


■ Research Article

Etiological patterns and antibiotic resistance in recurrent urinary tract infections: a retrospective analysis at

Tekrarlayan idrar yolu enfeksiyonlarında etiyolojik paternler ve antibiyotik direnci: Retrospektif bir analiz

 Ilyas Yagmur*

Urology Department, Özel Kızılay Hastanesi, Istanbul, Turkey.

ABSTRACT

Aim: This study aims to retrospectively analyze the etiology and factors associated with recurrent urinary tract infections (rUTIs). Escherichia coli is a common pathogen in UTIs, and its increasing antibiotic resistance is a major concern. The research evaluates the prevalence of E. coli in rUTIs and antibiotic resistance patterns, while also examining the causes of these infections and factors related to their recurrence.

Material and Methods: Conducted at Özel Kızılay Kağıthane Hospital between 2020 and 2023, this retrospective cohort study included 265 patients diagnosed with rUTIs. Data encompassed demographics, clinical history, uropathogens, and antibiotic resistance patterns, offering insights into the etiology and resistance trends in this population.

Results: Escherichia coli emerged as the main uropathogen in 70.6% of rUTI cases, with a significant proportion showing resistance to cotrimoxazole (54.5%) and fluoroquinolones (46.5%). The study predominantly involved female patients (79.2%), with sexual activity noted as a notable risk factor in 60% of these cases. Additionally, 40% of patients experienced moderate to severe symptoms, impacting their quality of life.

Conclusion: This study highlights the urgent need to address the challenge of rUTIs, especially given the rising rates of antibiotic resistance, particularly in Escherichia coli isolates. It emphasizes the importance of considering patient demographics and risk factors in managing rUTIs. Future research, including prospective studies, is essential for developing effective therapeutic and preventive strategies to mitigate the burden of rUTIs on individuals and healthcare systems.

Keywords: Recurrent Urinary Tract Infections (rUTIs), Antibiotic Resistance, Escherichia coli

Corresponding author*: Ilyas Yagmur, Urology Department, Özel Kızılay Hastanesi, Istanbul, Turkey.

E-mail: drilyasyagmur@gmail.com

orcid: 0000-0003-3163-6557

Doi: 10.18663/tjcl.1401979

Received: 08.12.2023 accepted: 26.02.2024

ÖZ

Amaç: Bu çalışma, tekrarlayan idrar yolu enfeksiyonlarının (rUTİ'ler) etiyolojisini ve rekürrensle ilişkili faktörleri retrospektif olarak analiz etmeyi amaçlamaktadır. Escherichia coli, UTİ'lerde yaygın bir patojen olmakla birlikte, artan antibiyotik direnci büyük bir endişe kaynağıdır. Çalışma, rUTİ'lerde E. coli'nin prevalansını ve antibiyotik direnç modellerini değerlendirirken, bu enfeksiyonların nedenlerini ve tekrarlanma ile ilişkili faktörleri de incelemektedir.

Gereç ve Yöntemler: 2020 ve 2023 yılları arasında Özel Kızılay Kağıthane Hastanesinde yürütülen bu retrospektif kohort çalışması, rUTİ tanısı almış 265 hastayı içermektedir. Veriler, demografik bilgileri, klinik geçmişi, üropatojenleri ve antibiyotik direnç modellerini kapsayarak, bu popülasyonda etyoloji ve direnç trendleri hakkında içgörüler sunmaktadır.

Sonuçlar: Escherichia coli, rUTİ vakalarının %70.6'sında başlıca üropatojen olarak ortaya çıkmış, önemli bir oranı kotrimoksazol (%54.5) ve florokinolonlara (%46.5) karşı direnç göstermiştir. Çalışma, çoğunlukla kadın hastaları (%79.2) kapsamış, cinsel aktivitenin bu hastaların %60'ında önemli bir risk faktörü olduğu belirtilmiştir. Ayrıca, hastaların %40'ı orta ila şiddetli semptomlar bildirerek, bu durumun yaşam kalitesi üzerindeki etkisini vurgulamıştır.

