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ORIGINAL ARTICLE

Antibiotic Sensitivity Patterns of Uropathogens in Children: The Current Trend

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ABSTRACT

Background: The emergence of antibiotic-resistant infections has led to increased health care costs and mortality among children. The purpose of this study was to determine the causative organisms responsible for urinary tract infection and their antibiotic sensitivity pattern among pediatric patients of Rawalpindi/Islamabad.

Material and Methods: This cross-sectional study was carried out from June 2014 to June 2015, in the Department of Microbiology, Army Medical College, Rawalpindi, affiliated with the Military Hospital, Rawalpindi. About 270 urine samples of children with UTI were analyzed through Analytical Profile Index (API) 20E and biochemical test strips system. Their antibiotic susceptibility was determined by using standard techniques. Data were assessed and analyzed by SPSS version 17.

Results: Most common uropathogen was *Escherichia coli* (61.48%), followed by *Proteus* (15.5), *Klebsiella* (12.3%), *Pseudomonas* (4.5%), *Enterococcus* (3.7%) and *Enterobacter* (2.5%). Gram-negative rods, were most sensitive to imipenem (100%), Gentamycin (86%) and Amikacin (78.3%). They were least sensitive to Ampicillin (4.2%) and Norfloxacin (5.5%). Gram-positive cocci showed highest sensitivity for Vancomycin (100%) while displayed relatively less sensitivity for Nitrofurantoin (61.2%) and Gentamycin (48.7%). Cephalosporins also showed increased resistance with only 14% of gram-negative rods showing sensitivity to Cefotaxime. These organisms were highly resistant to Penicillin, showing a sensitivity of only 12.4%.

Conclusion: Decreased sensitivity against penicillin and cephalosporins is seen in uropathogens causing UTI in children. High sensitivity towards Nitrofurantoin makes this drug an empirical treatment in UTI. Regular surveillance of the developing resistance in uropathogens due to inappropriate use of antibiotic is necessary to reduce complication in children with urinary tract infection.

Key words: Antibiotic resistance, Bacterial sensitivity, Cephalosporins, Multi-drug resistance, Urinary tract infection

Authors' Contribution:
[1,2] Conception, synthesis, planning of research and manuscript writing Interpretation, discussion, [3,4] Active participations in data collection [5,6] Data analysis.

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Introduction

One of the most common infections among children is urinary tract infections (UTI).[1] If ignored or untreated it can lead to a number of complications including pyelonephritis, renal scarring, hypertension, and end-stage renal disease. All these complications result in increased health care costs and mortality.[2] UTI mostly occurs during the first year of life, however in girls it can occur at any age[1]. Timely diagnosis and prompt treatment are essential to reduce life-threatening complications.[3]

Most common organisms in UTI originate from intestine[4], but causative agent is not limited to E. coli. Proteus

species, Pseudomonas, Klebsiella, Staphylococcus species, Streptococcus species, Chlamydia, Neisseria gonorrhea, Candida species and Mycoplasma are also involved in urinary tract infections.[5]

This is an unquestionable fact that the use of antibiotic reduces the complications and mortality related to urinary tract infections in childhood. However, the overuse or misuse of antibiotics results in the antibiotic resistance in the urinary pathogens.[6] Widespread use of antibiotics has led to an alarming rise of resistance against third-generation cephalosporins and aminoglycosides. Sensitivity patterns of uropathogens to different commonly used antibiotics show great historical and geographical variation. The awareness and the knowledge of the sensitivity pattern of common uropathogens in children is necessary for selection of an appropriate antibiotic for empirical treatment.[7] This is because resistant strains are becoming difficult to treat and will lead to therapeutic dead ends.[8] Antibiotic resistance in the treatment of UTI is a hurdle for health physicians, mainly in the developing countries where there is frequent use of spurious drugs.[9] Such practices not only endanger the health of the patient but also increase bacterial resistance to certain drugs thus leading to less available option for treatment of UTIs.[10] There are regional variations in drug resistance patterns.[11] To reduce treatment failure and health care costs[12] , it is important to understand the spectrum and resistance patterns, helping in effective empirical antibiotic therapies.[13] The epidemiological data of empiric antibiotic therapy must be updated regularly for monitoring of bacterial antibiotic resistance.[14] Despite these regional variations, no country can save itself[15] because resistant strains can be imported through travel and trade.[16]

