gram stain findings, culture characteristics, biochemical reactions and confirmed by antisera wherever indicated.

Antimicrobial susceptibility testing: Antimicrobial susceptibility testing was performed for all culture positive samples on Mueller Hinton agar plates by Kirby Bauer disc diffusion method, as per Clinical and Laboratory Standards Institute (CLSI) guidelines [7]. The antibiotic discs used for testing Gram negative isolates were Ampicillin 10µg, Cefazolin 30 µg, Gentamicin 10 µg, Tobramycin 10 µg, Amikacin 30 µg, Piperacillin-Tazobactam 100/10 µg, Cefuroxime 30 µg, Ceftriaxone 30 µg, Cefepime 30 µg, Cefotaxime 30 µg, Ciprofloxacin 5 µg, Norfloxacin 10 µg, Levofloxacin 5 µg, Trimethoprim-Sulfamethoxazole 1.25/23.75 µg, Imipenem 10 µg, Meropenem 10 µg, Aztreonam 30 µg and Ceftazidime 30 µg. The antibiotic discs used for testing Gram positive isolates were: Penicillin 10 units, Oxacillin 30 µg, Cefoxitin 30 µg, Teicoplanin 30 µg, Gentamycin10 µg, Amikacin 30 µg, Tobramycin 10 µg, Erythromycin 15 µg, Tetracycline 30 µg, Ciprofloxacin 5 µg, Norfloxacin 10 µg, Nitrofurantoin 300 µg, Clindamycin 2 µg, Trimethoprim-Sulfamethoxazole1.25/23.75 µg, Vancomycin (E strip), Linezolid 30 µg, Chloramphenicol 30 µg in Enterococcus spp. Antibiotic susceptibility was interpreted by measuring the inhibition zone diameters with a calibrated scale as per the CLSI criteria. Intermediate susceptible antibiotics were reported as resistant. *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 25923 were used as control strains.

Multidrug resistance: Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. [8].

Extended spectrum beta lactamase (ESBL) testing: Gram negative isolates showing resistance or reduced susceptibility to third generation cephalosporins (Ceftazidime zone ≤22 mm, Cefotaxime zone ≤27 mm, Ceftriaxone zone ≤25 mm) were tested for ESBL production. The phenotypic identification of ESBL producing pathogens was done by double disc combination method using ceftazidime and ceftazidime/clavulanic acid discs as per CLSI guidelines.[7] Double disc combination test for ESBL detection: Standard disc diffusion procedure was carried out using Ceftazidime 30µg, Ceftazidime-clavulanate 30/10 µg discs and the plates were incubated aerobically at 37^0C for 24 hrs. A ≥ 5-mm increase in a zone diameter for Ceftazidime tested in combination with clavulanate vs the zone diameter when Ceftazidime was tested alone was taken as indicative of ESBL production. E. coli ATCC 25922 and Klebsiella pneumoniae ATCC 700603 were used as negative and positive controls respectively.

Data analysis: Antimicrobial susceptibility results were compiled in an XL sheet and an antibiogram was prepared for all the positive samples. Antimicrobial susceptibility rates were presented as percentages. Numerical variables were expressed as mean.

RESULTS

Demography: A total of 3758 urine samples were collected during the study period, out of which 2034 (54.1%) were male and 1724 (45.9%) were female. The mean age of the study population was 58 years. 452 (12.0%) samples were culture positive, whereas 3306 samples were culture negative or were reported as contaminated or mixed bacterial species. The mean age of the culture positive patients was 62 years, of which 259 (57.3%) were females and 193 (42.7%) were males.

Isolated pathogens: Among the bacterial culture positive patients, 38 (8.4%) were Gram positive bacteria and 414 (91.6%) were Gram negative bacteria. The most commonly isolated pathogen was *Escherichia coli* (67%)), followed by *Klebsiella pneumoniae* (12.4%), *Enterococcus spp* (6.6%), *Pseudomonas aeruginosa* (2.9%), *Acinetobacter lwoffii* (2.7%) and *Klebsiella oxytoca* (1.8%). Citrobacter (2.0%), Morganella, Providencia, Proteus (1.8%), Enterobacter, *Staphylococcus aureus* (1.1%*)* and Coagulase negative Staphylococcus spp. (CoNS) were less frequently isolated. *E.coli* and *K. pneumoniae* were the organisms most frequently isolated from both male and female patients.

