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**“CAROL DAVILA” UNIVERSITY OF MEDICINE AND
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DOCTORAL SCHOOL
THE FIELD OF MEDICINE

***Clinical, Paraclinical, and Etiopathogenic Characteristics
and Evolution in Patients with Acute Obstructive
Pyelonephritis***

SUMMARY OF THE DOCTORAL THESIS

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LIST OF SCIENTIFIC PUBLICATIONS RELATED TO THE DOCTORAL THESIS

1. **Chițu, M.-C.**; Salmen, T.; Răducanu, P.-R.; Pălimariu, C.-M.; Salmen, B.-M.; Stoian, A.P.; Jinga, V.; Mischianu, D.L.D. Clinical Characteristics, Microbiological Spectrum, Biomarkers, and Imaging Insights in Acute Pyelonephritis and Its Complicated Forms—A Systematic Review. *Medicina* **2026**, *62*, 222. ISI Indexed - IF 2.4. Q1. Link: <https://doi.org/10.3390/medicina62010222>
2. **Chițu, M.-C.**; Caragea, D.-C.; Pălimariu, C.-M.; Salmen, T.; Marcu, R.-D.; Cimpeanu, R.-C.; Spînu, D.-A.; Jinga, V.; Stoian, A.P.; Mischianu, D.L.D. Epidemiology of Antimicrobial Resistance in Complicated Acute Pyelonephritis—A Romanian Cohort Study. *Microorganisms* **2026**, *14*, 767. ISI Indexed - IF 4.2. Q2. Link: <https://doi.org/10.3390/microorganisms14040767>
3. **Chițu, M.-C.**; Pălimariu, C.-M.; Salmen, T.; Nicodin, T.-P.; Reurean-Pintilei, D.; Spînu, D.-A.; Jinga, V.; Pantea Stoian, A.; Mischianu, D.L.D. A Cross-Sectional Analysis of Clinical and Biological Characteristics of Inpatients with Complicated Acute Pyelonephritis. *Antibiotics* **2026**, *15*, 363. ISI Indexed - IF 4.6. Q1. Link: <https://doi.org/10.3390/antibiotics15040363>

LIST OF ABBREVIATIONS AND SYMBOLS

AMR – Antimicrobial resistance	MRSA – Methicillin-resistant <i>Staphylococcus aureus</i>
AOPN – Acute Obstructive pyelonephritis	NLR – Neutrophil-to-lymphocyte ratio
APN – Acute pyelonephritis	<i>P. aeruginosa</i> – <i>Pseudomonas aeruginosa</i>
CFU – Colony-forming units	PCT – Procalcitonin
CS – Cephalosporins	PLR – Platelet-to-lymphocyte ratio
CRP – C-reactive protein	THP – Tamm–Horsfall protein
CT contrast (SC) – Contrast agent	TMP-SMX – Trimethoprim - sulfamethoxazole
CT – Computed Tomography	UB – Urinary bladder
DM – Diabetes mellitus	UT – Urinary tract
<i>E. coli</i> – <i>Escherichia coli</i>	UTI – Urinary tract infection
ESBL – Extended-spectrum beta-lactamases	UPEC – Uropathogenic <i>E. coli</i>
FQ – Fluoroquinolones	VRE – Vancomycin-resistant enterococci
GN – Gram-negative	XDR – Extensively drug-resistant
<i>K. pneumoniae</i> – <i>Klebsiella pneumoniae</i>	βL – Beta-lactams
MDR – Multi-drug-resistant	
MRI – Magnetic Resonance Imaging	

INTRODUCTION AND RATIONALE FOR CHOOSING THE TOPIC

Complicated acute pyelonephritis (APN) represents a clinical entity of major interest due to the complexity of the etiopathogenic mechanisms involved, the variability of the clinical presentation, and the significant risk of severe progression to sepsis and multiple organ failure. In daily medical practice, this pathology is a frequent cause of hospitalization in both Infectious Diseases and Urology departments.

The increasing prevalence of antimicrobial resistance (AMR) represents a major challenge, recognized by the World Health Organization as a global priority.

The rationale for choosing this topic derives from the need for an integrated approach to complicated acute pyelonephritis, including the correlated analysis of clinical, biological, microbiological, and imaging data.

The choice of this topic is justified by:

- the major clinical importance of complicated APN;
- the increasing prevalence of AMR;
- the need for local epidemiological data;
- the potential integration of clinico-biological and imaging data into a predictive model.

