Original Research Paper

Volume - 14 | Issue - 02 | February - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Paediatrics

"STUDY OF URINARY TRACT INFECTION CAUSED BY MULTIDRUG RESISTANT ORGANISMS"

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ABSTRACT **Objectives-** To know the prevalence of urinary tract infections caused by multidrug resistant organisms and risk factors for multidrug resistant urinary tract infections **Design-** Prospective observational study from August 2019 to August 2021 **Material and Method-** Total of 126 children less than 18 years of age diagnosed to have UTI by culture and sensitivity were recruited in this prospective observational study. Relevant history and examination was done as per the predesigned structured protocol. Antenatal records were reviewed for evidence of congenital anomalies of kidney and urinary tract. Physical examination was carried out to look for failure to thrive, toxicity, hypertension, palpable kidney or urinary bladder, genital and lumbosacral anomalies. Patients were enquired about exposure to antibiotics, and catheterisation of the urinary tract in the previous month. Records were reviewed for the previous episodes of UTI and details of the present medication was noted. Urine sample for microscopic examination and culture was collected by midstream clean catch or catheterization. Samples showing > 105 CFU /ml were considered to have significant growth. Antimicrobial susceptibility testing was done on samples showing significant growth by Kirby –Bauer disc diffusion method **Results:** Multidrug resistance was more prevalent among the age group of less than 5 years and more prevalent in males. The major risk factors are previous antibiotic exposure, previous hospitalization, underlying urological abnormalities. **Conclusion:** This study reveals that UTI caused by multidrug resistant organisms is on a significant rise and the major risk factor being previous exposure to antibiotics. This study showed that most of the isolates were resistant to cephalosporins and ampicillin. Lesser resistance to nitrofurantoin and amoxiclav was observed. As the susceptibility pattern is changing across the globe, regular monitoring of antibiotic resistance pattern is necessary.

KEYWORDS : Urinary Tract Infections, Multidrug Resistance, Children, E. Coli

INTRODUCTION

Urinary tract infections (UTI) are common in the paediatric population and an important cause of morbidity. Prevalence and clinical presentation of UTI may vary by gender and age. Often it may be difficult to diagnose UTI in children because of non-specific clinical features. Delay in the diagnosis and initiation of appropriate treatment adds to the morbidity.

Significant growth on urine culture confirms the diagnosis of UTI. E. coli, Klebsiella and Proteus are the most common cause of urinary tract infection in children [1]. Treatment is often started empirically based on the local prevalence of organisms and susceptibility pattern.

UTI caused by multidrug resistant organisms among children is on the rise across the globe [1]. Multidrug resistance (MDR) is defined as resistance to three or more different structural classes of antimicrobial agents [1]. Antibiotic resistance poses challenge in the management and may cause serious disease. There are a number of case-control studies regarding risk factors for UTI with antibiotic-resistant organisms in children [2-5].

Most frequently cited risk factors for multidrug resistant UTI are previous antibiotic use, underlying urinary tract anomalies and previous hospitalisation. To reduce the risk of resistance, it is pertinent to choose antibiotic therapy based on urine culture and sensitivity report [1,6,7,8].

This study was taken up to know the risk factors for multidrug resistant UTI and the bacteriological profile and susceptibility pattern of organisms causing UTI among children in central Karnataka.

MATERIALS AND METHODS

Total of 126 children less than 18 years of age diagnosed to have UTI by culture and sensitivity were recruited in this prospective observational study. This study was conducted from August 2019 to August 2021 in the hospitals affiliated to the department of Paediatrics.

Those children who were provisionally diagnosed to have UTI based on the clinical features but not showing significant growth on urine culture were excluded from the study. Those with urine samples showing polymicrobial growth on culture also were excluded from the study.

Relevant history and examination was done as per the predesigned structured protocol with emphasis on duration and grade of fever, pain abdomen, vomiting and voiding problems like urgency, frequency, strangury, post void dribbling and straining while passing urine. Antenatal records were reviewed for evidence of congenital anomalies of kidney and urinary tract.

Physical examination was carried out to look for failure to thrive, toxicity, hypertension, palpable kidney or urinary bladder, genital and lumbosacral anomalies. Patients were enquired about exposure to antibiotics, and catheterisation of the urinary tract in the previous month. Records were reviewed for the previous episodes of UTI. Details of the present medication was noted.