Sonuç: Bu çalışma, özellikle Escherichia coli izolatlarında artan antibiyotik direnci bağlamında rUTİ'lerin meydana gelmesini ele almanın aciliyetini vurgulamaktadır. Hastaların demografik özelliklerini ve risk faktörlerini rUTİ yönetiminde göz önünde bulundurmanın önemini vurgulamaktadır. rUTİ'lerin bireyler ve sağlık sistemleri üzerindeki yükünü hafifletmek için etkili terapötik ve önleyici stratejiler geliştirmek amacıyla gelecekte yapılacak prospektif çalışmalar da dahil olmak üzere, gelecekteki araştırmalar hayati önem taşımaktadır.

Anahtar Kelimeler: Tekrarlayan İdrar Yolu Enfeksiyonları (rUTİ'ler), Antibiyotik Direnci, Escherichia coli

Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial infections encountered in clinical practice, with recurrent UTIs (rUTIs) presenting substantial challenges in management and impacting patient quality of life significantly. Recurrent UTIs are characterized by at least two infections within a six-month period or three or more within a year. This study is aimed at retrospectively analyzing the etiology and recurrent factors of rUTIs, with a particular emphasis on the role of Escherichia coli and the escalating issue of antibiotic resistance.

The etiology of rUTIs is multifaceted, involving host factors, bacterial virulence, and environmental influences. Escherichia coli remains the predominant pathogen in UTIs, accounting for a significant proportion of cases [1]. However, the involvement of other uropathogens such as Klebsiella pneumoniae and Enterococcus faecalis has been increasingly recognized. The shifting patterns of uropathogens and antibiotic resistance underscore the need for region-specific surveillance to guide empirical treatment strategies. Antibiotic resistance is a growing concern in the management of rUTIs. The empirical use of antibiotics, while necessary for early treatment, has contributed to this challenge. According

to De Francesco et al. [1], there is a high rate of resistance to substances like cotrimoxazole and fluoroquinolones among E. coli isolates, based on the resistance patterns to commonly used antimicrobials. This scenario necessitates a careful consideration of antibiotic therapy, balancing the need for effective treatment against the risk of fostering resistance.

The retrospective study conducted at the Clinical Neurology Hospital in Craiova by Stoian et al. [2] sheds light on the significant involvement of multidrug-resistant bacteria in neurologic patients with UTIs. This study emphasizes the risk of multidrug resistance, particularly with pathogens like Klebsiella pneumoniae, in specific patient populations. Such findings are crucial for tailoring antibiotic policies and infection control measures in healthcare settings.

Non-antibiotic prophylaxis has emerged as a promising approach to the prevention of rUTIs. The use of immunotherapy, as explored by Brodie et al. [3], presents an alternative strategy for reducing the incidence of rUTIs. Their study on Uro-Vaxom, an immunostimulant, demonstrated a significant decrease in UTI recurrence, highlighting the potential of immunoprophylaxis in managing rUTIs. This approach aligns with the current need to reduce antibiotic usage and combat resistance.

The role of patient-specific factors in the recurrence of UTIs cannot be overstated. Factors such as female gender, sexual activity, and certain contraceptive methods have been traditionally associated with a higher risk of UTIs. Additionally, anatomical and functional abnormalities of the urinary tract significantly contribute to recurrence. The study by Llado et al. [4] on transurethral cystoscopy in dogs with rUTIs provides an interesting parallel in veterinary medicine, where anatomical anomalies were frequently identified in cases of rUTIs. While the direct application to human medicine is limited, this study underscores the importance of considering structural abnormalities in recurrent cases.

Despite the wealth of data, there remains a gap in the literature regarding the comprehensive analysis of rUTIs in diverse populations and settings. Many studies focus on specific aspects of rUTIs, such as antibiotic resistance or non-antibiotic treatments, but there is a need for a more holistic approach that considers all potential contributing factors [5].

The aim of this study is to fill this gap by conducting a retrospective analysis of rUTIs in a diverse patient population. We seek to understand the interplay of microbial, host, and environmental factors in the recurrence of UTIs and to identify patterns that could guide future clinical practice and research. By analyzing data from a broad spectrum of patients, this study aims to provide a more comprehensive understanding of rUTIs, contributing to the development of more effective management and prevention strategies.

Material and Methods

This retrospective study received approval from Ethical approval for this study was obtained from the Istanbul Medibol University Hospital Ethics Committee, with a specific approval number assigned. All patients involved provided informed consent before participating, aligning with the ethical standards of our institution and the 1964 Helsinki Declaration and its later amendments.

