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Original scientific paper

Research of Urinary Tract Infections in Family Medicine Physicians' Offices – Empiric Antimicrobial Therapy of Urinary Tract Infections – Croatian Experience

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A B S T R A C T

In the period between October 1st and November 30th, 2006, we investigated a total of 3188 episodes of UTI (802 among males; 2386 among females) recorded in 108 family medicine offices in 20 cities in Croatia. The most common UTIs in women were acute uncomplicated cystitis (62%), complicated UTIs – cystitis and pyelonephritis (14%), urethritis (9%), acute uncomplicated pyelonephritis (6%), recurrent cystitis (5%), asymptomatic bacteriuria (3%) and recurrent pyelonephritis. The most common UTIs in men were complicated UTIs – cystitis and pyelonephritis (48%), urethritis (25%), prostatitis (24%) and asymptomatic bacteriuria (3%). Etiological diagnosis was made in 999 (31%) UTI episodes before antimicrobial therapy was given. The most frequently isolated causative pathogens were Escherichia coli (77%), Enterococcus faecalis (9%), Proteus mirabilis (5%), Klebsiella spp (3%), Streptococcus agalactiae (3%) and Enterobacter (1%). Antimicrobial drug was administered in 2939 (92.19%) UTI episodes, in 1940 (66.01%) as empirical therapy, and in 999 (34%) as targeted antimicrobial therapy. The most commonly administered drug in empirical therapy for acute uncomplicated cystitis, recurrent cystitis and urethritis in women was cephalexin, for acute uncomplicated pyelonephritis and complicated UTIs in women co-amoxiclav, and for UTIs in males ciprofloxacin. The results of this research of 3188 UTI episodes in family medicine physicians' offices provide a confirmatory answer to question whether empirical antimicrobial therapy of UTI prescribed by Croatian family practitioners is in accordance with the national guidelines.

Key words: *urinary tract infections, epidemiology, etiology, clinical presentation, treatment, family medicine practitioners*

Introduction

Urinary tract infections (UTI) comprise a heterogeneous group of clinical syndromes and diseases. Except for location they differ in epidemiology, etiology, severity of disturbed general condition and general symptoms of infection, expressed local symptoms, frequency of recurrence and relapse, presence of complicating factors, necessary antimicrobial therapy, outcome and prognosis. UTI are among the most common bacterial infections in humans and one of the most common reasons for prescribing antimicrobial drugs[1].

Research of UTIs in family medicine practitioners' offices are rare, therefore the aim of this prospective research was to investigate the epidemiology, etiology, clinical presentation, complicating factors of UTIs treated by

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family physicinas and present the treatment of choice for empirical antimicrobial therapy of UTI used in family medicine offices in Croatia.

Patients and Methods

In the period from October 1st, 2006 until November 30th, 2006, a total of 108 family medicine offices in the following cities in Croatia – Buzet, Drniš, Gospić, Karlovac, Kaštel Sućurac, Križ, Labin, Novska, Ogulin, Ploče, Posedarje, Pula, Rijeka, Sesvete, Split, Umag, Viškovo, Vrsar, Zagreb, Zaprešić – participated in a prospective research of 3188 episodes of urinary tract infections (eUTI). Each particular episode was attributed to one patient; therefore the number of eUTI corresponded to the total number of patients.

Diagnostic criteria of clinical syndromes

Urethritis – clinical syndrome characterized by urethral inflammation and the following symptoms: dysuria, polakisuria, mucopurulent or purulent discharge, or urethral pruritis.

Acute uncomplicated cystitis – sporadic episode of cystitis in premenopausal, non pregnant women with clinical symptoms of dysuria, urgency, frequency, suprapubic pain, no fever, symptoms lasting less than 7 days, no urinary symptoms 4 weeks prior current episode. Urine culture should not be performed in young women. The diagnosis should be based on characteristic symptoms and leukocyturia (positive leukocyte esterase test or ≥10 WBC/mm^3) ± positive nitrite test.

