Original Article

CHANGING PATTERNS IN SENSITIVITY OF BACTERIAL UROPATHOGENS TO ANTIBIOTICS IN CHILDREN

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ABSTRACT

Objective: To determine the sensitivity/resistance of bacterial uropathogens to antibiotics in children and evaluate the changing pattern of their sensitivity over a six years period.

Methodology: Medical records of children between two moths to 14 years of age who admitted with symptomatic urinary tract infection were studied in two periods: First from 2006 to 2007 and the second from 2000 to 2001 in Children's Hospital of Tabriz/Iran. The sensitivity patterns of uropathogens were compared between two periods of study.

Results: The most frequently isolated germs were E.Coli, klebsiella, enterobacter, pseudomonas aeroginosa and proteus in a descending order. In study of 2006-2007: Among the oral agents, nitrofurantoin and ciprofloxacin, and among the parenteral agents, amikacin and gentamicin had the highest activity against E.coli. The highest sensitivity of klebsiella was to ciprofloxacin, nalidixic acid, cefixime, and amikacin in a descending order. The activity of ceftriaxone, ceftizoxime, nalidixic acid and cephalexin against E.coli has decreased significantly over six years ($P<0.05$). Also the activity of ceftriaxone, ceftizoxime, gentamicin, amikacin and nalidixic acid against klebsiella has decreased in comparison with results of six years ago ($P<0.05$). There was not any significant difference in sensitivity of enterobacter and pseudomonas with results of six years ago.

Conclusion: Increasing resistance of uropathogens to third generation cephalosporines and aminoglycosides raises an alarm for widespread use of these life saving drugs. The guidelines for empiric treatment of UTI should be revaluated periodically based on local studies.

KEY WORDS: Urinary tract infection, sensitivity, resistance, bacterial uropathogen (child).

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common causes of hospitalization and referral to out patient settings in children. It is estimated that at least 3% of girls and 1% of boys experience one episode of UTI before the 11th years of age.[1] About 30-50% of these patients will have another episode within three months to two years, particularly in girls.[2,3] Upper UTI (pyelonephritis) is a major cause of hypertension, renal insufficiency and end-stage renal failure in children. Early treatment of UTI with an effective antibiotic is essential for prevention from long-term consequences. Delay in treatment

increases the risk of scar formation in kidneys.[4] So in almost all children with UTI, antimicrobial therapy is initiated empirically before the result of urine culture is available. Sensitivity of bacterial uropathogens to antibiotics show a great geographical and historical variability due to different antibiotic treatments. So knowledge of the sensitivity pattern of common uropathogens according to local epidemiological studies is necessary for selection of an appropriate antibiotic for empirical treatment. Pape et al recommended that the policies for treatment of UTI in children should be re-evaluated every five years according to local resistance rates.[5] In our center data is limited on the susceptibility pattern of uropathogens to antibiotics.

The aim of this study was to determine the distribution and sensitivity pattern of uropathogens isolated from children and compare the findings with sensitivity pattern of 6 years ago in a tertiary care hospital in north-west of Iran.

METHODOLOGY

This study was conducted at the children's Hospital of Tabriz/Iran. Medical records of children between two months to 14 years of age with diagnosis of UTI (inpatient and outpatient) were evaluated from April 2006 to September 2007, and patients who had positive urine culture in association with pyuria were selected for study. Clinical diagnosis was based on the presence of one or more of followings: fever, flank pain, dysuria, frequency, urgency and suprapubic pain. Pyuria was defined as the presence of more than seven leukocytes in high power filed of centrifuged urine. Positive urine culture was defined as more than 10^5 colony forming units (CFU) of a single organism per milliliter of urine. Urine specimens were obtained by midstream collection in toilet trained children and sterile urine bags in younger children after disinfecting the perineum. Suprapubic sampling was carried out in selected patients. Blood agar was used for urine culture. Sensitivity/resistance of isolated microorganisms to commonly used antibiotics was detected by disc diffusion method.

Exclusion criteria were: patients without pyuria, asymptomatic patients and positive cultures with less than 10^5 CFU/ml or multiorganism growth. Also patients with insufficient data and repeat isolates from the same patient were excluded. Data from each patient including sex, age, clinical symptoms, and results of urine analysis, urine culture and antibiogram were collected in organized forms.

This study was repeated with the same method, from April 2000 to September 2001, and sensitivity pattern of uropathogens in these two periods of study were compared. The research ethics committee of Tabriz University of Medical Sciences approved the study. Data was analyzed by SPSS 14 software using Chi square test for comparisons. P.values less than 0.05 was considered as significant.

