

Demographic Characteristics of Patients with Community-Acquired Bacteriuria and Susceptibility of Urinary Pathogens to Antimicrobials in Northern Israel

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Abstract

Background: Urinary tract infection is one of the most common bacterial infections. Since antibiotics are given empirically, it is necessary to assess the distribution and susceptibility of the microorganisms in each case.

Objectives: To evaluate the demographic characteristics of ambulatory patients with UTI, the distribution and susceptibility of uropathogens, and the risk factors associated with trimethoprim-sulfamethoxazole resistant bacteria in women.

Methods: During 12 days in August 1997 all the urine cultures sent to the Tel-Hanan Laboratory (Haifa) were evaluated. Demographic characteristics of the patients, their underlying diseases and the previous use of antibiotics were obtained.

Results: During the 12 day survey 6,495 cultures were sent for evaluation. Of the 1,075 (17%) that were positive 950 were included in the study; 83.7% were from females, of whom 57% were ≥ 50 years old. *Escherichia coli* was the most common pathogen, with 74.7% in the female and 55% in the male population; 86.2% of the *E. coli* were resistant to amoxicillin, 38.8% to cephalexin and 46.8% to TMP-SMX. Cefuroxime (4.2%), ofloxacin (4.8%), ciprofloxacin (4.8%) and nitrofurantoin (0.4%) showed the lowest rates of resistance. By a multivariate analysis, post-menopause and recurrent UTI were found to be independent factors related to TMP-SMX resistance in women.

Conclusion: In northern Israel, ampicillin, cephalexin and TMP-SMX cannot be used empirically in the treatment of community-acquired UTI. Post-menopause and recurrent UTI are independent factors associated with TMP-SMX resistant pathogens in women.

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Urinary tract infection is one of the most common diseases encountered in medical practice. It is the second leading cause for the use of antibiotics in the community [1,2]. Physicians, after sending a urine culture, start antibiotic therapy empirically according to clinical symptoms. In order to choose an appropriate agent, the physician must be familiar with the antimicrobial susceptibility patterns of the uropathogens according to different demographic groups in each area.

The aims of the present study were to evaluate the distribution of community-acquired uropathogens among different age and gender groups and the susceptibility patterns of the infecting organisms. However, since UTI is a very common infectious disease in women, we decided to analyze specifically not only demographic characteristics but also distribution of microorganisms and susceptibility to antibiotics, according to the patients' clinical conditions. In addition, since TMP-SMX is recommended as the drug of choice in the treatment of UTI and since we know that there are high levels of resistance to this drug, we decided also to identify women at high risk of developing UTI associated with microorganisms resistant to TMP-SMX.

Material and Methods

During a 2 week period in August 1997 all the urinary cultures sent to the Tel-Hanan Microbiology Laboratory were examined. The Tel-Hanan laboratory is the largest community microbiological laboratory in Israel and serves a population of 700,000 inhabitants in northern Israel.

Urinary cultures were excluded from the study if they were sent from nursing homes or day-care centers. Only one sample from each patient was examined during the study period.

All the patients with a positive urinary culture were enrolled in the study without consideration of the clinical significance of the microbiological findings. Data on age and gender of all the patients were obtained by contacting the primary care physician of each patient. In addition,

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

clinical characteristics of the female population — such as underlying diseases, previous UTI, pregnancy and the use of antibiotics, especially TMP-SMX — were also recorded.

Urine was cultured by using the Uritest system (Hylab dipslides, Rehovot, Israel). A culture was defined as positive if $\geq 10^4$ cfu/ml of probable urinary pathogens were found. More than two microorganisms in one positive culture were considered as contamination. Susceptibility tests were performed using the Kirby-Bauer method (Mast Diagnostics, Merseyside, UK).

Statistical analysis

All the data were analyzed by the SPSS statistical package program. The relationships between categorical variables were examined using the Chi-square test. To assess the influence of different variables, univariate and multivariate logistic regression models were used. Odds ratio intervals were calculated from the models.

