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Review

Recurrent urinary tract infections in older adults: A systematic review of current challenges and emerging therapeutic strategies

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ABSTRACT

As global life expectancy continues to rise, urinary tract infections (UTIs) have become an increasing concern in older adults. The higher prevalence in this population is attributed to anatomical and physiological changes of the urinary tract, hormonal imbalances, immunosenescence, and the presence of comorbidities. These factors, combined with a distinct microbiological profile and rising antimicrobial resistance, create significant clinical challenges in diagnosis and treatment. We conducted a systematic review of clinical trials and observational studies on the epidemiology, pathogenesis, diagnosis, and management of recurrent urinary tract infections (rUTIs) in older adults. The prevalence of rUTIs increases with age, disproportionately affecting women, with 53 % of those over 55 years experiencing recurrences within one year. Healthcare-associated UTIs (HAUTIs) account for 20–30 % of nosocomial infections, primarily impacting older adults. The host microbiome seemed crucial in UTI pathogenesis, with *Escherichia coli* being the leading causative agent due to its ability to adhere, colonise, and evade the immune response. In elderly patients, atypical presentations – such as delirium, functional decline, or nonspecific abdominal symptoms – complicate diagnosis, underscoring the critical need to differentiate symptomatic infections from asymptomatic bacteriuria (ASB) to prevent misdiagnosis and overtreatment. Effective management requires accurate diagnosis, appropriate antibiotic selection, and careful monitoring of adverse effects, especially in patients with comorbidities. Emerging therapies, including faecal microbiota transplantation, bacteriophages, probiotics, and proanthocyanidins, offer promising adjuncts. While long-term antibiotic prophylaxis is effective, it increases the risk of bacterial resistance, particularly in catheterised patients. Behavioural modifications, such as increased fluid intake, aid pathogen clearance, and topical estrogen therapy in postmenopausal women provides additional preventive benefit. Managing recurrent UTIs in ageing populations requires addressing microbiological, diag-

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nostic, and antimicrobial resistance challenges. Despite resistance levels, the first-line treatment, nitrofurantoin, remains a viable therapeutic option, particularly in developed countries. An integrated approach combining individualised care, healthcare provider training, and rational antimicrobial use is essential to improving patient outcomes and quality of life. Future strategies should focus on novel antimicrobials targeting bacterial virulence factors, vaccines against uropathogens, and advanced diagnostic technologies.

Keywords: urinary tract infections, older adults, emerging therapeutic strategies

INTRODUCTION: INCREASING BURDEN OF URINARY TRACT INFECTIONS IN THE AGEING POPULATION

Urinary tract infections (UTIs), particularly those affecting the lower urinary tract, are the most frequent type of infection among long-term care residents and rank as the second most common infection among community-dwelling and hospitalised older adults, and it's also an important cause of sepsis (1, 2). With the continuous increase in global life expectancy, the prevalence and impact of chronic and recurrent UTIs in older populations have become significant healthcare challenges (3). These infections may be limited to the lower urinary tract or extend to the upper tract, with *Escherichia coli* identified as the predominant causative pathogen in numerous cases (4). The increased incidence of UTIs with advancing age is influenced by various factors, including anatomical abnormalities of the urinary tract, hormonal changes, urinary incontinence, weakened immune function, poor nutritional status, functional impairments and the presence of multiple chronic conditions (5).

Chronic or recurrent UTIs (rUTIs), typically characterised by two or more infections within a six-month period or three or more episodes in a year, are associated with substantial morbidity and increased healthcare resource use (6). According to some researchers, these recurrent cases pose a greater health burden than isolated infections due to their lasting negative impact on well-being (1). Recurrent lower urinary tract infections (rLUTIs) affect up to 30 % of women over 65 years old, a prevalence influenced by gender-specific anatomical factors and the cumulative effect of risk factors over a lifetime (7).

