„CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

PREVALENCE AND ANTIMICROBIAL RESISTANCE OF UROPATHOGENS IN THE FEMALE POPULATION IN ROMANIA

SUMMARY OF THE DOCTORAL THESIS

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LIST OF PUBLISHED SCIENTIFIC PAPERS

Articles published in scientific journals (from the doctoral thesis – first author):

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2. **Mareş, C.,** Petca, R.-C., Popescu, R.-I., Petca, A., Geavlete, B. F., & Jinga, V. (2023). Uropathogens' Antibiotic Resistance Evolution in a Female Population: A Sequential Multi-Year Comparative Analysis. *Antibiotics*, *12*(6), 948. https://doi.org/10.3390/antibiotics12060948
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Articles published in scientific journals (before and during the doctoral studies regarding the phenomenon of antibiotic resistance):

1. ***A Clinical Perspective on the Antimicrobial Resistance Spectrum of Uropathogens In a Romania Male Population,*** C.B. Chibelean, R.C. Petca, **C. Mares,** R.I. Popescu, B. Eniko, C. Mehedintu, A. Petca, Microorganisms 2020, 8, 848; doi:10.3390/microorganisms8060848

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2. ***Antibiotic resistance profile of common uropathogens implicated in urinary tract infections in Romania,*** R.C. Petca#, R.I. Popescu#, **C. Mares#**, A. Petca, C. Mehedintu, I. Sandu, N. Maru. Farmacia, 2019, 67(6): 994-1004.

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4. ***Heterogeneity of Antibiotics Multidrug-Resistance Profile of Uropathogens in Romanian Population,*** Răzvan-Cosmin Petca, Silvius Negoiță, **Cristian Mareș***, Aida Petca*, Răzvan-Ionuț Popescu and Călin Bogdan Chibelean, Antibiotics 2021, 10, 523. https://doi.org/10.3390/antibiotics10050523

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5. ***Urinary infections in a Romanian population: antimicrobial resistance of uropathogens – a multiregional study*** , Aurel Rusu#, Aida Petca#, Cristian Mares#, Razvan-Cosmin Petca*, Razvan-Ionut Popescu, Silviu Negoita, Razvan-Alexandru Danau, Calin Bogdan Chibelean, Viorel Jinga, Farmacia 2022, Vol 70, 5. https://doi.org/10.31925/farmacia.2022.5.19

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1. Notions of epidemiology and microbiology

Urinary tract infections (UTIs) are a common pathology, affecting mainly the female population, with early onset and relatively high recurrence rates. Incidence is influenced by age, sexual activity, pregnancy and institutionalization, and women are consistently at higher risk than men. UTIs are a major cause of presentation to the doctor both in outpatient and in hospital settings, with a significant impact on quality of life [1,2].

From an etiological point of view, most UTIs are of bacterial origin, with gram-negative uropathogens being dominant. Uropathogenic Escherichia coli (UPEC) is the main agent involved, responsible for most community-acquired infections, followed by Klebsiella spp., Proteus spp. and Pseudomonas spp., which are more frequently associated with complicated UTIs, urinary stones, catheterization and the hospital environment. Gram-positive uropathogens, such as Enterococcus spp. and Staphylococcus spp., have a lower share, but are relevant in certain risk groups [3,4].

UPEC is characterized by a complex arsenal of virulence factors, including adhesins, toxins, iron-binding systems and biofilm formation. These contribute to persistence, recurrence and treatment failure. Similarly, Klebsiella spp. and Pseudomonas aeruginosa exhibit advanced virulence and resistance mechanisms, including the production of extended-spectrum beta-lactamases (ESBLs) and multidrug-resistant phenotypes, while Proteus mirabilis, through its urease activity, promotes urine alkalinization, infection lithiasis and catheter obstruction [5,6].

In the hospital setting, healthcare-associated UTIs are frequently related to urinary devices and are characterized by an increased prevalence of multidrug-resistant strains, especially E. coli and Klebsiella spp., but also Enterococcus spp. These infections are often more severe, may progress to pyelonephritis or urosepsis and require complex, time-consuming and costly treatments [7].