Results

During 12 days in August 1997, 6,495 urine cultures were sent to the Tel-Hanan Laboratory, of which 1,075 (17%) were positive. Altogether, 125 cultures were excluded (95 cultures sent from nursing homes and 30 were repeated positive cultures). The survey included 950 positive urinary cultures, of which 83.7% were from females — 734 women and 61 girls (<16 years old). Inquiry results were obtained for 724 (98.6%) of them. The distribution of bacteriuria according to age and gender is shown in Table 1; 84% of the bacteriuria cases were women, and 56% of them were older than 50 years. *Escherichia coli* was the most common pathogen in community-acquired bacteriuria and comprised 71.4% of cases, with a significant statistical difference between males and females (55% vs. 74.2%, $P < 0.0001$). This was in marked contrast to other gram-negative bacteria such as *Klebsiella pneumoniae* that grew in 10.6% of all the cases, *Citrobacter*, *Enterobacter* and *Pseudomonas aeruginosa* in 2.9%, which are more common in males. Gram-positive microorganisms grew in only 3.8% of the positive cultures, with a moderate predominance in males.

Table 2 presents the distribution of pathogens according to gender and age. In the 1–15 year old male group, all isolates were *E. coli* with a constant reduction in favor of other gram-negative bacteria, and in the ≥ 65 year old group only 51% of the positive cultures were due to *E. coli*. However, in the female group, *E. coli* was the major pathogen, with 82% in the youngest group, and persisted in the other groups at about 74%.

Table 1. Distribution of bacteriuria according to age and gender

Gender	Age groups (yr)				Total
	1–15	16–49	50–64	>65	
Male	2.6%	13%	17.4%	67%	155 (16.0%)
Female	6%	38%	13%	43%	795 (84.0%)
Total	65 (6.8%)	320 (34%)	133 (14%)	432 (45%)	950 (100%)

Table 2. Distribution of gram-negative pathogens according to gender and age

Age group (yr)	Gender	<i>E. coli</i> (%)	Other gram-negative bacteria
1–15	Male	100	None
	Female	82	16.4
16–49	Male	63.2	36.8
	Female	74.1	20.5
50–64	Male	67	33
	Female	71.7	27.4
>65	Male	51	40
	Female	74	25.8

Table 3. Percentage of resistance of all the pathogens according to age

Antimicrobial agent	1–15 yr	16–49 yr	50–64 yr	>65 yr	Total
Ampicillin	87.9%	79.3%	88.7%	85.7%	83%
TMP-SMX	51.7%	39.3%	49.1%	51.2%	48.6%
Cephalexin	43.9%	34.2%	40.6%	38.7%	38.4%
Cefuroxime	0	3.7%	8.5%	7.6%	7.1%
Amoxicillin and clavulanic acid	14.3%	4.85%	16.1%	9.9%	9.9%
Nitrofurantoin	8.2%	4%	3.8%	7%	6.9%
Ofloxacin	0	1%	5.7%	7.9%	5.7%
Ciprofloxacin	0	0.7%	5.7%	7.9%	5.2%

The susceptibility of all the uropathogens according to age is presented in Table 3. The overall resistance to ampicillin was 83%, to TMP-SMX 48.6%, to cephalexin 38.4%, to cefuroxime 7.1%, and to amoxicillin-clavulanic acid 9.9%. Nitrofurantoin and quinolones showed the lower rates of resistance. In addition, it is noteworthy that even in patients aged 16–49 years the microorganisms were more sensitive to all the antibiotics, even though the percentage of resistance was considerably elevated. In Table 4 we can see the differences in susceptibility between *E. coli* and the other gram-negative bacteria. *Escherichia coli* was statistically significantly more sensitive to cefuroxime, augmentin and nitrofurantoin. Regarding quinolones, even though we did not find statistical significance, there is a trend towards high resistance rates of other gram-negative bacteria rather than *Escherichia coli*. No differences were observed with ampicillin, TMP-SMX and cephalexin.