The clinical presentation of UTIs ranges from asymptomatic bacteriuria (ASB) to symptomatic conditions such as cystitis, prostatitis and pyelonephritis, each presenting distinct diagnostic and therapeutic challenges (8). ASB is defined by the presence of bacteria in the urine (10^5 CFU mL^{-1}) without clinical symptoms (9). Pyuria, the presence of white blood cells in the urine, often complicates the diagnostic process since it can be observed in both ASB and UTIs (10). For diagnostic purposes, women require two consecutive urine samples, while men need only one. When samples are collected through catheterisation, a single specimen is sufficient for both genders. Screening for ASB in elderly patients is recommended only for those undergoing invasive urological procedures or surgeries involving implant materials (11). In other cases, urine testing is not advised if there are no urinary tract symptoms or signs. Studies have consistently shown that antibiotic treatment for ASB does not lower the risk of future complications and may paradoxically increase the likelihood of subsequent UTIs. Additionally, unnecessary antibiotic use

contributes to the emergence of drug-resistant pathogens, *Clostridium difficile* infections, and other medication-related adverse effects, highlighting the importance of adapted clinical strategies to distinguish true infections from just colonisation.

On the other hand, the diagnosis of symptomatic UTI generally requires the presence of pyuria, indicated by leukocyte esterase or white blood cells in a urinalysis, along with symptoms linked to the urinary tract, a positive urine culture confirming a pathogenic organism, and the exclusion of other infections or non-infectious conditions that could explain the patient's symptoms (12, 13). The range of symptoms associated with the urinary tract can vary widely, particularly in the geriatric population. Clear and specific diagnostic criteria for UTIs are particularly important in older adults. First, identifying ASB helps avoid unnecessary antibiotic use in a population already at heightened risk of adverse drug reactions due to polypharmacy and multiple comorbidities (14). Second, attributing clinical changes to a UTI without evaluating other potential diagnoses can delay proper treatment and increase the risk of harm by overlooking other medical conditions. Diagnostic approaches involve the McGeer and Loeb criteria, usually applied in long-term care settings (15). These guidelines recommend symptom-based triggers, including new-onset or worsening urgency, fever, suprapubic pain, or changes in mental status, to guide clinical decision-making, which will be discussed later. Some recent studies propose new criteria, but none have yet been widely or consistently adopted on a large scale.

Persistent infections exacerbate functional decline, reduce quality of life, and increase hospitalization rates. UTIs are among the leading causes of sepsis in elderly patients, with potentially fatal outcomes (16). Managing these infections requires a balance between appropriate antimicrobial use and the implementation of non-pharmacological strategies, such as hydration, improved hygiene, and estrogen therapy for postmenopausal women. This review will systematically explore the current evidence on effective management practices, aiming to enhance care outcomes and mitigate the impact of these infections on geriatric health.

AIMS AND METHODOLOGY: SYSTEMATIC REVIEW DESIGN, SEARCH STRATEGY, AND STUDY SELECTION CRITERIA

The present review focused on well-designed clinical trials and reviews concerning different aspects of recurrent UTI, especially pathogenesis, epidemiology and treatment focused on the elderly. Article research was conducted based on PubMed, Lilacs, Science Direct and Medline bases. The following key-words were used: “urinary tract infections", “new approaches", “pathogenesis", “recurrent”, “demographics and epidemiology”, “treatment”, “therapeutics”, “diagnosis”, “elderly”, “geriatric”, “HAUTI”, “pathogens”, “challenges”, “clinical trials”, “novel treatment” as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present. Five researchers independently performed study selection, data extraction, and quality assessment. Opinion articles and isolated case reports were excluded, with no restrictions on language, date, or geographical origin.

Entries and records identified in the electronic databases were exported to the Rayyan platform for screening and selection. Studies were initially filtered by title and abstract independently, and those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis. Full-text analysis and exclusion based on

eligibility for our paper were conducted independently by five researchers. Opinion articles and isolated case reports were the only automatic exclusion criteria, and no case complications were considered when differentiating among infection presentations. Articles were not excluded based on language, date or place of conduction.

