An-Najah National University

Faculty of Graduate Studies

PHARMACOLOGICAL MANAGEMENT OF RECURRENT URINARY TRACT INFECTION ON PALESTINIAN WOMEN: A RETROSPECTIVE STUDY

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This Thesis is Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Pharmacology, Faculty of Graduate Studies, An-Najah National University, Nablus - Palestine.

2026

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Dedication

The study is dedicated to my beloved family, especially to my mother, who was my first and greatest source of support, standing by my side with encouragement and assistance until I achieved my goal. I also dedicate this work to my colleagues and friends, and to everyone who offered support in my academic journey.

Acknowledgements

First and foremost, I thank GOD for granting me success and enabling me to complete this study. I would like to express my sincere gratitude and appreciation to my supervisor, Dr. Ramzi Shawahna, for his valuable guidance and continuous support. I also extend my thanks to An-Najah National University and its staff for providing the necessary facilities to conduct this study.

I am deeply grateful to my beloved parents for their constant encouragement, support, and assistance, which were instrumental in completing this work. I would also like to thank the examination committee for their time, effort, and valuable feedback in evaluating this research. Finally, I extend my sincere thanks to siblings, colleagues, friends, and everyone who contributed in any way to supporting me throughout this academic journey.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

PHARMACOLOGICAL MANAGEMENT OF RECURRENT URINARY TRACT INFECTION ON PALESTINIAN WOMEN: A RETROSPECTIVE STUDY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

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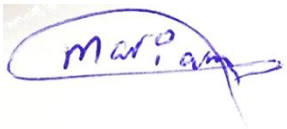
Signature: 

Date: **13/05/2026**

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List of Abbreviations

Abbreviation	Meaning
AMR	Antimicrobial Resistance
AUA	American Urology Association
AWMF	Arbeit gemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
COMEGO	College of Gynaecology and Obstetrics Specialists
CUA	Canadian Urological Association
DM	Diabetes Meletus
EAU	European Association of Urology
E. coli	Escherichia Coli
ESBL	Extended Spectrum Beta Lactamase
HF	Heart Failure
HTN	Hypertension
IVA	Intravesical Antimicrobial therapies
MDROs	Multi Drug Resistant Organisms
NICE	National Institute for Health and Care Excellence
PACs	Proanthocyanins
RUTIs	Recurrent Urinary Tract Infections
SEIMC	Spanish Society of Infectious Diseases and Clinical Microbiology
SOGC	Society of Obstetricians and Gynecologists of Canada
SSGO	Swiss Society of Gynecology and Obstetrics
SUFU	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction
TMP-SMX	Trimethoprim-sulfamethoxazole
UTIs	Urinary Tract Infections
WHO	World Health Organization

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PHARMACOLOGICAL MANAGEMENT OF RECURRENT URINARY TRACT INFECTION ON PALESTINIAN WOMEN: A RETROSPECTIVE STUDY

By
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Abstract

Background: Urinary tract infections (UTIs) are among the most common bacterial infections in women worldwide, with recurrent UTIs (rUTIs) creating major challenges for both clinical and public health. In Palestine, data on rUTIs and antimicrobial resistance (AMR) are still scarce.

Objectives: This study aimed to describe the pharmacological management of recurrent urinary tract infection (RUTI) and determine the prevalence of rUTIs among Palestinian women, identify the factors that are associated with increased risk of recurrent episodes, characterize antimicrobial resistance patterns, and evaluate the impact of culture-guided therapy on outcomes.

Methods: This study was a retrospective cohort study was conducted across four hospitals in the urology department in southern West Bank in Palestine (2016–2025). Medical records of 380 women aged ≥18 years with UTI were reviewed. Demographic, clinical, microbiological, and treatment variables were extracted. rUTI was defined as ≥2 symptomatic episodes within six months or ≥3 within twelve months. Descriptive and inferential statistics, including logistic regression, were performed by SPSS.

Results: The final analysis included 380 women diagnosed with UTI. The overall prevalence of rUTIs among Palestinian women was 27.4% (104/380). Older age (median 65 vs. 60 years, $p = 0.015$), diabetes mellitus ($p = 0.004$), asthma ($p = 0.012$), and prior UTI history ($p < 0.001$) were significantly associated with recurrence. Pregnancy was less frequent among rUTI cases ($p < 0.001$). The most dominant pathogen isolated from urine culture was Gram-negative Escherichia coli (40.5%) and Klebsiella spp. (9.7%) as leading isolates. ESBL-producing strains were common, diminishing the effectiveness of cephalosporin and fluoroquinolone. Empirical therapy was dominated by ceftriaxone (43.2%), while meropenem (23.9%) became most frequent after culture results. Culture-guided therapy was significantly associated with a reduced recurrence rate ($p <$

0.05). Clinical resolution occurred in 93.4%, but reinfection (14.2%) and MDR history (28.9%) continue to pose significant challenges.

Conclusion: rUTIs are prevalent among Palestinian women and represent a significant public health burden. rUTIs strongly associated with underlying comorbidities and resistant Gram-negative pathogens. Improved outcomes observed with culture-guided therapy, underscoring the need for a strengthened stewardship program and diagnostic infrastructure in resource-limited settings to enhance UTI management in Palestinian healthcare practices.

Keywords: Recurrent urinary tract infection; Escherichia coli; Antimicrobial resistance; Extended-spectrum beta-lactamase; Culture-guided therapy; Resource-limited settings

Chapter One

Introduction

1.1 Background

Urinary tract infections (UTIs) are one of the most common diseases in women, and are frequently diagnosed in outpatient care (1, 2). Based on recent estimates, UTIs affected more than 404.6 million cases in 2019 and caused nearly 236,786 deaths worldwide (1). Recurrent urinary tract infections (rUTIs) are considered one of the most pressing challenges in women's health due to their high prevalence and the growing threat of antimicrobial resistance (AMR) (3-6). According to a global estimate, up to one in four women with a first UTI will experience recurrence within a year (7). In resource-limited settings where broad-spectrum antibiotics are frequently used and culture-guided therapy is underutilized, the burden is magnified (5, 8-11).

The effectiveness of commonly used cephalosporins and fluoroquinolones has eroded due to the emergence of multidrug-resistant (MDR) Gram-negative pathogens, especially Escherichia coli (E. coli) and Klebsiella spp. leading to greater reliance on carbapenems and antifungals among clinicians (9-11). In Palestine, rUTIs impose clinical burden and substantial economic strain on the healthcare system because AMR surveillance is limited and preventive strategies remain underdeveloped. Understanding the epidemiology, risk factors associated with rUTIs, and treatment patterns in this context is necessary to optimize antibiotic stewardship, mitigate the escalating threats of AMR, and inform evidence-based practice.

Clinically, rUTIs are defined as ≥2 symptomatic episodes within six months or ≥3 within twelve months (10, 12). Pathophysiologically, rUTIs may manifest either as relapses or reinfections, the vast majority of recurrences represent reinfections. Relapse reflects incomplete eradication of the initial pathogen within 14 days of treatment, whereas reinfections occurring after 14 days typically require a new urine culture (9, 10). Importantly, reinfections are estimated at around 90%, underscoring the need for accurate diagnosis and tailored management strategies to achieve the successful eradication of these infections. Recurrent episodes impose a considerable burden at the individual level, often contributing to persistent urinary symptoms, disruption of daily activities, and a measurable decline in mental well-being (13, 14).

Epidemiological evidence demonstrates that rUTIs affect approximately 25-30% of women following an initial UTI episode, making them important as a public health concern (5, 15-17). According to the large cohort studies, have shown that older age, pregnancy, diabetes mellitus, and other chronic diseases increase susceptibility to recurrence (5, 6, 15-17). Pathogen-related factors, such as the predominant causative agent E. coli, followed by Klebsiella spp., contributing to treatment failure and recurrence with extended-spectrum beta-lactamase (ESBL)-producing strains (18).

Recent prevalence studies across different populations, including women of reproductive age, confirm that reinfections are responsible for the majority of rUTI cases, demonstrating the importance of accurate pathogen identification and culture-guided therapy (19). Collectively, these results showed that rUTIs are influenced by a multifactorial interplay of host susceptibility, pathogen virulence, and AMR, highlighting the need for tailored management strategies to balance effective treatment with stewardship principles.

1.1.1 Older age

Older age is one of the risk factors associated with rUTI disease because of anatomical and physiological changes occur in the body with aging. Impaired immune function, decreased ability of the body to clear infections, functional limitation, such as immobility and urinary incontinence contribute to the increased risk of infection. Postmenopausal women are more prone to rUTI than premenopausal women. Comorbidities also increase with age, such as DM, which causes an increase glucose in the urine and creates a suitable environment for the growth and recurrence of infections. All changes happen in the body with the age can contribute to the increased risk of rUTI.

1.1.2 E. coli

E. coli is the most common gram-negative bacterial pathogen that causes rUTI, and faces both clinical and epidemiological challenges due to increasing resistance. The growing use of antibiotics lead to the development of several strains of E. coli bacteria, such as extended-spectrum beta-lactamase (ESBL) E. coli, and carbapenemase-producing E. coli, these strains characterized by the ability to adaptations and pathogenicity (20). Understanding the mechanisms of bacterial resistance, such as the ability of bacteria to form biofilm or even how triggers mutation in antibiotic target sites, can help in

identifying potential targets for antibiotic development. There are several factors associated with increasing resistance of E. coli, including poor adherence to the treatment, empirical treatment without urine culture, and inappropriate or repeated antibiotic use, so an antibiotic stewardship program is crucial to minimize resistance problems. A study performed in 2020 showed that patients with rUTI are more likely to have ESBL-producing E. coli (21). E. coli can acquire resistance genes from other bacteria, the acquisition of resistance genes through horizontal gene transfer facilitated by mobile genetic elements, such as plasmids and transposons remain the most prevalent resistance mechanism (22). E. coli remains a public health concern because they continue to gain novel traits, resulting in more virulent strains (23).

For treatments the use of sensitive antibiotics is the best choice for cure, that can be done based on urine culture in the labs to determine the sensitive one for bacteria, empirical treatment should be started quickly after symptomatic UTI diagnosed and then the treatment tailored after urine culture result appear, such as modification on the type, the dose and the duration of antibiotics (24).

Nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX) and single dose of fosfomycin is a therapy for simple lower UTI used orally for short duration (3-7days) in outpatients (25), but for complicated UTI caused by multidrug resistance bacteria can be treated by using intravenous ciprofloxacin, levofloxacin, meropenem, imipenem and piperacillin-tazobactam for duration more than week and then orally (26), also for symptomatic relief can be used analgesic like non-steroidal anti-inflammatory drugs (diclofenac) (27).

Treatment strategies in rUTI focus on pharmacological treatment and preventive methods. Firstly, pharmacological treatment by using short course of antibiotics therapy to relive symptoms, without overuse of antibiotics to prevent generate resistance strain of bacteria which may lead to increase side effect and failure of antibiotics treatment (16). Secondly, preventive methods that can reduce the occurrence of this problem like take of probiotics, prophylaxis antibiotics, using of cranberry extract products, change in lifestyle habits like increase fluid intake, urination after sexual intercourse, avoid irritating feminine products, and take oral vaccine OM-89 (Uro-Vaxom) in Europe and where this vaccine is authorized, currently is licensed in 30 countries worldwide (28, 29).

One of the major challenges during UTI treatment is bacterial resistance, there are many factors that contribute to bacterial resistance to antibiotics such as over and misuse of antibiotics, lack of public awareness, patients doesn't finish antibiotics treatment course, lack of hygiene specially in poor countries, poor infection control in public health organization and lack of new antibiotics development, all these factors leads to develop the ability of bacteria to survive and continue to grow in the presence of antibiotics designated to kill them, making UTI treatment process more difficult and more susceptible to rUTI (30). Antibiotics resistance may intrinsic or acquired such as mutation, transformation, transduction and conjugation through several mechanisms like decrease uptake (porin loss), efflux pump, enzyme inactivation, altered target site and selection (death of probiotics) (31, 32).

Asymptomatic UTI and lower cystitis should be treated rapidly in pregnant women by suitable antibiotics like amoxicillin-clavulanic acid to minimize recurrent episode (33, 34). Unusual pathogens may cause UTI like Candiduria appear in the urinalysis it could be treated by fluconazole tab (35), also viral UTI are expected in child and immunocompromised patients (36).

The understanding of UTI pathophysiology can help in treatment, prevent the recurrent of the disease, decrease multi-drug resistance organisms and subsequent decrease of the economic burden (37). rUTI account for > 76 000 Australian hospitalization per year, the cost estimated for these hospitalizations was nine hundred and nine million Australian dollars (AUD$909 million) and more than $2 billion/year in the USA, so accurate diagnosis and optimal management can decrease the economic burden in the health sector (38-41).

1.1.3 Antibiotics treatment

Additional search and understanding of the pathophysiology of rUTI can lead to an accurate diagnosis and optimal treatment of rUTI. The patient's overall conditions should also be taken into consideration during the treatment process. According to the American guidelines, clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) for symptomatic UTI treatment because they are effective and less likely to produce side effects (42, 43). In rUTI cases, clinicians should treat women with antibiotics for a short duration of up to 7 days. However, in cases of rUTI where women experience acute cystitis associated with resistance to oral antibiotics, clinicians should

treat them with culture-guided parenteral antibiotics for a short duration of up to 7 days whenever possible. Resistance patterns of bacteria play a crucial role in choosing treatment and moving forward to second-line therapy.

1.1.4 Empirical vs. culture-guided treatment

Empirical therapy is reasonable in patients with typical cystitis and no risk factors for a resistant pathogen. Prioritize culture-guided therapy in patients with any history of multidrug resistance, recent hospitalization, structural or functional abnormalities, pregnancy, or severe infection. A study performed in 2022 compared empirical therapy with culture-directed antibiotics and found that, at 14 days, treatment failure rates were 31% for culture-based therapy and 17% for empirical therapy (44). This result indicates that delaying treatment until culture results are available may increase the rate of treatment failure, even when considering antimicrobial sensitivity profiles. Delaying treatment may also allow bacteria to invade the bladder wall and damage the urothelial layer (45, 46). In suspected pyelonephritis or complicated UTI, initiate empirical therapy with parenteral ceftriaxone, aminoglycosides, broad-spectrum beta-lactams, or oral fluoroquinolones, and adjust treatment as soon as culture results are available.