Moreover, bacteria are known to develop resistance against several antibiotics with time. Thus, it is important to determine the new resistance pattern in urinary pathogens to facilitate efficient management of urinary pathogens as well as to reduce complications in pediatric patients.[17] This study was undertaken to obtain current knowledge of the type of organisms responsible for UTIs among children in our population along with their antibiotic sensitivity patterns. We also explored age related gender variation among children presenting with UTI.

Material and Methods

It was a cross-sectional study, carried out in the Department of Microbiology, Army Medical College, Rawalpindi. Sample size was calculated using WHO sample size calculator. Keeping confidence interval at 95%, margin of error 5%, expected frequency of outcome factor as 82.3%, sample size was calculated to be 224.[18] In order to minimize bias and increase the strength of study a total of 270 samples of urine were studied. The evaluation included 270 urine specimens of children aged between I month to 12 years, that showed more than 100,000 colony-forming units/mL of a single pathogen on urine culture. Exclusion criteria was specimens showing multiple organisms on urine culture.

All samples were cultured on Cysteine Lactose Electrolyte deficient agar (CLED) (Oxoid UK) incubated at 37°C for 48 hours and bacteria were identified by standard biochemical methods. For antibiotic sensitivity, modified Kirby Bauer disc diffusion method was applied. A panel of antimicrobial agents depending on the identified causative organism was used and bacterial susceptibility zones against antibiotics were measured with help of Clinical Laboratory Standards Institute (CLSI) guidelines. Data were assessed and analyzed by SPSS version 17. Chi-square test was applied to assess gender variation among different age groups in children suffering from UTI. A *p*-value of <0.05 was considered significant.

Results

In our study, the total number of urine samples evaluated were 270, of which 133 were of girls and 137 of boys. Mean patient age was 41.11 ± 41.27 months. This study showed that the frequency of UTI in children was highest during the first year of life, which progressively decreased with age. In infants, boys (28.51%) were affected more; in contrast to girls (14.07%). Whereas between 1 to 5 years, a greater number of females were affected (1.28: 1).

Table I: Comparison of age groups and gender distribution in children with UTI					
Gender	**≤1 year n (%)**	**>1-5 years n (%)**	**>5-12 years n (%)**	**Total n (%)**	***P*-value**
Male	77 (28.51)	35 (12.96)	25 (9.26)	137 (50.74)	<0.001
Female	38 (14.07)	45 (16.66)	50 (18.51)	133 (49.26)	
Total	115 (42.59)	80 (29.62)	75 (27.77)	270 (100)	

This trend in UTI frequency between the two genders continued till the 12th year of life. This variation in gender between the three age groups in children was found to be highly significant (p <0.001). (Table I).

Among the positive urine culture, Gram-negative bacilli were most frequently isolated accounting for 97% (n=263) of infections, whereas gram-positive cocci comprised only 3% (n=7) of cases. Among the gram-negative rods, E. coli was the most frequently isolated pathogen followed by Proteus and Klebsiella. Among the gram-positive cocci, Enterobacter was the only pathogen isolated. (Figure 1).