Urine sample for microscopic examination and culture was collected by midstream clean catch or catheterization. Samples showing > 10^5 CFU /ml were considered to have significant growth. Antimicrobial susceptibility testing was done by Kirby-Bauer disc diffusion method as per the CLSI (Clinical and Laboratory Standards Institute) guidelines.

Antibiotic agents belonging to penicillins, cephalosporins, carbapenems, sulphonamides, quinolones, aminoglycosides, monobactams and polypeptides group were included. The isolates were reported as Susceptible (S), Intermediate (I) and Resistant ®.

Multidrug resistance was defined according to the 2011 international consensus statement as organisms with resistance to one or more antibiotics in three or more different antimicrobial categories [9]

Children with simple UTI were treated for 7 days and complicated for 14 days.

Simple UTI is defined as UTI with low grade fever, dysuria, frequency and absence of symptoms of complicated UTI. Complicated UTI is defined as presence of fever >39ºC, systemic toxicity, persistent vomiting, dehydration, renal angle tenderness and raised creatinine.

USG (Ultrasound sonography), MCU (Micturating cystourethrogram) and DMSA (Dimercapto succinic acid) were carried out according to the IAP guidelines [10] (figure 1). All patients with recurrent UTI of any age were evaluated with USG, MCU and DMSA.

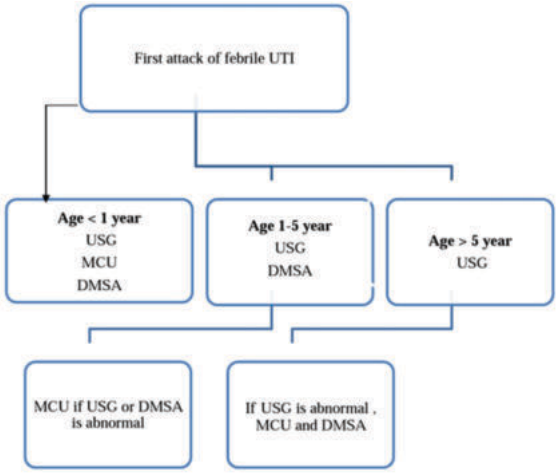

Fig 1. Evaluation following First UTI

Statistical Analysis

Data was analysed using SPSS version 20 (Statistical Package for Social Sciences). Descriptive variables were analysed by frequency and proportions. The statistical association between qualitative variables were assessed by Chi square test with the level of significance set at 5%.

RESULTS

A total of 250 urine samples were sent for urine culture, out of which 126 samples showed a significant growth. Males (53.2%) were marginally more affected than females (46.8%). UTI was predominantly seen in the age group between 0-5 years. Table 1 shows the age and sex distribution of UTI

Table 1: Age and sex distribution of UTI.

Age	Male	Female	Total
< 1 Year	26(39%)	15(26%)	41(33%)
1 to 5 year	31(46%)	35(59%)	66(52%)
> 5 year	10(15%)	9(15%)	19(15%)
Total	67(53.2%)	59(46.8%)	126(100%)

Among 126 children, 65(52%) had complicated UTI ,61 (48%) had simple UTI and 26(21%) had recurrent UTI.

Among 126 isolates, 86(68.3%) were found to be resistant to antibiotics of 3 or more classes and hence considered to be multidrug resistant.

Among 86 isolates which were multidrug resistant, 31(36%) were found in children below 1 year of age, 44(51.2%) between 1-5 years of age group and 11(13%) in more than 5 years of age group. 53(61.6%) of MDR isolates were found in males and 33(38.4%) were found in females. The age and sex wise distribution of MDR and sensitive isolate is shown in the table 2.

Table 2: Age and Sex distribution of MDR isolate and Sensitive isolate.

Age	Male		Female	
	MDR isolate	Sensitive isolate	MDR isolate	Sensitive isolate
< 1 year	20(38%)	6(42%)	11(33%)	4(15%)
1-5 year	28(53%)	3(21%)	16(49%)	19(73%)
> 5 year	5(9%)	5(37%)	6(18%)	3(12%)
Total	53(100%)	14(100%)	33(100%)	26(100%)

Among 86 MDR isolates, 54 (62.8%) were found in complicated UTI and 32(37.2%) were found in simple UTI. Among 26 children with recurrent UTI, 17 (65%) were found to have MDR isolate.