Among women with bacteriuria, several high risk groups were defined:

- 44 women who were immunosuppressed — 31 with malignancy and 13 with steroid or cytotoxic treatment for autoimmune diseases, comprising 8.2% of all women with bacteriuria
- 44 women (8.2%) with urogenital disorders — 25 with urolithiasis, 10 with urinary incontinence, 5 with permanent catheter, 2 with tuberculosis of the urinary tract and 2 with neurogenic bladder
- 82 women (15.4%) with diabetes mellitus
- 398 (74.8%) who were post-menopausal

Table 4. Percentage of resistance to antimicrobials between *E. coli* and other gram-negative bacteria

	% of resistance		P value
	<i>E. coli</i>	Other gram-negative bacteria	
Ampicillin	86.2	86.1	NS
TMP-SMX	46.8	47.8	NS
Cephalexin	38.8	40.4	NS
Cefuroxime	4.2	15.2	<0.005
Amoxicillin-clavulanic acid	7.3	18.2	<0.05
Nitrofurantoin	0.4	26.3	<0.0001
Ofloxacin	4.8	8.1	NS
Ciprofloxacin	4.8	6.2	NS

- 302 (57%) women who had two or more urinary tract infections in the last 6 months
- 57 women had received treatment with TMP-SMX during the preceding 6 months.

Table 5 shows the susceptibility to TMP-SMX in bacteriuric women according to risk factors. On univariate analysis, urogenital disorders, diabetes, post-menopause and recurrent UTI were statistically significant risk factors related to TMP-SMX resistant pathogens. However, by a multivariate model, only post-menopause and recurrent UTI were independent factors associated with TMP-SMX resistance ($P < 0.05$; odds ratio 1.42 and 1.47 respectively). Curiously, the use of TMP-SMX during the previous 6 months had no influence on the development of resistance. Of 724 women, 332 (45.8%) had taken antibiotics during the previous 6 months. The most common drugs were cephalexin (32.2%), nitrofurantoin (31.9%), cefuroxime and amoxicillin-clavulanic acid (24% each), and 123 women (17%) had taken ciprofloxacin. An obvious relation between exposure to specific antibiotics and the appearance of resistance was found only to ofloxacin ($P < 0.05$) and ciprofloxacin ($P < 0.0001$).

Table 5. Bacteriuria in women: susceptibility to TMP-SMX, and risk factors associated with resistance

Risk factor	% of resistance	O.R	95% C.I.	P value
Univariate analysis				
Immunosuppression	50	1.19	0.52, 3.28	<0.5
Urogenital disorders	59	1.76	1.05, 3.28	<0.05
Diabetes mellitus	58.5	1.78	1.17, 2.84	<0.05
Post-menopause	51	1.6	1.18, 2.14	<0.05
Recurrent UTI	53	1.6	1.21, 2.2	<0.05
Previous TMP-SMX treatment (within last 6 months)	51	1.2	0.73, 2.7	<0.1
Multivariate analysis				
Post-menopause		1.42	1.04, 1.94	<0.05
Recurrent UTI		1.47	1.08, 2.02	<0.05

*C.I. = Confidence Interval

Discussion

Community-acquired UTI is a predominant infectious disease in women. In the present study 84% of all the positive urinary cultures were found in women, and more than half of them were post-menopausal.

Since we did not know what method was used to collect the urine, we must be emphatic in the drawing of conclusions regarding several different patient populations, especially among children. Although *Escherichia coli* remains the most common pathogen, several studies have shown a constant reduction in the incidence of *E. coli* with a parallel increase of other microorganisms. Weber et al. [3] presented a surveillance study in southern Israel, showing that the incidence of *E. coli* dropped from 70.5% in 1991 to 61.2% ($P < 0.0001$), with a significant increase of *Enterococcus* from 1.7% to 7.2% in 1995 ($P < 0.0001$), respectively. We observed in a previous study [4] conducted in northern Israel that 69% of all the isolates were *E. coli* in 1991–92. However, these studies did not differentiate between the distribution of the microorganisms according to age and gender.