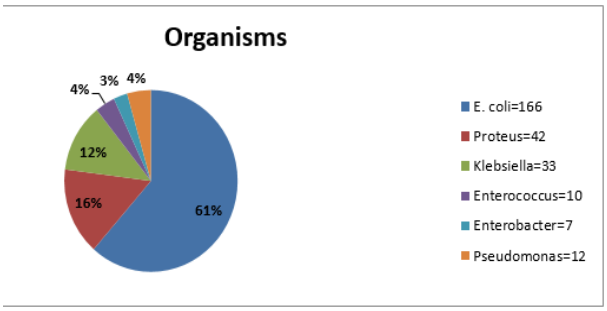

Figure 1: Percentage distribution of uropathogens in children

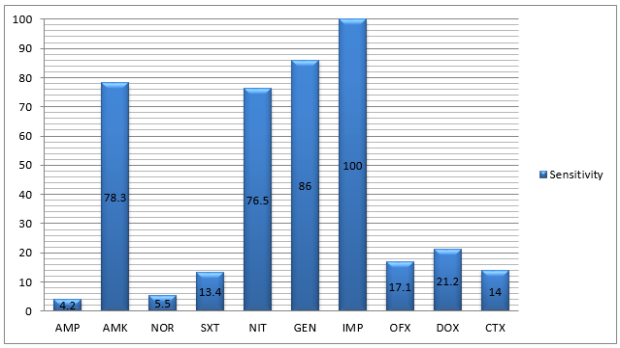

Figure 2: Antibiotic sensitivity pattern in gram-negative rods

**AMP, Ampicillin; AMK, Amikacin; NOR, Norfloxacin; SXT, Trimethoprim-sulphamethoxazole; NIT,Nitrofurantoin;GEN, Gentamicin;IMP, imipenem; OFX, OFloxacin; DOX, Doxycycline; CTX, Cefotaxime*

Among the isolated gram-negative rods, all of them were sensitive to imipenem. Greatest resistance was seen against ampicillin and only 4.2% of gram-negative rods were sensitive to this particular antibiotic. Cephalosporins also showed increased resistance with only 14% of gram-negative rods showing sensitivity to Cefotaxime (Figure 2). Gram-positive cocci were highly sensitive to vancomycin, followed by NIT and gentamycin. These organisms were least sensitive to Penicillin; showing a sensitivity of only 12.4%. (Figure 3).

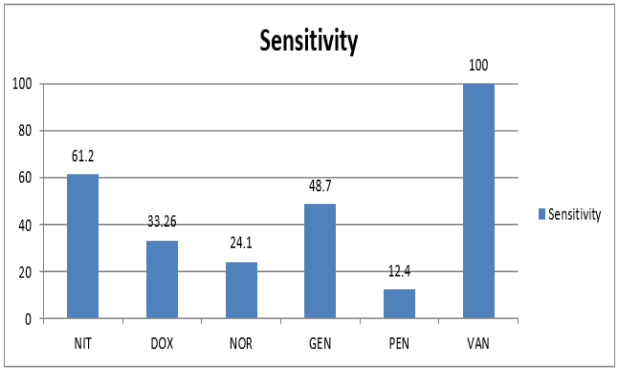

Figure 3: Antibiotic sensitivity pattern in gram- positive cocci

**NIT, Nitrofurantoin; DOX, Doxycycline; NOR, Norfloxacin; GEN, Gentamicin; PEN, Penicillin; VAN, Vancomycin*

Discussion

In the present study, the local status of antimicrobial susceptibility pattern in uropathogens was determined. It was done with a view to offer assistance in monitoring the continuous changing environment of bacterial resistance and bring improvements in UTI treatment. Urinary tract infection is the most common cause of fever of unknown origin and is one of the leading cause of infection and hospitalization among children.[19] To prevent potential sequels, like hypertension and recurrent or chronic pyelonephritis which results in renal scarring and renal

damage that may develop to chronic renal failure, it is important to start empirical antibiotic treatment before culture results.[3,15] Culture needs 24 to 48 hours to give microbiological growth, dipstick method is a reliable and less time-consuming method to diagnose complicated and uncomplicated UTI.[10] Antibiotic susceptibilities give direction for empirical treatment of urinary tract infection.[20] Awareness of the main uropathogens in the children and their antibiotic resistance patterns help in the selection of antibiotics.[13]