Among 74 children with h/o previous antibiotic exposure, 63 (85%) had MDR UTI. All the 11 children with h/o previous instrumentation had MDR UTI.

Among 86 children with MDR UTI, ultrasonogram of KUB region was abnormal in 56 (65.1%) children. PUV (posterior urethral valve) was seen in 7(8.1%) children and Primary VUR (vesicoureteral reflux) in 18(20.9%) on MCU. Table 3 shows prevalence of risk factors in MDR and sensitive UTI

Table 3: Prevalence of risk factors

Risk factors	Total number	MDR isolate	Sensitive Isolate
Previous antibiotic exposure	74	63(85%)	11(15%)
Previous hospitalization	49	38(77%)	11(23%)
Previous instrumentation	11	11(100%)	0(0%)
Abnormal USG	73	56(77%)	17(23%)

Among the 126 organisms isolated, E. Coli was the predominant isolate found in 94(74.6%) urine samples followed by klebsiella in 13 (10.3%), enterococci in 9 (7.1%). Among 86 MDR isolates, 66 (76.7%) were E. coli, 8(9.3%) were klebsiella, 8(9.3%) were enterococci, 2 (2.3%) were pseudomonas (table 4).

Table 4: Pattern of isolates

ORGANISMS	Total isolates	MDR isolates	Sensitive isolates
E.COLI	94(74.6%)	66(76.7%)	28(70%))
ENTEROCOCCI	9(7.1%)	8(9.3%)	1(2.5%)
KLEBSIELLA	13(10.3%)	8(9.3%)	5(12.5%)
PROTEUS	2(1.6%)	0(0.0%)	2(2.3%)
PSEUDOMONAS	5(4.0%)	2(2.3%)	3(3.4%)
ACETENOBACTER	2(1.6%)	2(2.3%)	0(0%)
CITROBACTER	1(0.8%)	0(0.0%)	1(2.5%)
Total	126(100%)	86(68%)	40(32%)

Table 5: Sensitivity pattern of isolates.

Organisms	E. Coli n=94(%)		Klebsiella n=13(%)		Enterococci n=9(%)		Pseudomonas n=5(%)		Proteus n=2(%)		Acenetobacter n=2(%)		Citrobacter n=1(%)	
Antibiotics	R	S	R	S	R	S	R	S	R	S	R	S	R	S
Ampicillin	66 (70)	28 (30)	9 (69)	4 (31)	4 (44)	5 (56)	3 (60)	2 (40)	0 (0)	2 (100)	2 (100)	0 (0)	1 (100)	0 (0)
Ceftriaxone	64 (68)	26 (32)	7 (54)	6 (46)	4 (44)	5 (56)	2 (40)	3 (60)	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)	1 (100)
Cefotaxime	62 (65)	32 (35)	5 (38)	8 (62)	5 (56)	4 (44)	3 (60)	2 (40)	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)	1 (100)
Nitrofurantoin	15 (16)	79 (84)	3 (23)	10 (77)	2 (22)	(78)	1 (20)	4 (80)	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)	1 (100)
Amikacin	55 (58)	39 (42)	5 (38)	8 (62)	2 (22)	7 (78)	1 (20)	4 (80)	1 (50)	1 (50)	2 (100)	0 (0)	1 (100)	0 (0)
Flouroquinolones	46 (50)	48 (50)	2 (15)	11 (85)	1 (11)	8 (89)	2 (40)	3 (60)	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)	1 (100)
Nalidixic Acid	56 (59)	38 (41)	6 (46)	7 (54)	4 (44)	5 (56)	4 (80)	1 (20)	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)	1 (100)
Amoxicillin-clavulinic acid	27 (29)	67 (71)	2 (15)	11 (85)	1 (11)	8 (89)	1 (20)	4 (80)	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)	1 (100)

Cotrimoxazole	50 (53)	44 (47)	2 (15)	11 (85)	4 (44)	5 (56)	2 (40)	3 (60)	1 (50)	1 (50)	0 (0)	2 (100)	0 (0)	1 (100)
Imepenam	10 (10)	84 (90)	2 (15)	11 (85)	1 (11)	8 (89)	1 (20)	4 (80)	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)	1(100)