ESBL production: Among the Gram negative isolates, 44.0% were found to be extended spectrum beta lactamase (ESBL) producers. Among the E. coli isolates, 48.2 % were ESBL producers. Among the K. pneumoniae isolates, 39.1% were ESBL producers.

Multidrug resistance (MDR): Among the Gram negative isolates, 65.5 % were found to be multi drug resistant. Among the ESBL positive organisms, 80.2% were multi drug resistant. 66.3% of the *E. coli* and 65.6% of the *Klebsiella spp* isolates were found to be multi drug resistant.

Antimicrobial susceptibility: Most Gram negative isolates were resistant to Cephalosporins (60-77%), Meropenem (76.7%), Fluoroquinolones (74%), Cotrimoxazole (68.5%) and Imipenem (46.7%). Maximum sensitivity was found to Colistin (92.0%), Polymyxin B (93.4%), Fosfomycin (89.9%), Piperacillin-Tazobactam (71.7%), Tobramycin (69.5%), Nitrofurantoin (68.7%) and Gentamicin (61.4%) (Figure 1). Most Gram positive isolates were resistant to Ampicillin (91.9%), Cefoxitin (87.5%), Erythromycin (86.8%), Penicillin (73.7%), Clindamycin (69.0%) and Tetracycline (65.7%).

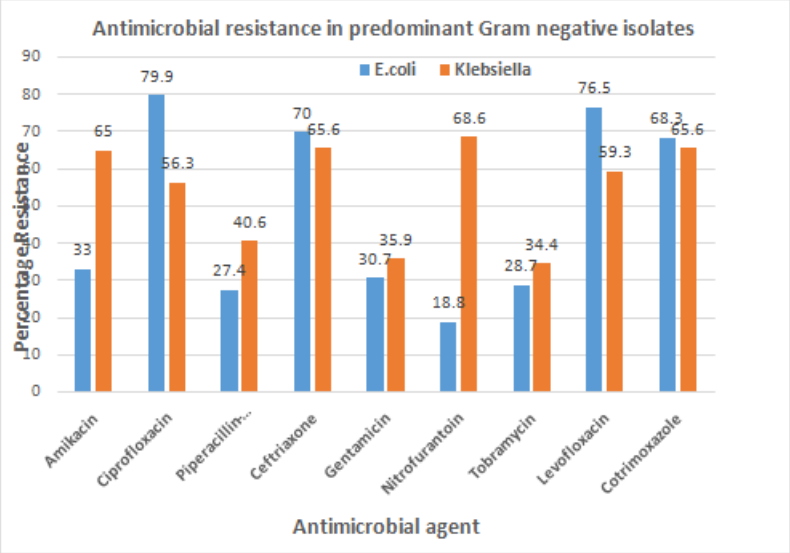

Figure 1. Antimicrobial resistance profile of Gram negative isolates

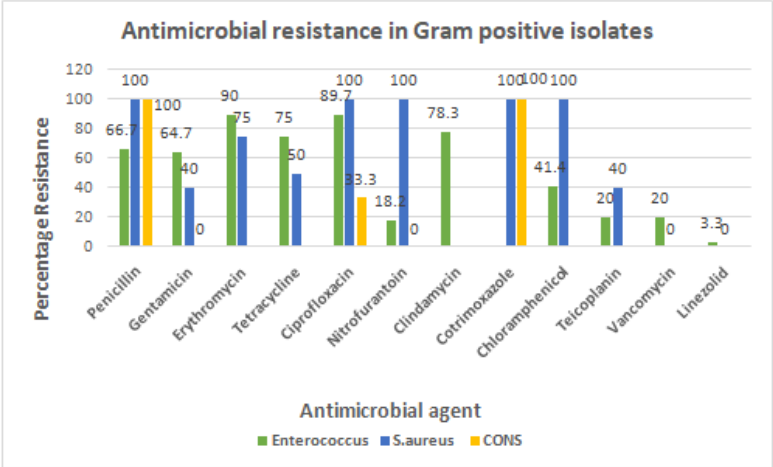

Figure 2. Antimicrobial resistance profile of Gram positive isolates

Maximum sensitivity was found to Linezolid (97.4%), Vancomycin (83.9%), Teicoplanin (76.3%) and Chloramphenicol (68.7%) (Figure 2).