I. CURRENT STATE OF KNOWLEDGE

1.1. HISTORY – Evolution of the Concept of UTI and Antimicrobial Therapy

Urinary tract infections (UTIs) are most frequently of microbial etiology, represent one of the most widespread infectious diseases, and predominantly affect the female population.

In the 19th century, the discoveries made by Louis Pasteur, Joseph Lister, and Robert Koch led to the formulation of the concept that infectious diseases have a microbial etiology, while in 1894, Nicolaier introduced the first urinary antiseptic (1).

An effective urinary antiseptic requires four essential characteristics:

1. chemical stability;
2. absence of toxicity and irritative effects on the urinary tract (UT);
3. preservation of antiseptic activity despite high urinary dilution;
4. predominantly unchanged renal excretion.

1.2. DEFINITIONS

UTIs represent some of the most common bacterial infections, both in the community and in hospital settings, where they are managed by multiple specialties, including internal medicine and related specialties, gynecology, urology, and intensive care medicine.

1.3. CLASSIFICATIONS – Modern Concepts

a. Acute uncomplicated UTI includes:

- acute cystitis;
- APN,

which occur in the absence of renal or urological comorbidities, generally in previously healthy women aged between 18 and 40 years.

Acute cystitis is a clinical syndrome characterized by dysuria, urinary urgency, increased urinary frequency, macroscopic hematuria, lumbar or hypogastric pain, and occasionally low-grade fever. Bacterial cultures are usually positive; however, one-third may remain below the detection threshold ($<10^5$ colony-forming units [CFU]/mL).

Uncomplicated APN is a clinical syndrome characterized by fever and chills, nausea, vomiting, flank pain, or costovertebral angle tenderness. Symptoms suggestive of lower urinary tract inflammation, such as dysuria, may be absent. Bacteriuria is inconsistently documented, generally with values $>10^4$ CFU/mL (2,3).

b. Complicated UTIs

Complicated UTIs are infections occurring in patients with a history of urinary catheterization or with anatomical and functional abnormalities of the urinary tract.

UTIs in male patients are considered inherently complicated. These infections may or may not be associated with local symptoms.

The term *complicated UTI* refers to acute UTI associated with symptoms suggestive of infection extending beyond the urinary bladder (UB), including fever ($T >37.7^\circ\text{C}$), chills, marked physical asthenia, anorexia, flank pain, costovertebral angle tenderness, and, in men, pelvic or perineal pain suggestive of associated prostatitis.

According to this definition, APN is considered a complicated UTI regardless of the patient's other characteristics. Patients with a history of urological diseases (nephrolithiasis, strictures, stents, urinary diversion), immunosuppression (neutropenia or advanced HIV infection), or poorly controlled diabetes mellitus (DM) are considered to have complicated UTI only if they present symptoms suggestive of upper UTI or systemic infection (4).

The 2025 guideline of the European Association of Urology proposes a new classification that no longer uses the terms *complicated* or *uncomplicated*, but rather emphasizes the distinction between localized and systemic UTI according to signs and symptoms.

a. Localized UTI

Localized UTI is defined as cystitis without other signs or symptoms of systemic infection, regardless of sex.

b. Systemic UTI

Systemic UTI presents signs and symptoms suggestive of systemic infection, while local symptoms may be absent, originating from any location within the urinary tract regardless of sex (e.g., pyelonephritis, prostatitis) (5).

1.4. EPIDEMIOLOGY

The incidence of complicated UTI ranges between 17.6% and 50.9% of all UTI cases (6).

1.5. URINARY TRACT ANATOMY

The urinary tract is an organ system whose primary function is the collection, transport, storage, and periodic coordinated elimination of urine. Thus, metabolic waste products and toxins filtered at the renal level are eliminated from the body through urine, which is transported via the ureters to the urinary bladder for temporary storage and subsequently evacuated through the urethra (7).

The principal function of the kidney is the elimination of nitrogenous waste products, toxins, and metabolites through urine formation and excretion. Additional functions include regulation of hydro-electrolytic balance and inorganic ions, maintenance of acid–base homeostasis, hormonal synthesis and secretion (erythropoietin, renin, 1,25-dihydroxycholecalciferol), and gluconeogenesis.