Acute uncomplicated pyelonephritis – sporadic episode of acute inflammation of kidney in women with significant bacteriuria with ≥10^4 cfu/mL uropathogens in midstream urine (MSU) and leukocyturia. Clinical symptoms are fever (>38°C), chills, flank pain, other diagnosis excluded, no history of clinical evidence of urological abnormalities (ultrasonography, radiography).

Complicated UTI – including cystitis and pyelonephritis are UTI with any combination of symptoms from cystitis or pyelonephritis and one or more factors associated with a complicated UTI. Laboratory criteria are leukocyturia and significant bacteriuria ≥10^5 cfu/mL uropathogens in women, ≥10^4 cfu/mL in men, and ≥10^3 cfu/mL in pregnant women.

Factors that suggest a potential complicated UTI are: male sex, pregnancy, hospital acquired infection, the presence of an indwelling catheter, stent or splint or the use of intermittent bladder catheterization, vesicoureteric reflux or other functional or anatomical abnormalities of the urinary tract, renal insufficiency, recent urinary tract intervention (in the last 15 days), recent antibiotic use (in the last 2–3 months), symptoms for >7 days at presentation, diabetes mellitus, immunosuppression or immunocompromised diseases.

Asymptomatc bacteriuria – is a significant bacteriuria and leukocyturia in a patient with no urinary symptoms. Significant bacteriuria for asymptomatic bacteriuria in females is ≥10^5 cfu/mL of the same bacterial strain in two consecutive MSU cultures ≥24 hours apart; in males ≥10^5 cfu/mL in a single MSU culture.

Recurrent UTI – are at least three episodes of uncomplicated infection documented by culture in the last 12 months or two episodes in the last 6 months, only in women with no structural/functional abnormalities. Laboratory criteria are leukocyturia and significant bacteriuria of ≥10^3 cfu/mL for uncomplicated cystitis or ≥10^4 cfu/mL for uncomplicated pyelonephritis.

Prostatitis – clinical entity manifested with urethral and urinary bladder symptoms (dysuria, polakisuria, urgency, nocturia, weaker and intermittent urine flow, urethral discharge), prostatic symptoms (pressure and pain in perineal and groin areas, discomfort in the low back and abdomen, tension in suprapubic, penile and scrotal areas, epididymis, anorectal sensitivity), sexual disturbances (difficult and painful erection, loss of libido), other symptoms (myalgia, headache, a low grade fever).

Methods

The following data were obtained for each patient: demographic data, medical history, clinical status including digitorectal prostatic examination when necessary and medical documentation analysis. Data was collected according to a specially designed questionnaire at the time of the patient's arival to family medicine office and were later on updated. This questionnaire proved suitable for another pilot research[2]. Before study initiation, family physicians were explained the aim of research, questionnaire and definitions necessary for filling it out.

Statistics

Data analysis was preformed by using Microsoft Excel/SAS, descriptive statistics and Mann-Whitney test.

Results

A total of 802 (25%) episodes were recorded among males and 2386 (75%) among females. Median age was

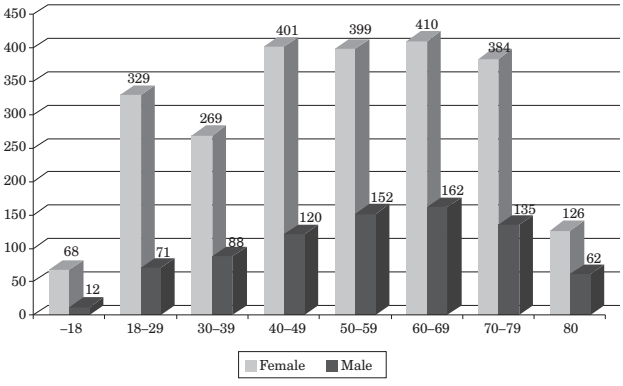

Fig. 1. Age and sex of patients with urinary tract infections examined at the family medicine physician's offices. Range min. 10.2 max. 99.4, Median age 52.8±18.8, n= 3188, F – 2386 (75%), M – 802 (25%).

