Antibiotic resistance pattern and empirical therapy for urinary tract infections in children

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ABSTRACT

الأهداف: دراسة أنواع البكتريا المسببة لالتهابات البول لدى الأطفال (UTI)، ونمط مقاومتها للمضادات الحيوية.

الطريقة: أجريت هذه الدراسة في مستشفى عسير المركزي – عسير – المملكة العربية السعودية، في الفترة مابين يناير 2003م وحتى 2006م ولمدة أربع سنوات. تمت المراجعة لسجلات المرضى من الأطفال الذين أُجريت لهم مزرعة للبول وذلك لمعرفة أنماط الاستجابة والمقاومة للمضادات الحيوية، ومدى استجابة ومقامة هذه الأنواع من البكتيريا للمضادات الحيوية.

النتائج: نتج عن البحث ما مجموعة 464 عينة شكلت بكتريا (E. coli) النسبة الأعلى بواقع 37.3% ، تبعتها (*Klebsiella*) و(*Pseudomonas*) بواقع 16.4%، 15.7% بالترتيب. بشكل عام كان هناك ارتفاع ملحوظ في نسب مقاومة هذه الأنواع من البكتيريا للمضادات الحيوية المختلفة.

خاتمة: بالرغم من الزيادة في مقاومة البكتيريا للمضادات الحيوية التي تسبب التهابات البول عند الأطفال (UTI) فإن (Imipenem)، (Ceftriaxone) وفي بعض الأحيان (Azactam) هي علاجات وريدية مبدئية مناسبة لالتهابات البول (UTI) قبل الحصول على نتائج مزرعة البول ويمكن إعطاء علاج (Nalidixic Acid) أوعلاج (Nitrofurantion) عن طريق الفم للحالات التي لا تستدعي التنويم.

Objectives: To study the type of bacterial pathogen causing urinary tract infection in children at Aseer Central Hospital, southwestern Saudi Arabia, and their antimicrobial resistance patterns.

Methods: A retrospective study of all the urine cultures carried out on children in the period from January 2003 to December 2006, for a total of 4 years were reviewed at the bacteriology laboratory, Aseer Central Hospital, southwestern region of Saudi Arabia. Their antimicrobial resistances as well as sensitivities were also analyzed.

Results: A total of 464 urine cultures were identified. *Escherichia coli* constitutes the most common pathogen isolated (37.3%), followed by *Klebsiella* (16.4%) and Pseudomonas species (15.7%). In general, there was a significant increase in the resistance rates of different bacterial pathogens to different antibiotics.

Conclusion: In spite of an increase in the resistance rates of bacterial pathogens causing UTI, ceftriaxone, imipenem, and to some extent Azactam are appropriate for initial empirical intravenous therapy in UTI. In patients with uncomplicated UTI not requiring hospitalization, Nalidixic acid, and Nitrofurantoin can be used as oral treatment.

Saudi Med J 2008; Vol. 29 (6): 854-858

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Received 27th November 2007. Accepted 26th April 2008.

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Urinary tract infection (UTI) is one of the common diseases in children. Urinary tract infection can cause significant morbidity in children including renal scarring and end-stage renal disease.[1-4] For that reason, UTI should be treated immediately, even before results of bacteriological cultures are available. The choice of empiric antibiotic therapy depends on the expected causative organism and its susceptibility pattern. Knowledge of the prevalence of causative organisms causing urinary tract infections in children and their sensitivity pattern is mandatory for effective treatment. Previous reports have shown that several countries experienced rising resistance rates for antibiotics particularly of *Escherichia coli (E. coli)* resistant to beta-lactam antibiotics.[5-9] The aim of this study is to investigate the local prevalence and resistance patterns of urinary pathogens in the southwestern region of Saudi Arabia.

Methods. A retrospective analysis was performed on all pediatric urine samples (534 samples) sent to the bacteriology laboratory at Aseer Central Hospital, Southwestern region of Saudi Arabia for culture and sensitivity in the period from January 2003 to December 2006.