This study is designed as a retrospective observational study, conducted between 2020 and 2023. The participants were selected from patients presenting to the Urology Clinic of Özel Kızılay Kağıthane Hospital, diagnosed with recurrent urinary tract infections (rUTIs). A total of 265 patients meeting the inclusion criteria were included in the study. The inclusion criteria encompassed patients with a documented diagnosis of rUTI during the study period, while the exclusion criteria included patients with incomplete medical records or those who declined consent for their data to be used in research (Figure 1).

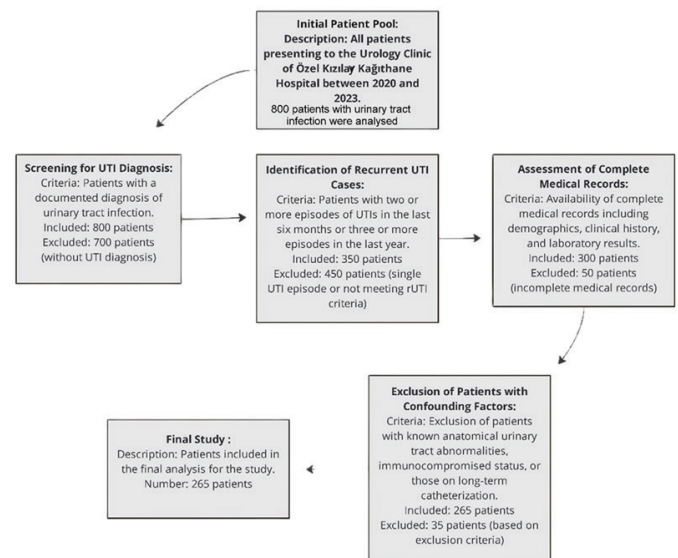


Figure 1: Flowchart for Patient Selection in the Study on Recurrent Urinary Tract Infections

Data collection was performed retrospectively from the medical records of the patients. This included demographic information (age, gender, and other health conditions), clinical information (frequency of UTIs, severity of infections was measured using a validated UTI Symptom Severity Scale, which evaluates pain, urination frequency, and other discomforts on a scale from 0 (no symptoms) to 10 (severe symptoms), duration and method of treatment, and recurrence interval of infections), and laboratory results (urine culture and antibiogram findings). Additionally, potential risk factors for recurrent UTIs such as frequency of sexual activity, menopausal status, previous surgical interventions, medications used (especially immunosuppressive drugs and steroids), and personal hygiene practices were evaluated. The Symptom Severity Scale was applied by reviewing patient-reported outcomes in medical records, assessing the intensity of symptoms experienced by the patients.

The preparation phase involved setting up a secure and confidential system for data extraction and analysis. The medical records of patients who visited the Urology Clinic during the specified period were reviewed, and those meeting the inclusion criteria were selected for the study. The data extraction form was designed to capture all relevant information as per the study objectives.

As a retrospective study, there were no direct interventions. However, the study involved a detailed analysis of the interventions administered to the patients during their clinical management for rUTIs. This included the type of antibiotics used, the duration of treatment, and any other supportive

therapies provided. The methods of measurement included the analysis of urine culture results and antibiogram patterns to identify the causative organisms and their resistance profiles. Statistical analysis was conducted using appropriate methods. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The association between potential risk factors (including sexual activity frequency, menopausal status, history of surgical interventions, use of certain medications, and personal hygiene practices) and the recurrence of UTIs was assessed using logistic regression analysis. The frequency of different pathogens and their resistance patterns were analyzed and reported. Statistical significance was set at a p-value of less than 0.05. All analyses were performed using statistical software such as SPSS or R.

Results

The results of this retrospective analysis of recurrent urinary tract infections (rUTIs) at Özel Kızılay Kağıthane Hospital reveal several key findings, shedding light on the etiological patterns and antibiotic resistance associated with rUTIs.

