Original Article

A retrospective study on the microbial spectrum and antibiogram of uropathogens in children in a secondary care hospital in Rural Vellore, South India

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Abstract

Background: Urinary tract infection (UTI) is common among children. Empiric antibiotics have to be started as early as possible or it may lead to an irreversible renal parenchymal damage and renal scarring in children. The objectives were to determine the prevalence and microbial profile of paediatric UTI and to determine the antimicrobial susceptibility pattern. **Methodology:** This is a retrospective study which looked at urine cultures of children below 15 years that were sent during the study period. **Results:** Among the total urine cultures sent only 21.2% showed significant growth of organisms. The most common organism isolated was *E. coli* (75.5%). *E. coli* was least sensitive to cefpodoxime and co-trimoxazole, whereas highly sensitive to nitrofurantoin. Of the total children who had significant growth, 46% had ESBL. **Discussion:** The prevalence of culture-proven UTI among children was found to be 21.2%. The most common organism isolated among the study population was *E. coli* (75.5%) followed by *Enterococcus* species (19.0%) and *Klebsiella* species (14.5%). It was also found that *E. coli* was least sensitive to cefpodoxime (31.6%) and co-trimoxazole (26.3%), moderately to amoxicillin-clavulanate (52.4%), whereas highly sensitive to nitrofurantoin (82.9%). This was similar with the studies done at other secondary care hospitals, in Oman and Oddanchathram, South India. **Conclusions:** With the increasing resistance, cephalosporins should not be used in treating paediatric UTI, whereas nitrofurantoin can be started as an empiric antibiotic, which can later be changed according to the susceptibility pattern.

Keywords: Antibiogram, antibiotic susceptibility pattern, UTI in children

Introduction and Justification

Urinary tract infection (UTI) is one of the most common infections among children. The risk of developing a UTI in childhood is approximately 1-3% in boys and 3-10% in girls.[1] This goes undiagnosed in many cases due to absence of specific signs and symptoms especially in infants and young children.[2] Delay in its diagnosis or inadequate treatment of UTI may cause an irreversible renal parenchymal damage and renal scarring in children which could lead to hypertension and renal failure in the long run.[3]

The prevalence of paediatric UTI differs with age, gender and certain predisposing factors like underlying systemic illness, structural and functional abnormalities of urinary tract like posterior-urethral valves, pelviureteric junction obstruction, neurogenic bladder and vesico-ureteral reflux.[4]

The microbial flora and antibiogram of paediatric UTI also differs from place to place and within the same place

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between different geographical areas.[5] Antimicrobial resistance among uropathogens has increased over the past few decades because of the widespread indiscriminate use, easy availability and over the counter sale of antibiotics.[6] Studies done at other tertiary care centres have shown that the most common organism isolated in children with UTI is *Escherichia coli* and that there is an increased resistance, chiefly, in the ESBL (Extended Spectrum Beta-Lactamase) producing uropathogens.[7,8]

There is plethora of information at the tertiary care level, but there is dearth of published information for the primary care physician and more precisely on UTI in children in India. This makes the management of UTI much more complicated especially in primary and secondary level hospitals, which is mainly due to a lack of accessible, affordable and quality-assured laboratory support with timely reporting. New primary care physicians at rural hospitals also require information for management purposes. Hence, the objectives of the proposed study were to determine the prevalence and microbial profile of paediatric UTI and to determine the antimicrobial treatment options through the susceptibility pattern of organisms causing paediatric UTI in a secondary care centre in South India.

Methodology

This is a retrospective study done in a 140-bedded secondary care hospital, covering a population of 115464, situated in rural Vellore in South India. Children less than 15 years of age, whose urine cultures were sent between January 2014 and December 2018, were included in the study. This included both hospitalized and out-patient cultures. Urine specimens were collected either by suprapubic aspiration method, urinary catheterization or by mid-stream clean catch method. Children on steroids or antibiotics prior to the culture were excluded from the study. The samples were transported to a nearby tertiary care facility for culture as early as possible. The study was approved by the Institutional Review Board (IRB) on 24-06-2020.

