Antimicrobial Susceptibility Pattern of Various Etiological Agents Causing Pediatric Urinary Tract Infection

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ABSTRACT

Introduction: Urinary tract infection (UTI) is one of the most common infections in children. The incidence of UTI varies with age and sex of the children. UTI is mainly due to ascending infection from the urethra. Timely diagnosis and treatment of UTI is important as it may be marker of urinary tract abnormalities, associated with high morbidity and mortality. Study aimed to determine the microbiological profile and their antimicrobial susceptibility pattern causing UTI among children.

Material and methods: A total of 386 urine samples were collected from the suspected cases of UTI. A calibrated loop method (semi quantitative method) was used for the isolation of bacterial pathogens from urinary samples. Significant isolates were identified by conventional methods according to the standard laboratory protocol. The antibiotic sensitivity test was performed by modified Kirby Bauer disc diffusion technique as per CLSI.

Result: A total of 386 urine samples from clinically suspected cases of UTI were enrolled in this study, out of which 138 (35.75%) showed significant growth and 248 (64%) were sterile. Out of 138 positive cases 77 (41.6%) were female and 61 (30.3%) were male. Majority of cases 43 (31.5%) were found in 0-5 years of age group. E. coli 61 (44.2%), and Staphylococcus aureus 45 (32.6%) was most common isolated Gram negative and Gram positive uropathogen among 138 positive cases. Gram negative organisms showed highest sensitivity to Nitrofurantoin (94.66%) while Gram positive organisms showed highest sensitivity to Nitrofurantoin (97.87%) followed by Vancomycin (91.46%).

Conclusion: Regular monitoring of the antibiotic sensitivity pattern of UTI pathogens for commonly used antimicrobial agents should be carried out in a particular region for optimal empirical therapy.

Keywords: Antimicrobial Susceptibility Testing (AST), Urinary Tract Infection (UTI).

INTRODUCTION

Urinary tract infection (UTI) is defined as the invasion of the genitourinary tract by the microorganisms, associated with high morbidity and mortality if left untreated. UTI is one of the most common infections in children.[1] The incidence of UTI varies with age and sex of the children. Approximately 5% of all children less than 2years of age have febrile illness due to UTI[2], remains undiagnosed[3], documented in cases associated with vesicoureteral reflex (VUR).[4]

Post urethral valves, pelvi-ureteric junction obstruction, neurogenic bladder, stricture urethra, vesicoureteral reflux are associated with pediatric UTI especially in infants (<1 year of age), differs all the way from adults.[5] The risk factors of UTI in children include low socioeconomic status, cultural habits like perineal cleaning method and diaper usage.[6] Small children are even more susceptible to have UTI which can be attributed to several predisposing factors such as changes in bacterial gut flora, immature immune system and urinary tract anomalies, among which vesicouretral reflex is the most common. VUR favors repeated infection and other complications like chronic pyelonephritis and eventual renal scarring.[7] Fever remains a most common presentation in neonates, infants and younger children, whereas older children present with classical sign of UTI.[8]

Escherichia coli and *Klebsiella spp.* are the predominant pathogens though *Enterococcus spp.*, yeasts and *Staphylococcus aureus* have emerged as prominent causative agents in recent years, many of them are resistant to multiple antibiotics.[5]

Accurate diagnosis and appropriate treatment by antimicrobials is vital to treat the present infection as well as to prevent the possible long term consequences like renal scarring, hypertension and eventually end stage renal disease (ESRD).[9] Appropriate antimicrobial therapy should be started promptly for rapid recovery and the avoidance of complications. Treatment of UTI should be started before the culture results are available and then changed to culture specific therapy. Overuse and use of incomplete course of antibiotics as well as empirical antibiotic therapy have been the major contributing factors in the development of multidrug resistant bacteria.[10] Therefore, this study is undertaken to determine the microbiological profile and their susceptibility pattern causing UTI among children and to formulate guidelines for the empirical treatment of

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childhood urinary tract infections in our region.

