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Research Article

Community acquired urinary tract infection in pediatric age-group with changing trends of antibiotic resistance pattern over 3 years: a clinico-epidemiological study

Baishali Chakroborty[1], Sumanta Kumar Dutta[2], Patralekha Ray Chaudhuri[3], Ranjita Santra (Dhali)[4]*

[1]Department of Microbiology, Calcutta Medical College, Kolkata, West Bengal, India, [2]Department of ENT, Calcutta National Medical College, Kolkata, West Bengal, India, [3]Department of Pharmacology, Calcutta National Medical College, Kolkata, West Bengal, India, [4]Department of Clinical and Experimental Pharmacology, Calcutta School of Tropical Medicine, Kolkata, West Bengal, India

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***Correspondence to:**
Ranjita Santra (Dhali),
Email: dsdrranjita@gmail.com

ABSTRACT

Background: Assessment of the antimicrobial sensitivity pattern in urinary isolates of the children suffering from urinary tract infection (UTI) and evaluation of the recent trends of multi-drug resistance in the isolates. The aim was to find out the antibiotics sensitivity of the organisms isolated from the urine samples of pediatric age-group with emphasis on their resistance pattern.
Methods: A clinico-epidemiological study comprising of 304 specimens of urine were collected among all the children with UTI below 12 years of age, attending pediatric outpatient department of a tertiary care teaching hospital in eastern India wet mount microscopy and semi quantitative culture were done to diagnose UTI. Organisms isolated were identified by standard biochemical tests, and antibiogram studies were done by standard Kirby-Bauer disc diffusion test statistical analysis, Microsoft excel and SPSS were used for analysis of data.
Results: Aminoglycosides had wider sensitivity pattern toward most of the uropathogens whereas tetracyclines and co-amoxyclav in particular were resistant for most of the organisms. Among all the organisms, *Pseudomonas* and *Enterococcus* species showed higher resistance pattern toward the conventional antimicrobials.
Conclusions: The changing trends in the anti-biograms of several Gram-positive and Gram-negative microorganisms in UTI demands reconsideration with respect to rational drug use in the pediatric age group.

Keywords: Urinary tract infection, Pediatric population, Antibiotic resistance, Empirical treatment

INTRODUCTION

Pediatric urinary tract infections (UTI) account for 0.7% of physician office visits and 5-14% of emergency department visits by children annually in India. UTI is defined as the persistent presence of actively multiplying organisms within the urinary tract.[1] Most UTIs in children result from ascending infections, although hematogenous spread may be more common in the first 12 weeks of life. Most cases of UTIs in children are caused by *Escherichia coli* (60-80%) *Proteus* (more common in boys and in children with renal stones), *Klebsiella*, *Enterococcus*, and coagulase-negative staphylococci.[2] UTIs occur in 3-5% of girls and 1% of boys of pediatric age-group. Some fungi like Candida, some virus like adenovirus (11, 21) may also be responsible for infection.[3] The prevalence of UTIs varies with age during

the 1st year of life with male:female ratio is 2.8-5.4:1. Beyond 1-2 years, there is striking female preponderance with a male:female ratio of 1:10.[3,4] UTI is a major cause of hospitalization of children in the developing countries.[5] Increased incidence of UTI-related complications can be prevented or reversed by early detection and treatment with proper administration of appropriate antimicrobial drug. Among the antimicrobial drugs, β-lactam (penicillin and cephalosporins) is effective against Gram-positive and Gram-negative organisms though resistance is increasing day by day.[6] Detection of pyuria and bacteruria may help in the diagnosis of UTI.[7] Diagnosis of UTI can be established only by quantitative or semi quantitative bacterial culture of measured amount of urine sample on solid media and counting the number of bacteria.[8] Spontaneous resolution rates of 50-70% for lower UTI without pharmacological intervention have been reported.[9] The purpose of this study was to assess the antimicrobial sensitivity pattern in urinary isolates of the children with suspected UTI over a period of 3 years to evaluate the changing trends of multi-drug resistance in those isolates.

