

**UNIVERSITY OF MEDICINE AND PHARMACY
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**DOCTORAL SCHOOL
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**PHD THESIS ABSTRACT
PREVALENCE AND ANTIMICROBIAL RESISTANCE OF
UROPATHOGENS IN THE MALE POPULATION OF
ROMANIA**

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Introduction

Urinary tract infections (UTIs) are among the most common infectious diseases encountered in clinical practice, affecting hundreds of millions of individuals annually and representing a major cause of antibiotic prescription worldwide [1–3]. Over recent decades, interest in this pathology has increased due to population aging, the widespread use of invasive medical procedures, and the growing phenomenon of antimicrobial resistance, which is currently recognized as one of the most significant threats to public health [2,4].

Although UTIs occur more frequently in women, they present distinct epidemiological and clinical characteristics in men. Their prevalence increases significantly with advancing age and is associated with benign prostatic hyperplasia, urolithiasis, urinary catheterization, and other obstructive urinary tract disorders [5,6]. Furthermore, prostatic involvement may promote the persistence and recurrence of infections by acting as a chronic bacterial reservoir, contributing to the development of more complex clinical presentations [6-8].

From a microbiological perspective, *Escherichia coli* remains the predominant etiological agent of UTIs. However, in male patients and in complicated infections, microorganisms such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterococcus spp.* are encountered more frequently [8,9]. At the same time, the increasing prevalence of antimicrobial resistance, particularly to fluoroquinolones, cephalosporins, and carbapenems, highlights the need for continuous adaptation of empirical therapy according to local epidemiological patterns [10,11].

In this context, the present doctoral thesis aims to investigate the epidemiological and microbiological characteristics of urinary tract infections in male patients, as well as the evolution of antimicrobial resistance in a tertiary urological center in Romania, with particular emphasis on the impact of the COVID-19 pandemic and the differences observed between male and female patients [6,10].

I. General Part

1. Urinary Tract Infections – Clinical and Epidemiological Background

Urinary tract infections (UTIs) are among the most common bacterial infections encountered in clinical practice and represent a significant cause of morbidity, antibiotic consumption, and healthcare resource utilization worldwide [1–3]. According to the current guidelines of the European Association of Urology (EAU), UTIs are classified as localized or systemic infections, as well as uncomplicated or complicated forms, a classification that directly influences diagnostic and therapeutic management [6]. Globally, UTIs affect hundreds of millions of individuals each year and remain one of the leading indications for antibiotic prescription in both outpatient and hospital settings [7].

From a microbiological perspective, *Escherichia coli* remains the predominant etiological agent responsible for urinary tract infections, accounting for the majority of cases reported worldwide. However, in complicated infections and among male patients, microorganisms such as *Klebsiella spp.*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterococcus spp.* are encountered more frequently, with their prevalence being influenced by age, comorbidities, and exposure to healthcare services [7,12]. At the same time, international surveillance systems have documented a continuous increase in antimicrobial resistance, particularly to fluoroquinolones, cephalosporins, and carbapenems, a phenomenon that represents one of the most important challenges in contemporary clinical practice [10,11].

Sex and age are major determinants in the epidemiology of UTIs. Although women are affected more frequently due to the anatomical characteristics of the urinary tract, the prevalence of UTIs in men increases significantly after the age of 55 years, mainly because of the association with benign prostatic hyperplasia, urolithiasis, and other obstructive urological conditions [6,11]. Furthermore, prostatic involvement plays an important role in the persistence and recurrence of male urinary tract infections, contributing to the development of more complex clinical presentations and the need for tailored therapeutic approaches [6,13].

The main risk factors associated with UTIs include anatomical and functional abnormalities of the urinary tract, diabetes mellitus, immunosuppression, urolithiasis, repeated antibiotic exposure, and urinary tract instrumentation. Urinary catheterization remains one of the most important predisposing factors, facilitating bacterial biofilm formation and the

emergence of antibiotic-resistant microorganisms [14]. In this context, understanding the epidemiological and microbiological characteristics of urinary tract infections is essential for optimizing diagnostic, therapeutic, and preventive strategies, as well as for limiting the impact of antimicrobial resistance [6,10,14].

2. Etiology and Pathogenesis of Urinary Tract Infections

The etiology of urinary tract infections is predominantly associated with microorganisms originating from the intestinal and perineal flora that colonize the urinary tract and develop specific mechanisms of adaptation and persistence. *Escherichia coli* is the leading etiological agent, accounting for the majority of community-acquired UTIs and a substantial proportion of healthcare-associated infections. Other frequently encountered uropathogens include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterococcus spp.*, and *Staphylococcus spp.*, whose distribution is influenced by age, sex, comorbidities, and clinical setting [8,15].

The pathogenesis of UTIs involves bacterial adhesion to the urothelium, subsequent multiplication, and, in certain cases, ascending spread to the upper urinary tract. Bacterial adhesins, pili, and other surface proteins play a crucial role in colonization and biofilm formation. These structures protect microorganisms from host immune responses and antimicrobial agents, contributing to the persistence and recurrence of urinary tract infections [16,17].

Uropathogenic *Escherichia coli* (UPEC) is characterized by specialized virulence factors, including type 1 fimbriae and the FimH adhesin, which facilitate attachment to uroepithelial cells and the formation of persistent bacterial reservoirs. Other pathogens exhibit distinct pathogenic mechanisms, such as urease production by *Proteus mirabilis*, biofilm formation by *Klebsiella pneumoniae*, and the ability of *Enterococcus spp.* to establish persistent infections associated with urinary devices [17,18].

The bacterial distribution differs between uncomplicated and complicated urinary tract infections. While *Escherichia coli* predominates in community-acquired infections, complicated UTIs are more frequently associated with *Klebsiella spp.*, *Proteus spp.*, *Pseudomonas aeruginosa*, and *Enterococcus spp.* [2,19]. In male patients, UTIs may also

involve the prostate and accessory genital organs, contributing to more complex clinical presentations and an increased risk of recurrence [20,21].

Understanding the microbiological characteristics and virulence mechanisms of the main uropathogens is essential for appropriate antimicrobial therapy selection and for the development of effective prevention and infection-control strategies [6,8].

3. Diagnosis and Treatment of Urinary Tract Infections

The diagnosis of urinary tract infections is based on the evaluation of clinical manifestations and microbiological confirmation through urine culture, which remains the gold standard for pathogen identification and antimicrobial susceptibility testing [6,22]. According to the current European Association of Urology (EAU) guidelines, urine culture is recommended in all systemic UTIs, complicated infections, male patients, and prior to invasive urological procedures, facilitating targeted therapy and reducing unnecessary antibiotic use [6].

The management of urinary tract infections is guided by the location and severity of infection, as well as local antimicrobial resistance patterns. EAU guidelines recommend empirical therapy only when prompt treatment initiation is required, followed by adjustment according to urine culture and susceptibility testing results [6]. For uncomplicated cystitis, first-line agents include fosfomycin trometamol and nitrofurantoin because of their favorable susceptibility profiles and limited ecological impact. Fluoroquinolones and cephalosporins should be used cautiously due to the increasing prevalence of antimicrobial resistance and their role in the selection of multidrug-resistant organisms [6,10,11].