TABLE 1
DISTRIBUTION OF URINARY TRACT INFECTION EPISODES ACCORDING TO DIAGNOSIS AND SEX OF PATIENT

Diagnosis	Patients					
	M		F		Total	
	n	%	n	%	n	%
Acute uncomplicated cystitis	–	–	1479	(61.99)	1479	46.39
Recurrent cystitis	–	–	125	(5.24)	125	3.92
Acute uncomplicated pyelonephritis	–	–	134	(5.62)	134	4.20
Recurrent pyelonephritis	–	–	23	(0.96)	23	0.72
Complicated UTI	385	(48)	337	(14.12)	722	22.65
Urethritis	201	(25.06)	218	(9.14)	419	13.14
Prostatitis	192	(23.94)	–	–	192	6.02
Asymptomatic bacteriuria	24	(2.99)	70	(2.93)	94	2.95

52.8±18.8 years, ranging from 10.2 to 99.4 years. There was no statistically significant difference recorded between age in males and females with UTI (Figure 1).

The most common UTIs in women were acute uncomplicated cystitis (62%), complicated UTIs – cystitis and pyelonephritis (14%), urethritis (9%), acute uncomplicated pyelonephritis (6%), recurrent cystitis (5%), asymptomatic bacteriuria (3%) and recurrent pyelonephritis (1%).

The most common UTIs in men were complicated UTIs – cystitis and pyelonephritis (48%), urethritis (25%), prostatitis (24%) and asymptomatic bacteriuria (3%) (Table 1).

Complicating factors of UTI are shown in Table 2.

An average number of complicating factors, except male sex, per eUTI in men with either cystitis or pyelonephritis was 1.95; in men with prostatitis, except for male sex 1.49; and in women with either cystitis or pyelonephritis 1.49.

Acute uncomplicated cystitis in women occurred in all age groups, more frequently in women over 40 years of age, with altogether 65% of episodes of acute uncomplicated cystitis recorded in the age group 40–79 years.

Episodes of complicated UTIs in women were equally distributed in all age groups from 18–79 years. In men, the presence of complicating factors was more frequently recorded in those older than 40 years of age.

Urethritis was common in age group 18–79 years in both sexes and most common in age group 40–69 years (male 56%, female 54%).

Altogether 68% of prostatitis episodes were recorded in the age group 50–79.

Acute uncomplicated pyelonephritis was frequent among women aged 50–79 years (57%).

TABLE 2
COMPLICATING FACTORS OF URINARY TRACT INFECTIONS RECORDED IN FAMILY MEDICINE PHYSICIAN'S OFFICES

Complicating factor	Episodes of complicating UTI (n=829)			
	Cystitis and pyelonephritis in males (n=385)	Prostatitis (n=107)	Women (n=337)	Total
Symptoms > 7 days	239	36	129	404
Diabetes mellitus	152	14	105	271
Urolithiasis	101	21	74	196
Antibiotic therapy in the past 3 months	83	51	46	180
History of pyelonephritis	34	5	65	104
Functional or anatomical abnormality of the urinary tract	33	20	18	71
Immunosuppression	52	2	5	59
Pregnancy	–	–	41	41
Urinary catheter	34	–	2	36
Surgical procedure on urogenital tract	17	5	2	24
Incontinence	–	–	23	23
Hospital acquired UTI	7	5	3	15
Total	752	159	513	1424

