Ten Years Surveillance of Antimicrobial Susceptibility of Community-Acquired *Escherichia coli* and Other Uropathogens in Northern Israel (1995–2005)

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Abstract

Background: In an era of increasing antimicrobial resistance, knowledge of local antimicrobial susceptibility patterns of common uropathogens is essential for prudent empiric therapy of community-acquired urinary tract infections.

Objectives: To define antimicrobial susceptibility of Gram-negative uropathogens in northern Israel over a 10 year period and to compare it with patterns of antibiotic use in the same community.

Methods: We tested the susceptibility of all Gram-negative urinary isolates from outpatients at HaEmek Medical Center over the years 1995, 1999, 2002 and 2005 to common antimicrobial agents. MIC_{90} of *Escherichia coli* to some of these agents was determined and antibiotic consumption data over the years 2000–2005 (DDD/1000/day) were obtained.

Results: We observed a rise in susceptibility rates of E. *coli* to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole and nitrofurantoin and of other Gram-negative isolates to amoxicillin-clavulanate, ceftriaxone and cephalothin. Susceptibility rates of all Gram-negative uropathogens to ciprofloxacin decreased significantly. MIC_{90} of E. *coli* for all drugs tested remained stable. There was a significant decrease in the use of nitrofurantoin and TMP-SMX and a significant increase in the use of ampicillin, cephalothin and ceftriaxone.

Conclusions: Antibiotic resistance patterns mostly remained unchanged or improved slightly. There was, however, a constant decrease in susceptibility of all Gram-negative uropathogens to ciprofloxacin. Antibiotic use patterns could not explain the changes seen in antibiotic susceptibility patterns.

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Urinary tract infection is a common clinical condition, especially among women, half of whom will suffer at least one episode at some point during adult life [1]. The management of uncomplicated UTI has traditionally been based on the predictability of two factors: the spectrum of organisms causing acute UTI (highly predictable) and the susceptibility patterns of these organisms (relatively predictable). However, antibiotic resistance is now becoming a major factor, not only in nosocomial UTIs but also in uncomplicated community-acquired UTI [2]. Thus, knowledge of local susceptibility patterns is essential for the optimal empiric therapy pending culture results. This study was aimed at evaluating and comparing susceptibility patterns of community-acquired UTI pathogens in northern Israel over a 10 year period. It follows a previous study by Chazan et al. [3] performed over the years 1995–2002.

TMP-SMX = trimethoprim-sulfamethoxazole
UTI = urinary tract infection

Patients and Methods

The laboratory at HaEmek Medical Center serves a population of approximately 450,000 patients. All Gram-negative uropathogens isolated from outpatients during the years 1995, 1999, 2002 and 2005 were included in this study. No significant demographic changes occurred during the study period.

Urine samples were processed as follows: 1 ml samples were seeded on Endo agar (Difco Laboratories, Detroit, MI, USA) and coliracin/nalidixic acid supplemented sheep blood agar plates (Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France) in 1995 and 1999. In 2002 and 2005, samples were inoculated on Chromagar Orientation Agar (Hy laboratories, Rehovot, Israel). Plates were read after 24 hours and 48 hours of incubation. Positive cultures were defined according to Cumitech guidelines [4]. The microbiology methods were the same over the different periods of the study. All the susceptibility data were obtained using the same Microscan Walakaway 96 System and processed with the same Microscan DM software.

Bacterial isolates were identified to the species level and antibiotic susceptibility was determined using Microscan Urine Combo 2 and Pos Combo 6 and 12 (Dade Behring, Sacramento, CA), for Gram-negative and Gram-positive organisms respectively. Panels were processed using a Microscan Walkaway 96 system. However, for data analysis, all Gram-negative organisms from E. *coli* were categorized as "other Gram-negative." Susceptibility of bacterial isolates to amoxicillin-clavulanate, cephalothin, cefuroxime, ceftriaxone, ciprofloxacin and nitrofurantoin was interpreted using the CLSI (Committee for Laboratory Standards Institute) breakpoints [5]. Antibiotic consumption data for the years 2000–2005 were obtained from the central computerized database of Clalit Health Services (largest of the four health management organizations in Israel). Antibiotic consumption was measured using Defined Daily Dose (DDD) per 1000 inhabitants, according to the 2003 version of World Health Organization definitions. Statistical comparisons between the groups were performed using the chi-square test.

Results

The numbers of urine samples received from outpatients during the years studied were as follows: 57,191 for 1995, 57,512 for 1999, 64,302 for 2002, and 66,293 for 2005. From those cultures, a total of 6212 (10.86%), 6519 (11.3%), 6272 (9.75%) and 6368 (9.6%) Gram-negative uropathogens were isolated respectively. Table 1 summarizes the prevalence and distribution of E. *coli* and other Gram-negative uropathogens during the four study years. E. *coli* remained the leading uropathogen with no significant change in prevalence over the study years.

