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Urinary Tract Infection in Male General Practice Patients: Uropathogens and Antibiotic Susceptibility

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OBJECTIVES: To evaluate uropathogens and their antibiotic susceptibility in male general practitioner (GP) patients presenting with an uncomplicated urinary tract infection (UTI).

MATERIAL AND METHODS: A population-based study was conducted among males, 18 years and older, general practice patients, who had symptoms indicative of an uncomplicated UTI. A UTI was defined as $\geq 10^3$ colony-forming units/mL (CFU/mL). The etiology of the infection, antimicrobial susceptibility, and treatment strategies used by the GP were determined.

RESULTS: *Escherichia coli* was most frequently isolated (48%), followed by other enterobacteriaceae (24%) and enterococci (9%). The etiology of infection was age-dependent; *E. coli* was more frequently isolated in younger patients and *Pseudomonas aeruginosa* in the elderly. The overall susceptibility rates were low for amoxicillin (63%) and trimethoprim (70%), and high for fluoroquinolones (91%) and amoxicillin-clavulanic acid (90%), which is similar to susceptibility rates in females with UTIs from the same population. Antibiotics were prescribed to 59% of the males with symptoms of UTI. Fluoroquinolones were given to 33% of the patients and trimethoprim-sulfamethoxazole to 24%. No difference in antibiotic prescription, nor in duration of therapy, was found between the different age groups.

CONCLUSIONS: In the male presenting with complaints of an acute uncomplicated UTI at the GP, *E. coli*, followed by other Gram-negative bacteria were the most frequently isolated uropathogens. Susceptibility rates in uncomplicated male and female UTIs were similar, indicating that data from UTI susceptibility studies in females from the same geographic region can be useful in the choice of empirical therapy in males.

Knowledge of male urinary tract infection (UTI) is less than that of female UTI, despite the fact that one-third of all 80-year-old men will have had an episode of bacteriuria.[1] and [2] The pathogenesis of uncomplicated UTI in men remains unclear, and it has been hypothesized that all UTI in men must be considered complicated because they result from an anatomic or functional anomaly. There is, however, little evidence to support this hypothesis.[1] and [2] Twenty percent of diagnosed uncomplicated UTI occur in men, with the prevalence escalating with increasing age.[3] Most male UTIs are seen and treated by the general practitioner (GP).[4] and [5]

Females with uncomplicated UTIs are managed effectively and safely by empirical antibiotic therapy without the need for a urine culture, but the diagnosis of uncomplicated UTI in men is still difficult. Therefore, in male patients, culture and targeted antibiotic therapy has been advocated before a treatment

decision is made,[5] although use of the nitrite dipstick method has been advocated and may result in earlier start of therapy.[6] Empirical antibiotic subscription by GPs should be based on the availability of actual antibiotic resistance data of the bacterial population to be treated. Unfortunately, most of the antibiotic resistance patterns are derived from uropathogens isolated from female patients.[7], [8], [9] and [10] Uropathogens causing UTIs in different age groups of male patients and the antibiotic susceptibility of the microorganisms involved are hardly available.[5], [11] and [12] Here, we evaluated uropathogens and their antibiotic susceptibility in male GP patients presenting with an uncomplicated UTI.

MATERIALS AND METHODS

Population

From January 2003 to December 2004, 21 general practices participating in the NIVEL (Netherlands Institute for Health Services Research) sentinel project, monitored personal, diagnostic, and therapeutic information of consecutive male patients 18 years and older, with symptoms indicative of a UTI (ie, acute signs of dysuria, urinary frequency, and/or urgency without the presence of temperature >38°C), without systemic complaints, foreign body, history of urological complaints, urine catheter, or suspicion of sexually transmitted disease. The design of the study did not differentiate between an uncomplicated UTI or the first UTI developing to a complicated or recurrent course. The patient population of these practices accounts for approximately 1% of the Dutch population and was representative for age, gender, regional distribution, and degree of urbanization. All patients received care as usual, ie, diagnostic tests and empirical therapy according to the daily practice of the GP.