In complicated and systemic urinary tract infections, antibiotic selection should be tailored to disease severity and individual risk factors. Carbapenems, aminoglycosides, and other broad-spectrum agents are generally reserved for severe infections or cases caused by resistant pathogens [6,11]. In male patients, therapeutic management presents specific challenges because prostatic involvement is frequently associated with urinary tract infections. In bacterial prostatitis, fluoroquinolones remain the first-line treatment owing to their excellent tissue penetration and high prostatic concentrations [23,24]. In the context of increasing antimicrobial resistance worldwide, adherence to antibiotic stewardship principles and continuous adaptation of treatment strategies to local epidemiological data are essential for optimizing clinical outcomes and limiting the emergence of resistant bacteria [6,10,11].

4. Evolution of Antimicrobial Resistance and the Impact of the COVID-19 Pandemic

Antimicrobial resistance represents one of the most significant challenges to modern healthcare, being associated with increased treatment failure rates, prolonged hospitalization, and the need for last-resort antibiotics [25,26]. In urinary tract infections, this phenomenon is particularly relevant because the main uropathogens, especially Gram-negative bacteria, develop complex resistance mechanisms and the ability to form biofilms, which promote infection persistence and reduce the effectiveness of antimicrobial therapy [25].

Current epidemiological data indicate a continuous increase in resistance to fluoroquinolones, cephalosporins, and other commonly prescribed antibiotics. Although women experience UTIs more frequently and receive antibiotics more often throughout their lifetime, several studies have reported higher antimicrobial resistance rates among male patients, particularly in the setting of complicated infections, obstructive urological conditions, and repeated exposure to healthcare services and urological procedures [6,24].

The surveillance of antimicrobial resistance is conducted through international monitoring programs such as GLASS, EARS-Net, and CAESAR, which provide essential data for the development of antibiotic stewardship strategies and the adaptation of empirical therapy to local epidemiological trends [10,27]. At the same time, the COVID-19 pandemic significantly influenced the evolution of antimicrobial resistance through the extensive use of antibiotics in hospitalized patients and the increased selective pressure exerted on bacterial populations. These changes have been associated with a higher prevalence of resistant pathogens, including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [28-29].

Despite advances in antimicrobial resistance surveillance, data focusing exclusively on male patients remain limited. This lack of information highlights the need for dedicated studies investigating the epidemiological and microbiological characteristics of urinary tract infections in men and their implications for antimicrobial treatment strategies [27,28,30].

II. Original Research

5. Working Hypothesis and General Objectives

Urinary tract infections represent one of the most common infectious diseases and remain a major challenge in the context of the global increase in antimicrobial resistance. Although less frequent in men, UTIs are often associated with complicated forms of disease, favored by conditions such as benign prostatic hyperplasia, urolithiasis, diabetes mellitus, and the need for invasive urological procedures.

The central hypothesis of this doctoral thesis is that the male population in Romania presents distinct epidemiological and microbiological characteristics compared to female patients, reflected by a specific distribution of uropathogens and higher rates of antimicrobial resistance. Furthermore, it is hypothesized that the COVID-19 pandemic has influenced the evolution of these resistance patterns.

The primary objective of this research was to evaluate the prevalence of uropathogens and antimicrobial resistance among male patients diagnosed with urinary tract infections in a tertiary referral center in Romania. Secondary objectives included assessing the impact of the COVID-19 pandemic on bacterial resistance patterns and comparing the microbiological characteristics and antimicrobial susceptibility profiles between male and female patients.

The original contribution of this thesis lies in providing updated epidemiological data on male urinary tract infections and highlighting differences in bacterial prevalence and antimicrobial resistance within an understudied population, with direct implications for optimizing empirical therapy and strengthening antibiotic stewardship programs.

6. General Research Methodology

This doctoral thesis is based on a series of retrospective, descriptive, and comparative studies conducted at the “Prof. Dr. Th. Burgele” Clinical Hospital in Bucharest, Romania, with the primary aim of evaluating uropathogen prevalence and antimicrobial resistance patterns in the male population. The research was performed in the context of the epidemiological changes associated with the COVID-19 pandemic and investigated both the

evolution of antimicrobial resistance during the pandemic and post-pandemic periods, as well as differences between male and female patients.

The original research section comprises three main studies: the evaluation of antimicrobial resistance among male patients during the COVID-19 pandemic, the comparative analysis of resistance patterns between the pandemic and post-pandemic periods, and the epidemiological and microbiological comparison between male and female patients in the post-pandemic era.

All studies were conducted in accordance with the principles of the Declaration of Helsinki and were approved by the Ethics Committee of the “Prof. Dr. Th. Burghele” Clinical Hospital (Approval No. 2/21.01.2019). Uniform inclusion and exclusion criteria were applied across all study cohorts. Adult patients with a positive urine culture ($\geq 10^5$ CFU/mL) and a single identified bacterial pathogen were included. Polymicrobial cultures, duplicate isolates, samples below the significance threshold, and patients with urinary catheters were excluded.

All urine samples processed by the hospital microbiology laboratory during the study periods were analyzed. To avoid data duplication, only the first positive urine culture for each patient was recorded. Available demographic data included age and sex; however, due to the retrospective design and the inclusion of outpatients, complete information regarding comorbidities and previous therapeutic history could not be consistently obtained.

Microbial identification and antimicrobial susceptibility testing were performed using standardized microbiological methods. Antimicrobial susceptibility was assessed using the Kirby–Bauer disk diffusion method, and results were interpreted according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). The analysis focused on the main bacterial species involved in urinary tract infections, including *Escherichia coli*, *Klebsiella spp.*, *Proteus spp.*, *Pseudomonas spp.*, *Enterococcus spp.*, and *Staphylococcus spp.*

Data were collected and organized using Microsoft Excel 2016 and statistically analyzed in Python 3.8.9 (JupyterLab 3.2.4 and Pandas 1.3.4). Continuous variables were analyzed using Student’s t-test or the Mann–Whitney U test, depending on data distribution, while categorical variables were compared using the Chi-square test or Fisher’s exact test. Statistical significance was defined as $p < 0.05$.

Through the large cohorts analyzed and the comparative evaluation of epidemiological and microbiological data, the methodology enabled a detailed assessment of uropathogen

distribution and antimicrobial resistance patterns in the male population, while also identifying the major changes associated with the post-pandemic period.

7. Study I: Antimicrobial Resistance of Uropathogens During the COVID-19 Pandemic in Male Patients

7.1.Introduction

The first study included in this doctoral thesis aimed to evaluate the prevalence of uropathogens and antimicrobial resistance patterns among male patients during the COVID-19 pandemic. The results were published in the *Journal of Medicine and Life* and indexed in PubMed [30].