EPIDEMIOLOGY, PATHOGENESIS, AND DIAGNOSTIC CHALLENGES OF RECURRENT URINARY TRACT INFECTIONS IN OLDER ADULTS

Urinary tract infections (UTIs) are among the most common infections in elderly adults, accounting for an average of 15.5 % of hospitalisations among patients aged 65 years and older (1, 4). Projections estimate a 20 % increase in the population over 65 years by 2050, alongside a rising incidence of UTI and bacteriuria in elderly patients. This underscores the significant clinical importance of addressing UTIs in this demographic, as ageing is associated with several factors that predispose individuals to infections, including comorbidities, reduced functional capacity, changes in innate and adaptive immunity, and an increased need for invasive procedures during hospitalisations (2, 5). Symptoms indicative of UTIs in older adults include suprapubic pain, dysuria with or without frequency, urgency or hematuria. These infections may manifest as cystitis, prostatitis, or pyelonephritis (4, 5).

Age- and sex-specific epidemiology of recurrent urinary tract infections in older adults

In terms of general UTI incidence among older men and women, studies suggest an infection rate of 5 to 7 % per person per year (17). The prevalence of bacteriuria in women over 65 years is approximately 20 %, whereas men in the same age group present a prevalence of 10 % (1, 2). Among women aged 65–70 years, bacteriuria was observed in 15 to 20 % of cases, increasing to 20–50 % in individuals over 80 years (8). For men, UTIs are frequent among those aged 65 years or older, and the increased prevalence of bacteriuria is often linked to urological interventions and prostatic disease, which can reduce the antibacterial activity of prostatic secretions (5, 7). UTI consultations occur twice as often among women of all ages compared to men, affecting up to 50 % of women during their lifetime, with nearly half experiencing recurrence within 6 to 12 months (18).

Recurrent UTIs (rUTIs), defined as three or more episodes within one year or two or more infections in the past six months (19, 20), represent a significant proportion of all UTIs. Approximately 95 % of rUTIs are thought to be caused by reinfection, while relapse accounts for only about 5 % (21, 22). rUTIs are more common in women, affecting up to 10 % of adult females and approximately 25 % of women with a history of isolated UTI. The prevalence of rUTIs in women increases with age, with around 53 % of women over 55 years reporting a recurrence within one year. Among men, as with UTIs in general, the prevalence of rUTIs increases with age. According to Schmiemann *et al*. (23), a U.S. study involving men with a mean age of 67.9 years found that nearly 10 % of those who had experienced a UTI developed another episode within 12 months, and approximately 2 % met the criteria for recurrent UTI.

Healthcare-associated urinary tract infections (HAUTIs) account for approximately 20 to 40 % of all healthcare-associated infections (24). It is estimated that 80 % of HAUTIs are associated with catheters. Patients with HAUTIs tend to be older, present more comorbidi-

ties, and have a history of more frequent antimicrobial treatments compared to those with community-acquired UTIs (25). Moreover, the highest rates of infectious complications are observed in older men with comorbidities (26). In this context, prostate biopsy (P-Bx) emerges as one of the most frequently performed urological procedures worldwide, with a direct impact on HAUTI rates. However, epidemiological data remain scarce, and infection rates may vary depending on the prophylactic measures applied during each approach.

Microbial spectrum and pathogenesis of urinary tract infections: role of uropathogens and host interactions

Beyond clinical presentations and patient demographics, the host microbiome plays a crucial role in UTI for the clinician, since treatment is established based on the pathogen causing the case (27). Although theoretically all pathogenic Gram-positive and Gram--negative bacteria (as well as some fungi) are able to cause UTI, bacteria from the Gram--negative *Enterobacteriaceae* family are considered to be the most common pathogens involved in UTI throughout population groups (28, 29). At least since 1980, *Escherichia coli*, a rod-shaped, motile, Gram-negative bacterium, has been recorded to excel among its pairs, accounting for the majority of cases (1). Since then, in all appreciable studies, *E. coli* – also referred to as uropathogenic *E. coli* (UPEC) – has been admitted to cause at least 50 % of UTIs, while the prevalence can reach up to over 90 % within some sections of the population, such as young women (2). Following UPEC, the main pathogens known to cause uncomplicated UTI in decreasing order of prevalence are *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococcus* (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida spp.* (Fig. 1) (4, 5, 7).