The functional unit of the kidney is the nephron, a tubular structure lined by a single layer of epithelial cells. In adults, the kidney contains approximately 1.2 million nephrons, of which 85% are cortical nephrons and 15% are juxtamedullary nephrons (8).

1.6. URINARY MICROBIOTA and the Gut–Urinary Tract Axis

At the urethral level, the microbiota is mainly composed of microorganisms belonging to the *Lactobacillaceae* family, coagulase-negative *Staphylococcus* (CoNS), *Streptococcus spp.* (viridans and non-hemolytic species), *Lactobacillus spp.*, *Diphtheroid spp.*, *non-pathogenic Neisseria*, coccobacilli, *Mycoplasma spp.*, anaerobic bacteria, and occasionally *Saccharomyces spp.* (9,10).

This microbiota maintains urinary tract homeostasis through the following mechanisms:

1. production of neurotransmitters interacting with the central nervous system;
2. competition with pathogens for energy sources;
3. regulation of epithelial molecular biomechanisms and maintenance of cellular homeostasis;

4. production of antimicrobial molecules;
5. enhancement of local defense mechanisms;
6. degradation of harmful factors, including certain bacterial toxins (11,12).

1.7. PATHOPHYSIOLOGY and Immune Response

The pathogenesis of UTI begins with contamination of the periurethral area by uropathogens originating from the intestinal microbiota, which subsequently colonize the urethra. Migration toward the urinary bladder and the expression of pili and adhesins facilitate colonization and invasion of superficial umbrella cells.

The host inflammatory response, including neutrophil migration, subsequently attempts to eliminate extracellular bacteria. Some bacteria evade this response either through intracellular invasion or through morphological changes conferring resistance to neutrophil-mediated activity, thereby initiating multiplication and biofilm formation.

These bacteria produce toxins and proteases that induce host cell injury, resulting in the release of essential nutrients required for bacterial survival and ascension toward the kidneys (13, 14).

1.8. INTRINSIC PROTECTIVE MECHANISMS AGAINST UTI

Urine possesses intrinsic antimicrobial properties that inhibit microbial growth, including acidic pH (<5), elevated urea concentrations, a hyperosmolar environment, and the presence of organic acids, proteins, and nitrites.

Urinary proteins, such as Tamm–Horsfall glycoprotein (THP), together with nitrites and urea, act synergistically as inhibitors of bacterial growth. Frequent urination and large urinary volumes also contribute to reducing the risk of UTI development.

1.9. RISK FACTORS

Risk factors for developing urinary tract infections (UTIs) caused by multidrug-resistant (MDR) Gram-negative (GN) bacteria include patients who, within the previous 3 months, fulfilled at least one of the following criteria:

1. isolation from the urinary tract (UT) of an MDR GN bacterium or fluoroquinolone (FQ)-resistant *Pseudomonas aeruginosa* (*P. aeruginosa*);

2. institutionalization/admission to another healthcare facility (hospital, nursing home, long-term care facility);
3. use of FQs, trimethoprim-sulfamethoxazole (TMP-SMX), or broad-spectrum beta-lactams (β Ls) (at least third-generation cephalosporins [CS]);
4. travel to countries with a high incidence of MDR pathogens (India, Israel, Spain, Mexico).

The European Association of Urology developed a classification system known as ORENUC, based on the clinical presentation of UTI and the associated host risk factors. In adults, uncomplicated UTIs include categories O, R, and partially E, while complicated UTIs include categories N, U, and C.

- O – absence of known risk factors;
- R – risk of recurrent UTI without risk of unfavorable outcome;
- E – extraurogenital risk factors;
- N – nephropathy;
- U – transient, resolvable urological risk factors;
- C – permanent urinary catheter or unresolved urological risk factors. (15,16)

1.10. BACTERIOLOGY

The bacterium most frequently involved in UTIs is uropathogenic *Escherichia coli* (UPEC); however, other bacteria such as *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus* spp., *Enterococcus* spp., Group B *Streptococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, as well as fungi such as *Candida* spp., may also cause UTIs. Worldwide, UPEC is responsible for approximately 75% of uncomplicated UTIs and 65% of complicated UTIs (17).

1.11. CLINICAL PRESENTATION

The classic signs and symptoms suggestive of acute cystitis include dysuria, increased urinary frequency, urinary urgency, suprapubic pain, and hematuria. The association of chills, myalgia, and marked physical asthenia suggests extension of the infectious process beyond the level of the urinary bladder (UB).

