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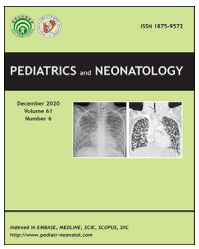

Original Article

# First UTI episode in life in infants < 1 year of age: Epidemiologic, clinical, microbiologic and disease recurrence characteristics

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**Key Words**
antibiotics;
ESBL;
infants;
recurrence;
UTI

*Background:* To examine the epidemiologic and microbiologic characteristics of first and recurrent UTI in young infants.
*Methods:* A retrospective study of all infants <1 year hospitalized during 2014–2017 with their first UTI and followed during their first year of life.
*Results:* 191 infants were enrolled; 69 (36.12%) patients were <2 months and 32 (16.8%) developed R-UTI during the follow-up. The five most common uropathogens were *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Proteus mirabilis* and *Staphylococcus aureus*. High resistance rates were recorded for ampicillin, amoxicillin/clavulanic acid, TMP/SMX, cefuroxime, ceftriaxone, piperacillin/tazobactam and gentamicin among *E. coli* and *Klebsiella* spp.; 29.15% *E. coli* and 42.9% *Klebsiella* spp. were ESBL-positive. 53.2% of recurrent UTI (R-UTI) episodes were diagnosed within 2 months after the initial UTI episode. *E. coli* (40.6%) and *Klebsiella* spp. (37.55) were the most frequent R-UTI pathogens. Twenty-five (78.1%) R-UTIs were caused by recurrent uropathogens representing new infections. Antibiotic resistance rates at recurrence were similar to those at initial UTI, except for a significant increase in *E. coli* and *Klebsiella* spp. resistance to piperacillin/tazobactam.

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*Conclusion:* We reported high antibiotic resistance rates to major antibiotic classes used in UTI treatment. Most R-UTI episodes were caused by uropathogens different than those isolated at the initial UTI episode and were caused by highly-resistant organisms. Our findings require frequent monitoring and possible modification of the empiric and prophylactic antibiotic therapy protocols in use. As a result of our findings, the protocol for initial empiric treatment of infants with suspicion of UTI was modified by changing gentamicin to amikacin in the treatment of infants <2 months of life and amikacin monotherapy (intravenous or intramuscular) was introduced as first-line therapy for infants >2 months of life.


## 1. Introduction

Urinary tract infection (UTI) is frequent in infants and children and is considered one of the most common causes of antibiotic prescriptions.[1–4] Among febrile infants, UTI was diagnosed in 7.5% of infants <8 weeks, 5.3% of infants <1 year, 4.1% of children <2 years and 1.7% of children <5 years.[5–7] In a prospective study enrolling 209 infants and children treated for first febrile UTI episodes, 21%, 37%, 18%, 6% and 19% of the episodes occurred at the ages 0–3, 4–12, 13–24, 25–36 and > 36 months.[8,9] Among infants aged 0–3 months, 74% were males, *Escherichia coli* was isolated in 88% and 21% had vesicoureteral reflux (VUR).[9]

Gram negative bacteria are the most common pathogens causing UTI in children and adults, with *E. coli* responsible for 70–90% of outpatients with UTI.[3,4,7–9] The overall burden of disease by caused *E. coli* is lower in neonatal UTI (about 50% of all positive cultures) compared with older patients.[11,12] Approximately 30%–50% of young infants with UTI may have urinary tract abnormalities, of which VUR is the most common. VUR is associated with approximately 20% of neonatal cases of UTI and its presence was reported to be 4-fold higher in infants with *Klebsiella* spp.-UTI compared with *E. coli*-UTI.[13,14]