METHODS

The study was a clinico-epidemiological type of study, which was non-invasive and cross-sectional in design and was spanned over a period of 1 year. The study population comprised of pediatric patients up to 12 years of age attending pediatric outpatient department (OPD) of a tertiary care teaching hospital of West Bengal with clinical features of UTI. Specimen of 304 cases of suspected UTI were collected among all the children attending pediatric OPD in a random method. Considering the following inclusion and exclusion criteria 304 children were incorporated into the study. Data analysis was performed with the help of Microsoft Excel and SPSS version 10 software.

Inclusion criteria

1. Neonates with one or more signs: fever, vomiting, diarrhea, lethargy, poor weight gain, and failure to thrive
2. Older children with one or more signs: difficulty in micturition, lower abdominal pain, frequency of micturition and burning sensation during micturition.

Exclusion criteria

Children with surgical intervention and other co-morbid conditions were excluded from this study.

A pre-designed form was used for this study consisting of two sections namely patient profile and disease profile. Specimens of urine from children with suspected UTI were collected. For aerobic culture of urine, MacConkey agar plate, blood agar plate, Mueller-Hinton agar plate and nutrient agar were utilized along with the liquid media - Peptone water, nutrient broth, 6.5% NaCl broth, and glucose phosphate broth. These media were prepared from the commercially available dehydrated media (HiMedia, Mumbai). All media were kept in the refrigerator at 4°C for further use. Examination of the urine specimen was done by microscopy of wet film and gram stain smear; isolation, identification and colony count. Determination of minimum inhibitory concentration (MIC) value was done for five antimicrobials viz. amikacin, cephalexin, amoxicillin/clavulanic acid (co-amoxyclav), norfloxacin, co-trimoxazole for *E. coli* in 10 samples - by epsilometer test ("E" test) with HiComb™ MIC test kit. The urine specimens were examined macroscopically for any abnormal color, presence or absence of haziness. Urine samples were tested for detecting the presence of reducing sugar and protein by Benedict's test, heat coagulation test, and biuret test respectively.[10,11] Preliminary screening test for evidence of UTI was done by examination of wet film and gram stain smear. Culture showing $>10^5$ colonies of a single pathogen or if there were 10^4 colonies in a symptomatic child, it was considered a UTI.[4] A pure culture of *Staphylococcus aureus* was considered to be significant regardless of the number of colony forming unit.[3] *In vitro* antimicrobial susceptibility pattern of the isolated uropathogen was determined by Kirby-Bauer disc diffusion test.[12] HiComb MIC test (E test) was done for the determination of MIC for the antibiotics viz. amikacin, cephalexin, co-trimoxazole, co-amoxyclav and norfloxacin. The inoculum was pure *E. coli*. Correlation of UTI and quantitative bacteriuria was done by many scientists like Rantz and Keefer in 1940, Marple in 1941, Harris, Murray, Paine, Kitham and Finland in 1947 and Sanfordt et al. in 1956.[13] The study was duly approved by the Institutional Ethics Committee (IEC) in accordance with the Declaration of Helsinki. Interpretation of antibiotic susceptibility testing was done following Clinical Laboratory Standards Institution (CLSI) criteria. Data analysis was performed with the help of Microsoft Excel and SPSS version 10 software. MIC was greatest with cephalexin followed by norfloxacin, cotrimoxazole and amikacin as evident from Table 3.

RESULTS

Male children correspond to 17,900/304 (58.88%) and female to 12,500/304 (41.12%) among 304 total cases of UTI. In both groups, most of the children in the age-group of 5-12 years showed clinical features of UTI (46.38%) (Figure 1).

E. coli was highly sensitive to AK (100%), G (89.09%) followed by FD (61%) as compared to the other antimicrobials.

For *Klebsiella* highest sensitivity was seen to AK (71.43%). *Proteus* was 100% sensitive to AK, G and QB and 80% sensitive to CH and RC.

