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Antibiotic resistance of urinary tract pathogens and rationale for empirical antibiotic therapy in children with urinary tract infection

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Abstract

Background and objective: Increased antimicrobial resistance of urinary tract pathogen is a matter of global public health concern. The purpose of this study was to identify the most common bacteria causing urinary tract infection and detection of antibiotics susceptibility of isolates to evaluate the options for empirical antibiotic therapy in children with urinary tract infection in Erbil city.

Methods: This study was conducted in Raparin Teaching Hospital on urine samples culture results over a one year period retrospectively. Hospital microbiology recording book was screened. Throughout the study period, 1622 children suspected to have urinary tract infection were investigated for urine culture. Disc diffusion technique according to clinical and laboratory standards institute (CLSI) was performed to determine antibiotics susceptibility of isolated bacteria species.

Results: Of 1622 children with suspected urinary tract infection, 514(31.69%) had a positive bacterial culture that included 104 males and 410 females. The most common isolates were E Coli (54.1 %), Staphylococcus (19.1%) and Proteus (12.5%). The most effective antibiotics against isolated pathogens were imipenem, ciprofloxacin and nitrofurantoin with sensitivity rate 95.2%, 78.8% and 74.1% respectively.

Conclusion: This study revealed that E. coli and staphylococcal strains were the most frequent isolated pathogens among our population; empirical antibiotic selection should be based on the knowledge of the local prevalence of bacterial organism and antibiotic sensitivity.

Keywords: Factors; Urinary tract infection; Antibiotic sensitivity; Uropathogens.

Introduction

Urinary tract infection(UTI) is one of the most common bacterial infections of childhood and it is associated with significant acute morbidity and long term illness such as arterial hypertension and chronic renal failure.[1] It has been suggested that early diagnosis, proper investigation, adequate therapy and prolonged careful follow up in children with UTI may well decrease the number of adults who present with chronic renal failure.[2] In a patient with suspected UTI, antibiotic treatment is usually started empirically before urine culture results are available. To ensure appropriate treatment, knowledge of organism that cause UTI and antibiotic susceptibility is mandatory.[3] In almost all cases there is a need to start treatment before the final microbiological results are available; this will contribute significantly to antimicrobial resistance in uropathogens due to frequent and sometimes repeated misuse of antimicrobials.[4] Area specific monitoring studies aimed to gain knowledge about the type of pathogens responsible for UTIs and their resistance pattern may help the clinician to choose the correct empirical treatment.[5] The start of empirical therapy ideally be supported by local epidemiological services at each institution to increase the likelihood of therapeutic success,[1] as the etiology of community acquired UTI, and their antibiotic sensitivity has shown geographical variation.[6] With

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growing problem of drug resistance worldwide as documented by published studies[5,7-8] as well as data on clinical, etiology of UTI and antimicrobial susceptibility of uropathogen in Iraq are scarce.[6] Hence, this study was undertaken to find out the distribution of the causative agents of UTI and their resistance rate at Raparin hospital in Erbil city and to ensure appropriate antibiotic selection.

Methods

This retrospective study involved children with UTI being treated in an inpatient department or an outpatient clinic of Raparin Teaching Hospital in Erbil. This is the only pediatrics hospital in the city covering a population of about 2 million people of which 755000 are children≤15 yearsold.[9] This study evaluated positive urine cultures in the microbiology laboratory between January 1stand December 31st,2014. UTI was defined as the growth of single pathogen of >10^5colony forming unit per ml [3].The choice of sampling (midstream urine samples versus clean urine samples collected into urine bag) was done in accordance with accepted guideline for each age group. The inclusion criteria included positive urine culture of children aged from birth till 13 years. Patients who underwent antibiotic treatment within last 24-72 hours and multiple micro-organisms were excluded from the study. From the database of microbiology laboratory, information was obtained from patients who met inclusion criteria for the study period including demographic data such as age in months at the time of diagnosis, gender, result of urine culture and antibiogram. The bacteria grown were defined with standard bacteriological methods and when findings were doubtful API-20E (bioMerieux) was used. Antimicrobial susceptibility of the isolates was tested by the disc diffusion technique according to clinical laboratory standard guideline (CLSI) [10] and also considering the availability of these drugs in the study area.[6] Organism with intermediate sensitivity were considered resistant.[3] Data were entered in a previously designed form and were analyzed with SPSS 21. A descriptive analysis of the data was performed including the calculation of frequency and proportion of variables in terms of means or medians with their standard deviation. Associations between two categorical variables were explored by cross tabulation. The statistical significance of such association was assessed by Chi-square test. An estimate was considered statistically significant if its *P* value was equal or less than a level of significance of 0.05. The study was approved by Ethics Committee of the College of Medicine of Hawler Medical University.

