

EPIDEMIOLOGY AND ANTIBIOTIC RESISTANCE PROFILE OF BACTERIAL UROPATHOGENS IN MALE PATIENTS: A 10-YEAR RETROSPECTIVE STUDY

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Abstract

The purpose of our present study was to establish the incidence of UTIs in adult male patients in the Southern region of Hungary over a long surveillance period (2008 - 2017). The antimicrobial susceptibility testing was performed using the disk diffusion method. Overall, n = 3750 of these outpatient samples (17.73%) and n = 5902 of inpatient samples (30.54%) originated from male patients. Members of the *Enterobacteriaceae* family were the most commonly isolated (outpatient: 64.4%, inpatient: 55.57%), with *E. coli* being the most common urinary pathogen in male patients (outpatient: 37.23%, inpatient: 27.40%), followed by *Enterococcus* spp. (outpatient: 22.72%, inpatient: 23.43%), and *P. aeruginosa* (outpatient: 7.15%, inpatient: 9.2%). Between 2010 and 2017, n = 501 (62.65 ± 13.51 per year) extended-spectrum β-lactamase (ESBL) - positive isolates were recorded from outpatients and n = 737 (105.28 ± 31.99 per year) from inpatients (p = 0.032). Similarly to other bacterial infections, patients affected by drug-resistant urinary pathogens may encounter a poor clinical outcome and complications.

Rezumat

Scopul studiului prezentat a fost de a stabili incidența infecțiilor de tract urinar (UTI) la pacienții de sex masculin adulți din regiunea sudică a Ungariei pe o perioadă lungă de supraveghere (2008 - 2017). Testul de sensibilitate antimicrobiană a fost efectuat folosind metoda de difuzie a discului. În ansamblu, 3750 dintre aceste probe au provenit de la pacienți tratați ambulator (17,73%) și 5902 de probe de la pacienți internați (30,54%) de sex masculin. Membrii familiei *Enterobacteriaceae* au fost cei mai frecvent izolați patogeni (ambulatoriu: 64,4%, internați: 55,57%), *E. coli* fiind cel mai frecvent agent patogen la pacienții de sex masculin (ambulatoriu: 37,23%, internați: 27,40%), urmat de *Enterococcus* spp. (ambulatoriu: 22,72%, internați: 23,43%) și *P. aeruginosa* (ambulatoriu: 7,15%, internați: 9,2%). Între 2010 și 2017, 501 (62,65 ± 13,51 pe an) izolate ESBL- pozitive au fost înregistrate de la pacienți din ambulator și 737 (105,28 ± 31,99 pe an) de la pacienți internați (p = 0,032). În mod similar cu alte infecții bacteriene, pacienții afectați de agenți patogeni rezistenți la medicamente pot avea rezultate clinice slabe și pot înregistra diferite complicații.

Keywords: urinary tract infections, UTIs, male patients, epidemiology, resistance

Introduction

Urinary tract infections (UTIs) are pathologies affecting a part of an individual's urinary system, including the bladder, urethra or the kidneys. UTIs are the second common type of infections in human medicine, representing around 10 - 30% of community-acquired and 25 - 50% of nosocomial infections worldwide [21, 32, 33, 37]. They are considered as an important factor of morbidity and mortality and an important economic burden (the medical care of these patients, together with the loss of productivity associated with UTIs is estimated to cost around 5 billion US\$ per year) [16, 35]. UTIs may also often correspond to serious complications, sequelae, recurrence and decreased quality of life (QoL) for the affected patients [15,

16, 21, 37]. Members of the *Enterobacteriales* order, including uropathogenic strains of *Escherichia coli* (UPEC) and *Klebsiella pneumoniae* (UPKP) are some of the most important causes of uncomplicated and community-acquired urinary tract infections, in addition to *Enterococcus* spp., *Staphylococcus saprophyticus* (so-called "honeymoon cystitis") and Group B streptococci [1, 15, 41]. Nevertheless, causative agents of UTIs in nosocomial settings (especially in case of immunocompromised patients) may be much more diverse, including non-fermenting Gram-negative bacteria, *S. aureus* and fungal species, facilitating the increasing occurrence of unconventional urinary pathogens [5, 10, 12, 15, 36].

The incidence of UTIs differs considerably among different patient populations, including different genders, age groups and immune status: symptomatic UTI are far more common in women than in men. 30 - 50% of women experience uncomplicated cystitis at least once in their lifetime, while this ratio is around 0.5 - 5% for males [21, 23, 24]. In addition, the incidence of UTIs in males between 18 - 50 years of age is very low (5 - 8 *per* 10,000 patient/years), compared to the sharp increase in incidence over 50 years of age [23, 24, 41]. This may be explained by anatomical differences between the two sexes (longer urethral lengths, the lack of moisture in the periurethral environment, antibacterial substances originating from the prostatic fluids, less pronounced colonization of the urethra by potential urinary pathogens); however, symptomatic UTIs in males may be more severe and harder to treat [21-24, 41, 44]. Risk factors for males include lack of circumcision, anatomical abnormalities, having recent urinary procedures, an immunocompromised state and high-risk sexual practice [21-24, 41, 44].