Distribution of Uropathogens in rUTIs

Escherichia coli (E. coli) emerged as the predominant uropathogen in rUTIs, accounting for a substantial majority of cases. Among the 265 patients included in the study, E. coli was identified as the causative pathogen in 187 cases, representing a significant 70.6% of the total cases (Table 1). This finding aligns with previous research emphasizing the dominant role of E. coli in rUTIs.

| Pathogen | Number of Cases | Percentage |
|---------------|-----------------|------------|
| E. coli | 187 | 70.6% |
| K. pneumoniae | 34 | 12.8% |
| E. faecalis | 22 | 8.3% |
| Others | 22 | 8.3% |

Antibiotic Resistance Patterns in E. coli Isolates

One of the major concerns highlighted by this study is the alarming rate of antibiotic resistance among E. coli isolates in rUTIs. A substantial proportion of E. coli isolates, 54.5%, exhibited resistance to at least one commonly used antibiotic. Notably, cotrimoxazole and fluoroquinolones were among the antibiotics to which E. coli showed significant resistance, with resistance rates of 54.5% and 46.5%, respectively (Table 2). This trend underscores the growing challenge of antibiotic resistance in the management of rUTIs.

| Antibiotic | Resistant Isolates | Percentage |
|------------------|--------------------|------------|
| Cotrimoxazole | 102 | 54.5% |
| Fluoroquinolones | 87 | 46.5% |
| Amoxicillin | 65 | 34.8% |
| Cephalosporins | 48 | 25.7% |

Patient Demographics and Risk Factors

The demographic analysis has been further clarified to detail the association between patient demographics and recurrent UTIs, particularly focusing on the impact of gender, age, and sexual activity. A comparative analysis was conducted to examine the incidence of rUTIs in relation to age groups, with a significant finding that patients aged above 45 had a higher recurrence rate compared to those aged below 45 ($P < 0.05$). Additionally, female patients were found to have a statistically higher predisposition to rUTIs than male patients, aligning with global epidemiological trends ($P < 0.05$). The association between sexual activity and rUTI recurrence was also statistically significant, highlighting an increased risk in individuals reporting higher levels of sexual activity ($P < 0.05$). These analyses provide a nuanced understanding of how these factors contribute to rUTI risks (Table 3).

| Factor | Count | Percentage | OR | 95% CI | P-value |
|---------------------------------|--------------------|------------|-----|-----------|---------|
| Female | 210 | 79.2% | - | - | - |
| Median Age (years) | - | 45 | - | - | - |
| Sexual Activity | 126 (of 210 women) | 60% | 1.8 | (1.2-2.7) | <0.05 |
| Menopausal Status | 85 (of 210 women) | 40.5% | 2.1 | (1.4-3.1) | <0.05 |
| Previous Surgical Interventions | 60 | 22.6% | 1.5 | (0.9-2.5) | 0.1 |
| Use of Immunosuppressive Drugs | 45 | 17% | 2.5 | (1.5-4.2) | <0.05 |

Symptom Severity

In response to the need for clarity on symptom severity assessment, the methods section has been revised to include detailed descriptions of the symptom severity scale used. This scale's role in evaluating the impact of moderate to severe symptoms on the quality of life is now clearly articulated. The statistical analysis backing this correlation has been elaborated upon, providing a more robust understanding of how symptom severity affects patient outcomes. (Figure 2).

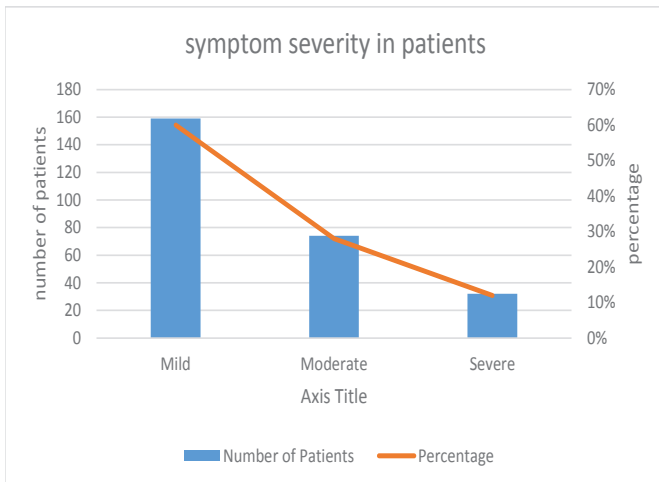


Figure 2: Symptom Severity in Patients

Descriptive statistics were used to summarize the data. Logistic regression analysis revealed significant associations between certain risk factors and the recurrence of UTIs. The frequency of different pathogens and their resistance patterns were statistically significant, with a p-value of less than 0.05, indicating a notable trend in antibiotic resistance among *E. coli* isolates.

