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Original Research Article

A clinical study of uropathogens causing urinary tract infection in children and adolescents in a tertiary care hospital

R. Abisha Rezia[1], R. Vijendra[1]*, Anjana Gopi[2]

[1]Department of Pharmacology, Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India
[2]Department of Microbiology, Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India

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***Correspondence:**
Dr. R. Vijendra,
Email: vijendra_ramaiah@yahoo.co.in

ABSTRACT

Background: Urinary Tract Infection (UTI) is one of the common infections in children. Incidence varies with age, race and gender. UTIs have become difficult to treat due to development of resistance among uropathogens. Regional data regarding the common uropathogens and their antimicrobial susceptibility pattern is required to guide the clinicians to start empirical therapy while treating UTIs.
Aims: This study is aimed to study the profile of uropathogens causing UTI in children and adolescents, assess their antimicrobial susceptibility, the clinical course and outcome.
Methods: All subjects with suspected UTI whose urine samples grew a positive culture of uropathogens were included in this prospective observational study. The study was done in the Department of Microbiology from July 2019 to December 2019. The urine samples were processed by standard methods (using 5% sheep blood agar and MacConkey agar) and antimicrobial susceptibility was performed using the Kirby-Bauer disk diffusion method. The details of the pathogens grown, and their antimicrobial sensitivity and resistance patterns were recorded, and the subjects were followed up during their course in the hospital.
Results: A total of 109 urine samples from paediatric and adolescent subjects showed positive cultures (97.32%). UTI was common among toddlers (46.7%). *E. coli* contributed to 40.3% of the cases, followed by *Enterococcus* and *Klebsiella pneumonaie. E. coli* was resistant to amoxicillin + clavulanic acid, cephalosporins and ciprofloxacin. The organisms were sensitive to meropenem, amikacin and piperacillin + tazobactam.
Conclusion: Incidence of UTI and the uropathogens causing UTI varies with age. Different uropathogens and their resistance to commonly used antimicrobials is a concern for future treatment options in UTI.

Keywords: Urinary tract infection, Children, Adolescents, Antimicrobial drug resistance

INTRODUCTION

Urinary tract infection (UTI) is infection involving any part of the urinary tract- kidneys, ureters, bladder and urethra. UTI is a common problem in children.[1] The incidence varies with age, race and gender.[2,3] UTI occurs in 1% boys and 3-5% girls.[4] It affects male children more than females in the first year of life and females after 1 year of age.[5] Three to five percent of febrile children are found to have UTI.[6] In infants and children, the symptoms of UTI may be minimal and non-specific.[7] Febrile children not suspected of having UTI are as likely to have UTI as those who are suspected of having UTI.[8] Hence diagnosis of UTI cannot be made on symptomatology alone. Urine examination and culture should be done in children even with minimal suspicion of UTI.[9,10] Complications of UTI include sepsis and renal scaring, which is the most common cause of hypertension in later childhood and renal failure in adulthood.[2,7]

Diagnosis should be made as early as possible to prevent these complications. At least 80% of UTI in children is caused by *Escherichia coli* followed by other uropathogens like *Proteus*, *Enterococcus*, *Pseudomonas*, *Klebsiella* species, *Citrobacter* and *Staphylococcus aureus*. Selection of antimicrobials is based on antimicrobial susceptibility patterns which vary over short periods.[11] Increasing antimicrobial resistance among uropathogens, to commonly prescribed drugs has become a global reality.[12] Use of antimicrobials by medical practitioners is rampant and has resulted in increase in resistance. Hence isolation of organisms causing UTI and their antimicrobial susceptibility pattern is essential for appropriate management. The objective of this study was to study the profile of uropathogens causing UTI in children and adolescents in a tertiary care hospital in South India and also assess their antimicrobial susceptibility pattern, clinical course and outcome.

METHODS

This study was a prospective, observational clinical study conducted in the Department of Microbiology at Kempegowda Institute of Medical Sciences and Research Centre, Bangalore. The study was conducted between July 2019 and December 2019 after approval by the Institutional Ethics Committee (IEC). The study was registered with Clinical Trial Registry- India (CTRI). All the subjects with suspected UTI (n=1445), whose urine samples were processed during the study period were examined for eligibility. (Non-probability sampling: convenience sampling). Data regarding the age, gender, reason for hospitalization, use of empirical antimicrobials, source of the urine samples, the organisms cultured, and their sensitivity and resistance patterns were noted. The subjects were followed up during their course in the hospital.