Signs and symptoms suggestive of pyelonephritis include fever, chills, flank pain, costovertebral angle tenderness, nausea, and vomiting; symptoms of cystitis are present in

most cases, but not obligatorily. Atypical presentations may also occur, in which patients report epigastric or lower abdominal pain.

1.12. DIAGNOSIS

In women with highly suggestive symptoms of cystitis, the clinical diagnosis alone is sufficient. If the patient presents risk factors for infection with AMR bacteria, such as urological abnormalities, immunosuppression, or poorly controlled DM, urine culture and antimicrobial susceptibility testing are recommended.

Furthermore, if symptoms raise suspicion of acute complicated UTI, urine culture with susceptibility testing is also recommended (18).

The ideal urine specimen for the diagnosis of UTI is one that accurately reflects the bacterial burden at the bladder level while minimizing bacterial contamination from the distal urethra and genital mucosa.

On microscopic examination, pyuria is defined as the presence of a significant number of leukocytes in the analyzed sample (>10 leukocytes/ μL or $>10,000$ leukocytes/mL). A value between 30–50 leukocytes/ μL is predictive of UTI (sensitivity = 92–94%, specificity = 42–47%).

In asymptomatic patients, the threshold suggestive of bladder bacteriuria is $\geq 10^5$ CFU/mL. However, in symptomatic women with pyuria, even counts $\geq 10^2$ CFU/mL have been associated with bladder-origin bacteriuria. Therefore, in such cases, colony counts $<10^5/\text{mL}$ but $\geq 10^2/\text{mL}$ may indicate UTI.

CFU counts $\leq 10^5/\text{mL}$ may also indicate infection rather than contamination in the following situations:

- patients who have already received antimicrobial therapy;
- male patients, in whom contamination is less likely (18-21).

1.13. SEROLOGICAL MARKERS

Laboratory investigations provide important data regarding patient evolution, and among the most commonly used tests in clinical practice are the complete blood count and C-reactive protein (CRP), as they provide information regarding the patient's immune response and inflammatory status.

Leukocytosis indicates bacterial infection in most cases, particularly through neutrophil recruitment, which plays a major role in phagocytosis.

Inflammatory markers such as CRP, absolute leukocyte count, and procalcitonin (PCT) have demonstrated usefulness in the diagnosis, prognosis, and monitoring of treatment response. There is, however, growing interest in the use of novel markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), whose relevance derives from the changes observed in neutrophils, platelets, and lymphocytes during the inflammatory response.

1.14. IMAGING METHODS

Imaging evaluation of UTI is mandatory in the following situations:

1. uncertain symptoms;
2. investigation of causes of complicated UTI, such as tumors and strictures;
3. persistent or recurrent symptoms despite appropriate treatment;
4. identification of complications requiring urgent intervention, such as renal abscess.

Computed tomography (CT) and magnetic resonance imaging (MRI) are imaging modalities used in the evaluation of patients with symptomatic and complicated UTIs.

Currently, contrast-enhanced CT is considered the gold standard for the diagnosis and characterization of APN complications. Abdominal radiography may be useful for screening emphysematous pyelonephritis by demonstrating gas bubbles. Abdominal ultrasonography may also serve as an initial screening modality, especially in pregnant women, and may guide subsequent interventions.

MRI is primarily indicated in pregnant women and in patients allergic to iodinated contrast agents (22).

1.15. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of UTI includes renal abscess, APN, obstructive acute pyelonephritis (OAPN), urinary bladder neoplasm, genitourinary infection with *Chlamydia* spp., cystitis, interstitial cystitis, herpes simplex infection, pelvic inflammatory disease, prostatitis, sexually transmitted infections, urethritis, urolithiasis, and vaginitis (23).

1.16. TREATMENT

Hospitalization is recommended for patients presenting severe comorbidities, pregnant women, patients unable to tolerate oral therapy (persistent vomiting, infection with AMR bacteria susceptible only to intravenous antibiotics, intolerance to orally administered agents), or those presenting high fever, dehydration, significant leukocytosis, or laboratory findings suggestive of sepsis.

Patients with upper urinary tract pathology requiring drainage of collections or surgical intervention should also be hospitalized (24).