With regard to sensitivity pattern, E. coli was found to be highly resistant to Ampicillin (70%), ceftriaxone (68%), cefotaxime (65%), followed by Nalidixic acid (59%), Amikacin (58%) and Cotrimoxazole (53%). Lesser resistance was seen for nitrofurantoin (16%), imipenam (10%) and Amoxicillin clavulanic acid (29%). Klebsiella was found to be highly resistant to ampicillin (69%) and ceftriaxone (54%) and has lesser resistance to fluoroquinolones (15%), amoxicillin-clavulanic acid (15%), imipenam (15%), co-trimoxazole (15%) and nitrofurantoin (23%). Enterococci and pseudomonas were found to be more resistant to ampicillin, ceftriaxone and nalidixic acid and lesser resistance to nitrofurantoin, amoxicillin-clavulanic acid and imipenam (table 5).

DISCUSSION

Total of 126 children less than 18 years of age who had visited OPD or admitted to the affiliated hospitals with the provisional diagnosis of UTI and subsequently confirmed by urine culture were analysed. The overall prevalence of MDR UTI was found to be 68.3%. These results were comparable with the results of the study conducted by Srinivasan et al where the prevalence of multidrug resistant isolates was 53% [1]**.**

UTI was predominantly seen in the age group between 0-1years (41%) and 1-5 years (52%). In a study conducted by Patel P et al, majority of cases were seen in less than 6 years of age group [9]. MDR UTI also was more prevalent in the age group between 0-1 year (36%) and 1-5 years (51.2%). A similar study conducted by Srinivasan et al showed majority of the MDR UTI were seen in children less than 5 years of age (57%).

Among 126 cases, males (53.2%) were marginally more affected than females (46.8%). MDR UTI also was more prevalent among male children (61.6%) compared to female children (38.4%) with P value 0.005 which is statistically significant. Similar results were seen in studies conducted by Patel P et al [12], and Srinivasan S et al [1].

Multidrug resistance was found to be more among the children with complicated UTI (83.07%) and recurrent UTI (65%) than with simple UTI (52.4%) with significant p value of 0.001. Multidrug resistance was more among children with previous antibiotic exposure (73.3%) with significant p value of 0.001. Similar results were seen in the study conducted by Srinivasan S et al (5,13,14). All the 11 children with h/o previous instrumentation were found to have MDR UTI.

Majority of children with MDR UTI had abnormal findings on USG or MCU (65.1%) compared to sensitive UTI (42%) but this association was not statistically significant (P value 0.027)

Among multidrug resistant isolates, E. coli was the predominant organism (76.7%), followed by enterococci (9.3%), klebsiella (9.3%). Similar results were reported by Eshwarappa et al and Patel P et al in their study on microbiological profile of urinary tract infections in south India. [7]. There are several other studies showing E. coli as the significant pathogen causing UTI. [1,15]. There are other studies which showed maximum MDR isolates were seen in E. coli [16,17,18] With regard to sensitivity pattern, E. coli was found to be highly resistant to ampicillin (70%), ceftriaxone (68%), cefotaxim (65%) followed by nalidixic acid (59%), amikacin (58%) and cotrimoxazole (53%) (figure 1). Similar results were seen in the study conducted by Flory et al in Mexico [19] and also in the study conducted by Gayathri Raman et al [5]. Our study showed that nitrofurantoin (16%) imipenam (10%) and amoxicillin –clavulanic acid (29%) having lesser resistance.

With the increasing resistance to ampicillin and cotrimoxazole, cephalosporins and fluoroquinolones are being increasingly used. But unfortunately due to excessive use of these antibiotics, resistance is emerging rapidly to these antibiotics also. In the recent years, use of cephalosporins like ceftriaxone has been drastically increased which appears to be the cause for increasing resistance.

CONCLUSION

This study reveals that UTI caused by multidrug resistant organisms is on a significant rise and the major risk factor being previous exposure to antibiotics. Previous instrumentation of urinary tract and underlying anatomical abnormalities of urinary tract were the other major risk factors though statistically significant association was not found in this study. This study showed that most of the isolates were resistant to cephalosporins and ampicillin. Lesser resistance to nitrofurantoin and amoxiclav was observed. As the susceptibility pattern is changing across the globe, regular monitoring of antibiotic resistance pattern is necessary.

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