Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Original Article

# Five-year assessment of causative agents and antibiotic resistances in urinary tract infections

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## Abstract

**Aim:** To show the distribution and changes of causative agents of urinary tract infections in children and resistance rates by years and select the most appropriate antibiotics.

**Material and Methods:** In this study, the Başkent University Alanya Research and Application Hospital automation system microbiology recording book was screened retrospectively. Growth of a single microorganism above 105 colonies (cfu/mL) was included in the assessment. Throughout the study, 10 691 urinary cultures were studies and growth was found in 392 (3.7%).

**Results:** Three hundred and nine (78.8%) of the samples with growth belonged to girls. Growth was found in the neonatal period in 32 patients (8.2%). The most commonly isolated microorganism was *Escherichia coli* (*E. coli*) which was found in 68.4% of the patients. *Klebsiella* spp. were found with a rate of 12.0%; *Enterobacter* spp. were found with a rate of 10.7% and proteus spp. were found with a rate of 5.1%. Resistance to cefalotin (62.1%), trimethoprim-sulfamethoxasole (43.1%), amoxycillin-clavulanate (34.8%), ampicillin (30.4%), cefixim (26.3%) and nitrofurantoin (3.6%) was found in *E. coli* species. The antibiotic which had the highest resistance rate was ampicillin with a rate of 93.2% for klebsiella and 83.4% for enterobacter. *Klebsiella* spp. were the most commonly grown pathogens in newborns (40.6%). In a follow-up period of 5 years, the resistance of *E. coli* to amoxycillin-clavulanate regressed from 40.3% to 31.3%, while the resistance to trimethoprim-sulfamethoxasole (TMP-SMX) regressed from 45.6% to 34.7%.

**Conclusions**: A high resistance against first-generation cephalosporins, ampicillin, amoxycillin-clavulanate and TMP-SMX which are the first-line antibiotics in childhood urinary tract infections was found. Carbapenem (meropenem, imipenem) resistance was not found in our center. Nitrofurantoin, aminoglycosides and cefixime can be recommended for empirical treatment in our hospital because of low resistance. Antibiotic treatment should be redecided according to in vitro antibiotic sensitivity results. (Türk Ped Arş 2014; 49: 124-9)

**Key words:** Antibiotic resistance, children, urinary culture, urinary tract infections, newborn

### Introduction

Urinary tract infection (UTI) is a common disease in children and it is observed in 3-5% of girls and in 1% of boys (1). While it is observed with a 5-fold higher rate in boys below the age of 5 years, after 5 years of age it is observed with a 10-fold higher rate in girls (2). Despite all advancements in diagnosis and treatment, UTI can recur frequently (3). It still continues to be a problem with its long-term complications including growth retardation, hypertension and renal failure (4, 5).

Amoxycillin, trimethoprim-sulfamethoxazole (TMP-SMX) and cephalosporins are generally used for urinary tract infection in children (6). Selection of appropriate emprical antibiotic initially will considerably decrease morbidity and mortality rates. We aimed to examine the distribution of the causative agents of UTI and resistance rates in our region and to ensure appropriate antibiotic selection by demonstrating changes in these.

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**Received:** 05.08.2013 **Accepted:** 18.03.2014



DOI:10.5152/tpa.2014.1505

## Material and Methods

Patiens aged between 0 and 6 years who presented to Başkent University Research and Application Hospital Pediatrics Outpatient Clinic between April 2008 and March 2013 were included in the study. The hospital automation system, patient files and microbiology recording books were screened retrospectively. Patients with a history of recurrent UTI and known urinary tract anomaly were not included in the study. Midstream urine samples or clean urine samples collected into urine bags were kept in 5% sheep blood agar and eosin methylene blue medium at 37 degrees for 24 hours; more than 100 000 colonies (cfu/mL) and growth of a single microorganism was considered positive culture. The bacteriae grown were defined with traditional methods and antibiotic sensitivities were tested by disc diffusion method in accordance with "The Clinical and Laboratory Standards Institute" (CLSI) methods (7).

### Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS ver. 11.0 Inc. Chicago, IL, USA) 11.0 package program and "Office Excel". Verbal informed consent was obtained from the families who could be reached.

## Results

In a 5-year follow-up period, 10 691 urine cultures were examined. Growth occured in 392 (3.7%) of the samples. 309 (78.8%) of the samples which had positive growth were taken from girls and 83 (21.2%) were taken from boys. Growth numbers by gender are shown in Table 1. The mean age of the patients was 54.19±47.91 (1-191) months. In the newborn period, growth occured in 32 (8.2%) patients. 123 (31.4%) of the subjects were younger than 12 months and 193 (49.2%) were younger than 48 months. 71 (57.7%) of the pediatric patients who were below the age of one year were female and 52 (42.3%) were male.

*E. coli* was the most commonly grown organism which was found in 268 (68.4%) patients. *Klebsiella* spp. were grown in 47 (12.0%) patients, *Enterobacter* spp. were grown in 42 (10.7%) patients and *Proteus* spp. were grown in 20 (5.1%) patients. *Staphylococcus epidermis* and *Pseudomonas* spp. were grown in 6 patients each (1.5%). *S. aureus*, Group B streptococci and candida were grown in three different patients seperately. The number of microorganisms by years are shown in Table 2.

Sensitivities of the microorganisms which were grown most commonly in urine cultures to various antibiotics are shown in Table 3 and Figure 1. *E. coli* was the most commonly grown microorganism excluding the neonatal period. It was resistant to cephalotin with a rate of 62.1%. The resistance rates for trimethoprim-sulfamethoxazole, amoxycillin clavulanate, ampicillin, cefixime and nitrofurantoin were found to be 43.1%, 34.8%, 30.4%, 26.3% and 3.6%, respectively. *Klebsiella* was found to be resistant to ampicillin with a rate of 93.2% and Enterobacter was found to be resistant to ampicillin with a rate of 83.4%. The resistance rate of *Klebsiella* spp. grown was found to be 34.1% for amoxycillin clavulanate, 17.8% for TMP-SMX, 14.7% for cefixime and 11.2% for nitrofurantoin. The resistance rate of Enterobacter was found to be 74% for cefixime, 53.9% for amoxycillin clavulanate, 20% for TMP-SMX and 5.6% for nitrofurantoin. Proteus was found to be resistant to nitrofurantoin with the higest rate (85.0%). The resistance rate of Proteus was found to be 46.7% for ampicillin, 35.3% for TMP-SMX, 17.7% for amoxycillin clavulanate and 5.6% for cefixime.

Comparison of the resistances of *E. coli* spp. grown in 2008 and 2012 is summarized in Figure 2. While resistance to amoxycillin clavulanate reduced from 40.3% to 31.3%, re-

**Table 1. Distribution of the microorganisms by gender**

| | Male | Female | Total |
|---|---|---|---|
| *Escherichia coli* | 44 (16.4%)† | 224 (83.6%) | 268 (68.4%) |
| *Klebsiella* spp. | 17 (36.1%) | 30 (63.9%) | 47 (12.0%) |
| *Enterobacter* spp. | 7 (16.6%) | 35 (83.4%) | 42 (10.7%) |
| *Proteus* spp. | 7 (35.0%) | 13 (65.0%) | 20 (5.1%) |
| Other* | 8 (53.3%) | 7 (46.7%) | 15 (3.8%) |
| Total | 83 (21.2%) | 309 (78.8%) | 392 (100%) |

†Growth number, percentage of microorganism, **Staphylococcus epidermidis*, *Pseudomonas* spp., *Staphylococcus aureus*, Group B strreptococci, *Candida*

