Antibiotic resistance of urinary tract pathogens and evaluation of empirical treatment in children with urinary tract infections in Thi-Qar Governorate

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ABSTRACT:

Background : There is global emergence of resistance against commonly prescribed antimicrobials . Empirical antibiotics Prescription should be directed by local antimicrobial susceptibility patterns .

Objective : To assess the resistance patterns of urinary isolates to commonly used antimicrobials and to evaluate the options for empirical treatment of UTI .

Methods : A prospective study was conducted in Bint Al-Huda teaching hospital for children ; Thi-Qar – Iraq ; From January 2011 to December 2012 . Urine specimens were obtained from patients younger than 15 years and cultured on appropriate bacteriological medias . Bacterial isolates were Identified by standard tests ; and antibiotic susceptibility was determined by disc diffusion method .

Results :From 1000 urine specimens (18 %) had positive results for bacterial cultures . Females out numbered males in all age groups with a ratio of 2.6 : 1 except in the first year of life . E-coli was the most common etiological agent of UTI (68.8 %) followed by proteus spp (12.7 %) ; Klebsiella (9.4 %) ; Enterobacter spp (6.6 %) , citrobacter spp (2.2 %) . High degree of resistance among pathogens to ampicillin (92.2 %); Amoxycillin (81.6 %) ; SXT (81.6 %) ; cephalothin (76.1%) ; 3rd generation cephaloporines (42.2 – 60.5%) . The lowest resistance was to imipenem (1.6 %) ;

Amikacin (6.1%) ; nitrofurantoin (12.7%) ; ciprofloxacin (15 %) .

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Conclusion :

Inspite of an increase in the resistance rates of bacterial pathogens causing UTI ; Amikacin is appropriate forintial empirical intra-venous therapy in simple febrile UTI , for complicated febrile UTI imipenem monotherapy is appropriate ; Nitrofurantion could be included as a reasonable alternative in the empirical treatment of lower UTI in older children . The results of this study and numerous observations regarding the increasing resistance to these antibiotics , in several countries ; emphasize the need for local population - specific surveillance for guiding empirical therapy for UTI in children .

Introduction :

Urinary tract infection (UTI) is a common problem in children [1] ; and many children with UTI are admitted to hospital [2] . The incidence varies according to age and sex of children [3,4] . It occurs in about 1% of boys and 3.5% in girls [4] . UTI mostly occurs during the first year of life in boys ; much more commonly in uncircumcised boys ; beyond 1 – 2 years ; there is strikling female preponderance with a 1 : 10 Male to female ratio[4]. Three to five percent of febrile children are found to have UTI [5] . Urinary tract infection has been considered an important risk factor for the development of progressive renal disease and long term complications [6] . The symptoms of UTI may be minimal and non specific infants and small children ; when the diagnosis of UTI is difficult [7] . Pathogens associated with uncomplicated UTI are E.coli identified in about 75 – 90 % of infection [8] ; staphylococcus saprohyticus (5 – 15 %) ; Klebsiella ; Proteus ; Enterococcus and Pseudomonas aeruginosa are seen in smaller percentages [9,10] . Most of infants and children receive empirical therapy before detecting antimicrobial sensitivity and resistance [11] . Recently Farrell [12] et al demonstrated high resistance to trimethoprim ; ampicillin ; and cephalosporines ; rendering them unsuitable for empirical use . Increasing resistance of bacterial pathogens is of world wide problem and concern that is varied in different regions and even countries [11,12] . It's necessary to identify the causative agent and spectrum of it's antimicrobial susceptibilities in order to treat UTI ; since this pectrum may

vary among geographical locations ; hospitals ; each institution should carefully plane their antibiotic therapy . The present study was performed to find out the frequency of different urinary tract pathogens and the antimicrobial susceptibility profile in children younger than 15 years ; who were admitted in Bint Al-Huda teaching hospital in Thi-Qar Governorate from January 2011 to December 2012 .

