ORIGINAL ARTICLE

Bacterial susceptibility to oral antibiotics in community acquired urinary tract infection

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Background: The most common oral antibiotics used in the treatment of urinary tract infection (UTI) are sulphonamides and cephalosporins, but emerging resistance is not unusual.
Aims: To assess the change in susceptibility of urinary pathogens to oral antibiotics during the past decade in children with community acquired UTI.
Methods: The study sample included two groups of children with a first community acquired UTI: 142 children enrolled in 1991 and 124 enrolled in 1999. UTI was diagnosed by properly collected urine specimen (suprapubic aspiration, transurethral catheterisation, or midstream specimen in circumcised males) in symptomatic patients. Antimicrobial susceptibility of the isolates was compared between the two groups.
Results: The pathogens recovered in the two groups were similar: in 1991—*E coli* 86%, *Klebsiella* 6%, others 8%; in 1999—*E coli* 82%, *Klebsiella* 13%, and others 5%. A slight but generalised decrease in bacterial susceptibility to common antibiotics in the two groups was shown: ampicillin 35% versus 30%; cephalexin 82% versus 63% (p < 0.001); nitrofurantoin 93% versus 92%. The only exception was co-trimoxazole, 60% versus 69%. Overall resistance to antibiotics in 1999 was as follows: ampicillin 70%, cephalexin 37%, co-trimoxazole 31%, amoxicillin-clavulanate 24%, nitrofurantoin 8%, cefuroxime-axetil 5%, nalidixic acid 3%.
Conclusions: This study shows a slight but generalised decrease in bacterial susceptibility to common oral antibiotics in the past decade in our population. Empirical initial treatment with co-trimoxazole or cephalexin is inadequate in approximately one third of UTI cases. A larger number of pathogens may be empirically treated with amoxicillin-clavulanate (24% resistance); 95% of organisms are susceptible to cefuroxime-axetil.

U rinary tract infection (UTI) is one of the most common bacterial diseases in children; it is acquired by an estimated 3–5% of girls and 1% of boys.[1] In girls, the average age at first diagnosis is 3 years; in boys, most cases occur during the first year of life. Early diagnosis and prompt antimicrobial treatment are required to minimise renal scarring and progressive kidney damage.

The American Academy of Pediatrics recommends that young children with culture proven UTI be treated with parenteral or oral antibiotics, depending on the clinical status.[2] The most common oral treatment is sulphonamides or first generation cephalosporins. However, there is growing concern regarding the resistance of urinary pathogens to these antibiotics because of the increasing number of therapeutic failures after empiric treatment.[3][4] This trend is part of the overall change in patterns of antimicrobial resistance. It is especially worrisome in children with UTI in whom quinolones are not accepted for routine use, leaving fewer oral treatment options than in adults.[5]

In patients with suspected UTI, antibiotic treatment is usually started empirically, before urine culture results are available. To ensure appropriate treatment, knowledge of the organisms that cause UTI and their antibiotic susceptibility is mandatory.[6] As both temporal and local variables can modify these data, they need to be constantly re-evaluated to achieve a maximal clinical response before the antibiotic susceptibility of the isolate is known. The aim of the present study was to assess the changing susceptibility of urinary pathogens to oral antibiotics in children with community acquired UTI.

PATIENTS AND METHODS
The study population consisted of children with first episode UTI being treated in an inpatient department or an outpatient

clinic of a tertiary paediatrics centre in Israel. The children were enrolled in the study during two periods: 1991 and 1999. All were referred because of urinary symptoms such as dysuria or unexplained acute febrile illness. In order to include only community acquired UTI, children with the following characteristics were excluded: previous history of urinary infection, known urinary malformations (according to prenatal ultrasound and previous medical records), chronic illness, or current prophylactic treatment with antibiotics.