Although several novel antibiotic agents have been approved for clinical use in recent 10 - 15 years, the therapy of UTIs (especially in outpatient settings) is becoming an important challenge for clinicians, due to the rapid development and spread of antimicrobial resistance (AMR) [19]. The growing prevalence of multidrug-resistant (MDR; i.e. exhibiting resistance to at least one agent, in at least three antibiotic categories) pathogens in UTIs limit therapeutic options considerably [1, 42]. The increasingly common occurrence of extended-spectrum β -lactamase (ESBL) genes (encoded on plasmids) in the members of the *Enterobacteriales* order is a cause of considerable worry both for clinicians and microbiologists worldwide; ESBLs confer resistance to classical penicillin-derivatives, such as broad-spectrum cephalosporins, which are all considered safe and effective therapeutic alternatives, forcing clinicians to utilize agents with a more pronounced toxicity profile (i.e. fluoroquinolones, such as ciprofloxacin or aminoglycosides, such as gentamicin) in the affected patients [14].

It is commonplace to treat patients with uncomplicated UTIs based on empirical antimicrobial therapy (without results of microbiological analyses or susceptibility-testing); nonetheless, decisions on drug therapy may also be influenced by social and monetary aspects (such as the price of the drugs, drug availability and predicted adherence of the patients), drug allergies and tolerability of these antibiotics [13]. In outpatient cases, publications reporting on local epidemiological data are useful to guide therapeutic choices. However, there is a lack of data for the epidemiology and resistance trends for UTIs of specific patient groups, namely for males, children and transplant patients, therefore the choice of appropriate empiric antibiotic therapy may be hindered by the inability of assess local patterns of resistance [23, 43]. Considering all these aspects, the

aim of this paper was to report on the epidemiology and resistance trends of UTIs among adult males in a tertiary-care teaching hospital in the Southern region of Hungary over a long study period of 10-years.

Materials and Methods

Study design, data collection methods

The present study was based on microbiological data collected for a 10-year surveillance period (2008.01.01 - 2017.12.31) at the Institute of Clinical Microbiology (University of Szeged, Hungary). The design of the study is retrospective. The Institute is the main diagnostic laboratory of the Albert Szent-Györgyi Health Centre, which is a primary- and tertiary-care teaching hospital in Szeged, Hungary. At the time of the study, the Centre had a capacity of 1,820-beds (1,465 acute and 355 chronic beds, respectively), with an annual patient turnover of over 400,000 patients in the region, according to the data of the Hungarian National Health Insurance Fund (NEAK), from general practitioner (GP) level care to specialized medical interventions [31]. Data for the study was collected by the study authors *via* the MedBakter laboratory system for urine samples originating from adult male patients, positive for bacterial pathogens. Samples with clinically-relevant colony counts (usually $10^5 <$ colony forming units (CFU)/mL) and bacteria (determined and interpreted by considering international guidelines for diagnosing UTIs and information supplied on microbiological analysis request forms), that were positive for the nitrite and leukocyte-esterase tests were included in the data for this survey [36]. Only the first isolate *per* patient was included in the study; isolates presenting with different antibiotic-susceptibility patterns were considered as different individual isolates. Samples from female patients and from patients < 18 years of age were excluded from data collection. In addition, the age of the male patients and inpatient/outpatient status were also collected.

Identification of bacterial isolates

The cultivation of relevant bacterial isolates was carried out using standard bacteriological protocols. 10 μ L of each un-centrifuged urine sample was cultured on various non-selective and selective-differentiating media (such as blood agar, eosine methylene blue agar and UriSelect chromogenic agar plates (Bio-Rad, Berkeley, CA, USA)) with a calibrated loop, according to the manufacturer's instructions; plates were incubated at 37°C for 24 - 48 h, aerobically. If the relevant pathogens presented in significant colony count, the plates went on for further processing. During 2008 - 2012, standard biochemical assays and the VITEK 2 Compact ID/AST (bioMérieux, Marcy-l'Étoile, France) were used for bacterial identification; from 2013 onward, this matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany) was also introduced

into routine ID practice. The methodology of sample preparation for MALDI-TOF MS measurements was described previously [12, 36]. MS assays were performed by the Microflex MALDI Biotyper (Bruker Daltonics, Bremen, Germany); spectrum analysis and ID were carried out by the MALDI Biotyper RTC 3.1 software (Bruker Daltonics) and the MALDI Biotyper Library 3.1.