Inclusion criteria included children and adolescents (11 to 19 years) whose urine sample when processed showed significant growth of one or more organisms (n=109).

Subjects whose urine sample was contaminated, subjects whose urine sample showed no growth and subjects whose urine sample showed insignificant bacteriuria were excluded from the study.

Samples were obtained by supra-pubic aspiration from neonates in the Neonatal Intensive Care Units (NICUs). Fresh midstream clean catch urine samples were collected aseptically in sterile containers, from the children and adolescents reporting to the various out-patient departments and from the in-patients of different wards. Each sample was plated onto 5% sheep blood agar and MacConkey agar plates using a calibrated loop, delivering 0.01 ml of the sample. This was incubated at 37°C overnight and the observation was made the next day. All plates showing significant growth (>105 CFU/ml) as per the Kass count were were subjected to antimicrobial sensitivity testing. For *Staphylococcus aureus*, even <10 colonies (10 CFU/ml) were further processed as this was considered significant. After biochemical identification of the organisms, anti-microbial sensitivity testing was done for the isolates using Kirby Bauer disc diffusion methods on Mueller Hinton agar and results were interpreted as per the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.

The data collected were analysed and the results were depicted in the form of percentages, graphs or bar charts.

RESULTS

Urine samples of 109 subjects showed positive urine culture. All the positive cultures were due to bacterial uropathogens and no candida species were reported.

Table 1 shows the demographic profile of the cases in the study. Table 2 shows the case distribution of the study subjects.

Table 1: Demographic profile of the cases in the study.

Demographic profile		N (%)
Age (years)*#	Toddlers (1 to 3 years)	51 (46.7)
	Pre-school and school age (4 to 10 years)	26 (23.9)
	Adolescents (11 to 19 years)	19 (17.4)
	Infants (1 month to 1 year)	11 (10)
	Neonates (less than 28 days)	2 (1.8)
Gender	Male	51 (46.7)
	Female	58 (53.2)

*Age of the subjects ranged from 4 days to 19 years; #Mean age 1867.5±2071.8 days

Table 2: Case distribution of the study subjects.

Variables		N (%)
Distribution of the cases	Culture positive	106 (94.6%)
	Multi-drug resistant (MDR) cases	2 (1.8%)
	Mixed infections (Culture of more than one organism)	1 (0.9%)
Source of the cases	In-patients	89 (81.7%)
	Out-patients	15 (13.7%)
	ICUs	5 (4.6%)
Source of the urine specimen	Fresh midstream urine	96 (88%)
	Suprapubic aspiration	13 (12%)

The reasons for hospitalization in the paediatric Intensive care unit (ICU) was acute gastroenteritis (n=1) and in the

NICU was fever with gastroenteritis (n=3) and sepsis (n=1).

Most in-patients were hospitalized for fever with suspected UTI (n=65). The other reasons were for acute gastroenteritis (n=7), viral fever (n=8), dengue fever (n=4) and enteric fever (n=2). Urine culture in the out-patients was done for fever with suspected UTI (n=15).

Table 3: Profile of culture positive uropathogens (n=109).

Culture positive organisms	N (%)
Escherichia coli	44 (40.3)
Enterococcus spp#	23 (21.1)
Klebsiella spp*	19 (17.43)
Proteus spp#	9 (8.25)
Acinetobacter spp#	5 (4.6)
Psedumonas aeruginosa	3 (2.8)
Staphylococcus aureus	2 (1.8)
Citrobacter spp#	2 (1.8)
Enterobacter spp#	2 (1.8)

**Klebsiella pneumoniae:* n=11, *Klebsiella oxytoca*: n=8
#Speciation was not conducted

Table 4: Culture positive uropathogens and resistance pattern.