TABLE 3
ETIOLOGY OF UTI EPISODES IN FAMILY MEDICINE PHYSICIAN'S OFFICES

Confirmed microorganism	UTI EPISODES (n=3188)									
	Acute uncomplicated cystitis	Complicated UTI	Urethritis	Prostatitis	Acute uncomplicated pyelonephritis	Recurrent cystitis	Asymptomatic bacteriuria	Recurrent pyelonephritis	Total	
									n	%
Escherichia coli	265	240	72	22	32	70	53	14	768	76.88
Enterococcus faecalis	11	50	5	7	–	2	17	–	92	9.21
Proteus mirabilis	16	9	5	11	2	–	5	2	50	5.0
Klebsiella spp	7	12	–	2	2	–	8	2	33	3.30
Streptococcus agalactiae	6	5	4	–	–	2	9	–	26	2.6
Enterobacter	4	5	2	1	–	–	–	–	12	1.2
Staphylococcus saprophyticus	4	–	–	–	–	–	1	–	5	0.5
Pseudomonas aer	1	3	–	–	–	–	–	–	4	0.4
Staphylococcus aureus	1	–	3	–	–	–	–	–	4	0.4
Serratia marcescens	–	2	–	–	–	–	1	–	3	0.3
Ureaplasma urealyticum	–	–	1	1	–	–	–	–	2	0.2
Total	315	326	92	44	36	74	94	18	999	100
Total episodes UTI	1479	722	419	192	134	125	94	23	3188	

Altogether 54% of recurrent cystitis episodes were recorded among age group 60–79 years.

Etiological diagnosis was made in 999 (31%) UTI episodes before antimicrobial therapy were given (Table 3). The most frequently isolated causative pathogens were *Escherichia coli* (77%), *Enterococcus faecalis* (9%), *Proteus mirabilis* (5%), *Klebsiella* spp (3%), *Streptococcus agalactiae* (3%) and *Enterobacter* (1%).

Out of 3188 analyzed eUTI, at the time of research, antimicrobial therapy was administered in 2939 (92.19%) episodes. Empirical antimicrobial therapy was applied in 1940 (66.01%) eUTI, and target antimicrobial therapy in 999 (33.99%) (Table 4).

The most commonly administered drug in empirical therapy for acute uncomplicated cystitis, recurrent cystitis and urethritis in women was cephalexin, for acute uncomplicated pyelonephritis and complicated UTIs in women co-amoxiclav, and for UTIs in males ciprofloxacin (Table 5). Altogether 151 (14.98%) female patient with acute uncomplicated cystitis received nitrofurantoin, and 36 (30.51%) men with urethritis doxycycline.

Discussion

The results of this research of 3188 UTI episodes in family medicine physicians' offices have shown that in practice, empirical antimicrobial therapy has to be used very often for the treatment of UTIs. The aim of UTI treatment is the disappearance of clinical symptoms and eradication of infection in order to prevent relapse. All symptomatic UTI and asymptomatic bacteriuria in certain individuals need to be treated. Antimicrobial spectrum of administered drug has to cover a range of detected or expected causative pathogens and as least as possible disturb normal human flora. Least toxic and at the same time the cheapest medication should be administered in adequate dosage and for a sufficient long period of time in order to eradicate infection. Empirical antimi-

TABLE 4
ANTIMICROBIAL TREATMENT OF URINARY TRACT INFECTIONS IN FAMILY MEDICINE PHYSICIANS' OFFICES

UTI episodes	Number
Analyzed	3188
Treated	2939 (92.19%)
Not treated at the time of research	249 (7.81%)
Etiologically confirmed (targeted therapy)	999 (33.99% of the total number of treated)
Empirical therapy	1940 (66.01% of the total number of treated)