Antimicrobial Susceptibility Testing (AST)

The evaluation of the resistance trends was carried out regarding the most prevalent UTI pathogens isolated from male patients, namely members of the order of *Enterobacterales*, *P. aeruginosa* and *Enterococcus* spp. Antimicrobial susceptibility testing (AST) was performed by standard disk diffusion methodologies on Mueller-Hinton agar plates (Liofilchem, Abruzzo, Italy) described by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), including. During AST, the susceptibility to the following antibiotics were tested (taking into consideration intrinsic resistance of isolates): ampicillin (10 µg), amoxicillin/clavulanic acid (20/10 µg), cefuroxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), piperacillin/tazobactam (30/6 µg), cefepime (30 µg), imipenem (10 µg), meropenem (10 µg), ciprofloxacin (5 µg), levofloxacin (5 µg), gentamicin (10 µg), amikacin (30 µg), trimethoprim-sulfamethoxazole (23.75/1.25 µg), vancomycin (5 µg) and linezolid (30 µg). The interpretation of the results was based on EUCAST Clinical Breakpoints 9.0.

Discrepant results were verified using the VITEK 2 Compact ID/AST (bioMérieux, Marcy-l'Étoile, France) automated system. The following bacterial strains were used as quality controls: *E. coli* ATCC 25922, *K.*

pneumoniae ATCC 700603, *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213. If AST results were indicative of ESBL-production among *Enterobacterales* (according to EUCAST recommendations), phenotypic detection was performed using ESBL Detection Set (MAST Diagnostica GmbH, Reinfeld, Germany) from 2010 onward, with adherence to manufacturer's instructions [17].

Statistical Analysis

Descriptive statistical analysis, normality tests (Shapiro-Wilk) and non-parametric tests (Mann-Whitney U test) with the SPSS software version 22 (IBM SPSS Statistics for Windows 22.0, Armonk, NY, USA, IBM Corp.) were used. p values < 0.05 were considered statistically significant.

Results and Discussion

The length of our surveillance study was 10-years, starting from 2008 and ending with 2017; in this period, the Institute had processed 21,150 positive urine samples from outpatient clinics and 19,325 positive urine samples from inpatient departments. Overall, n = 3750 of these outpatient samples (17.73%) and n = 5902 of inpatient samples (30.54%) originated from male patients who were 18 years or older at the time of sample submission. The sample distribution of the positive urine samples for males was the following: in outpatients 74.17% was midstream urine, while in inpatients 67.30% was catheter-specimen urine. Other samples types, such as first-stream urine, suprapubic bladder aspiration and urine obtained after a prostate massage were less common in both groups (4.01% and 1.64% overall) (Figure 1).

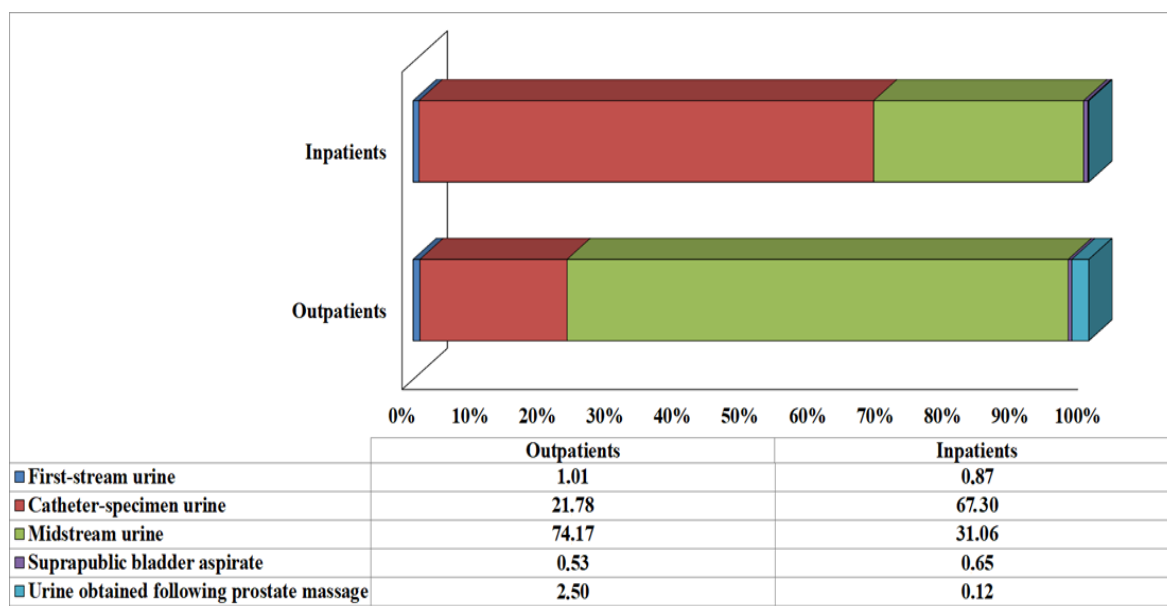


Figure 1.