Organisms	Resistance shown to antimicrobial agents
***Escherichia coli* (n=44)**	β-lactam antibiotics* (n=35)
	Fluoroquinolones# (n=9)
***Enterococcus spp* (n=23)**	β-lactam antibiotics* (n=4)
	Lincosamide† (n=7)
	Aminoglycoside‡ (n=12)
***Klebsiella spp* (n=19)**	β-lactam antibiotics* (n=10)
	Fluoroquinolones# (n=5)
	Urinary antiseptics§ (n=4)
***Proteus spp* (n=9)**	β-lactam antibiotics* (n=6)
	Urinary antiseptics§ (n=3)
***Acinetobacter spp* (n=5)**	β-lactam antibiotics* (n=4)
	Urinary antiseptics§ (n=1)
***Psedumonas aeruginosa* (n=3)**	β-lactam antibiotics* (n=2)
	Aminoglycoside‡ (n=1)
***Staphylococcus aureus* (n=2)**	β-lactam antibiotics* (n=1)
	Macrolides¶ (n=1)
***Citrobacter spp* (n=2)**	β-lactam antibiotics* (n=1)
	Urinary antiseptics§ (n=1)
***Enterobacter spp* (n=2)**	β-lactam antibiotics* (n=1)
	Urinary antiseptics§ (n=1)

*Amoxicillin, ampicillin, cefoperazone, cefepime, cefoxitin, cefuroxime, ceftriaxone, cefexime, ceftazidime, piperacillin + tazobactam, #Ciprofloxacin, levofloxacin, †Clindamycin, ‡Gentamicin, amikacin, §Nitrofurantoin, nalidixic acid, ¶Erythromycin

Table 3 denotes the profile of culture positive uropathogens.

No Candida species were reported in children.

There were two cases of Multi-drug resistant (MDR) uropathogens- one each of Klebsiella pneumoniae (n=1; 0.9%) and Klebsiella oxytoca (n=1; 0.9%). Both these multi drug resistant (MDR) cases were treated with ciprofloxacin.

Mixed infection was seen with *Escherichia coli* and *enterococcus* spp.

Table 5: Culture positive isolates and sensitivity pattern.

Organisms	Sensitive AMAs
***Escherichia coli* (n=44)**	Piperacillin + tazobactam (n=30)
	Meropenem (n=9)
	Gentamicin (n=5)
***Enterococcus spp* (n=23)**	Amoxicillin + clavulanic acid (n=10)
	Levofloxacin (n=7)
	Vancomycin (n=6)
***Klebsiella spp* (n=19)**	Amikacin (n=5)
	Tobramycin (n=4)
	Meropenem (n=10)
***Proteus spp* (n=9)**	Gentamicin (n=2)
	Amikacin, Netilmicin (n=2)
	Ciprofloxacin (n=2)
	Meropenem (n=3)
***Acinetobacter spp* (n=5)**	Amikacin, tobramycin (n=1)
	Meropenem (n=1)
	Piperacillin + tazobactam (n=3)
***Psedumonas aeruginosa* (n=3)**	Amikacin, netilmicin (n=1)
	Tobramycin (n=1)
	Meropenem (n=1)
***Staphylococcus aureus* (n=2)**	Gentamicin (n=1)
	Ciprofloxacin (n=1)
***Citrobacter spp* (n=2)**	Meropenem (n=1)
	Netilmicin (n=1)
***Enterobacter spp* (n=2)**	Meropenem (n=1)
	Tobramycin (n=1)

Table 6 depicts the empirical antimicrobials used. Empirical antimicrobials were used in 9.2% (n=10) and all the empirical antimicrobials were administered through the intravenous (IV) route.

Clinical outcome

The subjects responded to treatment with piperacillin + tazobactam (n=33), meropenem (n=26), gentamicin (n=8), amoxicillin + clavulanic acid (n=10), levofloxacin (n=7), vancomycin (n=6), amikacin (n=5), tobramycin (n=7), netilmicin (n=4) and ciprofloxacin (n=3). Repeat urine culture was negative in all the subjects and they were discharged after they fully recovered from the UTI.

Table 6: Empirical antimicrobials used.

Organism	Empirical antimicrobials (n=10)	Indication for use of the AMA
***Escherichia coli* (n=5)**	Ceftriaxone (n=1)	Febrile convulsion
	Amikacin (n=1)	Fever with suspected UTI
	Ciprofloxacin (n=1)	Enteric fever
	Ofloxacin (n=1)	Acute gastroenteritis
	Amoxicillin + clavulanic acid* (n=1)	Fever with suspected UTI
***Klebsiella oxytoca* (n=2)**	Ceftriaxone (n=1)	Viral fever
	Ofloxacin (n=1)	Acute gastroenteritis
***Klebsiella pneumoniae* (n=1)**	Ceftriaxone (n=1)	Viral fever
***Enterococcus* (n=1)**	Ceftriaxone (n=1)	Viral fever
***Proteus vulgaris* (n=1)**	Ceftriaxone (n=1)	Viral fever

*Fixed dose combinations (FDCs).