RESULTS

From April 2006 to September 2007, 232 patients and from April 2000 to September 2001, 205 patients who fulfilled the inclusion criteria were studied. Demographic features of patients have been demonstrated in Table-I. E.Coli, klebsiella pneumoniae and enterobacter were the most common isolated germs in both periods of study (Table-II). The invitro sensitivity of E.Coli and klebsiella to antibiotics has been shown in (Table-III&IV).

In study of 2006-2007 among the oral agents, nitrofurantoin and ciprofloxacin, and among the parenteral agents, amikacin and gentamicin had the highest activity against E.coli (Table-III). The

Table-I: Demographic features of patients with UTI

Period of study	*No. of patients*	*Mean age±SD (months)*	*No. of boys (%)*	*No. of girls (%)*
2006-2007	232	40.1±3.4	64 (27.6%)	168 (72.4%)
2000-2001	205	38.8±3.3	59 (28.8%)	146 (71.2%)

Table-II: Distribution of bacteria causing UTI in two periods of study

Microorganism	*No (%) in 2006-2007*	*No (%) in 2000-2001*
E.Coli	146(63%)	133 (64.9%)
Klebsiella Pneumoniae	45(19.4%)	38 (18.5%)
Enterobacter	14(6%)	15 (7.3%)
Pseudomonas aeroginosa	11(4.7%)	12 (5.85%)
Proteus mirabilis	9(3.9%)	5 (2.43%)
Enterococcus faecalis	5(2.2%)	2 (0.98%)
Staphylococcus aureus	1(0.4%)	_
Providentia	1(0.4%)	_
Total	232	205

antibiotics with highest activity against klebsiella were ciprofloxacin, nalidixic acid and cefixime in a descending order (Table-IV).

The activity of ceftriaxone, ceftizoxime, nalidixic acid and cephalexin against E.coli has decreased significantly over six years (P<0.05). Also the activity of ceftriaxone, ceftizoxime, gentamicin, amikacin and nalidixic acid against klebsiella has decreased in comparison with results of six years ago (P<0.05). There was not any significant change in susceptibility of E.coli and klebsiella to other antibiotics in two periods of study.

In study of 2006-2007, the sensitivity of enterobacter was 78.5% to gentamicin, 71.4% to ceftazidime, 57.1% to ciprofloxacin and ceftriaxone, 50% to amikacin and nitrofurantoin, 42.8% to nalidixic acid and 35.7% to cotrimoxazol. The sensitivity of pseudomonas was 100% to ciprofloxacin and ceftazidim, 81.8% to gentamicin and 63.6% to amikacin. All other antibiotics were totally inactive against pseudomonas.

There was not any significant difference in antibacterial sensitivity of enterobacter and pseudomonas in two periods of study (P>0.05).

Table-III: In vitro sensitivity of E.Coli to antibiotics in two periods of study

Antibiotic	*Sensitivity in 2006-2007(%)*	*Sensitivity in 2000-2001(%)*	*P.value*
Nitrofurantoin	132 (90.4%)	101 (75.9%)	P>0.05
Amikacin	123 (84.2%)	129 (97%)	P>0.05
Ciprofloxacin	119 (81.5%)	120 (90.2%)	P>0.05
Gentamicin	101 (69%)	96 (72.2%)	P>0.05
Ceftizoxime	93 (63.7%)	113 (85%)	*P<0.05*
Ceftriaxone	88 (60.2%)	119 (89.4%)	*P<0.05*
Nalidixic Acid	81 (55.4%)	120 (90.2%)	*P<0.05*
Ceftazidime	75 (51.3%)	71 (53.3%)	P>0.05
Cefixime	59 (40.4%)	59 (44.3%)	P>0.05
Cotrimoxazol	26 (17.8%)	32 (24%)	P>0.05
Amoxicillin	21 (14.3%)	23 (17.2%)	P>0.05
Cephalotin	14 (9.5%)	50 (37.5%)	*P<0.05*
Ampicillin	12 (8.2%)	12 (9%)	P>0.05
Total	146	133	-

Table-IV: In vitro sensitivity of klebsiella pneumoniae to antibiotics in two periods of study

