PATTERN OF ANTIBIOTIC RESISTANCE IN URINARY ISOLATES IN CHILDREN: WHAT COULD BE THE EMPIRICAL TREATMENT?

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ABSTRACT

Objective: *To assess the resistance patterns of urinary isolates to commonly used antimicrobials and to evaluate the options for empirical treatment of urinary tract infection (UTI) in our setup.*

Material and Methods: *A retrospective analysis of bacteria isolated from children with UTI was performed at Hayatabad Medical Complex, Peshawar, from January 2005 through June 2008. This evaluation did not consider whether UTI was complicated or uncomplicated, the first or recurrent infection, or nosocomial or community acquired. The data was based solely on laboratory findings.*

Results: *Mean patient age was 26 months and 67% of study population was females. Out of 519 positive urine samples, Escherichia coli (65.9%) was the leading uropathogen followed by Klebsiella pneumoniae (11.6%), Proteus mirabilus (07.1%) and Staphylococcus aureus (5.8%). Bacteria were frequently resistant to Ampicillin (86%), Trimethoprim-Sulfamethoxazole (99.5%), Gentamicin (81.6%), Cefalexin (60.2%) and Cefuroxime (52.5%) but had a resistance of less than 20% against Amikacin, Cefpirome, Ciprofloxacin, Sulzone, Meropenem and Tazocin. Uropathogens isolated below the age of one year are highly sensitive to amikacin, sulzone ($p<0.05$). No significant difference was noted between the children age less than and more than one year to cefixime, ceftazidime, ciprofloxacin, meropenem and tazocin.*

Conclusion: *Escherichia coli and Klebsiella pneumoniae are the commonest uropathogens causing UTI in children. Cefixime and ciprofloxacin could be the useful empirical oral treatment in children with afebrile UTI below and above one year of age respectively. Whilst amikacin (with/without ceftazidime/IV ciprofloxacin) might be the best empirical antibiotics for all age groups with febrile UTI.*

Key words: *Urinary Tract Infection, Antibiotic Resistance Pattern, Empirical Antibiotic Therapy, Escherichia Col, Uropathogens.*

INTRODUCTION

Antimicrobial resistance is now recognized as an increasingly global problem[1] which was observed for the first time in Escherichia coli (E. coli) in 1940. The primary factor responsible for the development and spread of bacterial resistance is the injudicious use of antimicrobial agents[2]. Resistance has emerged even to newer, more-potent antimicrobial agents[3]. Knowledge of drug resistance in bacteria is indispensable for the proper selection of antimicrobial drugs. Resistance studies assist health authorities in the formulation of their own drug policies. They are also important for the general practitioner in a remote area who may not have access to microbiology laboratory back-up and hence must depend on the prevailing knowledge of antibiotic-resistant bacteria.

Urinary tract infection (UTI) is one of the most common bacterial diseases in children and a common reason for antibiotic prescription and hospitalization, particularly in infancy[4]. Although the prognosis is usually favorable, long-term complications of UTI have been associated with renal scarring and include poor renal growth, impaired renal function, early hypertension, and chronic renal failure later in life[5]. In patients with UTI, initial antibiotic treatment is usually empirical, before urine culture results are available, in order to decrease the risk of renal damage[6]. Most of these children receive antibiotics

GENDER AND AGE DISTRIBUTION OF UROPATHOGENS ISOLATED

Organisms	Total Number of Isolates= 519				
	Gender		Age		Total
	Male	Female	<12 months (132)	>12 months (387)	
Escherichia coli	101 (59.1%)	241 (69.3%)	89	253	342 (65.9%)
Klebsiella pneumoniae	22 (12.9%)	38 (10.9%)	15	45	60 (11.6%)
Proteus mirabilus	14 (08.2%)	23 (06.6%)	11	26	37 (07.1%)
Staphylococcus aureus	12(07.0%)	18(05.2%)	08	22	30(05.8%)
Enterococcus species	07 (04.1%)	15 (04.3%)	03	19	22 (04.2%)
Pseudomonas aeruginosa	12 (07.0%)	08 (02.3%)	05	15	20 (03.9%)
Citrobacter species	03 (01.7%)	05 (01.4%)	01	07	08 (01.5%)
Total	171	348	132	387	519(100%)