Table 7: World Health Organisation (WHO) lists the following organisms as priority pathogens.[13]

Priority	Pathogens
Priority 1: Critical	*Acinetobacter baumannii*, carbapenam-resistant
	Pseudomonas aeruginosa, carbapenam-resistant
	Enterobacteriaceae, carbapenam-resistant, ESBL-producing
Priority 2: High	*Enterococcus faecium*, vancomycin-resistant
	Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
	Helicobacter pylori, clarithromycin-resistant
	Campylobacter spp, fluoroquinolone resistant
	Salmonellae, fluoroquinolone resistant
	Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: Medium	*Streptococcus pneumonia*, penicillin-non-susceptible
	Haemophilus influenza, ampicillin-resistant
	Shigella spp, fluoroquinolone-resistant

Table 7 gives information about the WHO priority pathogens. None of these organisms were encountered in our study.

DISCUSSION

The changing antimicrobial susceptibility patterns of the organisms is common in developing countries like India, where antimicrobials are prescribed irrationally and they are purchased from the chemists over-the-counter without a prescription.[14] Thus paediatricians should be aware of the rising trends of resistance of uropathogens to the commonly prescribed antibiotics as well as the profile of resistance within their community.[15] Periodic evaluation of the susceptibility pattern is essential for rational and appropriate use of antimicrobials.[11]

UTI incidence varies with age and gender. It occurs in one percent of boys and 3-5% of girls. However, in contrast to this, the present study showed a marginally higher positive rate among male children as compared with female children. Majority of the culture positive cases were in the toddler age group (1-3 years). This was in agreement with a study done in Iran.[16] The probable reason could be that children in this age group are not properly toilet trained and hence likelihood of ascending infection with fecal flora is more common.[4,7]

Escherichia coli was the most common uropathogen isolated and constituted 40.3% (n=44) of all the positive samples. This is less than the finding observed by Rimal et al *E.coli* constituted 59.4% of the nosocomial UTI in hospitalized patients as reported by Das et al.[17] Another study in children reported 96.4% urinary isolates of *E.coli.*[18] With regard to antibiotic sensitivity pattern of the isolates, *E.coli* was found to be most sensitive to amikacin, piperacillin and tazobactam, meropenem and netilmicin. Rajbhandari et al earlier reported nitrofurantoin as the most sensitive antibiotic followed by gentamicin, norfloxacin and ciprofloxacin.[19]

Proteus spp which includes *Proteus mirabilis* (1.8%; n=2) and *Proteus vulgaris* (6.4%; n=7) was identified as a causative agent for UTI only in a small number of cases in this study. This was similar to a study by Shrestha et al.[20] *Proteus* spp was found sensitive to ciprofloxacin, amikacin, gentamicin, meropenem and piperacillin + tazobactam. It was resistant to nalidixic acid and nitrofurantoin. In a study by Rajbhandari et al *Proteus* spp were reported to be sensitive to nalidixic acid.[19]

Klebsiella spp constituted the third most common uropathogen for UTI. It accounted for 17.43% (n=19) of the cases. On the contrary, Moderres et al found *Klebsiella* spp in 10.5% of the children.[16] It was sensitive to amikacin, gentamicin, tobramycin and meropenem and resistant to amoxicillin and clavulanic acid, cefepime, cefuroxime, ciprofloxacin, nitrofurantoin and nalidixic acid. This was contrary to the reports in another study which suggested that quinolone group- norfloxacin, nalidixic acid and nitrofurantoin was sensitive and most effective.[19]

The gram positive uropathogens isolated in our study were *Enterococcus* 21.1% (n=23), *Staphylococcus aureus* and *Methicillin Resistant Staphylococcus aureus* (MRSA) 0.9% (n=1) each. This is in contrast to another study report where *Staphylococcus aureus* was 2.7% to 12.2%.[19]

CONCLUSION

The incidence of UTI varies with age. Different uropathogens and their resistance to commonly used antimicrobials is a concern for future treatment options in UTI. The findings in this study suggest the need of periodic monitoring of antimicrobial susceptibility pattern of the bacterial isolates. This will help the clinicians in selecting empirical therapy for treatment of UTI in children and also in providing cost effective treatment in developing countries like India and elsewhere.

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