Ethnic Diversity and Increasing Resistance Patterns of Hospitalized Community-Acquired Urinary Tract Infections in Southern Israel: A Prospective Study

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ABSTRACT: **Background:** Little is known about the incidence of urinary tract infections (UTI) in the dispersed Bedouin population. UTIs are routinely treated empirically according to local resistance patterns, which is important when evaluating the risk factors and antibiotic resistance patterns in the Bedouin population.

Objectives: To analyze risk factors, pathogens, and antibiotic resistance patterns of UTIs in the Bedouin population compared to the general population in southern Israel. To compare data from this study to that from a previous study conducted at our center.

Methods: We prospectively followed all patients hospitalized with community acquired UTIs during a 4 month period at Soroka Medical Center. We also compared results from this study to those from a study conducted in 2000.

Results: The study comprised 223 patients: 44 Bedouin (19.7%), 179 (80.3%) non-Bedouin; 158 female (70.9%), 65 male (29.1%). The Bedouin were younger (51.7 vs. 71.1 years of age, $P < 0.001$) and had a lower Charlson Comorbidity Index (2.25 vs. 4.87, $P < 0.001$). Enterobacteriaceae were the most common pathogens identified, and *Escherichia coli* (*E. coli*) was the most common with 156 (70%) strains identified, followed by *Klebsiella* spp. with 29 (13%), *Proteus* spp. with 18 (8%), pseudomonas with 9 (4%), and other bacteria including enterococci with 11 (5%). The prevalence of *E. coli* increased significantly from 56% in 2000 to 70% in this study. We also noted an increase in community acquired extended spectrum beta lactamase (ESBL) pathogens from 4.5% in 2000 to 25.5% in the present study. No statistically significant difference was observed between the Bedouin and general populations in the causal pathogens, resistance to antibiotics, length of therapy, and readmission rate within 60 days.

Conclusions: The Bedouin population hospitalized for UTIs is younger and presents with fewer co-morbidities. Isolated pathogens were similar to those found in the general population as was the presence of drug resistant infections. Overall, a substantial percentage of pathogens were resistant to standard first-line antibiotics, driving the need to change from empiric therapy to aminoglycoside therapy.

IMAJ 2017; 19: 538–542

KEY WORDS: Bedouin, urinary tract infection (UTI), antimicrobials, antibiotic resistance, empiric therapy

Urinary Tract Infections (UTI) are some of the most common infectious diseases in adults, especially for women. The clinical signs of UTI range from an asymptomatic illness to a severe systemic disease including kidney infection, which could lead to septicemia. About 40% of women will experience at least one occurrence of UTI in their lifetime [1]. In the United States, UTIs lead to approximately 7 million visits to the doctor, at an annual cost of around 1.6 billion dollars [2]. In the medical literature there are a number of well-known risk factors for UTI in general and especially for recurring infections. These include a deformity of the urinary tract, the presence of a catheter in the urinary tract, an anatomical problem such as an enlargement of the prostate gland, or urine reflux [3].

In recent years, there has been an increase in bacterial resistance to antibiotics. There are reports in the literature of major differences between different geographical areas and between different populations because of previous exposure to antibiotics and other factors [4-5]. The problem of bacterial resistance to antibiotics has become so widespread that a report published by the World Health Organization in 2014 reported that in 5/6 of the world's regions over 50% of the bacteria that cause urinary tract and blood infections are resistant to third-generation cephalosporin [6]. The guidelines published by the Infectious Diseases Society of America recommend carrying out periodic local surveys of the causative factors of UTI to adjust the empirical treatment [7]. Resistance of bacteria to common antibiotics makes it difficult to treat UTI.

The Negev is a unique region, which occupies about half of the area of the State of Israel and has roughly 1 million residents. Of these, 20% are of Bedouin ethnicity, some living in urban conditions others without modern first-world facilities and

services such as running water and electricity. Hospitalization services in the Negev are provided by a single tertiary medical center: the Soroka Medical Center. Furthermore, the center's microbiology lab processes all of the tests that are performed in the region, providing researchers with a unique opportunity to observe the distribution of different pathogens and their sensitivity. To date, to the best of our knowledge, no comparison has been made between the Bedouin population and the general population as to which pathogens cause UTI, what their antibiotic resistance profile is, and whether it is different from the rest of the Negev community.