Patient and Methods:

The study population consisted of children younger than 15 years old who were admitted in Bint Al-Huda teaching hospital - Thi-Qar from the begning of January 2011 to the end of December 2012 . One thousand Urine specimens were obtained from patients ; only one hundred eighty patients with culture proven UTI were included in the study . The following cases had been already excluded : previous history of UTI ; the presence of urinary catheters ; urinary malformations (according to prenatal ultrasound and previous medical records) ; or current prophylactic treatment with antibiotics . Full history and complete physical examination conducted for all patients . Urine samples were collected by transurethral bladder catheter in

neonates (due to familial rejection of suprapubic aspiration) ; urine bag (using sterile methods) in infants aged one moth to 2.5 years ; and mid stream urine in children aged > 2.5 years Urine samples were subjected immediately for general urine and sent for culture . Auroculture was considered positive when it presented a bacterial count of more than 100,000 colong forming units (CFU) / ml in urine specimens collected mid stream and in urine bag or more than 10.000 CFU / ml for urine specimens collected by trans urethral bladder catheterization [13,14,15] . Urine cultures were done by spreading 0.1 ml of each sample on blood and Macconkey agars and incubated for 24 – 48 hours at 37 C . Identification of the isolated bacteria was performed according to a standard methods . Antimicrobial susceptibility was performed using the diffusion disc method [16] . The antimicrobial agents used in this study were :- Ampicilline ; Amoxycillin ; Trimethoprim-sulfa methoxazole (TMP-SMX) ; cephalothin ; ciprofloxacin ; ceftriaxone , cefotaxime ; ceftazidime ; Amikacin , Gentamicin ; nitrofurantoin ; Nalidixic acid and Imipenem .

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Results :

A total of 1000 urine specimens were collected from pediatric patients attending Bint Al-Huda teaching hospital ; cases that were fitting the criterias for exclusion had been excluded from the study ; and those with proven culture positive were enrolled in the study (180 cases) ; representing 18 % of total urine samples . The prevalence of uropathogens isolated on urine culture was shown in table (1) . E.coli represents 68.8 % of total number of the isolates followed by proteus spp (12.7 %) ; Klebsiella pneumoniae spp (9.4 %) ; Enterobacter spp (6.6 %) ; citrobacter spp (2.2 %) . The prevalence of UTI in different age groups was shown in table (2) . The highest number of cases were in the age group (13 – 60 month) representing 48.8 % of total number of the isolates and the lowest number were in the age groups (0 – 12 months) and (121 – 180 months) representing 5.6 % and 10% of total

number of the isolated uropathogens respectively . The distribution of uropathogens isolated according to sex in different age groups was shown in Table (3) . Females out numbered males with an all over ratio of 2.6 : 1 ; except in the first year of life when females : males ratio was 1 : 1.5 . Antibiotic resistance patterns of uropathogens was shown in Table (4) . High degree of resistance among uropathogens was noticed to commonly used antimicrobials ; with an all over resistance of 92.2 % ; 81.6% ; 81.6% ; 76.1% ; and (42.2 – 60.5 %) to ampicillin ; amoxycillin ; Tmp-smx ; cephalothin and 3rd generation cephalosporines respectively . Proteus spp showed a resistance rate of (30.4 – 34.7 %) to 3rd generation cephalopsporines . The lowest resistance rates among uropathogens were for imipenem (1.6 %) ; amikacin (6.1%) ; Nitrofurantoin (12.71%) and ciprofloxacin (15 %) . An all over resistance rates of (36.6 %) and (36.1 %) among uropathogens had been noticed for gentamicin and Nalidixic acid respectively .

Table (1)

The prevalence of uropathogens isolated on urine culture .