Overall, UTI represents a major public health problem through frequency, recurrence, severity and economic impact, and the central role of bacterial uropathogens, biofilm and antimicrobial resistance underlines the need for effective prevention strategies, correct etiological diagnosis and rational use of antibiotics, adapted to the clinical context and at-risk populations [8].

2. Understanding antibiotic resistance

Antimicrobial resistance (AMR) occurs when microorganisms no longer respond to antimicrobial treatments, transforming common infections into difficult or impossible to treat diseases. Although AMR is a natural process linked to the genetic adaptation of pathogens, the excessive and uncontrolled use of antibiotics in human, veterinary medicine and agriculture has dramatically accelerated this phenomenon, making it a major public health emergency worldwide [9].

At the microbiological level, antibiotic resistance can be intrinsic or acquired and varies between bacterial species and strains. Its assessment is made by the minimum inhibitory concentration, and bacteria can acquire resistance genes including through horizontal transfer. There are pathogens with natural resistance to certain classes of antibiotics, and repeated exposure to antimicrobials favors the selection and expression of induced resistance mechanisms [10].

The main mechanisms of resistance include limiting antibiotic absorption, inactivation of the substance, modification of the target of action and active efflux. Gram-negative bacteria possess all these mechanisms, including an outer membrane barrier, modified porins and biofilm, while in Gram-positive bacteria, target modification and efflux predominate. Inactivating enzymes, such as beta-lactamases, and efflux pumps play a central role in the emergence of multidrug-resistant strains [11].

The global impact of antibiotic resistance is alarming: millions of deaths are attributed annually to infections with multidrug-resistant bacteria, exceeding the mortality of other major infectious diseases. International reports highlight high rates of resistance to common uropathogens, such as Escherichia coli, Klebsiella spp., Staphylococcus spp. or Pseudomonas spp., including the emergence of pan-drug-resistant strains, which severely limit therapeutic options and increase medical costs [12,13].

At regional level, knowledge of local resistance rates is essential to guide empirical treatment, especially in severe urinary tract infections. In Romania, excessive antibiotic use, low levels of health education, and poor reporting of AMR contribute to high mortality associated with this phenomenon. Effective control of AMR requires coordinated measures of antibiotic stewardship, public education, epidemiological surveillance, and interdisciplinary collaboration, both at national and international levels [14].

3. Clinical risk factors and the influence of the Covid-19 pandemic on antibiotic resistance

Urinary tract infections (UTIs) can be classified into localized and systemic types, the differentiation being closely related to the presence of risk factors. Localized UTIs usually occur in young, healthy women without structural or neurological abnormalities, without pregnancy or immunosuppression, while systemic UTIs are associated with urinary obstruction, chronic kidney disease, kidney transplantation, pregnancy, urinary stones, neurological diseases and the use of urinary devices such as catheters or stents [15].

General risk factors for UTIs include low fluid intake, decreased urine output, urinary stones, constipation, urinary retention and catheterization. In women, the risk is increased by anatomical features, sexual activity, use of spermicides or diaphragms, pregnancy and postmenopausal hormonal changes such as vaginal atrophy or genital prolapse, which are often accompanied by hospitalization and antibiotic use [16].

The development of bacterial resistance, especially in the community setting, is closely linked to the excessive use of antibiotics in human, veterinary and agricultural medicine. Certain factors are associated with an increased risk of UTI with multidrug-resistant organisms, the most important being urinary catheterization, institutionalization, recent hospitalizations and history of antimicrobial treatment, while other factors, such as age or history of UTI, have a possible or contributory role [17,18].

The COVID-19 pandemic has significantly accentuated the problem of antibiotic resistance through the unjustified use of antimicrobials, frequently prescribed prophylactically for viral infections. Although concomitant bacterial infections were rare, antibiotics were administered in most cases, favoring the selection and spread of multidrug-resistant strains, especially in the hospital setting [19].

Recent data show an alarming increase in MDR strains during the pandemic and post-pandemic period, including Enterobacteriaceae resistant to reserve antibiotics. This evolution has been amplified by the reliance on empirical therapy, diagnostic limitations, disruption of infection control programs and antibiotic stewardship, underlining the need to resume and strengthen strategies for prevention, surveillance and rational use of antibiotics to limit the long-term impact of AMR [20].