Table 1

without knowledge regarding the causative organism or its sensitivity to antibiotics[7]. The changing pattern of antimicrobial resistance in the causative microorganisms of UTI in childhood is also a growing problem[8]. To ensure effective treatment, knowledge of the organisms responsible for UTI in children and their antibiotic susceptibility patterns is mandatory. Thus, empirical antibiotic treatment in UTI in children must rely on surveillance data on the epidemiology and resistance patterns of common uropathogens[9].

Updated knowledge of the prevailing causal bacteria and their susceptibility patterns is important for the proper selection and use of antimicrobial drugs and for the development of an appropriate prescribing policy. The aim of this retrospective study was to assess the resistance patterns of urinary isolates to commonly used antimicrobials and to evaluate the options for empirical treatment of UTI.

MATERIAL AND METHODS

This retrospective analysis was performed on all urine samples sent to the bacteriology laboratory of the Postgraduate Medical Institute, Hayatabad Medical Complex, Peshawar, for culture and sensitivity testing from January 2005 through June 2008. Strains were isolated from inpatients and outpatients with symptoms of UTI. *The retrospective evaluation did not consider whether UTI was complicated or uncomplicated, the first or recurrent infection, or nosocomial or community acquired. The data were based solely on laboratory findings.* Urine samples were collected by midstream clean catch, catheterization, suprapubic aspiration, and urine collecting bag. All samples were collected in sterile disposable containers and were delivered to the laboratory within 1 hour of collection at room temperature. In case of delay the urine samples was kept at 4°C and analyzed within 6 hours of the collection. Cultures were performed by standard techniques. Briefly, 1 µl of urine was streaked on Blood and McConkey agar plates using a calibrated standard loop. The plates were incubated for 18–24 hours at 37°C. Bacterial identification was done by hand lens and standard biochemical tests. Where multiple growths were obtained the culture was repeated again before accepting the results. A colony count of 10^5 or more colony forming units (CFU) is the criterion used to define significant bacteriuria. The *in vitro* susceptibility to Isolated urinary organisms were tested against amikacin, gentamicin, cotrimoxazole, ampicillin, amoxicillin/clavulanate, cephalexin, cefuroxime, ceftizoxime, cefixime, cefpirome, ceftazidime, cefatoxime, ceftriaxone, nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, enoxacin, gatifloxacin, sulzone (cefoperazone+sulbactam), meropenem and tazocin (piperacillin + tazobactam), determined by the disk diffusion method. Strains defined as having intermediate resistance were classified in the resistant group for the purposes of this analysis. The details of each patient were recorded in a proforma.

Inclusion criteria: Urinary tract infection was defined as any bacterial growth in specimens obtained by suprapubic aspiration and the growth of $>10^5$ colony forming units /ml in specimens obtained by other methods.

Exclusion criteria: All cases with no growth or growth of $<10^5$ colony forming units /ml were excluded from the study.

Data Analysis: Data was analyzed for the pattern of growth of the uropathogens and their resistant to the tested antibiotics. Data was then divided into 2 groups on the basis of age: below one and