PATIENTS AND METHODS

After obtaining informed consent from our institution's ethics review board, we prospectively screened all consecutive patients from April 2015 until July 2015 who presented with a urine culture positive for UTI. We included hospitalized patients with a positive urine culture (> 105 colony-forming units) of a single pathogen obtained at admission who had fever of ≥ 38.2°C and at least one of the following symptoms: dysuria, frequency, urgency, flank pain, or costovertebral tenderness. We excluded all patients with a permanent urinary catheter and asymptomatic bacteriuria as well as patients with other suspected or proven sources of infection.

Data collected included demographic details, underlying disease, Charlson Comorbidity Index (CCI), symptoms and signs related to the present infection, diagnosis upon admission, and other relevant clinical information. Etiological pathogens and their sensitivity to antibiotic therapy were evaluated. Urine cultures were conducted by our microbiology laboratory according to standard techniques [8]. Antimicrobial susceptibility tests were performed using the Kirby–Bauer disk diffusion method [9] or the VITEK® 2 (bioMérieux, France) microbial identification system and antibiotic susceptibility testing. Interpretation of these test results were according to the guidelines proposed by the Clinical Laboratory Standards Institute [10]. We conducted an observational study and did not interfere with clinical decisions or with the selection of antibiotics. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

DATA ANALYSIS

Statistical analysis was performed using IBM SPSS statistics software, version 23 (IBM Corp, Armonk, New York, USA). Risk ratios (RRs), 95% confidence intervals (CIs), and *P* values on categorical outcomes were calculated with univariate log-binomial regression models and with Pearson's chi-square test. Continuous variables were compared using a 2-sample *t* test or Mann–Whitney U test. Variables were initially assessed by univariate analysis. Multivariate analysis was performed using a multiple log-binomial regression model to control for confounding and effect modification. A *P* value of 0.05 or less was considered to be statistically significant.

RESULTS

From 1 April 2015 until 31 July 2015, 673 patients with urine cultures positive for UTI were identified by the Soroka Medical Center's microbiology lab. Of these, 223 (33%) were determined to be true UTIs; whereas, 450 (67%) were not included: 36 due to the presence of a permanent catheter in the urinary tract, 78 children under the age of 18, and 336 in whom another source of the fever was identified so that it was impossible to attribute the illness to UTI with any certainty.

In the study group, most of the patients were women (70.9%) with an average age of 67.2 ± 21.1 years, with a CCI of 4.41 ± 2.6. In most of the patients (71.7%), components of complicated UTI were found, such as diabetes (36%), pregnancy (7.6%), and male gender (29.1%). Compared to a similar study that was carried out at the same medical center in 2000 [11] [Table 1], there were more Bedouin, diabetics, and patients defined as suffering from complicated UTI.

In this study, 19.7% were of Bedouin origin, similar to the percentage in the population of the Negev area, no significant difference was found in terms of the time of diagnosis. Compared to the general population, in the Bedouin population [Table 2] a younger population was observed: 51.725 ±

Table 1. Demographic and clinical baseline characteristics of patients with urinary tract infections and distribution of microorganism identified in urine cultures at the Soroka Medical Center: 2015 vs. 2000 [11]

	2015 N (%)	2000 N (%)	*P* value
All cases	223 (100)	223 (100)	1
Female	70.9 (158)	146 (65.5)	0.22
Bedouin	19.7 (44)	11 (5)	< 0.01
Age, years	67.2 ± 21.1	64.9 ± 19.2	
CCI	4.41 ± 2.6	n/a	n/a
Complicated UTI	71.7 (160)	136 (60)	0.01
Diabetes	35 (78)	57 (25.6)	0.03
Pregnancy	7.6 (17)	9 (4)	0.1
E. Coli	156 (70)	146 (65.5)	n/a
Klebsiella spp.	13 (29)	23 (10)	n/a
Proteus spp.	8 (18)	16 (7)	n/a
Pseudomonas spp.	9 (4)	15 (7)	n/a
Other bacteria*	10 (4)	24 (11)	n/a
Enterococci	1 (≤ 1)	20 (9)	n/a
ESBL	57 (25.5)	10 (4.5)	n/a

CCI = Charlson Comorbidity Index, n/a = no available data, UTI = urinary tract infection, *E. coli* = *Escherichia coli*, ESBL = extended-spectrum beta-lactamas

*other bacteria include *Acinetobacter* spp., coagulase negative Staphylococci, *Citrobacter* spp., Enterobacter, Morganella, and *Streptococcus B*