4. Working hypothesis and general objectives

The paper starts from the hypothesis that the regional variability of antibiotic resistance of uropathogens, insufficiently documented in Romania in recent decades, significantly influences the effectiveness of the treatment of urinary tract infections in women, with the objective of evaluating the prevalence of etiological agents, resistance profiles, evaluating multi-drug resistant (MDR) strains, clinical risk factors and integrating these data into a comparative model that allows the optimization of therapeutic strategies based on current epidemiological evidence.

5. General research methodology

The research methodology consists of a cross-sectional retrospective study conducted on consecutive patients with UTI presented as outpatients or hospitalized in a tertiary urological center, in three distinct time intervals, with systematic collection of ethically approved demographic, clinical and bacteriological data, analysis of urine samples according to CLSI/EUCAST standards and descriptive and inferential statistical processing using SPSS and Excel, to evaluate the dynamics of antibiotic resistance of uropathogens and associated risk factors.

6. Study: Evaluation of antibiotic resistance and susceptibility rates of uropathogens in the female population in Romania – in relation to clinical data

The doctoral thesis study is a cross-sectional retrospective study, which analyzed anonymized medical data from patients evaluated in a tertiary urological center, including 1,708 cases with significant bacteriuria selected from 15,863 urine cultures, during three comparative intervals, pre-, intra- and post-pandemic, with the integration of demographic information for the entire batch and detailed clinical data for hospitalized patients, for final statistical processing.

Urinary cultures were processed by seeding on selective media (Columbia blood agar, lactose agar and, if necessary, Chapman), incubated for 24 hours at 37°C, only pure cultures with significant bacteriuria >10^5 CFU/mL determined automatically by the Vitek 2 system or manually in certain cases were included in the analysis, and the identification of bacterial species was performed phenotypically, based on standard morphological and biochemical characteristics, by the microbiologist, the data obtained being subsequently integrated into the study analysis.

The antimicrobial susceptibility of bacterial strains was determined by the disk diffusion method (Kirby–Bauer), according to CLSI and EUCAST standards, using the standardized inoculum at 0.5 McFarland and the controlled placement of antibiotic disks on appropriate culture media, followed by 18–24 hour incubation and interpretation of the diameters of the inhibition zones by reference to the official sensitivity thresholds, especially for enterobacteria such as E. coli, Klebsiella spp. and Proteus spp.

6.1 Results

6.1.1 General data and age group stratification

The study, conducted between 2018 and 2023 in a tertiary urology center in Bucharest, at the “Prof. Dr. Th. Burghele” Clinical Hospital, comparatively analyzed the evolution of antibiotic sensitivity and resistance of uropathogens in 1,708 patients with UTI over three distinct six-months intervals, highlighting the predominance of Escherichia coli infections and the majority share of gram-negative bacteria in the global etiological structure. In the studied group, gram-negative uropathogens predominated (80,15%), with Escherichia coli as the main etiological agent, and the analysis by age groups and periods revealed a progressive increase in the incidence of UTI with advancing age, the distribution of cases following an approximately Gaussian model, with a peak between 50–70 years and a mean age of approximately 60 years, which suggests a relatively homogeneous population impact and a concentration of infections among middle-aged and elderly women.

6.1.2 Evaluation of total resistance and sensitivity rates of gram-negative uropathogens to common antibiotics

In the analyzed group, Gram-negative uropathogens were dominant and included mainly Escherichia coli (the most frequent agent), followed by Klebsiella spp., Proteus spp. and Pseudomonas spp., each with a distinct sensitivity/resistance profile. For E. coli, minimal resistances to reserve antibiotics (carbapenems - imipenem 0.43% and meropenem 0.21%)