NUMBER (PERCENT) OF COMMON URINARY PATHOGENS RESISTANT TO ANTIMICROBIAL AGENTS

Antibiotics	E. coli (342)	Klebsiella (60)	Proteus (37)	S. aureus (30)	Enterococcus (22)	Pseudomonas (20)	Citrobacter (08)	Total Resistant Pattern
Amikacin	58/342(16.9)	11/60(18.3)	09/37(24.3)	12/30(40.0)	03/22(13.6)	03/20(15.0)	02/8(25.0)	98/519(18.9%)
Gentamicin	219/264(82.9)	45/53(84.9)	15/23(65.2)	25/27(92.6)	10/19(52.6)	17/19(89.5)	05/7(71.4)	336/412(81.6%)
TMP-SMX*1	111/112(99.1)	12/12(100)	23/23(100)	19/19(100)	09/9(100)	07/7(100)	04/04(100)	185/186(99.5%)
Ampicillin	188/223(84.3)	16/18(88.9)	18/18(100)	21/21(100)	10/16(62.5)	08/8(100)	04/4(100)	265/308(86.0%)
Amo/cla*2	108/288(37.5)	28/49(57.1)	15/35(42.9)	12/27(44.4)	09/21(42.9)	12/20(60)	03/8(37.5)	187/448(41.7%)
Cephalexin	102/170(60.0)	16/27(59.3)	11/19(57.9)	07/16(43.8)	09/13(69.2)	08/9(88.9)	NT*5	153/254(60.2%)
Cefuroxime	123/234(52.6)	12/17(70.6)	07/20(35.0)	04/19(21.1)	12/17(70.6)	07/8(87.5)	01/1(100)	166/316(52.5%)
Ceftizoxime	22/98(22.4)	06/25(24.0)	10/17(58.8)	05/27(18.5)	04/18(22.2)	03/12(25.0)	NT*5	50/197(25.4%)
Cefixime	67/331(20.2)	17/54(31.5)	09/34(26.5)	07/23(30.4)	08/19(42.1)	03/18(16.7)	02/5(40.0)	113/484(23.3%)
Cefpirome	35/198(17.7)	09/52(17.3)	04/32(12.5)	08/27(29.6)	03/17(17.6)	04/18(22.2)	01/4(25.0)	64/348(18.4%)
Ceftazidime	77/340(22.6)	08/60(13.3)	05/37(13.5)	10/27(37.0)	04/21(19.0)	03/20(15.0)	02/8(25.0)	109/513(21.2%)
Cefatoxime	97/329(29.5)	16/56(26.8)	19/37(51.4)	11/30(36.7)	04/21(19.0)	08/20(40.0)	03/8(37.5)	158/501(31.5%)
Ceftriaxone	118/340(34.7)	09/60(15.0)	04/37(10.8)	05/30(16.7)	07/20(35.0)	06/20(30.0)	03/8(37.5)	152/515(29.5%)
Nalidixic acid	69/178(38.8)	12/51(23.5)	05/22(22.7)	09/17(52.9)	06/16(37.5)	04/13(30.7)	02/6(33.3)	107/303(35.3%)
Norfloxacin	76/211(36.0)	10/39(25.6)	07/21(33.3)	17/19(89.5)	04/18(22.2)	08/20(40.0)	04/7(57.1)	126/335(37.6%)
Ciprofloxacin	47/342(13.7)	09/58(15.5)	04/37(10.8)	04/30(13.3)	02/22(09.1)	02/20(10.0)	01/8(12.5)	69/517(13.3%)
Ofloxacin	37/201(18.4)	11/39(28.2)	07/33(21.2)	10/27(37.0)	02/20(10.0)	03/20(15.0)	01/6(16.7)	71/346(20.5%)
Levofloxacin	11/96(11.5)	02/21(09.5)	04/23(17.4)	06/22(27.3)	02/15(13.3)	02/14(14.3)	01/5(20.0)	28/196(14.3%)
Sparfloxacin	07/101(06.9)	02/26(07.7)	03/27(11.1)	05/27(18.5)	02/16(12.5)	01/12(08.3)	01/7(14.3)	21/216(09.7%)
Enoxacin	15/88(17.1)	04/25(16.0)	03/19(15.8)	05/15(33.3)	02/17(11.8)	02/12(16.7)	01/6(16.7)	32/182(17.6%)
Gatifloxacin	06/47(12.8)	02/18(11.1)	03/19(15.8)	05/13(38.5)	03/16(18.8)	02/10(20.0)	NT*5	21/123(17.1%)
Sulzone*3	29/235(12.3)	04/43(09.3)	04/32(12.5)	01/23(04.3)	01/17(05.9)	00/9 (Nil)	00/3(Nil)	39/362(10.8%)
Meropenem	08/193(04.2)	05/32(15.6)	03/25(12.0)	03/27(11.1)	00/8(Nil)	01/8(12.5)	00/4(Nil)	20/297(06.7%)
Tazocin*4	07/108(06.5)	03/17(17.6)	01/12(08.3)	01/14(07.1)	00/9(Nil)	00/9(Nil)	NT*5	12/169(07.1%)