Urinary tract infections are among the most common infectious diseases worldwide, affecting more than 150 million individuals annually and generating a substantial healthcare burden [3]. At the same time, the continuous rise in antimicrobial resistance has reduced available treatment options and increased the risk of treatment failure, prolonged hospitalization, and severe complications [31]. Although UTIs occur more frequently in women, their prevalence increases significantly in men with advancing age, mainly because of benign prostatic hyperplasia, urinary tract obstruction, and other underlying urological conditions [15,32].

Given the limited data available regarding bacterial distribution and antimicrobial resistance among male patients in Romania, the objective of this study was to evaluate the prevalence of the main uropathogens and their resistance profiles to commonly used antibiotics in male patients diagnosed with urinary tract infections during the COVID-19 pandemic [30,33].

7.2. Materials and Methods

This retrospective descriptive study was conducted at the “Prof. Dr. Th. Burghel” Clinical Hospital in Bucharest, Romania. The study included exclusively male patients aged ≥ 18 years with a positive urine culture ($\geq 10^5$ CFU/mL) collected between September 1, 2021, and February 28, 2022. Of the 3,789 positive urine cultures identified during the study period, 733 belonged to male patients.

Only monomicrobial cultures were included in the analysis. Duplicate isolates, polymicrobial cultures, patients with urinary catheters, and cases of asymptomatic bacteriuria were excluded. To avoid data duplication, only the first positive urine culture from each patient was recorded.

Data were collected and organized using Microsoft Excel 2016 and statistically analyzed in Python 3.8.9 (JupyterLab 3.2.4 and Pandas 1.3.4). Variables were expressed as frequencies and percentages and were used to evaluate the bacterial distribution and antimicrobial resistance profiles of the main uropathogens identified during the COVID-19 pandemic period.

7.3. Results

A total of 733 positive urine cultures from male patients were included in the analysis. These were initially classified as Gram-negative (579 cases; 78.99%) and Gram-positive isolates (154 cases; 21.01%). Among Gram-negative bacteria, *Escherichia coli* was the most prevalent pathogen, followed by *Klebsiella spp.*

Within the Gram-positive group, *Enterococcus spp.* was the most frequently isolated microorganism, accounting for the majority of cases.

Table 7.3.1. Bacterial prevalence			
	Bacteria	Nr.	%.
Gram-negative	<i>E. coli</i>	240	32.74
	<i>Klebsiella spp.</i>	199	27.15
	<i>Proteus spp.</i>	96	13.1
	<i>Pseudomonas spp.</i>	44	6.0
Gram-positive	<i>Enterococcus spp.</i>	129	17.6
	<i>Staphylococcus spp.</i>	25	3.41
Total		733	100

The primary objective of this study was to evaluate antimicrobial resistance among uropathogens isolated from male patients across different antibiotic classes. Therefore, the

resistance profiles of the identified bacterial species were analyzed and subsequently grouped into two major categories: Gram-negative and Gram-positive.

Table 7.3.2. Resistance and sensitivity in Gram-negative																
Antibiotic	<i>E.coli</i>				<i>Klebsiella spp.</i>				<i>Pseudomonas spp.</i>				<i>Proteus spp.</i>			
	R		S		R		S		R		S		R		S	
	N r.	%.	Nr .	%.	Nr .	%.	Nr .	%.	N r.	%.	N r.	%.	N r.	%.	N r.	%.
Amoxicillin-clavulanic ac.	78	35.78	14	64.20	11	57.20	82	42.71	7	87.5	1	12.5	28	31.46	61	68.54
Ampicillin	0	0.0	1	100.0	3	42.86	4	57.14	0		0		0		0	
Aztreonam	28	12.44	19	87.56	77	40.74	11	59.26	19	46.34	22	53.66	10	10.99	81	89.01
Trimethoprim-Sulfamethoxazole	9	47.37	10	52.63	11	50.0	11	50.0	0		0		4	66.67	2	33.33
Ceftazidime	23	10.0	20	90.0	74	38.95	11	61.05	15	35.71	27	64.29	11	11.83	82	88.17
Fosfomycin	3	1.44	20	98.56	2	20.0	8	80.0	0	0.0	3	100.0	0	0.0	7	100.0
Imipenem	1	0.43	23	99.57	25	13.59	15	86.41	21	50.0	21	50.0	11	11.7	83	88.3
Levofloxacin	84	36.52	14	63.48	76	40.0	11	60.04	20	51.28	19	48.72	35	38.89	55	61.11

Linezolid	1	50.0	1	50.0	0	0.0	4	100.0	0		0		0		0	
Meropenem	1	0.46	218	99.54	24	12.9	162	87.1	21	47.73	23	52.27	3	3.19	91	96.81
Nitrofurantoin	10	6.45	145	93.55	45	56.96	34	43.04	1	100.0	0	0.0	3	25.0	9	75.0
Penicillin	0	0.0	4	100.0	0	0.0	4	100.0	0		0		0	0.0	3	100.0
Vancomycin	0	0.0	4	100.0	0	0.0	4	100.0	0		0		0	0.0	3	100.0
R – Resistant; S – Sensitivity; Nr. – Number; %. - Percentage																

Within the Gram-positive group, *Enterococcus spp.* was the predominant pathogen identified. The antimicrobial susceptibility analysis demonstrated high resistance rates to levofloxacin (56.7%), whereas resistance to penicillin remained comparatively lower (19.67%).

Table 7.3.3. Resistance and sensitivity in Gram-positive								
Antibiotic	<i>Enterococcus spp.</i>				<i>Staphylococcus spp.</i>			
	R		S		R		S	
	Nr.	%..	Nr.	%..	Nr.	%..	Nr.	%
Amoxicillin-clavulanic ac.	5	83.33	1	16.67	0		0	
Ampicillin	8	6.67	112	93.33	0	0.0	1	100.0
Aztreonam	2	66.67	1	33.33	0		0	

Trimethoprim-Sulfamethoxazole	0	0.0	3	100.0	8	33.33	16	66.67
Ceftazidime	2	66.67	1	33.33	0		0	
Fosfomycin	4	3.6	107	96.4	0	0.0	1	100.0
Imipenem	1	33.33	2	66.67	0		0	
Levofloxacin	55	56.7	42	43.3	9	52.94	8	47.06
Linezolid	1	0.9	110	99.1	1	4.0	24	96.0
Meropenem	0	0.0	3	100.0	0		0	
Nitrofurantoin	2	1.72	114	98.28	2	10.53	17	89.47
Penicillin	24	19.67	98	80.33	13	68.42	6	31.58
Vancomycin	0	0.0	125	100.0	0	0.0	1	100.0
R – Resistance; S – Sensitivity; Nr. – Number; %. - Percentage								

This study included an analysis of overall antimicrobial resistance rates across different age groups for both Gram-negative and Gram-positive bacterial isolates.

Among Gram-negative uropathogens, resistance rates exceeding 30% were observed for amoxicillin–clavulanic acid (43.98%) and levofloxacin (39.16%).

Similarly, the Gram-positive group demonstrated high resistance rates to levofloxacin (56.14%) and penicillin (26.24%), highlighting the limited effectiveness of these agents against a substantial proportion of isolates.