Results

We reviewed retrospectively the Raparin Teaching Hospital records for 2014. Total urine samples received in the laboratory in the study period were 1,622.Five hundred and fourteen (31.69%) of the samples were positive and evaluated of which 410(79.76%) samples were taken from girls and 104 (20.23%) were taken from boys. The mean patient age was 54.13 months. The most common bacterial isolate was *E Coli* (54.1%), followed by Staphylococcus sp.(19%) and Proteus sp.(12.5%) (Figure 1). There was a statistically significant difference between males and females in susceptibility to *E Coli* infection in different age groups, 41.3% of males in infancy (<12 months) had *E Coli* in comparison to 45.3% of females who suffered from E Coli in older age group >60 months (*P*<0.001). The same difference was noted for Klebsiella species were 100% of infection with Klebsiella which occurred in males was in infant group while it was distributed in all age groups in females (*P* = 0.002). Regarding Proteus species, 50% of infection occurred in males of infant age group while 54.3% of infection in females were in 12-60 month age group (*P*= 0.017)

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as shown in Table1.

Table 1: Distribution of isolated pathogen by age group and gender.

Micro-organism	Age group (months)	Male	Female	Total	*P* value
Ecoli	<12	19(41.3)	28(12.1)	47(16.9)	<0.001
	12-60	18(39.1)	99(42.7)	117(42.1)	
	>60	9(19.6)	105(45.3)	114(41)	
	Total	46(100)	232(100)	278(100)	
Klebsiella sp.	<12	10(100)	9(34.6)	19(52.8)	0.002
	12-60	0(0)	8(30.8)	8(22.2)	
	>60	0(0)	9(34.6)	9(25)	
	Total	10(100)	26(100)	36(100)	
Proteus sp.	<12	9(50)	10(21.7)	19(29.7)	0.017
	12-60	3(16.7)	25(54.3)	28(43.8)	
	>60	6(33.3)	11(23.9)	17(26.6)	
	Total	18(100)	46(100)	64(100)	
Staphylococcus sp.	<12	6(28.6)	12(15.6)	18(18.4)	0.393
	12-60	6(28.6)	27(35.1)	33(33.7)	
	>60	9(42.9)	36(49.4)	47(48)	
	Total	21(100)	77(100)	98(100)	
Pseudomonas sp.	<12	3(37.5)	1(10)	49(22.2)	0.332
	12-60	4(50)	6(60)	10(55.6)	
	>60	1(12.5)	3(30)	4(22.2)	
	Total	8(100)	10(100)	18(100)	
Others*	<12	1(100)	2(10.5)	3(15)	0.051
	12-60	0(0)	11(57.9)	11(55)	
	>60	0(0)	6(31.6)	6(30)	
	Total	1(100)	19(100)	20(100)	
Total		104	410	514	

*Others (citrobacter, enterobacter, kluyvera, morganellamorganii, monilia and streptococcus)

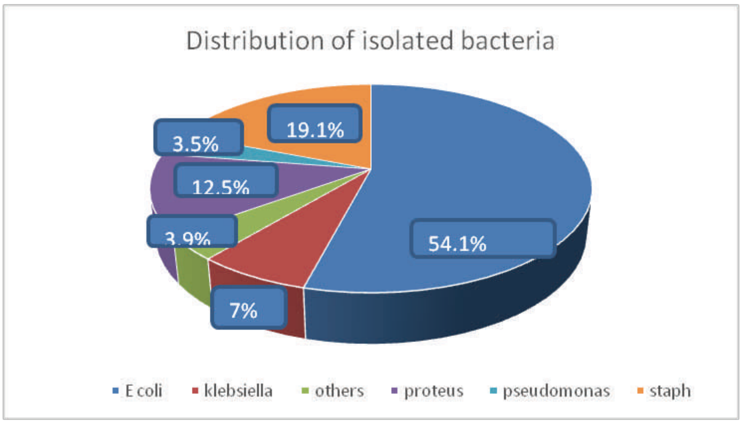

Figure 1: Distribution of isolated bacteria.

