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Etiological profile and antibiotic sensitivity pattern of uropathogens in children at a teaching hospital, Thrissur

Catherine Simon[1], Parvathy VK[2], Liaquat Roopesh Johnson[3*], Rajany Jose[4]

Affiliation: 1Assistant Professor, Dept. of Community Medicine, Azeezia Institute of Medical Sciences and Research, Kollam ,2Professor and Head of Dept. of Paediatrics, Amala Institute of Medical Sciences, Thrissur,3Associate Professor, Dept. of Community Medicine, Azeezia Institute of Medical Sciences and Research, Kollam.4Associate Professor, Dept. of Community Medicine, Government Medical College, Thrissur

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***Author for correspondence**: Dr. Liaquat R. Johnson, Associate Professor, Dept. of Community Medicine, Azeezia Institute of Medical Sciences and Research, Meeyyannoor PO, Kollam, Kerala 691537. E-mail: liaquat99@gmail.com

Abstract

Background: Urinary tract infection (UTI) is very common among community-based and hospitalized children. Approximately 3-8% of girls and 1% of boys are diagnosed with UTI, and may lead to serious complications if not treated appropriately. Empirical treatment of UTI with antibiotics leads to antibiotic resistance. The choice of antibiotics should be based on a basic knowledge about current causative uropathogens and their susceptibility patterns. **Objectives:** To determine the aetiologic profile and antibiotic susceptibility of uropathogens in children at a teaching hospital. **Methodology:** A record-based retrospective study was conducted using a total of 129 positive urine culture and sensitivity reports (bacterial count $\geq 10^5$ CFU / ml of urine) of children with suspected UTI between February 2011 and January 2012 at a teaching hospital in Thrissur. Data were entered using Microsoft Excel 97, and analyzed by Epi-Info, EZR. **Results:** E. coli (2(63.6%)) and Klebsiella(23(17.8%))were the commonest uropathogens followed by Enterococci (8.5%) and Proteus (6.2%). Infants (54(41.9%)) were more frequently affected than the older age-groups. More males (74(57.4%)) were affected as compared to females. E.coli isolates were found predominantly in boys while Klebsiella isolates were more frequent in girls. Over 80% of both isolates were sensitive to Amikacin, Cefoperazone and Piperacillin-Tazobactam while >70% were sensitive to Gentamicin and Nitrofurantoin. Klebsiella also showed more than 80% sensitivity to Ciprofloxacin and Norfloxacin. Both organisms were highly (>90%) resistant to ampicillin. **Conclusion:** E.coli was the commonest uropathogen, followed by Klebsiella. Treatment strategies and antibiotic policy should be informed by the etiology and sensitivity patterns of uropathogens.

Key-words: Urinary tract infection, etiology, antibiotic sensitivity, children

Introduction

Urinary tract infections (UTI) are one of the most common bacterial infections seen in children. It has been estimated that UTI are diagnosed in 1-2% of boys and 3-8% of girls.[1-5] Although the true incidence of urinary tract infections (UTIs) in children is difficult to estimate, they are one of the most common bacterial infections seen by paediatricians. Except for the first 8 to 12 weeks of life, when infection of the urinary tract may be secondary to a haematogenous source, UTI is believed to arise by the ascending route after entry of bacteria via the urethra.[6]

Approximately 3% of prepubertal girls and 1% of prepubertal boys are diagnosed with UTI, and is a major cause of morbidity, that may lead to urosepsis, urolithiasis, permanent renal parenchymal damage, HTN and end-stage renal disease if not treated appropriately.[7-10] The fact that 30% of children with urinary tract anomalies first present with a UTI, underscores the importance of appropriate early management.[11] All age groups, and both hospitalized and non-hospitalized individuals are affected by UTI, often with serious impacts on their socioeconomic life. It accounts for a large proportion of antibacterial drug consumption and treatment failure due to increasing resistance to common antibiotics.[1,6,12] UTI is a major public health problem worldwide that is commonly encountered in medical practice. However, in resource-poor settings, its treatment is usually empiric due to the high cost and long duration required for culture and antibiotic susceptibility testing.[13] In most cases, family physicians provide empirical treatment without the benefit of a pre-therapy urine culture.[6] Nevertheless, the use of an appropriate antibiotic is essential to prevent development of long-term complications.[14]