In recent years the development of bacterial strains resistant to various antibiotics has been increasingly reported.[15–17] A meta-analysis of 58 studies published during 1955–2015 from developed and developing countries analyzed the antibiotic resistance of 77,783 *E. coli* isolates from community-acquired UTI in children <17 years and found that in developed countries the overall resistance of *E. coli* was significantly lower than in the developing countries.[18] In a survey on 4745 positive urine cultures from both hospitalized and non-hospitalized infants from 18 units in 10 European countries, *E. coli* was the most frequent pathogen; however, in 10/16 hospitals and 6/15 community settings it was isolated in <50% of the total positive urine cultures.[19]

The information about the microbiological picture and antibiotics resistance in UTI in young children in Romania is limited. In the present study we examined the epidemiologic, microbiologic and recurrent disease characteristics in young infants aged 0–1 years hospitalized at our medical center during 2014–2017 with their first UTI.

## 2. Material and methods

This retrospective study was performed during 2014–2017 and included all infants <1 year of age admitted to the Children's Clinic Hospital, Transilvania University Brasov, Romania, with UTI (confirmed by urine culture) and followed during their first year of life. Our hospital is the only primary and tertiary medical center in the city of Brasov (located in Central Romania) and takes care of a population of approximately 300,000 patients (of whom around 100,000 are children).

Diagnosis of UTI was made on the basis of the presence of at least 50.000 colonies/ml of one or two uropathogenic organisms in a specimen of urine obtained by bladder catheterization. The medical records of the infants, laboratory findings from the bacteriological laboratory and imaging data from the radiology department were searched, both for the index episode and also for the first recurrent UTI episode.

The departmental protocol for the initial empiric treatment of infants with suspicion of UTI included: 1) ampicillin (100 mg/kg/day tid plus gentamicin (5 mg/kg/day once/day) for the patients aged 0–2 months and 2) cefuroxime (100 mg/kg/day tid) or 3) ceftriaxone 50 mg/kg/day once/day for patients aged 2–12 months. The intravenous treatment was continued for a minimum of 5–7 days and changed to an oral antibiotic (cefuroxime axetil 30 mg/kg/day bid or cephalexin 50 mg/kg/day tid in most cases) for 7 additional days in infants aged 0–2 months and for 3–5 additional days in patients aged 2–12 months. Following the switch to oral antibiotics, the patients could be discharged if asymptomatic and afebrile and if normalization of inflammatory blood parameters (CRP and WBC count) was documented.

The antibiotic prophylaxis policy was not well-defined during the study period, leaving at the physicians' discretion whether to administer antibiotic prophylaxis and the specific antibiotic to be administered. The recommended imaging studies during the study period included the completion of an ultrasound examination during or after hospitalization in all cases of infants <1 year with UTI.

The study was approved by the ethics committee of the hospital.

### 2.1. Statistical analysis

Data were recorded using the Access Microsoft Office software. Statistical analysis was performed using the SPSS 22.0 software. Contingency table analysis for comparing rates between unmatched samples was performed using the Chi-square or Fisher's exact test, as appropriate. Student's independent samples *t*-test or ANOVA was used to compare continuous variables.

## 3. Results

Overall, 191 patients <1 year of age were hospitalized with their first UTI and 32 (16.8%) of them were diagnosed with a recurrent UTI episode during the follow-up period.

Among the 191 patients with the first UTI episode, there were more male patients (115, 60.2%) than female patients (76, 39.8%). Median age at admission was 3 months (mean ± SD 4.14 ± 3.24 months, range 2 days−11 months); 44 (23.03%), 25 (13.09%), 66 (34.55%) and 56 (29.3%) of the patients were aged 0−1, 1−2, 3−6 and 7−12 months, respectively. Overall, 69 (36.12%) patients were <2 months of age at admission.

Eighty-seven (45.5%) patients were delivered by caesarian section and 43 (22.5%) were premature. Background diseases included malnutrition, ano-rectal malformations, epilepsy, cardiomyopathy and cardiac insufficiency in 2.6%, 1.0%, 0.5%, 0.5%, 0.5% and 0.5% of patients, respectively. None of the patients had known renal or genitourinary anomalies at the time of admission; no bowel/bladder dysfunction were previously diagnosed in the study patients.