Sample distribution from the outpatient and inpatient departments over the 10-year period

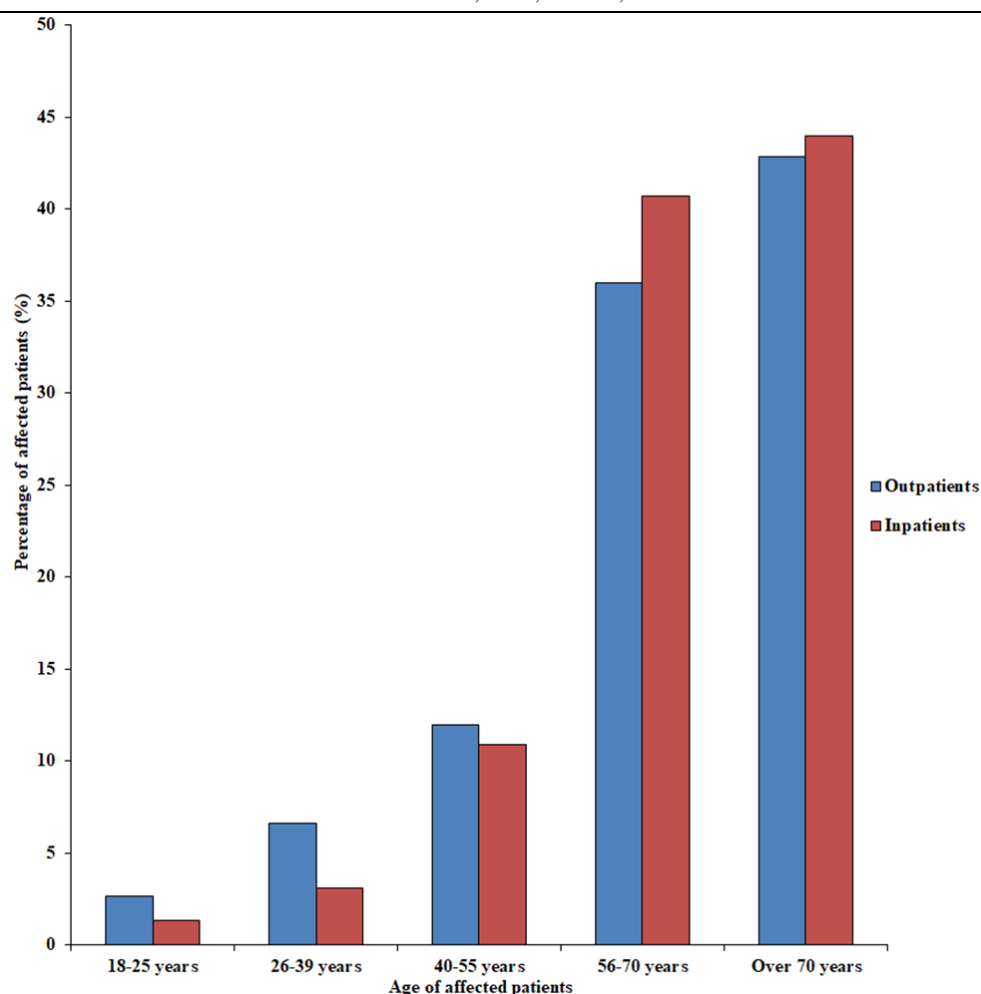


Figure 2.

Age distribution of the affected patients in the outpatient and inpatient groups

The median age of affected patients was 55 years (range: 18 - 97) in the outpatient group, while in the inpatient group, the median age was 58 years (range: 18 - 96). In both inpatient and outpatient groups, patient aged 56 years or older constituted the overwhelming majority of patients (78.81% and 84.68%, respectively); patients over 70 years presented in the highest numbers (42.84% and 43.98%, respectively) (Figure 2).