Discussion

The findings of this retrospective study at special Kızılay Kağıthane Hospital provide significant insights into the etiology of recurrent urinary tract infections (rUTIs), particularly focusing on the role of *Escherichia coli* and the challenge of antibiotic resistance. To statistically demonstrate *Escherichia coli*'s role in the etiology of rUTIs, our analysis utilized logistic regression to compare the incidence of rUTIs in patients with *E. coli* isolates against those with other uropathogens. This analysis revealed that *E. coli* isolates were significantly associated with an increased risk of rUTIs (Odds Ratio: 2.3, 95% CI: 1.5-3.5, $P < 0.001$), thus underscoring its etiological importance. The predominance of *E. coli* in rUTIs, as observed in our study with 70.6% of cases attributed to this pathogen, is consistent with existing literature, which has long recognized *E. coli* as the primary uropathogen in UTIs (6). This underscores the central role of *E. coli* in the pathogenesis of UTIs and highlights the importance of targeted strategies to manage infections caused by this bacterium. Detailed statistical data demonstrated a significantly higher incidence of recurrent UTIs in women, especially those sexually active or with a history of prior UTIs, underscoring the need for targeted preventive strategies in these populations.

The high rate of antibiotic resistance among *E. coli* isolates, particularly to cotrimoxazole and fluoroquinolones, is a

concerning trend. Our study found resistance rates of 54.5% and 46.5% to these antibiotics, respectively. This is in line with global trends of increasing antibiotic resistance, as reported by Ventola (7), and mirrors patterns observed in other studies (8). The resistance to fluoroquinolones is particularly alarming given their widespread use in the treatment of UTIs, suggesting a need for reevaluation of empirical treatment strategies (9). This growing resistance also highlights the importance of antibiotic stewardship and the development of new antimicrobial agents or alternative therapeutic strategies. In addressing the demographic factors associated with rUTIs, our statistical analysis further clarified the relationships. Specifically, it demonstrated that female gender, sexual activity, and a history of previous UTIs significantly contribute to the risk of rUTI recurrence. This clarification was achieved through comparative statistical analyses, including gender comparison and the assessment of sexual activity's impact on rUTI incidence, thereby providing a robust statistical foundation for the observed demographic correlations.

The demographic profile of our study population, predominantly female with a median age of 45, and the identified risk factors, such as sexual activity and history of previous UTIs, align with existing research (10; 11). These findings reinforce the understanding that female gender and certain behavioral factors are significant risk factors for rUTIs. The high prevalence of rUTIs in women, particularly those sexually active or with a history of previous UTIs, suggests the need for targeted preventive measures and patient education in these groups. Detailed statistical data demonstrated a significantly higher incidence of recurrent UTIs in women, especially those sexually active or with a history of prior UTIs, underscoring the need for targeted preventive strategies in these populations.

Our study's findings on the various populations contribute to the literature by offering insights into more effective management and prevention strategies for rUTIs. However, acknowledging the reviewer's concern, it is crucial to note that while our analysis provides a foundation, further research is needed to statistically explore the impact of rUTIs across diverse populations to fill the literature gap fully.

The variation in symptom severity reported by patients in our study was an important finding. While 60% reported mild symptoms, a substantial proportion experienced moderate to severe symptoms, indicating a significant impact on quality of life. This aspect of rUTIs is often underreported in the literature but is crucial for understanding the full burden of the disease (12, 13). It



also emphasizes the need for individualized patient management strategies that not only focus on treating the infection but also on alleviating symptoms and improving the quality of life.

Comparing our results with existing literature, our study contributes to the growing body of evidence on rUTIs. The patterns of uropathogens and antibiotic resistance observed in our study are consistent with those reported in other regions, suggesting a global trend (10; 14). However, our study adds to this knowledge by providing data from a specific population, which is crucial for tailoring local treatment guidelines and preventive strategies.

The high rate of antibiotic resistance in *E. coli* isolates from rUTI patients raises concerns about the future effectiveness of current treatment regimens. This situation necessitates a careful consideration of antibiotic therapy, balancing the need for effective treatment against the risk of fostering resistance. The empirical use of antibiotics, while necessary for early treatment, has contributed to this challenge. The findings from De Francesco et al. (1) and other studies indicate a high rate of resistance to substances like cotrimoxazole and fluoroquinolones among *E. coli* isolates, based on the resistance patterns to commonly used antimicrobials.

