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IP International Journal of Medical Microbiology and Tropical Diseases

Journal homepage: https://www.ijmmtd.org/

Original Research Article

A retrospective study on antimicrobial resistance pattern of uropathogenic *E. coli* in rural paediatric population attending tertiary care centre in Tamil Nadu

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ARTICLE INFO

Article history:
Received 11-08-2024
Accepted 14-10-2024
Available online 12-12-2024

Keywords:
coli
Klebsiella spp
Citrobacter spp
Enterobacter cloacae
Proteus mirabilis & Pseudomonas aeruginosa Among the grampositive organisms
Enterococcus spp
Streptococcus group B
Staphylococcus aureus
Staphylococcus epidermidis &
Staphylococcus

ABSTRACT

Introduction: Urinary tract infections are one of the commonest infections occurring in pediatric population. The diagnosis of UTI is difficult due to lack of proper history and absence of typical clinical symptoms as in the adult population. The most common reasons for development of UTI are the anatomical proximity in female and surface area of the prepuce in male uncircumcised children. The most common bacteria associated with infections are *E. coli*, *Klebsiella spp*, *Citrobacter spp*, *Enterobacter cloacae*, *Proteus mirabilis* & *Pseudomonas aeruginosa*. Among the gram-positive organisms, *Enterococcus spp*, *Streptococcus group B*, *Staphylococcus aureus*, *Staphylococcus epidermidis* & *Staphylococcus saprophyticus* have been documented to cause infections.

Materials and Methods: Urine samples processed for culture and sensitivity, from January 2021 to December 2023 from patients ranging from zero days to 18 years were included in the study. Repeat urine samples were excluded from the study. Sample showing no growth or insignificant growth or more than two types of bacterial colonies were excluded from the study. All samples of patients above the age of 18 years were also excluded. Those samples which fit the inclusion criteria were tabulated according to age, gender, bacterial species and antimicrobial resistance. The above data was collected using the ERP software Sage 300. The samples were divided based on the age group of the patients into four groups comprising of Group I: 0 days to 2 years, Group II: 2 to 5years, Group III – 6 to11 years & Group IV: 12 to 18 years.

Results: The study revealed a significant prevalence of urinary tract infections (UTIs) in the pediatric population, with *E. coli* being the primary causative agent. The highest incidence was observed in the 0-2 age group, with a notable decline in *E. coli* infections in male children as they aged. Female children, however, exhibited a more persistent *E. coli* infection rate across different age groups. Alarmingly, increasing antibiotic resistance was observed, particularly against ampicillin, cephalosporins, and fluoroquinolones. In contrast, aminoglycosides, carbapenems, nitrofurantoin, and fosfomycin demonstrated higher sensitivity rates, highlighting their potential as effective treatment options.

Conclusion: There needs to be a separate antibiotic policy for paediatric patients according to the age group and gender so that age & gender-based antibiotics can be selected for empirical therapy. This will in turn lead to a better antibiotic usage which will be cost effective as well as handle the emerging drug resistant organisms of the Enterobacteriaceae family.

1. Introduction

Paediatric population is challenging when it comes to diagnosis of Urinary Tract Infections (UTI). UTI is one of the most common infections resulting in approximately

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https://doi.org/10.18231/j.ijmmtd.2024.059

5-8% of infants and children requiring inpatient care.[1–3] UTI is the infection involving any part of the renal system from the kidneys to the urethra. It is classically divided into lower UTI and upper UTI. The upper UTI comprises of infections of the kidney and ureter whereas the lower UTI comprises of the infections of bladder and urethra. The clinical presentation in the pediatric population is different from adults and so does the method of sample collection & culture reporting. Infants most commonly present with primarily unexplained fever. Other symptoms may include lethargy, poor feeding, irritability, vomiting, diarrhoea, failure to thrive, cloudy or malodorous urine, crying while passing urine & haematuria. A detailed history, physical examination and correlating the culture findings can help in effective management of UTI. Infants and young children have a higher chance of developing urosepsis following UTI.[4] Older children can give history on the most troubling symptoms like lower abdominal pain, dysuria, urinary incontinence & suprapubic pain. Although theoretically many symptoms have been described none of the sign or symptom or a combination of them is sufficient to identify UTIs without any doubt. Culture & sensitivity is considered as the gold standard for diagnosis of Urinary Tract Infection and takes around 24-48 hours for the results to be available.[5]