In developing countries, area-specific monitoring studies about the aetiopathogenesis of UTI and their resistance patterns can help clinicians to choose the correct empirical treatment.[1] Moreover, since antibiotic resistance in children hospitalized with UTI is high, susceptibility testing should be carried out periodically on the clinical isolates and the empirical antibiotic treatment should be altered accordingly.[15] With the problem of antimicrobial resistance on the rise,[16] a knowledge of antibiotic susceptibility pattern is essential for successful eradication of invading pathogens and evaluation of effective therapeutic options at the primary health care level.[1,2,12,15,16] Even in a single geographical area, antibiotic sensitivity patterns change over time.[17-19] Ideally, continuous regional surveillance should be performed to detect these changes.[9] However, this may not be feasible due to various practical and logistical reasons. Serial measurements offer a less resource-intensive alternative to continuous surveillance.[18] Thrissur is the cultural capital of Kerala, and boasts of several tertiary care institutions. Although there is a recent interest in studying antibiotic sensitivity patterns of uropathogens, there is scant past data for comparison. It is in the above-mentioned context that this study was conducted at a teaching hospital in Thrissur with the following objectives:

1. To determine the aetiologic profile of uropathogens in children at a teaching hospital.
2. To assess the antibiotic susceptibility pattern of the causative uropathogens.

MATERIALS AND METHODS

Study design: A record based retrospective study of urine culture and sensitivity reports of children who had presented with symptoms of UTI at the paediatrics department of a teaching hospital in Thrissur.

Study setting: A 1000 bedded (teaching) hospital in Thrissur district of central Kerala.

Study period: Data was collected during September 2012 to October 2012 to assess the culture and sensitivity reports of uropathogens in children with UTI, pertaining to a one-year period from 1st February 2011 to 31st January 2012. **Study procedure:** There were 129 positive urine culture and sensitivity reports of pediatric patients with UTI, pertaining to the above-mentioned period were obtained from among 477 urine samples given for testing. **Ethical considerations:** Ethical approval was obtained from the institutional ethics committee. Permissions for the study were obtained from the departments of Paediatrics and Microbiology. All data were coded to exclude personal identifying information, and stored in a password protected computer. Access to the data were restricted to the investigators. **Inclusion criteria:** Positive urine culture reports of children attending the paediatric out-patient (OP) or in-patient (IP) department with suspected UTI were included in this study. Based on the fact that five bacteria per HPF represents roughly 100,000 colony-forming units (CFU) per ml, which is the classic diagnostic criterion for asymptomatic bacteriuria and certainly compatible with UTI. A reported bacterial count of $\geq 10^5$ CFU / ml of urine was therefore considered as the cut-off for a positive urine culture.[20]

Statistical analysis: Age-wise data of all 129 paediatric patients who had tested positive for urine culture were collected and the prevalence of the uropathogens and their antibiotic susceptibility pattern was tabulated by noting their frequency and percentage. Data entry was done using Microsoft Excel 97 and the results were analyzed by using Epi-Info Statistical package Version 16 and EZR (version 1.36) [R Commander version 2.4-0; R version 3.4.1].[21] The Chi-square test was applied to determine whether there was any statistically significant difference in sensitivity between the various drug classes ($p < 0.05$) for the two most common uropathogens in this study, namely E. coli and Klebsiella at the 5% level.[22,23]

RESULTS

Out of a total of 477 urine samples that were collected during a one-year period from January 2011 to February 2012, there were 129 urine samples that were reported to be culture positive (bacterial count $\geq 10^5$ CFU / ml of urine). Among the 129 children study subjects who were culture positive, there were 73 (57.4%) males and 56 (42.6%) females. Their age-wise distribution showed that the majority (54) of the culture-positive urine samples were those of infants, while 41 samples belonged to children in the 1– 5 year old age-group and the remaining 34 were those of children above 5 years of age **(Table 1).**

Table 1: Age-wise distribution of study subjects

Age in years	Frequency	Percentage
Up to 1yr	54	41.90%
1 – 5 yrs	41	31.80%
> 5 yrs	34	26.30%
Total	**129**	**100%**

Table 2: Frequency of uropathogens in study subjects

Organism	Frequency	Percentage
Escherichia coli	82	63.60%
Klebsiella	23	17.80%
Enterococci	11	8.50%
Proteus	8	6.20%
Staphylococcus	4	3.10%
Pseudomonas	1	0.80%
Total	**129**	**100%**

In this study, there were six different types of uropathogens that were isolated, namely Escherichia coli (E. coli), Klebsiella, Enterococci, Proteus, Staphylococcus and Pseudomonas. The most common uropathogen was E. coli which was found in 82 (63.6%) children, followed by Klebsiella in 23 (17.8%), Enterococci in 11 (8.5%) and Proteus in 8 (6.2%) of the patients. Staphylococcus was responsible for 4 cases of UTI while there was only a single case of UTI due to Pseudomonas (**Table 2**).