1.1.5 Intravesical antimicrobial therapies (IVA)

Intravesical instillation of antimicrobials directly into the bladder via a urinary catheter is a localized treatment that is infrequently used and is a last-line treatment for rUTI (47). IVA short-term seems to be safe and effective as a prophylaxis and treatment of rUTI. The silent pandemic of antibiotic resistance has demanded an urgent need for a novel solution for the treatment of rUTI. IVA has been shown to have a greater effect on bacteria at a local level while reducing systemic absorption and its associated side effects. Gentamycin was the most common IVA used and effective in the bladder (48). IVA decreased the frequency of symptomatic infections and reduced the need for oral antibiotics. Furthermore, new studies are needed to give sufficient evidence to use IVA in the prevention and treatment of rUTI.

rUTIs are managed by various specialists, including general practitioners, gynecologists, geriatricians, infectious disease specialists, and urologists. According to the European Association of Urology (EAU) 2022 guidelines, which recommend a short course of antibiotic treatment (no longer than 7 days) in uncomplicated cystitis, continuous and

postcoital prophylaxis antibiotic and use of Immuno-prophylaxis (OM-89) vaccine is strongly recommended, but no recommendation about the use of cranberry as prevention (49).

1.1.6 Antibiotics resistance

A worldwide crisis due to the rapid increase of multidrug-resistant bacteria, antibiotic is the cornerstone in the management of UTI patients. In the treatment of rUTI, there are growing concerns regarding antibiotic resistance. The World Health Organization (WHO) considers antibiotic resistance threats of the global security and published the Global Action Plan on Antimicrobial Resistance (AMR) in 2015 to increase awareness about the antimicrobial resistance problem (42, 50). If broad-spectrum antibiotics become ineffective can lead to devastating implications, making the treatment process more difficult. The highest resistance rates of uropathogens in worldwide and in Europe were cephalosporin, fluoroquinolone, and aminoglycosides, which are used in the treatment of UTI, and the best susceptibility rate was for nitrofurantoin, fosfomycin, and carbapenem (50). Antibiotic resistance is a serious problem for all physicians who treat UTI, and clinical medicine needs frequent updates to guide antibiotic therapy.

1.1.7 Prevention methods

Prevention methods are important to reduce rUTI frequency and morbidity. Behavioral modifications in UTI prevention are strongly recommended by Arbeit gemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), whereas the majority of guidelines provide a weak recommendation. Increasing oral fluid intake is recommended by the American Urology Association (AUA), Canadian Urological Association (CUA), and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guidelines. Wiping front to back after defecation, postcoital voiding, and not delaying urination is recommended by the UK National Institute for Health and Care Excellence (NICE) guidelines. Vaginal estrogen replacement is strongly recommended by the EAU, Swiss Society of Gynecology and Obstetrics (SSGO), and Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) in postmenopausal women or those with vaginal atrophy to prevent rUTI episodes, while other guidelines provide a weak-moderate recommendation. The Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines strongly recommended the use of cranberry extract as prevention in susceptible women, whereas other guidelines provided a weak-moderate

recommendation. Insufficient evidence about the use of probiotics and lactobacillus products to prevent UTI, as agreed to all guidelines. D-mannose is strongly recommended by the SEIMC guidelines, while EUA, SSGO, and AWMF provides a weak-moderate recommendation. Immunoactive prophylaxis (OM-89) is recommended by the EUA, Mexican College of Gynecology and Obstetrics Specialists (COMEGO), SEMIC, AWMF, and SSGO guidelines. Acupuncture is recommended for women who are unresponsive to antibiotic prophylaxis according to the SOGC guidelines. The SSGO recommended the use of methenamine Hippurate for short-term therapy, and the SSGO and AWMF guidelines briefly included phototherapeutics (49).

1.1.7.1 Antibiotic prophylaxis

The physicians use prophylactic antibiotics to prevent future recurrent UTI episodes in women previously diagnosed with UTI. A low dose of antibiotics for a long time can decrease the recurrence of episodes. Nitrofurantoin is commonly prescribed for women with UTIs. All antibiotics have side effects, nitrofurantoin can cause hepatic and pulmonary toxicity during long-term use. TMP, TMP-SMX, cephalexin, and fosfomycin are all used as a prophylactic drug in a daily dose, the duration of prophylaxis ranged from 3 to 6 to 12 months. A single dose of postcoital antibiotic prophylaxis is strongly recommended in women who experience rUTI linked to intercourse (42, 51).

1.1.7.2 Non-Antibiotic prophylaxis

Exacerbation of antibiotic resistance in the world has led to shift the treatment of rUTI with antibiotics towards preventive methods to decrease undesirable side effect.

1.1.7.3 Cranberry

Cranberries are one of the most important edible plants that can be used to decrease recurrent episodes in susceptible patients (52). This plant is processed to become available as tablets, juice, and other formulations (53). The active component in cranberry extract is proanthocyanins (PACs). It works by preventing the adhesion of bacteria to the urinary tract epithelium and reducing biofilm formation by washing out through the urine (54-58). Cranberry products don't kill bacteria and cause resistance. It works as a prevention, not as a treatment. It can be used as an adjunctive therapy with other products, such as D-mannose. Sometimes cranberry juice isn’t effective in treatment because most juices are heavily diluted and PCA is reduced, added sugar can encourage bacterial growth, potency

varies from batch to batch, and poor long-term adherence due to taste. Cranberry juice contains sugars and should not be used in diabetic patients. The number of clinical trials on cranberry extract used to prevent rUTI has increased. According to the systematic review and meta-analysis studies showed that the use of cranberry extract significantly lowers the rate of developing UTIs in susceptible populations and decreases antibiotic use (59, 60).

1.1.7.4 Estrogen

Vaginal estrogen therapy should be recommended in postmenopausal women with rUTI to decrease the number of recurrent episodes (61, 62). Systematic estrogen therapy should not be recommended to treat rUTI to avoid side effects. Low estrogen after menopause can lead to thinning of vaginal and urethral epithelium, loss of lactobacillus flora, increased vaginal PH, and increased colonization by uropathogens. Topical Vaginal estrogen therapy helps in restoring healthy vaginal PH, vaginal epithelium, and normal flora, and reducing bacterial adherence to the urinary tract. There are several forms of vaginal estrogen, such as cream, vaginal tablet, and vaginal ring, which may cause vaginal irritation or discharge when used. Women with estrogen-dependent cancer should not use this agent unless approved by an oncologist (63, 64).

1.1.7.5 Uro-Vaxom (OM-89)

This vaccine stimulates the immune system in the body to recognize on bacteria that causes future UTI, made from killed extracts of E. coli bacteria. According to EAU 2022 guidelines, Immuno-prophylaxis (OM-89) vaccine is strongly recommended because it doesn't lead to antibiotic resistance, and this can decrease a big problem that threatens the world. Available as an oral capsules or tablet formulation, it can help reduce recurrent episodes for many people, but not guarantee success for everyone, and further research need to be done to confirm the effectiveness of this vaccine because limited evidence is available about that. This vaccine is not a replacement for antibiotics during an active UTI and is used as a prophylactic agent in rUTI (65-67).

1.1.7.6 Lactobacillus

Probiotics are good bacteria that are normally available in the vagina and the urinary genital area, used as a prevention in rUTI patients, because they maintain vaginal PH acidic and prevent the growth of bacteria in this acidic environment. A decrease in

probiotics can lead to an increase in vaginal pH so bacterial colonization becomes easier, and the risk of recurrent episodes increases. Patients with comorbidities like DM are more susceptible to decreased probiotics. Probiotic bacteria decreased by excessive use of antibiotics, menopause, pregnancy, poor hygiene, and hormonal changes. Probiotics can help in decrease rUTI by preventing bacteria from sticking to vaginal and urinary cells, maintaining acidic media which inhibit uropathogens, and enhancing local immune defense. It can be used especially in women with frequent antibiotic use and postmenopausal women. This prevention method is good as an adjunctive therapy or for long-term use because of fewer side effects and no antibiotic resistance. The probiotics don't substitute for antibiotics in active infection, and the actual reduction in rUTI in susceptible women remains inconclusive, the duration and dose remain unknown, more comprehensive research is still needed (68-70).

1.1.7.7 D-mannose

D-mannose is a simple natural sugar found in some fruits, like cranberries, and is excreted in urine. This sugar is used in the prevention of rUTI and reduce the frequency of episodes in people with repeated infections. Work by binds to E. coli in the urine and prevents the bacteria from sticking to the bladder lining, then pushes bacteria out during urination. It works through a mechanical anti-adhesion effect, so no antibiotic resistance is developed, and it can be used for long term because it is safe and well tolerated. It may have some disadvantages because it doesn't work effectively for all bacteria, works mainly for UTIs caused by E. coli, and is not a treatment for severe or complicated UTIs. It should be used carefully in diabetic patients (71).

1.1.7.8 Methenamine Hippurate

Methenamine Hippurate is a urinary antiseptic used for the prevention of rUTI in women with frequent episodes. It is a non-antibiotic that works through hydrolysis in acidic urine to produce formaldehyde, which is a broad-spectrum bactericidal agent. Formaldehyde denatures bacterial proteins and nucleic acids, leading to non-specific inhibition of bacterial growth, and is therefore effective against both Gram-positive and Gram-negative pathogens. It can be used with pregnant women and may cause mild gastrointestinal symptoms, it should be used with caution in cases of dehydration, renal, and hepatic disease (72). It doesn't induce antibiotic resistance, therefore the use of methenamine is considered crucial, further research is needed to test the effectiveness in preventing UTIs in susceptible women (73).

Physicians should take complete history from patients to confirm the diagnosis of rUTI, including symptoms such as dysuria, frequent urination, urgency, suprapubic pain, tenderness, urethral discharge, cloudy urine, foul-smelling, hematuria, chills, fever, costovertebral tenderness, and flank pain. Physicians should assess risk factors, older age, pregnancy, presence of comorbidities, such as DM, hypertension (HTN), and heart failure (HF), and the family history. UTI history, including UTI frequency, number of UTIs in the last year, positive urine culture associated with previous episodes, type of microorganisms appearing in the culture, and antimicrobials used in treatment, must all be documented by the Physician. The physicians select the appropriate antimicrobial therapy based on urine culture results and sensitivity tests. Therefore, doctors should obtain urinalysis, urine culture, and sensitivity tests in symptomatic UTIs prior to initiating treatment. In rUTI patients with acute episodes, physicians may initiate empirical treatment while awaiting the urine culture results.

1.2 Literature Review

By search on Google schooler and PubMed

The recurrent of infection and misuse of antibiotics is an active area for scientific research, so it's important to understand the factors that associated with the recurrent of the disease.

In the Middle East and North Africa (MENA) region, UTIs represent a major public health concern, with incidence rising steadily over the past three decades (1, 2). UTIs accounted for substantial morbidity and mortality among women according to a recent regional analysis, and showed that the burden is disproportionate in countries with lower socio-demographic indices (8). Studies from the West Bank of Palestine, the Gaza Strip, and neighboring countries have consistently shown high resistance rates to first-line antibiotics such as ampicillin, trimethoprim–sulfamethoxazole, and fluoroquinolones, with ESBL-producing E. coli and Klebsiella spp. increasingly prevalent (74, 75). In other resource-limited settings, similar results have been reported, where recurrent infections are often attributed to limited access to culture-guided therapy, limited preventive strategies such as vaccines or prophylactic regimens, and overuse of broad-spectrum agents in this setting (8-12, 18, 76). The association between comorbidities such as diabetes and pregnancy with an increased risk of recurrence is well supported by the evidence from regional reviews. However, a restricted diagnostic structure contributes to delayed or inappropriate treatment, particularly in low-income countries (8).

According to the previous studies, including studies conducted in Nablus and Israel showed that UTI disease is more common in women than men, and they linked recurrent disease with several demographic and clinical factors, including older age, postmenopausal status, comorbidities, pregnancy, urinary tract abnormalities, obesity, and previous history of UTI (77-79). This study included only women to give more specific results and improve the generalizability of the findings. The results of this study were compatible with previous studies. This study confirmed that there is a relationship between older age, the presence of comorbidity, pregnancy, and a previous history of UTI with recurrent episodes.

According to previous microbiological studies performed in Nablus and Middle East showed that the most common pathogen isolated from urine samples was Gram-negative bacteria especially E. coli, and most UTIs is community-acquired, also defined some type of bacteria and their resistance profile, but the resistance rate in HA-UTI is higher than in CA-UTI, and hospital-acquired infections are more likely to be associated with resistant organisms and complicated disease (80, 81). The findings of this study are consistent with previous findings. This study demonstrates that the most isolated pathogens from urine culture was Gram-negative E. coli and then Klebsiella, and the most common UTI was community-acquired infection.

To date, no studies have been conducted in Palestine about systematically investigating the pharmacological management of rUTI on Palestinian women. This study involved the prevalence, risk factors, antimicrobial resistance patterns, and treatment outcomes of rUTIs among women. Unlike previous studies that focused on limited aspects of rUTI among Palestinian women, and there is a significant gap in the Palestinian context regarding comprehensive data on the pharmacological management of rUTIs in women, particularly in relation to antimicrobial resistance and treatment practices. This study addresses this gap. The findings of this study demonstrate that the most used empirical antibiotics were Ceftriaxone, then followed by Meropenem, Levofloxacin, and Cefuroxime, but after the urine culture results appeared, Meropenem became the most used antibiotic then followed by Levofloxacin, Cefuroxime, Cefpodoxime, and Fluconazole. These findings emphasize that treatment of rUTI should be guided by urine culture and susceptibility testing to decrease antibiotic resistance.

According to the previous studies more than 50% of women experience at least one UTI in their lifetime, and approximately one-quarter of them will experience rUTI (82). The results of this study are consistent with previous findings, showed that the overall prevalence of rUTIs among Palestinian women with UTI was 27.4% (104/380).