and fosfomycin (0.21%), moderate resistances to amikacin (8.11%) and ceftazidime (9.95%), respectively a less robust sensitivity to nitrofurantoin (73.8%), while the highest resistances were to amoxicillin–clavulanic acid (26.83%) and levofloxacin (30.41%), with statistically significant differences in the distribution of the response between periods for most of the antimicrobials evaluated (Chi-square test). Klebsiella spp. showed relatively low resistance to carbapenems (imipenem 4.94%, meropenem 6.09%) and amikacin (10.26%), but increased resistance to ceftazidime (23.57%), levofloxacin (27.37%) and especially to amoxicillin–clavulanic acid (41.44%), some variations being dependent on the period analyzed. Proteus spp. maintained a good profile for amikacin (R=4.06%), ceftazidime (R=8.94%) and carbapenems (imipenem R 4.06%, meropenem R 1.62%), but had relevant resistance to amoxicillin–clavulanic acid (26.01%) and levofloxacin (33.33%). In contrast, Pseudomonas spp., although the least common Gram-negative, had an alarming resistance profile, with no antibiotic with resistance below 30% (amikacin 30.5%, meropenem 35.59%, imipenem 38%, ceftazidime 44.06%, levofloxacin 52.54%), suggesting selection pressure and major therapeutic difficulties.

Among Gram-positives, Enterococcus spp. was the main uropathogen, with very good sensitivities to linezolid (91.76%) and fosfomycin (91.76%), high sensitivity to vancomycin (91.38%) and nitrofurantoin (89.55%), and a favorable profile to ampicillin (80.52%); instead, the highest resistances were observed to penicillin (31.83%) and especially to levofloxacin (41.94%), some antimicrobials (e.g. fosfomycin, linezolid, vancomycin) showing statistically significant variations between periods. Staphylococcus spp., less common, had a preserved efficiency for linezolid (S=87.5%) and nitrofurantoin (S=75%), but showed the highest resistance to penicillin (R=52.77%), with an intermediate profile for trimethoprim-sulfamethoxazole (S=70.83%), ceftazidime (S=71.42%) and levofloxacin (S=69.44%); in addition, for some antibiotics (e.g. amikacin, ceftazidime) statistically significant changes in the sensitivity/resistance distribution over time were observed, suggesting a resistance dynamics that should be carefully monitored in clinical practice.

6.1.3 Overall assessment of antibiotic resistance rates of all uropathogens

In the total group analyzed, Gram-negative uropathogens were predominant (80.15%), presenting overall the lowest resistance rates to fosfomycin (0.21%) and to carbapenems - meropenem (2.99%) and imipenem (3.21%) - followed by nitrofurantoin (7.59%), amikacin (9.13%) and ceftazidime (13.95%), while considerably higher resistances were observed for amoxicillin–clavulanic acid (29.07%) and especially for fluoroquinolones, levofloxacin having the highest resistance rate (31.04%); In parallel, Gram-positive uropathogens maintained very good sensitivity to fosfomycin, linezolid and vancomycin, as well as to nitrofurantoin and ampicillin, but showed significant resistance to penicillin (36.28%) and, similar to Gram-negative germs, to levofloxacin (37.75%), and Chi-square statistical analysis confirmed significant differences between the two bacterial groups for common antibiotics (fosfomycin, levofloxacin, nitrofurantoin), highlighting the existence of distinct antimicrobial response patterns with direct implications in the choice of empirical therapy.

6.1.4 Trends in the evolution of antibiotic resistance rates of uropathogens during the evaluated periods.

The evolution of resistance showed for Escherichia coli a progressive increase especially to common antibiotics, especially to fluoroquinolones (approximately 30% resistance in the last period evaluated), while fosfomycin and carbapenems remained with resistances below 1%. For Klebsiella and Proteus spp. there were fluctuating variations without overall statistical significance, but with consistently high levels of resistance to frequently used antibiotics. Pseudomonas spp. was the only pathogen with a statistically significant increase in resistance, reaching peaks of over 60–80% during the pandemic period, which represents the most important epidemiological signal of the study.

Enterococcus spp. maintained a relatively stable profile, but with persistently high resistance to fluoroquinolones (approximately 35–50%), while sensitivity to linezolid and fosfomycin remained high. Staphylococcus spp. also showed overall stability, with consistently high resistance to penicillin (approximately 50%) and retained efficiency for reserve antibiotics. Overall, Gram-positive germs did not demonstrate a statistically significant increase in resistance, but the maintenance of these values warrants continued monitoring.