1.17. RECURRENT UTIs

More than 1.5 million women annually suffer from recurrent UTIs, which reduce quality of life and substantially increase morbidity and mortality, particularly in hospital settings.

Recurrent UTIs are defined as ≥ 2 episodes of acute UTI within 6 months or at least 3 episodes within one year and predominantly affect women.

These are classified into reinfection and relapse. Reinfection is considered when the interval between two episodes exceeds two weeks, a different pathogenic microorganism is isolated, or a sterile urine culture collected without antibiotic treatment has been documented between the two episodes.

1.18. UTI PROPHYLAXIS

Antibiotics represent the mainstay of treatment for UTIs and are also used as prophylaxis in women with recurrent UTIs. However, in the context of the rapid global emergence of AMR uropathogens, effective non-antibiotic preventive therapies are increasingly being investigated.

Recent discoveries regarding the female urinary microbiome and the capacity of probiotics to reduce the uropathogenic burden have generated significant interest. Probiotics inhibit uropathogen ascension through mechanisms including interference with adhesion, biofilm formation, invasion and multiplication, virulence factor expression, and modulation of host defense mechanisms.

Intravaginal probiotic formulations containing lactobacilli produce anti-infective agents, including hydrogen peroxide.

In women with frequent cystitis episodes (≥ 2 episodes within 6 months) unrelated to sexual activity, who present symptoms affecting quality of life and who understand and accept the adverse effects, antibiotic prophylaxis may be initiated.

The susceptibility profile of previously isolated pathogens, possible allergies, and drug interactions with chronic treatment should be considered. Agents used for prophylaxis include nitrofurantoin, TMP-SMX, TMP, cephalexin, cefaclor, and fosfomycin (administered as sachets).

II. PERSONAL CONTRIBUTIONS

2. WORKING HYPOTHESIS AND GENERAL OBJECTIVES

2.1. WORKING HYPOTHESIS

The working hypothesis of the present study is that there are significant correlations between clinical characteristics, biological parameters, microbiological profile, and imaging findings identified in patients with complicated APN. Therefore, the integration of these data may allow:

- risk stratification for progression toward clinical worsening or development of complications;
- early identification of patients with poor prognosis;
- optimization of empirical and targeted antimicrobial therapy.

2.2. AIM OF THE STUDY

The main aim of the research is the integrated evaluation of clinico-paraclinical and etiopathogenic aspects in patients with complicated APN, in order to identify determinants of disease severity, characterize AMR patterns, and optimize diagnostic and therapeutic strategies.

2.3. MAIN OBJECTIVES

The general objectives are:

- detailed characterization of the clinical profile of patients hospitalized with complicated APN;
- analysis of biological parameters and evaluation of the role of inflammatory biomarkers in assessing severity in AOPN;
- determination of the microbiological spectrum and analysis of AMR profiles in AOPN;
- correlation of imaging findings with clinical severity and disease evolution;
- identification of risk factors for complications and unfavorable outcomes;
- integration of obtained data into a conceptual model applicable in clinical practice;

- comparison of results with international literature and highlighting personal contributions;
- proposal of an integrative predictive model for evaluation and management.

3. GENERAL METHODOLOGY OF THE RESEARCH

The study included consecutively hospitalized patients diagnosed with complicated APN. The inclusion period was between 1 January 2021 and 31 December 2025 and comprised patients admitted to the Urology and Infectious Diseases Departments of the Central Military Emergency University Hospital “Dr. Carol Davila”.

The study cohort included patients hospitalized with complicated APN who underwent clinical, biological, imaging, and microbiological evaluation.

A total of 588 patients were initially included; 22 patients had incomplete medical records for the variables of interest, and 13 patients were excluded due to an alternative diagnosis. Therefore, 553 patients were included in the final analysis.

3.1. STUDY DESIGN

The research followed two main directions:

- a systematic literature review assessing current knowledge on the clinical, paraclinical, and microbiological aspects of complicated APN;
- a retrospective cohort study evaluating antimicrobial resistance in cases of complicated APN;
- a cross-sectional observational study analyzing the clinical and paraclinical characteristics of hospitalized patients with complicated APN.

3.2. INCLUSION CRITERIA

- adult patients >18 years;
- confirmed diagnosis of complicated APN / AOPN;
- hospitalization in the Urology or Infectious Diseases Departments of the Central Military Emergency University Hospital “Dr. Carol Davila”;
- availability of complete clinical and paraclinical data in medical records.