Antibiotic	*Sensitivity in 2006-2007*	*Sensitivity in 2000-2001*	*P.Value*
Ciprofloxacin	35 (77%)	31 (81.5%)	P>0.05
Nalidixic Acid	29 (64%)	35 (92%)	*P<0.05*
Cefixime	28 (62.2%)	25 (65.7%)	P>0.05
Amikacin	18 (40%)	26 (68.4%)	P>0.05
Nitrofurantoin	17 (37.7%)	13 (34.2%)	P>0.05
Ceftazidime	17 (37.7%)	15(39.4%)	P>0.05
Cotrimoxazol	16 (35.5%)	14 (36.8%)	P>0.05
Gentamicin	14 (31%)	20 (52.6%)	*P<0.05*
Ceftizoxime	10 (22.2%)	25 (65.7%)	*P<0.05*
Ceftriaxone	9 (20%)	20 (52.6%)	*P<0.05*
Cephalotin	5 (11%)	6 (15.7%)	P>0.05
Ampicillin	0%	0%	_
Total	45	38	_

DISCUSSION

Escherichia-coli is the most common cause of UTI and accounts for 75-90% of UTIs in children.[6,7] However its relative frequency varies in different areas. 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 UTIs,[8-11] that is similar to our results.

In empiric treatment of acute febrile UTI, suggestive of pyelonephritis, broad spectrum antibiotics such as ceftriaxone or a combination of ampicillin with an aminoglycoside such as gentamicin is conventionally recommended.[6,12] However in some studies from Iran,[4,13] Mexico[9] and Sudan,[14] microbial resistance to ampicillin is high and varies from 75% to 89.3%. In present study, resistance to ampicillin is very high (91.8%). So adminstration of ampicillin in empiric treatment of UTI is not reasonable in our center. Most studies show a high sensitivity of E.coli to gentamicin.[15] In the study of Goldstein et al in France, the susceptibility of E.coli to gentamicin was 98.4%.[16] In our study the susceptibility of E.coli is 69.9% to gentamicin and 84.4% to amikacin which is lower than other studies. Also present study showed that the activity of ceftriaxone against E.coli and klebsiella and activity of aminoglycosides against klebsiella has significantly decreased over six years. Decreaseing trend in activity of aminoglycosides and third generation cephalosporines against uropathogens raises a great concern regarding the empiric treatment of pyelonephritis, in our institution.

Among oral antibiotics for ambulatory management of uncomplicated lower UTI, cotrimoxazol was a drug of choice for a long time. During the past decades resistance of E.coli to cotrimoxazol increased from 0-5% before 1990 to 9-15% in 1999 in Western countries.[17] In recent years resistance of E.coli to cotrimoxazol has increased and varies from 21% to 76.7% in different studies.[8-10,13-15,18-22] In our study, resistance of E.coli to cotrimoxazol (82.2%) is higher in comparison with literature that may be related to inappropriate prescription of cotrimoxazol in upper respiratory infections in our country. From other oral agents fluoroquinolones (FQs) such as ciprofloxacin have the highest activity against E.Coli in most studies.[14,16,18-20] So in the past few years use of cotrimoxazol has decreased whereas use of FQs has increased dramatically in adults.[23] Guneysel et al observed that FQs were the most prescribed antibiotics for UTI of adults in Turkey.[20] The activity of ciprofloxacin against E.coli has been reported up to 93.3% in children[4] and is 81.5% in our study. However the safety of ciprofloxacin in children is under study because

of potential cartilage damage that occurred in research with immature animal.[6]

In our study, nitrofurantoin has the highest activity against E.coli (90.4%). The susceptibility of E.coli to nitrofurantoin has been reported from 83.6% to 98.8%.[18-20] Although this agent may be used for treatment of lower UTI, its use in pyelonephritis is not recommended because of inadequate tissue levels.[6]

CONCLUSION

This study has showed a decreasing susceptibility of E.coli and Klebsiella to some antibiotics over a six years period. If this trend continues, the antimicrobial drugs are likely to become less effective not only for treating of UTI, but also for treating of other life threatening infections. However, it should be noted that our hospital is a referral center for most complicated UTIs. Further community based studies in general hospitals and outpatient settings are required to determine the resistance pattern of uropathogens in uncomplicated UTIs.