Uropthogens	Number	Percentage
E. coli	124	68.8
Proteus spp	23	12.7
Klebsiella pneumoniae spp	17	9.4
Enterobacter spp	12	6.6
Citrobacter spp	4	2.2
Total	180	100 %

Table (2)

The prevalence of UTI in different age groups

Age group (Months)	Number of patients with UTI	Percentage
0 – 12 months	10	5.6 %
13 – 60 months	88	48.8 %
61 – 120 months	64	35.5 %
121 – 180 months	18	10 %
Total	180	100 %

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Table (3)

The distribution of uropathogens isolated according to sex in different age groups

Age group in months	Sex			
	Male		Female	
	N	%	N	%
0 – 12	6	3.33	4	2.22
13 – 60	25	13.88	63	35
61 – 120	14	7.77	50	27.77
121 – 180	5	2.77	13	7.22
Total	50	27.75	130	72.21

Table (4)

Antibiotic resistance pattern of uropathogens isolated

	Isolated uropthogens n (%)					
	E.coli 124 (68.8)	Klebsiella 17 (9.4)	Proteus 23 (12.7)	Enterobacter 12(6.6)	Citrobacter 4(2.2)	Total Resistance (%)
	Antimicrobial resistance (%)					
Ampicilline	116(93.5)	16 (94)	18 (78.3)	12 (100)	4 (100)	92.2
Amc	100(80.6)	14 (82.4)	18 (78.3)	11 (91.7)	4 (100)	81.6
Tmp – smx	106(85.4)	13 (76.4)	17 (73.9)	8 (66.6)	3 (75)	81.6
Cephalothin	94(75.8)	12 (70.5)	17 (73.9)	11 (91.6)	3 (75)	76.1
Ciprofloxacin	13(10.4)	6 (35.2)	3 (13)	4 (33.3)	1 (25)	15
Cefriaxone	75(60.4)	10 (58.8)	7 (30.4)	7 (58.3)	2 (50)	56.1
Cefotaxime	81(65.3)	10 (58.8)	8 (34.7)	8 (66.6)	2 (50)	60.5
Ceftazidime	56(45.1)	7 (41.1)	7 (30.4)	5 (41.6)	1 (25)	42.2
Amicacin	6(4.8)	1 (5.8)	2 (8.6)	1 (8.3)	1 (25)	6.1
Gentamicin	48(38.7)	5 (29.4)	8 (34.7)	3 (25)	2 (50)	36.6

Nitrofurantoin	13(10.4)	4 (23.5)	3 (13)	2 (16.6)	1 (25)	12.7
Nalidixicacid	25(20.1)	11 (64.7)	17 (73.9)	10 (83.3)	2 (50)	36.1
Imipenem	2 (1.6)	1 (5.8)	0 (0)	0 (0)	0 (0)	1.6

Discussion:

According to the results of our study , most of infections were observed in females with an over all males to females ration of 1 : 2.6 . Males out numbered females during the first year of life with a ratio of 1.5 : I ; this is similar to findings in other studies [17,18] . Majority of patients (48.8%) belong to the age group (13 – 60 months) as shown in Table (2) . This is in full agreement with studies from Turkey [19] ; united states [20] ; Kuwait [21] . This could be because of the reason as reported by others that this age group is more susceptible to infections due to their toilet training problems [22] . The most common agent infecting the urinary tract were E.coli (68.8 %) followed by proteus spp (12.7 %) ; Klebsiella pneumniae spp (9.4 %) ; enterobacter spp (6.6 %) ; citrobacter spp (2.2 %) as shown in table (1) . The above results are similar to the results in other studies [23,24] . In the last decades ; antimicrobial resistance phenomenon has been growing rapidly among uropathogens world wide [25,26] . The number of reports about occurrence of antibiotic resistance has been increasing over the world . In our study as shown in table (4) ; isolated uropathogens showed high degree of resistance to commonly used antibiotics ; with an all over resistance of 92.2 % ; 81.6 % ; 81.6 % 76.1 % (42.2 – 60.5 %) to ampicillin ; amoxicillin ; Tmp – smx ; cephalothin and 3rd generation cephalosporins respectively . high resistance rates against ampicillin ; amoxycillin ; 1st generation cephalosporines and Tmp – smx have been reported reported in Turkey [27] and other international studies [28,29] ; this could be attributed to the wide spread use of these antibiotics in the treatment of variety of infectious diseases in our country . Our findings of high resistance rates to ampicillin , amoxycillin and Tmp – smx under scores the fact that the above antibiotics should no longer be used for empiric treatment . High resistance rate to 3rd generation cephalosporines observed among the isolates in our study (42.2 – 60.5 %) ; except for