Urine Sampling and Processing

Male patients suspected of having a UTI provided a fresh voided (midstream) urine sample as part of usual care. Subsequently, a dipslide (Uriline, 56 508, bioMérieux, Plainview, NY) was performed according to the manufacturer's instructions and sent by mail to the laboratory of Medical Microbiology of the University Hospital Maastricht, The Netherlands, for identification and antibiotic susceptibility testing of the uropathogens. On the day of arrival, the dipslide was incubated at 37°C overnight. The growth of bacteria was recorded according to the manufacturer's instructions. Growth of $\geq 10^3$ colony-forming units(CFU)/mL was considered a positive urine culture[11] and indicative of a UTI in male. The isolated uropathogens were stored at −70°C for further analysis. In case of more than one cultured bacteria, only the predominant microorganism was counted.

Antimicrobial Susceptibility

Minimum inhibitory concentrations (MICs) were determined according to the NCCLS (CLSI) criteria[13] using the microbroth dilution method with Mueller Hinton II broth cation adjusted (Becton Dickinson & Company, Sparks, MD), an inoculum of 5×10^5 CFU/mL, and overnight incubation at 37°C. MCS Diagnostics provided the MIC plates with freeze-dried antibiotics (NLDMCS1, MCS Diagnostics BV, Swalmen, The Netherlands). The following antimicrobial agents (range in mg/L) were tested: amoxicillin (0.06-128), amoxicillin-clavulanic acid (0.06-128), trimethoprim (0.03-64), trimethoprim-sulfamethoxazole (0.03-64), norfloxacin (0.03-64), ciprofloxacin (0.008-16), and nitrofurantoin (0.5-512). Breakpoints for susceptibility were according to the NCCLS (CLSI) guidelines.[13] Norfloxacin, ofloxacin, levofloxacin, and ciprofloxacin were grouped in the fluoroquinolone group.

Statistical Analysis

For the analysis of the culture results and the susceptibility percentages, the patients were divided in the age groups 18-50, 51-70 and >70 years. For statistical analysis, the program SPSS 15.0 for Windows was used (SPSS, Inc., Chicago, IL). The susceptibility was coded as present or absent and analyzed per uropathogen with the chi-square test.

An outcome was significant if the *P* value was >.05.

RESULTS

Population and Culture Results

In total, 422 male patients were included in the study. The age of the patients ranged from 18-104 years, with mean and median ages of 58 years. A positive urine culture was found in 236 (56%) men (mean age 60 years, median age 62 years). Positive urine cultures increased with age; 68 of 150 patients in the age

category of 18-50 years (45%) had a positive urine culture. In the age category of 51-70 years, 90 of 163 patients (55%) had a positive urine culture, and in the age category >70 years, 78 of 109 men (72%) had a positive urine culture ($P = .03$). In most of the samples (91%), one species was cultured. None of the samples were contaminated, ie, contained more than 2 microbial species. Overall, *Escherichia coli* was the most frequently isolated uropathogen (48%) ([Table 1]).

[TABLE 1.]

In the different age categories, different predominant uropathogens were cultured ($P = .025$) ([Table 1]). *E. coli* was significantly more isolated in younger patients compared with other Gram-negative bacteria ($P = .04$), and *Pseudomonas aeruginosa* was more frequently isolated in the elderly compared with other Gram-negative bacteria ($P = .005$). The mean age of patients with a positive urine culture with *P. aeruginosa* was 73 year, *Klebsiella pneumoniae* 74 years, *Enterococcus faecalis* 54 years, and *E. coli* 59 years.

Antibiotic Susceptibility

The antibiotic susceptibility of *E. coli* ranged from 75% for amoxicillin to 100% for amoxicillin-clavulanic acid ([Table 2]). For both nitrofurantoin and the fluoroquinolones, the susceptibility of *E. coli* was 97%. However, susceptibility for trimethoprim-sulfamethoxazole was only 81%, whereas this drug was prescribed to 24% of the men ([Table 2] and [Table 3]).

[TABLE 2. AND TABLE 3.]

Antibiotic Therapy

Of all 422 patients, antibiotics were prescribed in 60% (253 patients). The most frequently prescribed antimicrobial agent in patients of all age groups were fluoroquinolones 33% (83/253). Its prescription ranged from 35% in the oldest to 31% in the younger patients (NS). One-fourth of the patients received trimethoprim-sulfamethoxazole (24%). Nitrofurantoin and amoxicillin-clavulanic acid were prescribed for 16% and 11%, respectively ([Table 3]). Of the patients who received antibiotics, 71% had a positive urine culture. One-hundred two patients with a positive nitrite test received antibiotics, and 113 patients with a negative nitrite test (NS). The treatment duration was 6-7 days in 44% but ranged from 3 to >21 days ([Fig. 1]). No correlation between duration of antibiotic use and age was found ($P = .64$) ([Fig. 1]).