The species distribution of outpatient and inpatient isolates did not present high variance, 36 and 37 different pathogens were identified on the species-level, respectively (Table I and Table II). 72.96% of isolates were Gram-negative, 26.0% were Gram-positive,

0.67% were yeasts and 0.37% were atypical bacteria in the out-patient group (Table I). As a comparison, 66.88% of urinary pathogens were Gram-negative, 26.92% were Gram-positive, 6.15% were yeasts and 0.05% were atypical bacteria (Table II) in the inpatient group. Species-wise, the members of the *Enterobacteriales* family were the most commonly isolated (outpatient: 64.4%, inpatient: 55.57%), with *E. coli* being the most common urinary pathogen in male patients (outpatient: 37.23%, inpatient: 27.40%), followed by *Enterococcus* spp. (outpatient: 22.72%, inpatient: 23.43%), and *P. aeruginosa* (outpatient: 7.15%, inpatient: 9.2%) (Table I and Table II).

Table I

Species-composition of the urinary isolates from outpatient samples, 2008 - 2017

Isolated species	Study year										N	%
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017		
<i>Achromobacter xylosoxidans</i>									2		2	0.05
<i>Acinetobacter baumannii</i>	3	1			2		5	4	2	5	22	0.59
<i>A. lwoffii</i>	3			1	2	4	2			1	13	0.35
<i>A. junii</i>		1							1	1	3	0.08
<i>Burholderia cepacia</i>			3			2					5	0.13
<i>Candida albicans</i>			2				5	8	2	2	19	0.51

Isolated species	Study year										N	%
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017		
<i>C. glabrata</i>				1						1	2	0.05
<i>C. parapsilosis</i>									1		1	0.03
<i>C. tropicalis</i>						2	1				3	0.08
<i>Citrobacter freundii</i>	1	3	2		2	2				1	11	0.29
<i>C. koseri</i>	1		1	2	2	5		5	7	8	31	0.83
<i>Enterobacter asburiae</i>						3	1		1	1	6	0.16
<i>E. cloacae</i>	3	7	5	5	6	5	3	10	11	9	64	1.71
<i>E. kobei</i>						1	6	4		2	13	0.35
<i>Enterococcus faecalis</i>	85	62	60	61	72	68	83	111	100	131	833	22.21
<i>E. faecium</i>		2		4	3	2		2	1	5	19	0.51
<i>Escherichia coli</i>	80	63	123	117	111	144	176	196	186	200	1396	37.23
<i>Klebsiella aerogenes</i>	1	2	3	4	1	2		3	3	8	27	0.72
<i>K. oxytoca</i>	4		4		5	11	9	11	6	12	62	1.65
<i>K. pneumoniae</i>	27		74		42	71	39	74	67	90	484	12.91
<i>Mycoplasma hominis</i>				2							2	0.05
<i>Morganella morganii</i>			1	2	2	4	1	3	7	4	24	0.64
<i>Proteus mirabilis</i>	5	4	14	18	18	25	32	38	40	55	249	6.64
<i>P. vulgaris</i>	3	4	6	2	2	3	5	4	5		34	0.91
<i>Providencia rettgerii</i>									1		1	0.03
<i>P. stuartii</i>										1	1	0.03
<i>Pseudomonas aeruginosa</i>	28	25	21	37	25	32	23	24	25	28	268	7.15
<i>Serratia marcescens</i>		1					1	3	6	1	12	0.32
<i>Staphylococcus aureus</i>		1		8	8	7	8	8	10	9	59	1.57
<i>S. saprophyticus</i>					1				3		4	0.11
<i>S. epidermidis</i>		3	5	1		4					13	0.35
<i>S. hominis</i>	4	2									6	0.16
<i>S. haemolyticus</i>						1					1	0.03
<i>Stenotrophomonas maltophilia</i>	1			1		2		2	1	1	8	0.21
<i>Streptococcus agalactiae</i>	5	5	3	2	3	4	2	6	5	5	40	1.07
<i>Ureaplasma urealyticum</i>	2			2		4	1	1	2		12	0.32

Table II
Species-composition of the urinary isolates from inpatient samples, 2008 - 2017