1.3 Problem statement

Throughout history, the treatment of UTI has not been considered complex, but the recurrence of these infections has made them more complex and requires further investigation. Complicated UTI has a higher risk for treatment failure and recurrence of infection. According to the cohort study performed in the USA, the overall incidence of uncomplicated UTI was 102 per 100,000 women ages 18-64 from 2003-2011 (83), so UTI disease have several medical and financial implication.

Generally, UTI is treated with antibiotics, but the misuse of antibiotics can lead to the generation of resistant strain of bacteria and increase antibiotic resistance, which consider global public health dilemma in 21st century and forecast of 10 million deaths per year globally by 2050 (84), antibiotic resistance can cause UTI treatment failure or recurrent of infection. The overall prevalence of rUTI in premenopausal women was 23.4% according to a study performed in Israel between June 2012 and May 2014 (77). So asymptomatic UTI doesn't always require antibiotics for treatment, and if necessary, it is used for a short duration as much as possible (85), and in rUTI cases, it can focus on preventive methods.

This study is necessary because there is no study performed about the pharmacological management of rUTI on Palestinian women previously. Indeed, the study help in improving local clinical guidelines, suggest recommendation to the health sector about the regulation of antibiotic use in UTI treatment, and optimize therapeutic modalities and strict policies in the hospitals about continuous monitoring of antibiotic sensitivity test or establishment of new model in west bank in Palestine. Furthermore, the study contributes to improve community awareness about limited use of non-prescribing antibiotics and highlight the causes of rUTI and simple non-pharmacological prevention strategies.

1.4 Research questions

1. Is there a significant relationship between the use of culture-guided therapy and the reduction of recurrent episodes in Palestinian women?
2. Is there a significant relationship between age and rUTI?
3. Is a patient with comorbidity is more susceptible to the rUTI?

1.5 Objectives

This study aimed to describe the pharmacological management of rUTI in current Palestinian Hospitals, show the prevalence of rUTI among women in Palestine, identify the causative microorganism and characterize their antimicrobial resistance pattern, clarify the main risk factors that associated with rUTI, describe the treatment before and after urine culture, and evaluate the impact of culture-guided therapy on outcomes.

1.6 Significance of the study

The findings of this study contribute to the development of local clinical guidelines in the health sector in Palestine for UTI treatment. Optimizing therapeutic modalities and strict policies in hospitals about continuous monitoring of antibiotic sensitivity tests. They help in understanding the prevalence of rUTI among Palestinian women and quantifying the disease burden. The results highlight the importance of limiting antibiotic use, or returning to the pre-antibiotic era if possible during the treatment of UTI to protect patients from severe complications. This approach can reduce morbidity and mortality, decrease the economic burden in the health sector, and improve women's quality of life. Furthermore, the study seeks to improve community awareness about the limited use of non-prescribed antibiotics and strengthening prevention strategies, and highlights the causes of rUTI.

Chapter Two

Methods

2.1 Study design

The study was a retrospective cohort study conducted in adherence to the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) statement, with adherence to the checklist provided in Supplementary Table. The retrospective design was chosen for its efficiency and feasibility, allowing the use of existing electronic medical records and laboratory data to minimize cost, time, and effort while ensuring efficient data collection and analysis. By utilizing routinely collected data, the study provided a robust framework to evaluate real-world management practices and AMR trends in a resource-limited setting. This design enabled systematic identification of women diagnosed with UTI, evaluation of their treatment approach, and assessment of recurrence patterns over defined follow-up periods. Importantly, the design facilitated analysis of antibiotic utilization patterns, the effectiveness of sensitive agents, and the clinical outcomes of women who experienced recurrent infections within six months.

2.2 Study settings

The study was conducted in the health care system in the urology department of four private hospitals in Hebron city in Palestine (Al-Ahli Hospital, Al-Mizan Hospital, Red Crescent Specialized Hospital, and Nasser Hospital), where UTI patients are found in large numbers and electronic medical record databases are available. This setting provided a robust framework to evaluate real-world management practices, antimicrobial resistance trends, and clinical outcomes in a resource-limited context. The data was collected over the nine-year period from January 2016 to December 2025, facilitating the inclusion of a diverse and representative cohort of women with acute and recurrent UTIs.

2.3 Patients

All Palestinian women aged ≥ 18 years diagnosed with UTI and admitted to the participating hospitals included in the study. Eligible patients were identified through electronic medical records and confirmed by clinical and laboratory documentation while exclusion criteria were applied to ensure validity of the findings. Women with incomplete or missing data, or those with indwelling urinary catheter, HIV infection, chronic use of

corticosteroid therapy, children, and men were excluded from the study. Through this approach allowed for the creation of cohort representative of Palestinian women with UTIs, suitable for evaluating recurrence patterns, antimicrobial resistance, and treatment outcomes.

2.4 Variables and Data Collection

Women are at higher risk of developing UTIs. There are several factors that can contribute to the development of this disease. Many variables associated with UTI disease were assessed in this study, including demographic, clinical, microbiological, and treatment variables. From patients' medical records, women's ages, and preexisting comorbidities, such as HTN, DM, chronic kidney disease, HF, cardiac catheterization, asthma, cardiovascular disease, acute kidney injury, thyroid goiter, and cervical adenocarcinoma were obtained. Clinical symptoms in women, such as dysuria, suprapubic pain, urinary frequency, urgency, fever, vomiting, flank pain, nausea, hematuria, and costovertebral pain, were evaluated. Another risk factor associated with the progression of UTI, such as pregnancy and a previous history of UTI, was assessed. Laboratory tests and their results were required to confirm the diagnosis and ensure the results as urine culture.

Based on clinical presentation, UTI is classified as complicated occur in high risk patients, such as pyelonephritis and severe urosepsis, and uncomplicated, such as simple cystitis and urethritis occur in healthy individuals. UTI in pregnant women, immunocompromised patients, kidney stones, catheters, urinary obstruction, sepsis, and males are considered complicated UTI (86). Anatomical location of UTI (cystitis / pyelonephritis) and UTI classification (complicated / uncomplicated) were obtained from the medical records of the patients. In this study, rUTI was defined as ≥ 2 episodes within six months or ≥ 3 episodes within twelve months (10, 12), and patients were categorized accordingly. The appearance of different types of pathogens in a urine culture leads to the use of different types of treatment. Therefore, the type of pathogen available in the urine culture (Gram-positive bacteria/ Gram-negative bacteria / yeast) was obtained.

The number of UTIs in the last year and the source of infection (community-acquired / hospital-acquired) were extracted from the recorded patient files. Specific causative microorganisms, sensitivity/ resistance profile, and type of multidrug resistance organisms were included. The factors that influencing the outcome and improves the validity of the findings were assessed, such

as treatment related variables, empirical and after urine culture treatment used in women with UTI. Other variables were obtained, such as coinfection presented, outcome variables included disease resolution or progression, reinfection after discharge from hospital, readmission within 30 days, and discharge status (alive / died). Data were collected retrospectively from electronic medical record databases of the participating hospitals using a standardized data collection form (Supplementary Table).

2.5 Bias

The study may have some information bias because it depended on medical records that may contain missing data and incomplete documentation. May also contain selection bias because the study included documented women diagnosed with UTI in the hospital, while excluded women with milder symptoms who were managed outside the hospital. Reducing bias in this study was achieved through using standardized data collection form, takes a sufficient and representative sample size, and reviewed the hospital extracted sheet by experts in the urology department to ensure the validity and reliability of the measurements.

2.6 Study size

The required sample size was estimated using the RaoSoft calculator (www.raosoft.com), based on an annual population of approximately 20,000 women diagnosed with UTIs in the West Bank. With a 95% confidence interval and a 5% margin of error, the minimum representative sample size was calculated to be 377 patients, which was considered statistically sufficient. In practice, the study enrolled 380 women, exceeding this threshold and thereby strengthening the reliability of the findings. This sample conducted in similar resource-limited settings. size is consistent with global epidemiological estimates, which report that UTIs affect nearly half of all women during their lifetime, with recurrent episodes occurring in 25-30% of cases (6, 87). These statistics underscore the adequacy of the current cohort size for evaluating prevalence, risk factors, and antimicrobial resistance patterns in Palestinian women, while ensuring comparability with studies.

2.7 Quantitative variables

Quantitative variables in this study, such as age and the number of UTIs in the last year, were analyzed using descriptive and inferential statistical methods. Descriptive statistics were summarized as medians and interquartile range (Q1, Q3). For inferential statistics, the comparison between two groups was performed using a two independent sample t-test, and the association between continuous variables and the presence of rUTI was conducted by using the Mann-Whitney U test, allowing assessment of whether the association is statistically significant. A p-value of <0.05 was considered statistically significant.

2.8 Statistical method

All analyses were performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics and clinical variables. Categorical variables were expressed as counts (n) and percentages (%), while continuous variables were reported as medians with interquartile ranges (Q1, Q3) due to non-normal distribution.

Inferential statistics were applied to evaluate associations between patient variables and the occurrence of rUTI. Initially, univariate analyses were conducted to explore crude associations between individual patient variables and the occurrence of rUTI. The chi-square test was used to compare categorical variables, while the Mann-Whitney U test was employed for continuous variables. p-value ≤ 0.05 was considered statistically significant. Subsequently, multivariable logistic regression analysis was constructed to identify independent predictors of rUTI and discharge outcomes. Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs), providing effect size estimates for each associated variable. Clinically relevant variables were entered into the regression models, respecting the rule of at least 10 events per outcome. Diagnostics of the regression models were systematically assessed.

2.9 Ethical approval

This study was conducted in accordance with international and local principles, including those outlined in the Declaration of Helsinki. Official and ethical approval was obtained

from the research committee and the Institutional Review Board (IRB) at An-Najah National University to conduct the research. The IRP protocol number for this research was Med. July. 2025/5, also formal permission was obtained from participating hospitals to access patient records and collect data, all collected data encoded as much as possible and used only for the purpose of this research, while maintaining patient privacy and data confidentiality. Analyses were performed by de-identified datasets, and access was restricted to the research team. A waiver of informed consent was approved by the IRP because this study involved a retrospective review of existing medical records without direct patient contact or intervention. Minimal risk to participant, the exclusive use of data for research purposes, and impractically of obtaining consent from all patients over a nine-year period make the waiver justified.

2.11 Funding

This research was conducted without financial support.

Chapter Three

Results

3.1 Baseline Characteristics and Admission Variables

A total of 380 women diagnosed with UTI were included in this study. The median age of the women was 62 years (IQR: 33–76). Comorbidities were common and reported in 255 (67.1%) women, with HTN present in 215 (56.6%) and DM in 179 (47.1%). Most women had at least one urinary symptom, the most frequent being dysuria presented in 278 (73.2%) women, followed by suprapubic pain presented in 236 (62.1%) women, and urinary frequency in 214 (56.3%). Pregnancy was documented in 61 (16.1%) women, while 113 (29.7%) had a prior history of UTI. Urine culture was performed in 376 (98.9%) patients, yielding positive results in 300 (78.9%). Of these, 266 (70.0%) were bacterial isolates and 34 (8.9%) were yeast (Candida spp.). Most infections were classified as cystitis (n = 346, 91.1%), with pyelonephritis in 34 (8.9%). Complicated UTIs accounted for 320 (84.2%), while 60 (15.8%) were uncomplicated. rUTI was identified in 104 (27.4%) women. The majority of infections were community-acquired (374, 98.4%), with only 6 (1.6%) hospital-acquired. The baseline characteristics and admission variables are shown in Table 1.

Table 1: *Baseline characteristics and admission variables of women with UTI (n = 380)*

Variable	Median (Q1, Q3) or n (%)
Age (years), median (Q1, Q3)	62.0 (33.0, 76.0)
Comorbidities	255 (67.1)
Hypertension, n (%)	215 (56.6)
Diabetes mellitus, n (%)	179 (47.1)
Chronic kidney disease, n (%)	64 (16.8)
Heart failure, n (%)	58 (15.3)
Cardiac catheterization, n (%)	37 (9.7)
Asthma, n (%)	21 (5.5)
Cardiovascular diseases, n (%)	1 (0.3)
Acute kidney injury, n (%)	1 (0.3)
Thyroid goiter, n (%)	1 (0.3)
Cervical adenocarcinoma, n (%)	1 (0.3)
Non-prescribed antibiotics, n (%)	29 (7.6)
Presenting signs and symptoms	372 (97.9)
Dysuria, n (%)	278 (73.2)
Suprapubic pain, n (%)	236 (62.1)
Urinary frequency, n (%)	214 (56.3)
Urgency, n (%)	105 (27.6)
Fever, n (%)	74 (19.5)
Vomiting, n (%)	73 (19.2)
Flank pain, n (%)	60 (15.8)
Nausea, n (%)	37 (9.7)
Hematuria, n (%)	20 (5.3)
Costovertebral pain, n (%)	14 (3.7)
History of previous UTI, n (%)	113 (29.7)
Pregnancy, n (%)	61 (16.1)
Urine culture test	
No, n (%)	4 (1.1)
Yes, n (%)	376 (98.9)
Urine culture result	
Negative, n (%)	76 (20.0)
Positive, n (%)	300 (78.9)
UTI location	
Lower (Cystitis), n (%)	346 (91.1)
Upper (Pyelonephritis), n (%)	34 (8.9)
UTI classification	
Uncomplicated, n (%)	60 (15.8)
Complicated, n (%)	320 (84.2)
RUTI (> 2 in 6 months or > 3 in 12 months)	
No, n (%)	276 (72.6)
Yes, n (%)	104 (27.4)
Type of pathogen	

Continued

Variable	Median (Q1, Q3) or n (%)
Bacteria, n (%)	266 (70.0)
Gram-positive, n (%)	33 (8.7)
Gram-negative, n (%)	233 (61.3)
Yeast, n (%)	34 (8.9)
Yeast, n (%)	34 (8.9)
Number of UTIs in the last year	
1, n (%)	67 (17.6)
2, n (%)	17 (4.5)
3, n (%)	4 (1.1)
Source of infection	
Community acquired infection, n (%)	374 (98.4)
Hospital acquired infection, n (%)	6 (1.6)

UTI: urinary tract infection, Q1: lower quartile, Q3: upper quartile

3.2 Microbiological Findings from Urine Cultures

Among the 300 women with positive urine cultures (78.9%), the majority of isolates were bacterial (n = 266, 70.0%). Gram-negative organisms predominated (n = 233, 61.3%), while Gram-positive bacteria accounted for 33 (8.7%). Yeast growth, primarily *Candida spp*., was identified in 34 (8.9%). The most frequently isolated pathogen was *Escherichia coli* (*E. coli*) (n = 154, 40.5%), followed by *Klebsiella spp.* (n = 37, 9.7%). These findings highlight that the most isolated uropathogen was Gram-negative E. coli in rUTIs among Palestinian women. The types of microorganisms isolated from urine cultures are shown in Table 2.