Table 7.3.4. Overall resistance and sensitivity rates												
Antibiotic	Gram-negative				Gram-positive				Total			
	R		S		R		S		R		S	
	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.

Amoxicillin-clavulanic ac.	223	43.98	284	56.02	5	83.33	1	16.67	228	44.44	285	55.56
Ampicillin	3	37.5	5	62.5	8	6.61	113	93.39	11	8.53	118	91.47
Aztreonam	134	24.54	412	75.46	2	66.67	1	33.33	136	24.77	413	75.23
Trimethoprim-Sulfamethoxazole	24	51.06	23	48.94	8	29.63	19	70.37	32	43.24	42	56.76
Ceftazidime	123	22.16	432	77.84	2	66.67	1	33.33	125	22.4	433	77.6
Fosfomycin	5	2.19	223	97.81	4	3.57	108	96.43	9	2.65	331	97.35
Imipenem	58	10.47	496	89.53	1	33.33	2	66.67	59	10.59	498	89.41
Levofloxacin	215	39.16	334	60.84	64	56.14	50	43.86	279	42.08	384	57.92
Linezolid	1	16.67	5	83.33	2	1.47	134	98.53	3	2.11	139	97.89
Meropenem	49	9.02	494	90.98	0	0.0	3	100.0	49	8.97	497	91.03
Nitrofurantoin	59	23.89	188	76.11	4	2.96	131	97.04	63	16.49	319	83.51
Penicillin	0	0.0	11	100.0	37	26.24	104	73.76	37	24.34	115	75.66
Vancomycin	0	0.0	11	100.0	0	0.0	126	100.0	0	0.0	137	100.0
R – Resistance; S – Sensitivity; Nr. – Number; %. - Percentage												

A global analysis of antimicrobial resistance across all investigated antibiotic classes was also performed according to age groups. Patients younger than 40 years exhibited lower resistance rates to most of the tested antibiotics; however, this subgroup included a relatively small number of cases. Overall, antimicrobial resistance showed an increasing trend with advancing age in the male population, suggesting a cumulative effect of comorbidities, healthcare exposure, and previous antibiotic use.

Table 7.3.5. Overall resistance and sensitivity resistance rates by age				
Antibiotic	< 40 years	41-55 years	>55 years	Total

	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S
	N r.	%.	N r.	%.	N r.	%.	N r.	%.	Nr .	%.	Nr .	%.	Nr .	%.	Nr .	%.
Amoxicillin-clavulanic ac.	6	37.5	10	62.5	26	50.0	26	50.0	19 6	44.0 4	24 9	55.9 6	22 8	44.4 4	28 5	55.5 6
Ampicillin	0		0		4 4	44.4 4	5	55.5 6	7	5.83	11 3	94.1 7	11	8.53	11 8	91.4 7
Aztreonam	0	0.0	15	100. 0	8	14.2 9	48	85.7 1	12 8	26.7 8	35 0	73.2 2	13 6	24.7 7	41 3	75.2 3
Trimethoprim-Sulfamethoxazole	0		0		4	100. 0	0	0.0	28	40.0	42	60.0 0	32	43.2 4	42	56.7 6
Ceftazidime	0	0.0	17	100. 0	12	21.4 3	44	78.5 7	11 3	23.3	37 2	76.7	12 5	22.4	43 3	77.6
Fosfomycin	0	0.0	8	100. 0	0	0.0	30	100. 0	9	2.98	29 3	97.0 2	9	2.65	33 1	97.3 5
Imipenem	0	0.0	17	100. 0	5	8.77	52	91.2 3	54	11.1 8	42 9	88.8 2	59	10.5 9	49 8	89.4 1
Levofloxacin	4	26.6 7	11	73.3 3	15	24.1 9	47	75.8 1	26 0	44.3 7	32 6	55.6 3	27 9	42.0 8	38 4	57.9 2
Linezolid	0		0		0	0.0	8	100. 0	3	2.24	13 1	97.7 6	3	2.11	13 9	97.8 9
Meropenem	0	0.0	17	100. 0	5	9.26	49	90.7 4	44	9.26	43 1	90.7 4	49	8.97	49 7	91.0 3
Nitrofurantoin	1	20.0	4	80.0	7	25.0	21	75.0	55 6	15.7 4	29 4	84.2 4	63 9	16.4 9	31 9	83.5 1

Penicillin	0		0		4	44.4	5	55.5	33	23.0	11	76.9	37	24.3	11	75.6
					4		6			8	0	2		4	5	6
Vancomycin	0		0		0	0.0	6	100.	0	0.0	13	100.	0	0.0	13	100.
							0				1	0			7	0
R – Resistance; S – Sensitivity; Nr. – Number; %. - Percentage																

7.4. Discussion

The results of the present study confirm that urinary tract infections in the male population exhibit distinct epidemiological and microbiological characteristics compared to those observed in women. *Escherichia coli* remained the predominant etiological agent; however, its prevalence of approximately 33% was considerably lower than the values reported in most studies conducted in female populations, where it frequently exceeds 60%. In contrast, *Klebsiella spp.* and *Enterococcus spp.* accounted for a significantly larger proportion of cases, a finding that may be explained by the more frequent occurrence of complicated UTIs in men and their association with obstructive urological conditions, urinary instrumentation, and repeated hospitalizations [33,34]. Furthermore, age distribution analysis revealed a clear predominance of cases among patients older than 55 years, confirming the major role of aging and associated comorbidities in the development of male UTIs [35].

Analysis of antimicrobial resistance profiles demonstrated high resistance rates among Gram-negative bacteria, particularly to levofloxacin and amoxicillin–clavulanic acid. These findings are consistent with international epidemiological trends and support the need to reconsider the empirical use of these antibiotics. *Escherichia coli* and *Klebsiella spp.* exhibited substantial resistance to fluoroquinolones and β -lactams, whereas *Pseudomonas spp.* displayed the least favorable susceptibility profiles, including resistance to carbapenems. In contrast, fosfomicin and aminoglycosides maintained high levels of activity, suggesting that they remain valuable therapeutic options for the treatment of UTIs caused by Gram-negative bacteria [36,37].

Regarding Gram-positive bacteria, *Enterococcus spp.* was the predominant uropathogen identified. Although elevated resistance rates to fluoroquinolones were observed, high susceptibility to fosfomicin, vancomycin, and linezolid was preserved. These results are

consistent with those reported in other studies conducted in male populations and international cohorts, confirming the role of these antibiotics in the management of enterococcal urinary tract infections [33,38].

Comparison with data available for female populations consistently demonstrated higher resistance rates among men for most of the antibiotics analyzed. These differences were particularly evident for *Escherichia coli* and *Klebsiella spp.*, suggesting that male UTIs are more frequently associated with predisposing factors and complex clinical settings. These findings support the need for sex-specific therapeutic strategies and emphasize the importance of local microbiological surveillance data when selecting empirical treatment [33,38,39].