UTI was defined as the growth of a single pathogen of >10^5 colony forming units/ml by properly collected urine specimen (suprapubic aspiration, transurethral catheterisation, or midstream specimen in circumcised boys) in children with febrile disease or urinary symptoms. Bag collected specimens were considered inadequate for diagnosis. Antimicrobial susceptibility of the isolates was tested by the disc diffusion technique, according to the National Committee for Clinical Laboratory Standards. For statistical analysis, organisms with intermediate susceptibility were considered resistant. The two groups (1991 and 1999) were compared for demographic data, epidemiological factors, and antibiotic susceptibility of pathogens. A sonogram and voiding cystourethrogram were performed in each case following urinary infection. Children with pathological results (reflux, anatomic malformations, or obstructions) were referred for further nephrological follow up. Statistical analysis was performed with Pearson's χ^2 test as well as Fisher's exact test, ANOVA, and the Mann-Whitney test.

RESULTS
A total of 142 children were enrolled in 1991 and 124 in 1999.

Table 1 Urine collection technique in children with UTI

	1991 Number (%)	1999 Number (%)
Suprapubic aspiration	33 (23.3)	13 (10.5)
Catheterisation	99 (69.7)	74 (59.7)
Midstream specimen	10 (7)	37 (29.8)
Total	142	124

Demographic data

Mean age of the first group was 20 months and of the second, 17 months. Median age of all children was 4.5 months (range 2 weeks to 15 years), without gaussian distribution. Females were affected more often than males (70% in 1991 and 63% in 1999) and were highly significantly older (mean 24 months v 6 months for males, $p < 0.001$).

The technique of urine collection was slightly different in the two groups. Suprapubic aspiration was performed in 23% of the patients in 1991 versus 10.5% in 1999; catheterisation in 70% versus 59.7%; and midstream collection in 7% versus 29.8% (table 1).

Urinalysis

In all children, microscopic examination (for leucocytes and bacteria) and urine nitrite testing were performed. There was a highly significant association between the presence of nitrites and pyuria (≥ 5 WBC/high power field; $p < 0.0001$). In 23% of the positive culture specimens, no leucocytes were present, and in 65%, no nitrites were found. Just one specimen without leucocytes was positive for nitrites; in 22% of cases, therefore, urinalysis was normal despite bacterial growth in urine culture. When these cases were compared to the general study population, no statistically significant differences were observed in demographic data (age and sex), pathogens, and antibiotic susceptibility.

Pathogens

The pathogens recovered in the two groups (1991 v 1999) were similar. Of the 142 children with UTI in 1991, 86% were infected by *Escherichia coli*, 6% by *Klebsiella* sp., and 8% by other pathogens. In 1999, *E coli* was identified in 82%, *Klebsiella* in 13%, and other pathogens in 5%. It is noteworthy that *E coli* grew in 91% of the specimens from females but in only 67% of those from males. Corresponding rates for *Klebsiella* were 6.4% and 21.7% ($p < 0.001$). Patients in whom UTI was caused by *E coli* were older than those with UTI caused by *Klebsiella* (mean age (SEM): 20.3 (3.2) v 1 (0.14) months; $p < 0.001$). They also tended to have more urine leucocytes (mean leucocyte count (SEM): 21.8 (1.8) v 4.5 (2.2); $p < 0.001$).

Antibiotic susceptibility

Table 2 shows the antibiotic susceptibility of the specific uropathogens in the two groups. The overall resistance to antibiotics in 1999 was as follows: ampicillin 70%, cephalexin 37%, co-trimoxazole 31%, amoxicillin-clavulanate 24%, nitrofurantoin 8%, cefuroxime 5%, nalidixic acid 3% (fig 1). In addition, the routinely tested antibiotics included third generation cephalosporins, aminoglycosides, monobactams, piperacillin, and quinolones.
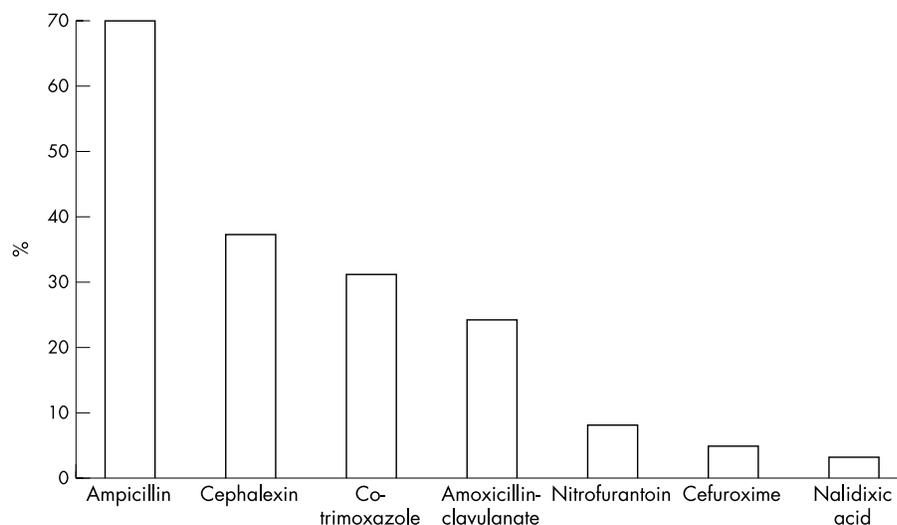
Table 2 Antibiotic susceptibility of uropathogens

