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ORIGINAL ARTICLE

Etiology, Sensitivity and Resistance Pattern of Urinary Tract Infection Among Children (0 To 16 Years)

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ABSTRACT

Objective: To determine etiology, sensitivity and resistance pattern of urinary tract infection in pediatrics age group 0 to 16 years at tertiary care hospital.

Methodology: It was a cross-sectional study conducted inPediatric department of Aga khan university hospital and its affiliated secondary care centers in Karachi and Hyderabad. All urine culture proven children aged 0-16 years were included in the study. Urine culture showed growth of single pathogen and pathogen had more 10,000 colonies. Urine samples were obtained by SPA, clean catch, urinary catheter. Pre-designed proforma was used to note down the etiology and resistance pattern of urinary tract infection. SPSS version 25 was used to analyse data.

Results: Of 177 patients, 70.1 % were females and 29.9% were males. Most common organism was E.coli 71.2% (n=126) followed by Klebsiella pneumonia 16.9% (n=30). Proteus Mirabilis 6.8% (n=12), and Pseudomonas aeruginosa 5.1% (n=9). Most common organism E.coli was 78% and 72.7% sensitive to nitrofurantoin and amikacin respectively and 85.1%, 91.4% and 77.3% resistance to ceftriaxone, ciprofloxacin and ampicillin respectively. This study will help in choosing choice of antibiotic on empirical basis for better outcome in resources limited setting like in remote areas and reduced financial burden on community.

Conclusion: E.coli was the most common bacterial isolates among children with UTI. Nitrofurantoin and Amikacin showed higher sensitivity against E.coli., while Ciprofloxacin, Ceftriaxone and Ampicillin showed high resistance against E.coli.

Keywords: Bacterial resistance, E.coli, urinary tract infection, paediatric population, antimicrobial sensitive

INTRODUCTION

A urinary tract infection (UTI) is defined as the presence of actively proliferating bacteria in the urinary system.[1] The incidence of UTI among children is reported to be 30% all over the world [2, 3] Almost 50% of the children with UTI remained misdiagnosed due to lack of standard therapeutic guidelines and treated with empirical antimicrobial therapy.[4]The inappropriate use and dosage of antibiotic, cause treatment failure and increased antibiotic resistance.[4]As a result, recurrent UTIs can lead to consequences, such as chronic renal failure, hypertension, and renal scarring.[3, 5]In addition, urinary tract abnormalities and antibiotic use are possible risk factors for antibiotic resistance.[5]

Even though there are regional variations, resistance to antimicrobials used in empirical treatment of UTIs is gradually increasing all around the world and in Pakistan as well.[5, 6] In Nepal, E.coli shows the highest resistance to ampicillin and cephalexin (87%).[7] In Brazil, Trimethoprim-Sulfamethoxazole shows 51% resistance to E.coli.[8] In Iran, E. coli had a sensitivity of 79.7% to amikacin, 77.1% to ciprofloxacin, and 83.5% resistance to ampicillin.[9] Danger of antibiotic resistance is spreading across the world, ranging from America to Australia. As per CDC, antibiotic-resistance caused a minimum of 2.8 million infections and 35,000 deaths only in the US. A study of trends of AMR in Europe observed that GNR uropathogens showed significant resistance to the most commonly used antibiotics. A north-to-south gradient in AMR exists in Europe, with higher resistance among southern European states like Greece, Cyprus, France, and Italy. One study from Asia pacific, showed "reduced sensitivity to commonly prescribed antibiotic including advanced-generation cephalosporin, piperacillin-tazobactam, and levofloxacin, among the studied gram-negative pathogens -While in Pakistan, E. coli shows 100% resistance to cotrimoxazole, 95% to ampicillin and 91% resistance to amikacin.[6]

Antibiotic resistance is a global problem that the WHO has classified as an emerging disease.[10] However, judicious use of antibiotics can effectively combat bacterial resistance. As a result, it is recommended that microbiological analysis and antibiotic sensitivity testing of urine samples be performed on a regular basis in a specific geographic location.[5] This study would help pediatricians in implying the judicious use of broad spectrum antibiotics and choosing suitable antibiotic empirical therapy according to the local prevalence of pathogens and their antimicrobial resistance pattern. This research will aid pediatricians in recommending the prudent use of broad-spectrum antibiotics and selecting appropriate antibiotic empirical therapy based on the local prevalence of pathogens and their antimicrobial resistance patterns.