**Table 2. Distribution of microorganism growths by years**

| | 2008 | 2009 | 2010 | 2011 | 2012 | Total |
|---|---|---|---|---|---|---|
| *Escherichia coli* | 59 (22.0%)† | 62 (23.1%) | 53 (19.8%) | 44 (16.4%) | 50 (18.7%) | 268 (100%) |
| *Klebsiella* spp. | 7 (14.9%) | 15 (31.9%) | 11 (23.4%) | 10 (21.3%) | 4 (8.5%) | 47 (100%) |
| *Enterobacter* spp. | 4 (9.5%) | 7 (16.7%) | 15 (35.7%) | 12 (28.6%) | 4 (9.5%) | 42 (100%) |
| *Proteus* spp. | 4 (20.0%) | 8 (40.0%) | 1 (5.0%) | 5 (25.0%) | 2 (10.0%) | 20 (100%) |
| Other* | 4 (26.7%) | 6 (40.0%) | 3 (20.0%) | 0 | 2 (13.3%) | 15 (100%) |
| Total | 78 (19.9%)‡ | 98 (25.0%) | 83 (21.2%) | 71 (18.1%) | 62 (15.8%) | 392 (100%) |

†Growth number, percentage of microorganism, **Staphylococcus epidermidis*, *Pseudomonas* spp., *Staphylococcus aureus*, Group B strreptococci, *Candida*, ‡annual total growth number, percentage in five years

**Table 3. Sensitivity rates of gram negative microorganisms obtained in urine cultures against various antibiotics**

| | *Escherichia coli* 268 | | *Klebsiella* spp. 47 | | *Enterobacter* spp 42 | | *Proteus* spp. 20 | |
|---|---|---|---|---|---|---|---|---|
| Amikacin | 242/250 | 96.8% | 45/45 | 100% | 12/12 | 100% | 18/18 | 100% |
| Amoxycilline-clavulanate | 165/253 | 65.2% | 29/44 | 65.9% | 6/13 | 46.1% | 14/17 | 82.3% |
| Ampicillin | 172/247 | 69.6% | 3/44 | 6.8% | 2/12 | 16.6% | 8/15 | 53.3% |
| Phosphamycine | 194/242 | 80.1% | 18/43 | 41.8% | 13/21 | 61.9% | 12/18 | 66.6% |
| Gentamycin | 220/253 | 86.9% | 43/45 | 95.5% | 33/35 | 94.2% | 18/19 | 94.7% |
| Imipenem | 251/251 | 100% | 41/42 | 97.6% | 13/13 | 100% | 19/20 | 95.0% |
| Meropenem | 254/254 | 100% | 45/46 | 97.8% | 13/13 | 100% | 20/20 | 100% |
| Nitrofurantoin | 244/253 | 96.4% | 40/45 | 88.8% | 34/36 | 94.4% | 3/20 | 15.0% |
| Norfloxacin | 227/251 | 90.4% | 42/43 | 97.6% | 24/32 | 75.0% | 19/19 | 100% |
| Piperacillin | 118/227 | 51.9% | 25/40 | 62.5% | 10/13 | 76.9% | 13/17 | 76.4% |
| Cefalotin | 90/237 | 37.9% | 27/42 | 64.2% | 5/16 | 31.2% | 11/15 | 73.3% |
| Cefoperazone | 177/229 | 77.2% | 33/41 | 80.4% | 9/13 | 69.2% | 15/16 | 93.7% |
| Cefazoline | 169/243 | 69.5% | 32/41 | 78.0% | 4/7 | 57.1% | 13/18 | 72.2% |
| Cefepime | 221/230 | 96.0% | 38/39 | 97.4% | 12/12 | 100% | 17/17 | 100% |
| Cefixime | 180/244 | 73.7% | 35/41 | 85.3% | 6/23 | 26.0% | 17/18 | 94.4% |
| Ceftazidime | 228/256 | 89.0% | 43/45 | 95.5% | 12/13 | 92.3% | 19/20 | 95.0% |
| Ceftriaxone | 215/259 | 83.0% | 43/46 | 93.4% | 10/13 | 76.9% | 19/20 | 95.0% |
| Cefuroxim | 188/236 | 79.6% | 32/44 | 72.7% | 4/10 | 40.0% | 16/18 | 88.8% |
| Ciprofloxacin | 232/256 | 90.6% | 45/46 | 97.8% | 31/37 | 83.7% | 20/20 | 100% |
| TMP-SMX | 147/258 | 56.9% | 37/45 | 82.2% | 12/15 | 80.0% | 11/17 | 64.7% |

