

## Research Article



## Antibiotic Sensitivity of Uropathogens in Acute Pyelonephritis Children

Halimeh L\*, Al-Amouri M

\*Dept. of Biochemistry and Microbiology, Faculty of Pharmacy, Damascus University, Syria.

\*Corresponding author's E-mail: [lina.halimeh@hotmail.com](mailto:lina.halimeh@hotmail.com)

Accepted on: 01-05-2014; Finalized on: 30-06-2014.

## ABSTRACT

Acute pyelonephritis (APN) is a common childhood infection, which localizes in the upper urinary tract. Our aim in this study was to investigate the most common uropathogens in APN children and their antibiotic sensitivity patterns. Urine samples were taken from 65 children who were diagnosed with APN, from which uropathogens were isolated and identified by selective culture media and biochemical tests, and antibiotic sensitivity trends were evaluated on Muller Hinton agar by disk diffusion method. *E. coli* was the leading isolate (66.7%) followed by *Klebsiella pneumonia* (13.98%), *Proteus mirabilis* (7.53%), *Pseudomonas aeruginosa* (4.3%), *Staphylococcus aureus* (4.3%) and *Enterococcus faecalis* (3.2%). The highest sensitivity rates were against imipenem, nalidixic acid, nitrofurantoin and amikacin (97.8%, 84.9%, 82.8% and 78.5% respectively), whereas the least were against augmentin and amoxicillin (30% and 4.3% respectively). Children younger than one year old had higher resistance rates than older ones. Imipenem, nalidixic acid, nitrofurantoin and amikacin were the most effective antibiotics, and higher resistance rates were found in younger children, who were suffering from more frequently recurrent infections.

**Keywords:** Acute pyelonephritis, Antibiotic, Children, Sensitivity, Uropathogens.

## INTRODUCTION

Acute pyelonephritis (APN) is an urinary tract infection in which bacteria usually reach the kidney by ascending from lower urinary tract.<sup>1</sup> The incidence of APN in children is difficult to ascertain, but it has been demonstrated that it is a common problem and the cause of 5-7% of their febrile episodes.<sup>2</sup> Vesicoureteral reflux (VUR) is one of the most urinary tract abnormality associated with APN diagnosed children.<sup>3</sup> In this reflex, the valve mechanism normally prevent back ward flow of bladder urine into the ureter and kidney is not working properly, which increases their recurrent infections.<sup>3,1</sup> APN is associated with severe complications like permanent renal scarring and renal failure, which can be reduced by prompt and proper treatment.<sup>4</sup> However, the resistance to antibiotics is increasing nowadays, due to the careless and irregular use of antibiotics especially in children with recurrent urinary tract infections.<sup>5</sup> So our aim in this study was to investigate the most common uropathogens that can lead to APN in children and their antibiotic resistance patterns for later use of this information in proper antibiotic treatment.

## MATERIALS AND METHODS

Urine samples were collected from 65 children with APN, who were admitted to Children Hospital in Damascus, Syria, between July 2012 and September 2013. The patients ages were between 1 month to 12 years. We obtained samples either by midstream clean catch method from urination controlled children, or by urethral catheters from urination uncontrolled ones. Children who had another infection or receiving antibiotic had been excluded from the study. Isolation of urine

microorganisms was made on nutrient agar and next identification depended on gram staining, colonies characters on MacConkey, EMB and blood agar, in addition to biochemical tests like indole, methyl red-Voges Proskauer, Simmon's citrate, urease broth, oxidase, catalase and coagulase tests. We investigated the microorganism's resistance rates against amoxicillin, augmentin, trimethoprim and sulfamethaxazole, cefoxitin, cefazoline, nitrofurantoin, ceftriaxone, Gentamicin, amikacin, cefotaxime, ceftazidime, nalidixic acid and imipenem on Muller Hinton agar by disk diffusion method.