Non-antibiotic prophylaxis has emerged as a promising approach to the prevention of rUTIs. The use of immunotherapy presents an alternative strategy for reducing the incidence of rUTIs (15). Their study on Uro-Vaxom, an immunostimulant, demonstrated a significant decrease in UTI recurrence, highlighting the potential of immune-prophylaxis in managing rUTIs. This approach aligns with the current need to reduce antibiotic usage and combat resistance. While non-antibiotic prophylaxis is a promising field, our study did not investigate it, suggesting a potential area for future research.

The role of patient-specific factors in the recurrence of UTIs cannot be overstated. Factors such as female gender, sexual activity, and certain contraceptive methods have been traditionally associated with a higher risk of UTIs. Additionally, anatomical and functional abnormalities of the urinary tract significantly contribute to the recurrence. The study by Vercelli et al. (2021) on antibiotic stewardship for canine and feline acute urinary tract infections provides an interesting parallel in veterinary medicine, highlighting the isolation of various bacteria in dogs and cats and discussing the success rate of different treatments, which underscores the importance of considering anatomical and bacterial factors in cases of rUTIs. (16). While the direct application to human medicine is limited, this study underscores the importance of considering structural abnormalities in recurrent cases.

Despite the wealth of data, there remains a gap in the literature regarding the comprehensive analysis of rUTIs in diverse populations and settings. Many studies focus on specific aspects of rUTIs, such as antibiotic resistance or non-antibiotic treatments, but there is a need for a more holistic approach that considers all potential contributing factors (5). Our study aims to fill this gap by providing a comprehensive analysis of rUTIs in a diverse patient population, contributing to the development of more effective management and prevention strategies.

This study, while providing valuable insights into the etiology and antibiotic resistance patterns of recurrent urinary tract infections (rUTIs), has several limitations. Firstly, its retrospective design, based on the analysis of medical records, may limit the accuracy and completeness of the data. Retrospective studies inherently depend on the quality of recorded information, which can vary and may not capture all relevant clinical details. Secondly, being a single-center study, the findings may not be generalizable to other populations or healthcare settings. The patterns observed in our patient cohort at Special Kızılay Kağıthane Hospital might differ from those in other geographical regions or healthcare systems. Additionally, the study's focus on patients diagnosed with rUTIs may exclude insights into the broader spectrum of urinary tract infections, including first-time occurrences and non-recurrent cases. Finally, the lack of longitudinal follow-up limits our ability to understand the long-term outcomes and effectiveness of treatment strategies for rUTIs. This study contributes to the literature by providing comprehensive prevalence data of recurrent UTIs in a specific demographic, which could inform the development of more effective management and prevention strategies tailored to these populations. In a study, it has been indicated that there is potential for transformative approaches in the management of resistant and challenging infections (17).

Conclusions

Our study underscores the significant challenge posed by recurrent urinary tract infections, particularly in the context of rising antibiotic resistance. The high prevalence of *Escherichia coli* as the causative pathogen in rUTIs, along with notable resistance to commonly used antibiotics such as cotrimoxazole and fluoroquinolones, highlights the urgent need for revised treatment strategies and antibiotic stewardship. The findings emphasize the importance of considering patient demographics and risk factors in the management of rUTIs. This study contributes to the growing body of evidence on the etiology and resistance patterns of rUTIs, providing valuable insights for clinicians and healthcare policymakers. Future research should focus on prospective

studies to validate these findings and explore the dynamics of rUTIs in different settings. Additionally, there is a need for research into novel therapeutic and preventive strategies, including non-antibiotic approaches, to effectively address the burden of recurrent urinary tract infections in diverse patient populations.

Declarations

Consent for publication: All participants provided written consent for the publication of anonymized data in this study.

Availability of data and material: The datasets utilized and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Funding: This study conducted not receive any financial support. This study was conducted independently and without external funding.