In our study, the most common pathogen isolated was Escherichia coli (61.48%), followed by Proteus (15.5%) and Klebsiella (12.3%). Parveen et al in a recent study at Children Hospital, Lahore, observed that Klebsiella (40.0%) was the most frequent pathogen followed by E.Coli (26.0%)amongst children with complicated UTI. [21] Studies by Kalsoom and Bashir showed E. coli to comprise 46.98% and 66% of all bacteria causing UTI respectively.[22,23]

A number of other studies conducted worldwide have also demonstrated E. coli to be the number one cause of urinary tract infections in children and adults alike. Klebsiella was usually found to be the second most frequent uropathogen unlike our study in which Proteus was more frequently isolated.[24- 26]

In our study, gram-negative rods demonstrated the highest resistance against ampicillin followed by Norfloxacin. Previous studies from Pakistan have also demonstrated high resistance against ampicillin.[22] However, a study by Bashir et al in 2008 demonstrated intermediate-level resistance against third-generation cephalosporins (35-50%) and about 40% of gram-negative bacilli were still susceptible to second-generation cephalosporins.[23] Over the years, this resistance against antibiotics seems to have increased tremendously. The research by Shahnaz et al published in 2016 concluded that about 80-90% of gram-negative rods were resistant to third-generation cephalosporins.[21] This trend is supported by our study which showed that 86% of gram-negative pathogens were resistant to cefotaxime. Similarly, resistance to quinolones has gone up from 62% in 2008[23] to 80% in 2011.[22] In this study, we observed the resistance of more than 90% against norfloxacin which is quite alarming.

Researches conducted in South Asia have also shown increasing trends of antimicrobial resistance among children with UTI. Research by Ghorashi et al[27] in 2011 showed a low level of resistance by E. coli against ciprofloxacin (14.5%) and intermediate-level resistance to third-generation cephalosporins, while they were strongly resistant to ampicillin, cotrimoxazole, and cephalexin. However, a later study conducted by Sharan et al[28] in India demonstrated markedly increased resistance by E. coli to third-generation cephalosporins (73%) and quinolones (63%). These uropathogens have, throughout the years, shown increased susceptibility to Amikacin, Nitrofurantoin, and Imipenem, which is also supported by our study. [19,21,26] Tseng et al[29] who conducted his study in 1991-2000 and 2001-2005 in Taiwan found that Ampicillin resistance is increasing in children. This should be a matter of great concern especially in Asian countries and adequate measures must be taken, including the prescription of over the counter medications, so that this resistance can be avoided in our country.

As regards the gram-positive cocci, our study showed enterococci to be most susceptible to vancomycin, whereas greatest resistance was seen against penicillin. Nitrofurantoin showed intermediate-level resistance of up to 40%. Previous studies in Pakistan have also shown increased sensitivity of enterococci to Vancomycin.[21] Catal et al[26] also showed that leading causative organism of urinary tract infection in children in Istanbul was *Escherichia coli* (81.7%). In his study, gram-positive cocci, e.g. *Enterococcus* showed resistant to all antimicrobials but were sensitive to vancomycin. The latest study carried out in Turkey showed that only 10% of enterococci were resistant to Nitrofurantoin whereas in our study the resistance seen is up to 40%.[30]

Our study has a few limitations. Firstly, in vitro testing of antibiotics does not ensure similar results in patients. Secondly, we are uncertain of the empirical or definite treatment offered to patients because there was no follow up.

Conclusion

Decreased sensitivity against penicillin and cephalosporins is seen in children with urinary tract infection. Nitrofurantoin

with a high sensitivity makes this drug an empirical treatment in UTI. Regular surveillance of the developing resistance in uropathogen due to inappropriate use of antibiotic is necessary to reduce complication in children with urinary tract infection.

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