MATERIAL AND METHODS

This cross sectional study was conducted from December 2018 to November 2019 at Rohilkhand Medical College and hospital, Bareilly. Study was conducted after taking the approval from ethical committee of the institute. The clean catch urine samples with no additional stimulation[11] were collected in children < 1 years and clean catch mid-stream urine in children over 2 years, respectively from indoor and outdoor patients suspecting UTI. Children having age between 0 to 18 years were enrolled in this study. A total of 386 urine samples of clinically suspected urinary tract infection were included in this study. A calibrated loop method (semi quantitative method) was used for the isolation of bacterial pathogens from urinary samples. A loopful urine sample was inoculated on Mac-Conkey agar and Blood agar (Hi Media Laboratories, Mumbai, India). The inoculated plates were incubated at 37^{O}C for 24 hours. The number of isolated bacterial colonies were multiplied by 1000 for the estimation of bacterial load/mL of the urine sample. A specimen was considered positive for UTI if growth detected at a concentration of $\geq 10^5$ CFU/mL.[12] Significant isolates were identified by conventional methods according to the standard laboratory protocol, including colony morphology, gram staining and biochemical reactions. All gram-negative bacilli were identified to species level by their characteristic appearances on the media, Gram's stain, Oxidase test, Motility and biochemical reactions as per standard laboratory protocol. All gram positive organisms were identified to species level by their characteristic appearances on the media, Gram's stain, and Catalase test followed by Coagulase test. Enterococcus was identified by Bile Esculin disc test and also confirmed by Salt tolerance test (6.5% NaCl). *Candida species* grown on conventional media was identified by their characteristic colony morphology and Gram's stain.

Antimicrobial Susceptibility Testing

The antibiotic sensitivity test was performed by modified Kirby Bauer disc diffusion technique with commercially available Hi-Media antibiotic discs on Mueller Hinton agar plates, the zone size was interpreted as Susceptible (S), Intermediate (I), Resistant (R) according to Central Laboratory Standard Institute (CLSI 2019) guidelines.[13]

RESULT

A total of 386 urine samples from clinically suspected cases of UTI were enrolled in this study, out of which 138 (35.75%) showed significant growth and 248 (64%) were sterile (table 1). Out of 138 positive cases 77 (41.6%) were female and 61 (30.3%) were male. Majority of cases 43 (31.5%) were found in 1-5 years of age group followed by 6-10 years of age group (Table 2).

E. coli 61 (44.2%), and *Staphylococcus aureus* 45 (32.6%) was most common isolated Gram negative and Gram positive uropathogen among 138 positive cases respectively. Out of total 61 outdoor and Indoor patients, *E. coli* was present in 22 (36.06%) and 39 (63.93%) respectively (*p-value* 0.04, statistically significant), followed by S. *aureus* in which 18 (51.2%) were from outdoor and 27 (48.8%) from indoor (p-*value* not significant). *Klebsiella pneumoniae* was present only in one (12.5%) outdoor and in 7 (87.5%) indoor patients respectively (p-*value* < 0.001, statistically highly significant). *Pseudomonas aeruginosa* was present 1 each in both the outdoor and indoor patient. *Proteus mirabilis* was

Urine culture	Number of samples	Percentage
Significant growth	138	35.75%
Sterile	248	64.28%
Total	386	100%

Table-1: Total number of sample tested (n=386)

Age group (years)	Male		Female		Total	
	Number	%	Number	%	Number	%
0-5 yrs	16	26.22	27	35.06	43	31.15%
6-10 yrs	18	29.50	20	25.97	38	27.53%
11-15yrs	12	19.67	20	25.97	32	23.18%
16-18 yrs	15	24.59	10	12.98	25	18.11
Total	61	100%	77	100%	138	100%

Table-2: Age and gender distribution of culture positive urine samples (n=138)

Organisms	Outpatient (%)	Inpatient (%)	Total (%)	p value
E. coli	22 (36.06%)	39 (63.93%)	61 (44.2%)	0.040*
S. aureus	18 (51.2%)	27 (48.8%)	45 (32.6%)	0.233
K. pneuminiae	1 (12.5%)	7 (87.5%)	8 (5.8%)	<0.001*
K. oxytoca	3 (60%)	2 (40%)	5 (3.6%)	0.057
P. aeruginosa	1 (50%)	1 (50%)	2 (1.9%)	1.00
Proteus mirabilis	1 (100%)	0	1 (0.7%)	<0.001*
Enterococcus species	0	2 (100%)	2 (1.5%)	<0.001*
Candida spp.	0	14 (100%)	14 (10.2%)	<0.001*
Total	46	92	138	