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The antibiogram of isolated pathogen is shown in Table 2. The highest susceptibility was for imipenem(95%), ciprofloxacin (78.8%) and nitrofurantoin (74.1%) and the least was to amoxiclav, ceftazidime, ampicillin and cloxacillin.

Table 2: Sensitivity to antibiotic.

Antibiotic	No of Sensitive organism/ no of examined	%
Imipenem	458/481	95.2
Ciprofloxacine	78/99	78.8
Nitrofurantoin	357/482	74.1
Gentamycine	277/465	50.6
Amikacin	123/264	46.6
Cefipime	116/302	38.4
Cefotaxime	107/329	32.5
Nalidixic acid	45/144	31.3
Azithromycine	120/435	27.6
Cotrimoxazole	119/461	25.8
Meropenem	88/396	22.2
Ceftriaxone	36/167	21.6
Cephalothin	43/207	20.8
Cefixim	34/185	18.4
Amoxiclav	32/246	13
Ceftazidime	31/341	9.1
Ampicillin	36/437	8.2

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The results of susceptibility of isolated bacteria to antibiotics are presented in Table 3. *E Coli* present sensitivity rate to imipenem of 95.8% followed by 87.9% to nitrofurantoin and 63% to gentamicin. The susceptibility of Staphylococcus sp., the second highest prevalent pathogen, was 98.9% sensitive to imipenem followed by nitrofurantoin (88.6%) and 73.7% for ciprofloxacin. The susceptibility rate of Proteus sp. was 93.2% to imipenem followed by 85 %and 63.9% for ciprofloxacin and cefipim, respectively. For Klebsiella sp, it was 91.2% to imipenem followed by 80% and 60% to ciprofloxacin and amikacin, respectively. The least common pathogen Pseudomonas sp. showed 88%,62.5%and 55.6% sensitivity to imipenem, gentamicin and amikacin, respectively.

Table 3: the sensitivity of different micro organism to antibiotics.

Antibiotic	*E coli**	Staphylococcus sp. *	Proteus sp.*	Klebsiella sp.*	Pseudomonas sp.*	Others*
Cefixim	19/89 (21.3)	1/36(2.8)	11/27(40.7)	2/13(15.4)	1/9(11.1)	0/11 (0)
Amikacin	63/142 (44.4)	32/52(61.5)	11/33(33.3)	9/15(60)	5/9(55.6)	3/13 (23.1)
Amoxicillin	9/147 (6.1)	14/56(25)	5/36(13.9)	0/21(0)	0/13(0)	2/13 (15.4)
Cotrimoxazole	58/252 (23)	31/85(36.5)	16/59(27.1)	6/31(19.4)	2/15(13.3)	6/19 (31.6)
Imipenem	249/260 (95.8)	91/92(98.9)	55/59(93.2)	31/34(91.2)	16/18(88.9)	16/18 (88.9)
Nitrofurantoin	232/264 (87.9)	78/88(88.6)	15/61(24.6)	19/33(57.6)	4/17(23.5)	9/19 (47.4)
Ceftriaxone	23/95 (24.2)	2/32(6.3)	7/20(35)	2/9(22.2)	0/5(0%)	2/6 (33.3)
Ceftazidime	16/93 (8.3)	3/53(5.7)	11/46(23.9)	0/30(0)	1/11(9.1)	0/8 (0)
Nalidixic acid	25/74 (33.8)	2/15(13.3)	11/26(42.3)	4/15(26.7)	0/4(0)	3/10 (30)
Meropenem	53/212 (25)	13/75(17.3)	10/51(19.6)	3/28(10.7)	3/13(23.1)	6/16 (37.5)
Cephalothin	7/105 (6.7)	28/44(63.6)	6/23(26.1)	1/15(6.7)	0/10(0)	1/10 (10)
Ampicillin	10/233 (4.3)	16/85(18.8)	8/55(14.5)	0/30(0)	0/17(0)	2/17 (11.8)
Amoxiclavulanic acid	7/124 (5.6)	17/51(33.3)	6/33(18.2)	0/15(0)	0/8(0)	2/15 (13.3)
Azithromycin	90/239 (37.7)	11/73(15.1)	5/58(8.6)	5/29(17.2)	4/17(23.5)	5/19 (26.3)
Gentamicin	152/252 (60.3)	58/89(65.2)	29/58(50)	19/33(57.6)	10/16(62.5)	9/17 (52.9)
Rifampin	2/169 (1.2)	15/19(78.9)	0/37(0)	0/22(0)	0/12(0)	0/1 (0)
Cefipim	70/175 (40)	7/47(14.9)	23/36(63.9)	10/24(41.7)	1/11(9.1)	5/9 (55.6)
Cefotaxime	59/182 (32.4)	10/56(17.9)	24/43(55.8)	9/29(31)	1/11(9.1)	4/8 (50)
Ciprofloxacin	36/44 (81.8)	14/19(73.7)	17/20(85)	8/10(80)	2/4(50)	1/2 (50)