	E coli 1991	E coli 1999	Klebsiella 1991	Klebsiella 1999	Total† 1991	Total† 1999
Percentage of UTI	86%	82%	6%	13%		
Ampicillin	37%	32%	1%	7%	35%	30%
Cephalexin	90%	64%*	50%	71%*	82%	63%*
Co-trimoxazole	59%	67%	67%	78%	60%	69%
Amoxicillin-clavulanate	ND	78%	ND	78%	ND	76%
Nitrofurantoin	100%	98%	89%	73%	93%	92%
Cefuroxime	ND	99%	ND	78%	ND	95%
Nalidixic acid	98%	99%	100%	93%	97%	97%

*$p<0.001$ for difference between the two periods.
†*E coli*, *Klebsiella*, and other pathogens.
ND, not done.

Figure 1 Overall resistance of urinary pathogens to oral antibiotics in 1999.

The antibiotic susceptibility of the urinary pathogens was also evaluated by patient sex. Bacterial specimens in male patients tended to be more sensitive to each antimicrobial agent, although this difference did not reach statistical significance. The agents with the most prominent differences were ampicillin (male susceptibility 37% *v* female susceptibility 26%, p = 0.3); amoxicillin-clavulanate (80% *v* 74%, p = 0.7); and co-trimoxazole (80% *v* 63%, p = 0.1).

DISCUSSION

This study shows a slight but generalised decrease in bacterial susceptibility of urinary pathogens to common oral antibiotics from 1991 to 1999 in children with community acquired UTI. Because young patients with a first episode of UTI are usually referred for in-hospital treatment, our group is probably representative of the general population in Israel.

According to the demographic data, females are affected more often than males, but males are significantly younger than females at the first UTI episode; they are also more frequently infected by *Klebsiella* sp. The relatively low percentage (63–70%) of female patients in our study can be explained by the younger median age of the patients; in an older sample, the relative rate of females would probably be higher. The question of an underlying urinary pathology in males compared to females and/or *Klebsiella* versus *E coli* infection is beyond the scope of this study, but it is known that children with urinary malformation have a decreased number of *E coli* infections and an increased number of infections by other Gram negative organisms.[6]

Studies have established that a normal urinalysis does not rule out UTI in children.[2] Indeed, 22% of our specimens that were positive on urinary culture were normal on urinalysis. The specific contribution of nitrites to the diagnosis of UTI was very low, in that there was just one patient without pyuria who was positive for nitrites. This observation supports previous studies indicating that the sensitivity of microscopic identification of white blood cells is so low (73%, range 32–100%), it makes the risk of missing UTI unacceptably high.[2] Asymptomatic bacteriuria should be considered in these patients[7]; however, all patients included in our study presented with a febrile illness or urinary complaints. Moreover, when we compared the subgroup of children with normal urinalysis to the whole study population, no statistically significant differences were observed in any of the parameters examined (data not shown).

The technique of sterile urine specimen collection in young children has been extensively discussed in the medical literature. Sterile midstream collection of urine in circumcised males is now performed more frequently in our institution, avoiding the need for more invasive procedures such as catheterisation or suprapubic aspiration. In populations with a high percentage of circumcised males, midstream collection is highly recommended as a reliable, non-invasive procedure for the diagnosis of UTI.[8] Furthermore, the American Academy of Pediatrics recognises that the low a priori rate of UTI in this population (0.2–0.4%) does not justify the routine use of an invasive, potentially traumatic diagnostic procedure.[2]

The most common oral antibiotics prescribed in Israel for UTI are first generation cephalosporins and co-trimoxazole. Aminoglycosides are the most common parenteral treatment. For secondary prophylaxis, first generation cephalosporins, co-trimoxazole, and nitrofurantoin are commonly prescribed.