*1 TMP-SMX = trimethoprimsulfamethoxazole *2 Amo/cla= (Amoxicillin/clavulanate) *3Sulzone (cefoperazone/sulbactam)
*4 Tazocin= (piperacillin/tazobactam) *5NT=Not tested

Table 2

above one year and compared for above mentioned indicators. To test significance of the difference between the two groups, chi-squared tests was applied and p value was calculated. $P<0.05$ was considered statistically significant.

RESULTS

Our record review revealed that over a period of three and half years (study period), a total of 937 urine specimens from infants and children investigated for bacterial etiologic agents, 519 had proven urinary tract infection and were included in this study. The patient population was 67% (348) female. The ages of the children in our population ranged from 1 week to 15 years. The median age was 6.5 months and the mean age was 26 months (mean age, 25 months for boys and 28 months for girls). 67 specimens were collected by suprapublic aspiration, 56 by catheterization, and 205 by clean catch (mid-stream collection); while in 191 urinary bag was used to collect the urine. The spectrum of urinary tract pathogens identified is shown in Table 1. The most common organisms were Escherichia coli (65.9%), followed by Klebsiella pneumoniae (11.6%), Proteus mirabilus (07.1%), Staphylococcus aureus (5.8%), Enterococcus species (04.2%), Pseudomonas aeruginosa (03.9%), and Citrobacter species. More than 25% of episodes occurred below the age of one year. The rates of resistance for uropathogens isolated to selected antibiotics agents are shown in Table 2. These uropathogens showed high resistance when they were tested against ampicillin, cotrimoxazole, cephalexin, gentamicin, cefuroxime. In comparison, low resistance rates were found against amikacin, cefpirome, ciprofloxacin, levofloxacin, sparfloxacin, enoxacin, gatifloxacin, sulzone, meropenem and tazocin. Age wise distribution (below and above one year of age) of antibiotic resistance pattern is shown in