Table 2. Baseline characteristics of the patient population

	Bedouin, N (%)	Non-Bedouin, N (%)	*P* value
All cases	44 (19.7)	179 (80.3)	< 0.01
Female	33 (75)	125 (69.8)	0.5
Age, years	51.7 ± 25	71.1 ± 18.4	< 0.001
CCI	2.25 ± 2.6	4.87 ± 2.4	< 0.001
Dysuria	9 (20.5)	27 (15.1)	0.26
Urgency	6 (13.6)	9 (5)	0.05
Frequency	5 (11.4)	7 (3.9)	0.064
Flank pain	12 (27.3)	18 (10.1)	0.005
Abnormal urine dipstick	22 (50)	71 (39.7)	0.14
Diabetes	13 (29.5)	65 (36.3)	0.25
Pregnancy	11 (25)	6 (3.4)	< 0.001
Readmission within 60 days	7 (15.9)	40 (22.3)	0.41
Mean antibiotic therapy days (SD)	8.9 (6.5)	8 (5.7)	0.345

CCI = Charlson Comorbidity Index, SD = standard deviation

vs. 71.1 ± 18.4 ($P < 0.001$) as well as a lower CCI of 2.25 ± 2.6 vs. 4.87 ± 2.4 ($P < 0.001$). The Bedouin population reported more flank pain and included significantly more pregnant women; however, there was no significant difference in the length of antibiotic therapy (8 vs. 8.9 days) and no difference in the readmission rate within 60 days.

Enterobacteriaceae were the most common pathogens identified [Table1]. Among them, the most common pathogen was *Escherichia coli* (*E. coli*) (156 cases, 70%), followed by *Klebsiella* spp. (29 cases, 13%), *Proteus mirabilis* (18 cases, 8%), and *Pseudomonas aeruginosa* (9 cases, 4%). *Enterococcus fecium* was isolated in only one case (< 1%), other uncommon pathogens included acinetobacter and citrobacter (10 cases, 4%). There was no difference in the occurrence of the pathogens and their resistance to antibiotics between the Bedouin population and the total population [Table 3].

Compared to the prospective study that was conducted at our institution in 2000 [Table 4] [11], a significant increase was found in the occurrence of the *E. coli* bacteria, together with a significant decrease in the incidence of

Table 3. Distribution of pathogens according to sensitivity in Bedouin and non-Bedouin population in 223 patients

	E coli			Klebsiella spp.			Proteus spp.			Other bacteria*			Pseudomonas spp.			Enterococci		
	Bedouin	Non-Bedouin	*P* value	Bedouin	Non-Bedouin	*P* value	Bedouin	Non-Bedouin	*P* value	Bedouin	Non-Bedouin	*P* value	Bedouin	Non-Bedouin	*P* value	Bedouin	Non-Bedouin	*P* value
Patients, N	33	123		4	25		3	15		3	7		0	9		0	1	
Cefuroxime, n (%)	23 (69)	78 (63)	NS	2 (50)	9 (36)	NS	2 (66)	11 (73)	NS	2 (66)	4 (57)	NS	n/a	n/a	n/a	n/a	n/a	n/a
Ceftriaxone, n (%)	22 (66)	81 (65)	NS	2 (50)	11 (44)	NS	2 (66)	11 (73)	NS	3 (100)	4 (57)	NS	n/a	n/a	n/a	n/a	n/a	n/a
Aminoglycoside, n (%)	29 (87)	99 (80)	NS	1 (25)	12 (48)	NS	3 (100)	11 (73)	NS	2 (66)	5 (71)	NS	0	6 (66)	NS	0	1	NS
Fluoroquinolone, n (%)	22 (66)	80 (65)	NS	2 (50)	12 (48)	NS	1 (33)	9 (60)	NS	2 (66)	4 (57)	NS	0	5 (55)	NS	0	0	NS
TMP/SMX, n (%)	21 (63)	77 (62)	NS	2 (50)	11 (44)	NS	2 (66)	11 (73)	NS	1 (33)	5 (71)	NS	n/a	n/a	n/a	n/a	n/a	n/a
Nitrofurantoin, n (%)	23 (69)	89 (72)	NS	1 (25)	7 (28)	NS	0	1 (6)	NS	2 (66)	4 (57)	NS	n/a	n/a	n/a	n/a	n/a	n/a

E. coli = *Escherichia coli*, TMP/SMX = trimethoprim sulfamethoxazole. NS = non-significant, n/a = no available data
*other bacteria include *Acinetobacter* spp., coagulase negative Staphylococci, *Citrobacter* spp., Enterobacter, Morganella, and *Streptococcus B*