Considering complicated UTI, some pathogens are more successful, meaning more prevalent, such as *Proteus mirabilis*, which is estimated to cause around 7 % of complicated cases (8). Nevertheless, there is no dispute regarding the overwhelmingly dominant distribution of *E. coli*, responsible for 65 % of complicated infections (30). Also, in the absence of confirming data, there seems to be no reason to think that recurrent UTI should present a radically different distribution from uncomplicated infection, since their conceptual difference is not one of presentation, but rather of frequency. In fact, the utter preponderance of *E. coli* among all UTI allows for an archetype study of its pathogenesis, which should prove instrumental to further discuss antibiotic treatment agents and their target mechanisms.

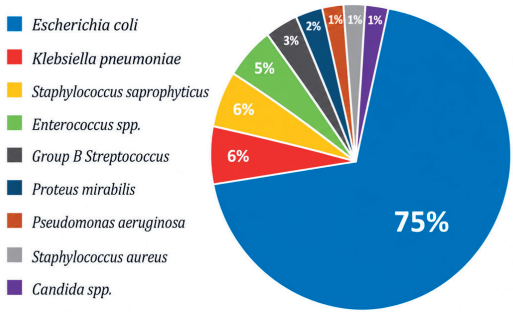

Fig. 1. Prevalence of uncomplicated UTI pathogens.

Virulence mechanisms of uropathogenic Escherichia coli: adhesion, *biofilm formation, and immune evasion strategies*

As with all microbiological environments, the mechanisms by which *E. coli* is able to colonise the human urinary tract are multivariate (31, 32). However, recent studies have provided a comprehensible pathway preferred by *E. coli* (as well as other uropathogens) to conquer the urinary tract (33, 34). This strategy consists of three main fronts: adhering to the uroepithelium, enabling colonisation, and evading the host's immune response (35). Uropathogens have a wide arsenal of molecules which serve their colonisation purposes over human tissue and are called virulence factors (36). We shall study in detail each step for its establishment and survival in infecting the urinary tract, as briefly as convenient, for further discussing clinical approaches to UTI.

Adhesion. – *E. coli* is native to the human gut microbiota (4). It must reach the urethral external introitus in order to cause a UTI. The means of this early contact serve as a watershed moment in distinguishing between uncomplicated and complicated UTIs in elderly populations (8). This is due to the high prevalence of catheterised older adults, who may develop complicated UTIs following physical urothelial injury from a contaminated catheter, which serves as a shortcut to the bladder, rather than the typical ascending route of accidental urethral contamination in a catheter-free urinary tract (37). Once the bacteria form contact with the human lower urothelium, multiple bacterial adhesins recognise receptors and mediate colonisation. *E. coli* has structures called pili and fimbriae, namely F1C pili, P pili, S pili and Type 1 pili (shared by many uropathogens), capable of adhering directly to protein components of the urothelial umbrella cells' apical membrane called uroplakins (38).

Another sophisticated pili mechanism employed to facilitate adherence and also to begin biofilm formation (which enables colony survival) revolves around the chaperone-usher pathway (CUP) pili, a large family of adhesive fibres. The CUP pilum allows for the individual binding of bacteria, as subunits, which form a complex between neighboring bacteria and the urothelium (39). CUP pili are a significant challenge for antimicrobial agents to overcome, mainly due to their structural variety. Over thirty distinct CUP pili have been identified in *E. coli*, and a genomic analysis shows one of its decoding genes to be highly mutable, enabling a single strain to produce over twelve different CUP pili.