The incidence of UTIs is more in female and uncircumcised male infants. This is probably due to the increased bacterial skin flora in use of nappy pads during infancy and shorter urethral distance in female anatomically and foreskin surface area in uncircumcised males.[2] During the toddler years, the toilet training can lead to voluntary holding and bladder stasis. This bladder stasis could be structural due to urogenital abnormalities or functional which can due to a neurogenic bladder, constipation, and behavioural withholding. Other factors include worm infestation, enuresis, wiping from back to front, and urethral instrumentation.[6,7] The most common reason for higher incidence in female patients is the increase in colonization of female perineum by uropathogens. This is mainly helped by the pH of the vagina which ranges about 4.8-5.7 the first week of birth and stabilizes to 7.0-8.0 in 2-6 weeks after birth remaining so till puberty. The pH drops to 3.5-4.5 with onset of menstruation.[8] This is accompanied by the increased adhesiveness of bacteria to vaginal cells and decreased cervicovaginal antibodies. In boys, the preputial space acts as a reservoir. Apart from this, urinary catheterization can introduce the bacteria into the urinary tract and rarely the hematogenous spread can also occur in early months of life and a very small portion can lead to the invasion of the kidney, inflammation, and renal scarring.[9]

The pathogenic virulence factors involved most in the establishment of infections are the Alpha hemolysin, M-hemagglutinin, Bacterial endotoxin, Cytotoxic necrotizing factor 1, K-capsular antigen, a rigid cell wall, and an adhesive capacity which is provided by the type 1 pili, P-fimbriae, and Alpha adhesins. Due to the action of these virulence factors, the bacteria can adhere to the uroepithelium despite the flushing action of urine. Once the uroepithelium has been invaded, slowly there is a biofilm formation which will protect the bacteria against the host defence mechanisms.[10,11]

The risk factors in the host which allow the establishment of UTI are vesicoureteric reflex which allows the bacteria to ascend into the upper renal system and development of post-void residual urine. This is an important risk factor in recurrent UTI and renal scarring. There can be some anatomical obstructions which can lead to stasis and this includes Phimosis, Meatal stenosis, Labial fusion, Posterior Urethral Valves, Urethral strictures, Ureterovesical or Ureteropelvic Junction Obstruction, Renal Stone, Faecal Impaction, Tumor or Cyst. The presence of a foreign body, stone or a catheter provide a nidus for the bacteria to establish and multiply in the renal system. Apart from this, the other risk factors are Parenchymal Renal Anomalies, Dysfunctional Bladder Emptying, Detrusor Muscle Instability, Constipation, Diabetes Mellitus, Immunodeficiency, Obesity and Vitamin D deficiency. The genetic predisposition for recurrent UTI and renal scarring has also been identified and most associated genes are Angiotensin-Converting Enzyme Insertion/Deletion (ACE I/D) gene, Interleukin (IL)-8 receptor CXCR1 and CXCR2 genes, IL-10-1082 A/G gene, heat shock protein 72 (HSPA1B) gene, Transforming Growth Factor (TGF)-β1 gene, Toll-Like Receptor (TLR) pathway genes, and Vascular Endothelial Growth Factor (VEGF) gene.[10,12]

The UTIs in paediatric patients can range anywhere from a mild dysuria to life-threatening urosepsis. These life-threatening complications are more common in neonates. Typically, they can have poor oral intake, dehydration, and sometimes rare complications like perinephric abscess formation and spread of the bacteria from the urinary tract into the bloodstream or into the CSF causing bacteraemia or meningitis. Long term complications following UTI in early childhood are renal injury and scarring leading to renal dysfunction, hypertension, and chronic kidney disease in later years of life. However, the probability of developing long-term complications of UTI induced renal injury is still being debated.[6]