Table-3: Organism isolated in urine culture positive samples (n=138)

Antibiotics	Number of isolates	Percentage (sensitivity)
Amoxicillin	25	33.33%
Amikacin	31	41.33%
Cefepime	21	28
Cefotaxime	18	24%
Ceftazidime	24	32%
Ceftriaxone	18	24%
Cefoperazone-sulbactum	46	61.33%
Co-trimoxazole	21	28%
Imipenem	29	38.66%
Norfolxacin	21	28%
Nitrofurantoin	71	94.66%

Table-4: Antibiotic sensitivity pattern of Gram negative Uropathogen (n=75)

Antibiotics	Number of isolates	Percentage (sensitivity)
Amikacin	2	100%
Aztreonam	2	100%
Ciprofloxacin	1	50%
Ceftazidime	1	50%
Cefepime	2	100%
Colistin	2	100%
Gentamicin	1	50%
Imipenem	2	100%
Levofloxacin	1	50%
Piperacillin-tazobactum	2	100%
Tobramycin	2	100%

Table-5: Antibiotic sensitivity pattern of *Pesudomonas aeruginosa* (n=2)

Antibiotics	Number of isolates	Percentage (sensitivity)
Ampicillin	21	44.6%
Amikacin	33	70.2%
Cefoxitin	16	34%
Ciprofloxacin	23	48.93%
Cotrimoxazole	23	48.93%
Gentamycin	28	59.57%
Norfloxacin	11	24.44%
Nitrofurantoin	46	97.87%
Vancomycin	43	91.46%
Linezolid	42	89.36%

Table-6: Antibiotic sensitivity pattern of Gram positive bacteria (n=47)

present only in 1 outdoor (p-value < 0.001). *Enterococcus sp.* in 2 (100%) and *Candida sp*. in 14 (100%) was isolated in indoor patients, (p-*value* < 0.001, statistically highly significant (Table 3).

Gram negative uropathogen showed highest sensitivity to Nitrofurantoin (94.66%), followed by Cefoperazone-sulbactum (61.33%), Amikacin (41.33%) and Imipenem (38.66%). They showed least sensitivity (24%) to Cefotaxime and Ceftriaxone (Table 4).

Pseudomonas species showed highest sensitivity (100%) to Colistin, Amikacin, Aztreonam, Imipenem, Piperacillin-tazobactum and Tobramycin. They showed (50%) sensitivity to Ciprofloxacin and Levofloxacin (Table 5).

Gram positive bacteria showed highest sensitivity to Nitrofurantoin (97.87%) followed by Vancomycin (91.46%), Linezolid (89.36%) and Amikacin (70.2%). They showed least sensitivity to Norfloxacin (24.44%) (Table 6).

DISCUSSION

In our study 386 urine samples were processed, out of which 138 (35.75%) showed significant growth of pathogen. Shrestha et al.[14], Palak Gupta et al.[15] also observed bacterial growth in 35.4% and 35.7% of urine samples respectively. However, Prakash D et al.[16] (53.82%), Rangari A et al.[17] (58.82%) showed high while kumar S et al.[18] (17.7%), Dalal P et al.[19] (18.5%) found low prevalence of UTI. Such variation might be due to inclusion of children having specific age group, certain locality and variation in sample size.

In this study, occurrence of UTI was higher in female (41.6%) as compared to the male children (30.3%). The male to female ratio was 1:1.3. Our findings are in accordance with other studies who also shown a female preponderance with male to female ratio of 1:1.2[20] and 1:2[21] respectively. UTI is more common in females, probably due to their characteristic anatomical and physiological changes like short urethra, its proximity to anus.

In our study UTI was more common in 0-5 years (31.15%) followed by 6-10 years (27.53%) of age group. Our observations are consistent with Sharma et al.[22] G K Rai et al.[23] and Singh et al.[24] also found 35-50% of patients in this age group, while Gautam G et al.[25] found maximum number of cases in 6-10 years of age group. This might be due to lack of education for proper toilet training and ascending infection with fecal flora in this age group.