TABLE 5
EMPIRICAL ANTIMICROBIAL THERAPY OF 1490 UTI EPISODES RECORDED IN FAMILY MEDICINE PHYSICIANS' OFFICES

UTI episodes		Patients / Empirical therapy									
		Cephalexin		Co-amoxiclav		Ciprofloxacin		Other		Total	
		n	%	n	%	n	%	n	%	n	%
Acute uncomplicated cystitis		818	79.57	16	1.56	–		194	18.87	1028	100
Acute uncomplicated pyelonephritis		2	1.6	95	76	12	9.6	16	12.8	125	100
Recurrent cystitis		51	85	7	11.67	2	3.33	–		60	100
Recurrent pyelonephritis		3	15	15	75	2	10	–		20	100
Complicated UTI	males	15	8.29	32	17.68	124	68.51	10	5.52	181	100
	females	45	22.17	114	56.16	34	16.75	10	4.93	203	100
Urethritis	males	18	15.25	21	17.8	38	32.30	41	34.75	118	100
	females	48	60	2	2.5	2	2.5	28	35	80	100
Prostatitis		10	8	15	12	88	70.4	12	9.6	125	100
Total		1110		317		302		211		1940	

crobial therapy is determined on the basis of local data on the most common pathogens causing most frequent clinical syndromes and their susceptibility to most commonly administered antimicrobial drugs.

Whenever possible, before starting antimicrobial therapy, midstream urine for urine culture should be collected. First morning sample or urine sample after four hours of non urination should be collected. Urine should be cultured within two hours from collection, if not, than urine sample should be stored at +4°C up to 24 hours.

Empirical therapy should be modified according to antibiogram as soon as urine culture results are available – antibiotic therapy should be switched to antibiotic with the narrowest spectrum and most effective against the causative pathogen.

Since 1997, the resistance of bacterial pathogens to antibiotics, in the most common clinical syndromes, has been regularly monitored in Croatia. In the last five years, we recorded no significant changes in the susceptibility of *E. coli* to the most commonly administered antimicrobial drugs (Table 6).

Local antibiotic resistance data were obtained from the Committee for Antibiotic Resistance Surveillance of the Croatian Academy of Medical Sciences[3–7].

Croatian national guidelines for antimicrobial treatment and prophylaxis of UTI were published in 2004[8]. With the help of the Croatian Ministry for Health and Social Welfare, the Dutch Government and international consultants, they were updated and via Internet and a two-month-piloting period, widely presented to general practitioners and specialists in urology, gynecology, infec-

TABLE 6
THE RESISTANCE OF *E. COLI* TO THE MOST COMMON ANTIBIOTICS IN CROATIA IN THE PERIOD FROM 2002–2006

Antibiotic	Resistant (intermediate) %				
	2002	2003	2004	2005	2006
Nitrofurantoin	4 (1)	3 (1)	3 (1)	3 (1)	2 (1)
Trimethoprim-sulfamethoxazole	25 (0)	22 (0)	25 (0)	24 (1)	24 (0)
Amoxicillin	47 (1)	47 (1)	44 (1)	49 (1)	52 (1)
Cephalexin	11 (5)	9 (4)	9 (6)	11 (8)	8 (5)
Co-amoxiclav	8 (4)	6 (4)	5 (3)	5 (4)	4 (4)
Cefuroxim	5 (1)	3 (1)	3 (1)	3 (2)	2 (2)
Ceftibuten	3 (0)	2 (0)	2 (0)	1 (0)	2 (0)
Ceftriaxone	3 (0)	2 (0)	2 (0)	1 (0)	2 (0)
Gentamicin	7 (1)	5 (0)	5 (0)	6 (0)	6 (0)
Norfloxacin	8 (0)	8 (0)	7 (0)	10 (0)	10 (1)
Ciprofloxacin	7 (0)	8 (0)	7 (0)	10 (0)	10 (1)