UTI may be caused by any pathogen that colonizes the urinary tract. The causative agent differs based on age, geographic location, and associated comorbidities. E coli is the most frequently isolated uropathogen. Few important other pathogens include *Pseudomonas aeruginosa*, *Klebsiella spp*, *Citrobacter spp*, *Enterobacter cloacae* & *Proteus mirabilis*. Among the gram-positive organisms, *Enterococcus spp*, *Streptococcus group B*, *Staphylococcus aureus*, *Staphylococcus epidermidis* &

Staphylococcus saprophyticus have been documented to cause infections. In immunocompromised children and children with indwelling catheters, *Candida* may be isolated from the urine. Nosocomial infections are typically more difficult to treat and are caused by various organisms which may be drug resistant, including *E. coli*, *Candida*, *Enterococcus*, *Enterobacter,* and *Pseudomonas spp*.[13]

They have been various types of urine collection documented over a period. They can be broadly classified into non-invasive methods and invasive methods. There are three types of non-invasive methods. One is a nappy pad method where the pad is placed inside the diaper and the advantage of this method is that it is convenient and it can be used directly for dipstick screening. But the contamination rates are high and therefore, it is not very reliable for urine culture. The next method is urine bag where the bag is directly fixed over the genitalia. That is also a convenient method, again it is highly unreliable for culture. The third method is the clean catch midstream urine sample collection. The problem is that we must wait till the child voids spontaneously and we should have the correct opportunity to catch hold, to catch off the urine sample. The chances of contamination are comparatively less and some methods to stimulate voiding can increase the success rate of a sample for good culture.

The invasive methods comprise of two main methods, one is using a urinary catheter where the catheter is inserted into the bladder via the urethra and the sample can be obtained. The advantage is it has very less rates of contamination and problem is that the disadvantage is that it is invasive and painful, it requires expertise to catheterize a child. The second method which is again an invasive method is a suprapubic aspiration where a needle is inserted into the bladder through the skin of the lower abdomen above the pubic symphysis and this is the best sample where the levels of contamination are very low and the chance of success can be increased by using ultrasound to ensure the filling of the bladder. The disadvantage is that it is invasive, painful and requires a specialized care for obtaining a suprapubic aspiration sample.

UTI is diagnosed based on urine culture performed on the clean catch Midstream urine sample which after incubation shows Significant number of single type of species along with the presence of clinical signs and symptoms. This can be supplemented with urine analysis showing more than 10 leukocytes per mm^3 in a uncentrifuged sample or more than five leukocytes per high power field in a centrifuged sample. The leukocytes can also be present if the child has glomerulonephritis, Renal stones, or foreign body in the urinary tract. The significance of the number of colony forming units changes with the type of sample. In some cases when the urine sample has been obtained by Supra pubic aspiration any number of colonies formed on culture becomes significant. In the same way Sample obtained via urinary catheter around 1000 – 5000 CFU is treated as significant.[14]

The Importance of diagnosis of paediatric UTI lies in the fact that the renal cortex of young children is prone to renal scarring even after a single episode of UTI. The renal scarring may lead to hypertension and chronic renal failure in the later years of life. Thus, a proper diagnosis and immediate treatment is warranted to prevent long term morbidities in young children.

2. Materials and Methods

This study was conducted at Chettinad Hospital and Research Institute after obtaining the Institutional Human Ethics Committee (IHEC) clearance. All urine samples processed for culture and sensitivity from January 2021 to December 2023 and collected from patients ranging from zero days to 18 years of age, were included in the study. Repeat urine samples were excluded from the study. Sample showing no growth or insignificant growth or more than two types of bacterial colonies were excluded from the study. All patient samples above the age of 18 years were also excluded. Those samples which fit the inclusion criteria were tabulated according to age, gender, bacterial species, and antimicrobial resistance. The antibiotic data was analysed asper the CLSI 2024 guidelines. The above data was collected using the ERP software Sage 300 [previously known AACPAC] after obtaining the requisite permissions from the institution. The samples were divided based on the age group of the patients into four groups comprising of Group I: 0 days to 2 years (Neonates, Infants & toddlers), Group II : 2-5 years, Group III : 6-11years (Middle childhood) & Group IV : 12-18 years (Early adolescence) based on National Institute of Child Health and Human Development guidelines.[15]