A semi-quantitative culture was performed on 7% Sheep Blood agar, Mac Conkey agar and the organisms were identified using conventional biochemical tests. Reports were generated based on the clinical presentation, specimen type, Gram stain microscopy plus culture growth.[9,10]

The growth of organism was considered as significant, only if there were up to two organisms in significant number of colonies. Significant bacteriuria was defined as more than 1,00,000 CFU (Colony Forming Unit)/ml in a mid-stream clean catch specimen, or more than 50,000 CFU/ml in a sample taken by urethral catheterization, or any number of colonies, if sample was collected by suprapubic aspiration. Probably significant bacteriuria was defined as 1000 – 1,00,000 CFU/ml in a mid-stream specimen.[1]

First-line antimicrobials that were tested for susceptibility included, for the Gram-negative bacilli belonging to order *Enterobacterales*, cefpodoxime, co-trimoxazole, nitrofurantoin, ciprofloxacin, amoxicillin-clavulanate and gentamicin, the second line antimicrobials tested were amikacin, piperacillin-tazobactam, cefeperazone-sulbactam, meropenem and imipenem. For *Enterococcus*spp, the first-line antimicrobials tested were ampicillin, nitrofurantoin and high-level gentamicin, the second-line antimicrobials tested were vancomycin, teicoplanin and linezolid. For *Staphylococcus*spp, the first-line antimicrobials tested were cefoxitin, co-trimoxazole, nitrofurantoin, norfloxacin and rifampicin. The second-line drugs were vancomycin and teicoplanin.

The data were maintained and analysed with Microsoft Office Excel 2007.

Results

Total number of urine cultures sent from both hospitalized and out-patients below the age of 15 years, during the study period of 5 years (from January 2014 to December 2018) were 1561.

In our study, 1289 (82.6%) urine cultures were collected by mid-stream clean catch method, 65 (4.2%) were catheter sample and 207 (13.3%) were collected by supra pubic aspiration method. Among the urine cultures that were sent, 888 (56.9%) did not have growth of any organisms and 342 (21.9%) had insignificant CFU. Only 331 (21.2%) of the total urine cultures sent during the study period showed significant growth of organisms.

No gender predilection was found among patients with significant bacteriuria [Table 1].

According to the guidelines given by Indian Society of Paediatric Nephrology (ISPN), significant pyuria was defined as >10 leucocytes per cubic mm in a fresh uncentrifuged urine sample. In our study, among the total urine cultures sent (1561), only 1452 study subjects had been screened with urine uncentrifuged WBCs (White Blood Cells). Out of the 1452 subjects, 1357 (93.45%) had >10 leucocytes estimated manually, in the uncentrifuged urine, of which only 304 (22.47%) had significant bacteriuria and 130 (9.5%) had probably significant bacteriuria [Table 2].

The most common organism isolated was *E. coli* constituting 75.5% (250). This was followed by *Enterococcus*spp 19% (63) and *Klebsiella*spp 14.5% (48) [Table 3].

E. coli was isolated in 250 (75.5%) urines cultures but susceptibility was done only in 244 patients. Out of this, 77 (31.5%) were found to be susceptible to cefpodoxime, 203 (83.1%) were susceptible to nitrofurantoin, 65 (26.6%) were susceptible to co-trimoxazole, 91 (37.2%) susceptible to ciprofloxacin, 128 (52.4%) susceptible to amoxicillin-clavulanate and 132 (54.0%) were susceptible to gentamicin. The second line antimicrobial testing was required in only 32 of 244 patients. Out of this, 32 (100%) were susceptible to amikacin, meropenem and imipenem, 28 (87.8%) to piperacillin-tazobactam and 31 (96.9%) were susceptible to cefeperazone-sulbactam [Table 4].

Enterococcus was the second most common organism in our study 63 (19%). Antimicrobial susceptibility test was done only in 50 patients. Out of this 42 (84%) were susceptible to nitrofurantoin, 20 (40%) to high-level gentamicin and 38 (76%) were susceptible to ampicillin [Table 4].

Klebsiella was isolated in 48 urine cultures. Out of this antimicrobial susceptibility test was done only in 34 patients, which showed that 16 (47.1%) susceptible to amoxicillin-clavulanate, 5 (14.7%) to nitrofurantoin, 19 (55.9%) to co-trimoxazole, 26 (76.5%) to gentamicin, 16 (47.1%) susceptible to cefpodoxime and 24 (70.6%) were to ciprofloxacin [Table 4].

Sensitivity results were available for 302 samples. Among this, 244 samples had *E. coli,* of which 128 (52.45%) were ESBL producing organisms. Among *Klebsiella*, 14 out of 34 samples were ESBL producing organisms (41.17%). Of the total 302 children who had significant growth and whose susceptibility pattern was available, 142 (47%) had ESBL producing organisms.

Discussion

In children, aggressive evaluation and management of the first episode of UTI at an early stage prevents the development of chronic kidney disease and hypertension.[1,11] Hence, empiric antibiotics are to be initiated as early as possible while waiting for the urine culture and susceptibility report. This empiric drug choice to treat the UTI should be based on the local antimicrobial susceptibility patterns.