7.5. Conclusions

The present study confirms that urinary tract infections in men predominantly affect the elderly population, with more than 80% of cases identified in patients older than 55 years. *Escherichia coli* remained the most common uropathogen, although with a lower prevalence than that typically reported in women, whereas *Klebsiella spp.* and *Enterococcus spp.* contributed more substantially to the overall bacterial distribution. High resistance rates were observed for commonly prescribed antibiotics, particularly levofloxacin and amoxicillin–clavulanic acid, and resistance levels were generally higher than those reported in female populations. In contrast, fosfomycin, aminoglycosides, vancomycin, and linezolid maintained favorable activity. These findings highlight the need to adapt empirical therapy to the specific characteristics of the male population, particularly elderly patients, and underscore the importance of continuous antimicrobial resistance surveillance.

8. Study II: Comparative Analysis of Antimicrobial Resistance Among Uropathogens in Male Patients During and After the COVID-19 Pandemic

8.1. Introduction

The second part of this doctoral thesis aimed to evaluate the impact of the COVID-19 pandemic on bacterial prevalence and antimicrobial resistance among uropathogens isolated from male patients. The results of this study were published in the journal *Medicina* [40].

Urinary tract infections are among the most common bacterial infections worldwide, accounting for more than 150 million cases annually, while the continuous increase in antimicrobial resistance represents a major public health concern [7,41]. During the COVID-19 pandemic, extensive antibiotic use, prolonged hospitalizations, and the increased utilization of invasive medical devices were associated with important changes in infection epidemiology and bacterial resistance patterns [42]. Given the high levels of antibiotic consumption and the elevated resistance rates reported in Romania [10,43], the primary objective of this study was to compare the antimicrobial resistance profiles of uropathogens isolated from male patients during the pandemic and post-pandemic periods. The secondary objective was to evaluate changes in bacterial prevalence between these periods.

8.2. Materials and Methods

A retrospective, observational, single-center study was conducted at the “Prof. Dr. Th. Burghel” Clinical Hospital in Bucharest, one of the leading tertiary urological centers and academic institutions in Romania. The study included exclusively male patients aged ≥ 18 years with positive urine cultures processed in the hospital’s microbiology laboratory.

To evaluate the impact of the COVID-19 pandemic on bacterial prevalence and antimicrobial resistance, the analysis was structured into four distinct six-month intervals: two corresponding to the pandemic period (September 1, 2020–February 28, 2021, and September 1, 2021–February 28, 2022) and two corresponding to the post-pandemic period (September 1, 2023–February 29, 2024, and September 1, 2024–February 28, 2025). The use of identical intervals, including the autumn and winter seasons, was intended to minimize the influence of seasonal variation on bacterial distribution and resistance patterns [31,33].

Only urine cultures with significant bacterial growth ($\geq 10^5$ CFU/mL) and identification of a single microorganism were included. Polymicrobial cultures, duplicate isolates from the same patient, patients with urinary catheters, and cases with incomplete microbiological data were excluded. For each patient, only the first positive urine culture recorded during the study period was included in the analysis. The prevalence of the main uropathogens and their antimicrobial resistance profiles to commonly used antibiotics were evaluated.

Data were collected and organized using Microsoft Excel 2016, while statistical analyses were performed in Python 3.8.9 using JupyterLab 3.2.4 and the Pandas 1.3.4 library.

8.3. Results

Following the analysis of the demographic characteristics of the study population, patients were stratified into two age groups using 55 years as the cutoff value, which has been considered by several authors a relevant threshold for the onset of lower urinary tract symptoms and the increased prevalence of urinary tract infections. The present results demonstrated a higher prevalence of urinary tract infections among elderly patients, with the majority of cases occurring in individuals older than 55 years.

Table 8.3.1. Age distribution			
	<55 years Nr./%.	>55 years Nr./%.	Total
Group I (Pandemic)	173/11.21	1370/88.78	1543
Group II (Post-pandemic)	174/10.77	1441/89.22	1615
Nr. – Number; % . - Percentage			

Regarding the distribution of bacterial pathogens across the two study periods, Gram-negative bacteria showed the highest prevalence, with similar patterns observed in both groups. *Escherichia coli* remained the most frequently isolated uropathogen among male patients, followed closely by *Klebsiella spp.*. A higher prevalence of *Pseudomonas spp.* was observed during the post-pandemic period (10.90%) compared to the pandemic period (7.26%), suggesting a potential increase in healthcare-associated urinary tract infections. Among Gram-positive bacteria, *Enterococcus spp.* remained the most commonly isolated pathogen throughout both periods.

Table 8.3.2. Bacterial prevalence					
		Pandemic Nr.	Pandemic %.	Post-pandemic Nr.	Post-pandemic %.
	<i>E. coli</i>	507	32.86	520	32.20

Gram negative	<i>Klebsiella</i>	400	25.92	397	24.58
	<i>Pseudomonas</i>	112	7.26	176	10.90
	<i>Proteus</i>	154	9.98	129	7.99
Gram positive	<i>Enterococcus</i>	300	19.44	299	18.51
	<i>Staphylococcus</i>	67	4.34	77	4.77
Others		3	0.19	15	1.06
Nr. – Number; %. - Percentage					

This study focused on determining antimicrobial resistance rates among both Gram-negative and Gram-positive bacterial isolates.

Overall resistance rates among Gram-negative uropathogens showed concerning increases during the post-pandemic period, particularly for amoxicillin–clavulanic acid (43.24% vs. 50.37%) and levofloxacin (39.36% vs. 44.55%) when compared with the pandemic period. These findings suggest a progressive decline in the effectiveness of commonly prescribed antibiotics used in the treatment of urinary tract infections.

Among Gram-positive bacteria, resistance patterns remained relatively stable, with only minor variations observed between the pandemic and post-pandemic periods. Notably, levofloxacin exhibited persistently high resistance rates throughout both periods, highlighting the limited utility of this antibiotic against Gram-positive uropathogens.

Table 8.3.3. Overall resistance rates in Gram-negative						
Antibiotic	Gram negative R		Gram negative R		Gram negative R	
	Pandemic		Post-Pandemic		Total	
	Nr.	%.	Nr.	%.	Nr.	%.
Amikacin	126	11.17	170	14.3	296	12.78
Amoxicillin-clavulanic ac.	441	43.24	473	50.37	914	46.66

Aztreonam	241	22.8	123	31.54	364	25.16
Trimethoprim-Sulfamethoxazole	16	38.1	402	46.69	418	46.29
Ceftazidime	246	21.83	318	27.11	564	24.52
Fosfomycin	13	2.73	14	2.8	27	2.76
Imipenem	104	9.41	121	20.1	225	13.18
Levofloxacin	442	39.36	511	44.55	953	41.98
Meropenem	99	8.89	80	24.02	179	12.38
Nitrofurantoin	171	29.58	167	27.97	338	28.77
R – Resistance; Nr. – Number; %. - Percentage						

Tabelul 8.3.4. Overall resistance in Gram-positive						
Antibiotic	Gram positive R		Gram positive R		Gram positive R	
	Pandemic		Post-Pandemic		Total	
	Nr.	%.	Nr.	%.	Nr.	%.
Amikacin	4	6.9		5.56	5	6.58
Ampicillin	39	14.39	35	13.06	74	13.73
Trimethoprim-Sulfamethoxazole	24	39.34	25	29.76	49	33.79

Fosfomycin	12	4.2	14	5.49	26	4.81
Levofloxacin	166	50.46	176	49.16	342	49.78
Linezolid	6	1.77	13	3.83	19	2.8
Nitrofurantoin	13	3.86	20	5.92	33	4.89
Penicillin	137	40.41	164	48.66	301	44.53
Vancomycin	1	0.34	8	2.87	9	1.57
R – Resistance; Nr. – Number; %. - Percentage						

Escherichia coli, the most frequently identified urinary pathogen, exhibited higher resistance rates during the post-pandemic period compared with the pandemic period to several commonly used antibiotics, including levofloxacin, amoxicillin–clavulanic acid, and ceftazidime.