3.3. EXCLUSION CRITERIA

- uncomplicated UTIs;
- incomplete clinical or paraclinical data in medical records;

- severely immunocompromised patients under immunosuppressive, radiotherapy, chemotherapy, or biologic treatment;
- severe concomitant pathologies potentially influencing clinical evolution (active malignancies under oncologic treatment, tuberculosis under antituberculous therapy, autoimmune diseases treated with high-dose corticosteroids);
- lack of microbiological confirmation (absence of urine culture at admission or prior to antibiotic administration).

4. STUDY 1 – Clinical Characteristics, Microbiological Spectrum, Biomarkers, and Imaging Findings in Complicated AP – Systematic Review (25)

4.1. RESULTS

APN is clinically characterized by fever and flank pain and is confirmed through laboratory methods, including macroscopic pyuria and bacteriuria quantified by CFU counts, while blood cultures remain essential in complicated or obstructive cases.

Elderly patients or those with multiple comorbidities present with more pronounced risk factors, atypical clinical presentations, bacteremia, and a higher frequency of infections caused by extended-spectrum beta-lactamase (ESBL)-producing organisms. Predisposing factors such as DM and thrombocytopenia require early diagnostic and therapeutic intervention in order to reduce morbidity and mortality associated with sepsis.

Laboratory biomarkers that should be assessed and monitored in AOPN include elevated PCT, presepsin (PSEP), NLR, as well as thrombocytopenia and hypoalbuminemia. These parameters act as independent predictors of disease severity, sepsis, and septic shock in APN and AOPN. The combined use of PCT–PSEP–NLR has shown superior performance compared to conventional parameters such as CRP or leukocytosis, enabling early risk stratification, particularly in elderly patients and those with comorbidities, even in resource-limited clinical settings.

The microbiological spectrum is predominantly represented by *E. coli*, which remains the leading uropathogen in APN and OAPN. However, increasing rates of ESBL-producing and MDR strains have been observed, associated with broad cross-resistance to FQs and CS.

Although ultrasonography (US) is an accessible first-line screening method with moderate sensitivity for detecting APN and AOPN, studies demonstrate that contrast-enhanced CT remains the gold standard and the most accurate imaging modality for identifying parenchymal and perirenal complications, including calculi, abscesses, and emphysematous changes.

4.2. DISCUSSION

The present study identified that APN predominantly affects young, sexually active women, whereas AOPN is more frequent in elderly patients and in those with comorbidities such as DM and urinary retention. These findings are consistent with those reported by Chang et al. (26), who observed that elderly women with community-acquired APN present higher rates of bacteremia, elevated CRP, and infections caused by ESBL-producing organisms compared to younger cohorts.

Similarly, Lee et al. (27) demonstrated that atypical presentations such as confusion, oliguria, or altered general condition were more prevalent among elderly patients with obstructive urolithiasis, contributing to delayed diagnosis and consequently higher rates of sepsis.

Current data confirm that DM and thrombocytopenia are strong predictors of septic shock, in agreement with Yamamichi et al. (28) and Kakinoki et al. (29), who emphasized the importance of early decompression in obstructive cases.

Studies highlight the prognostic value of inflammatory biomarkers in assessing severity in APN and AOPN, including PCT $>1.12 \mu\text{g/L}$, PSEP, NLR ≥ 8.7 , thrombocytopenia, and hypoalbuminemia. Similar findings were reported by Baboudjian et al. (30), who demonstrated that PCT is an early predictor of septic complications, superior to CRP and leukocytosis.

In a complementary manner, Tambo et al. (31) confirmed the independent predictive role of PSEP and PCT in sepsis and septic shock, highlighting the faster kinetic response of PSEP, but also its limitations in patients with renal dysfunction.

The role of NLR as an accessible and cost-effective biomarker has been validated by multiple studies (32,33), which associated it with increased risk of septic shock and prolonged hospitalization.

E. coli remains the predominant uropathogen in APN and AOPN, accounting for 60–95% of community-acquired infections. Non-*E. coli* Enterobacterales such as *K. pneumoniae*, *Proteus mirabilis*, *Enterobacter cloacae*, and *Citrobacter* spp. represent a smaller but clinically significant proportion due to their frequent AMR. Other pathogens, including *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *P. aeruginosa*, and fungi such as *Candida albicans*, have been occasionally implicated, particularly in catheterized patients or those exposed to broad-spectrum antibiotics (34–38).