Table 3: Age-wise distribution of uropathogens

Organism	< 1 yr n (%)	1-5 yrs n (%)	> 5 yrs n (%)
Eschericia coli	34 (63%)	29 (70.7%)	19 (55.9%)
Klebsiella	11 (20.4%)	6 (14.6%)	6 (17.7%)
Enterococci	7 (13%)	3 (7.3%)	1 (2.9%)
Proteus	1 (1.8%)	2 (4.9%)	5 (14.7%)
Staphylococcus	1 (1.8%)	0	3 (8.8%)
Pseudomonas	0	1(2.5%)	0
Total	**54**	**41**	**34**

The ages of the children with positive UTI reports were stratified into 3 groups (>1 year, 1-5years and >5 years) so as to indicate the age-wise distribution of uropathogens. It was noted that E. coli was the most common organism followed by Klebsiella and Enterococci. Even among infants, the most common uropathogen was E. coli which was found in 34 (63%) of infants, followed by Klebsiella in 11 (20.4%) and Enterococci in 7 (13%) infants. Proteus and Staphylococcus isolates were found in 5 (14.7%) and 3 (8.8%) respectively, of samples from among the older age group (>5 years) as compared to the younger age-groups. (**Table 3**).

Table 4: Antibiotic susceptibility pattern of uropathogens

Antibiotic susceptibility	E.coli (n=82)		Klebsiella (n=23)	
	S* %	R** %	S* %	R** %
Nitrofurantoin	97.1	2.9	75	25
Amikacin	95.7	4.3	94.1	5.9
Piperacillin + Taxobactam	90.5	9.5	91.7	8.3
Cefopirazone	85	15	100	0
Gentamicin	76.8	23.2	70	30
Ciproflox	57.4	42.6	87.5	12.5
Ceftrioxone	55.1	44.9	52.6	47.4
Norflox	52.7	47.3	82.4	17.6
Cefpirome	52.2	47.8	55.6	44.4
Bactrim	51.4	48.6	56.5	43.5
Cefotaxim	50.9	49.1	41.2	58.8
Cefuroxime	46.4	53.6	27.5	72.5
Cefixime	46.4	53.6	37.5	62.5
Cefazolin	27.6	72.6	60	40
Ampicillin	9	91	4.8	95.2

S* : Sensitive; R** : Resistant

Data on antibiotic susceptibility showed that E. coli was highly sensitive to Nitrofurantoin (97.1%), Amikacin (95.7%), Piperacillin + Tazobactam (90.5%), Cefoperazone (85%) and Gentamicin (76.8%).

Klebsiella was found to be highly sensitive to Cefopirazone (100%), Amikacin (94.1%), Piperacillin + Tazobactam (91.7%), Ciprofloxacillin (87.5%), Norfloxacillin (82.4%), Nitrofurantoin (75%) and Gentamicin (70%). On the other hand, both E. coli and Klebsiella were highly resistant to Ampicillin (91% and 95.2% respectively). It was noted that E.coli was also resistant to Cefazolin (72.6%) while Klebsiella showed resistance to Cefuroxime (72.5%). The susceptibility of E.coli and Klebsiella to other antibiotics such as Ciprofloxacin, Ceftrioxone, Norflox, Cefpirone, Bactrim, Cefotaxim, Cefuroxime and Cefixime were in the intermediate range of 45% to 55% (**Table 4**).

To find out the association between antibiotic sensitivity of uropathogens and class of drugs, the urinary antibiotics tested in this study were classified and grouped as follows: Nitrofurans (eg. Nitrofurantoin), Aminoglycosides (eg. Amikacin and Gentamicin), Cephalosporins (eg. Cefopirazone, Ceftrioxone, Cefpirome, cefotaxim, Cefuroxine, and Cefixime), Fluoroquinalones (eg. Ciprofloxacin, Norfloxacin), Extended spectrum Penicillins (eg. Piperacillin+Tazobactam), Oral Penicillin (eg. Ampicillin) and Sulpha combinations (eg. Bactrim). The details of statistical analyses to determine if there is any difference in sensitivity among the various groups of antibiotics for the two commonest uropathogens, E.coli and Klebsiella, are presented in Table 5. Statistically, there was a highly significant difference ($p < 0.0001$) in sensitivity between drug classes for both E. coli and Klebsiella.