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REFERENCES

1. Gulati S, Kher V. Urinary tract infection. Indian Pediatrics 1996;33:211-17.
2. Yildiz B, Kural N, Durmaz G, Yarar C, Ak I, Akcar N. Antibiotic resistance in children with complicated urinary tract infection. Saudi Med J 2007;28(12):1850-4.
3. Mangiarotti P, Pizzini C, Fanos V. Antibiotic prophylaxis in children with relapsing urinary tract infections: review. J Chemother 2000;12 (2):115-23.
4. Sharifian M, Karimi A, Tabatabaei SR, Anvaripour N. Microbial sensitivity pattern in urinary tract infections in children: A single center experience of 1177 urine cultures. Jpn J Infect Dis 2006;59:380-2.
5. Pape L, Gunzer F, Ziesing S, Pape A, Offner G, Ehrich JH. Bacterial pathogens, resistance patterns and treatment options in community acquired pediatric urinary tract infection. Klin Padiatr 2004;216(2):83-6.
6. Elder JS. Urinary tract infections in: Kliegman RM, Behrman RE, Jenson HB, Stanton B. Nelson textbook of pediatrics. 18th ed. Philadelphia; Saunders 2007;2224-6.
7. McLoughlin TG Jr, Joseph MM. Antibiotic resistance patterns of uropathogens in pediatric emergency department patients. Acad Emerg Med 2003;10(4):347-51.
8. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnik LP, et al. Antibiotic resistance in outpatient urinary isolates: final results from the North American urinary tract infection collaborative alliance (NAUTICA). Int J Antimicrob Agents 2005;26(5):380-8.
9. Hernandez-Porras M, Salmeron-Arteage G, Medina-Santillan R. Microbial resistance to antibiotics used to treat urinary tract infection in Mexican children. Proc West Pharmacol Soc 2004;47:120-121.
10. Shaikh D, Ashfaq S, Shaikh K, Shaikh M, Naqavi BS, Mahmood ZA, et al. Studies on resistance/sensitivity pattern of bacteria related with urinary tract infections. Medical J Islamic World Academy of Sciences 2005;15(4):129-133.
11. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections In JNMC Hospital Aligarh, India, Ann Clin Microbiol Antimicrob 2007;6:4. (Online).
12. Haller M, Brandis M, Berner R. Antibiotic resistance of urinary tract pathogens and rationale for empirical intravenous therapy. Pediatr Nephrol 2004;19(9):982-6.
13. Haghi Ashteiani M, Sadeghi far N, Abedini M, Soroush S, Taheri-Kalani M. Etiology and antibacterial resistance of bacterial urinary tract infections in children Medical center, Tehran, Iran. Acta Medica Iranica 2007;45(2):153-7.
14. Ahmed AA, Osman H, Mansour AM, Musa HA, Ahmed AB, Karrar Z, et al. Antimicrobial agent resistance in bacterial isolation from patients with diarrhea and urinary tract infection in the Sudan. Amm J Trop Med Hyg 2000;63(5,6):259-63.
15. Allen UD, MacDonald N, Fuite L, Chan F, Stephens D. Risk factors for resistance to "first-line" antimicrobials among urinary tract isolates of Escherichia coli in children. CMAJ JAMC 1999;160(10):1436-40.
16. Goldstein FW. Antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections in France. Multicentre Study Group. Eur J Clin Microbiol Infec Dis 2000;19(2):112-17.
17. Radalski VV, Strachunskii LS, Krechikova OI, Eidelshtein IA, Akhmetova LI, Babkin PA, et al. Resistance of ambulatory urinary infection pathogens according to the data of multicenter microbiological studies UTIAP-I and UTIAP-II. Urologiia 2004;2:13-17.
18. Rafal'skii VV, Rokhikov IM, Strachunskii LS. Clinico microbiological characteristics of community-acquired infections of the urinary tracts in Moscow. Urologiia 2007;(5)18:20-3.
19. Farrell DJ, Morrissey I, Rubeis D, Robbins M, Felmingham D. A UK multicentre study of the antimicrobial susceptibility of bacterial pathogens causing urinary tract infection. J Infect 2003;46(2):94-100.
20. Guneysel O, Onur O, Erdede M, Denizbasi A. Trimethoprim/sulfamethoxazol resistance in urinary tract infections. J Emergency Medicine 2009;36(4):338-341.
21. Prelog M, Schiefecker D, Fille M, Wurzner R, Brunner A, Zimmerhackl LB. Febrile urinary tract infection in children: ampicillin and trimethoprim insufficient as empirical monotherapy. Pediatr Nephrol 2008;23(4):597-602.
22. Gaspari RJ, Dickson E, Karlowsky J, Doern G. Multi drug resistance in pediatric urinary tract infections. Microb Drug Resist 2006;12(2):126-9.
23. Hooton TM, Besser R, Foxman B, Fritsche TR, Nicolle LE. Acute uncomplicated cystitis in an era of increasing antibiotic resistance: A proposed approach to empirical therapy. Clinical Infectious Dis (CID) 2004;39:75-80.