*calculated by number of sensitive microorganisms/number of samples studied.
TMP-SMX: trimethoptim-sulfamethoxazole

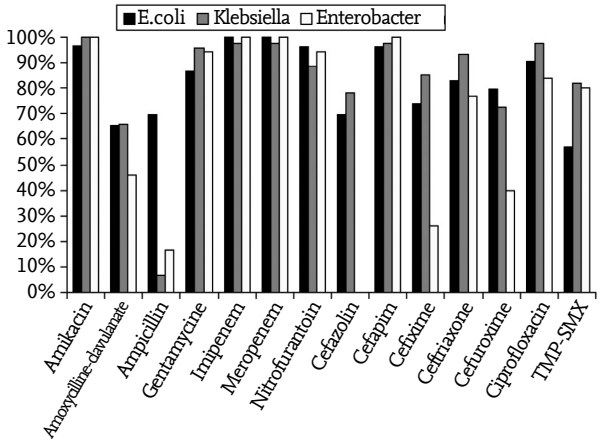


**Figure 1. Antibiotic sensitivities of the three most common microorganims**

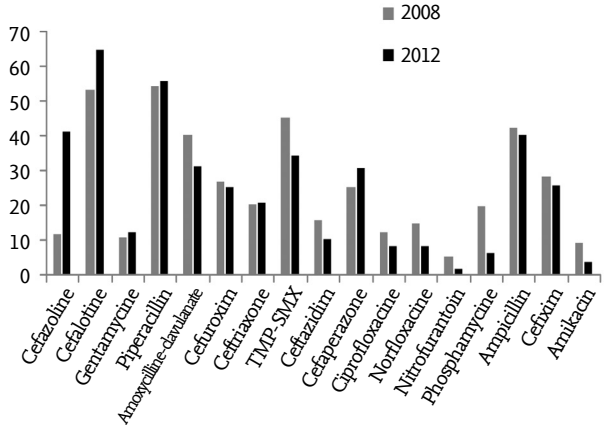


**Figure 2. Comparison of E.coli resistances of some antibiotics in 2008-2012**

sistance to TMP-SMX reduced from 45.6% to 34.7%. A reduction of 13.5%, 5.3%, 3.5% and 2.5% was observed in resistance to phosphomycin, amikacin, nitrofurantoin and cefixime, respectively. While ceftiraxon resistance remained the same, cefoperazone and cefalotin resistance increased.

Growth occured in 32 newborns 12 of whom were male and 20 of whom were female. The most commonly grown agents included *Klebsiella* spp. in 13 patients (40.6%, 8 boys, 5 girls), *E. coli* in 11 patients (34.4%, 8 girls, 3 boys) and *Enterobacter* in 6 patients (18.8%, 4 girls, 2 boys). *Staphylococcus epidermis*

and *Pseudomonas* spp. were grown in two different male patients. The sensitivity rates of some of the antibiotics which are used frequently in the neonatal period are shown in Table 4. Ampicillin resistance was found with a rate of 100% for Enterobacter, 90,9% for *Klebsiella* and 44,4% for *E. coli*.

## Discussion

Urinary tract infection is an important infectious disease which is observed commonly in children. UTI is responsible of 5-6% of the infections in children evaluated because of fever. Colonization of the periurethral region with enteric pathogens is the first step of UTI. Inflammatory response starts when these microorganisms gain pathogenic properties by way of virulance factors and the infection may progress up to the bladder and kidney (8). Vesicoureteral reflux, neuromuscular dysfunction, mixion disorder, constipation, bladder neck stenosis and presence of catheter facilitate development of UTI (9). Familial and genetic predispositions have also been reported (10).