DISCUSSION

The prevalence of urinary tract infections has been reported to be 25-35% in India. [9,10]In the present study, 12.0% patients clinically suspected to be having urinary tract infections showed the presence of culture positive UTI. *Escherichia coli* was the predominant organism causing UTI among most of the patients in the present study. *E. coli* has been reported to be the main pathogen associated with community acquired urinary tract infections in various previous studies.[11-17] In the present study, *Klebsiella sp*p were isolated from 12.4% of the culture positive samples. Previous Indian studies have also suggested *Klebsiella spp* to be less frequently associated with community acquired UTI. [16, 18] A study in South India also found *E. coli, K. pneumoniae* and *P. aeruginosa* to be the most common gram negative isolates associated with community acquired UTI. [12] A similar organism profile has been reported in other studies from India and worldwide. [13-17]. In the present study, Gram positive organisms were associated with only 8.4% of the UTI cases, with a higher prevalence of *Enterococcus spp* (6.6%) and *Staphylococcus aureus* in only 1.1% of the positive samples.

Another study in Aligarh, India reported Gram positive organisms in 8.0% of the urine samples.However, in this study, *Staphylococcus aureus* was the predominant Gram positive isolate (7.0%) and *Enterococcus faecalis* was isolated in 1.0% of the samples. [14] Similar findings have been reported in previous studies [19]. ESBL production in urine isolates has been reported to be 40-70% among recent Indian studies.[20-23] We found the ESBL production to be 44% among the Gram negative urinary isolates. Among the Gram negative isolates, highest production of ESBL was observed in E. coli (48.2 %), followed by K. pneumoniae (39.3%). Recent studies have reported ESBL production around 50-55% among Gram negative isolates and 70% in *E. coli*. A study in East India in 2012 reported ESBL strains in 23.2% *E. coli* and 9.4% K. pneumoniae. [10] Researchers from Jaipur reported an increasing trend of ESBL producing *Escherichia coli* strains (from 9.52% to 30.08%) over a period of 3 years (2007-2009). [24]. The antimicrobial resistance has been a major concern over the years, and has been on the rise every year. Moreover, the resistance trends vary form country to country, and region to region. [25] The antimicrobial susceptibility tests among urine isolates show resistance to higher antibiotics. Resistance observed to commonly prescribed antibiotics like fluoroquinolones, third generation cephalosporins and cotrimoxazole is an important finding as these are the antibiotics recommended for empirical therapy of urinary tract

Table 2. Resistance pattern of Gram negative isolates (%) in Indian studies

Author	Ak	Ctr	Ctx	Cip	Lev	Of	Nx	Nit	Cot	Gen	Tob	Mer	Imp	PIT	CFS	F
Present study 2018	34.5	67.3	67.7	73.9	72.3	-	73.3	31.3	68.1	38.6	30.5	86.7	21	28	11	18
Bharara et al 2018	25	61	71	67	50	-	75	38	75	-	-	-	-	45	13	-
Batabyal et al. 2018	4.5% in E.coli	66	68	63.2	57.4	63	-	27	63.2	22.0	-	-	-	-	-	24
Sukumar et al. 2017	7.8 in E.coli	-	70	66	-	-	67	18	59	35	-	-	8	26	-	-
Niranjan et al. 2014	17.4	-	-	75-89	75-89	75-89	75-89	-	-	-	-	-	1	-	-	-
Dash M et al. 2013	5.3	-	-	51.2	-	45	-	-	53.4	14.6	-	-	-	-	-	-
Gupta et al. 2015	9.3 in E.coli	74.2	-	77.4	-	-	-	-	-	52.6	-	21.7	-	-	8.3	-
Somashekara et al. 2014	26	-	37	57.8	51.4	-	62	-	75.2	-	-	-	15	-	-	-
Krishna et al. 2013	15	-	-	23	-	-	-	-	-	-	-	-	-	-	-	-
Murugan et al. 2012	33.4	-	44	43.5	45	-	47	-	-	-	-	-	-	-	-	-
Mandal et al. 2012	39.1	-	62	57.3	-	-	-	-	-	-	-	-	18	-	-	-
Manjunath et al. 2011	6.9	-	47	73	-	7.7	53	-	47.9	-	-	-	8	-	-	-
Shalini et al. 2011	12.6	-	-	26.6	26.6	-	27	-	81.8	-	-	-	-	-	-	-
Akram et al. 2007	51 in E.coli	55	56	69	-	-	69	80	76	64	73	-	-	-	-	-