In imaging investigations performed in the present study, 57.9% of patients exhibited abnormalities on ultrasonography, with the *renal pyramid prominence sign* observed in approximately one quarter of cases. CT detection rates exceeding 70% are consistent with literature data, which identify CT as the reference standard for the evaluation of parenchymal and perirenal complications (28,39).

5. STUDY 2 – Epidemiology of AMR in Complicated AP – A Romanian Cohort Study (40)

5.1. RESULTS

The distribution of the main bacterial species in the studied cohort was as follows: *E. coli* — 46.84%, *Enterococcus faecalis* — 13.74%, *K. pneumoniae* — 11.39%, and *P. aeruginosa* — 6.87%.

Out of a total of 553 isolates evaluated, *E. coli* accounted for 46.8% (259 cases), followed by *Enterococcus faecalis* (13.7%), *K. pneumoniae* (11.4%), and *P. aeruginosa* (6.9%).

Among all isolates, 109 exhibited identifiable resistance phenotypes. *P. aeruginosa* showed the highest proportion of resistant phenotypes (67.5%), followed by *Klebsiella aerogenes* (66.7%), *K. pneumoniae* (46.88%), and *Staphylococcus epidermidis* (100%), although this latter result was based on a single isolate. *E. coli* demonstrated a resistant phenotype proportion of 12.74%.

The dominant resistance mechanisms included ESBL production (55 cases), MDR phenotypes (39 cases), XDR phenotypes (15 cases), and isolated cases of vancomycin-resistant enterococci (VRE), KPC-producing organisms, and methicillin-resistant staphylococci (MRS).

Gender-based analysis revealed that resistance phenotypes were present in 27.8% of isolates from male patients compared to 15.2% in female patients.

5.2. DISCUSSION

In this cohort, *E. coli* remained the predominant pathogen, accounting for nearly half of all isolates, consistent with previous observational studies (41,42). However, growing evidence indicates that infections caused by non-*E. coli* organisms, including *K. pneumoniae*, *P. aeruginosa*, and *Enterococcus faecalis*, are associated with more severe clinical outcomes, including higher rates of bacteremia, prolonged hospitalization, and increased treatment failure rates.

A considerable level of resistance was observed, particularly among *K. pneumoniae* (46%) and *P. aeruginosa* (65.8%), likely reflecting the fact that these organisms are

frequently associated with healthcare exposure and are well known for their ability to acquire multiple resistance mechanisms.

In the present cohort, male patients exhibited a higher proportion of resistant isolates compared to female patients. Logistic regression analysis suggested that male sex remained independently associated with resistant phenotypes after adjustment for available variables in the dataset.

The resistance phenotypes identified in this dataset—including ESBL-producing, MDR, and XDR strains—reflect the broader global challenge of AMR in UTIs. These findings highlight the limitations of traditional empirical therapies, such as FQs and third-generation CS, in regions with a high prevalence of resistant organisms (43). This underscores the importance of local epidemiological surveillance in guiding empirical antibiotic selection, thereby necessitating judicious use of carbapenems or combination therapy in selected cases (44,45).

Overall, the patterns identified in the present cohort are consistent with a broader global epidemiological shift characterized by the progressive emergence of MDR Gram-negative pathogens in urinary tract infections. Although *E. coli* remains the dominant etiological agent, surveillance programs consistently demonstrate that resistant pathogens are disproportionately concentrated among non-*E. coli* organisms, particularly *K. pneumoniae* and *P. aeruginosa* (46,47).

This phenomenon has important clinical implications, as empiric treatment strategies historically optimized for *E. coli* may fail to provide adequate coverage in regions where resistant *Enterobacterales* and non-fermenting GN bacilli significantly contribute to infection complexity (43, 48-52).

6. STUDY 3 – A Cross-Sectional Analysis of the Clinical and Biological Characteristics of Patients Hospitalized with Complicated PA

(53)

6.1. RESULTS

A total of 553 adult patients diagnosed with complicated APN were included in the biological analysis. The underlying pathology responsible for complicated APN was urinary tract obstruction. The causes of obstruction consisted of ureteral lithiasis (n=489), malignant obstruction (n=58), and ureteral strictures (n=6).