Strains were isolated from inpatients and outpatients with symptoms of UTI. All complete bacteriological reports of children aged 0-17 years were included in this study. The hospital is a primary to tertiary care center covering an urban and rural population of approximately 1,000,000 people. The retrospective evaluation did not consider whether UTI was complicated or uncomplicated, the first, or recurrent infection, nosocomial or community acquired. The collected data were solely based on laboratory findings. In order to study the changing pattern of resistance, a comparison was made between the 2 periods: from January 2003-December 2004 and from January 2005-December 2006. Urine samples were collected by either midstream clean catch, catheter suprapubic aspiration or bag urine samples. Bacteriuria was considered if more than 10^5 colony forming units/ml. Samples were cultured and incubated according to standard methods. Interpretation of antimicrobial susceptibility followed the international criteria.[10] All cultures with candida growth (70 samples) were excluded, thus, the total number of samples was 464 samples.

Statistical analyses were performed using SPSS program, version 13. Bivariant chi-square tests were calculated taking $p<0.05$ as the cut off point for significant values.

Results. **Table 1** demonstrates the prevalence of urinary pathogens detected during the period of study that extended from the year 2003 to 2006. Pathogens like *Acinetobacter*, *Enterococcus Cloaca*, *Streptococcus*, and *Provedentia saturatii* were rarely detected. **Table 2** compared the prevalence of the main pathogens during the periods 2003-2004 and 2005-2006. There were no significant differences in the prevalence of all pathogens except for *Proteus,* which raised significantly ($p=0.01$) from 5.4-12.2%. **Table 3** describes the resistance rates (in percentages) of the main urinary pathogen to some antibiotics during the total period of the study (2003-2006). Most antibiotics tested for *Enterococcus fecalis* were ineffective. For *Pseudomonus*, resistance to Cefaclor, Nitrofurantoin, Nalidixic acid, and Cotrimoxazole was noticed. As for *Proteus*, resistance to Amikacin was not noticed in Cefaclor and Cotrimoxazole of cases. **Table 4** shows the significant increases in resistance to some antibiotics between the 2 periods of study. Thus, *E. coli* exhibited a significant increase in resistance to Piperacillin from 67-84%. Also, the resistance to Cefotriaxone raised significantly from 11-33%. *Klebsiella* showed significant increase in resistance to Piperacillin, Ceftazidime, Aztreonam, and Nalidixic acid. Lastly, *Pseudomonus* showed a significant increase in resistance to Nitrofuration to the alarming level of 100%. However, neither *Staphylococcus aureus* nor *Enterococcus fecalis* or *Proteus* showed any significant increase in resistance to the tested antibiotics.

Table 1 - Prevalence of urinary pathogens during the period of study 2003-2006 (N=464).

Pathogen	n (%)
Escherichia coli	173 (37.3)
Klebsiella spp.	76 (16.4)
Pseudomonas aeruginosa	73 (15.7)
Enterococcus fecalis	57 (12.3)
Proteus spp.	34 (7.3)
Staphylococcus aureus	29 (6.3)
Acinetobacter	10 (2.2)
Others	12 (2.5)
Total	**464 (100)**

Table 2 - Comparison of the prevalence of main urinary pathogens in the periods 2003-2004 and 2005-2006.

Pathogen	2003 -2004 (n=295)	2005-2006 (n=147)
	n (%)	
Escherichia coli	121 (41)	52 (35.4)
Klebsiella species	46 (15.6)	30 (20.4)
Pseudomonas aeruginosa	53 (18)	20 (13.6)
Enterococcus fecalis	42 (14.2)	15 (10.2)
Proteus species	16 (5.4)	18 (12.2)*
Staphylococcus aureus	17 (5.8)	12 (8.2)
Total	**295 (100)**	**147 (100)**