## Statistical analysis

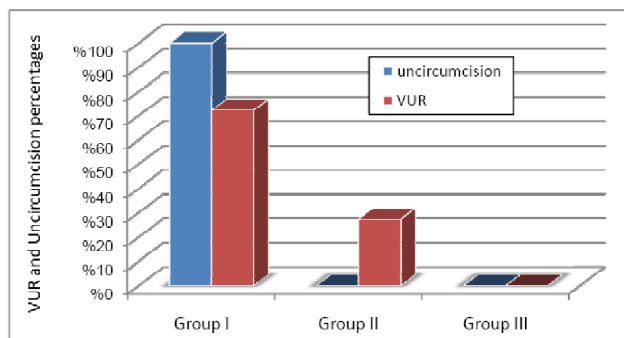
SPSS program and Chi square test were used to analyze the results, which were presented as percentage rates (%). A P value less than 0.05 was considered statistically significant.

## RESULTS AND DISCUSSION

65 patients had been classified into 3 groups according to their age, Group I: children under one year (27 patients, 41.5%), Group II: children between one and four years (31 patients, 47.7%) and Group III: older children (7 patients, 10.8%). By reviewing patient files we found that 18.2% of boys were uncircumcised (100% in first group), and 33.8% of children had VUR (72.7% in the first group and 27.3% in the second group), as it is described in figure 1. Both VUR and uncircumcision are considered to be important infection risk factors, while the former is the most frequent APN associated abnormality, in which the urine reflux promotes the ascending of infection into the kidneys,<sup>3</sup> the latter increases the risk by 10-12 folds.<sup>1</sup>



The girls (43, 66.2%) were twice the number of boys (22, 33.8%), but 70% of Group I was only boys and girls increased after this age (95%), (P value<0.001). This can be explained by increasing boys risk factors at this age, because 21% of boys younger than a year old were uncircumcised and 72.7% had VUR. Most of boys were also at younger ages in Huang et al<sup>6</sup> and Peng et al<sup>3</sup> studies, but not in Czaja et al<sup>7</sup> one, in which girls were predominant in all ages.



**Figure 1:** Distribution of uncircumcised and VUR children on groups of APN patients.

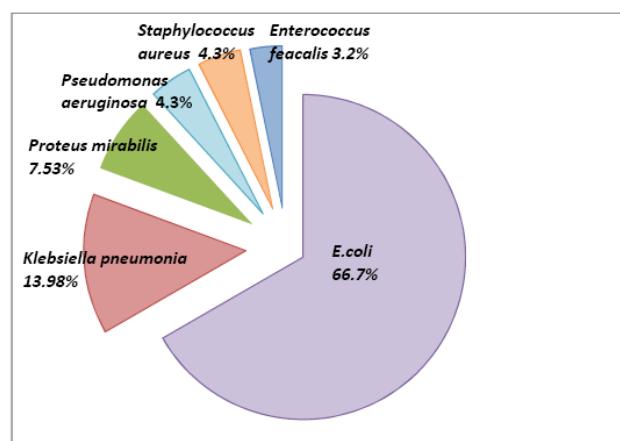
Among 65 urine sample, 93 bacterial isolates were found. In most of the samples we isolated one bacterial type (66.24%), but also more than one were isolated (33.76%). 77% of infections with more than one bacterial type were in the Group I, whereas 76% of one bacterial type infections were in older children, (P value=0.001). Increase the isolates in children younger than a year old is explained by their weak immune response,<sup>1</sup> and higher rates of VUR and being uncircumcised, which increase the number of opportunistic bacteria reaching the kidneys.

*E.coli* was the leading isolate in our study (66.7%), because of its ability to form biofilm against the immune response,<sup>8</sup> in addition to its high virulence, which helps it ascend along ureters to the kidneys, in spite of opposite urine flow and defending immune response.<sup>9</sup> These results are similar to those in previous studies in Turkey<sup>5</sup>, Iran<sup>10</sup>, Serbia<sup>4</sup>, India<sup>11</sup>, Iraq<sup>12</sup> and Saudi Arabia.<sup>13</sup> *Klebsiella pneumonia* was the second isolate in the study (13.98%), that it is opportunistic bacteria and a common isolate in nosocomial infections.<sup>14</sup> We also isolated *Proteus mirabilis* (7.53%), *Pseudomonas aeruginosa* (4.3%), *Staphylococcus aureus* (4.3%) and *Enterococcus faecalis* (3.2%), as it is described in the figure 2.