Pseudomonas was 100% sensitive to AK, resistant to CH, FD, PR, AG, B, T. *S. aureus* was highly sensitive to

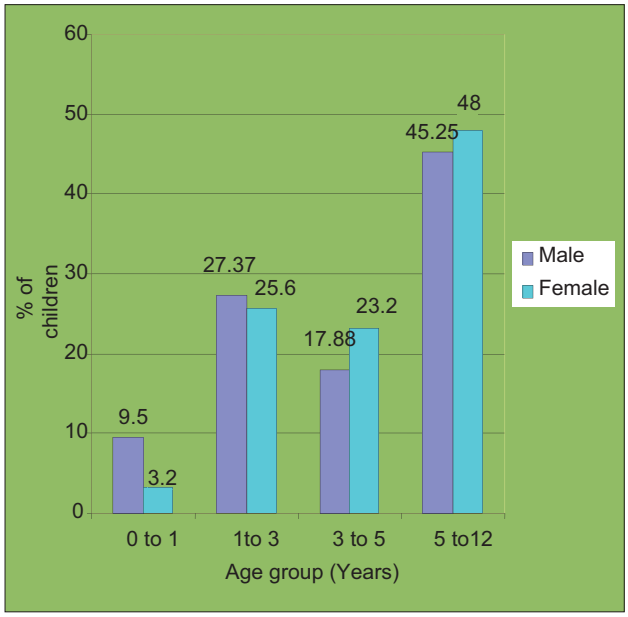

Figure 1: Paired bar diagram on age and gender-wise distribution of study population.

G (100%), AK (90%). *Staphylococcus saprophyticus* was highly sensitive to AK and CF (100% each) followed by G (78.78%). *Enterococcus* species was resistant to most of the antimicrobials except AK. Considering the whole scenario, it can be commented that AK and G remain sensitive for most of the uropathogens, whereas T and AG have shown a marked degree of resistance. *Pseudomonas* and *Enterococcus* had emerged to be the most resistant organisms in children with UTI in the present study (Table 1).

DISCUSSION

In this study, 168 children out of 304 diagnosed cases of UTI received empirical antimicrobial therapy. Those children who did not receive empirical antimicrobial therapy showed 44.12% growth positivity in comparison to 24.40% in those who received empirical therapy. The difference in growth was found to be statistically significant ($p<0.05$). In findings of another study[14] where *E. coli* was sensitive to amikacin and gentamicin (90-100%), cefotaxime (70-80%), cephalexin and chloramphenicol (40-50%), *Proteus* by 100% sensitive to amikacin, gentamicin, it has been found that it correlates well with our study. *Klebsiella* in the present study has the highest sensitivity toward amikacin (71.43%), followed by gentamicin, chloramphenicol, nitrofurantoin, ciprofloxacin (42.86% each). In a recent study, *Klebsiella* was sensitive to amikacin, co-trimoxazole, gentamicin by 60-80%, levofloxacin by 80%, chloramphenicol and ciprofloxacin, cefotaxime by 40%[15] while cefotaxime showed greater resistance in our study. Here, *Pseudomonas* showed the highest sensitivity to amikacin, then toward gentamicin and absolute resistance to chloramphenicol, nitrofurantoin, cephalexin, co-amoxyclav, and tetracycline. While in another study, amikacin and gentamicin showed mild sensitivityto it.[16] Again mean resistance rate for *E. coli* with cephalexin was 24% whereas it is as high as 87.27% in our study. They also concluded that, cefotaxime has the highest sensitivity followed by sulfonamides and fluoroquinolones which are inconsistent with our results. *S. aureus* showed the highest sensitivity to gentamicin (100%) and amikacin (90%), whereas lowest sensitivity towards norfloxacin and co-amoxyclav. *S. saprophyticus* was highly sensitive to amikacin and cefotaxime (100%) followed by gentamicin (78.78%) and least sensitive to co-trimoxazole and chloramphenicol. *Enterococcus* species was universally resistant to most of the antimicrobials except the amikacin. All the microorganisms are extremely resistant towards tetracycline. In the present study, resistance pattern is lowest towards aminoglycosides and higher toward quinolones specially norfloxacin. Almost all the pathogens show higher resistance toward β-lactam antibiotics. In a similar study, considerably low level of resistance pattern was found for gentamicin, ciprofloxacin, co-trimoxazole and nitrofurantoin which is not in agreement with us.[17] Another study showed overall lower resistance pattern of pathogens toward ciprofloxacin, co-trimoxazole, nitrofurantoin compared to our study and significantly less resistance was found towards co-trimoxazole, cephalexin and co-amoxyclav in a different study which is not in agreement with this study.[10] Maximum resistance emerged with the use of tetracycline followed by co-amoxyclav, co-trimoxazole and cephalexin as evident from Table 2.