Table 5: Association between antibiotic sensitivity of uropathogens and drug class

Antibiotic class	E. coli		P value	Klebsiella		P value
	S* n (%)	R** n (%)		S* n (%)	R** n (%)	
Nitrofurans (Nitrofurantoin)	80 (10.9%)	2 -0.40%		17 -7.90%	6 -4.60%	
Aminoglycosides	141 (19.2%)	23 -4.60%		38 - 17.70%	8 -6.20%	
Extended spectrum penicillins	74 (10.1%)	8 -1.60%		21 -9.80%	2 -1.50%	
Cephalosporins	299 (40.8%)	275 (55.3%)	<0.0001	86 -40%	75 -57.70%	<0.0001
Fluoroquinolones	90 (12.3%)	74 -14.90%		39 - 18.10%	7 -5.40%	
Sulphonamides (Combination)	42 (5.7%)	40 -8.00%		13 -6.00%	10 -7.70%	
Penicillin (Ampicillin)	7 -1.00%	75 -15.10%		1 -0.50%	22 -16.90%	
Total	**733 (100%)**	**497 (100%)**		**215 (100%)**	**130 (100%)**	

DISCUSSION

In this retrospective record-based hospital study conducted during September to October 2012, there were a total of 129 culture-positive urine sample reports (with bacterial count $\geq 10^5$ CFU / ml of urine), of children who had attended the paediatric department of a teaching hospital in Thrissur.

The majority (54) culture positive urine samples were those of infants, followed by those in the older age groups. The sex-wise distribution of UTI indicated a higher prevalence (57.4%) among male children as compared to females (42.6%). A higher prevalence of UTI in boys in the first year of life is consistent with another study wherein boys had higher UTI rates during infancy and majority of the UTI in boys occurred in the first three months of life.[24] Both the patients' age and gender are significant factors in determining the etiology of UTI and can increase accuracy in defining the causative uropathogen as well as provide useful guidance for empiric treatment.[25]

The most common uropathogens in our study were Escherichia coli (63.6%) and Klebsiella (17.8%), followed by a few cases of Enterococcus, Proteus, Staphylococcus and Pseudomonas. Similar findings were also observed in several other studies.[6,12,25,26] Gram negative organisms are the most commonly isolated organisms, with E. coli accounting for 70 to 90% of infections.[27] Studies carried out in infants and children to determine the type of organisms causing UTI have shown that E. coli was the most commonly cultured organism followed by other organisms including Klebsiella, Pseudomonas, Proteus and Enterobacter.[28]

In a retrospective hospital-based study of urine culture records of patients diagnosed with UTI in Singapore, the commonest organism isolated for all age groups and gender was Escherichia coli (74.5%) followed by Klebsiella (8.7%).[29] In a community-based study,[30] of urine culture and sensitivity reports from outpatients clinics of an urban area of north Italy over a 22-month period, it was seen that E. coli accounted for 67.6% of all isolates, followed by Klebsiella pneumoniae (8.8%), Enterococcus faecalis (6.3%) and Proteus mirabilis (5.2%). This trend was also noted in an 11-year analysis of prevalent uropathogens and the changing pattern of antibiotic resistance by E coli in a community-based study at Dublin, wherein the prevalence of E. coli was seen to be increasing in recent years in community UTIs with 70.4 % of UTIs in the community caused by E. coli in 2009.[31]

Our study on antibiotic susceptibility showed that the most common uropathogen namely E. Coli was highly sensitive to Nitrofurantoin (97.1%), Amikacin (95.7%), Piperacillin + Tazobactam (90.5%) and Cefoperazone (85%), along with moderate sensitivity to Gentamicin (76.8%). Klebsiella, the second most common uropathogen in this study, showed a high degree of sensitivity to Cefapirazone (100%), Amikacin (94.1%), Piperacillin +Taxobactam (91.7%), Ciproflox (87.5%) and Norflox (82.4%) with considerable sensitivity to Nitrofurantoin (75%) and Gentamicin (70%). Similar findings of high susceptibility of E. coli and Klebsiella to Amikacin, Nitrofurantoin, Piperacillin + Tazobactam and Gentamicin have been reported from many studies.[6,12,15,16,20,24,32]