The prevalence of culture-proven UTI among children in our hospital was found to be 21.2%. Studies with variable prevalence of paediatric UTI ranging from as low as 7.8% in Iran to as high as 26.7% in India have been reported from among tertiary level hospitals.[11-15]

With this similar burden in secondary hospital care, confirming a UTI is the first challenge. Our study showed that only 22.47% of children with significant pyuria in urine microscopy had significant bacteriuria in urine culture, whereas another 9.5% had probably significant bacteriuria. Pyuria although a feature of UTI may appear in other conditions as well.[15] Secondary set ups relying on only a microscopy to guide treatment may inadvertently aid the growing burden of drug resistance. This finding strongly suggests that antibiotics should not be administered based only on urine microscopy alone.[16] Pyuria may be used as a guide to start empiric antibiotics based on the local susceptibility pattern which needs to be altered once the patient's culture and susceptibility reports are available.

Most of the secondary care hospitals lack appropriate laboratory facility for urine cultures. The urine samples for culture have to be transported to another facility.[17] There may be problems not only in storage of such temperature-sensitive samples but also logistic issues in transporting the samples to another facility. There is a need for secondary care hospitals to be better equipped with either culture facility or institution of proper transport systems to transfer the samples within an acceptable time limit.

To understand the treatment of these UTI's, the most common organism isolated among the study population was *E. coli* (75.5%) followed by *Enterococcus species* (19.0%) and *Klebsiella* species (14.5%). This was similar with the studies done at other secondary care hospitals outside of India, in Oman and Oddanchathram, South India.[18,19]

Antimicrobial susceptibility test was done only in 302 (91.23%) patients with significant bacteriuria in our secondary care hospital. This was due to financial constraints.

Table 1: Prevalence of UTI in different age groups and genders

Variables	Category	Significant growth (*n*=331)		No growth/ Insignificant growth (*n*=1230)	
		n	Percent	*n*	Percent
Gender	Male (*n*=781)	166	21.2	615	78.7
	Female (*n*=780)	165	21.2	615	78.8
Age	Neonate (*n*=49)	16	32.7	33	67.3
	29 days-1 year (*n*=709)	176	24.8	533	75.2
	>1 year-5 years (*n*=563)	109	19.4	454	80.6
	>5 Years (*n*=240)	30	12.5	210	87.5

Table 2: WBC count in un-centrifuged urine sample compared to growth of organisms on culture

WBC cells in un-centrifuged urine sample per cubic mm (*n*=1452)		Growth of organisms *n* (%)		
		No growth/Insignificant growth (*n*=998)	Probably significant growth (*n*=136)	Significant growth (*n*=318)
Cell counts				
<10	95 (100%)	75 (78.9)	6 (6.3)	14 (14.7)
10-49	781 (100%)	591 (75.7)	87 (11.1)	103 (13.2)
50-99	241 (100%)	180 (74.7)	21 (8.7)	40 (16.6)
100-999	203 (100%)	111 (54.7)	19 (9.4)	73 (36.0)
>1000	132 (100%)	41 (31.1)	3 (2.3)	88 (66.7)
Total	1452 (100%)	998 (68.7)	136 (9.4)	318 (21.9)

In our study, it was found that *E. coli* was least sensitive to cefpodoxime (31.6%) and co-trimoxazole (26.3%), moderately to amoxicillin-clavulanate (52.4%), whereas highly sensitive to the underutilised drug, nitrofurantoin (82.9%). Despite various studies showing nitrofurantoin as being highly sensitive to *E. coli*, GI intolerance limits its regular use in children. *E. coli* was also found to be highly sensitive to the second line antibiotics like amikacin, piperacillin-tazobactam, cefeperazone-sulbactam, meropenem and imipenem. The increased resistance of *E. coli* to cephalosporins, co-trimoxazole and amoxicillin-clavulanate was also reported in the studies done in secondary care hospitals in Oman and Oddanchathram, South India[18,19] and also in tertiary care hospitals in India as reported by Pooja *et al.* and Lok Bahadur *et al.* Their studies also showed that *E. coli* was highly sensitive to nitrofurantoin.[11,20] Similar findings were reported by Demir *et al.* in a tertiary care hospital in Turkey and Vazouras *et al.* in Greece.[21,22]

*Enterococcus*spp was also found to be highly sensitive to nitrofurantoin (84%) and to ampicillin (73.5%) and high-level gentamicin (73.5%). This was contradictory to the study done in secondary care hospital at Oman, where they found high resistance to ampicillin.[18]

Table 3: Organisms identified (*n*=331 urine samples)

Organism	*n*	Percentage
E. coli	250	75.5
Enterococcus spp	63	19.0
Klebsiella spp	48	14.5
Proteus spp	20	6.0
Pseudomonas aeruginosa	6	1.8
Citrobacter spp	5	1.5
Staphylococcus aureus	5	1.5
Morganella morganii	3	0.9
Non-fermenting GNB	1	0.3