The acute pathologies at admission and during hospitalization included acute gastroenteritis, pneumonia, bronchiolitis, sepsis syndrome, acute otitis media, herpetic gingivostomatitis, hepatitis, omphalitis and measles in 20.4%, 15.2%, 9.9%, 4.2%, 1.0%, 1.0%, 1.0% and 0.8% of patients, respectively.

A temperature <38.0 °C was recorded in 101 (52.9%) patients; 35 (18.3%) patients had fever >39.0 °C. The main clinical symptoms at admission included diarrhea, vomiting, irritability, refusal to eat and convulsions in 29.8%, 25.7%, 16.8%, 16.8% and 3.4% of patients, respectively.

### 3.1. Microbiological picture

A total of 217 uropathogens were recovered from the 191 enrolled patients diagnosed with first UTI episode in life. The five most commonly isolated uropathogens were *E. coli*, *Klebsiella* spp., *Enterococcus* spp., *Proteus mirabilis* and *Staphylococcus aureus* (Table 1). Among patients with isolation of one uropathogen, the five most commonly isolated organisms were *E. coli*, *Klebsiella* spp., *Enterococcus* spp., *P. mirabilis* and *S. aureus* (63.6%, 23.0%, 5.5%, 3.0% and 1.2% of all pathogens, respectively). Fifty-two uropathogens were isolated in the 26 patients with growth of 2 uropathogens: *E. coli* plus *Klebsiella* spp. was the mostly commonly reported dual-uropathogen infection (13 patients, 50% of all patients), followed by *E. coli* plus *P. mirabilis* (4, 15.4%). *E. coli* was more frequently isolated among single pathogen-episodes (63.6% *vs.* 42.3%, $P = 0.006$) (Table 1). *Enterococcus* spp. were isolated more frequently among patients with dual growth-episodes compared with single pathogen-episodes growth (13.5% *vs.* 5.5%. $P = 0.05$).

No differences were found between male and female patients in the distribution of the 3 main pathogens: *E. coli* (32.3% *vs.* 26.6%, $P = 0.17$), *Klebsiella* spp. (15.2% *vs.* 9.2%, $P = 0.06$) and *Enterococcus* spp. (5.07% *vs.* 2.3%, $P = 0.12$).

### 3.2. Laboratory data

Leukocytosis >15.000 WBC/mm$^3$ was recorded in 77/188 (41%) evaluable patients. The total WBC count at admission was 14.8 ± 6.7 cells/mm$^3$, without differences between the patients with UTI caused by *E. coli*, *Klebsiella* spp. or *Enterococcus* spp. CRP was determined in 147 (77.0%) patients and was abnormal (>5 mg/d/L) in 39 (26.5%) of them.

Urinalysis (dipstick) was performed in 159/191 (83.2%) patients and was positive in 120 (75.5%) of them.

Blood cultures were performed in 50 patients and were positive in 2 of them for *E. coli* isolates identical to those isolated in urine.

### 3.3. Imaging

Ultrasound examination of kidneys and urinary tract was performed in 109/191 (57.1%) patients during hospitalization and revealed hydronephrosis of grades 1, 2 and 3 in 3, 2 and 3 patients, respectively; 3 additional patients had uretherolithiasis, swollen kidneys and double pyeloureteral system (1 each).