Table 4. Antibiotic sensitivity of bacteria identified in the urine cultures. Comparison between 2000 study [11] and current study (2015) at Soroka Medical Center

	E coli			Klebsiella spp.			Proteus spp.			Other bacteria*			Pseudomonas spp.		
	2000	2015	*P* value	2000	2015	*P* value	2000	2015	*P* value	2000**	2015*	*P* value	2000	2015	*P* value
Patient, N (%)	125 (56)	156 (70)	< 0.05	23 (10)	29 (13)	NS	16 (7)	18 (8)	NS	24 (10)	10 (4)	< 0.05	15 (6)	9 (4)	NS
Cefuroxime, n (%)	114 (91)	101 (65)	< 0.05	18 (78)	11(38)	< 0.05	12 (75)	13 (72)	NS	12 (50)	6 (60)	NS	n/a	n/a	n/a
Aminoglycoside, n (%)	108 (86)	128 (82)	NS	17 (74)	14 (48)	< 0.05	7 (44)	14 (78)	NS	18 (75)	7 (70)	NS	1	6	NS
Fluoroquinolone, n (%)	107 (85)	102 (65)	< 0.05	17 (74)	10 (34)	< 0.05	12 (75)	10 (55)	NS	16 (66)	6 (60)	NS	10	5	NS
TMP/SMX, n (%)	72 (57)	98 (63)	NS	17 (74)	13 (45)	< 0.05	7 (44)	13 (72)	NS	18 (75)	6 (60)	NS	n/a	n/a	n/a

E. coli = *Escherichia coli*, TMP/SMX = trimethoprim sulfamethoxazole, NS = non-significant, n/a = no available data
*other bacteria include *Acinetobacter* spp., coagulase negative Staphylococci and *Citrobacter* spp., Enterobacter, Morganella, *Streptococcus B*

enterococci and other pathogens. Likewise, a significant change was observed in the sensitivity profile of the bacteria. A significant decrease in the sensitivity of *E. coli* to second generation cephalosporin and fluoroquinolones, and a significant decrease in the sensitivity of Klebsiella to all the antibiotics that were tested. An additional finding of the comparison of the data from the different years was a significant rise in the prevalence of bacteria capable of producing extended-spectrum beta-lactamases (ESBLs), from 10 patients (4.5%) in 2000 to 57 patients (25.5%) in 2015.

DISCUSSION

A number of distinct differences can be seen between the Bedouin population and the general population. The Bedouin population that was hospitalized due to a UTI was younger, with fewer co-morbidities and more often pregnant. In addition, this population expressed more urinary complaints upon admission than the rest of the population. However, the occurrence of diabetes, the ratio of men, and indicators of complicated disease were similar in both populations. The length of antibiotic therapy and the re-admission rates were also comparable, thus implying similar failure of therapy rates. There are a number of possible reasons for these differences: the distance from the place of residence to the medical center, living conditions that are mostly not in organized settlements with less access to public health services, and the concern of the medical staff at the emergency department about discharging the patients without proper outpatient follow-up. Contrary to these differences between the Bedouin population and the rest of the population, there were no observed differences in the distribution of the bacteria that caused the urinary tract inflammation or their resistance patterns to antibiotics. This finding implies that the Bedouin population is exposed to antibiotics at the same rate as the rest of the population.

In the study population it can be seen, as expected, that most of the patients were women who mostly suffered from complicated infections of the urinary tract with background diseases. This result is to be expected in light of the inclusion of only hospitalized patients in this prospective study, making it predisposed to choosing a more complex patient population. During the period of the current study, the impression was that the hospitalized patients were sicker, with a significant rise in the number of diabetics, and also in the number of patients with complicated UTI. It should be noted that we saw a higher percentage of Bedouin who were hospitalized with UTI, but it should also be noted that since 2000, the Bedouin population of the Negev has doubled in size.

Looking at long term trends of different pathogens that cause true UTI that lead patients to be hospitalized, we can see changes over time: the prevalence of *E. coli* declined from 70% in 1995 to 56% in 2000, parallel to a rise in the level of *Klebsiella pneumoniae* and other bacteria. In the present study we noted a significant reversal of the trend with the prevalence of *E. coli* rising again and a simultaneous decrease in enterococci. However even though the specific pathogens may change, we observed a steady increase in resistance patterns in the antibiotics commonly used for empirical treatment of UTI, such as second generation cephalosporin and quinolones [12-13]. These changes affected the choice of empirical coverage at our institution, which are similar to those observed in various medical centers around the world [14].