3. Results

This retrospective study was conducted to understand the spectrum of bacterial pathogens infecting the paediatric group and the associated antimicrobial resistance. During the study period of 3 years, 7153 pediatric urine samples were received for culture & sensitivity testing in the clinical microbiology laboratory of Chettinad Hospital and Research Institute. Out of these samples, 6060 samples did not show any growth after 48 hours of incubation, or showed less than 10^3 bacterial colonies (insignificant growth) or yielded mixed bacterial growth. These samples were excluded from the study. From the clean catch midstream urine samples received in the laboratory, 1093 isolates or samples which match our study criteria were included in the study and further analysis was carried out. Among the 1093 samples, majority of the samples grew Gram negative bacteria amounting to 80.15% (876 isolates) and 19.85% (217 isolates) of samples grew Gram positive

cocci. Among the gram-negative bacteria, 73.65% (805 isolates) belonged to the Enterobacteriaceae family and 6.5% (71 isolates) belonged to the genus Pseudomonas. Among the Enterobacteriaceae, the major contributor of UTIs in paediatric population was *E. coli* amounting to 41.63% (455 isolates) and the next most predominant isolate was the Klebsiella species of around 12.17% (133 isolates) as shown in (Table 1).

Another interesting fact noted during the study was that among the 19.85% of Gram-positive cocci including *Enterococcus spp*, *Staphylococcus aureus*, Streptococcus spp (217 isolates), 18.21% were *Enterococcus species* (199 isolates). the infection with Enterococci is seen to affect male patients more commonly compared to their female counterparts. The male patients showed about 59% to 81% among the four age groups compared to females in whom 4% to 34.4% Enterococci was isolated. A similar pattern was noted in Proteus species wherein the male patients seem to be affected more compared to females. the male patients from 0 day to 2 years age group were mainly affected by Proteus spp. Similarly, the patients in age group of 0 days to 2 years had a higher incidence of Enterococci infection with slight male predominance.

As most infections were caused by *E. coli* (41.63%) in all four age groups, further analysis was restricted to *E. coli*. Out of the 1,093 samples which showed significant bacterial growth, 455 samples yielded *E. coli* (41.63%). Considering the age wise group distribution of samples showing significant *E. coli* growth, the maximal number of E coli isolates was seen during the 0 to 2 years category (121) among males (26.6%). Among females, it was 102 isolates (22.4%). In the male children, from the age of 2 to 5 years, the isolation of *E. coli* drastically dropped to 5.7% of the isolates which further reduced to 2.6% isolates in the 6 to 11 years age group, followed by a slight increase in the 12-to-18-year age group to 4.6% isolates. Whereas in the female population, there was a drop but around 15% isolates were seen to spread across the 2 to 11 years age group after which a reduction in prevalence of infection was noticed in the 12-to-18-year age group to 8.6%. (Table 2)

When we consider the gender wise distribution among groups, in the 2 to 5 years age group, the male patients showed a slight increase in *E. coli* infections which was around 54.3% whereas in female population it was 45.7%. The male patients had a drastic drop to 28.2% and among the females rate of infection was 2.5 times more at 71.7%. in a similar manner the male population continued to experience a drop in the rate of infections with E coli in the 6 to 11 years age group to around 15% whereas the female population experienced nearly 6 times increased incidence of *E. coli* infections compared to their male counter parts at 85%. In the age group of 12 to 18 years the male population showed on 35% of isolates growing Ecoli whereas in the females, the incidence was nearly double at around 65%. so, the rate of infections although they decrease from the 0 to 2 age group to 12 to 18 years age group the number of infections continue to increase and remain the same which is in line with the literature that the incidence of e coli infections in female population is more compared to the male population.

When we consider the antibiotic sensitivity pattern of the isolates of *E. coli*, Ampicillin, Cephalosporins and Fluroquinolones showed a sensitivity percentage of 17.61%, 36.41% & 45.63% respectively. Among the cephalosporins, cefepime showed the highest sensitivity of 48.29% compared to cefazolin, cefuroxime & cefotaxime (26.01, 33.17 & 38.20). Cotrimoxazole resulted in a total sensitivity of 56.45%. Among aminoglycosides Amikacin showed a sensitivity of 72.06% and Gentamicin showed an overall sensitivity of 82.23%. Piperacillin Tazobactam showed a sensitivity of 88.47%. Among the carbapenems, Imipenem showed an overall sensitivity of 88.37%, and to Meropenem, the overall sensitivity was 94.10%. The urinary antiseptic Nitrofurantoin showed overall sensitivity of 95.66% which is around 94.82% among males and 96.5% among female isolates. In a similar manner, Fosfomycin showed overall sensitivity of 96.86% which is around 95.61% among males and 98.11% among females. The gender wise and age group wise sensitivity pattern is presented in (Table 3).