[Figure 1.]

COMMENT

This study reports on the uropathogens in male patients with symptoms indicative of UTI in a GP population.[5] The uropathogens that were isolated were mainly Gram-negative, with *E. coli* as the predominant pathogen. The uropathogens were highly susceptible for amoxicillin-clavulanic acid and for fluoroquinolones.

The frequency of male UTI increases with age, probably secondary to voiding problems.[2], [14] and [15] Remarkably, symptoms of UTI were more predictive for culture-proven UTI in the elderly. Although it cannot be excluded that some of the patients presenting to the GP had a complicated UTI, the acute onset of symptoms, lack of systemic symptoms, or history of urological complaints suggests that the majority of men had cystitis.[2] This diagnosis remains difficult, especially in men. In women, growth of $\geq 10^5$ CFU/mL is usually considered a positive urine culture. In well-instructed collection of clean midstream urine, lower growth could be considered positive in females. The anatomy of the male urethra makes the midstream urine probably unnecessary.[11] The Dutch guidelines advise to use growth of $\geq 10^3$ CFU/mL as a positive urine culture in men.[16] and [17]

E. coli is the important uropathogen in the general population.[12] and [18] In females of all age categories, *E. coli* is the most frequently isolated uropathogen.[9], [10] and [19] In accordance with the literature, we found that *E. coli* causes most male UTIs, followed by other enterobacteriaceae and enterococci[1] and [2] whereas in female UTIs, *Proteus mirabilis* was more frequently isolated in the younger and *K. pneumoniae* in the elderly patients[10]; in elderly males, isolation of *P. aeruginosa* increased.

The diagnosis of a UTI in male patients is not always straightforward. Previously, we showed that a positive nitrite test has a high probability of disease (96%) in male UTIs, and empirical antibiotic treatment should be considered awaiting culture results.[6] The choice of empirical therapy depends on the distribution of uropathogens and their antibiotic susceptibility patterns. Most studies on uropathogens and their

susceptibility have been performed in female patients with UTIs[7], [8], [9] and [10] or a case mix of female and male patients.[12], [20], [21] and [22] In other studies describing uropathogens in men with symptoms indicative of UTI, 40% had negative urine cultures, *E. coli* was isolated in half of the UTIs, and Gram-positive cocci caused 20% of the UTIs,[5] and [12] which is comparable to our results. Twenty-four percent of men with culture-proven UTI were not treated at the first consultation on clinical grounds, suggesting that additional diagnostic tests are needed.

In The Netherlands, females with an uncomplicated UTI originating from the same population that we studied showed the lowest susceptibility percentages for the 3 most frequently isolated uropathogens (*E. coli*, *P. mirabilis*, and *K. pneumoniae*) for amoxicillin and trimethoprim, and more then 96% of the *E. coli* isolates were susceptible for amoxicillin-clavulanic acid, fluoroquinolones, and nitrofurantoin.[9] and [10] In male patients with UTI, deriving from the same GPs in the same period, the highest susceptibility rates were also found for amoxicillin-clavulanic acid, nitrofurantoin and fluoroquinolones (this study), suggesting that uropathogens in community-acquired UTIs have a similar susceptibility pattern in male and female patients. This supports the choice for the same empiric antibacterial therapy for symptoms of an uncomplicated UTI in both male and female patients.

Antibiotic resistance has become a consideration in the treatment of community-acquired UTIs.[23] and [24] To our knowledge, sparse studies on antibiotic resistance in male UTIs have been reported.[5] In a population study in Spain, including both complicated and uncomplicated UTIs in male and female patients, the susceptibility percentages for *E. coli* were low for amoxicillin (41%), trimethoprim-sulfamethoxazole (66%), and ciprofloxacin (77%).[12] In Spain and Latin American men with uncomplicated UTIs, the susceptibility percentages for *E. coli* were lower for trimethoprim-sulfamethoxazole and fluoroquinolones compared with our Dutch population,[12] and [18] and fluoroquinolone resistance increased with age.[21] In Europe, *E. coli*, susceptibility for multiple drugs varied from 9%-40% in uncomplicated UTIs[7] and [25]; in women, resistance to fluoroquinolones varied from 9%-16%,[7] and [25] and in men it was as high as 25%.[25] However, these susceptibility percentages may be higher than in the community because most cultures are done when treatment fails or in the case of complicated UTI.[26] Because susceptibility varies with geographic region and population (nosocomial or community), empiric antibiotic prescription should be dependent on the susceptibility percentages of a specific community over time[12], [21], [27], [28], [29] and [30]