As shown in Table 2, the susceptibility rates of E. *coli* for ampicillin, cefuroxime and ceftriaxone remained stable during the study period, while susceptibility to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole and nitrofurantoin showed a significant increase. Susceptibility rates of E. *coli* to ciprofloxacin showed a significant decrease. For cephalotin, following a decrease in 1999, a continuous increase in susceptibility rates was observed until 2005.

Table 3 presents the susceptibility of other Gram-negative pathogens for the same antibacterials. Susceptibility to cefuroxime, TMP-SXZ and nitrofurantoin remained stable. There was a significant increase in the susceptibility to amoxicillin-clavulanate, ceftriaxone and cephalothin. There was lowered susceptibility to ampicillin and ciprofloxacin. The MIC_{90} of E. *coli* for amoxicillin-clavulanate, cephalothin, cefuroxime, ceftriaxone and ciprofloxacin remained stable during the study period.

The antibiotic consumption in the community for ampicillin, amoxicillin-clavulanate, cephalothin, cefuroxime, ceftriaxone, TMP-SMX, fluoroquinolones (ciprofloxacin and ofloxacin) and nitrofurantoin during the years 2000–2005 in our area is shown in Table 4. There was a significant decrease in the use of nitrofurantoin and TMP-SMX, and a significant increase in the use of ampicillin, cephalothin and ceftriaxone. There was also a small increase in the use of fluoroquinolones, amoxicillin-clavulanate and cefuroxime.

Discussion

The susceptibility of uropathogens in northern Israel has been reported previously [3,6]. However, the present study provides information on the frequency and antibiotic susceptibility of Gram-negative uropathogens responsible for community-acquired UTI over a 10 year period in our geographic region. The study demonstrates that E. *coli* remains the leading uropathogen responsible for community-acquired UTI in our area, and no change in its prevalence among all Gram-negative uropathogens was observed.

The results show a significant increase in susceptibility of E. *coli* to amoxicillin-clavulanate (89% to 96%), TMP-SXZ (70.9–71.88%) and nitrofurantoin (93.9–96.99%) over the 10 year period. Susceptibility of E. *coli* to ampicillin (~45%), cefuroxime (~97%) and ceftriaxone (~98%) did not change significantly. Furthermore, for cefuroxime and ceftriaxone the MIC_{90} remained stable.

During the years 2000–2005 there was a significant reduction in the use of TMP-SXZ and nitrofurantoin in our area. We speculated that this might explain the increased susceptibility of E. *coli* to these antibacterials. However, the data also reflected a non-significant increase in the use of amoxicillin-clavulanate for which E. *coli* susceptibility has increased significantly. On the other hand, susceptibility rates of E. *coli* to cephalotin increased significantly since 1999 despite a significant increase in the use

Table 1. Distribution of Gram-negative uropathogens over the four study years

	1995 n (%)	1999 n (%)	2002 n (%)	2005 n (%)	*P*
E. *coli*	4179 (67.3)	4404 (67.5)	4190 (66.8)	4329 (68.0)	NS
Other Gram-negative pathogens	2033 (32.7)	2115 (32.5)	2082 (33.2)	2039 (32.0)	NS
Gram-negative total	6212 (100%)	6519 (100%)	6272 (100%)	6368 (100%)	

NS = not significant

Table 2. Susceptibility rates in % for E. *coli*

	AMC	AMP	CAX	CRM	CF	CP	T/S	FD
1995	89	45	98	96	74	94	70.9	93.9
1999	90	44.1	99	96	60.1	94	73	95
2002	95	46	99	97	70	93	74.9	97
2005	96	46	98	96.7	72.1	89.5	71.88	96.99
P	< 0.001	0.36	0.94	0.088	0.03	< 0.001	0.01	< 0.001

AMC = amoxicillin-clavulanate, AMP = ampicillin, CAX = ceftriaxone, CRM = cefuroxime, CF = cephalotin, CP = ciprofoloxacin, T/S = trimethoprim-sulfamethoxazole, FD = nitrofurantoin.

Table 3. Susceptibility rates in % for other Gram-negative uropathogens

	AMC	AMP	CAX	CRM	CF	CP	T/S	FD
1995	68.5	24.1	91.7	74.9	58.3	92	80.6	44.4
1999	74.8	14.7	90.9	79.6	61.9	95.7	82.5	37.6
2002	80.1	14.5	92.4	85.3	68	91.3	85.8	51.2
2005	73.8	19.5	94.93	76.46	68.31	89.34	80	43.73
P	< 0.001	< 0.001	< 0.001	0.25	< 0.001	0.004	0.61	0.67

AMC = amoxicillin-clavulanate, AMP = ampicillin, CAX = ceftriaxone, CRM = cefuroxime, CF = cephalotin, CP = ciprofoloxacin, T/S = trimethoprim-sulfamethoxazole, FD = nitrofurantoin.