### 3.4. Antibiotic susceptibility (Figs. 1 and 2)

The resistance rates of the *E. coli* isolates (127 isolates) to the most commonly used antibiotics were 103/127 (81.1%), 80/127 (63.0%), 43/121 (35.5%), 40/127 (31.5%), 38/127 (29.9%), 23/118 (19.5%), 18/127 (14.2%), 9/118 (7.6%) and 4/112 (3.6%) for ampicillin, amoxicillin/clavulanic acid, TMP/SMX, cefuroxime, ceftriaxone, piperacillin/tazobactam, gentamicin, ciprofloxacin and amikacin, respectively. The antibiotic resistance of *Klebsiella* spp. isolates (53 isolates) was 53/53 (100%), 31/53 (58.5%), 31/53 (58.5%), 25/53 (47.2%), 23/53 (43.4%), 15/47 (31.9%), 8/50 (16.0%), 5/45 (11.1%) and 3/53 (5.7%) for ampicillin, cefuroxime, ceftriaxone, amoxicillin/clavulanic acid, gentamicin, TMP/SMX, piperacillin/tazobactam, amikacin and ciprofloxacin, respectively. The antibiotic resistance rates of the *Enterococcus* spp. (16 isolates) were 11/16 (68.8%), 11/15 (73.3%), 8/12 (66.7%) and 8/14 (57.1%) for ampicillin, gentamicin, TMP/and amoxicillin/clavulanic acid, respectively. All isolates were susceptible to vancomycin and teicoplanin.

Meropenem was tested for 11 patients and 10/11 pathogens isolated (6/6 *E. coli* and 5/6 *Klebsiella* spp.) were found susceptible to this antimicrobial.

Thirty-seven (29.15%) of the 127 *E. coli* isolates and 15/35 (42.9%) of the *Klebsiella* spp. tested isolates were ESBL-positive.

### 3.5. Management

Thirty-three infants received antibiotics during the month before the present hospitalization with UTI.

The mean (±SD) hospitalization length was 7.77 ± 4.03 days (median 7 days, range 2−30 days).

Sixty-five (31.4%) patients did not receive empiric antibiotic therapy and were started on antibiotic therapy only after the urine culture results were available. In the 131 patients started on antibiotics on the day of hospitalization, the most commonly used antibiotics were ceftriaxone (66 patients, 50.4%, 57 as single therapy), ampicillin (32, 24.4%, 17 alone and 15 in combination with gentamicin) and

**Table 1** Pathogen distribution: total pathogens recovered in first UTI episode (191 patients, 217 pathogens).

| Pathogen | No. isolates (total) | % | Single pathogen | % | Two pathogens | % |
|---|---|---|---|---|---|---|
| *Escherichia coli* | 127 | 58.5 | 105 | 63.6 | 22 | 42.3 |
| *Klebsiella* spp. | 53 | 24.4 | 38 | 23.0 | 15 | 28.9 |
| *Enterococcus* spp. | 16 | 7.4 | 9 | 5.5 | 7 | 13.5 |
| *Proteus mirabilis* | 6 | 2.8 | 2 | 1.2 | 4 | 7.7 |
| *Staphylococcus aureus* | 6 | 2.8 | 5 | 3.0 | 1 | 1.9 |
| *Enterobacter* spp. | 2 | 0.9 | 1 | 0.6 | 1 | 1.9 |
| *Pseudomonas aeruginosa* | 2 | 0.9 | 2 | 1.2 | – | – |
| Other | 5 | 2.3 | 3 | 1.9 | 2 | 3.8 |
| **Total** | **217** | | **165** | | **52** | |

cefuroxime (26, 19.8%, 22 as single therapy). The initial antibiotic therapy was modified according to the urine culture results and/or clinical condition in 34 (25.5%) patients.

### 3.6. UTI recurrence

Recurrent UTI episodes were recorded in 32/191 (16.8%) patients (75% males) (Table 2); 21.9% and 53.2% of the recurrent UTI episodes were diagnosed within 1 and within 2 months following the discharge after the initial UTI episode. Seven patients had a previously diagnosed renal abnormality (5 with hydronephrosis).

Fifteen (50%) of 30 the patients on whom data were available received antibiotic prophylaxis following the initial UTI episode.