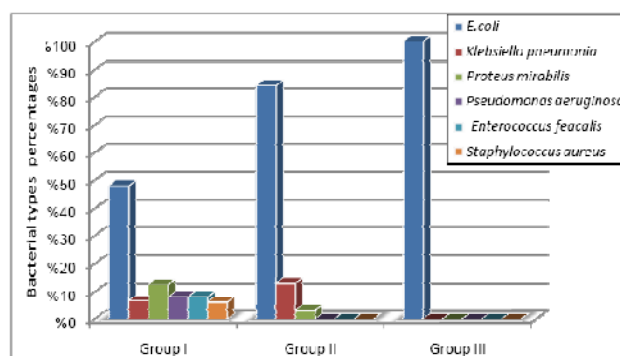
*E.coli* was predominant in all age groups, while 80% of non *E.coli* isolates were found in Group I, which are described in figure 3.

This can be explained by the highest rate of VUR founded in Group I, which is also seen in Johanson et al<sup>15</sup> and Park et al<sup>16</sup> whom submitted the increase of infection with non *E.coli* bacteria in VUR children. In addition Cascio et al<sup>17</sup> found increase of these bacterial concentration around preputial sac of VUR children, in whom urine reflux push them into the kidneys. Non *E.coli* isolates were similarly

predominant in newborns in some previous study,<sup>4,18</sup> but Ipek et al<sup>19</sup> concluded differently that there wasn't age-bacterial type correlation.



**Figure 2:** Types and percentage of bacteria isolated from APN children.



**Figure 3:** Distribution of bacterial type on age groups.

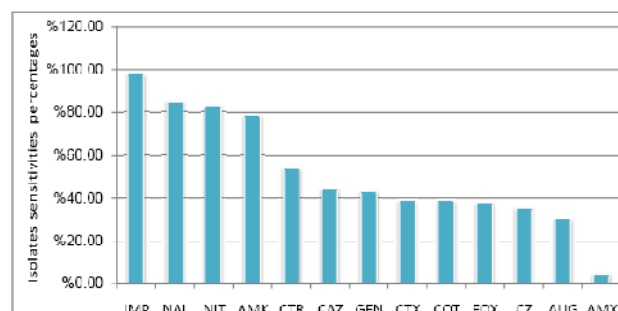
Although hospital isolates are considered highly resistance, we investigated high sensitivity against imipenem, nalidixic acid, nitrofurantoin and amikacin (97.8%, 84.9%, 82.8% and 78.5% respectively), as they are described in figure 4, which may explained by their limited and medically controlled uses in our country. Nitrofurantoin spread poorly into infected renal tissues, so it is not used in the treatment.<sup>20</sup> However, its high efficacy promotes its use in prophylaxis of APN in VUR and other high risk children, as it produces an antibacterial urine environment without affecting intestinal micro flora.<sup>21</sup> Similar high sensitivities against imipenem, nalidixic acid and nitrofurantoin were reported in previous study,<sup>4,19,22</sup> while lower sensitivities were found in others.<sup>10,13,23,24</sup> Although high amikacin sensitivity had been demonstrated in our study (78.5%), the Gentamicin sensitivity was much lower (43%) and lower than that reported in AL-Omar study in our country in 2008 (78%)<sup>25</sup> and in other regional studies (>60%).<sup>5,12,19,20,26</sup> This may be related to increase gentamicin use, which develop bacterial resistance and its tendency to prevent its intracellular accumulation up to the level.<sup>27</sup>