TABLE 7
CROATIAN RECOMMENDATIONS FOR EMPIRICAL ANTIMICROBIAL THERAPY OF UTI IN FAMILY MEDICINE PHYSICIANS' OFFICES

	Empirical antimicrobial therapy*	
Category of UTI	First choice	Alternative choice
Acute uncomplicated cystitis	nitrofurantoin/ 7 days	co-amoxiclav/ 7 days cephalexin/ 7 days norfloxacin/ 3 days
Acute uncomplicated pyelonephritis	co-amoxiclav/ 10–14 days	II and II generation cephalosporins/ 10–14 days ciprofloxacin/ 7–10 days
Complicated UTI	co-amoxiclav/ 10–14 days	II and II generation cephalosporins/ 10–14 days ciprofloxacin/ 7–10 days
UTI in males with systemic symptoms	ciprofloxacin/ 14 days	co-amoxiclav/ 14 days II and II generation cephalosporins/ 14 days
UTI in males with systemic symptoms and symptoms of prostatitis	ciprofloxacin/ 4 weeks	co-amoxiclav/ 4 weeks II and II generation cephalosporins/ 4 weeks
Asymptomatic bacteriuria	no empiric therapy – treatment according to antibiogram for 3–7 days	
Recurrent UTI	the same as sporadic episodes except that previous isolates and their sensitivity patterns should be taken into account	

*doses are stated for an average adult body weight and normal kidney function

tious diseases and nephrology working in primary health care and hospitals[9]. The evidence for these guidelines was based on a systemic review of the literature, local antibiotic resistance data and local and international guidelines for the treatment of UTI[10–17]. Recommendations for empirical antimicrobial therapy of UTI in family medicine physicians' offices are shown in Table 7[8,9,18].

The results of this research of 3188 UTI episodes in family medicine physicians' offices suggest that empirical antimicrobial therapy of UTI prescribed by Croatian family practitioners is in accordance with the national guidelines.

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ISTRAŽIVANJE INFEKCIJA MOKRAĆNOG SUSTAVA U ORDINACIJAMA LIJEČNIKA OBITELJSKE MEDICINE – EMPIRIJSKA ANTIMIKROBNA TERAPIJA INFEKCIJA MOKRAĆNOG SUSTAVA – HRVATSKA ISKUSTVA

S A Ž E T A K

U razdoblju od 1. listopada do 30. studenog 2006. godine istražili smo ukupno 3188 epizoda infekcija mokraćnog sustava (IMS) (802 u muškaraca; 2386 u žena) zabilježenih u 108 ordinacija liječnika obiteljske medicine u 20 gradova u Hrvatskoj. Najčešće IMS u žena bile su: akutni nekomplicirani cistitis (62%), komplicirane IMS – cistitis i pijelonefritis (14%), uretritis (9%), akutni nekomplicirani pijelonefritis (6%), rekurentni cistitis (5%), asimptomatska bakteriurija (3%) i rekurentni pijelonefritis. Najčešće IMS u muškaraca su bile komplicirane IMS – cistitis i pijelonefritis (48%), uretritis (25%), prostatitis (24%) i asimptomatska bakteriurija (3%). Etiološka dijagnoza postavljena je u 999 (31%) epizoda IMS prije započete antimikrobne terapije. Najčešći izolirani uzročnici bili su Escherichia coli (77%), Enterococcus faecalis (9%), Proteus mirabilis (5%), Klebsiella spp (3%), Streptococcus agalactiae (3%) i Enterobacter (1%). Antimikrobna terapija primijenjena je u 2939 (92.19%) epizoda IMS, u 1940 (66.01%) kao empirijska, a u 999 (34%) kao ciljana antimikrobna terapija. Najčešće primjenjivani lijek u empirijskoj terapiji akutnog nekompliciranog cistitisa, rekurentnog cistitisa i uretritisa u žena bio je cefaleksin, za liječenje akutnog nekompliciranog pijelonefritisa i komplicirane IMS u žena koamoksiklav, a za IMS u muškaraca ciprofloksacin. Rezultati ovog istraživanja 3188 epizoda IMS u ordinacijama liječnika obiteljske medicine daju potvrdan odgovor na pitanje o podudarnosti propisane empirijske antimikrobne terapije IMS s nacionalnim preporukama.