Table 2: *Microorganisms isolated from urine cultures of women with UTI*

Microorganism	n (%)
No pathogenic growth	76 (20.0)
Pathogenic growth	300 (78.9)
Gram positive	33 (8.7)
Streptococcus	1 (0.3)
Streptococcus viridians	1 (0.3)
Streptococcus group B	6 (1.6)
Streptococcus group D	1 (0.3)
Staphylococcus aureus	1 (0.3)
Staphylococcus saprophyticus	2 (0.5)
Enterococcus	13 (3.4)
Enterococcus D	6 (1.6)
Methicillin-resistant Staphylococcus aureus	2 (0.5)
Gram negative	233 (61.3)
Escherichia coli	154 (40.5)
Klebsiella	37 (9.7)
Enterobacter	4 (1.1)
Citrobacter	12 (3.2)
Proteus	3 (0.8)
Pseudomonas	18 (4.7)
Acinetobacter	3 (0.8)
Serratia	1 (0.3)
Moraxella	1 (0.3)
Fungal	34 (8.9)
Yeast	34 (8.9)

E. coli: Escherichia coli

3.3 Antimicrobial Therapy Patterns

Management of UTI cases required a range of antimicrobial agents, prescribed either empirically or guided by urine culture results. Empirical therapy was dominated by ceftriaxone (n = 164, 43.2%), followed by meropenem (n = 50, 13.2%), levofloxacin (n = 30, 7.9%), and cefuroxime (n = 29, 7.6%). Other antimicrobial agents were used less frequently. Treatment patterns shifted after urine culture results were obtained. Meropenem was most frequently prescribed (n = 91, 23.9%), followed by levofloxacin (n = 38, 10%), cefuroxime (n = 36, 9.5%), cefpodoxime (n = 33, 8.7%), and fluconazole (n = 31, 8.2%). These findings highlight the reliance on broad-spectrum antibiotics, particularly carbapenems, and the notable use of antifungal therapy in cases with yeast isolation. The antimicrobial agents used are shown in Table 3.

Table 3: *Antimicrobial agents used in the treatment of women with UTI*

Treatment	n (%)
Empirical Therapy	
Penicillin	
Amoxicillin and Clavulanic acid	13 (3.4)
Cephalosporins	
Cefuroxime	29 (7.6)
Cefpodoxime	10 (2.6)
Cefotaxime	1 (0.3)
Ceftriaxone	164 (43.2)
Cefixime	1 (0.3)
Carbapenems	
Ertapenem	3 (0.8)
Meropenem	50 (13.2)
Fluoroquinolones	
Ciprofloxacin	4 (1.1)
Levofloxacin	30 (7.9)
Aminoglycosides	
Amikacin	1 (0.3)
Glycopeptide	
Vancomycin	19 (5)
Macrolide	
Azithromycin	1 (0.3)
Nitroimidazole	
Metronidazole	1 (0.3)
β-Lactamase inhibitor	
Tazobactam	17 (4.5)
Phosphonic acid derivatives	
Fosfomycin	2 (0.5)
Nitrofuran	
Nitrofurantoin	2 (0.5)
Antifungals	
Polyene	
Nystatin vaginal ovules	1 (0.3)
Treatment after urine culture	
Penicillin	
Amoxicillin and Clavulanic acid	19 (5)
Cephalosporins	
Cefuroxime	36 (9.5)
Cefpodoxime	33 (8.7)
Cefdinir	7 (1.8)
Cefixime	5 (1.3)
Ceftriaxone	12 (3.2)
Carbapenems	
Ertapenem	2 (0.5)

Continued

Treatment	n (%)
Meropenem	91 (23.9)
Fluoroquinolones	
Ciprofloxacin	5 (1.3)
Levofloxacin	38 (10)
Aminoglycosides	
Amikacin	1 (0.3)
Gentamycin	1 (0.3)
Glycopeptide	
Vancomycin	8 (2.1)
Sulfonamide	
Sulfamethoxazole and Trimethoprim	2 (0.5)
Nitrofuran	
Nitrofurantoin	15 (3.9)
Nitroimidazole	
Metronidazole	2 (0.5)
β-Lactamase inhibitor	
Tazobactam	30 (7.9)
Phosphonic acid derivatives	
Fosfomycin	3 (0.8)
Glycylcyclines	
Tigecycline	1 (0.3)
Antifungals	
Azoles	
Fluconazole	31 (8.2)
Miconazole nitrate vaginal ovules	1 (0.3)
Miconazole gel	1 (0.3)
Clotrimazole and Hydrocortisone acetate cream	1 (0.3)
Polyene	
Nystatin vaginal ovules	1 (0.3)
Plant extract	
Cranberry	1 (0.3)

3.4 Clinical Outcomes and Multidrug Resistance

Among the 380 women included, UTI resolved in 355 (93.4%), while 25 (6.6%) experienced disease progression. After hospital discharge, 54 (14.2%) were re-infected with a different pathogen, whereas 316 (83.2%) remained infection-free. Readmission within 30 days occurred in 13 (3.4%) patients. A history of UTIs caused by MDR pathogens was documented in 110 (28.9%) women. Extended spectrum beta-lactamase (ESBL)-producing bacteria were the predominant resistant pathogens (n = 107, 28.2%), Antibiotic Resistance Profiles of Uropathogens followed by Carbapenem-resistant Enterobacteriaceae (CRE) (n = 4, 1.1%) and methicillin-resistant Staphylococcus aureus

(MRSA) (n = 2, 0.5%). At discharge, 363 (95.5%) patients were alive, while 17 (4.5%) had died. The clinical outcomes and multidrug resistance are shown in Table 4.

Table 4: *Clinical outcomes and multidrug resistance among women with UTI*

Outcome	n (%)
The patient is re-infected after discharge from hospital with	
same type of pathogen	10 (2.6)
different type of pathogen	54 (14.2)
Not re-infected	316 (83.2)
Re-infected with different type of pathogen	
Streptococcus viridians	1 (0.3)
Enterococcus	2 (0.5)
Staphylococcus saprophyticus	1 (0.3)
Lactobacillus	1 (0.3)
E. coli	11 (2.9)
E. coli (ESBL)	6 (1.6)
E. coli (CRE)	1 (0.3)
Klebsiella	8 (2.1)
Klebsiella (ESBL)	6 (1.6)
Klebsiella (CRE)	5 (1.3)
Proteus	3 (0.8)
Proteus (ESBL)	1 (0.3)
Pseudomonas	4 (1.1)
Pseudomonas (CRE)	1 (0.3)
Citrobacter	2 (0.5)
Citrobacter (ESBL)	2 (0.5)
Acinetobacter	3 (0.8)
Yeast	20 (5.3)
Co-infection present	
Yes	12 (3.2)
No	368 (96.8)
Has multi drug resistance history (MDRO)	
Yes	110 (28.9)
No	270 (71.1)
Type of multi drug resistance history (MDRO)	
Methicillin-resistant Staphylococcus aureus (MRSA)	2 (0.5)
Extended Spectrum Beta-Lactamase (ESBL)-producing bacteria	107 (28.2)
Carbapenem-resistant Enterobacteriaceae (CRE)	4 (1.1)
UTI disease resolved or progressed	
Resolved	355 (93.4)
Progressed	25 (6.6)
Readmission within 30 Days with UTI	
Yes	13 (3.4)
No	367 (96.6)
Discharge Status	
Alive	363 (95.5)
Died	17 (4.5)

3.5 Antibiotic Resistance Profiles of Uropathogens

A total of 376 urine cultures were collected, and 300 were positive. Microorganisms were investigated for their antibiotic resistance profiles, and antibiotic susceptibility testing of Gram-positive uropathogens demonstrated different resistance patterns across various antibiotic classes. According to this study, ampicillin showed no resistance cases,

amoxicillin and clavulanic acid resistance is moderate, with 2 cases of resistance Enterococcus and 11cases sensitive (Resistance Rate (RR) 15.4%), cefuroxime resistance is high, with 7 cases of resistance Enterococcus and 3 cases sensitive (RR 70%), cefotaxime resistance is high, with 6 cases of resistance of Enterococcus and 3 cases sensitive (RR 66.7%), ceftriaxone resistance is high, with 6 cases of resistance Enterococcus and 3 cases sensitive (RR 70%), meropenem resistance is low to moderate, with 1 case of resistance Enterococcus and 9 cases sensitive (RR 10%), tazobactam resistance is low to moderate, with 1 case of resistance Enterococcus D and 9 cases sensitive (RR 10%), ciprofloxacin resistance is high, with 5 cases resistance of Enterococcus and one case sensitive (RR 83.3%), levofloxacin resistance is high, with 5 cases of resistance Enterococcus and 2 cases sensitive (RR 71.4%), gentamycin resistance is high, with 3 cases of resistance Enterococcus and 1 case sensitive (RR 75%), vancomycin and colistin showed no resistance, and nitrofurantoin resistance is low, with 1 resistance case of Enterococcus and 9 cases sensitive (RR 10%). In recurrent UTI, nitrofurantoin may also be used as prophylactic therapy in selected patients. However, its use as empirical therapy is relatively limited and is mainly restricted to uncomplicated lower UTIs. A summary of the resistance and sensitivity profile for Gram-positive bacteria is shown in Table 5.

Table 5: *Antibiotic resistance and sensitivity ratios for Gram-positive uropathogens isolated from urine cultures*

	Gram-positive uropathogens: resistant/sensitive (R/S)									
Antibiotics / Bacteria	Streptococcus	*Streptococcus viridans*	Streptococcus group B	Streptococcus group D	Staphylococcus aureus	Staphylococcus saprophyticus	Enterococcus	Enterococcus D	Methicillin-resistant Staphylococcus aureus	Lactobacillus
Ampicillin							0/3	0/1		
Oxacillin									1/0	
Amoxicillin and Clavulanic acid Cefazolin	0/1	1/0	0/6	0/1	0/1	0/2	2/11	0/6	1/0	0/1
Cefoxitin						0/1			1/0	
Cefuroxime	0/1	1/0	0/6	1/0	0/1	1/1	7/3	5/0	1/0	
Ceftazidime			0/1				2/0			
Cefotaxime	0/1	1/0	1/5	1/0	0/1	1/1	6/3	4/0	1/0	0/1
Ceftriaxone	0/1		0/5	1/0	0/1	1/1	6/3	4/0	1/0	0/1
Imipenem		1/0	0/2			0/1				
Meropenem	0/1	0/1	0/6	0/1	0/1	0/2	1/9	1/5	1/0	
Ertapenem										
Tazobactam	0/1	0/1	0/5	0/1	0/1	0/2	1/9	1/5	1/0	
Ciprofloxacin	1/0		0/1	1/0	0/1	0/2	5/1	3/1	1/0	
Levofloxacin	1/0		1/3	1/0	0/1	0/2	5/2	4/1	1/0	
Moxifloxacin										
Gentamycin			3/0	1/0	0/1	1/1	3/1	2/0	1/1	
Amikacin	1/0		3/2		0/1	1/1	7/0	2/0	1/0	
Teicoplanin		0/1	0/1	0/1	0/1	0/1	1/7	0/4	0/1	
Vancomycin	0/1	0/1	0/5	0/1	0/1	0/2	0/11	0/6	0/2	
Colistin			0/1				0/1			
Nitrofurantoin		0/1	0/3	0/1		0/1	1/9	0/5	1/0	
Metronidazole									1/0	
Sulfamethoxazole and Trimethoprim Tigecycline				1/0				2/0	0/1	

* R- Resistance, S- Sensitive

Among 233 urine cultures with gram-negative bacteria, ampicillin resistance was high: there were 2 cases of E. coli resistance and no sensitive case (RR 100%), 1 case of resistance and 1 case sensitive of Klebsiella (RR 50%). Amoxicillin and clavulanic acid resistance are high in E. coli (88 resistant, 58 sensitive, RR 60.3%), and in Klebsiella (27 resistant, 10 sensitive, RR 73%), often involving ESBL-producing bacteria. Cefuroxime resistance is also high: E. coli showed 75 resistant and 76 sensitive cases (RR 49.7%), while Klebsiella had 23 resistant and 12 sensitive (RR 65.7%). Ceftazidime resistance is high in E. coli (19 resistant, 29 sensitive, RR 39.6%), and Klebsiella (9 resistant, 8 sensitive, RR 52.9%). Ceftriaxone resistance is high too: E. coli showed 67 resistant, 83 sensitive (RR 44.7%), and Klebsiella had 25 resistant, 12 sensitive (RR 67.6%).

Meropenem resistance is low: E. coli had no resistance and 152 cases were sensitive (RR zero), while Klebsiella had 2 resistant, 34 sensitive (RR 5.6%). Tazobactam resistance is low in E. coli (4 resistant, 136 sensitive, RR 2.9%). Ciprofloxacin resistance is high in E. coli (46 resistant, 42 sensitive, RR 52.3%) and in Klebsiella (15 resistant, 4 sensitive, RR 78.9%).