Fifteen (50%) of the 30 evaluable patients were afebrile at the diagnosis of recurrent UTI, 7/30 (23.3%) had a WBC count $>$15.000 cells/mm$^3$ and the urinalysis (by dipstick) was positive in 17/28 (60.7%) samples analyzed.

Thirty-two uropathogens were isolated at recurrence. *E. coli* was the most frequent uropathogen (13 patients, 40.6% of all recurrent UTI episodes), followed by *Klebsiella* spp. (12, 37.5%). The percentages of *E. coli* isolation (among all pathogens) at the initial UTI episode were higher compared with those reported at the recurrent UTI episode (127/217, 58.5% *vs.* 13/32, 40.6%, $P = 0.057$). No differences were recorded in the percentages of *Klebsiella* spp. among the pathogens isolated in the index UTI episode compared with recurrent UTI episodes (53/217, 24.4% vs. 12/32, 37.5%, $P = 0.116$).

Twenty-five (78.1%) of the 32 recurrent UTI episodes were caused by uropathogens different (phenotypically) from the pathogens isolated at the initial UTI episode. The seven cases of recurrent UTI where the recovered uropathogen was identical to the initial uropathogen were caused by *E. coli* (5), *Klebsiella* spp. (1) and *Enterococcus* spp. (1). ESBL were reported in 7 (21.9%) isolates at the initial episode and in 10 (31.3%) at the UTI recurrence. Nine (90%) of the ESBL-producing uropathogens isolated at recurrence represented (phenotypically) new infections.

The antibiotic resistance rates of the *E. coli* (13 isolates) isolates were 76.9%, 58.3%, 46.2%, 38.5%, 38.5%, 38.5%, 30.8%, 0% and 0% for ampicillin, piperacillin/tazobactam, amoxicillin/clavulanic acid, TMP/SMX, cefuroxime, ceftriaxone, gentamicin, ciprofloxacin and amikacin, respectively (Fig. 1). The antibiotic resistance of *Klebsiella* spp. isolates (12 isolates) was 83.3%, 66.7%, 50.0%, 41.7%, 41.7%, 36.4%, 33.3%, 8.3% and 8.3% for ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefuroxime, ceftriaxone, TMP/SMX, gentamicin, amikacin and ciprofloxacin, respectively (Fig. 2).

**Table 2** 32 recurrent UTI episodes: epidemiologic and microbiologic characteristics.

| | No patients (%) |
|---|---|
| Age at initial episode (months, mean ± SD, median) | 3.02 ± 2.39 (2) |
| Age at first recurrence (months, mean ± SD, median) | 5.1 ± 2.81 (5) |
| Time of recurrence after index UTI episode (months) | |
| - 0–1 months | 7 (21.9) |
| - 1–2 months | 10 (31.3) |
| - 3–6 months | 13 (40.6) |
| - 7–12 months | 2 (6.2) |
| Gender M/F | 24 (75)/8 (25) |
| Renal pathology (on Ultrasound at recurrence)[a] | |
| - Hydronephrosis[b] | 5 (16.1) |
| - Double pyeloureteral system | 1 (3.2) |
| - Megaureter | 1 (3.2) |
| Uropathogens isolated ($n = 32$) | |
| - *E. coli* | 13 (40.6) |
| - *Klebsiella* spp. | 12 (37.5) |
| - *Enterococcus* spp. | 4 (12.5) |
| - *Enterobacter* spp. | 2 (6.3) |
| - *P. mirabilis* | 1 (3.1) |
| - ESBL–producing uropathogens[c] | 10 (31.3) |
| No. patients with normal urinalysis (dipstick)[d] | 11 (39.2) |
| Antibiotic prophylaxis since index episode[e] | 15 (50) |

[a] Data available on 31 patients.
[b] Degree 2, 3 and 4 in 2, 2 and 1 patients, respectively.
[c] 5 *E. coli*, 1 *Klebsiella* spp.
[d] Data available for 28 patients.
[e] Data available for 30 patients.