In the present study 71.4% of the microorganisms were *E. coli*, but there was a significant difference between males and females: among males only 55% of the pathogens were *E. coli* compared to 74.2% among females ($P < 0.05$). The incidence of *Enterococcus* in our area is low – 3%, with a predominance in men at 5.8% vs. 2.4% in women. This low incidence can be explained by the restrictive use of cephalosporins in our region [5]. Curiously, *Staphylococcus saprophyticus* is a very uncommon pathogen, as we previously described [6].

The distribution of the pathogens in the current study was not only different by gender but by age groups as well. Whereas there were no significant differences in females in the prevalence of *E. coli*, 100% of bacteriuria cases among boys were due to *E. coli* but its incidence decreased, and in elderly men there were only 51% due to other gram-negative microorganisms.

In our previous study we observed that in 1991 the rate of resistance to ampicillin, TMP-SMX and cephalexin was high (68%, 49% and 40%, respectively), and no significant differences were noted in the present survey (83%, 48.6% and 38.4%). Since our previous study presented microbiological data without differentiating distribution of the microorganisms and their susceptibility according to age or gender, we presumed that significant differences would be found between men and women, and specifically between young and post-menopausal patients. For example, we presume that young women with UTI will have more susceptible microorganisms than post-menopausal women or men with prostatitis.

The high rate of ampicillin resistance to gram-negative bacteria justifies its use only in UTI due to gram-positive microorganisms, which represent a very low percentage of our uropathogens. TMP-SMX has been the drug of choice for treating UTI in the USA and several European

countries [2]. However, in our area half of the positive cultures were resistant *in vitro*. One of the hypotheses of this study was that probably in the group of young women with uncomplicated cystitis we might find a better microbiological profile, which will allow us to treat those women empirically with TMP-SMX. Unfortunately, in spite of the fact that patients aged 16–49 years presented a lower rate of resistance than children and elderly patients, the 39.3% resistance is extremely high when considering treatment with TMP-SMX in these patients.

We also looked for clinical risk factors associated with TMP-SMX resistant organisms. In a univariant analysis we observed that diabetes, urogenital disorders, post-menopause, and recurrent UTI are significantly associated with the development of resistant TMP-SMX organisms, however the use of this drug during the previous 6 months had no influence on the development of resistance. This finding supports the theory that microorganisms acquired resistance to TMP-SMX a long time before. Yet, in the multivariant analysis only post-menopause and recurrent UTI were independent factors related to TMP-SMX resistance.

Gupta et al. [7] also found that in women with uncomplicated cystitis the resistance of *E. coli* to ampicillin, TMP-SMX and cephalexin was considerably increased,

and similar to our findings the levels of resistance to nitrofurantoin and quinolones were very low.

References

1. Kunin CM. Urinary tract infections in females. *Clin Infect Dis* 1984;18:1–12.
2. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am* 1997;11(3):551–81.
3. Weber G, Reisenberg K, Schlaeffer F, Peled M, Borer A, Yagupsky P. Changing trends in frequency and antimicrobial resistance of urinary pathogens in outpatient clinics and a hospital in Southern Israel, 1991–1995. *Eur J Clin Microbiol Infect Dis* 1997;16:834–8.
4. Oren B, Raz R, Hefter H, Kennes Y, Pottesman P. Antimicrobial resistance of urinary isolates in the community and its relation to antibiotic use. *Isr J Med Sci* 1993;29:207–13.
5. Felmingham D, Wilson A, Quintana A, Grüneberg R. *Enterococcus* species in urinary tract infection. *Clin Infect Dis* 1992;15:295–301.
6. Raz R, Mersbach C, Sobeh J, Finkelstein R. Absence of *Staphylococcus saprophyticus* in urinary tract infections in Israel. *Isr J Med Sci* 1983;19:566–7.
7. Gupta K, Scholes D, Stamm W. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA* 1999;8:736–8.

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