* Significant at $p=0.01$

Discussion. The UTI resistance pattern should be considered when selecting empirical treatment. Thus, the antibiotic policy should be formulated according to local surveillance data. In our study, the spectrum and resistance pattern of uropathogens to common antimicrobial agents were analyzed. The 2 periods from January 2003-December 2004 and from January 2005-December 2006, showed that the most common pathogen was *E. coli* followed by Gram-ve bacteria (*Klebsiella*, *Pseudomonas*, and *Proteus*). The spectrum pattern of uropathogens between the 2 periods showed no significant difference in the prevalence of all pathogens except for *Proteus,* which rose significantly ($p=0.3$) from 4.5-10.25%. There is a high resistance rate to oral cephalosporin (Cefaclor) by *E. coli* and other

Table 3 - Resistance rates of different urinary pathogens to some antibiotics during the total period of study 2003-2006 (N=464).

Antibiotic	*Escherichia coli* n=173	*Klebsiella Species* n=76	*Pseudomonus aeruginosa* n=73	*Enterococcus fecalis* n=57	*Proteus species* n=34	*Staphylococcus aureus* n=29
			%			
Ampicillin				83.6		77.8
Cefaclor	75.6	74.7	88.2	96.4	50	44.8
Cotrimoxazole	61.3	62.2	85.7	98.2	50	50
Ceftriaxone	10.4	27.3	60.4		41.2	
Ceftazidime	15.0	61.3	48.2		31.3	
Gentamycin	48.4	36.2	36.4	89.6	34.6	50
Amikacin		62.5	30		82.4	
Aztreonam	36.1	60	51.7		25	
Nalidixic acid	24.5	23	87.5		21.9	
Nitrofurantoin	4.3	19.4	88.4		21.9	
Piperacillin	74.6	73.3	39		29.4	
Ciprpofloxacin	22.8	22.2	28.8		16.7	

Table 4 - Resistance rates of different urinary pathogens to some antibiotics during the 2 period of study 2003-2004 and 2005-2006 (N=464).

Antibiotic	*Escherichia coli*		*Klebsiella species*		*Pseudomonusaeruginosa*		*Enterococcus fecalis*		*Proteus species*		*Staphylococcus aureus*	
							%					
	2003-2004	2005-2006	2003-2004	2005-2006	2003-2004	2005-2006	2003-2004	2005-2006	2003-2004	2005-2006	2003-2004	2005-2006
Ampicillin							85.4	78.6			82.4	70
Cefaclor	75.8	75	71.1	80	90.3	85	97.5	93.3	43.8	55.6	41.2	50
Cotrimoxazole	62.6	58.3	53.3	75.9	90	78.9	100	93.3	40	58.8	35.3	58.3
Cefotriaxone	11.1	33.3*	30.8	14.3	66.7	41.7						
Cefrazidime	41.2	37.5	41.7	73.7*	53.5	30.8				33.3		
Gentamycin	41.6	48.3	31	50	44.4		91.7	83	33.3	36.4	50	50
Amikacin	52.9	43.3	50	70	33.3	20			100	76.9		
Aztreonam	37.1	34.6	41.7	72.2*	57.8	33.3			50	16.7		
Nalidixic acid	20.7	34	13.3	37.9*	79.2	100			13.3	29.4		
Nitrofurantoin	4.2	4.3	20.9	17.2	81.5	100*			13.3	29.4		
Piperacillin	67.6	84*	45.5	89.5*	48.9	7.1				23.1		
Imipinam					26.8							
Ciprofloxacin	25.6	19.4	13.3	28.6	32.6	11.1			20	15.4		

*significantly higher at $p<0.05$ than the previous period 2003-2004.