Table 4. Defined daily dose (DDD) per 1000 inhabitants for selected antibacterials during 2000–2005

	AMP	CF	FD	T/S	AMC	FLQ	CAX	CRM
2000	6.49	0.61	0.75	0.15	2.98	0.84	0.005	2.15
2001	6.41	0.58	0.82	0.18	3	0.83	0.005	2.09
2002	6.68	0.65	0.93	0.15	3.27	0.78	0.005	2.3
2003	7.39	0.71	1.06	0.13	3.32	0.81	0.008	2.33
2004	7.85	0.81	0.61	0.21	3.57	0.93	0.011	2.25
2005	8	0.87	0.57	0.071	3.7	0.99	0.008	2.46
P	< 0.001	0.003	< 0.001	< 0.001	0.37	0.74	< 0.001	0.13

AMC = amoxicillin-clavulanate, AMP = ampicillin, CAX = ceftriaxone, CRM = cefuroxime, CF = cephalotin, CP = ciprofoloxacin, T/S = trimethoprim-sulfamethoxazole, FD = nitrofurantoin.

of this antimicrobial in the last few years. Thus, at least in some cases, the change in susceptibility rates of uropathogens to certain antibacterials could not always be explained by changing trends in the use of the same drug.

An alarming finding was a significant decline in susceptibility of E. *coli* and other Gram-negative pathogens to ciprofloxacin, in contradiction to the results of Chazan and co-authors in 2002 [3], which showed stability of susceptibility to ciprofloxacin over the years 1995–2002. Susceptibility of E. *coli* decreased from 94% in 1994 to 89.5% in 2005 and the susceptibility of other Gram-negative pathogens declined from 92% in 1995 to 89.34% in 2005. These results are compatible with those of Karaca et al. [7] who studied the resistance of E. *coli* to TMP-SMX and fluroquinolones in Turkey over a 10 year period (1994–2003), and showed a decrease in resistance to TMP-SMX and an increase in resistance to fluroquinolones as the use of TMP-SMX in Turkey diminished and fluroquinolones became the drugs of choice for community-acquired UTI.

The resistance to fluroquinolones is regional, as shown by the ECO-SENS study that investigated the prevalence and antimicrobial susceptibility of pathogens causing uncomplicated community-acquired UTI in 16 different European countries and Canada [8]. Overall resistance to ciprofloxacin was 2.3%, with 0% in Austria and up to 14.7% in Spain.

Since their introduction to clinical practice, fluroquinolone-resistant E. *coli* (QREC) strains are being isolated with increasing frequency. Such strains also show higher rates of cross-resistance with antimicrobial classes other than fluroquinolone-susceptible strains, and they are associated with increased mortality [8]. Risk factors for acquisition of QREC include prior fluroquinolone use, old age and recurrent urinary tract infections [9,10]. The increased frequency of QREC UTIs is probably due to selection of resistant strains from the endogenous flora of the patients [9].

Although resistance of E. *coli* to fluroquinolones is on the rise it remains highly susceptible to nitrofurantoin. Given the fact that nitrofurantoin has no role in the treatment of other infections, it should be especially useful for the treatment of uncomplicated community-acquired UTI [8]. The data obtained for other Gram-negative uropathogens demonstrate a significantly increased susceptibility of these pathogens to amoxicillin-clavulanate (65.8–73.8%), ceftriaxone (91.7–93.93%) and cephalothin (58.3--68.3%). Susceptibility for cefuroxime (~75%), TMP-SXZ (~80%) and nitrofurantoin (~44%) did not change significantly over the 10 years, but a significant decrease in susceptibility to ciprofloxacin was observed.

QREC = fluroquinolone-resistant E. *coli*

In an era of increased antibiotic resistance in general and Gram-negative uropathogens in particular, our study demonstrates that over a 10 year period the susceptibility of E. *coli* and other Gram-negative uropathogens responsible for community-acquired UTI in northern Israel has remained stable or showed a small but significant increase. However, there has been a constant decrease in susceptibility of uropathogens to fluroquinolones. In our opinion, antibiotic consumption patterns in our area cannot explain the changes in antibiotic susceptibility. As susceptibility of E. *coli* to nitrofurantoin remains high, it should be used more frequently in the treatment of uncomplicated community-acquired UTI caused by this pathogen and the use of fluroquinolones should be curtailed in the community as in the hospital setting.

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Nature's laws affirm instead of prohibit. If you violate her laws, you are your own prosecuting attorney, judge, jury, and hangman.

Luther Burbank (1849-1926), U.S. horticulturist who developed more than 800 strains and varieties of plants, including the well-known Russett-Burbank potato, the world's predominant processing potato