Similar sensitivity decreasing was found against cephalosporins, that was intermediate against

ceftriaxone, ceftazidime (53.8%, 44.1% respectively), while was lower against cefotaxime, cefoxitin and cefazolin (38.7%, 37.6%, 35.5% respectively). Higher cephalosporins sensitivities were reported in AL-Omar study in 2008 (67-70%)<sup>25</sup> and in other regional ones (60-80%).<sup>5,19,22,26</sup> Decreased cephalosporins sensitivity may be resulted from the development of resistance strains that produce extended spectrum  $\beta$ -lactamases (ESBLs),<sup>27</sup> especially after the increase of their uses in the treatment of nosocomial and even community-acquired bacterial infections. The resistance rates against cefoxitin and cefazolin were even higher than that of other examined cephalosporins, because of their oral dosage forms which are more commonly used in children.

Sensitivities to trimethoprim and sulfamethaxazole, augmentin and amoxicillin were low (38.7%, 30% and 4.3% respectively), and they are not effective any more in the APN treatment similarly to what demonstrated in many previous study.<sup>5,10,23,26</sup> Amoxicillin and augmentin are rapidly excreted and the duration of their significant urine concentration is short,<sup>28</sup> in addition the bacterial resistance against them like that against trimethoprim and sulfamethaxazole is constantly increasing, because of the increase use without prescriptions in the treatment of bacterial infections or even the common cold. Haward et al<sup>29</sup> submitted that there is linked resistance between cephalosporins, trimethoprim and sulfamethaxazole,

augmentin and amoxicillin, which may describe their associated resistance increasing in our study.



**Figure 4:** Percentages of isolates sensitivities against examined antibiotics.

IMP: imipenem, NAL: nalidixic acid, NIT: nitrofurantoin, AMK: amikacin, GEN: gentamicin, CTR: ceftriaxone, CTX: cefotaxime, CAZ: ceftazidime, FOX: cefoxitin, CZ: cefazoline, AUG: augmentin, AMX: amoxicillin and COT: trimethoprim and sulfamethoxazole.

The resistance against nalidixic acid, nitrofurantoin and gentamicin were higher in children younger than one year old in statistically significant manner ( $P$  value < 0.05), and against amikacin and cephalosporins in statistically insignificant manner ( $P$  value > 0.05), which are documented in the table 1.

**Table 1:** antibiotic resistance in children younger than one year old and older ones

Antibiotics	Number and percentage of resistance isolates						P value
	Younger than 1 year		Older than 1 year		total		
	n = 27	%	n = 38	%	n = 65	%	
IMP	2	2.1%	0	0%	2	2.1%	-
NAL	13	14.1%	1	1.1%	14	15.2%	0.005
NIT	14	15.1%	2	2.1%	16	17.2%	0.003
AMK	15	16.1%	5	5.4%	20	21.5%	> 0.05
GEN	33	35.5%	20	21.5%	53	57%	0.049
CTR	24	25.8%	19	20.4%	43	46.2%	> 0.05
CTX	32	34.4%	25	26.9%	57	61.3%	> 0.05
CAZ	31	33.3%	21	22.6%	52	55.9%	> 0.05
FOX	32	34.4%	26	28%	58	62.4%	> 0.05
CZ	34	36.5%	26	28%	60	64.5%	> 0.05

Haward et al<sup>29</sup> and Peco-Antić et al<sup>4</sup> indicated that bacterial resistance was higher in newborns and neonates, because of their weak immune responses which lead to increase their recurrence infections and so treatment rates. In addition, Valavi et al<sup>26</sup> and Taneja et al<sup>30</sup> submitted that bacterial resistance was higher in children with urinary tract abnormality, because of their higher recurrence and treatment rates. Similarly the resistance in our study was higher in first group children, in whom the immune system was weak and the rates of VUR, uncircumcision and antibiotic treatment were higher. Differently from our study Caraciolo et al<sup>18</sup> found bacterial resistance was similar in all children ages.