70 samples (21.1%) had 2 organisms in culture

*Klebsiella*spp, was found to be quite highly sensitive to gentamicin (76.5%), ciporofloxacin (70.6%) however, of lowered susceptibility to cefpodoxime (47.0%) and nitrofurantoin (14.7%). This was similar to the study done in Oddanchathram, South India.[19]

There were 52.45% of ESBL producing organisms among *E. coli* and 41.17% of ESBL producing organisms among *Klebsiella*. Of the total 302 children who had significant growth and whose susceptibility pattern was available, 142 (47%) had ESBL producing organisms. This is similar to certain studies done in tertiary care hospitals at Nagpur and Aligarh, India, where ESBL was seen in 48.3%[23] and 42%[24] but is higher than in the studies done at Chandigarh, India and Nepal, where the ESBL producing bacteria were between 35 and 40%.[7,11,12] There was no data available, as per our knowledge, from secondary care hospitals regarding this.

In current practice, oral third-generation cephalosporins (cefixime) are the commonly prescribed empiric antibiotics in UTI in children. This 5-year study shows that the organisms are least sensitive to cephalosporins. Therefore, it may be prudent to best avoid it in the treatment of UTI in children and in its place, the lesser used drug, nitrofurantoin is suggested as the empiric antibiotic option. Treatment may be tailored according to the susceptibility patterns.[11,18-20]

According to several studies, the best response to treatment of UTI with ESBL producing organisms is with carbapenems. According to an RCT (Randomized Controlled Trial) done between 2013 and 2015, in Korea among adult patients, which compared piperacillin-tazobactam (PTZ), ertapenem and cefepime in treating UTI caused by ESBL producing organism, PTZ was found to have higher microbiological response of 94% and this response was comparable to treatment with ertapenem.[25] Thus, currently, with the high treatment costs of carbapenems and PTZ, the variable efficacy of cephalosporins and the side effects due to nitrofurantoin, the available choice

Table 4: Antimicrobial susceptibility pattern among isolated bacterial isolates

Pathogen	*n*	Cefpodoxime	Nitrofurantoin	Co-trimoxazole	Ciprofloxacin	Amoxicillin-clav ulanate	Gentamicin
E. coli	244	77 (31.5%)	203 (83.1%)	65 (26.6%)	91 (37.2%)	128 (52.4%)	132 (54.0%)
Klebsiella spp	34	16 (47.1%)	5 (14.7%)	19 (55.9%)	24 (70.6%)	16 (47.0%)	26 (76.5%)
Proteus spp	16	13 (81.3%)	15 (93.8%)	7 (43.8%)	10 (62.5%)	13 (81.3%)	11 (68.8%)
Citrobacter spp	4	2 (50.0%)	0 (0%)	3 (75.0%)	4 (100%)	3 (75.0%)	4 (100%)
Second line antimicrobials for *E. coli*							
Pathogen	***n***	**Amikacin**	**Piperacillin-Tazobactam**	**Cefeperazone-Sulbactam**	**Meropenem**	**Imipenem**	
E. coli	32	32 (100%)	28 (87.8%) 4 IS*	31 (96.9%)	32 (100%)	32 (100%)	
Pathogen	***n***	**Amikacin**	**Cefoperazone-sulbactam**	**Ceftazidime**	**Levofloxacin**	**Tobramycin**	**Piperacillin-Tazobactam**
Pseudomonas aeruginosa	6	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)
Pathogen	***n***	**Nitrofur antoin**	**High level Gentamicin**	**Ampicillin**			
Enterococcus species	50	42 (84.0%)	20 (40.0%)	38 (76.0%)			

*Intermediate susceptible

of antibiotics in a secondary care hospital to treat paediatric UTI is limited.[18,19]

Conclusion

In a resource-limited setting, it is essential to have a point of care culture facility in secondary care hospitals, to understand the burden of infections, spectrum of organisms we are dealing with and to choose the correct antibiotics. If significant pyuria in urine microscopy alone is used as an indicator of urinary tract infection in children, then it may lead to unnecessary use of antimicrobials.

In the secondary care hospitals, with the increasing levels of antimicrobial resistance, it is worthwhile doing antimicrobial susceptibility testing prior to prescribing antibiotics, which not only helps to choose and tailor the empiric antibiotics but also helps in decreasing the resistance of organisms. The susceptibility pattern allows a primary care physician to administer geographically relevant empiric antimicrobials in the age of growing resistance. This study reinforces the scope for improvement in terms of sample collection, storage and transport at the primary care level.

In the current scenario, with the increasing resistance, cephalosporins should not be used in treating UTI in children whereas nitrofurantoin, being the most sensitive antibiotic can be started as an empiric antibiotic, which can later be changed according to the susceptibility pattern.

Limitation

The study has focussed on the burden of antimicrobial resistance. Thus, the clinical presentations have not been described.

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Conflicts of interest

There are no conflicts of interest.

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