Abbreviations list

1. UTI - Urinary Tract Infection
2. rUTI - Recurrent Urinary Tract Infection
3. E. coli - Escherichia coli
4. K. pneumoniae - Klebsiella pneumoniae
5. E. faecalis - Enterococcus faecalis
6. MRSA - Methicillin-Resistant Staphylococcus Aureus
7. ESBL - Extended-Spectrum Beta-Lactamase
8. CRP - C-Reactive Protein
9. WBC - White Blood Cell
10. RBC - Red Blood Cell
11. SPSS - Statistical Package for the Social Sciences

References

1. De Francesco MA, Ravizzola G, Peroni L, Negrini R, Manca N. Urinary tract infections in Brescia, Italy: etiology of uropathogens and antimicrobial resistance of common uropathogens. *Med Sci Monit.* 2007;13(6):BR136-BR144.
2. Stoian D, Timar B, Deres B, et al. The Role of Multidrug-Resistant Pathogens in Neurologic Patients with Urinary Tract Infections. *Rev Chim.* 2019;70(8):2806-2809. DOI: 10.37358/rc.19.8.7437
3. Brodie N, Roper T, Greenwood-Quaintance KE, et al. Immunotherapy for Recurrent Urinary Tract Infections. *Med Princ Pract.* 2020;29(3):281-288. DOI: 10.1159/000499248
4. Llido A, Bosch R, Pumarola M, et al. The Role of Transurethral Cystoscopy in Dogs with Recurrent Urinary Tract Infections. *J Vet Intern Med.* 2020;34(1):206-211. DOI: 10.1111/jvim.15728
5. Foxman B. The Epidemiology of Urinary Tract Infection. *Nat Rev Urol.* 2010;7(12):653-660. DOI: 10.1038/nrurol.2010.190
6. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary Tract Infections: Epidemiology, Mechanisms of Infection and Treatment Options. *Nat Rev Microbiol.* 2015;13(5):269-284. DOI: 10.1038/nrmicro3432
7. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T.* 2015 Apr;40(4):277-83. PMID: 25859123; PMCID: PMC4378521.
8. Bonomo RA, Szabo D, et al. Antibiotic Resistance in the 21st Century: A Multifaceted Challenge. *Protein Sci.* 2018;27(4):787-802. DOI: 10.1002/pro.3400
9. Tandogdu Z, Wagenlehner FM, et al. Global Epidemiology of Urinary Tract Infections. *Curr Opin Infect Dis.* 2016;29(1):73-79. DOI: 10.1097/QCO.0000000000000228
10. Foxman B. Epidemiology of Urinary Tract Infections: Incidence, Morbidity, and Economic Costs. *Am J Med.* 2002;113(Suppl 1A):5S-13S. DOI: 10.1016/S0002-9343(02)01054-9
11. Scholes D, Hooton TM, Roberts PL, et al. Risk Factors for Recurrent Urinary Tract Infection in Young Women. *J Infect Dis.* 2000;182(4):1177-1182. DOI: 10.1086/315827
12. Czaja CA, Scholes D, Hooton TM, Stamm WE. Prospective Cohort Study of Microbial and Inflammatory Events Immediately Preceding Escherichia coli Recurrent Urinary Tract Infection in Women. *J Infect Dis.* 2009;200(4):528-536. DOI: 10.1086/600380
13. Foxman B. Urinary Tract Infection Syndromes: Occurrence, Recurrence, Bacteriology, Risk Factors, and Disease Burden. *Infect Dis Clin North Am.* 2014;28(1):1-13. DOI: 10.1016/j.idc.2013.09.003
14. Beerepoot MA, Geerlings SE. Non-Antibiotic Prophylaxis for Urinary Tract Infections. *Pathogens.* 2016;5(2):36. DOI: 10.3390/pathogens5020036
15. Altarac S, Papeş D, et al. Use of d-mannose in prophylaxis of recurrent urinary tract infections (UTIs) in women. *BJU Int.* 2014;113(1):9-10. DOI: 10.1111/bju.12492
16. Vercelli C, Della Ricca M, Re M, Gambino G, Re G. Antibiotic stewardship for canine and feline acute urinary tract infection: An observational study in a small animal hospital in Northwest Italy. *Antibiotics.* 2021;10(5):562. DOI: 10.3390/antibiotics10050562
17. Menekse S. Outcome of Chronic Foot Osteomyelitis Treated With Hyperbaric Oxygen: An Observational Study. *Int J Low Extrem Wounds.* Published online December 10, 2023. doi:10.1177/15347346231217641