METHODOLOGY

It was a cross-sectional study carried out from September 2018 to March 2019 at the pediatric ward and outpatient department of Aga Khan University Hospital (AKUH) Karachi and its secondary care hospitals at Karimabad, Hyderabad, and Garden.By using WHO sample size calculator takings statistics for pseudomonas11.6%[11], margin of error as 4.72% and 95% confidence level. The calculated sample size came out as 177.Children aged 0-16 years who had any symptoms (fever > 38 degree Centigrade, dysuria increased urinary frequency, abdominal painand back pain (Wong baker pain scale >4) hematuria, new day time incontinence or asymptomatic child withculture proven urinary tract infections were included in the study. Children with congenital renal anomalies andchildren having neurological disorders (like cerebral palsy CP, neurogenic bladder, spinal deformities) were excluded from the study. Non-probability consecutive sampling technique was employed.

After taking approval of study from ethical review committee of AKUH and informed consent from parents or guardians, eligible children were enrolled in the study. Urine samples were obtained from children by SPA, clean catch, and urinary catheter. Urine culture showed growth of single pathogen and pathogen had more 10,000 colonies.Data regarding age, gender, etiologic agent and antibiotic resistant pattern were obtained. All research was conducted under supervision of experience fellow consultant paediatrician and data was recorded in designed Performa.

Antimicrobial sensitivity, intermediate sensitivity, and resistance were categorised using CLSI 2016 standards.[12] Sensitivity: This category showed that antibiotic dosages prescribed to treat infection inhibited isolates. The susceptible breakpoint for Ampicillin, Amikacin, and Nitrofurantoin is >17 mm, for Ceftriaxone>23 mm, Ciprofloxacin>21 mm, and for

Pseudomonas susceptible breakpoint for amikacin is >17 mm and Ciprofloxacin>21 mm in Enterobacteriaceae (E.coli, Klebsiella, and Proteus) disc diffusion method zone diameter. Intermediate: Isolates in this group required a higher dose of antibiotic than the MIC to halt bacterial growth. The intermediate breakpoint for Ampicillin 14-16 mm, Amikacin 15-16 mm, ceftriaxone 20-22 mm, ciprofloxacin 16-20 mm, Nitrofurantoin 15-16 mm, and for Pseudomonas intermediate breakpoint for amikacin is 15-16 mm, and for ciprofloxacin 16-20 mm in the disc diffusion method zone diameter interpretative criteria for Enterobacteriaceae (E.coli , Klebsiella, Proteus). The resistant category indicated that isolates were not inhibited by the prescribed antibiotic dose to treat infection. Enterobacteriaceae (E.coli, Klebsiella,, Proteus) disk diffusion method zone diameter interpretative criteria, the resistance breakpoint for amikacin and nitrofurantoin is <14 mm, ceftriaxone <19 mm, Ciprofloxacin is <15 mm and ampicillin <13 mm. For Pseudomonas resistance breakpoint for amikacin is <14 mm and ciprofloxacin is <15 mm.

Data was analyzed using SPSS version 23. Mean and SD was reported for age. Frequency and percentage were reported for gender, resources, mode of collection, etiology and susceptibility pattern of antibiotics. Bacterial isolates were also compared with susceptibility pattern of antimicrobials using cross-tabulation. Bacterial isolates were stratified with respect to age and gender. Post-stratification chi-square/Fisher exact test was applied. A p-value≤0.05 was considered as statistically significant.

RESULTS

A total of 177 urine samples from children were obtained during the study period. Of 177 patients, 124 were girls (70.1%) and 53 were boys (29.9%). The mean age was 4.31±4.82 years. Most of the children of age 0-2 years were affected (n=91, 51.4%), followed by age group 3-12 years (n=69, 39%) and the least affected age group was 13-16 years (n=17, 9.6%), respectively. About 122 samples were collected from outpatient department (68.9%) and 55 samples were collected from inpatient department (31.1%). About 172 samples were received via clean catch or mid-stream urine (97.2%) and only 5 samples were taken from catheter.

E.coli (n = 126, 71.2%) was the most common microorganism followed by Klebsiella pneumonia (n = 30, 16.9%). The details of microorganisms are displayed in fig 1.

The microorganism profile with respect to age groups and gender are detailed in Table 1. The proportion of Protens Mirabilis was significantly higher in children of age>2 years as compared to children aged 0-2 years (p=0.001). While, proportion of Klebsiella Pneumonia was significantly higher in infant as compared to children aged>2 years (p=0.038). The difference between males and female in the frequency of positive samples of each agent was analysed. The proportion of E.coli was significantly greater in females as compared to males (p=0.013), whereas, proportion ofPseudomonas Aeruginosa was significantly less among females as compared to males (p=0.022).