An increase was recorded from the initial to the recurrent UTI episodes in the resistance rates of *E. coli* and *Klebsiella* spp. isolates to piperacillin/tazobactam (Figs. 1 and 2): from 15.5% to 58.3% ($P = 0.002$) for *E. coli* and from 16% to 50% ($P = 0.001$) for *Klebsiella* spp.

## 4. Discussion

In a recent study, we reported on 151 infants $<$3 months of age hospitalized during 2010–2013 with UTI and showed

that 48.7% were <2 months, 6% had renal anomalies and only 28.2% were febrile at admission.[20] *E. coli*, *Klebsiella* spp., *Enterococcus* spp., *M. morganii* and *Proteus* spp. were the most common pathogens and the antibiotic resistance rates of *E. coli* and *Klebsiella* spp. were high (45.6—61.8% and 54.3—82.9%, respectively) for ceftriaxone, cefuroxime, gentamicin and ciprofloxacin. 80.9% and 42.9% of the *E. coli* and *Klebsiella* spp. isolates were ESBL-producers. The resistance rates of the 2 major pathogens to piperacillin/tazobactam, meropenem, nalidixic acid, chloramphenicol and colistin were low.[20]

The aim of the present study was to extend the previous information and to study the epidemiologic and microbiologic characteristics of infants aged 0—1 years diagnosed with their first UTI and hospitalized at our academic medical center in Central Romania during 2014—2017, with special emphasis on the characteristics of the first recurrent UTI episode. This study analyzed the first 191 UTI episodes and the 32 first UTI recurrence episodes occurring in these patients. The diagnosis was done following an examination of urine collected by catheterization of the bladder and we included in our study children whose urine culture grew one and also two organisms considered true uropathogens, following a thorough analysis of the microbiological, clinical and laboratory findings and after consultation with infectious disease experts.

We found the following in this study: 1. The five most commonly isolated uropathogens were *E. coli*, *Klebsiella* spp., *Enterococcus* spp., *P. mirabilis* and *S. aureus*; 2. The resistance rates of *E. coli* and *Klebsiella* spp. isolates were high for ampicillin, amoxicillin/clavulanic acid, TMP/SMX, cefuroxime, ceftriaxone and gentamicin, moderate for piperacillin/tazobactam and low for ciprofloxacin, amikacin and meropenem; 3. High ESBL production rates were recorded among *E. coli* and *Klebsiella* spp. isolates; 4. More than 50% of the recurrent UTI episodes were diagnosed within 2 months following the discharge after the initial UTI episode; 5. The percentages of *E. coli* isolation at the recurrent UTI episode were lower than those reported at the initial UTI episode; 6. The majority (78.1%) of the recurrent UTI episodes were caused by uropathogens different phenotypically from the pathogens isolated at the initial UTI episode and most ESBL-producing uropathogens isolated at recurrence represented new infections; 7. No differences were recorded between the initial and recurrent UTI episodes in the resistance rates of *E. coli* and *Klebsiella* spp., except for increased resistance rates of both pathogens to piperacillin/tazobactam at the recurrent episode.