Levofloxacin resistance is high in E. coli (49 resistant, 83 sensitive, RR 37.1%), and in Klebsiella (11 resistant, 16 sensitive, RR 40.7%). Gentamycin resistance is intermediate: E. coli had 15 resistant, 81 sensitive (RR 15.6%). Amikacin resistance is low: E. coli had 1 resistant, 147 sensitive (RR 0.68%), Klebsiella had 3 resistant, 33 sensitive (RR 8.3 %), and Pseudomonas had 1 resistant, 16 sensitive (RR 5.9%). Vancomycin resistance is low E. coli had no resistance with 8 sensitive cases. Nitrofurantoin resistance is low: E. coli had 2 resistant, 60 sensitive (RR 3.2%). Sulfamethoxazole and trimethoprim resistance are high in E. coli (20 resistant, 9 sensitive, RR 69%). A summary of the resistance and sensitivity profile for Gram-negative bacteria is shown in Table 6.

Table 6: *Antibiotics resistance and sensitivity ratios for Gram-negative uropathogens isolated from urine cultures*

Antibiotics / Bacteria	Gram-negative uropathogens: resistant/sensitive (R/S)								
	Escherichia coli	*Klebsiella*	Enterobacter	Citrobacter	Proteus	Pseudomonas	Acinetobacter	Serratia	Moraxella
Ampicillin	2/0	1/1							
Oxacillin									
Amoxicillin and Clavulanic acid	88/58	27/10	4/0	5/7	2/1	12/0	2/0	0/1	0/1
Cefazolin	4/0	1/0	1/0						
Cefoxitin	1/0								
Cefuroxime	75/76	23/12	4/0	4/8	2/1	12/0	2/0	0/1	0/1
Ceftazidime	19/29	9/8	1/0	0/3		4/11	1/0		0/1
Cefotaxime	66/78	25/12	2/1	3/8	2/1	9/3	2/0	0/1	0/1
Ceftriaxone	67/83	25/12	3/1	3/9	2/1	10/2	2/0	0/1	0/1
Imipenem	0/38	1/13	0/1	0/3	0/1	0/6	2/0		
Meropenem	0/152	2/34	0/4	0/12	0/3	2/15	2/1	0/1	0/1
Ertapenem	0/25	0/10	0/2	0/1	0/2		1/0		
Tazobactam	4/136	5/27	0/3	0/12	0/3	0/16	2/0	0/1	0/1
Ciprofloxacin	46/42	15/4	0/1	5/4	1/1	4/5		0/1	
Levofloxacin	49/83	11/16	1/0	5/6	1/2	5/9	1/1	0/1	0/1
Moxifloxacin		1/0							
Gentamycin	15/81	6/16	1/2	3/6	0/2	5/11	3/0	0/1	1/0
Amikacin	1/147	3/33	0/4	0/12	0/3	1/16	2/0	0/1	1/0
Teicoplanin	0/2								
Vancomycin	0/8								
Colistin	1/55	0/21	0/3	0/4	0/1	0/6	0/3		
Nitrofurantoin	2/60	2/3		0/4	2/0	3/1	1/0		
Metronidazole									
Sulfamethoxazole and Trimethoprim	20/9	7/0		1/0	1/1	2/0	1/0		
Tigecycline	0/4	0/1		0/1			0/2		

* R- Resistance, S- Sensitive

3.6 Variables Significantly Associated with rUTIs

Univariate analysis identified some significant associations between women's variables and occurrence of rUTIs (as shown in table 7.). Women with rUTI were older, with a median age of 65.0 years (Q1: 45.0, Q3: 78.0), compared to 60.0 years (Q1: 30.0, Q3: 74.0) in non-rUTI cases ($p = 0.015$).

Presenting symptoms differed between groups. Suprapubic pain was reported in 56 (14.7%) rUTI patients versus 180 (47.4%) non-rUTI ($p = 0.045$). Flank pain was more frequent in rUTI, 35 (9.2%) vs. 39 (10.3%) ($p < 0.001$), as was hematuria, 28 (7.4%) vs. 32 (8.4%) ($p < 0.001$). Fever occurred in 10 (2.6%) rUTI patients compared to 10 (2.6%) non-rUTI ($p = 0.035$), and costovertebral pain was more common in rUTI, 10 (2.6%) vs. 4 (1.1%) ($p = 0.001$). UTI location showed strong associations as cystitis was more frequent in non-rUTI, 263 (69.2%) vs. 83 (21.8%) ($p < 0.001$), while pyelonephritis was more common in rUTI, 21 (5.5%) vs. 13 (3.4%). Previous UTI was reported in 93 (24.5%) rUTI patients vs. 20 (5.3%) non-rUTI ($p < 0.001$).

Diabetes mellitus was present in 62 (16.3%) rUTI vs. 117 (30.8%) non-rUTI ($p = 0.004$), and asthma in 11 (2.9%) vs. 10 (2.6%) ($p = 0.012$). Pregnancy was less frequent in rUTI, 5 (1.3%) vs. 56 (14.7%) ($p < 0.001$). Empirical meropenem use was documented in 23 (6.1%) rUTI vs. 27 (7.1%) non-rUTI ($p = 0.003$).

Culture-guided therapy included nitrofurantoin (8, 2.1% vs. 7, 1.8%; $p = 0.034$), vancomycin (5, 1.3% vs. 3, 0.8%; $p = 0.038$), meropenem (33, 8.7% vs. 58, 15.3%; $p = 0.032$), tazobactam (15, 3.9% vs. 15, 3.9%; $p = 0.009$), and cefpodoxime (2, 0.5% vs. 31, 8.2%; $p = 0.003$). E. coli was isolated in 7 (1.8%) rUTI vs. 4 (1.1%) non-rUTI ($p = 0.012$).

Klebsiella spp. appeared in 6 (1.6%) vs. 2 (0.5%) ($p = 0.006$), ESBL-producing Klebsiella in 5 (1.3%) vs. 1 (0.3%) ($p = 0.007$), and Candida spp. in 16 (4.2%) vs. 4 (1.1%) ($p < 0.001$). Disease resolution occurred in 90 (23.7%) rUTI vs. 265 (69.7%) non-rUTI ($p = 0.002$), while progression was more frequent in rUTI, 14 (3.7%) vs. 11 (2.9%). Readmission within 30 days was documented in 13 (3.4%) rUTI vs. none in non rUTI ($p < 0.001$). Mortality was higher in rUTI, 11 (2.9%) vs. 6 (1.6%) ($p = 0.001$).

Table 7. *Univariate analysis of variables associated with occurrence of RUTIs*

Variable	RUTI No n (%)	RUTI Yes n (%)	p-value
Age (in years), median (Q1, Q3)	60.0 (30.0, 74.0)	65.0 (45.0, 78.0)	0.015
Suprapubic pain	180 (47.4)	56 (14.7)	0.045
Flank pain	39 (10.3)	35 (9.2)	< 0.001
Hematuria	32 (8.4)	28 (7.4)	< 0.001
Fever	10 (2.6)	10 (2.6)	0.035
Costovertebral pain	4 (1.1)	10 (2.6)	0.001
UTI location			
(Cystitis)	263 (69.2)	83 (21.8)	< 0.001
(Pyelonephritis)	13 (3.4)	21 (5.5)	
History of previous UTI	20 (5.3)	93 (24.5)	< 0.001
Number of UTIs in the last year, median (Q1, Q3)	0.0	1.0 (1.0, 2.0)	0.024
Pregnant women	56 (14.7)	5 (1.3)	< 0.001
Presence of comorbidities	177 (46.6)	78 (20.5)	≤ 0.05
Diabetes mellitus	117 (30.8)	62 (16.3)	0.004
Asthma	10 (2.6)	11 (2.9)	0.012
The patient takes non-prescribed antibiotics	14 (3.7)	15 (3.9)	0.004
Meropenem administered as empirical antimicrobial therapy	27 (7.1)	23 (6.1)	0.003
Source of infection			
Community acquired infection	274 (72.1)	100 (26.3)	≤ 0.05
Hospital acquired infection	2 (0.5)	4 (1.1)	
Antibiotics administered after urine culture result and drug treatment	234 (61.6)	98 (25.8)	0.015
Nitrofurantoin administered after urine culture result	7 (1.8)	8 (2.1)	0.034
Vancomycin administered after urine culture result	3 (0.8)	5 (1.3)	0.038
Meropenem administered after urine culture result	58 (15.3)	33 (8.7)	0.032
Tazobactam administered after urine culture result	15 (3.9)	15 (3.9)	0.009
Cefpodoxime administered after urine culture result	31 (8.2)	2 (0.5)	0.003
Has multi drug resistance history (MDRO)	71 (18.7)	39 (10.3)	0.031
The patients re-infected with the different type of pathogen after discharge from hospital	16 (4.2)	38 (10.0)	< 0.001
Re-infected with E. coli	4 (1.1)	7 (1.8)	0.012
Re-infected with Klebsiella	2 (0.5)	6 (1.6)	0.006
Re-infected with Klebsiella (ESBL)	1 (0.3)	5 (1.3)	0.007
Re-infected with Yeast	4 (1.1)	16 (4.2)	< 0.001
UTI disease resolved or progressed			
Resolved	265 (69.7)	90 (23.7)	0.002
Progressed	11 (2.9)	14 (3.7)	
Readmission within 30 days with UTI	0 (0.0)	13 (3.4)	< 0.001
Discharge status			
Alive	270 (71.1)	93 (24.5)	0.001
Died	6 (1.6)	11 (2.9)	

Logistic regression was conducted to adjust potential confounding variables (Table 8). History of previous UTI was a strong factor associated with occurrence of rUTIs (OR = 106.45, 95% CI: 46.13 245.62, $p < 0.001$). Age, suprapubic pain, flank pain, hematuria, fever, costovertebral pain, UTI location, diabetes mellitus, and asthma were not significantly associated with rUTI ($p > 0.05$). The model demonstrated excellent overall fit. The omnibus test of model coefficients was highly significant ($\chi2 = 261.4$, df = 10, $p < 0.001$), indicating that the predictors collectively contributed to the model. The model explained a substantial proportion of variance, with Cox & Snell R2 = 0.497 and Nagelkerke R2 = 0.720. The Hosmer-Lemeshow goodness-of-fit test was non-significant ($\chi2 = 5.33$, df = 8, $p = 0.722$), confirming good calibration between observed and predicted outcomes. Classification accuracy was high, correctly classifying 91.8% of cases overall, with sensitivity of 89.4% and specificity of 92.8%.

Table 8: *Factors associated with occurrence of rUTIs after controlling confounding variables*

						95% CI for OR	
Variable	B	SE	Wald	p-value	OR	lower	upper
Age (in years), median (Q1, Q3)	0.00	0.01	0.01	0.94	1.00	0.98	1.02
Suprapubic pain	0.05	0.44	0.01	0.91	1.05	0.44	2.50
Flank pain	-0.72	0.75	0.93	0.34	0.49	0.11	2.11
Hematuria	0.01	0.86	0.00	0.99	1.01	0.19	5.38
Fever	-0.84	0.52	2.55	0.11	0.43	0.16	1.21
Costovertebral pain	0.19	1.39	0.02	0.89	1.21	0.08	18.34
UTI location	-0.76	1.02	0.55	0.46	0.47	0.06	3.46
History of previous UTI	4.67	0.43	119.72	0.00	106.45	46.13	245.62
Diabetes mellitus	-0.67	0.46	2.14	0.14	0.51	0.21	1.25
Asthma	0.13	0.77	0.03	0.86	1.14	0.25	5.14

*CI: confidence interval, OR: odds ratio, SE: standard error

3.7 The association between patient variables and discharge status (Alive / Died)

Regression models were used to identify factors independently associated with the mortality, as shown in table 8. Mortality reflects all causes of death, not exclusively attributable to UTI, but the main cause of death due to urosepsis. Mortality was significantly associated with advanced age, the median age of died patients was 77 (68, 81), while the median age was 61 (32, 75) in surviving patients ($p = 0.002$).

Clinical symptoms, including suprapubic pain, urinary frequency, fever, vomiting, flank pain, costovertebral pain, and hematuria more frequent among patients who died (all $p < 0.05$). Pyelonephritis is strongly associated with mortality compared with cystitis ($p < 0.001$), as well as a history of previous UTI and a higher number of UTI episodes in the

last year. Mortality was significantly linked to rUTI (p = 0.001), presence of comorbidities, particularly HTN, DM, and heart failure (HF) (all p < 0.05), and presence of coinfection (p = 0.001). In addition, patients who died were more likely to receive meropenem empirically and after urine culture results (all $p < 0.05$). All deaths occurred among patients who had disease progression, whereas complete resolution occurred in surviving patients ($p < 0.001$).

Table 9: *The association between patient variables and discharge status (died / alive)*

	Outcome		
Variable	Died n (%)	Alive n	p-value
Age (in years), median (Q1, Q3)	77 (68, 81)	61 (32, 75)	0.002
Suprapubic pain	4 (1.1)	232 (61.1)	0.001
Urinary frequency	4 (1.1)	210 (55.3)	0.01
Fever	11 (2.9)	63 (16.6)	< 0.001
Vomiting	10 (2.6)	63 (16.6)	< 0.001
Flank pain	10 (2.6)	50 (13.2)	< 0.001
Costovertebral pain	9 (2.4)	5 (1.3)	< 0.001
Hematuria	5 (1.3)	15 (3.9)	0.001
UTI location			
Lower (Cystitis)	4 (1.1)	342 (90)	< 0.001
Upper (Pyelonephritis)	13 (3.4)	21 (5.5)	
History of previous UTI	11 (2.9)	102 (26.8)	0.002
Number of UTIs in the last year, median (Q1, Q3)	2 (1, 2)	1 (1, 1)	0.019
The patient suffers from recurrent UTI (>2 in 6 months or >3 in 12 months)	11 (2.9)	93 (24.5)	0.001
Presence of comorbidities	17 (4.5)	238 (62.6)	0.001
Hypertension	14 (3.7)	201 (52.9)	0.042
Diabetes mellitus	15 (3.9)	164 (43.2)	0.001
Heart failure	8 (2.1)	50 (13.2)	0.001
Meropenem administered as empirical antimicrobial therapy	8 (2.1)	42 (11.1)	0.001
Co-infection present	4 (1.1)	8 (2.1)	0.001
Vancomycin administered after urine culture result	4 (1.1)	4 (1.1)	< 0.001
Meropenem administered after urine culture result	9 (2.4)	82 (21.6)	0.008
UTI disease resolved or progressed			
Resolved	0	355 (93.4)	< 0.001
Progressed	17 (4.5)	8 (2.1)	

Chapter Four
Discussion and Conclusion

4.1 Discussion

rUTIs represent a major challenge in women's health worldwide, yet evidence from resource-limited settings remains scarce (5, 8, 18). To our knowledge, this is the first large-scale study in Palestine to systematically investigate the prevalence, risk factors, antimicrobial resistance patterns, and treatment outcomes of rUTIs among women. Our findings are notable as nearly one in three women with UTI experienced recurrence, E. coli was the dominant uropathogen, and ESBL production was common, eroding the effectiveness of widely used cephalosporins and fluoroquinolones. Indeed, our findings suggest that culture-guided therapy was associated with decreased recurrence rates, underscoring its critical role in successful treatment and better outcomes.