In our study, almost all the bacteria tested showed a tendency to increased resistance to common antibiotics. The only exception was co-trimoxazole (40% *v* 31%, p < 0.01). One third of the urinary pathogens were resistant to co-trimoxazole or cephalexin, whereas only 25% were resistant to amoxicillin-clavulanate. Overall, 95% of the urinary pathogens in our population were sensitive to cefuroxime-axetil.

The failure rate in girls with UTI is expected to be greater than in boys. In our series, 80% of the specimens from the boys with UTI were sensitive to co-trimoxazole and to amoxicillin-clavulanate, compared to 63% and 74%, respectively, in the girls. Empiric treatment with co-trimoxazole is therefore inadequate in girls with UTI, but can be considered in boys. The reason for this disparity is not clear, but the younger age of the boys compared with the girls probably indicates a lower exposure to antimicrobial agents during life. The different pathogens involved in each group may also explain this finding.

Two other oral antimicrobial agents maintained their very high efficacy against urinary pathogens: nitrofurantoin and nalidixic acid (92% and 97%, respectively). These drugs remain a good option for prophylactic treatment. They should not be used to treat UTI in febrile infants because they are excreted in the urine and do not achieve therapeutic concentrations in the bloodstream.[2]

The increased isolation rate of *Klebsiella* sp. in the late period at the expense of a reduction in the isolation of *E coli* (probably as a consequence of the increased rate of male patients) is noteworthy. This may serve as an explanation for the increment in resistance to ampicillin and first generation cephalosporins, given that *Klebsiella* sp. are almost uniformly resistant to those antibiotics. Another possible cause of the increased resistance is the widespread use of β lactam agents in paediatric populations, especially for otitis media and pharyngitis.

As expected, in patients with community acquired UTI, expanded spectrum β lactamase bacteria were not recovered in our sample. All specimens were susceptible to at least one of the third generation cephalosporins or monobactams. Since our paper focuses on oral antibiotic treatment, these data are not shown.

Higher rates of susceptibility to many antibiotics have been reported in the general population with UTI worldwide. The trend of increasing resistance of urinary pathogens during the past few years is similar to our findings.[3 9–13] However, in the reports that were laboratory focused, the overall resistance of uropathogens was lower than in our study. This disparity may be attributed to differences in the study samples (paediatric *v* mixed population). In addition, laboratory studies may include specimens from asymptomatic patients or patients with external contamination, whereas our study was limited to properly collected urine samples in symptomatic paediatric patients.

In a recent study of UTI in northern Israel[4] in children aged 1–15 years, the percentage of uropathogen resistance to ampicillin, trimethoprim-sulfamethoxazole, and cephalexin was even higher than in our study (88%, 52%, 44%, respectively), though the resistance to amoxicillin-clavulanate and cefuroxime was similar (14% and 0%, respectively). These differences were probably caused by our restricting the sample to children with first episode UTI. The massive use of antibiotics in the paediatric population is probably a risk factor for increased resistance of uropathogens in our study. Moreover, we considered only the fully susceptible specimens as sensitive; all intermediate ones were classified as resistant, leading to lower susceptibility rates.

In 1999, Hoberman and colleagues[14] recommended oral cefixime for the treatment of young children with fever and UTI instead of hospitalisation and intravenous antimicrobials. Cefixime was not included in our study, but the published data support the efficacy of this third generation cephalosporin. We did not address the issue of hospitalisation versus outpatient treatment, but as a rule, the narrowest spectrum of antibiotics should be used as the drugs of choice.

In conclusion, in children with a first episode of community acquired UTI, we found only a slight increase in bacterial resistance to oral antibiotics during the past decade. Empirical treatment with co-trimoxazole or cephalexin as the initial

drug is inadequate in approximately one third of cases. A larger number of pathogens may be empirically treated with amoxicillin-clavulanate (24% resistance); 95% of organisms are sensitive to cefuroxime-axetil.

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