Ak:Amikacin, Ctr:Ceftriaxone, Ctx:Cefotaxime, Cip:Ciprofloxacin, Lev:Levofloxacin, Of:Ofloxacin, Nx:Norfloxacin, Cot:Cotrimoxazole, Gen:Gentmicin, Tob:Tobramycin, Mer:Meropenem, Imp:Imipenem, PIT:Piperacillin-Tazobactam, CFS:Cefoperazone-Sulbactam, F:Fosfomycin

Table 3. Resistance pattern of Gram positive isolates (%) in Indian studies

Author		Amp	Pen	Cot	Nit	Cip	Lev	Of	Nx	Gen	Ak	Lz	Van	Cx
Present study 2018		52	100	100	10.6	86.5	85.7	-	94.7	-	40	2.6	17	75
Sukumar et al. 2017	SA	97		44	0	74	-	-	74	56	72	0	0	80
	Ent	35		80	18	78	-	-	77	56	59	0	0	-
Gupta et al. 2015	SA	50	50	-	0	50	-	-	-	-	-	-	0	83
	Ent	38	-	-	3	75	-	-	-	-	-	-	22	-
Somashekara et al. 2014	SA	78		64		46	38	68	62	-	-	-	-	-
	Ent	34.6		24.2	-	67	56	54	68	-		-	-	-
Dash et al. 2013		65		38.3	5.8	13.3	-	15	-	9.2	10	-	22	-
Akram et al. 2007		-	-	40	20	40	-	-		20	20	-	-	-

infections in various national and international guidelines. The National Centre for Disease Control (NCDC) guidelines recommend nitrofurantoin, cotrimoxazole or ciprofloxacin for the treatment of acute uncomplicated cystitis and amikacin or gentamicin for acute uncomplicated pyelonephritis. [26] The antibiotic policy at our institution recommends fluoroquinolones or ceftriaxone for the treatment of uncomplicated urinary tract infections. The resistance to fluoroquinolones observed in our study was nearly 74.0%, to ceftriaxone, was 65.2%, to nitrofurantoin was 26.4%, to amikacin was 27.0% and to gentamicin was 27.8%. The widespread use of fluoroquinolones to treat urinary infections has led to the increase in resistance. Resistance to cotrimoxazole has been declared in the eighties. [27] (Table 1,2). Another study in India conducted on children with urinary tract infections found high degree of resistance to third generation cephalosporins (Ceftriaxone=68%, Cefotaxime=68.0%, Cefotaxime=90.0%), Cotrimoxazole (72.0%), Fluoroquinolones (66.0%), and nitrofurantoin (76.0%).[12] A study in East India showed *E.coli* and Klebsiella isolates to be quite sensitive to aminoglycosides (72-76%) and nitrofurantoin (52%). However, the study reported high resistance to all quinolones except levofloxacin (52%) and all cephalosporins and cotrimoxazole [10]. In the present study, 66.3% of the *E. coli* isolates were multi drug resistant. A study by researchers in Puducherry found 76.5 % *E. coli* isolates in urine to be MDR. [26] Another study by Hasan et al reported a 52.9% prevalence of ESBL *E. coli* in urine isolates. [39] In contrast, a study in South India conducted in 2008 reported an MDR prevalence of 8.4% in *E. coli* isolates. [40] A study in Aligarh found almost all isolates being resistant to four or more antibiotics [16].

Conclusion

Rising trends in antimicrobial resistance to the commonly prescribed antibiotics warrant the need to curb the menace of over prescription. The treatment for community acquired urinary tract infections should be tailored as per the antimicrobial susceptibility result with the use of the narrowest spectrum of antibiotic. Moreover, the present study emphasizes on the need to develop and regularly update the antibiotic policy in each hospital, as the antimicrobial resistance trends are changing rapidly and the trends vary in each region. The study also raises a question whether the current treatment guidelines for community acquired urinary tract infection are outdated and need a revision.

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