4. Discussion

UTIs in the paediatric age group are tricky to diagnose, as many of the characteristic clinical features are not always present, and the patient is not able to express their symptoms like the adult patients. Secondly the paediatric patients are at risk of developing renal abnormalities which may affect the child in later stages of life. There is also a risk of recurrent infections which increases the chances of developing hypertension and chronic kidney disease in later stage of life. The initial step of analysing the root cause of UTI is to screen for abnormalities of the urogenital tract, like distended bladder, palpable enlarged kidneys, tight phimosis, urinary incontinence, previous surgery in the urinary tract, anorectal malformation or meningomyelocele. Other factors like shorter urethra and increased chance of Bacterial entry from the in female children higher bacterial skin flora under the nappy in infancy should also be considered.

Urinary sample collection in paediatric patients is more difficult compared to adult patients. But the quality of sample must be reemphasized for obtaining a reliable culture report which reflects the real status of the patient. Samples obtained via Supra pubic aspiration or catheterized samples have a higher probability of revealing true infections. In clinical practise the most obtained sample is the clean catch midstream urine and this sample needs expertise to ensure that only the organism responsible

Table 1: Gender wise distribution of isolates (N- 1093)

Bacterial groups	Group I		Group II		Group III		Group IV		Total
	M	F	M	F	M	F	M	F	
Acinetobacter spp.	10	5	9	12	1	9	2	7	55
Citrobacter spp.	9	6	2	4	1	1	6	5	34
Enterobacter spp.	4	1	3	2	1	4	2	6	23
E. coli	121	102	26	66	12	68	21	39	455
Klebsiella spp.	29	31	8	13	5	16	9	22	133
Morganella	21	3	9	0	3	0	3	0	39
Proteus spp.	34	4	11	1	5	1	3	2	61
Providencia spp.	0	1	2	0	0	0	1	0	4
Salmonella spp.	0	0	0	0	0	1	0	0	1
Pseudomonas spp.	14	3	12	5	12	7	13	5	71
Staphylococcus spp.	1	1	0	0	2	0	0	3	7
Enterococcus spp.	59	31	40	15	26	6	13	9	199
Streptococcus spp.	0	4	0	3	0	1	2	1	11
Total	302	130	122	121	68	114	75	99	1093

Group I: 0-2years, Group II: 2-5 years, Group III: 6-11 years, Group IV: 12 -18 years M: Male F: Female

Table 2: Age & Gender wise distribution of *E.coli* isolates (n-455)

Age in years	Male	Female
0-2	121 (26.59%)	102 (22.41%)
2-5	26 (5.71%)	66 (14.50%)
6-11	12 (2.63%)	68 (14.94%)
12-18	21 (4.61%)	39 (8.57%)

Table 3: Antibiotic sensitivity of *E.coli* (n-455)

	Males				Females			
Antibiotics	I	II	III	IV	I	II	III	IV
Amikacin	68.3	61.5	66.7	71.4	80.2	86.4	68.6	73.3
Ampicillin	6.03	23.1	11.1	15	13	15.2	27.8	29.7
Cefazolin	10	26.9	16.7	25	22.6	25.8	28.4	52.8
Cefuroxime	54.6	26.9	16.7	23.8	27.5	34.9	32.4	48.7
Cefotaxime	22.7	38.5	45.5	20	34.3	45.5	40.3	59
Cefepime	29.5	45.8	60	47.6	43	53.2	42.4	64.7
Gentamicin	68.4	79.2	83.3	90.5	77.2	87.7	85.1	86.5
Cotrimoxazole	52.1	70.8	58.3	61.9	40.6	50	53.7	64.1
Ciprofloxacin	43.4	38.5	58.3	40.9	46.3	36.9	45.5	55.3
Imipenem	93.3	90	100	73.7	83.5	90.6	86.5	89.3
Meropenem	94.3	95.5	100	79	95.5	96.2	92.5	100
Pip-tazobactam	88.3	85.7	91.7	80	87.8	93.7	88.3	92.3
Nitrofurantoin	90.8	88.5	100	100	97.1	94	100	94.9
Fosfomycin	91.5	90.9	100	100	96.8	100	98.4	97.2