Oral UTI treatment is as efficient as parenteral treatment (11). Hospitalization or parenteral treatment is indicated in infants younger than 2 months with toxic appearance who can not take fluid or medication by the oral route, in immune deficiencies and when there is social justification (8, 11). Empirical antibiotic which can be selected for oral administration include amoxycillin clavulanate, TMP-SMX, cefixime, sefpodoxim, cefprozil, cefuroxime axetil and cefalexin. Emprical parenteral treatment options include ceftriaxon, cefotaxim, ceftazidim, gentamycin, tobramycin and piperacillin (12). The total treatment time is 7-14 days (13). Although there are different approaches, urinary tract ultrasonography is consistently recommended after the first UTI (14). The risk of recurrence is higher in the first 6 months. Use of prophylactic antibiotic decreases recurrence in patients with recurrent UTI, but it has little contribution to the patient and the decision should be made considering the possibility of development of resistance (15).

**Table 4. Sensitivity rates of the microorganisms grown in newborns against various antibiotics**

| | *Escherichia coli* 11 | | *Klebsiella* spp. 13 | | *Enterobacter* spp. 6 | |
|---|---|---|---|---|---|---|
| Ampicillin | 5/9 | 55.6*% | 1/11 | 9.1% | 0/5 | 0% |
| Amikacin | 10/11 | 90.9% | 12/12 | 100% | 5/6 | 83.3% |
| Amoxycilline-clavulanate | 10/10 | 100% | 8/12 | 66.7% | 2/5 | 40% |
| Gentamycine | 10/11 | 90.9% | 10/11 | 90.9% | 6/6 | 100% |
| Cefixim | 9/10 | 90% | 8/11 | 72.7% | 2/5 | 40% |
| Ceftriaxone | 9/10 | 90% | 11/12 | 91.7% | 5/5 | 100% |
| Ceftazidim | 10/10 | 100% | 11/12 | 91.7% | 5/5 | 100% |

*calculated by number of sensitive microorganisms/number of samples studied

78.8% of the patients who had a positive urine culture were female. Although UTI is observed with a higher rate in boys below the age of 1 year, it was found with a higher rate in girls at all age groups.

*E. coli* which is one of the gram negative microorganisms has been found as the most common causative agent in studies performed in our country. In our study, *E. coli*, *Klebsiella* and *Enterobacter* were the most commonly grown microorganisms. In the studies conducted in İzmir (16), Bursa (17), Tokat (18) and Ankara (19), the same three agents were in the first three orders. While *Proteus* spp. were in the fourth order in our study, İpek et al. (20) and Senel et al. (21) found the same agent in the second order. Güneş et al. (22) found coagulase negative staphylocicci to be in the second order, whereas eneterococci were the second most common microorganism in the study of Küçükbasmacı et al. (23).

While *Klebsiella* spp. were found to be resistant to amikacin with a rate of 100% in our study, they were found to be resistant to ampicillin with a rate of 93,2%. Aydemir (24) found an ampicillin resistance of 100% and an amikacin sensitivity of 94.3%. Resistance of *Klebsiella* spp. to empirical TMP-SMX was found to be 17.8%. This rate of resistance was found to be 47.8% in the study of Gündüz et al. (25), whereas it increased up to 67% in the study of Mir et al. (26). Güner et al. (27) found resistance rates similar to our study for all these three antibiotics (amikacin 1.1%, ampicillin 88.2%, TMP-SMX 20%).

In our study, Enterobacter had a sensitivity of 100% against amikacin, imipenem, meropenem and cefepim. The resistance rate was found to be 83.4% for ampicillin which is frequently prescribed for oral administration, 74% for cefixim and 53.9% for amoxycillin clavulanate. While Salduz et al. (28) found ampicillin resistance to be 100%, amikacin resistance was found to be 39.25% in the study performed by Mir et al. (16).

Proteus species grown in our hospital did not develop resistance to amikacin, ciprofloxacin, norfloxacin, cefepim and meropenem. An ampicillin resistance of 46.7% and a TMP-SMX resistance of 35.3% was found. Since *Proteus* spp. have intrinsic resistance to nitrofurantoin, this antibiotic is not used in treatment. In the study of Şahin et al. (29), ampicillin resistance was found to be 92.6% and TMP-SMX resistance was found to be 37.0%.