6.1.5 Trends in antibiotic susceptibility rates of uropathogens during the evaluated periods.

Escherichia coli remained the dominant uropathogen, with generally good sensitivities to reserve antibiotics, but with a visible decrease in common antibiotics: amoxicillin–clavulanic acid decreased from approximately 79% to 66%, and levofloxacin from 69% to just under 67%. In contrast, fosfomycin increased steadily to over 95% sensitivity, and carbapenems remained high, above 90%, although with a slight downward trend. Klebsiella and Proteus spp. showed undulating variations, with unstable sensitivity to beta-lactams and fluoroquinolones, but maintaining good values for aminoglycosides and carbapenems. Pseudomonas spp. showed the greatest fluctuations, with a decrease in sensitivity during the pandemic period (for example, for levofloxacin up to 13%) followed by partial recovery, being the only pathogen with statistically significant changes, which indicates an unstable microbiological profile that is difficult to predict clinically.

Enterococcus spp. maintained high susceptibility to linezolid, fosfomycin and nitrofurantoin (approximately 90%), but consistently lower values to fluoroquinolones, which dropped towards 50% in the final period. Ampicillin even showed an increase in susceptibility to over 85%, while vancomycin showed a significant post-pandemic decrease, to almost 80%. Staphylococcus spp. had a weaker overall profile, with low susceptibility to penicillin (40%) and wide fluctuations for other classes, but linezolid remained stably effective (between 85 and 90%). Although statistically these variations are not generalizable, the clinical trend suggests a slow decrease in susceptibility to commonly used antibiotics and the need for continuous monitoring.

6.1.6 Evaluation of multidrug resistance (MDR) rates of uropathogens in the female population

Multidrug resistance (MDR) of uropathogens is a major public health problem, defined as non-susceptibility to ≥3 classes of antibiotics and associated with prolonged hospitalizations and limited therapeutic options. In the study group, MDR strains were dominated by Gram-negative bacteria, especially Escherichia coli and Klebsiella spp., to which the most frequent resistances involved the common antibiotics: amoxicillin–clavulanic acid (over 100 MDR cases in E. coli and almost universal resistance in Klebsiella MDR) and fluoroquinolones. The phenotypic profile was extremely heterogeneous, with 25 unique combinations of resistance to E. coli and 20 to Klebsiella, suggesting complex adaptive mechanisms and the possible presence of the ESBL phenotype. In contrast, fosfomycin and nitrofurantoin were rarely involved in these patterns, and resistance to carbapenems remained exceptional (only 2 strains resistant to imipenem), which maintains them as reserve options in complicated infections; these data support the need for continuous epidemiological monitoring and strict antibiotic stewardship.

6.1.7 Antimicrobial resistance profile in relation to clinical data

Integrating clinical factors is essential for understanding the incidence of UTI and the risk of selection of resistant strains, as comorbidities can influence both susceptibility to infection, the distribution of uropathogens, and the likelihood of MDR; in the post-pandemic analysis (2022–2023) of 524 patients, the most common associated factors were UTI in the past 12 months (187 cases), diabetes (148 cases), chronic kidney disease (95 cases), and active urogenital neoplasia (74 cases). Pearson Chi-square test revealed significant associations between the type of uropathogen and several clinical factors, including recent UTI ($p<0.05$) and diabetes ($p<0.001$), suggesting that these comorbidities shape the etiology of the current episode and should be considered in risk stratification and choice of empirical treatment; In contrast, recent urogenital surgery and immunocompromised status did not demonstrate significant associations in this group.

6.2 Discussions

UTIs remain some of the most common bacterial infections in medical practice, with a major impact especially in women, where anatomical particularities, hormonal variations and behavioral factors increase susceptibility; although most episodes are localized in the lower urinary tract (cystitis), lack of treatment or inadequate treatment can allow the ascent to the upper tract, with pyelonephritis and complicated, systemic forms, which increase morbidity and the need for hospitalization [21]. In addition, the incidence of UTIs and the microbiological profile are influenced by age: in young groups the frequency is lower, then increases in perimenopause and especially after 60 years, when comorbidities and predisposing factors are more often associated, which also explains the increase in recurrences; in the same direction, the literature shows an increase in asymptomatic bacteriuria with advancing age, with much higher values in the elderly and in institutionalized people, similar data to the work published with thesis data in 2024 [22, 23].