The mean leukocyte count was $15.6 \pm 5.8 \times 10^3/\mu\text{L}$, indicating moderate to severe leukocytosis in the majority of patients. Neutrophils represented the dominant leukocyte subtype, with a mean value of $10.1 \pm 4.7 \times 10^3/\mu\text{L}$, consistent with an acute bacterial etiology.

Markers associated with coagulation activation and endothelial dysfunction were frequently altered. Plasma D-dimer levels showed a median value of 1249 ng/mL (IQR: 777–1831 ng/mL); 58% of patients had values exceeding 1000 ng/mL, and approximately 12% had values above 2000 ng/mL, suggesting significant activation of the coagulation cascade in a large subset of cases.

Mean serum urea was 50.4 ± 23.9 mg/dL, while mean creatinine reached 1.69 ± 0.76 mg/dL, suggesting transient renal impairment related to infection severity, dehydration, or systemic inflammatory effects.

In accordance with systemic involvement, liver enzymes showed variable but frequently abnormal values. Alanine aminotransferase (ALT) had a median value of 83 U/L, while aspartate aminotransferase (AST) reached a median value of 66 U/L. Gamma-glutamyl transferase (GGT) was also elevated, with a median value of 93 U/L.

Empirical antimicrobial therapy was initiated in all patients within the first two hours from presentation and clinical evaluation. The majority of patients received third-generation CS (80%), followed by βL /beta-lactamase inhibitor combinations (approximately 10%), FQs (approximately 5%), and carbapenems in a minority of cases. Additionally, 15 cases (2.71%) required antimicrobial therapy adjustment based on antibiogram results.

6.2. DISCUSSION

The present study highlights a pronounced and relatively homogeneous inflammatory response among patients with complicated APN. Leukocytosis, neutrophilia, and elevated acute-phase reactants emphasize the systemic nature of this infection, extending beyond localized renal involvement (52).

The NLR represents an easily obtainable and accessible early marker of sepsis. Although it was not explicitly calculated in the present study due to incomplete patient records, it can be inferred that this ratio was elevated, given the degree of neutrophilia and systemic inflammation (54).

In this cohort, CRP values >60–90 mg/L were frequent, indicating moderate to severe inflammation (33,52). Resistant pathogens are often associated with delayed initiation of effective therapy, prolonged bacterial replication, and an intensified host inflammatory response, all of which may contribute to elevated CRP concentrations (52).

The increase in fibrinogen levels further supports this observation. Fibrinogen is both an acute-phase reactant and a key coagulation factor.

Serum PCT levels are significantly elevated in bacterial APN. These values correlate with infection severity and systemic complications, including sepsis. In complicated APN, PCT has independent prognostic value.

The high prevalence of elevated D-dimer levels represents one of the most notable biological findings. Although traditionally associated with thromboembolic disease, increased D-dimers in acute infections are increasingly interpreted as markers of systemic coagulation activation and endothelial dysfunction. These findings suggest that APN induces coagulation activation primarily through inflammatory mechanisms rather than representing a true thrombotic event. More than half of the patients exhibited D-dimer levels >1000 ng/mL.

More intense inflammatory and coagulation profiles observed in infections caused by resistant pathogens underline the need for early recognition and appropriate empirical therapy. The 2024 Infectious Diseases Society of America (IDSA) guidelines on GN AMR infections emphasize the importance of individualized risk assessment and early escalation of therapy in patients with severe presentations or risk factors for resistance (54).

7. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

7.1. GENERAL CONCLUSIONS

The results of the study highlight:

- the clinical heterogeneity of patients presenting with and diagnosed with this condition;
- the importance of biomarkers (leukocytes, neutrophils, D-dimers, fibrinogen, CRP, PCT) in assessing disease severity;
- the predominance of Enterobacterales with high rates of AMR, such as *E. coli*, *K. pneumoniae*, and *P. aeruginosa*;
- the need to adapt empirical antimicrobial therapy to the local epidemiological context.

7.2. PERSONAL CONCLUSIONS

Personal contributions include:

- the conduct of original clinical studies;
- the analysis of AMR profiles;
- the integration of data into an applicable conceptual model;
- the identification of epidemiological particularities in Romania.

7.3. RESEARCH PERSPECTIVES

Future research directions include:

- development of validated predictive scoring systems;
- multicenter prospective studies;
- identification and utilization of novel or existing biomarkers;
- evaluation of antimicrobial stewardship strategies.

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