* Number of sensitive pathogen/ number of examined pathogen (% of sensitive pathogen)

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The antibiotic susceptibility of the urinary pathogens was also evaluated by patient gender (Table 4). There was no significant difference between genders regarding sensitivity pattern to antibiotics except for nitrofurantoin and ceftriaxone where females were more sensitive to these antibiotics (*P* = 0.027and 0.023, respectively). Males were more sensitive to ciprofloxacin (*P*=0.019).

Table 4: Antibiotic sensitivity with respect to gender.

Antibiotic sensitivity	Gender (No sensitive/No examined (% within gender)		*P* value
	Male*	Female*	
Cefixime	3/34 (8.8)	31/151 (20.5)	0.111
Amikacin	29/54 (53.7)	94/210 (44.8)	0.240
Amoxicilline	5/61 (8.2)	25/225 (11.1)	0.510
Cotrimoxazole	24/98 (24.5)	95/363 (26.2)	0.736
Imipenem	94/100 (94)	364/381 (95.5)	0.521
Nitrofurantoin	64/98 (65.3)	293/384 (76.3)	0.027
Ceftriaxone	2/31 (6.5)	34/136 (25)	0.023
Ceftazidime	7/78 (9)	24/263 (9.1)	0.967
Meropenem	12/82 (14.6)	76/314 (24.2)	0.063
Cephalothin	8/37 (21.6)	35/170 (20.6)	0.888
Amoxiclav	7/47 (49)	25/199 (12.6)	0.669
Gentamicin	52/95 (54.7)	225/370 (60.8)	0.282
Cefipime	20/68 (29.4)	96/234 (41)	0.08
Cefotaxime	17/65 (26.2)	90/264 (34.1)	0.221
Ciprofloxacin	23/24 (95.8)	55/75 (73.3)	0.019

* Number of sensitive pathogen/ number of examined pathogen (% of sensitive pathogen)