Antibiotic susceptibility showed variable pattern of resistance. About 77.3% of E.coli were resistant to ampicillin, 91.4% to ciprofloxacin, 50% to amikacin 50%, 85.1% to ceftriaxone, and 24.2% to nitrofurantoin 24.2%. Klebsiella Pneumonia isolates resistance to amikacin was 41.7%, ciprofloxacin 6.2%, ceftriaxone 15%, and nitrofurantoin 27.3%. Isolates of Proteus Mirabilis 37% resistance to ampicillin followed by nitrofurantoin 30.3%. Strains of pseudomonas were sensitive to Amikacin 5.5%, ampicillin 25.9%, ciprofloxacin 9%, and ceftriaxone 12.7%, no sensitivity but resistance of 18.2% to nitrofurantoin, respectively. (Table 2)

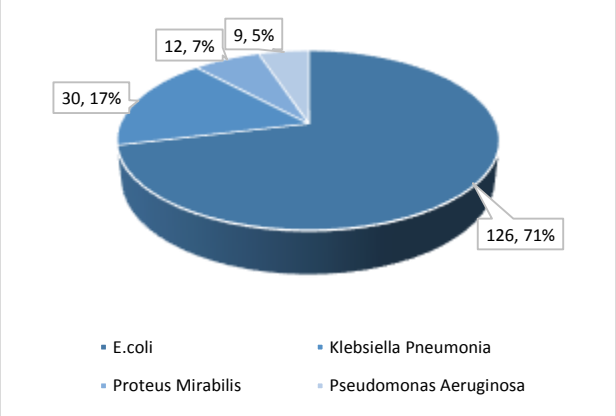

Figure 1: Frequency distribution of bacterial isolates from urine samples of children

Table 1: Distribution of bacterial isolates from urine samples in children with respect to age and gender

	E.coli	Klebsiella Pneumonia	Proteus Mirabilis	Pseudomonas Aeruginosa
Age groups				
Infant (0-2 years)	62 (49.2)	22 (73.3)	3 (25)	4 (44.4)
Childhood (3-12 years)	54 (42.9)	6 (20)	6 (50)	3 (33.3)
Adolescents (13-16 years)	10 (7.9)	2 (6.7)	6 (50)	2 (22.2)
p-value	0.186	0.038	0.001*	0.419
Gender				
Male	30 (23.8)	13 (43.3)	4 (33.3)	6 (66.7)
Female	96 (76.2)	17 (56.7)	8 (66.7)	3 (33.3)
p-value	0.013*	0.079	0.753	0.022*
Data presented as n (%) Chi-square/Fisher exact test was applied *Significant at 0.05 level of significance				

Table 2: Suspectibility pattern of bacterial isolates from urine samples to antibiotics

Antibiotics	Susceptibility pattern	Microorganism			
		E.coli	Klebsiella Pneumonia	Proteus Mirabilis	Pseudomonas Aeruginosa
Amikacin	S	120 (72.7)	25 (15.2)	11 (6.7)	9 (5.5)
	R	6 (50)	5 (41.7)	1 (8.3)	0
Ampicillin	S	10 (37)	0	10 (37.1)	7 (25.9)
	R	116 (77.3)	30 (20)	2 (1.3)	2 (1.3)
Ciprofloxacin	S	48 (53.9)	22 (24.7)	11 (12.4)	8 (9)
	R	74 (91.4)	5 (6.2)	1 (1.2)	1 (1.2)
	I	4 (57.1)	3 (42.9)	0	0
Ceftriaxone	S	29 (46)	15 (23.8)	11 (17.5)	8 (12.7)
	R	97 (85.1)	15 (13.2)	1 (0.9)	1 (0.9)
Nitrofurantoin	S	78 (86.7)	12 (13.3)	0	0
	R	8 (24.2)	9 (27.3)	10 (30.3)	6 (18.2)
	I	9 (90)	1 (10)	0	0
	NA	31 (70.5)	8 (18.2)	2 (4.5)	3 (6.85)
S=Sensitivity, R=Resistance, I=Intermediate, NA=Not assessed Data presented as n (%)					

DISCUSSION

Globally one of the most common infections in children is UTI, causing significant morbidity and mortality, specifically in the children of aged 0-2 years.[10, 13]Early diagnosis and treatment with the right antibiotics can help to alleviate symptoms and avoid kidney damage. Because antibiotic treatment is frequently started before the causative microorganism and its sensitivity to antibiotics are identified, the decision is based on local data. Hence, in the current study we have evaluate the etiology and susceptibility pattern of UTI among children aged 0 to 16 years.

This is very common practice to start antibiotics empirically if there is a suspicion of UTI which lead to resistance on larger scale. According to Shah et al., annually 5 to 14% of emergency visits and 0.7% outpatient department visits were due to pediatric UTI.[6] In our study, 68.9% samples were derived from IPD and OPD accounts for 31.1% of urine samples.

Urine collection method is very important as this determines the colony forming units' number that are significant as the urethra distally may be colonized by the same bacteria that cause UTI.[14] In our study significant numbers of urine samples were clean catch or midstream urine sample which account for 97.2% and only 2.8% samples were received from catheter.