In this study most common isolated Gram negative uropathogen was E. coli (44.2%). Our result is in accordance with other studies.[17,19,26] but differs from others in which *P. aeruginosa*[27] and *Klebsiella spp*.[28] were reported as the predominant bacteria in UTI. *Escherichia coli* is a major normal flora in the gut and poor hygiene will lead urinary tract infection due to cross contamination. Other Gram negative isolated organisms in our study were *K. pneumoniae* (5.8%), *K. oxytoca* (3.6%), *P. aeruginosa* (1.9%) and *P. mirabilis* (0.7%).

Recently Gram positive organism has seeking more attention as a cause for bacteuria and urinary tract infection. In our study *Staphylococcus aureus* (32.6%) was the predominant among gram positive and second most common isolated uropathogen. Neha shah et al.[29] and Gupta et al.[15] found *Enterococcus spp*. as the second most common organism in UTI. This could be due to different geographical distribution of pathogen. In our study *Escherichia coli*, *K. pneumoniae, Enterococcus species* and *Proteus mirabilis* were isolated more significantly in indoor patient as compared to outdoor patient. Similar results were reported by Taneja N.et al.[5]

In this study, the occurrence of candiduria in UTI was 10.2% and all patients were from indoor and no patient was

from outdoor (p-*value* <0.001) (Table 3). Candiduria is the presence of yeast cells in urine. It is an increasingly common finding in hospitalized patients. It has been observed that nosocomial urinary tract infection caused by *Candida species* may vary from 11 to 52%. Hiral K P et al.[30] also found candiduria in 13% of patients and majority of the patients were from indoor. Some of the clinicians believe that the presence of *Candida species* in urine samples is harmless colonization, or lower tract infection. On the other hand, candiduria is well known as an important risk factor for invasive candidiasis with considerable morbidity and mortality.[30]

The antimicrobial susceptibility testing (AST) pattern differs in different studies because of the wide availability of over the counter antibiotics and different hospital based antibiotic policies. The antimicrobial resistance among uropathogen is one of the barricades that may interfere with effective treatment. The antimicrobial resistance pattern of the microorganism causing UTI varies in their susceptibility to antimicrobials from place to place and from time to time.[20]

In our study majority of Gram negative uropathogen showed highest sensitivity to Nitrofurantoin (94.66%), followed by Cefoperazone-sulbactum (61.33%), Amikacin (41.33%) and Imipenem (38.66%) which was in accordance with Beena Sharma et al.[20], A Sharma et al.[22] Gupta P et al.[15] found highest sensitivity to Nitrofurantoin (74.5%), followed by Amikacin (55.4%), Imipenem (48.5%), while GK Rai et al.[23] showed that *E. coli* was most sensitive to Amikacin, Chloramphenicol and Nitrofurantoin. These findings suggest that the antibiotic susceptibility patterns of uropathogen to different drugs may vary geographically.

In this study the highly sensitive drug for *Pseudomonas spp.* was Colistin, Amikacin, Aztreonam, Imipenem, Piperacillin-tazobactum and Tobramycin (100% sensitive) but showed (50%) sensitivity to Ciprofloxacin and Levofloxacin which was in accordance with Beena Sharma et al.[20]

In this study, most common Gram positive organism was *Staphylococcus aureus* and was sensitive to Nitrofurantoin (97.87%) followed by Vancomycin (91.46%), Linezolid (89.36%) and Amikacin (70.2%) but showed least sensitivity to Norfloxacin (24.44%) while other studies found *Enterococcus species* as common Gram positive organism, sensitive to Linezolid (100%) followed by Vancomycin, Teiocplanin (92.8%) and Piperacillin+Tazobactum (84.6%) whereas least sensitive to Norfloxacin (17.8%).[15,20]

It has been observed that every study has its own susceptibility pattern of that region, which relies on factors related to difference in antibiotic use, patient population and prescribing rate. Treatment of patients suffering from UTI depends on selection of an effective antibiotic agent to the causative organism.

CONCLUSION

This study highlights the better efficacy of Nitrofurantoin, aminoglycosides and Imipenem, can be included as empirical therapy. There should be development of protocol for rationale use of antibiotics with regular monitoring to identify the reliable information about resistance pattern of urinary pathogen for optimal empirical therapy. It should be based on the knowledge of local occurrence of bacterial organisms and their antibiotic sensitivities rather than on universal guidelines.

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