Organism	AMAKACIN					CEFIXIME					CEFPIROME					CEFTAZIDIME				
	<1 year		>1 year		P	<1 year		>1 year		P	<1 year		>1 year		P	<1 year		>1 year		P
	T	R	T	R	Value	T	R	T	R	Value	T	R	T	R	Value	T	R	T	R	Value
E.coli	89	11	253	47	**0.23**	82	13	249	54	**0.28**	77	9	121	26	**0.12**	87	19	253	58	**1.00**
K. pneumonia	15	2	45	9	**0.18**	13	3	41	14	**0.11**	11	1	41	8	**0.04**	13	2	47	6	**0.83**
P. mirabilus	11	1	26	8	**0.001**	9	3	25	6	**0.21**	9	1	23	3	**0.82**	10	2	27	3	**0.11**
S. aureus	8	2	22	10	**0.003**	6	1	17	6	**0.006**	8	1	19	7	**0.000**	8	3	19	7	**1.00**
Enterococcus	3	0	19	3	**0.000**	3	1	16	7	**0.14**	3	0	14	3	**0.000**	3	1	18	3	**0.01**
Pseudomonas	5	0	15	3	**0.000**	5	1	13	2	**0.45**	5	1	13	3	**0.73**	5	1	15	2	**0.25**
Citrobacter	1	0	7	2	**0.000**	NT**	---	5	2	**NA**	1	0	3	1	**0.000**	1	0	7	2	**0.000**
Total	**132**	**16**	**387**	**82**	**0.007**	**118**	**22**	**366**	**91**	**0.72**	**114**	**13**	**234**	**51**	**0.05**	**127**	**28**	**386**	**81**	**1.00**
Organism	**CIPROFLOXACIN**					**SULZONE**					**MEROPENEM**					**TAZOCIN**				
	<1 year		>1 year		P	<1 year		>1 year		P	<1 year		>1 year		P	<1 year		>1 year		P
	T	R	T	R	Value	T	R	T	R	Value	T	R	T	R	Value	T	R	T	R	Value
E.coli	76	15	266	32	**0.17**	53	3	182	26	**0.09**	43	2	150	6	**1.00**	29	1	79	6	**0.33**
K. pneumonia	15	2	43	7	**0.68**	9	0	34	4	**0.001**	13	1	19	4	**0.01**	9	0	8	3	**0.000**
P. mirabilus	10	0	27	4	**0.000**	6	0	26	4	**0.000**	7	0	18	3	**0.000**	5	0	7	1	**0.000**
S. aureus	8	1	22	3	**0.83**	5	0	18	1	**0.07**	6	1	21	2	**0.14**	4	0	10	1	**0.003**
Enterococcus	3	0	19	2	**0.07**	3	0	14	1	**0.02**	2	0	6	0	**NA**	3	0	6	0	**NA**
Pseudomonas	4	0	16	2	**0.001**	3	0	6	0	**NA**	2	0	6	1	**0.000**	3	0	6	0	**NA**
Citrobacter	1	0	7	1	**0.000**	1	0	2	0	**NA**	NT	---	4	0	**NA**	NT	---	NT	---	**----**
Total	**117**	**18**	**400**	**51**	**0.83**	**80**	**3**	**282**	**36**	**0.04**	**73**	**4**	**224**	**16**	**0.76**	**53**	**1**	**116**	**11**	**0.06**

Table 3

Table 3. Only those antibiotics were compared that could be used in pediatric age group. It was found that uropathogens isolated below the age of one year were significantly least resistant to amikacin ($p<0.007$), sulzone ($p<0.04$) and even to cefpirome ($p\leq 0.05$). There was no significant difference in the resistance pattern of rest of 5 antibiotics between two age groups.

DISCUSSION

The goals of treatment of urinary tract infections are to eliminate the pathogen, to prevent urosepsis, and to reduce the risk of renal scarring[10]. Epidemiology and resistance patterns of bacterial pathogens in pediatric urinary tract infection show large interregional variability, and rates of bacterial resistances are changing due to different antibiotic treatment[11]. Knowledge of spectrum of pathogens and their patterns of drug resistance is indispensable for the empirically select an effective therapeutic agent prior to availability of culture results[12].

As expected, *E. coli is* still the major causative organism in pediatric urinary tract infections as affirmed in this study accounting for almost 66% of all cases, followed by *Klebsiella* spp. (11.6%), *Proteus* spp. (7.1%), *S. aureus* (5.8%), *Enterococcus* spp. (4.2%), *Pseudomonas aeruginosa* (3.9%), and *Citrobacter* spp. (1.5%) and these results are comparable to those reported by others earlier[13-15].

In our study, urinary tract infection is highly prevalent under the age of one year. As reported in literature[5], initial episodes of urinary tract infection occur more commonly in infancy, when the renal parenchyma is highly susceptible to the injurious effect of infection and is at greatest risk of developing renal scars. However, according to a recent prospective study[16], the development of cortical scarring does not decrease with age and this review has a considerable effect on recommendations for the initial treatment of urinary tract infection among febrile children prior to availability of culture results.