Isolated species	Study year										N	%
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017		
<i>Achromobacter xylosoxidans</i>			1								1	0.02
<i>Acinetobacter baumannii</i>	2	3	7	3	14	11	8	9	6	5	68	1.15
<i>A. lwoffii</i>		1						10	2		13	0.22
<i>A. junii</i>								1			1	0.02
<i>Burholderia cepacia</i>	8	1	2	4	2	1	2			1	21	0.36
<i>Candida albicans</i>	10	15	18	8	11	22	33	30	33	60	240	4.07
<i>C. glabrata</i>	3	4	2	4	2	2	8	20	5	11	61	1.03
<i>C. parapsilosis</i>		3	1		3	1	2	5		4	19	0.32
<i>C. krusei</i>			1	2	2	4	2	2	2	4	19	0.32
<i>C. tropicalis</i>	3		6	1	3	1	2	4		4	24	0.41
<i>Citrobacter freundii</i>	2		1	1				2	2	2	10	0.17
<i>C. koseri</i>		2	2	1		5		6	2	5	23	0.39
<i>Enterobacter asburiae</i>						1					1	0.02
<i>E. cloacae</i>	9	10	19	9	12	14	14	11	7	8	113	1.91
<i>E. kobei</i>			1					4	2	4	11	0.19
<i>Enterococcus faecalis</i>	108	92	95	105	120	142	152	138	161	158	1271	21.54
<i>E. faecium</i>	5	14	7	7	7	13	13	7	21	18	112	1.90
<i>Escherichia coli</i>	105	103	142	174	165	164	208	209	192	155	1617	27.40
<i>Klebsiella aerogenes</i>	3	3	4	6	5	1	4	1	3	2	32	0.54
<i>K. oxytoca</i>	6	4	6	9	6	9	14	9	15	15	93	1.58
<i>K. pneumoniae</i>	42	43	73	68	87	72	110	99	117	79	790	13.39
<i>Mycoplasma hominis</i>				3							3	0.05
<i>Morganella morganii</i>	3	2	1				3	6	17	5	37	0.63
<i>Proteus mirabilis</i>	16	20	30	54	44	45	72	79	58	52	470	7.96

Isolated species	Study year										N	%
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017		
<i>P. vulgaris</i>	3	6	6	10	7	4	11	4	7	5	63	1.07
<i>Providencia rettgeri</i>						1		1		4	6	0.10
<i>P. stuartii</i>								1	3	1	5	0.08
<i>Pseudomonas aeruginosa</i>	45	65	47	58	76	45	55	46	52	54	543	9.20
<i>Serratia marcescens</i>	1	1		2	2	1	5	2	1	4	19	0.32
<i>Staphylococcus aureus</i>	10	13	9	11	9	11	8	6	13	8	98	1.66
<i>S. saprophyticus</i>	3		1		3	3	2		2	4	18	0.30
<i>S. epidermidis</i>	6	7		1		3	1		2		20	0.34
<i>S. hominis</i>	9		2	3	3						17	0.29
<i>S. haemolyticus</i>						4			2		6	0.10
<i>S. hominis</i>	9										9	0.15
<i>Stenotrophomonas maltophilia</i>		1	1	1		1	4			2	10	0.17
<i>Streptococcus agalactiae</i>	5	7	3	5	3	4	3	5	1	2	38	0.64

Susceptibility results were collected for the isolates that were the most numerous in the adult male patients, namely members of the *Enterobacteriaceae* family, *Enterococcus* spp. and *P. aeruginosa* (Table III), in addition, the distribution of ESBL-producing isolates was also assessed over the 8-year period, where data was available (2010 - 2017; Figure 3). During our study, intrinsic non-susceptibility of relevant bacteria was considered during the assessment. The highest resistance rates were seen for fluoroquinolones in all three groups of uropathogens (*Enterobacterales*, enterococci and *P. aeruginosa*); additionally, high levels of resistance were also shown in regards to 3rd generation cephalosporins (3GS) and trimethoprim-sulfamethoxazole in *Enterobacterales* (e.g., *E. coli* and *Klebsiella* spp.). For *P. aeruginosa*, both imipenem and

meropenem resistance rates were > 10% for outpatients and > 20% for inpatients. Pronounced differences were observed when comparing the resistance levels of outpatient and inpatient isolates, in the following cases: 3GCs, ciprofloxacin, levofloxacin, gentamicin and trimethoprim-sulfamethoxazole-resistance in *Enterobacterales*, ciprofloxacin and levofloxacin resistance in *Enterococcus* spp., and ciprofloxacin, levofloxacin and ceftazidime-resistance in *P. aeruginosa* (Table III). Between 2010 and 2017, n = 501 (62.65 ± 13.51 per year) ESBL-positive isolates were recorded from outpatients and n = 737 (105.28 ± 31.99 per year) from inpatients (p = 0.032) (Figure 3). No carbapenem-resistant isolates in *Enterobacterales* or vancomycin- and linezolid-resistant *Enterococcus* isolates were detected from these samples.