gram-ve organisms. Moreover, *E. coli* showed significant increase in resistance to Cefotriaxone in the second period. Although the rate is not high, this finding is to be considered as Cefotriaxone is a frequently used antibiotic (compared to Cefotaxime) as empirical treatment. Moreover, as the other gram-ve uropathogens showed lower rate of resistance to Cefotriaxone (especially in the second period), it is still to be used for these pathogens empirically. The pattern of resistance to the highly active Cephalosporins (Cefotriaxone and Ceftazidime) was still promising although there was a significantly increased rate of resistance in the second period for Cefotriaxone by *Klebsiella* and *E. Coli,* however, the range is still acceptable if we compare it to the aminoglycosides. Ceftazidime, one of the widely used Cephalosporins, encountered significantly raising

resistance by *Klebsiella*. This finding calls for limiting its use in UTI especially when *Klebsiella* is suspected to be the main pathogen. The trend of increasing resistance of urinary pathogens during the past few years is well recognized as in our findings.[11-13] Cephalosporins are favorite antimicrobial agents for the empirical treatment of not only UTI, but also community acquired respiratory tract infection. Moreover, in secondary and tertiary centers, Cephalosporins are widely used.[14] Therefore, it seems rational to make any effort to reduce the widespread use of Cephalosporins.[15]

Our data indicate that it is appropriate for initial empirical intravenous therapy in UTI to use Cefotriaxone, imipenum and to some extent, Aztrionam (except for *Klebsiella*). There is much evidence suggesting a relationship between prescribing habits and antibiotics resistance.[16] The less frequently used antibiotics, Imipenum and Ciprofloxacin, showed a lower rate of resistance for almost all tested urinary pathogens. Although Ciprofloxacin is still not licensed for pediatric use, both antibiotics are to be reserved for complicated UTI. When comparing the resistance rate of the 2 Aminoglycoside (Gentamicin and Amikacin) it seems that the resistant rate of gram-ve bacteria to Amikacin is more than to Gentamicin, a finding not noticed in an other study.[17] This may be due to the frequent use of Amikacin in our institution to treat UTI and other pediatric infections. If the need arises for using Aminoglycosides, we think that using Gentamicin will be more effective than Amikacin. In this aspect, *Pseudomonas* is still showing lower resistance rate to both Aminoglycosides. Azactam, Ampicillin, and Aminoglycosides (Amikacin) showed in this study relatively high resistance rate, which was not found in other centers studies.[8-14] However, the resistance rate of *Pseudomonas* to Nalidixic acid and Nitrofurantoin was almost total and raising significantly in the second period of the study. This pattern was less obvious for the other gram-ve organisms, where the 2 antibiotics can still be used as an alternative oral treatment or prophylaxis, if the patient is not a febrile infant as it is known that at this age they do not achieve therapeutic concentration in the blood stream, and they are readily excreted in the urine.[2]

The data from this study, showed that it may be inappropriate to continue using oral Cefaclor, Cotrimoxazol, or Ampicillin as treatment or prophylaxis of urinary infections, as there is significant resistance to these antibiotics while still Nitrofurantoin and Nalidixic acid have relatively more efficacy to uropathogens (except with pseudomonas). It seems wise to use them first with oral Cefixime for both treatment and prophylaxis as this antibiotic showed efficacy in UTI treatment in some studies.[13] Unfortunately, Cefixime was not included in our study. In patients with uncomplicated UTI who do not require hospitalization, Nalidixic acid, and Nitrofurantoin can be used as an oral treatment.

Some reports suggested that oral treatment, even for febrile young children with UTI are safe and effective compared to IV therapy.[17] Extreme caution should be taken in young children, as IV treatment is still mandatory in severely affected children.[18] The limitation of this study is, being a retrospective and laboratory based study, it was not possible to differentiate between first or second attack, neither complicated nor uncomplicated UTI. The main goal of this study was to define a rational treatment option for patients that would cover most of the urinary pathogens in children who require oral or IV treatment irrespective of their history and the nature of UTI.

We recommend that, because of the variation of resistance patterns in different regions, it is important for each hospital to formulate their antibiotics policy according to their local resistance pattern, which can be assessed by hospital and laboratory - based surveillance studies.

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Related topics

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