These results hold significant value not only for clinicians and pharmacists in Palestine but also policymakers, public health authorities, and international stakeholders seeking to strengthen antimicrobial stewardship in resource-limited settings. By highlighting the burden of rUTIs and the pressing need for evidence-based management, this study provides practical guidance for improving women's health and alleviating the economic strain on healthcare systems. Furthermore, the study contributes to improve community awareness about the limited use of non-prescribing antibiotics and highlights the causes of rUTI and simple non-pharmacological prevention strategies.

The prevalence of rUTIs in our cohort was 27.4%, which is consistent with global estimates reporting recurrence in one quarter to one third of women following an initial UTI episode (5, 6, 16). This burden is similar to the findings from large epidemiological studies in Europe and North America, where the rate of recurrence ranges between 25–30% (3, 87). The prevalence of rUTI disease provides insight into a substantial clinical and economic public health burden. Multicenter studies are needed to further explore the preventive strategies and optimize management for rUTI in Palestine.

Our study further confirmed that older age, comorbidities such as DM and asthma, and pregnancy significantly increased the risk of rUTIs, reflecting similar observations reported across high-income and resource-limited settings (15, 17, 18). Notably, the identification of these risk factors in Palestinian women underscores the universality of

host-related determinants of recurrence, while also highlighting the need for tailored preventive strategies in populations with limited access to culture-guided therapy and stewardship programs. These findings are particularly relevant for clinicians, pharmacists, and public health authorities in the Middle East, where the rising prevalence of chronic diseases such as DM may further amplify the risk of recurrent infections (8).

The microbiological profile of our cohort showed that E. coli was still the predominant uropathogen, accounting for (40.5%) of isolates, followed by Klebsiella spp. (9.7%). This distribution aligns with international epidemiological patterns, where E. coli consistently represents the leading cause of both acute and rUTIs (9-11). In agreement with reports from the Middle East and other resource-limited regions, our research underscores a notably high prevalence of ESBL-producing strains, especially among E. coli and Klebsiella. (8, 74, 75). The emergence of these resistance patterns has eroded the effectiveness of widely used cephalosporins and fluoroquinolones, leaving clinicians increasingly reliant on carbapenems, as noted in our cohort and in similar studies worldwide (5, 18).

The detection of fungal pathogens in nearly 9% of cases, particularly Candida spp., emphasizes the increasing complexity of rUTI management in Palestine, potentially attributable to extensive broad-spectrum antibiotic use and the difficulties associated with antimicrobial stewardship in resource-limited settings (19, 76). Collectively, these findings underscore the urgent need for robust and comprehensive surveillance systems and rely on culture-guided therapy to mitigate the escalating impact of AMR in uropathogens.

Antimicrobial therapy approaches in our cohort demonstrated a heavy reliance on broad-spectrum antibiotics, particularly ceftriaxone for empirical treatment and meropenem after culture results. These approaches reflect the erosion of cephalosporin and fluoroquinolone effectiveness due to widespread ESBL production, a trend consistently reported in both local and international studies (9-11). While carbapenems are still highly effective against MDR E. coli and Klebsiella spp., their increasing use raises concerns about the emergence of CRE, which have already been identified in the region (74, 75).

Our findings showed that culture-guided therapy was significantly associated with a reduced recurrence rate, underscoring the importance of diagnostic stewardship, as similar evidence from large cohort studies in Europe and North America, where targeted therapy improved outcomes and decreased unnecessary exposure to broad-spectrum antibiotics (6, 88). The notable detection of fungal pathogens, particularly Candida spp., further underscores the unintentional consequences of empirical broad-spectrum prescribing, as prolonged or inappropriate antibiotic use predisposes women to opportunistic infections (19, 76). All these results further emphasize the urgent need for antimicrobial stewardship programs in Palestine, where culture-guided therapy could serve as a cornerstone for reducing recurrence rate, preserving antibiotic effectiveness, and alleviating the financial burden of rUTIs in health sectors.

While most women in our cohort achieved clinical resolution, recurrence and reinfection continue to be significant challenges, reflecting the sophisticated interplay between host factors, pathogen resistance, and treatment practices. Reinfection after discharge from hospitals and early readmission, though relatively infrequent, underscore the vulnerability of women with comorbidities such as DM and asthma, as well as those with prior UTI history, all of which were identified as predictors of poor outcomes (6, 16). Mortality, documented in 4.5% of cases, is similar to reports from other resource-limited areas where delayed diagnosis, empirical reliance on ineffective antibiotics, and limited access to culture-guided therapy contribute to deleterious outcomes (8, 11).

Crucially, the presence of MDR pathogens, particularly ESBL-producing E. coli and Klebsiella spp., was strongly associated with recurrence and treatment failure, emphasizing the urgent need for stewardship interventions. These findings suggest that while short-term resolution is achievable, long-term outcomes are compromised by recurrent infections and resistance, making culture-guided therapy and preventive strategies remain essential components of effective management in Palestine and similar settings.

The findings of this study provide distinct insights from those documented in other areas, reflecting the specific challenges of managing rUTIs in Palestine. While recurrence rates in our cohort were widely consistent with global estimates, the higher prevalence of ESBL-producing E. coli and Klebsiella spp., the dependence on empirical broad-spectrum antibiotics, and the notable detection of fungal pathogens made our

findings different from studies in high-income countries where culture-guided therapy is routine and stewardship programs are well established (3, 6, 19). These differences highlight the importance of context: in settings with limited diagnostic infrastructure and inconsistent stewardship, treatment practices and outcomes differ from global criteria.

Through reporting these patterns in a large, multi-center Palestinian cohort, our study provides evidence that is both locally relevant and globally informative. For physicians, the results underscore the need to prioritize culture-guided therapy; for policymakers, they provide a basis for strengthening stewardship and diagnostic capacity; and for researchers, they provide active areas where further investigation is required to tailor interventions to resource-limited settings.

The findings of this study showed that risk factors, such as women with older age, the presence of comorbidity, especially DM, a history of previous UTI, an increasing number of UTIs in the preceding year, pregnancy, and pyelonephritis were significantly associated with rUTI. The findings of this study are consistent with those of previous studies (89-94). Based on these findings, women with a high risk of rUTI should be early identified, closely monitored, receive early follow-up, and be educated about prevention strategies. Optimal management of comorbidities is essential to reduce the development of UTI.

The median age of the women was 62 [33, 76] years, indicating most of the sample was older. Women with rUTI had a median age of 65 [45, 78] years, while controls had a median age of 60 [30, 74] years. A Chi-square test found a significant relationship between rUTI and older age ($p = 0.015$).

This suggests that increasing age is associated with increased rUTI risk, possibly due to changes like declining immune function, higher comorbidity rates, functional impairment, and greater exposure to healthcare interventions. With increasing age estrogen level decline especially during the postmenopausal periods, this led to structural and functional changes in the urogenital tract, including thinning of the vaginal and urethral epithelium, loss of mucosal elasticity, and alters the vaginal microbiota by reducing protective flora and increasing vaginal pH, these changes facilitate colonization by uropathogens such as E. coli, making older women more susceptible to recurrent episodes.

Our findings revealed that clinical symptoms experienced by the patients like dysuria, suprapubic pain, urinary frequency, urgency, fever, nausea, vomiting flank pain, hematuria, and costovertebral pain contribute to impaired daily functioning and have a significant impacts on the physical health, increase financial burden, and reduce overall quality of life among affected women, particularly in recurrent and frequent cases, as the previous studies mentioned also (95-97).

Therefore, health care providers should prioritize early recognition and management of these symptoms so that comprehensive patient assessment and appropriate symptoms control can reduce disease burden and the suffering of patients.

Anatomical location of UTI was significantly associated with RUTI ($p < 0.001$). Cystitis was predominantly observed among women without RUTI 263 (69.2%), compared with those with RUTI 83 (21.8%), indicating that lower urinary tract infections are more commonly associated with non-recurrent episodes.

In contrast, pyelonephritis among women without RUTI was 13 (3.4%), and among women with RUTI was 21 (5.5%), indicating that upper urinary tract infections are more strongly associated with recurrent episodes. This pattern suggests that more severe and ascending infections are more likely to be associated with RUTI. These findings highlight the importance of early diagnosis and rapid management with suitable antibiotics to prevent progression and repeated episodes.

Patients may engage in practices that can impact the outcome of their treatment. Taking non-prescribed antibiotics can lead to incomplete eradication of bacteria because the type, dose, and duration are often inappropriate for the specific bacterial infection. Antibiotics should be taken under medical guidance to prevent the emergence of resistant bacterial strains, which can occur with repeated unsupervised use.

These strains are well-known contributors to rUTI. Sometimes, patients can't distinguish between bacterial and yeast infections, and taking antibiotics in this case is not correct because antibiotics don’t kill candida and destroy normal flora, which allows candida to overgrow, leading to a worsening of the condition. For a yeast infection, the recommended treatment is antifungal, such as fluconazole. Patients who self-medicate may be more prone to treatment failure because irregular use of non-prescribed antibiotics can disrupt the normal urogenital microbiota and facilitate bacterial colonization and

reinfection. The results of this study indicate that taking non-prescribed antibiotics is strongly associated with rUTI ($p = 0.004$).

When patients take non-prescribed antibiotics, they may suppress the symptoms without treating the cause, delaying urine culture and targeted therapy, which increases the risk of recurrent episodes. If the resistance developed, the rate of future treatment failures increased, resulting in recurrent episodes and additional hospital visits. Therefore, the guidelines strongly emphasize culture-guided therapy and avoid self-initiated antibiotics, especially in recurrent cases.

UTIs are among the most common diseases that occur in women, the source of infection is either community-acquired or hospital-acquired. The findings of this study showed that most UTIs in women were community-acquired infections, accounting for 374 (98.4%), whereas hospital acquired, accounting for 6 (1.6%).

Most previous studies shown that community-acquired infection occur more than hospital acquired in women with UTI, but the proportions different from one study to another. Community-acquired UTIs often occur in healthy individuals outside the hospital and mostly respond well to empirical therapy.

In contrast, hospital-acquired UTIs, which develop after hospital admission, often occur in patients with underlying comorbidities, they are often caused by multidrug-resistant organisms, such as ESBL-producing bacteria and carbapenem-resistant bacteria, and are generally more severe and more associated with morbidity. Hospital-acquired infections have a worse impact on epidemiology and leads to increase economic burden in healthcare settings.

Urine culture may yield a variety of bacterial pathogens due to differences in patient characteristics, the source of infection, and healthcare exposure. Gram-negative organisms, such as Escherichia coli, Klebsiella, Enterobacter, Citrobacter, Proteus, Pseudomonas, Acinetobacter, Serratia, and Moraxella, and Gram-positive organisms, such as Streptococcus, Streptococcus viridians, Streptococcus group B, Streptococcus group D, Staphylococcus aureus, Staphylococcus saprophyticus, Enterococcus, Enterococcus D, and Methicillin-resistant staphylococcus aureus can appear in urine culture in UTI women. Optimal treatment decisions should be guided based on precise microbiological identification and targeted antimicrobial susceptibility testing due to the

diversity of bacterial isolates identified in urine culture.

The microbiological findings for this study revealed a predominance of Gram-negative bacteria, including E. coli accounting for 154 (40.5%), and Klebsiella, accounting for 37 (9.7%), and a predominance of Gram-positive bacteria, including Enterococcus accounting for 13 (3.4%). The findings of this study are consistent with those of previous studies (78, 80, 81).

A study performed in 2020 showed that the predominant isolates from urine culture were gram-negative E. coli, accounting for (68.9%), followed by Klebsiella pneumoniae (8.9%) and Staphylococcus aureus (6.7%) (98). Another study performed in 2022 showed that the most isolates from urine culture were E. coli, accounting for (68.3%), followed by Klebsiella pneumoniae, accounting for (31.7%) (99). In Uganda, another study performed and showed that the most prevalent bacterial uropathogens were E. coli, accounting for (41.9%), followed by Staphylococcus aureus (31.4%) and Klebsiella pneumoniae (11.6%) (100).

AMR it is a major global public health threats, occurs when bacteria, virus, fungi, and parasites no longer respond to antimicrobial drugs, this can hinder the treatment process and reduces the effectiveness of medication leads to long-lasting illness. AMR is accelerated due to the misuse and overuse of antimicrobial medicines. All countries in the world try to minimize AMR, and some countries are moving towards prevention strategies and returning to pre-antibiotics era in the treatment of infections.

Some European countries have also turned to using vaccines to management of UTI. Understanding local AMR plays a fundamental part in selecting appropriate antibiotic treatment and successfully eradicating the infection and preventing its recurrence. The findings of this study show that ciprofloxacin, gentamycin, levofloxacin, cefuroxime, and ceftriaxone resistance are high in Enterococcus, while meropenem and nitrofurantoin resistance are low in Enterococcus.