## CONCLUSION

*E.coli* was the most common uropathogen that lead to APN in children. High sensitivity was found against imipenem, nalidixic acid, nitrofurantoin and amikacin, which promote imipenem, nalidixic acid and amikacin usage in the treatment of APN and nitrofurantoin usage in the prophylaxis in children suffering from recurrent infections. On the other hand, the highest resistance was found against cefazolin, cefoxitin, trimethoprim and sulfamethaxazole, augmentin and amoxicillin which are frequently prescribed for treatment in children. Therefore these information should be considered while prescribing antibiotics for treatment and further studies are needed to follow the development of antibiotic resistance with time.



## REFERENCES

- Chang SL, Shortliffe LD, Pediatric urinary tract infections, *Pediatr Clin North Am*, 53(3), 2006, 379-400.
- Godfroid N, Levchenko E, Magerman K, Raes A, Schurmans T, Hoyweghen EV, Management of urinary tract infection in children: Belgian consensus, *Belgische Kinderarts*, 12(2), 2010, 26-29.
- Peng NJ, Hu C, Wu CS, Tsay DG, Chiou YH, Incidence and relationship of vesicoureteral reflux and acute pyelonephritis in children with first urinary tract infection., *Ann Nucl Med Sci*, 22, 2009, 67-74.
- Peco-Antić A, Paripović D, Buljugić S, Krusčić D, Spasojević B, Cvetković M, Kostić M, Laban-Nestorović S, Milosevski-Lomić G, Antibiotic resistance of uropathogens in newborns and young children with acute pyelonephritis, *Srp Arh Celok Lek*, 140(3-4), 2012, 179-183.
- Kayaş L, Yolbaş İ, Ece A, Kayaş Y, Balık H, Kocamaz H, Causative agents and antibiotic susceptibilities in children with urinary tract infection, *Journal of Microbiology and Infectious Diseases*, 1(1), 2011, 17-21.
- Huang DT, Huang FY, Tsai TC, Tsai JD, Chiu NC, Lin CC, Clinical differentiation of acute pyelonephritis from lower urinary tract infection in children, *J Microbiol Immunol Infect*, 40(6), 2007, 513-517.
- Czaja CA, Scholes D, Hooton TM, Stamm WE, Population-based epidemiologic analysis of acute pyelonephritis, *Clin Infect Dis*, 45(3), 2007, 273-280.
- Khamees SS, Urinary Tract Infection: Causative Agents, the Relation Between Bacteriuria and Pyuria, *World Applied Sciences Journal*, 20 (5), 2012, 683-686.
- Bergstena G, Wullt B, Svanborg C, *Escherichia coli*, fimbriae, bacterial persistence and host response induction in the human urinary tract, *International Journal of Medical Microbiology*, 295, 2005, 487-502.
- Aghamahdi F, Hashemian H, Shafiei M, Akbarian Z, Nejad MR, Karkan MF, Etiologies and antibiotic resistance patterns in Infants with urinary tract infections hospitalized in children medical center, Rasht, Iran, *Iranian Journal of Neonatology*, 4(2), 2013, 21-25.
- Ghadage DP, Nale SS, Kamble DS, Muley VA, Wankhade AB, Mali RJ, Bhore AV, Study of aetiology and anti-biogram of uropathogens in children-a retrospective analysis, *Journal of Clinical and Diagnostic Research*, 8(1), 2014, 20-22.
- AL-Geborry GM, Etiology of bacterial pathogens caused urinary tract infections in children of Al-Nasseria city, *AL-TAQANI*, 23(3), 2010, 72-80.
- AL-Harthi AA, Al-fifi SH, antibiotic resistance pattern and empirical therapy for urinary tract infections in children, *Saudi Med J*, 29(6), 2008, 854-858.
- Damian M, Usein CR, Palade AM, Ceciu S, Cosman M, Molecular epidemiology and virulence characteristics of *Klebsiella pneumoniae* strains isolated from hospital-associated infections, *The Open Epidemiology Journal*, 2, 2009, 69-78.