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Proteus spp when the resistance rate was (30.4 – 34.7 %) . This high resistance rate to 3rd generation cephalosporines rendering them un suitable choice for empiric treatment . Despite of being in agreement with other studies in Iran [30] , Nepal [31] , our findings of high resistance rate to cephalosporines are significantly higher than other new studies [32,33] . Such resistance against cephalosporins may be suggestive of the extended spectrum betalactamase (ESBL) mechanism of resistance [34] ; which is an emerging problem in Enterobacteriaceae and Hydrolyze extended spectrum cephalosporins with an oxyimino side chain [35] . These include ceftazidime ; ceftriaxone ; cefotaxime ; and the oxyimino-monobactam aztreonam . In many countries including Iraq ; cephalosporins are the favorite antimicrobial agents for the empirical treatment of not only UTI but also community – acquired respiratory tract infections . More ever ; in secondary and tertiary care centers cephalosporins are widely used ; e.g ; in intensive care units and hematology / oncology words . The high rate of resistance to gentamicin and Nalidixic acid in our study is in agreement with other studies [30,36] . The best activity against uropathogens achieved with imipenem ; amikacin ; Nitrofurantoin ; ciprofloxacin with their resistance rates of (1.6 %) ; 6.1 % ; 12.7 % ; 15 % as shown in table (4) . This may be attributed to restriction and limited prescription of these agents in children in contrast to amino penicillins that are frequently used . Our findings are in agreement with other study [37] . Imipenem was the most active antibacterial agent tested in this study (mean susceptibility level of 98 : 4%) as shown in Table (4) . These levels of efficacy make this antibiotic suitable choice for initial empirical treatment of cases with toxicity or difficult – to treat UTI [38] . Amikacin is the second most active agent tested and hence its appropriate for initial empirical treatment of patients with simple febrile UTI . Ciprofloxacin is not the first line drug for initial treatment of UTI in children ; However this drug may be considered a reserved alternative for children with difficult-to-treat UTI . Nitrofurantoin is an oral drug that is not systemic antibacterial agent is widely used to treat cases with uncomplicated cystits (a febrile UTI) . This drug usually achieve excellent urinary concentration and exceeding MIC for the respective

uropathogens and its multiple mechanisms of action enable it be to potent against uropathogens despite nearly 50 years of use [39] , and hence this antibiotic is an appropriate option for initial empirical therapy for older children with cystitis . As a rule this agent should not be used for febrile UTI . It's quite alarming to note that uropathogens isolated in this study are resistance to most routine antibiotics that were tested . Therefore ; this is an important issue to be considered by drug makers to formulate a strict antibiotic prescription in our country and region ; because the uropathogens resistance pattern to antimicrobials vary from time to another and among different locations ; empiric therapy with antibiotics for infections should be based on local experience of susceptibility and resistance profiles .

Conclusions :

According to findings of our study for children with simple eystitis nitrofurantoin monotherapy is appropriate . For patients with simple febrile UTI ; Amikacin monotherapy is appropriate .For complicated UTI (young infants ; critically ill and toxic patients ; underlying urinary tract malformations ; the prolonged use of urinary catheter or antibiotic prophylaxis) parenteral imipenemtherapy is indicated .

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