Table 8.3.5. Resistance and sensitivity rates in <i>E. coli</i>									
Antibiotic	<i>E. coli</i> R		<i>E. coli</i> S		<i>E. coli</i> R		<i>E. coli</i> S		p Value
	Pandemic				Post-Pandemic				
	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	
Amikacin	23	4.69	467	95.31	24	4.82	474	95.18	1.00
Amoxicillin-clavulanic ac.	164	33.81	321	66.19	191	40.13	285	59.87	0.049
Aztreonam	60	12.99	402	87.01	25	19.23	105	80.77	0.098
Trimethoprim-Sulfamethoxazole	3	23.08	10	76.92	193	45.09	235	54.91	0.196
Ceftazidime	59	12.04	431	87.96	85	17.21	409	82.79	0.027
Fosfomycin	7	1.55	444	98.45	5	1.07	461	98.93	0.728

Imipenem	4	0.83	479	99.17	2	0.83	238	99.17	1.0
Levofloxacin	181	37.24	305	62.76	221	45.57	264	54.43	0.010
Meropenem	3	0.63	474	99.37	0	0.0	51	100.0	1.0
Nitrofurantoin	48	13.33	312	86.67	39	9.58	368	90.42	0.128
R – Resistance; S – Sensitivity; Nr. – Number; %. - Percentage									

Klebsiella spp., the second most frequently isolated pathogen, demonstrated a notable increase in antimicrobial resistance during the post-pandemic period, particularly to nitrofurantoin, reaching 68.51%.

The most significant increase in resistance following the COVID-19 pandemic was observed for imipenem and meropenem, exceeding 30%, highlighting the potential emergence of resistance to last-line carbapenem antibiotics.

Table 8.3.6. Resistance and sensitivity rates in <i>Klebsiella spp.</i>									
Antibiotic	<i>Klebsiella</i> R		<i>Klebsiella</i> S		<i>Klebsiella</i> R		<i>Klebsiella</i> S		p Value
	Pandemic				Post-Pandemic				
	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	
Amikacin	64	16.71	319	83.29	86	22.11	303	77.89	0.07
Amoxicillin-clavulanic ac.	222	57.81	162	42.19	223	63.35	129	36.65	0.144
Aztreonam	135	38.35	217	61.65	45	39.13	70	60.87	0.969
Trimethoprim-Sulfamethoxazole	8	36.36	14	63.64	144	44.17	182	55.83	0.622
Ceftazidime	139	36.2	245	63.8	145	37.47	242	62.53	0.771

Imipenem	56	15.09	315	84.91	60	32.09	127	67.91	<0.001
Levofloxacin	159	41.3	226	58.7	160	42.67	215	57.33	0.757
Meropenem	55	14.4	327	85.6	26	33.33	52	66.67	<0.001
Nitrofurantoin	110	56.7	84	43.3	124	68.51	57	31.49	0.02
R – Resistance; S – Sensitivity; Nr. – Number; %. - Percentage									

Following the evaluation of antimicrobial susceptibility patterns among Gram-negative uropathogens, the antibiotic susceptibility profile of Gram-positive bacteria was also examined. *Enterococcus spp.*, the most frequently isolated pathogen in this group, showed relatively stable results between the pandemic and post-pandemic periods. Although no major differences were observed, several antibiotics exhibited concerning resistance profiles. The most notable resistance rates were recorded for levofloxacin (48.7% vs. 47.89%), followed by penicillin (32.26% vs. 38.64%) and ampicillin (14.5% vs. 13.06%).

Table 8.3.7. Resistance and sensitivity rates in <i>Enterococcus spp.</i>									
Antibiotic	<i>Enterococcus</i> R		<i>Enterococcus</i> S		<i>Enterococcus</i> R		<i>Enterococcus</i> S		p Value
	Pandemic				Post-Pandemic				
	No.	%.	No.	%.	No.	%.	No.	%.	
Ampicillin	39	14.5	230	85.5	35	13.06	233	86.94	0.720
Fosfomycin	10	3.57	270	96.43	14	5.53	239	94.47	0.377
Levofloxacin	131	48.7	138	51.3	136	47.89	148	52.11	0.915
Linezolid	5	1.82	270	98.18	11	4.1	257	95.9	0.186
Nitrofurantoin	12	4.26	270	95.74	17	6.27	254	93.73	0.382
Penicillin	90	32.26	189	67.74	102	38.64	162	61.36	0.143
Vancomycin	1	0.35	285	99.65	8	2.87	271	97.13	0.040

8.4. Discussion

The results of this study confirm that urinary tract infections in men predominantly affect the elderly population, with a mean age of approximately 70 years. This finding supports the major role of age-related predisposing factors, including benign prostatic hyperplasia, urinary retention, and complex urological conditions, in the development of male UTIs [7,44].

The principal finding of the study was the change in antimicrobial resistance patterns between the pandemic and post-pandemic periods. The results demonstrated a significant increase in resistance among Gram-negative bacteria, a phenomenon that may be explained by the extensive use of antibiotics and the increased selective pressure exerted during the COVID-19 pandemic [45,46]. The most important changes were observed for fluoroquinolones and β -lactams, two antibiotic classes frequently used in the treatment of urinary tract infections.

A particularly important finding was the increase in carbapenem resistance observed during the post-pandemic period, especially among Enterobacterales. This trend is concerning because carbapenems represent one of the last therapeutic options available for severe infections caused by resistant bacteria. In contrast, Gram-positive bacteria showed only limited changes in susceptibility patterns, while vancomycin and linezolid maintained favorable activity [47,48]. These findings highlight the impact of the COVID-19 pandemic on antimicrobial resistance and emphasize the need for continuous local surveillance and periodic updates of therapeutic strategies.

8.5. Conclusions

This study demonstrated that urinary tract infections in men predominantly affect the elderly population and that the COVID-19 pandemic influenced the evolution of antimicrobial resistance. The post-pandemic period was associated with increased resistance, particularly among Gram-negative bacteria, to fluoroquinolones, β -lactams, and carbapenems. These

findings underline the importance of continuous surveillance of local resistance patterns and the adaptation of empirical therapy to current epidemiological trends.