Furthermore, the prevalence of ESBL resistance patterns at the Soroka Medical Center has increased significantly relative to 2000. In the past, acquiring this resistance mechanism was mostly attributed to infections contracted in the hospital environment [15] but in the present study, all of the infections were contracted in the community. We saw a disturbing increase in their occurrence, thus shifting the risk factors to exposure in the community and not just prior hospitalization. This finding impacts the selection of empiric therapy for hospital-treated UTI, implying a greater need to use aminoglycoside therapy for empiric treatment for severe UTI.

The main limitation of this study is the sample size. Since this work was done on a period of only 3 months, the number of patients included in the study is relatively small and one should be cautious about reaching broad and comprehensive conclusions about the general population of the Negev based on this work. However, this data support our overall impression of increasing resistance in community-acquired infections that we have seen in internal data from the microbiology lab (that were not confirmed as true UTI). In spite of these limitations, in light of the prospective character of the work, the presented data has clinical significance regarding the choice of empirical antibiotic treatment for a patient who is hospitalized with ascending UTI that was contracted in the community in the Negev area.

CONCLUSIONS

We are witnessing a disturbing change in the Negev area, characterized by a decline in the sensitivity to antibiotics of the bacteria that cause ascending UTI contacted in the community. In addition, a significant rise in the prevalence of pathogens that produce ESBL enzymes has been observed.

No difference has been observed between Bedouin patients and the rest of the Negev population in terms of pathogens and their sensitivity profile.

According to the present sensitivity profile, our recommendation for empirical antibiotic treatment of patients hospitalized with ascending urinary tract infection is a medication from the aminoglycoside family, in light of the sensitivity of over 80% of the different pathogens.

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Capsule

Habitual coffee consumption and genetic predisposition to obesity: gene – diet interaction analyses in three U.S. prospective studies

Whether habitual coffee consumption interacts with the genetic predisposition to obesity in relation to body mass index (BMI) and obesity is unknown. Wang and colleagues analyzed the interactions between genetic predisposition and habitual coffee consumption in relation to BMI and obesity risk in 5116 men from the Health Professionals Follow-up Study (HPFS), in 9841 women from the Nurses' Health Study (NHS), and in 5648 women from the Women's Health Initiative (WHI). The genetic risk score was calculated based on 77 BMI-associated loci. Coffee consumption was examined prospectively in relation to BMI. The genetic association with BMI was attenuated among participants with higher consumption of coffee than among those with lower consumption in the HPFS ($P_{interaction}$ = 0.023) and NHS ($P_{interaction}$ = 0.039); similar results were replicated in the WHI ($P_{interaction}$ = 0.044). In the combined data of all cohorts, differences in BMI per increment of 10-risk allele were 1.38 (standard error [SE], 0.28), 1.02 (SE, 0.10), and 0.95 (SE, 0.12) kg/m^2 for coffee consumption of ‹ 1, 1–3 and › 3 cup(s)/day, respectively ($P_{interaction}$ ‹ 0.001). Such interaction was partly due to slightly higher BMI with higher coffee consumption among participants at lower genetic risk and slightly lower BMI with higher coffee consumption among those at higher genetic risk. Each increment of 10-risk allele was associated with 78% (95% confidence interval [CI], 59–99%), 48% (95%CI, 36–62%), and 43% (95%CI, 28–59%) increased risk for obesity across these subgroups of coffee consumption ($P_{interaction}$ = 0.008). From another perspective, differences in BMI per increment of 1 cup/day coffee consumption were 0.02 (SE, 0.09), -0.02 (SE, 0.04), and -0.14 (SE, 0.04) kg/m^2 across tertiles of the genetic risk score. The authors concluded that higher coffee consumption might attenuate the genetic associations with BMI and obesity risk, and individuals with greater genetic predisposition to obesity appeared to have lower BMI associated with higher coffee consumption.

BMC Med 2017; 15: 97
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"I believe that anyone can conquer fear by doing the things he fears to do, provided he keeps doing them until he gets a record of successful experience behind him"

Eleanor Roosevelt, (1884–1962), American politician, diplomat, and activist. Wife of former U.S. President Franklin D. Roosevelt. Served as United States delegate to the United Nations General Assembly from 1945 to 1952