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Discussion

Urinary tract infection (UTI) is a relatively common problem in children and accounts for a significant number of pediatric hospital admission.[2] Antibiotic resistance is a major clinical problem in treating infections caused by uropathogens.[11] The appropriate antibiotic choice for UTI requires an adequate understanding of the epidemiology and the profile of local antimicrobial resistance of associated uropathogen which is not applicable to all geographical region.[1] Bacterial resistance to the antibiotics becomes a complicated issue in the UTI treatment especially with the emergence of new strains resistant to a high range of antibiotics.[12] This study describes the sensitivity profile of uropathogen causing UTI in a pediatric population of Raparin Teaching Hospital in Erbil city, Iraqi Kurdistan. The most common uropathogen isolated in this study was E Coli (54.1%).A similar result was obtained in Hilla(Iraq),[13] India[11]and Nepal[5] (49%, 61% and 59.4%, respectively). However, E Coli was found in only (33.8%) of patients in another study from the same hospital.[14] This might be due to the smaller sample size of the previous study. Staphylococcus sp. was the second most common uropathogen isolated in this study (19.1%).This was in concordance with a study done in the same hospital[14] but much higher than Theqar,[15] Nepal[5] and Spain[1] (5.3%, 5.5% and 0.7%, respectively). According to the age and sex distribution of the patients diagnosed with UTI, young male children were frequently affected by Klebsiella (100% occur in infant age group). The question of an underlying urinary pathology in males compared to females regarding Klebsiella infection is beyond the scope of this study, but it is known that children with urinary malformation have a decreased number of E Coli infections and an increased number of infections by other Gram negative organisms.[3] There is good evidence of historical and emerging resistance patterns; therefore, rationalization of prescription patterns by knowledge of sensitivities coupled with the re-examination of empirical antibiotic choices is clearly important. Local formularies should reflect geographical resistance patterns along with the best evidence on the duration and choice of antibiotic to maximize therapeutic effect while minimizing the development of resistant strains.[16] Drugs such as cephalosporin, sulfamethoxazole, trimethoprim and amoxicillin-clavulanate are the most utilized oral antibiotics.[1] In developing countries, the low sensitivity for commonly used antibiotics because these antibiotics have been extensively used in treatment of community acquired UTI and other infections in the past years.[6] The results obtained from this study showed a high resistance of almost all uropathogens to multiple antibiotics like ampicillin (91.8%), trimethoprim (74.2%) and cephalothin (79.2%).The same results were obtained from series of studies inside and outside Iraq[4,6,14]. Inappropriate clinical practices, unsupervised use, overuse, over the counter availability, lack of awareness and self- medication have worsened the condition in developing countries. Unqualified practitioners, untrained pharmacist, and nurses all over the country use antimicrobials indiscriminately.[4] All these might contribute to increasing resistance of isolated uropathogens. Similar practices have also been reported in India, Vietnam and Nepal.[17-18] Another possibility is that the high level of multidrug resistance was most probably due to production of extended spectrum beta lactamases in these isolates.[19-20] All the isolates were found to be sensitive to imipenem (95.2%).This is because this group is highly stable against beta lactamase and has unusual property of causing a post antibiotic effect on gram negative bacteria.[2] The best choices for treatment of UTI in our region include nitrofurantoin (sensitivity is 78.8%). In general *E Coli* and staph were highly sensitive for nitrofurantoin (87.9% and

86.7%, respectively) and Klebsiella moderately sensitive for it (57.6%) and low sensitivity for Proteus and Pseudomonas. It is a bacteriostatic agent for gram positive but a bactericidal for gram negative and can be used as an oral alternative for urinary infection[1,21] in addition to its low cost. It is active against many organisms including E. coli, Staphylococcus saprophyticus, Enterobacter, and Klebsiella species. It is also useful for the treatment of infection caused by ESBL E Coli. Nitrofurantoin only achieves an antibiotic concentration in the urine with low circulating blood levels and poor tissue penetration making it unsuitable for the treatment of upper UTIs. Nitrofurantoin is well absorbed, but it should be taken with food, as this improves its bioavailability. It is metabolized by the liver and eliminated by the kidneys. It is a useful antibiotic choice in pregnancy apart from at term when it is contraindicated. Other contraindications are renal failure and neonates and children with G6PD deficiency.[16] There was no statistically significant difference between genders regarding sensitivity pattern to antibiotics except for nitrofurantoin and ceftriaxone where females were significantly more sensitive to these antibiotics, while male was significantly more sensitive to ciprofloxacin. In the present study, a large number of E. coli and K. pneumonia were multidrug resistant and ESBL producers. ESBLs are β-lactamases capable of conferring bacterial resistance to the penicillins; first-, second- and third-generation cephalosporins; and aztreonam (but not the cephamycins or carbapenems) by hydrolysis of these antibiotics.[22] Monitoring of ESBL production and antimicrobial susceptibility testing are necessary to avoid treatment failure in patients with UTI.

Conclusion

It is quit alarming to note that most of the isolates included in this study were found resistant to four or more antibiotic. Therefore, it is an important issue to be addressed by policy-makers to restrict antibiotic prescription in our country. Empirical treatment with trimethoprim and ampicillin or amoxicillin-clavulanic acid for community acquired UTI may be insufficient due to the elevated rate of resistance of E Coli and other isolated uropathogens in our hospital. Conversely, nitrofurantoin is the only oral agent that remains relatively active against most uropathogens and can be used for empiric therapy in uncomplicated UTI, particularly in the community setting.

Conflicts of interest

The author reports no conflicts of interest.

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