8. Study III: Comparative Evaluation of Antimicrobial Resistance Among Uropathogens in Male and Female Patients

9.1. Introduction

The third part of this doctoral thesis aimed to compare bacterial prevalence and antimicrobial resistance profiles between male and female patients with urinary tract infections. The results of this study were published in the journal *Microorganisms* [49,50]. Urinary tract infections are among the most common bacterial infections worldwide, affecting more than 150 million individuals annually and being associated with extensive antibiotic use [1]. At the same time, the increasing prevalence of antimicrobial resistance has become one of the major challenges facing healthcare systems, particularly regarding the main uropathogens such as *Escherichia coli* and *Klebsiella spp.* [41,51].

Anatomical and functional differences between sexes influence both the prevalence of urinary tract infections and the distribution of the pathogens involved. While women experience a higher incidence of uncomplicated UTIs, infections in men are more frequently associated with obstructive urological conditions, urolithiasis, urinary tract instrumentation, and other complex urological disorders [7,52]. Furthermore, data from Eastern Europe continue to demonstrate high levels of antimicrobial resistance, highlighting the need for local studies that separately evaluate male and female populations [10,43].

The primary objective of this study was to compare bacterial distribution and demographic characteristics between male and female patients, while the secondary objective was to evaluate differences in antimicrobial resistance profiles among the main uropathogens.

9.2. Materials and Methods

A retrospective, observational, single-center study was conducted at the “Prof. Dr. Th. Burghel” Clinical Hospital in Bucharest, a tertiary referral center and one of the leading academic urological institutions in Romania. Male and female patients aged ≥ 18 years with positive urine cultures were included and evaluated during three consecutive six-month periods (September 1–February 28) between 2023 and 2025. The use of identical study intervals was intended to minimize the influence of seasonal variations and allowed direct comparison with previous studies performed within the same institution [39,53].

Only cultures with significant bacterial growth ($\geq 10^5$ CFU/mL) and identification of a single microorganism were included. Cases with lithangiuria, polymicrobial cultures, duplicate results, and patients with urinary catheters were excluded. For each patient, only the first positive urine culture recorded during the study period was included in the analysis. The study evaluated the distribution of the main uropathogens, demographic characteristics, and antimicrobial resistance profiles to commonly used antibiotics.

Data were collected using Microsoft Excel 2016, while statistical analyses were performed in Python 3.8.9 using JupyterLab 3.2.4 and the Pandas 1.3.4 library.

9.3. Results

This study included 3,978 patients with positive urine cultures. Of these, 2,270 were male (57.1%) and 1,708 were female (42.9%). Patients older than 55 years accounted for 79.3% of the total study population, while 20.7% were younger than 55 years.

	<55 years	>55 years	
Female-Sex	575	1133	1708
Male-Sex	247	2023	2270
Table 9.3.1. Age distribution			

Following microbiological analysis of the processed samples, differences were observed in the distribution and prevalence of the identified bacterial pathogens. *Escherichia coli* was the predominant etiological agent in both groups. Among female patients, it showed a higher prevalence of 54.1%, compared with 32.42% among male patients. In contrast, *Klebsiella spp.* was diagnosed more frequently in men (25.81% vs. 15.4% in women).

The observed variations in prevalence according to patient sex are likely influenced by differences in the underlying clinical conditions. Unlike Gram-negative species, which demonstrated important sex-related differences, *Enterococcus spp.* was identified at comparable rates in the two groups (15.63% in women versus 18.68% in men).

		Female		Male	
Group	Gram	Nr.	%.	Nr.	%.
Bacteria	Gram Negative	1369	80.15	1752	77.18

	Gram Positive	339	19.85	518	22.82
Table 9.3.2 Overall bacterial distribution					

		Female Nr.	Female %.	Male Nr.	Male %.
Gram Negative	<i>E. coli</i>	924	54.1	736	32.42
	<i>Klebsiella</i>	263	15.4	586	25.81
	<i>Proteus</i>	123	7.2	201	8.85
	<i>Pseudomonas</i>	59	3.45	229	10.09
Gram Positive	<i>Enterococcus</i>	267	15.63	424	18.68
	<i>Staphylococcus</i>	72	4.22	94	4.14
Table 9.3.3 Bacterial prevalence by species					

The distribution of the different bacterial species did not differ significantly between inpatient and outpatient subgroups in either sex.

Table 9.3.4. Uropathogens' distribution according to hospitalization					
		Females		Males	
		Hospitalized No./%	Ambulatory No./%	Hospitalized No./%	Ambulatory No./%
Gram Negative	<i>E. coli</i>	326/35.3	598/64.7	191/39.5	445/60.5
	<i>Klebsiella</i>	101/38.4	162/61.6	275/46.9	311/53.1
	<i>Proteus</i>	57/46.3	66/53.7	84/41.8	117/58.2
	<i>Pseudomonas</i>	23/39.0	36/61.0	103/45.0	126/55.0
Gram Positive	<i>Enterococcus</i>	112/41.9	155/58.1	179/42.2	245/57.8
	<i>Staphylococcus</i>	28/38.9	44/61.1	33/35.1	61/64.9
Pearson Chi-Square		8.364		10.077	
p Value		0.137		0.073	

Regarding susceptibility to different antibiotic classes, *Escherichia coli* demonstrated important differences between the two sexes. As the predominant etiological agent in both populations, it exhibited higher resistance rates to trimethoprim–sulfamethoxazole among male patients (44.65% vs. 32.89%). Similarly, higher resistance rates were identified in men for levofloxacin (43.27% vs. 30.78%) and amoxicillin–clavulanic acid (40.18% vs. 27.19%).

Antibiotic	<i>E. coli</i> R	<i>E. coli</i> S	<i>E. coli</i> R	<i>E. coli</i> S	p Value
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	Females				Males				
	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	
Amikacin	75	8.29	830	91.71	33	4.69	670	95.31	0.239
Amoxicillin-clavulanic ac.	248	27.19	664	72.81	272	40.18	405	59.82	0.012
Aztreonam	53	8.94	540	91.06	50	16.34	256	83.66	<0.001
Trimethoprim-Sulfamethoxazole	98	32.89	200	67.11	196	44.65	243	55.35	0.001
Ceftazidime	92	10.07	822	89.93	113	16.17	586	83.83	<0.001
Fosfomycin	2	0.23	861	99.77	10	1.53	644	98.47	0.004
Imipenem	4	0.45	891	99.55	5	1.13	438	98.87	0.151
Levofloxacin	281	30.78	632	69.22	296	43.27	388	56.73	0.023
Meropenem	2	0.23	858	99.77	2	0.82	242	99.18	0.178
Nitrofurantoin	38	5.28	682	94.72	49	8.86	504	91.14	0.012
Table 9.3.5. Resistance and sensitivity rates in <i>E. coli</i>									

For *Klebsiella spp.*, the second most frequently isolated urinary pathogen among male patients, a distinct resistance profile was observed within the study cohort (Table 9.3.9). Significantly higher antimicrobial resistance rates were identified in men for amoxicillin–clavulanic acid (60.6% vs. 43.25%), levofloxacin (40.18% vs. 27.91%), aztreonam (37.4% vs. 27.27%), and ceftazidime (36.23% vs. 24.03%).