In the present study, we also found that the most frequent microorganism among children with UTI was E.coli (71.2%). Other common microorganisms were Klebsiella pneumonia (16.9%) and Proteus Mirabilis (6.8%). However, its prevalence differs in various areas.[2, 6, 11]In studies carried out in Canada, Mexico, Pakistan and India, E.coli accounted for 57.7%-69.9% and Klebsiella for 12.4%-29% of UTI and this range is similar to our study.[15-18]

According to Konca et al.,E. coli (60.1%), and Klebsiella spp. (16.5%) were the most common uropathogens affecting children with mean age group 3.36 ± 3.38 years.[19] This study is very much near to our study as E.coli was 71.2% followed by 16.9% isolates of Klebsiella species affecting mean age group 4.31 ± 4.82 years. Riccaboma et al. stated that approximately 1% of boys and 3-8% of girls are diagnosed with UTI, but during first year of life 2.7% males are affected as compare to 0.7% females.[20] But as age increases school age girls are more affected than school age boys.[13] According to our study 29.9% male and 70.1 % females were diagnosed with UTI.

Enrico et al in 2012 establish a statistically significant relationship ($p<0.05$) between gender and type of organism affecting them, 71% females and 55%males were affected by E.coli whereas Klebsiella affects 9.1% females and 7.3% males in the relevant study.[21]In our study, 76.2% females and 23.8% males were affected by E.coli and Klebsiella affect 56.7% females and 43.3% males. However relative frequency of organism differs in different geographical location and same goes for antimicrobial resistance pattern. In some studies, from Iran, Mexico and Sudan microbial resistance to ampicillin is high and varies from 75% to 89.3%.[2, 6, 22, 23]In Iranian study the susceptibility of E.coli is 84.4% to amikacin as compare to our study which shows susceptibility of 72.7.2 %.[15]

The susceptibility of E.coli to nitrofurantoin has been reported from 83.6% to 98.8%.[15] Our study falls to the range and 86.7% bacterial isolates were sensitive to nitrofurantoin. One of the studies conducted in Peshawar, E.coli was 39.2% sensitive to ciprofloxacin.[24]But this study done in Karachi shows sensitivity pattern of 53.9% to ciprofloxacin. Study conducted between 2016-2017 shows 100% isolates of E.coli was sensitive to ceftriaxone[25] as compare to our study which shows 46% sensitivity to ceftriaxone. Another similar study conducted at Nepal shows antimicrobial sensitivity pattern to Klebsiella Pneumonia which are as follows: Amikacin 100%, Nitrofurantoin 50%,and Ciprofloxacin 100%.[26]As compare to result of our study which are as follows amikacin 15.2%, ciprofloxacin 24.7%, and ceftriaxone 23.8%, and nitrofurantoin 13.3%. Eleven year prolong study conducted from 2005-2016 at Iran shows resistance pattern of Pseudomonas as follows 6.9 % resistance to amikacin, 100% resistance to ampicillin, 46.15% resistance to ceftriaxone, 4% resistance to ciprofloxacin, and 83.87% resistance to nitrofurantoin.[27] Following is the resistance pattern of our study for Pseudomonas: none of the isolates of pseudomonas was resistance to amikacin 1.3 % resistant to ampicillin, 1.2% and 0.9% resistance to ciprofloxacin and ceftriaxone respectively and 18.2% isolates were resistant to nitrofurantoin.

Hence, when there is suspicion of UTI it is standard practice to start antibiotic empirically. Such routine use increases the probability of antibiotic resistance which add burden to health system. The aim of this study was therefore to provide a proper guide regarding treatment of UTI so that children are properly managed.In low income countries like Pakistan affordability and reduced access to healthcare can result in growing concerns for increased morbidity and mortality from antibiotic resistant infections. At national level policies should be generated regarding antibiotic stewardship and their implementation should be made. Parents should be educated regarding proper hygiene practices regular hand washing, toilet training and proper cleaning techniques after urination can prevent UTI and its related morbidity.Few limitations of our study is that we did not collected data on the presence of urinary tract malformation, previous UTI and use of antibiotic prophylaxis. This could have confounding effect on outcomes. Furthermore, sample size of the study was small, therefore findings of the study lacks generalizability. In future more

CONCLUSION

E.coli was the most common bacterial isolates among children with UTI. Nitrofurantoin and Amikacin showed higher sensitivity against E.coli., while Ciprofloxacin, Ceftriaxone and Ampicillin showed high resistance against E.coli. Hence, antibiotic resistance of uropathogen is increasing and this increase is due to frequent use of broad spectrum antibiotics. Regular observation should be carried out to determine the local prevalence of organisms and antimicrobial susceptibilities in order to guide the proper management.

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