*E. coli* is the most common problem. While it has a sensitivity of 100% to imipenem and meropenem, it has a resistance of 62.1% to cefalotin and a resistance of 48.1% to piperacillin. The resistance rate was found to be 43.1% for TMP-SMX which is preferred for empirical treatment, 30.4% for ampicillin, 26.3% for cefixim and 34.8% for amoxycillin clavulanate. While Cebe et al. (30) found TMP-SMX resistance to be 43.6% and amoxycillin clavulanate resistance to be 28.6%, Motor et

al. (31) found the same rates to be 61% and 65%, respectively. In our study, ceftriaxone resistance was found to be 17%, whereas Abuhandan et al. (32) calculated this resistance to be 39.5%. Üstün et al. (33) found no resistance to meropenem and amikacin. In our study, no resistance to meropenem was found and amikacin resistance was found with a rate of 3.2%.

When the resistances of some antibiotics in *E. coli* growhts in 2008 and 2012 were compared, it was pleasing that resistances to most antibiotics were reduced. However, cefazolin resistance increased from 32.2% to 41.6%, cefalotin resistance increased from 53.5% to 65% and cefaperazon resistance increased from 25.5% to 31.1%. It was observed that trimetoprim sulfametoxazole resistance was reduced from 45.6% to 34.6%, amoxycillin clavulanate resistance was reduced from 40.3% to 31.2% and nitrofurantoin resistance was reduced from 5.6% to 2.1%. Çetin et al. (34) found an increase in TMP-SMX resistance in their thre-year follow-up and observed a reduction in amoxycillin clavulanate resistance similar to our study. In the study performed by Erdoğan et al. (35) from our center covering the year of 2004, ampicillin resistance was found to be 71.7%, TMP-SMX resistance was found to be 54.3% and amoxycillin clavulanate resistance was found to be 43.5%. Amikacin and nitrofurantoin resistances are similar. Although ampicillin resistance reduced from 71.7% to 42.6% between 2004 and 2008, it regressed to 40.5% in a five-year follow-up period. The fact that enteric bacteria can produce large-spectrum beta lactamase which inactivates third and fourth generation cephalosporins is an important problem and this rate ranges between 1% and 10% in community-acquired UTI (35). When the two studies were compared, it was observed that cefixim resistance increased from 4.3% to 26.3% and ceftriaxon resistance increased form 4.3% to 17%.

In newborns, treatment is initiated after obtaining blood sample for culture. The first-line options in treatment include ampicillin, gentamycin and third generation cephalosporins (36). *E. coli* is resistant to ampicillin with a rate of 44.4% and the general ampicillin resistance in newborns has been found to be 76%. In newborns, amikacin and ceftriaxon sensitivity was found to be 93.1% and cefixim sensitivity was found to be 73%. In the study of Arıkan et al. (37), *E. coli* was the most common causative agent, the rate of renal damage was high in these patients and the authors recommended long-term follow-up for these patients. Some authors definetely forbid use of ceftriaxon in newborns (38).

Since this study was a retrospective study, reliable information related with clinical data and antibiotic use of the patients could not be reached. There were also patients with a possibility of asymptomatic bacteriuria. These are the limitations of our study. Conclusively, a high rate of resistance was found to first generation cephalosporins, ampicillin, amoxycillin clavulanate and TMP-SMX which are the first-line agents in childhood UTI. In our center, no resistance to carbapenem (meropenem, imipenem) was found. Nitrofurantoin, aminoglycosides and cefixime can be reccomended in emprical treatment in our hospital because of low resistance. Antibiotic treatment should be redecided according to the results of in vitro antibiotic sensitivity tests.

**Ethics Committee Approval:** Due to the retrospective design of the study, the ethics committee approval was waived.

**Informed Consent:** Written informed consent was obtained from the parents of the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - B.Ç., E.B.; Design - B.Ç., N.Ü., H.K.; Supervision - B.Ç., H.E.; Funding - B.Ç., B.T.; Materials - B.Ç.; H.E.; Data Collection and/or Processing - B.Ç., B.T., H.K., N.Ü.; Analysis and/or Interpretation - B.Ç., N.Ü., H.K., B.T.; Literature Review - B.Ç., E.B.; Writer - B.Ç.; / Critical Review - B.Ç., N.Ü., B.T., H.K., E.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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