Most cases of UTI are uncomplicated, and family physicians may thus provide empirical treatment for these patients without the benefit of a pre-therapy urine culture. Ideally, antibiotics have to be given for seven days and the child reviewed after two days.[33] Guidelines for the management of UTI and appropriate empirical therapy rely on the predictability of these agents causing the infection and knowledge of their antimicrobial susceptibility patterns. Empiric selection of antimicrobial agents should be based on the antibiotic sensitivity pattern of the uropathogens prevalent in that area, which is derived from epidemiological studies carried out in that environment. This must be guided by clinical evidence as well as the safety profile and appropriateness of the drug.[34] Nitrofurantoin has been used for more than five decades for the treatment of uncomplicated cystitis and it was found to remain active against most of the uropathogens. Recent data suggests that nitrofurantoin has retained a good amount of sensitivity (90.98%) against both E. coli and Klebsiella. The absorption of oral nitrofurantoin is 40-50% and is enhanced when taken with food. The drug has minimal side effects and can be safely used for the treatment of uncomplicated cystitis even during pregnancy.[35] Even though antibiotics such as Amikacin, Cefaperazone, Gentamicin were also found to be highly sensitive, they are injectable drugs and therefore, are used more often in hospital settings than in the community, thereby increasing the risk of development of resistant strains in the hospital surroundings.[36]

In this study, both E. coli and Klebsiella were found to be highly resistant to Ampicillin (91% and 95.2%) respectively, and this trend was observed in many other studies with varying degrees of resistance.[28-31] More importantly, a similar pattern has been recently reported from the same geographical area where this study was conducted. However, the resistance of Klebsiella to ampicillin was 100%. There was a reduction in sensitivity of E. coli to Nitrofurantoin, from 97.5% in this study, to 90% in the other study.[37] This change would not have been identified without the benefit of the findings of this study, and underlines the need for suitable baseline data. Both E.coli and Klebsiella showed varying degrees (40-60%) of moderate resistance to antimicrobials such as Ceftrioxone, Cefpirone, Bactrim, Cefotaxim, Cefuroxime and cefixime. A cut-off point of 20 % has been suggested as the level of resistance at which an agent should no longer be used empirically.[33]

The fact that both E. coli and Klebsiella showed the highest resistance (more than 90%) to Ampicillin is an indicator of the increasing rate of antibiotic resistance to the commonly prescribed antimicrobial agents and is a matter of concern. The antibiotic resistance pattern of the two principal UTI pathogens, E. coli and Klebsiella appears in general to be as that found in other parts of India and the globe.[39-41] but the trend of antibiotic susceptibility pattern has to be detected periodically to select appropriate treatment regimen and especially to identify those children at risk for recurrent UTI in developing countries through referring children with two or more UTI episodes in the past year for definitive urine testing and paediatric consultation.[33]

Limitations of the study:

This study was hospital-based, and so the results may not be generalized to the community at large.

Being a retrospective study that was limited to one particular teaching hospital may have lead to bias. Since the method of collection of urine has not been clearly specified, there may have been errors in the urine susceptibility results.

Conclusion:

The results of our study have indicated that E. coli and Klebsiella are the main aetiological agents in paediatric UTI in a tertiary care hospital in central Kerala. Even though the role of these two uropathogens as major contributors in UTI children has not changed, their antibiotic susceptibility pattern has changed considerably. Our study has revealed a high statistically significant difference in the susceptibility (<0.0001) between the different drug groups for the two predominant uropathogens namely E. coli and Klebsiella. Drugs such as Ampicillin and Bactrim which were frequently used in the treatment of UTIs are now showing considerable resistance. To avoid this situation, surveillance of antibiotic resistance patterns should be done periodically and an antibiotic policy should be made accordingly. This will facilitate the introduction of appropriate changes in the effective management of UTI in general, and in children in particular. Among the oral urinary antibiotics, Nitrofurantoin has been found to be highly effective against both E. coli and Klebsiella and can be considered as an appropriate drug for empiric treatment of UTI, while awaiting the culture and sensitivity results.

Recommendations:

The aetiology and resistance patterns of organisms in UTIs are not predictable, necessitating reappraisal by culture and sensitivity testing from time to time. Since the antibiotic sensitivity pattern of uropathogens is changing, it must be taken into account when selecting treatment plans. Antibiotic policies should be formulated as per local surveillance data.

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