In parallel, antimicrobial resistance has become a central determinant of UTI management in the last two decades, with the emergence of MDR strains and the increasing difficulty of empirical treatment; therefore, resistance surveillance is no longer just an epidemiological tool, but a practical benchmark for empirical therapy recommendations and locally adapted “antibiotic stewardship” programs [15]. In the Romanian context, the issue is amplified by the high level of resistance reported at European level and the still insufficient underreporting, which reduces the quality of decision-making support and may maintain antibiotic pressure through non-optimized empirical uses [24], and the present studies with loco-regional data represent a real tool of help to clinicians in our country in the treatment of these infections [25,26].

Against this background, the discussed work aims to evaluate the resistance and sensitivity of uropathogens involved in UTI in the female population in Romania, to describe the distribution by age groups, to follow the short and medium-term evolution (including in the context of pandemic pressures) and to estimate the burden of MDR, while integrating associated clinical factors (e.g. UTI in the last year, diabetes, chronic kidney disease, neoplasia) for risk stratification and individualization of therapy. From the perspective of the discussed results, the etiology is dominated by gram-negatives, with Escherichia coli as the main uropathogen (approximately 54% of the total), followed by Klebsiella spp., and in the case of gram-positives, Enterococcus spp. and, much less frequently, Staphylococcus spp. (approximately 4% of cases) predominate. Consequently, updating the guidelines based on loco-regional data and strengthening standardized reporting become essential for optimizing empirical treatment and reducing the selection of resistant strains.

Conclusions and personal contributions

The paper confirms that UTI in women is a critical area in the current context of antimicrobial resistance, and the integrated microbiological, clinical and epidemiological analysis provides a current picture of the pressure exerted by resistant strains in urological practice. The results corroborate international trends, but highlight important loco-regional particularities, highlighting the decrease in susceptibility to frequently used antibiotics and the increase in the incidence of MDR strains. By correlating microbiological data with associated clinical factors, the study supports the need for a personalized approach to treatment, with an emphasis on prevention, reducing recurrences and limiting the inappropriate use of antibiotics. In this sense, modern management of UTI must be multidisciplinary, guided by updated local data and integrated into stewardship strategies adapted to the epidemiological reality.

The major objectives of the research were achieved by detailed characterization of the distribution of uropathogens and susceptibility profiles in the female population. Escherichia coli remains the dominant agent (approximately 54% of cases), followed by Enterococcus spp. and Klebsiella spp. (approximately 15% each), with a clear increase in the incidence of UTI with age, especially after 60 years. The highest resistances were consistently observed to fluoroquinolones and beta-lactam combinations frequently used empirically, while carbapenems, aminoglycosides and certain reserve molecules retain better susceptibilities. The short- and medium-term evolutionary analysis suggested a generally negative trend, with clear statistical significance for Pseudomonas spp., but with percentage signals of worsening also for the other pathogens. The MDR assessment demonstrated an important burden (264 strains out of 1708), with repetitive resistance profiles centered on aminopenicillins and fluoroquinolones, and the analysis of clinical factors confirmed the major role of UTI recurrence, diabetes and chronic kidney disease in the selection of resistant strains.

The personal contribution of the work consists in providing a coherent set of loco-regional data useful directly in clinical practice, facilitating the orientation of empirical treatment when it is inevitable, without substituting the fundamental principle of antibiogram-guided therapy. The study raises an alarm regarding the unfavorable position of Romania in the European resistance landscape and argues for the need to strengthen stewardship programs. The limitations of the research are represented by the monocentric character, the absence of behavioral data and the exclusively phenotypic analysis indicating clear directions of development, represented by multicentric national databases, the integration of socio-behavioral factors and the use of genomic methods (WGS) for mapping resistance mechanisms. These future directions do not only represent a continuation of research, but an essential condition for the long-term control of the antimicrobial resistance phenomenon.

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