Antibiotic	Klebsiella R		Klebsiella S		Klebsiella R		Klebsiella S		p Value
	Femei				Bărbați				
	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	
Amikacin	27	10.38	233	89.62	109	19.33	455	80.67	0.069
Amoxicillin-clavulanic ac.	109	43.25	143	56.75	323	60.6	210	39.4	0.034
Aztreonam	48	27.27	128	72.73	98	37.4	164	62.6	0.027
Trimethoprim-Sulfamethoxazole	23	31.08	51	68.92	151	43.64	195	56.36	0.046

Ceftazidime	62	24.03	196	75.97	204	36.23	359	63.77	<0.001
Imipenem	13	5.24	235	94.76	82	23.1	273	76.9	0.012
Levofloxacin	72	27.91	186	72.09	223	40.18	332	59.82	<0.001
Meropenem	16	6.45	232	93.55	46	18.18	207	81.82	0.014
Nitrofurantoin	61	55.96	48	44.04	180	65.69	94	34.31	0.075
Table 9.3.6. Resistance and sensitivity rates in <i>Klebsiella</i>									

Enterococcus spp. exhibited a similar antimicrobial resistance profile, with the highest resistance rates observed for levofloxacin and penicillin (Table 9.3.12). Among the male population, resistance exceeded 30% for penicillin and reached 48.83% for levofloxacin. In contrast, fosfomycin, linezolid, nitrofurantoin, and vancomycin maintained high susceptibility rates.

Antibiotic	Enterococcus R		Enterococcus S		Enterococcus R		Enterococcus S		p Value
	Female				Male				
	Nr.	%.	Nr.	%.	Nr.	%.	Nr.	%.	
Ampicillin	41	16.02	215	83.98	46	12.23	330	87.77	0.176
Fosfomycin	11	4.3	245	95.7	18	4.92	348	95.08	0.718
Levofloxacin	112	42.75	150	57.25	187	48.83	196	51.17	0.128
Linezolid	9	3.54	245	96.46	14	3.67	367	96.33	0.931
Nitrofurantoin	17	6.61	240	93.39	22	5.68	365	94.32	0.628
Penicillin	85	33.6	168	66.4	126	33.33	252	66.67	0.945
Vancomycin	12	4.69	244	95.31	9	2.26	390	97.74	0.085
Table 9.3.7. Resistance and sensitivity rates in <i>Enterococcus</i>									

9.4. Discussion

The results of this study revealed important demographic and microbiological differences between male and female patients. Male patients had a significantly higher mean age, with most cases diagnosed after the age of 55 years, consistent with the role of obstructive conditions, prostatic disease, and increased healthcare exposure associated with aging [11,52].

Although *Escherichia coli* remained the predominant uropathogen in both sexes, its prevalence was significantly lower in men than in women, whereas *Klebsiella spp.*, *Pseudomonas aeruginosa*, and *Enterococcus spp.* were more frequently identified in the male population. These findings support the existence of a distinct epidemiological profile of male urinary tract infections, characterized by a higher proportion of complicated and healthcare-associated infections.

The analysis of antimicrobial resistance demonstrated that male patients exhibited significantly higher resistance rates for most Gram-negative bacteria and for the antibiotics most commonly used in clinical practice, particularly fluoroquinolones, amoxicillin–clavulanic acid, and trimethoprim–sulfamethoxazole. These differences were especially evident for *Escherichia coli* and *Klebsiella spp.*, the latter displaying the most unfavorable resistance profile, including resistance to carbapenems. These findings are consistent with recent epidemiological data and suggest that male urinary tract infections are more frequently associated with predisposing factors such as urinary retention, prostatic involvement, urological procedures, and repeated antibiotic exposure [54,55]. In contrast, aminoglycosides and carbapenems generally maintained good activity against the major Gram-negative uropathogens.

For Gram-positive bacteria, sex-related differences were less pronounced. *Enterococcus spp.* and *Staphylococcus spp.* exhibited relatively stable resistance patterns, maintaining high susceptibility to vancomycin, linezolid, fosfomycin, and nitrofurantoin. These findings suggest that the impact of sex on antimicrobial resistance is more evident among Gram-negative bacteria, which also represent the predominant etiological agents of urinary tract infections in the studied population [30,47].

9.5. Conclusions

This study demonstrated significant differences between male and female patients regarding age, bacterial distribution, and antimicrobial resistance profiles. Men showed a higher prevalence of uropathogens associated with complicated infections and significantly higher resistance rates among most Gram-negative bacteria, particularly *Escherichia coli* and *Klebsiella spp.*. In contrast, Gram-positive bacteria exhibited relatively stable susceptibility profiles, with preserved activity of vancomycin and linezolid. These findings

highlight the importance of local epidemiological surveillance and a sex-specific approach to optimizing empirical treatment strategies for urinary tract infections.

10. Conclusions and Original Contributions

This doctoral thesis contributes to the current understanding of urinary tract infection epidemiology and antimicrobial resistance by analyzing a large cohort of patients evaluated at a tertiary urological center in Romania. The originality of the research derives from its integrated assessment of bacterial prevalence and antimicrobial resistance patterns, with a particular focus on the male population, which remains underrepresented in the scientific literature.

One of the main contributions of this thesis is the development of one of the largest studies dedicated exclusively to urinary tract infections in men in Romania. The results confirmed the predominant role of *Escherichia coli* in the aetiology of UTIs while also highlighting the increased prevalence of microorganisms commonly associated with complicated infections, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterococcus spp.*, thereby defining a distinct microbiological profile of the male population.

An important contribution is represented by the comparative analysis between male and female patients, which demonstrated significant differences in both bacterial distribution and antimicrobial susceptibility profiles. Male patients exhibited a higher prevalence of pathogens associated with complicated infections and higher resistance rates to several antibiotic classes commonly used in clinical practice. These findings support the need for sex-specific therapeutic strategies and adaptation of empirical treatment according to patient characteristics.

Another major contribution of this thesis is the evaluation of the impact of the COVID-19 pandemic on antimicrobial resistance. The comparative analysis of pandemic and post-pandemic periods revealed significant changes in susceptibility patterns among the main uropathogens, demonstrating that the evolution of bacterial resistance may be influenced by changes in medical practice and antibiotic use during this period.

Through the individual analysis of the principal bacterial species, distinct resistance and susceptibility patterns were identified, with direct implications for empirical therapy

selection and the development of local antibiotic stewardship programs. The data generated provide updated information regarding the local epidemiology of urinary tract infections and offer scientific support for optimizing therapeutic protocols in urological practice.

The scientific value of this research is further supported by the publication of the results in internationally indexed journals and their integration into the international scientific literature. Through the size of the analyzed cohorts, the practical applicability of the findings, and their relevance to clinical practice, this thesis contributes to strengthening current knowledge on urinary tract infection epidemiology and antimicrobial resistance, while providing a foundation for the development of modern diagnostic, therapeutic, and antibiotic stewardship strategies.

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