- Johansen TE, Cek M, Naber KG, Stratchounski L, Svendsen MV, Tenke P, Hospital acquired urinary tract infections in urology departments: pathogens, susceptibility and use of antibiotics. Data from the PEP and PEAP-studies, *Int J Antimicrob Agents*, 1, 2006, S91-107.
- Park S, Song SH, Lee C, Kim JW, Kim KS, Bacterial pathogens in first febrile urinary tract infection affect breakthrough infections in infants with vesicoureteral reflux who receive prophylactic antibiotics, *Urology*, 81(6), 2013, 1342-1345.
- Cascio S, Colhoun E, Puri P, Bacterial colonization of the prepuce in boys with vesicoureteral reflux who receive antibiotic prophylaxis, *The Journal of Pediatrics*, 139(1), 160-162.
- Caracciolo A, Bettinelli A, Bonato C, Isimbaldi C, Tagliabue A, Longoni L, Bianchetti MG, Antimicrobial resistance among *Escherichia coli* that cause childhood community-acquired urinary tract infections in Northern Italy, *Italian Journal of Pediatrics*, 37(3), 2011, 1-4.
- Ipek İÖ, Bozaykut A, Arman DC, Sezer RG, Antimicrobial resistance patterns of uropathogens among children in Istanbul, Turkey, *Southeast Asian J Trop Med Public Health*, 42(2), 2011, 355-362.
- Mortazavi F, Shahin N, Changing patterns in sensitivity of bacterial uropathogens to antibiotics in children, *Pak J Med Sci*, 25(5), 2009, 801-805.
- Song SH, Kim KS, Antibiotic prophylaxis in pediatric urology, *Indian J Urol*, 24(2), 2008, 145-149.
- Jafari HM, Saffar MJ, Nemate I, Saffar H, Khalilian AR, Increasing antibiotic resistance among uropathogens isolated during years 2006-2009: Impact on the empirical management, *Int Braz J Urol*, 38, 2012, 25-32.
- Afsharpaiman S, Bairaghdar F, Torkaman M, Kavehmanesh Z, Amirsalari S, Moradi M, Safavimirmahalleh MJ, Bacterial pathogens and resistance patterns in children with community-acquired urinary tract infection: a cross sectional study, *J Compr Ped*, 3(1), 2012, 16-20.
- Rai GK, Upreti HC, Rai SK, Shah KP, Shrestha RM, Causative agents of urinary tract infections in children and their antibiotic sensitivity pattern: a hospital based study, *Nepal Med Coll J*, 10(2), 2008, 86-90.
- Al-Omar AS, Bacterial culture results and susceptibility test of uropathogens isolated from outpatients referred from clinics in community, *Tashkhis al-Mukhtabari*, 3(7), 2008.
- Valavi E, Nikfar R, Ahmadzadeh A, Kompani F, Najafi R, Hoseini R, The Last three years antibiotic susceptibility patterns of uropathogens in southwest of Iran, *Jundishapur J Microbiol*, 6(4), 2013, 1-5.
- Muhsin EA, The efficacy of antibiotics reduction activity against chronic kidney diseases caused bacteria, *Journal of Genetic and Environmental Resources Conservation*, 1(1), 2013, 56-62.
- Kashef N, Djavid GE, Shahbazi S, Antimicrobial susceptibility patterns of community-acquired uropathogens in Tehran, Iran, *J Infect Dev Ctries*, 4(4), 2010, 202-206.
- Howard AJ, Magee JT, Fitzgerald KA, Dunstan FDJ, Factors associated with antibiotic resistance in coliform organisms from community urinary tract infections in Wales, *Journal of Antimicrobial Chemotherapy*, 47, 2001, 305-313.
- Taneja N, Chatterjee SS, Singh M, Singh S, Sharma M, Pediatric urinary tract infections in a tertiary care center from north India, *Indian J Med Res*, 131, 2010, 101-105.

Source of Support: Nil, Conflict of Interest: None.