Amoxicillin and clavulanic acid, cefuroxime, ceftazidime, ceftriaxone, ciprofloxacin, levofloxacin, and sulfamethoxazole and trimethoprim resistance are high in E. coli and Klebsiella involving ESBL-producing bacteria, whereas resistance to meropenem, tazobactam, amikacin, and nitrofurantoin is low in E. coli and Klebsiella. The findings of this study build on the findings of the previous study (75, 101-103). The result of a

previous study performed in 2022 showed that E. coli was highly resistant for ceftriaxone, ampicillin, levofloxacin, cefotaxime, aztreonam, ceftazidime, gentamycin, piperacillin, and trimethoprim-sulfamethoxazole, but showed low resistance to imipenem, cefepime, and ciprofloxacin (99). Another study performed in southern Italy in 2023 showed that low resistance rates were recorded against nitrofurantoin, fosfomycin, piperacillin-tazobactam, and gentamycin (104). The findings of this study confirm the need for routine urine culture and susceptibility testing in healthcare settings to guide the treatment. Knowledge of resistance patterns is essential in determining appropriate antibiotics in the treatment of UTI and decreasing multidrug-resistant organisms.

Doctors have many antibiotic options available to treat UTIs. Including penicillin, such as amoxicillin and clavulanic acid, cephalosporins, such as cefuroxime, cefpodoxime, cefotaxime, ceftriaxone, and cefixime, carbapenems such as ertapenem and meropenem, fluoroquinolones, such as ciprofloxacin and levofloxacin, aminoglycosides, such as amikacin and gentamycin, glycopeptide, such as vancomycin, macrolide, such as azithromycin, nitroimidazole, such as metronidazole, β-lactamase inhibitor, such as tazobactam, phosphonic acid derivatives, such as fosfomycin, nitrofuran, such as nitrofurantoin, sulfonamide, such as sulfamethoxazole and trimethoprim, glycylcyclines, such as tigecycline, but their choice depends on the patient overall condition.

The treatment findings showed that the most used empirical antibiotics were ceftriaxone, then followed by meropenem, levofloxacin, and cefuroxime, but after the urine culture results appeared, meropenem became the most used antibiotic then followed by levofloxacin, cefuroxime, cefpodoxime, and fluconazole.

Delay in effective treatment allows the infection to become severe and complicated. The findings of this study were consistent with previous studies (105-107). Timing and effective culture-guided therapy by healthcare providers is essential to reduce recurrence and antibiotic resistance. Also, should choose empirical therapy based on patient demographics/medical history, and strengthening antimicrobial stewardship program to limit unnecessary use of broad-spectrum antibiotics.

The high reliance on ceftriaxone as empirical therapy in resource-limited settings may be attributed to its relatively low cost and its wide availability in healthcare centers compared to other antimicrobial agents. However, the excessive dependence on ceftriaxone may

contribute to the emergence and progression of AMR, leading to a gradual decline in its effectiveness, as shown in the (resistance/sensitivity ratio), as well as the effectiveness of other cephalosporins.

Therefore, the antimicrobial stewardship program plays a crucial role in promoting the rational use of ceftriaxone through encouraging culture-guided, limiting unnecessary empirical prescribing, and optimizing antibiotic selection based on local susceptibility patterns in order to preserve the efficiency of cephalosporins for future use. All health care providers should collaborate with each other to minimize this problem and improve patient outcomes.

The role of pharmacists in the antimicrobial stewardship program

Pharmacists play an essential role in combating the growing problem of antimicrobial resistance through participation in the antimicrobial stewardship program. Through effective patient counseling and education, they help patients understand the appropriate use of antibiotics, the importance of adherence to prescribed therapy, and demonstrate the risks associated with the misuse of antibiotics or self-medication. Pharmacists contribute to improving community awareness about the rational use of antibiotics and strengthening prevention strategies. In resource-limited settings and areas where oversight is lacking, pharmacists can contribute to reducing the AMR problem by avoiding the dispensing of antibiotics without a prescription. Additionally, active involvement of infectious disease pharmacist's and collaboration with medical centers is essential to reduce the dispensing of antibiotics as much as possible, and to continue following patients and relaying feedback to doctors and policymakers who are seeking to minimize the AMR problem.

The findings of this study reflect heterogeneous policies in our hospitals. In resource-limited settings, the availability of antimicrobial agents is often restricted, leading to a heavy reliance on a limited number of antibiotics such as ceftriaxone. However, in severe and complicated infections, particularly emphysematous pyelonephritis, the use of ceftriaxone monotherapy may be insufficient to provide adequate antimicrobial coverage.

Patients presenting with severe disease, sepsis, or significant comorbidities frequently require early initiation of broad-spectrum antimicrobial therapy, such as carbapenem or a combination of therapy, guided by infection severity, local resistance patterns, and culture and susceptibility results. These infections are associated with substantial morbidity and

mortality, and delays in administering effective therapy may significantly worsen clinical outcomes. Therefore, the implementation of strict antimicrobial stewardship policies within our hospitals is essential to ensure the rational and appropriate use of broad-spectrum antibiotics, especially in severe complicated infections such as emphysematous pyelonephritis. Such policies may optimize empirical antibiotic selection, reduce inappropriate antibiotic exposure, improve patient outcomes, and potentially decrease mortality.

Several comorbidities have been strongly associated with an increased risk of rUTI. Conditions such as DM is a well-established risk factors for UTIs (94). Patients with DM are more susceptible to UTIs because of impaired immune function, autonomic bladder dysfunction leading to urinary stasis, microvascular complications, and elevated urinary glucose concentrations that enhance bacterial growth. Poor glycemic control further increases both the frequency and severity of recurrent infections.

In addition, DM has a particularly strong association with emphysematous pyelonephritis (108), hyperglycemia may facilitate the proliferation of gas-forming microorganisms and contribute to impaired host immune responses, thereby increasing susceptibility to severe renal infections. The majority of patients diagnosed with emphysematous pyelonephritis have underlying DM (108), particularly those with poorly controlled blood glucose level. Moreover, DM is associated with worse clinical outcomes in patients with emphysematous pyelonephritis, including septic shock, renal impairment, and higher mortality rates. These findings emphasize the importance of adequate glycemic control, early diagnosis, and prompt management of urinary tract infections in diabetic patients to reduce the risk of developing emphysematous pyelonephritis.

rUTI was significantly associated with antibiotics administered after urine culture (p = 0.015). Patients with rUTI are more likely to receive antibiotics after urine culture testing compared to those without rUTI. Meropenem, vancomycin, and nitrofurantoin demonstrate a higher utilization in the rUTI group.

Reflecting the complexity of managing recurrent infections and suggesting increased disease severity and a higher rate of resistant pathogens, the use of tazobactam was comparable between both the rUTI and non-rUTI groups. Cefpodoxime was prescribed more often in patients without the rUTI group. The use of meropenem as empirical

antimicrobial therapy was significantly associated with the rUTI status (p = 0.003). Empirical meropenem was administered more frequently in women with rUTI 23 (6.1%), compared with those without rUTI 27 (7.1%). These findings highlight the need for careful antimicrobial stewardship and guide clinicians about the initial antibiotic choice.

rUTI was observed in both hospital-acquired infection and community-acquired infection, a higher proportion of rUTI cases was associated with hospital-acquired infection, and this may be due to prolonged hospitalization and exposure to a highly contaminated environment (high bacterial load). Hospitalized patients usually have weak immunity and have an underlying disease, leading to a reduced body's ability to fight infection. Hospitals use many invasive devices that create a direct pathway for bacteria, and the bacteria in hospitals are more dangerous and resistant (ESBL, MRSA, CRE, Pseudomonas, Acinetobacter), more virulent, and harder to treat, because they survive in a high antibiotic environment. Patients in the hospital often take broad-spectrum antibiotics or multiple courses of antibiotics, and this kills normal flora and allows resistant bacteria to dominate.

MDROs were found to be associated with rUTI (p = 0.031). A higher proportion of MDROs was observed among those with rUTI 39 (10.3%), compared with women without rUTI 71 (18.7%). This association suggest that infection with resistance pathogens may contribute to persistence of infection, decrease the effectiveness of antibiotics, limited antibiotic treatment options, and an increased risk of recurrence. These findings confirmed the importance of targeted therapy in patients with a history of MDROs and strengthen of antimicrobial stewardship program.

rUTI is a disease that requires follow-up after treatment, even if the patient has completely recovered, because these patients are susceptible to reinfection. The results of this study demonstrated that the rUTI cases are attributable to reinfection with different types of pathogens after discharge from the hospital, emphasizing the need for preventive strategies that target modifiable risk factors and microbial colonization rather than solely focusing on the eradication of the initial infection. Patients in the rUTI group showed a higher frequency of reinfection with E. coli, Klebsiella, ESBL-producing Klebsiella, and Yeast infection. These findings indicate that rUTI is strongly associated with reinfection by both bacterial and fungal infections. Patients with rUTI should be considered a high-risk group and followed closely after discharge from the hospital, antimicrobial therapy

should be guided strictly by culture and susceptibility results to minimize inappropriate antibiotic use and decrease resistant organisms. Preventive strategies should be strengthened by patient education about these prevention methods to minimize reinfection as much as possible.

Clinical outcome was significantly associated with rUTI (p = 0.002). Resolution of infection was more frequent in women without rUTI 265 (69.7%) compared with those with rUTI 90 (23.7%). In contrast, disease progression was more frequent in women with rUTI group 14 (3.7%) than in women without rUTI 11 (2.9%). These results suggest that rUTI is associated with poorer clinical outcomes and a lower rate of complete resolution. rUTI may lead to disease progression due to more frequent exposure to repeated courses of antibiotics and a higher prevalence of resistant or difficult to eradicate pathogen in patients with recurrent infections. Recurrent episodes are often associated with persistent uropathogens, making them difficult to eradicate and increasing the inflammation and tissue damage. Patients with underlying diseases allow infection to persist or worsen.

Rapid readmission of the patient to the hospital within 30 days with UTI after discharge from the hospital indicates that the patients not fully recovered or more susceptible to recurrent episodes. The results of this study showed that readmission of the patients within 30 days with UTI was strongly associated with the rUTI group compared to those without rUTI ($p < 0.001$). Patients with rUTI experienced a notable readmission within 30 days. In contrast, there was no readmission in patients without rUTI. This result indicates that rUTI is strongly associated with early hospital readmission may be due to ineffective eradication of infection, higher rates of antimicrobial resistance in this patient population, inappropriate or inadequate treatment, non-adherence to medications, presence of chronic disease, poor discharge planning and unclear instructions. This finding underscores the need for targeted discharge planning and close discharge follow-up.

Mortality is an indicator of the disease burden and a measure of healthcare effectiveness. They provide valuable insight into patient prognosis and treatment outcomes. Although UTIs are commonly associated with low mortality, complications may develop, such as urosepsis and AMR, which can significantly increase mortality rates, particularly among vulnerable women. The survival rate was considerably higher among patients without rUTI 270 (71.1%) compared to those with rUTI 93 (24.5%). Otherwise, mortality was

higher among patients with rUTI 11 (2.9%) compared to those without rUTI 6 (1.6%). These findings demonstrated that rUTIs are associated with worse clinical outcomes, maybe due to repeated infection, AMR, and the presence of underlying comorbidities, which amplify the disease severity. Monitoring mortality in rUTI women is essential for assessing healthcare interventions and guiding treatment strategies to reduce factors that contribute to death. Advanced age was significantly associated with mortality. The median age of women who died was higher than that of survivors (77 [68, 81] years vs 61 [32, 75] years, $p = 0.002$), indicating that elderly patients are at greater risk of mortality.

Clinical signs and symptoms, including fever, vomiting, and flank pain, were significantly associated with mortality, suggesting that severe infection and upper urinary tract involvement may increase mortality risk. Additionally, hematuria and costovertebral pain reflect a more complicated infection. However, suprapubic pain and urinary frequency were documented more frequently among survivors than those who died, possibly because these symptoms are more typical of less severe infections. Notably, Pyelonephritis was reported frequently in patients who died, whereas cystitis was markedly more common among survivors. These differences in UTI location between dead and alive patients were statistically significant ($p < 0.001$). suggesting that pyelonephritis was associated with increased mortality, while cystitis was associated with lower mortality.

4.2 Strengths of the study

This study has several strengths. First, it represents the biggest multi-center cohort of Palestinian women with UTIs, covering a nine-year period, which provides large and representative data in a setting where such evidence has been rare. Second, the use of standardized electronic medical records through four hospitals decreased information bias and confirmed consistency in data collection. Third, the incorporation of demographic, clinical, microbiological, and treatment variables allowed for a comprehensive analysis of both host and pathogen factors, providing a multifactorial perspective on recurrence. Fourth, the study employed culture-guided therapy analysis, allowing for the assessment of its impact on recurrence and outcomes, which is particularly relevant in resource-limited countries where empirical therapy dominates. Fifth, the inclusion of detailed AMR profiles for both Gram-positive and Gram-negative pathogens strengthens

the clinical relevance of the findings, as it relates to rUTIs. Immediately informs stewardship policies. Sixth, the study adhered to STROBE reporting guidelines and conducted regression diagnostics, optimizing methodological transparency and validity. All these strengths position the study as a valuable contribution to both local and global literature on rUTIs.

4.3 Limitations of the study

This study may have some limitations that should be acknowledged. First, the retrospective design may introduce some selection bias, as only women admitted to the hospitals with complete records were included; however, the large sample size and multi-center approach minimize this concern. Second, the dependence on hospital-based data may underrepresent women treated in outpatient clinics, which allowed for detailed microbiological and treatment information that is often unavailable in primary care. Third, the study did not capture patient-reported outcomes such as symptom burden or quality of life, but clinical endpoints such as recurrence, reinfection, and readmission provide meaningful predictions for disease impact. Fourth, while antibiotic prescribing patterns were analyzed, the study could not completely account for prior community prescriptions or self-medication, though this limitation reflects a wider challenge in AMR research in resource-limited areas. Fifth, the number of patients who take non-prescribed antibiotics may be an underestimation of the actual prevalence because non-prescribed antibiotic use might not have been fully documented in patient medical records. Sixth, the findings are context-specific to Palestine, which may limit generalizability; however, this uniqueness is also a strength, as it fills a critical gap in regional evidence and highlights challenges that are shared across similar healthcare systems. Through acknowledging these limitations while emphasizing the methodological rigor and breadth of data, the study provides a balanced and reliable account of rUTIs in Palestinian women. The strengths exceed the limitations, and the findings remain highly relevant for informing clinical practice, stewardship programs, and future research in both local and international contexts.