Table III

Ratio of resistant isolates among common urinary tract pathogens isolated from male patients over the 10-year surveillance period

Tested antibiotics	<i>Enterobacteriaceae</i>			<i>Enterococcus</i> spp.			<i>P. aeruginosa</i>		
	Outpatients (%)	Inpatients (%)	Statistics*	Outpatients (%)	Inpatients (%)	Statistics*	Outpatients (%)	Inpatients (%)	Statistics*
Ampicillin	39.85	51.11	n.s.	0.17	0.21	n.s.	-		
Amoxicillin/clavulanic acid	18.16	20.05	n.s.	0.17	0.21	n.s.	-		
Cefuroxime	25.64	32.18	p = 0.043	-			-		
Ceftriaxone	24.91	31.97	p = 0.041	-			-		
Ceftazidime	24.86	31.97	p = 0.04	-			11.13	18.81	p = 0.041
Piperacillin/tazobactam	24.86	31.97	p = 0.04	0.17	0.21	n.s.	-		
Cefepime	16.31	19.10	n.s.	-			13.56	20.01	n.s.
Imipenem	0.0	0.0	n.s.	0.03	0.07	n.s.	13.26	24.91	
Meropenem	0.0	0.0	n.s.	-			12.50	21.07	
Ciprofloxacin	22.17	34.57	p = 0.029	34.15	19.28	p = 0.019	33.00	43.78	p = 0.039
Levofloxacin	20.10	31.96	p = 0.31	32.05	17.17	p = 0.022	33.00	43.78	p = 0.039
Gentamicin	10.17	19.35	p = 0.02	-			-		
Amikacin	5.52	7.23	n.s.	-			15.56	18.21	n.s.
Trimethoprim-sulfamethoxazole	25.45	36.68	p = 0.03	-			-		
Vancomycin	-			0.0	0.0	n.s.	-		
Linezolid	-			0.0	0.0	n.s.	-		

*Comparison of resistance levels among isolates originating from outpatients and inpatients; n.s.: not significant

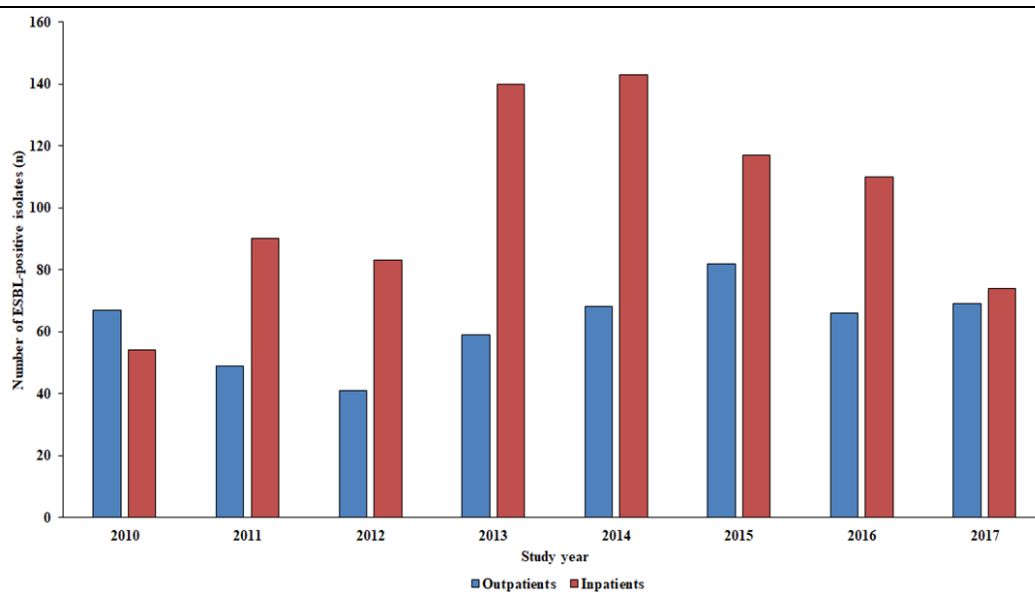


Figure 3.
Distribution of ESBL-producing isolates

The principal aim of our research was to provide reliable epidemiological information regarding UTIs in adult male patients in the southern region of Hungary over a long surveillance period, focusing on bacterial composition and resistance trends in the most numerous isolates. The epidemiology and resistance of urinary pathogens from female patients in the geographic region has been described previously: in these reports, similar resistance trends were observed for the most common urinary pathogens [12, 17, 25, 34, 36]. Nevertheless, the ratio of ESBL-positivity was higher in isolates from male patients than in females. The data presented here may contribute to the creation of a national/transnational surveillance program for male UTIs, as previously, international surveillance reports (e.g., SENTRY [22, 26], SMART [29], ESGNI-003 [8], PEP-study [22, 26], MYSTIC [45]) mainly focus on data on nosocomial UTIs, affecting both genders. In comparison with the already-published data in the available literature, our has provided similar conclusions, both regarding the species-composition of the relevant pathogens (*E. coli*, *K. pneumoniae* and *Enterococcus*, which are constituents of the normal intestinal microbiota and *P. aeruginosa*, a common colonizer in nosocomial environments) and the prevalence of UTIs in different age groups (> 40% of affected patients were over 70 years of age) [24, 26]. In male patients, the critical assessment of the symptoms is important for differential-diagnostics, as urinary frequency, urgency, dysuria and pyuria may also indicate bacterial prostatitis. If the symptoms of the patients persist for a long period of time, or they are coupled with malaise, myalgia, pain from the perineal region, with fever, chills and urinary retention, there is a high-risk that the prostate is affected (e.g., benign prostate hyperplasia) [19, 24].