Summarizing the whole picture it can be said that amikacin is the most appropriate antimicrobial which can be prescribed for all the pediatric cases of UTI empirically without awaiting the results for culture and sensitivity, followed by gentamicin, third and fourth generation cephalosporins, fluroquinolones and other beta-lactam antibiotics. The changing trend in resistance pattern is seen in all the bacteria responsible for UTI in the pediatric population, and all of them have acquired 100% resistance to tetracycline (Table 2).

CONCLUSION

With increasing trend of resistance to the antimicrobials and the possibility of re-emergence of sensitivity to some among the microorganisms, the policy of empirical treatment of UTI in children needs to be rationalized. The changing trends in the anti-biograms of several Gram-positive and Gram-negative microorganisms probably demands reconsideration for the use of proper drug therapy to prevent the emergence of multidrug resistance.

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Table 1: Sensitivity pattern of the uropathogens towards the antimicrobials.

Types of microorrganisms	Sensitivity and resistance	Antimicrobial drugs (N (%))												
		AK	G	CH	FD	NX	QB	RC	PR	CF	SF	AG	B	T
E. coli	S	55 (100)	49 (89.09)	22 (40)	34 (61.81)	12 (21.81)	23 (41.81)	13 (23.63)	7 (12.72)	25 (45.45)	14 (25.45)	0 (0)	6 (10.90)	0 (0)
	R	0 (0)	6 (10.91)	33 (60)	21 (38.18)	43 (78.18)	32 (58.18)	42 (76.36)	48 (87.27)	30 (54.55)	41 (74.55)	55 (100)	49 (89.09)	55 (100)
Klebsiella	S	5 (71.43)	3 (42.86)	3 (42.86)	3 (42.86)	2 (28.57)	2 (28.57)	3 (42.86)	0 (0)	2 (28.57)	1 (14.29)	0 (0)	1 (14.29)	0 (0)
	R	2 (28.57)	4 (57.14)	4 (57.14)	4 (57.14)	5 (71.43)	5 (71.43)	4 (57.14)	7 (100)	5 (71.43)	6 (85.71)	7 (100)	6 (85.71)	7 (100)
Proteus	S	5 (100)	5 (100)	4 (80)	-	2 (40)	5 (100)	4 (80)	0 (0)	2 (40)	0 (0)	0 (0)	0 (0)	0 (0)
	R	0 (0)	0 (0)	1 (20)	-	3 (60)	0 (0)	1 (20)	5 (100)	3 (60)	5 (100)	5 (100)	5 (100)	5 (100)
Pseudomonas	S	4 (100)	2 (50)	0 (0)	0 (0)	2 (50)	2 (50)	2 (50)	0 (0)	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)
	R	0 (0)	2 (50)	4 (100)	4 (100)	2 (50)	2 (50)	2 (50)	4 (100)	3 (75)	3 (75)	4 (100)	4 (100)	4 (100)
S. aureus	S	10 (90.91)	11 (100)	4 (36.36)	4 (36.36)	1 (9.09)	6 (54.55)	3 (27.27)	3 (27.27)	8 (72.72)	4 (36.36)	2 (18.18)	0 (0)	0 (0)
	R	1 (9.09)	0 (0)	7 (63.63)	7 (63.63)	10 (90.91)	5 (45.45)	8 (72.72)	8 (72.72)	3 (27.27)	7 (63.63)	9 (81.82)	11 (100)	11 (100)
Staphylococcus saprophyticus	S	9 (100)	7 (78.78)	1 (11.11)	4 (44.44)	2 (22.22)	2 (22.22)	2 (22.22)	4 (44.44)	9 (100)	3 (33.33)	2 (22.22)	1 (11.11)	0 (0)
	R	0 (0)	2 (22.22)	8 (88.89)	5 (55.56)	7 (77.78)	7 (77.78)	7 (77.78)	5 (55.56)	0 (0)	6 (66.67)	7 (77.78)	8 (88.89)	9 (100)
Enterococcus species	S	9 (90)	5 (50)	0 (0)	1 (10)	0 (0)	2 (20)	2 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	R	1 (10)	5 (50)	10 (100)	9 (90)	10 (100)	8 (80)	8 (80)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)	10 (100)