Since delay in initiation of antibiotic therapy is associated with an increased risk of renal scaring,[21] infants and children with suspicion of UTI should be started on empiric antimicrobial therapy pending culture results.[3,4,11,22] *E. coli* organisms producing ESBL are reported with increased frequency and associated with recent hospitalization, preexisting neurological disease, presence of VUR and prior exposure to antimicrobial treatments.[23,24] Standard antimicrobial agents for initiation of treatment of UTI in infants <2 months of age include ampicillin plus an aminoglycoside and a parenteral second/third generation cephalosporin or aminoglycoside for older infants.[3,4,7,10,22] In the present study we found high rates of ESBL-producing *E. coli* and *Klebsiella* spp. organisms at the initial UTI episodes, associated with high resistance rates of these two pathogens to cefuroxime, ceftriaxone, piperacillin/tazobactam and gentamicin. These findings are of major concern and may warrant modifications in the empiric antibiotic treatment protocols used at our institution. As a first step towards improvement of the coverage of *E. coli* and *Klebsiell*a spp. (together with other *Enterobacteriaceae* spp.) in infants with UTI and also aiming to spare the use of carbapenems in order to limit the emergence of carbapenemase-producing *Enterobacteriaceae* spp., we decided (following the present study and in accordance to published studies on the good efficacy, safety and microbiologic profile of amikacin in the treatment of infections caused by this group of pathogens[25,26]) to modify the departmental protocol for the initial empiric treatment of this infants. According to the new protocol, gentamicin was changed to amikacin in the treatment of UTI in infants <2 months of life and amikacin monotherapy (intravenous or intramuscular) was introduced as first-line therapy for infants with UTI older than 2 months of life.

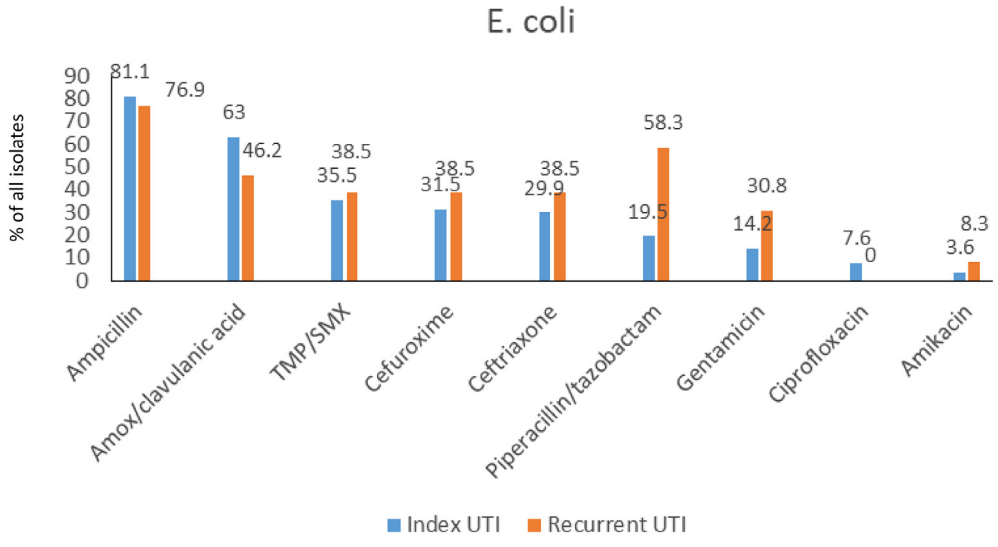


**Figure 1** Resistance percentages of *E. coli* to main antibiotics at the index UTI episode and at the recurrent-UTI episode.