In contrast to female patients,[9] and [10] the GP did not rely on the outcome of the nitrite dipstick test for the prescription of antimicrobial therapy, because only 47% of the treated patients had a positive dipstick test. Blinded for the culture results, the decision to treat was based on clinical grounds. The most prescribed antibiotics in all age groups were fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and amoxicillin-clavulanic acid. Given the susceptibility percentages, it is justifiable that amoxicillin and trimethoprim are prescribed in the minority of patients. The prescription of nitrofurantoin is according to guidelines that state that males without a previous history of UTIs, systemic complaints, or signs of tissue invasion could be treated with nitrofurantoin.[16] and [17] Both the choice of antibiotic and duration of therapy indicate that patients were treated for uncomplicated UTIs, because treatment for complicated UTI favors the choice of fluoroquinolones and a longer duration of therapy.[2]

CONCLUSIONS

In the adult male presenting to the GP with acute symptomatic complaints of uncomplicated UTI, *E. coli* and other Gram-negatives are the most prevalent uropathogens. Empirical treatment in a male with suspected UTI may be started awaiting culture results based on susceptibility rates for uropathogens in the geographic region. Because susceptibility rates seem to be similar in community-acquired male and female UTIs, these rates may be obtained in either male or female UTIs. In elderly male patients with a suspicion of *P. aeruginosa* as the causative uropathogen, a fluoroquinolone should be given.

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TABLES AND FIGURE

Table 1. Percentage of isolated uropathogens found according to the age category

	Age Category in Years			
	18-50 n = 68	51-70 n = 90	>70 n = 78	Total N = 236
E. coli	59	42	45	48
P. mirabilis	4	6	8	6
K. pneumoniae	0	3	4	3
Pseudomonas spp.	1	2	13	6
Acinetobacter spp.	9	6	5	6
Other gram neg.	9	21	14	15
Enterococcus	16	8	5	9
Other gram post.	1	12	6	7

N = total number of cases.

Table 2. Susceptibility percentages of the uropathogens for the different antibiotics

		Antibiotic Susceptibility %					
Uropathogen	N*	AMX	AMC	NF	TMP	TMP-SMX	FQ
E. Coli	113	75	100	97	81	81	97
P. mirabilis	14	93	100	0	50	86	100
K. pneumoniae	6	0	100	100	83	83	100
E. faecalis	22	100	100	100	82	91	55
P. aeruginosa	13	15	15	0	0	0	100
Acinetobacter spp.	15	73	87	33	20	93	100
Other gram neg†	36	22	72	89	81	86	94
Other gram post‡	17	47	100	100	77	94	71
All uropathogens	236	63%	90%	82%	70%	85%	91%

AMX = amoxicillin; AMC = amoxicillin-clavulanic acid; NF = nitrofurantoin; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole; FQ = fluoroquinolone.

* N = total numbers of cases.

† Consisting of *Klebsiella oxytoca, Enterobacter cloacae, Enterobacter aerogenes, Citrobacter koseri, Citrobacter freundii, Morganella morganii, Stenotrophomonas maltophilia, Serratia marcescens.*

‡ Consisting of *coagulase-negative Staphylococcus, Staphylococcus aureus,* group B *Streptococcu, Staphylococcus saprophyticus.*

Table 3. Percentage of patients that received antibiotic treatment shown per age category

Antibiotic Treatment	Age Category 18-50 y n = 86	51-70 y n = 99	>70 y n = 68	Total N = 253
Amoxicillin	1	3	0	2
Co-amoxicillin	10	12	10	11
TMP-SMX*	26	24	21	24
Trimethoprim	3	1	1	2
Nitrofurantoin	14	15	19	16
Quinolones	31	32	35	33
Other	14	12	13	13
Total %	100	100	100	100

N = Total number of cases.
* Trimethoprim-sulfamethoxazole.

Figure 1. Percentage of all patients with antibiotic therapy in that age category treated for a specified amount of days.