AK: Amikacin, G: Gentimicin, CH: Chloramphenicol, FD: Nitrofurantoin, NX: Norfloxacin, QB: Levofloxacin, RC: Ciprofloxacin, PR: Cephalexin, CF: Cefotaxime, SF: Cefixime, AG: Co-amoxyclav, B: Co-trimoxazole, T: Tetracycline, *E. coli: Escherichia coli, S. aureus: Staphylococcus aureus, S. saprophyticus: Staphylococcus saprophyticus*, S: Sensitivity, R: Resistance

Table 3: MIC (MIC in µg/ml) of five antimicrobials in growth of the major pathogen *E. coli.*

Number of *E. coli* growth	MIC of antimicrobials (µg/ml)				
	Amikacin	Cephalexin	Norfloxacin	Co-amoxyclav	Co-trimoxazole
1	0.256	-	-	-	-
2	0.256	7.5	-	-	-
3	0.256	-	-	-	0.1
4	0.256	15	0.5	-	0.5
5	0.256	-	-	-	-
6	0.256	-	0.5	-	-
7	0.256	7.5	0.001	-	0.1
8	0.128	7.5	0.05	-	0.5
9	0.256	7.5	-	-	-

MIC: Minimum inhibitory concentration, *E. coli: Escherichia coli*

Table 2: Changing trend of antimicrobial resistance pattern over 2010 July-2013 June.

Antimicrobials	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)
Amikacin	2 (2.27)	3 (2.22)	1 (0.9)	4 (3.96)
Chloramphenicol	61 (69.32)	56 (41.48)	33 (29.73)	67 (66.34)
Gentamicin	20 (22.73)	60 (44.44)	31 (27.93)	19 (18.81)
Cephalexin	74 (84.09)	131 (97.04)	109 (98.2)	87 (86.14)
Levofloxacin	21 (23.86)	35 (25.93)	23 (20.72)	59 (58.42)
Cefotaxim	32 (36.36)	75 (55.56)	61 (54.95)	54 (53.47)
Ciprofloxacin	45 (51.14)	92 (68.15)	84 (75.68)	72 (71.29)
Norfloxacin	49 (55.68)	129 (95.56)	96 (86.49)	80 (79.21)
Nitrofurantoin	40 (45.45)	67 (49.63)	44 (39.64)	55 (52.08)
Co-amoxyclav	83 (94.32)	131 (97.04)	108 (97.3)	97 (96.04)
Tetracycline	87 (98.86)	135 (100.00)	111 (100.00)	101 (100.00)
Co-trimoxazole	86 (97.73)	133 (98.52)	111 (100.00)	93 (92.08)
Cefixime	74 (84.09)	122 (90.37)	97 (87.39)	78 (77.23)

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