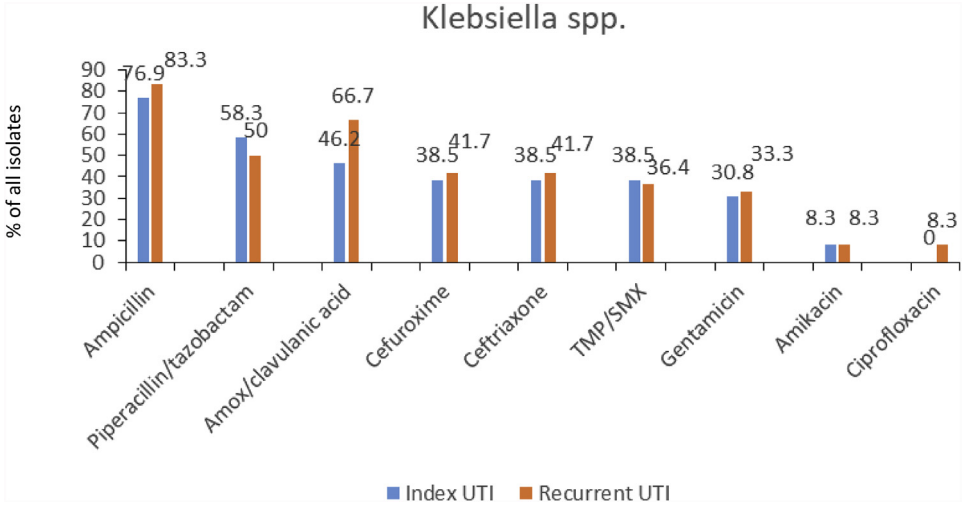


**Figure 2** Resistance percentages of *Klebsiella* spp. to main antibiotics at the index UTI episode and at the recurrent-UTI episode.

The recurrence rates after an initial UTI episode may reach 20—30% and most occur in the first 6 months after the initial episode.[7,27—30] In 611 children aged <6 years with a first UTI episode occurring during 2001—2006 in 27 primary pediatric practices in the United States, 83 (13.6%) were diagnosed with a recurrent UTI.[27] Factors associated with an increased risk of recurrent UTI included white race, age 3—5 years and grade 4—5 VUR. Antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI but was a risk factor for antimicrobial resistance among children with recurrent UTI.[27] During the first year of life, in patients with VUR receiving antibiotic prophylaxis, 48.4% developed recurrent UTI after a mean of 2.6 months after initiation of antibiotic treatment.[31] Higher grades of VUR, bilateral VUR, initial UTI caused by a non-*E. coli* strain and a delayed contrast passage on VCUG were all found to increase the risk of recurrent UTIs in patients with VUR.[31,32] In the present study, we report a 16.8% rate of recurrent UTI episodes which occurred in more than half of the cases at a time interval shorter than 2 months from the initial episode. The majority of the recurrent episodes represented infections with pathogens different to those isolated at the initial UTI. Therefore, in respect to the antibiotic choices for the treatment of the recurrent cases, it is clear to us, following the present study, that a therapeutic escalation is not needed and the same antibiotic protocol used for the initial episode should be used in these cases as well. However, most recurrent UTI episodes were caused by multidrug-resistant *E. coli* and *Klebsiella* spp. and were characterized by high rates of ESBL-producing organisms. The antibiotic resistance at recurrence of these two uropathogens was high and it was not different from the resistance reported for the initial UTI episode, with the exception of the resistance to piperacillin/tazobactam, which increased significantly compared with the initial episode.

The main limitation of this work derives from its retrospective nature, and some data could have been missing or incomplete. Some of the enrolled patients were admitted with other diagnoses (like bronchiolitis, pneumonia, otitis media or gastroenteritis, conditions associated with low UTI rates and not requiring urine examination or culture) and they received antibiotics targeting the initially diagnosed condition and their diagnosis of UTI was made only after the results of urine cultures became available. Therefore, it is plausible that in some cases contamination of the urine sample or presence of asymptomatic bacteriuria occurred on the background of fever or other symptoms related to other medical conditions requiring hospitalization. In addition, our data addressed only the microbiological picture of hospitalized infants with UTI and did not reflect the microbiological picture in children diagnosed in the community. The imaging data presented here represented the ultrasound examination performed during the hospitalization for the initial UTI episode and we were not able to provide information on possible renal abnormalities diagnosed after discharge.

In conclusion, we reported high antibiotic resistance rate to major antibiotic classes used in the treatment of UTI. R-UTIs were characterized by early occurrence, different uropathogens and increased antibiotic resistance. Our findings make the choice of the appropriate antibiotic treatment for UTI more difficult and challenging, particularly in geographic areas like ours, characterized by considerable antibiotic abuse and high antibiotic resistance rate, and our study emphasizes the need for tight epidemiologic follow-up and active, efficacious antibiotic stewardship.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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