The development of UTIs in consequence of urinary pathogens is dependent on the presence of various virulence-determinants, that associated with host colonization, tissue invasion and damage, the evasion of mucosal immunity and elimination of the host's humoral immune response [4, 6, 15, 32, 33, 38]. The abovementioned virulence determinants include protein-based agents, such as adhesins, toxins, capsule-production, biofilm (especially in catheter-associated infections), siderophore (iron-uptake) systems, lipopolysaccharide (LPS), and O- and H-antigens (in select Gram-negative bacteria) [4, 6, 15, 32, 33, 38]. Most of these are associated with UPEC and UPKP; however, the majority may also be found in *P. aeruginosa* and *Enterococcus* spp.

Similarly to other bacterial infections, patients affected by drug-resistant urinary pathogens may observe a poor clinical outcome and complications [3, 27]. Nevertheless, with the extensive clinical use of antibiotics, the development of bacterial resistance simultaneously and inevitably occurs; thus the prudent use of these drugs in all settings is of critical relevance [3, 18, 27]. The most common pathogens isolated in this study are all members of the so-called "ESKAPE" pathogens, designated by the World Health Organisation as the most important drug resistant bacteria, warranting attention from pharmaceutical companies and national infection control experts [7, 19, 40]. Trimethoprim-sulfamethoxazole, fosfomycin and nitrofurantoin (in case of *E. coli*) are regarded as first-choice antibiotics in uncomplicated UTIs; while if there are allergies or intolerance to these agents, several β -lactam antibiotics and fluoroquinolones also offer viable alternatives, although the relevance of fluoroquinolones has been called into question many times, due to the mounting evidence of their serious, debilitating adverse effects

[39, 43]. However, it must be noted that if an isolate shows resistance to the abovementioned drugs, there are essentially no other orally-available options left for treat UTIs in the outpatient settings; this is especially true in case of *P. aeruginosa* and enterococci, as the list of clinically-useful drugs is already limited in wild-type strains [4, 14, 21]. There has been renewed interest in the acidification of urine and the use of urinary disinfectants (e.g., methenamine) to spare antibiotics [2, 20]. For Gram-negative bacteria, the presence of β -lactamases is one of the most significant mechanisms of resistance, although alterations in porin channels and the cell wall may also lead to resistance for β -lactam antibiotics [2, 3, 27]. In the *Enterobacterales* order, ESBL-production (sometimes together with chromosomally-encoded or plasmid-mediated AmpC-enzyme production) is an important therapeutic concern; since the 21st century, the *bla*_{CTX-M}-type enzymes have become the most prevalent worldwide [9, 11, 14, 28, 30]. In addition, ESBL-positivity is also alarming from the standpoint of infection control, as these genes are found on large plasmids or integrons, which may include other resistance-determinants, leading to the rapid development of MDR in these isolates [11, 28, 30].

Although our study highlight the importance of this research field and provides valuable data, several limitations of the research methods should be considered: the study design was retrospective, and the medical records of the individual patients could not be accessed; subsequently, the correlation between bacterial isolation and other laboratory parameters, signs and symptoms, and the immune status of the patients could not be assessed. Selection bias is also present for this study (similarly to other epidemiological studies from tertiary-care hospitals), because our data presumably corresponds to patients with more severe conditions or underlying illnesses. In addition, during laboratory analyses, our study did not include the genotypic characterization of the causative isolates, such as determination of the presence of resistance genes or virulence factors.

Conclusions

This study presents the epidemiological trends and resistance levels of the main urinary pathogens associated with urinary tract infections (UTIs) in adult males. The study was carried out in the Southern region of Hungary over a long surveillance period (10 years). In the present study, Gram-negative strains were most prevalent in the UTIs of male patients, unsurprisingly, *E. coli* was the most common uropathogen detected. The study also revealed that all the major strains showed high levels of resistance against fluoroquinolones and in the case of *Enterobacteriaceae*, also for broad-spectrum cephalosporins, due to the production of ESBL-enzymes. The renaissance of old urinary antibiotics, e.g., nitrofurantoin and fosfomycin

is warranted. To ensure safe and effective antimicrobial therapy to treat UTIs (empirically) in male patients, the continuous surveillance of causative agents and their resistance rates in these infections is definitely warranted.

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Conflict of interest

The authors declare no conflict of interest.

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