Group I: 0-2years, Group II: 2-5 years, Group III: 6-11 years, Group IV: 12 -18 years Values mentioned in percentage

for causing the UTI is identified and antibiotic sensitive reported so that the child is not exposed to unnecessary antibiotics and has a chance of developing antimicrobial resistance due to selection pressure.

As per the national treatment guidelines for antimicrobial usage in common syndromes 2019, 2022 as well as Guidance to antimicrobial therapy published by the Directorate of Medical education & Research, government of Tamil Nadu in the year 2023 clearly recommend Nitrofurantoin & Fosfomycin as first line therapy and the clinical usage of these two antibiotics is a matter of debate.

Nitrofurantoin is known as a urinary antiseptic which is used in the treatment of uncomplicated lower UTIs. It is active against both gram positive and gram-negative organisms. Nitrofurantoin mainly concentrates in the lower urinary tract, has a very low serum concentration and does not affect the bowel flora.

Nitrofurantoin has several mechanisms of action. The most accepted one is that the Nitrofurantoin is taken up by the bacterial intracellular riboproteins which reduce

Nitrofurantoin to reactive intermediates, which bind to the bacterial ribosomes and inhibit bacterial enzymes involved in the synthesis of DNA, RNA, cell wall proteins and other metabolic enzymes.

Nitrofurantoin is contraindicated in patients with clinical suspicion of acute pyelonephritis, pregnant women in the third trimester and in patients above 65 years of age, for the fear of inducing hepatotoxicity, renal toxicity and peripheral neuropathy when used long term. Recent study conducted in paediatric patients with follow-up renal studies showed that oral nitrofurantoin could be effectively used for lower UTI caused by ESBL-producing *E. coli* in paediatric patients without any side effects in paediatric patients.[16,17]

Fosfomycin is a broad-spectrum bactericidal antibiotic. The studies regarding the usage of Fosfomycin are limited but the available studies show promising response even in multidrug resistant bacteria. The drug disseminates in tissues very well and has shown efficacy in experimental biofilm models as well. The antibiotic works well with other antibiotics and has been proven to be safe in children even on prolonged usage. In children it is easy to dose, achieves high concentrations in urine, has no major adverse effects, does not affect the intestinal flora and finally it has an excellent activity against *E. coli* and other Enterobacteriaceae.[18]

5. Conclusion

The outcome of the retrospective study is that *E. coli* has developed mechanisms of resistance against the commonly used drugs in the geographical area and hence antibiotic cycling can be implemented to combat resistance. There are not many antibiotics in the pipeline and the cost of therapy with available antibiotics is on the rise. Our focus must be to provide our patients with affordable and yet reliable options of treatment against the ESBL *E. coli* and other members of the Enterobacteriaceae and hence widening the tunnel vision on usage of antibiotics like Nitrofurantoin & Fosfomycin should be considered after taking up large population studies in paediatric population.

Ideally a separate antibiotic policy for paediatric patients according to the age group and gender can be developed, so that age & gender-based antibiotics can be selected for empirical therapy. This will in turn lead to a better antibiotic usage which will be cost effective as well as handle the emerging drug resistant organisms of the Enterobacteriaceae family.

6. Ethical Approval

This study was conducted after taking approval from the Institute of Ethical Review Committee, reg. no. ECR/1589/Inst/TN/2021.

7. Conflict of Interest

None.

8. Source of Funding

None.

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Cite this article: Sheriff R, Shanmugam P, Alice Peace Selvabai R, Jayakaran J, Thayikkannu AB. A retrospective study on antimicrobial resistance pattern of uropathogenic *E. coli* in rural paediatric population attending tertiary care centre in Tamil Nadu. *IP Int J Med Microbiol Trop Dis* 2024;10(4):350-356.