Resistance among uropathogens to a variety of antibiotics is increasing. Prior studies[17] have shown increasing rates of resistance to ampicillin, gentamicin, cotrimoxazole and first-generation cephalosporins. Our study also found high rates of resistance to all of these antibiotics. More than 35% of uropathogens of this study are resistant to those antibiotics once considered to be the best oral substitutes to injectables i.e., nalidixic acid and amoxicillin+clavulanate. Almost 30% uropathogens have developed resistant to the third-generation cephalosporins except ceftazidime (21.2%) and cefpirome (18.4%). Higher resistance rate to all antibiotics used in this study with the exception of amikacin, ciprofloxacin, sulzone (cefoperazone+sulbactam), meropenem and tazocin (piperacillin+tazobactam) may be explained by widespread and injudicious use of antimicrobial agents during the past decade in our region. A comparison of our results with those of recent paediatric studies from the Turkey[18], India[3], Germany[11] and Yemen[19], shows a broadly similar picture.

In the present study, only three antibiotics, sulzone, meropenem and tazocin, have resistance of 10 or less than 10%. The emergence of antibiotic-resistant strains is multifactorial and that could be explained by several nonexhaustive hypotheses. The influence of excessive and/or

inappropriate antibiotic use, particularly of broad-spectrum agents prescribed empirically, has been demonstrated. Reducing the number of prescriptions of a particular antibiotic can lead to a decrease in resistance rates. Conversely, it has been observed an increase in the rate of ciprofloxacin resistance among *E. coli* strains from 3 to 20%; this was observed concomitantly with a tripling in the rate of consumption of fluoroquinolones during the same period. Transmission of resistant isolates between people and/or by consumption of food from animals that had received antibiotics and greater mobility of individuals worldwide have also contributed to the extension of antibiotic resistance[20].

Age wise distribution of antibiotic resistance pattern revealed that uropathogens isolated from the children of different age groups showed slight variation in percent resistance against different antibiotics. It is found that out 24 antibiotics against which the resistance is checked, 8 which can be used in children have resistance of less than 20%. Uropathogens isolated below the age of one year are highly sensitive to amikacin, sulzone and even to cefpirome with a p value of 0.007, 0.04 and 0.05 respectively. There is no significant difference noted between the children age less than one and more than one year to cefixime, ceftazidime, ciprofloxacin, meropenem and tazocin, all having p value of more than 0.05.

Our study may have significant implications for outpatient as well as inpatient treatment of UTI. Lutter SA, et al[21] has reported that children with a first febrile UTI may safely be managed as outpatients with an oral third-generation cephalosporin, thereby reducing health care costs. Cefixime in our study has a resistance of 23% and can be used in selected cases, especially when a child with suspected urinary tract infection is afebrile. We demonstrated a high rate of susceptibility of the uropathogens to amikacin, thus children of all ages may be treated with this drug. The combination of ceftazidime, a cephalosporin with Pseudomonas coverage, and amikacin also provided excellent coverage in children less than one year of age[22]. Cefpirome, cefoperazone+sulbactam, meropenem or an extended-generation penicillin such as piperacillin-tazobactam might be considered as alternative in febrile urinary tract infection as demonstrated in many studies[23]. Aminoglycosides have the advantage of a much lower cost, but they do require monitoring of drug levels and there is a risk of nephrotoxicity or ototoxicity. Nonetheless, aminoglycosides have a long record of safety and efficacy for the inpatient management of urinary tract infection in children[24].

In this study, rate of resistance to ciprofloxacin in children with age more than one year is almost 13% which is comparable to the studies conducted earlier and is now recommended in children with urinary tract infection after the age of one year[25]. This antibiotic is available both in oral and injectable preparation and may be considered in this age group children. In resistance cases and febrile urinary tract infection, amikacin, cefpirome, cefoperazone+sulbactam, meropenem or piperacillin-tazobactam might be considered as alternative to ciprofloxacin in this age group children.

At the end, we believe that our findings may be useful to physicians in clinical practice regarding the selection of the appropriate empirical antimicrobial regimen for patients in the primary care setting with urinary tract infections. Moreover, they highlight the increasing problem of antimicrobial resistance even in the primary care setting.

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