4.4 Conclusion

In this large multi-center cohort of Palestinian women, rUTIs were common, affecting more than one in four patients, and were strongly associated with older age, pregnancy, DM, asthma, and prior UTI history. Gram-negative uropathogens, particularly ESBL-producing E. coli and Klebsiella spp., dominated the microbiological profile, contributing to high resistance against cephalosporins and fluoroquinolones and increasing reliance on carbapenems. Importantly, culture-guided therapy was associated with reduced recurrence rate, underscoring its value in enhancing outcomes and limiting unnecessary broad-spectrum antibiotic use. While most infections resolved, reinfection and multidrug resistance are still significant challenges, underscoring the urgent need for strengthened antimicrobial stewardship programs, diagnostic infrastructure, and preventive strategies. These findings provide specific evidence that can inform clinical practice and policy in Palestine and offer insights relevant to other resource-limited settings facing s AMR and similar burdens of rUTIs.

4.5 Recommendations

Based on the findings of this study, targeted strategies should be implemented to reduce the burden of recurrent urinary tract infection among women. Firstly, patient counseling and making educational sessions about early symptom recognition, adherence to treatment, hygiene practices, taking of non-prescribed antibiotics, and preventive strategies is essential to improve outcomes and reduce recurrence of infection. Secondly, women with high-risk groups, such as pregnancy, women with comorbidities, and older women, should receive closer follow-up and an individualized care plan. Thirdly, improve community awareness and local clinical guidelines about the misuse of antibiotics and advise to use of antibiotics in a regular manner. Fourthly, in health care practices, routine use of urine culture and antimicrobial susceptibility testing is recommended, especially during treatment of recurrent and complicated cases. Fifth, strengthening antimicrobial stewardship to minimize inappropriate use of broad-spectrum antibiotics and decrease antibiotic resistance. Ultimately, physicians, scientists, and patients should collaborate to enhance disease management.

4.6 Future research extensions

Future studies are needed to continue surveillance of antimicrobial resistance patterns of bacteria to guide therapy. Longitudinal and multi-center studies are needed to better understand long-term risk factors associated with rUTI. In addition, interventional studies are needed to evaluate the effectiveness of prevention strategies, such as cranberry extract and vaccination. Also, further studies are needed to explore behavioral, lifestyle, and socioeconomic factors, which are not available in retrospective files, to improve the generalizability of the findings.

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financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2026, StatPearls Publishing LLC.; 2026.

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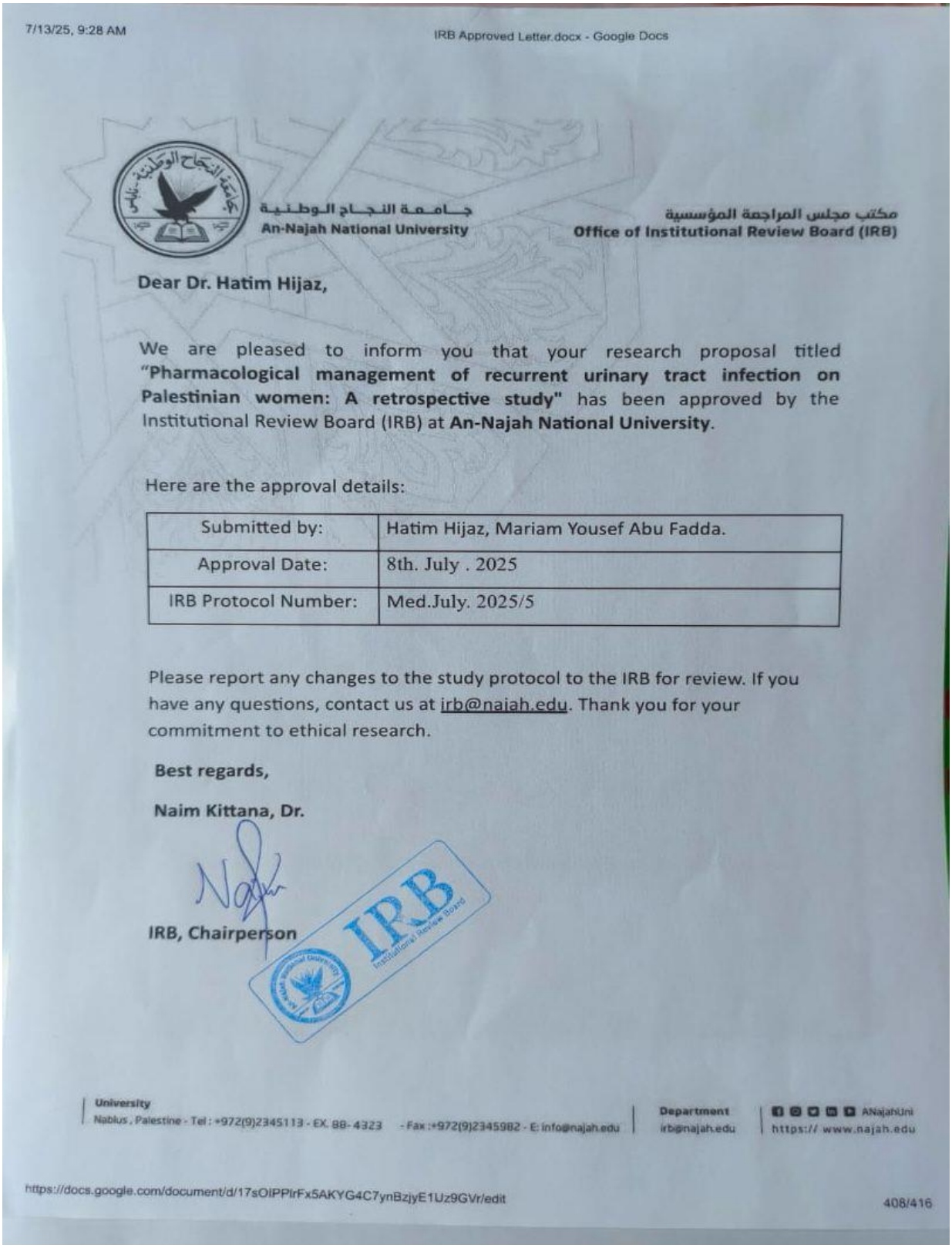
Appendices

In APA style, the appendix appears after the References list. If you have more than one appendix you would name the first one Appendix A, the second one Appendix B and so on. The appendices would appear in the order that you mention them in your study. Each Appendix begins on a new page.

Appendix A

An-Najah National University Institutional Review Board (IRB) approval



7/13/25, 9:28 AM IRB Approved Letter.docx - Google Docs

جـامـعـة النـجـاح الـوطـنـيـة
An-Najah National University

مكتب مجلس المراجعة المؤسسية
Office of Institutional Review Board (IRB)

Dear Dr. Hatim Hijaz,

We are pleased to inform you that your research proposal titled **"Pharmacological management of recurrent urinary tract infection on Palestinian women: A retrospective study"** has been approved by the Institutional Review Board (IRB) at **An-Najah National University**.

Here are the approval details:

Submitted by:	Hatim Hijaz, Mariam Yousef Abu Fadda.
Approval Date:	8th. July . 2025
IRB Protocol Number:	Med.July. 2025/5

Please report any changes to the study protocol to the IRB for review. If you have any questions, contact us at irb@najah.edu. Thank you for your commitment to ethical research.

Best regards,

Naim Kittana, Dr.

IRB, Chairperson

IRB Institutional Review Board

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Appendix B

Semi Structured interview

Semi Structured interview

Demographic information:

1. Gender: male, female (don't ask the child)
   الجنس: ذكر، انثى؟
2. Age: (7-17 years)
   قديش عمرك؟
3. Current Grade:
   بأي صف انت؟
4. City/governorate (don't ask the child)
   المحافظة:
5. Type of residency: Village, camp, city (don't ask the child)
   نوع مكان السكن: مخيم، قرية، مدينة
6. Number of siblings:
   كم اخ واخت عندك؟
7. Type of school: public, private, UNRWA
   شو نوع مدرستك، خاصة، حكومة، ولا وكالة؟
8. Do you receive/have you received online schooling: yes, no
   عم تاخذ حصص اونلاين/ او اخذت حصص اونلاين؟

Interview questions:

1. What do you know about the Covid 19? Why are we in Lockdown?
   شو بتعرف عن فيروس كورونا؟ ليش احنا في الحجر البيتي/ في البيت؟
2. How would you describe your feeling at the beginning of the Lockdown? Has it changed now?
   شو كنت حاسس في بداية الحجر اني البيت؟ طيب كيف هلا حاسس؟
3. What are your feelings about all of this situation? Are you afraid/worried?
   شو رأيك بالي عم يصير او بهذا الوضع؟ كيف حاسس؟ خايف؟ قلقان؟
4. How the lockdown changed your life?
   شو تغير عليك في الحجر؟ كيف تغيرت حياتك؟
5. How is your daily routine nowadays?
   شو بتعمل كل يوم؟ كيف روتينك بالبيت؟
6. What is the worst and the best thing about this lockdown?
   شو احسن شي واسوأ شي في هذا الحجر؟
7. Can you tell me what do you miss the most?
   بتقدر تحكيلي شو اكتر شي اشتقتلو وانت بالبيت بالحجر؟
8. What is the first thing you will do when the lockdown will end?
   شو اول شي رح تعملو لما نخلص من الحجر البيتي؟

جامعة النجاح الوطنية

كلية الدراسات العليا

دراسة مرجعية حول علاج التهابات المسالك البولية المتكررة لدى النساء الفلسطينيات

إعداد

مريم يوسف محمود أبو فضه

إشراف

د. حاتم حجاز

أ.د. رمزي شواهنة

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في علم الأدوية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس- فلسطين.

2026

دراسة مرجعية حول علاج التهابات المسالك البولية المتكررة

لدى النساء الفلسطينيات بالأدوية

اعداد

مريم يوسف محمود أبو فضه

إشراف

أ. د. رمزي شواهنة

د. حاتم حجاز

الملخص

الخلفية: تعد التهابات المسالك البولية من أكثر العدوى البكتيرية شيوعا بين النساء حول العالم، حيث تخلق التهابات المسالك البولية المتكررة تحديات كبيرة لكل من الصحة السريرية والعامة. في فلسطين، لا تزال البيانات حول التهابات المسالك البولية المتكررة ومقاومة المضادات الحيوية (AMR) نادرة.

الأهداف: هدفت هذه الدراسة إلى وصف الإدارة الدوائية لعدوى المسالك البولية المتكررة (RUTI) وتحديد انتشار التهابات المسالك البولية بين النساء الفلسطينيات، وتحديد العوامل المرتبطة بزيادة خطر النوبات المتكررة، وتوصيف أنماط مقاومة المضادات الحيوية، وتقييم تأثير العلاج الموجه بالزراعة على النتائج.

المنهجية: كانت هذه الدراسة دراسة جماعية بأثر رجعي أجريت عبر أربعة مستشفيات في قسم المسالك البولية في جنوب الضفة الغربية في فلسطين .(2025–2016) تمت مراجعة السجلات الطبية ل 380 امرأة تبلغ من العمر 18≤ عاما مصابات بعدوى المسالك البولية .تم استخراج المتغيرات الديموغرافية والسريرية والميكروبيولوجية والعلاجية .تم تعريف التهاب المسالك البولية بأنه 2≤ نوبة عرضية خلال ستة أشهر أو 3≤ خلال اثني عشر شهرا .تم إجراء الإحصاءات الوصفية والاستدلالية، بما في ذلك الانحدار اللوجستي، بواسطة SPSS.

النتائج: شمل التحليل النهائي 380 امرأة تم تشخيصهن بعدوى المسالك البولية .بلغ انتشار التهابات المسالك البولية بين النساء الفلسطينيات٪27.4 (104 /380). كان العمر الأكبر (الوسيط 65 مقابل 60 سنة، p = 0.015) السكري (p = 0.004)، الربو(p = 0.012)، وتاريخ التهاب المسالك البولية السابق p) (0.001 > مرتبطة بشكل ملحوظ بعودة المرض .كان الحمل أقل تكرارا بين حالات التهاب المسالك البولية المتكررة (p < 0.001).

كان أكثر مسببات الأمراض المسيطرة التي تم عزلها من زراعة البول هي الإشريكية القولونية سالبة الغرام (40.5%)و وأنواع كليبسييلا (9.7%) كعزلات رئيسية .كانت السلالات المنتجة ل ESBL شائعة، مما قلل من فعالية السيفالوسبورين والفلوروكينولون .هيمن العلاج التجريبي على السيفترياكسون (43.2%) ، بينما أصبح الميروبينيم (23.9%) الأكثر شيوعا بعد نتائج الزراعة. العلاج الموجه بالزراعة كان مرتبطا بشكل ملحوظ بانخفاض معدل التكرار(p < 0.05). الحل السريري حدث بنسبة (93.4%) ، لكن إعادة العدوى (14.2%) وتاريخ مقاومة الأدوية المتعددة (28.9%) لا يزالان يشكلان تحديات كبيرة.

الاستنتاجات: التهابات المسالك البولية المتكررة تنتشر بين النساء الفلسطينيات وتمثل عبئا كبيرا على الصحة العامة. التهابات المسالك البولية المتكررة ترتبط ارتباطا وثيقا بالأمراض المصاحبة الكامنة ومسببات الأمراض السالبة غرام المقاومة. لوحظت نتائج أفضل مع العلاج الموجه بالزراعة، مما يؤكد الحاجة إلى تعزيز برنامج الرعاية والبنية التحتية التشخيصية في بيئات محدودة الموارد لتعزيز إدارة عدوى المسالك البولية في الممارسات الصحية الفلسطينية.

الكلمات المفتاحية: عدوى المسالك البولية المتكررة؛ الإشريكية القولونية؛ مقاومة مضادات الميكروبات؛ بيتالاكتاماز واسعة الطيف؛ العلاج الموجه بالزراعة؛ بيئات محدودة الموارد