Enabling colonization. – Following this bacterial protein chain, *E. coli* crafts over umbrella cells. These extracellular polymeric substances form a bacterial community known as biofilm. Biofilm formation – which occurs simultaneously as adherence progresses – is a key mechanism for colony survival in UTI (40). It is basically a scaffold of bacterial proteins that provides a physical barrier towards aggression and immune responses, as well as aids in obstructing the urinary tract (41). The biofilm formation is usually a predictor of recurrence in many different infections, and it is presumed to be an important way by which bacteria can evade antimicrobial therapy and cause recurrent UTIs (42).

Evading host immunity. – Multiple strategies have been identified by which *E. coli* escapes innate immune response against its aggression (43). One which is better understood is mediated by Type 1 pili, which bind to uroplakins (together with all other discussed adhesins), enabling the zippering invasion (or engulfing) of umbrella cells by *E. coli via* Rho

GTPases in a transduction cascade, which, of course, serves as an escape route that perfectly counters humoral response (44). Once *E. coli* invades the cell, urothelial Toll-like receptor 4 (TLR4) signalling activates adenylyl cyclase 3, leading to increased intracellular cyclic AMP (cAMP) levels and triggering the exocytosis of the bacteria-containing 'Trojan horse' vesicle. However, the bacteria can escape the vesicle towards the cytoplasm and begin rapidly multiplying, forming an intracellular biofilm-like community (IBC) (45, 46). This intracellular community successfully evades neutrophil aggression, and similarly to viruses' lytic cycle, may destroy umbrella cells by physical lysis, after which cells are ultimately exfoliated (47).

The IBCs were once theorised to be another important aetiology for chronic infections. If bacteria could occupy the host cell for a sort of non-lytic cycle, surviving in umbrella cells' cytoplasm and succeeding in evading exocytosis efforts, it would be relatively (although temporarily) safe from immune aggression, serving as seeds for endlessly recurrent infections (48).

Synergistic pathological mechanisms. – Despite the formidable arsenal displayed to infect the human urinary tract, many other mechanisms are employed and synergise with tissue colonisation (49). Some of the most important treatments are *E. coli* proteases and toxins, especially alpha-haemolysin, which result in porous formations in umbrella cell membranes, ultimately causing osmotic death, facilitating nutrient acquisition by bacteria and also providing for an initial route towards deep tissue and structures (4).

Among these nutrients, iron is a crucial factor in the virulence mechanisms of *E. coli* (50, 51). An interesting mechanism for iron scavenging in such a scarce environment as the bladder involves siderophores, which are Greek for "iron transporters". These proteins are produced by *E. coli* to bind to host cell membranes, providing the colony with sufficient ions to support its metabolism. These proteins are widely studied in vaccine development and are an important target in investigating the role of cranberries as an antibiotic agent, as it is understood that colonies cannot survive and progress without their function (52). Urease is also produced by uropathogens to catalyse the hydrolysis of urea, producing ammonia and thus resulting in elevated urine pH and precipitation of apatite and struvite crystals (53). Together with other biofilm elements, these crystals shield the colony against aggression and stresses, and can also obstruct urine flow and catheters, promote urine stasis and thus enable the infection to further.

An intriguing perspective on the aetiology of chronic infections centres on the host's own immune response (54). While it is intuitive to attribute chronic infections to immune deficiencies in combating microorganisms – a notion that is not entirely incorrect – an alternative mechanism involves a self-perpetuating immune response. If the host's defence relies heavily on lymphocyte-mediated immunity, collateral damage to the urothelium may occur as a bystander effect (55). This tissue damage could predispose the urinary tract to recurrent infections, especially if the source of contamination is not effectively eliminated.

Clinical presentation and diagnostic challenges of urinary tract infections in older adults

In older adults, the clinical presentation of urinary tract infection differs significantly from younger populations, often complicating diagnosis (56). In cases of cystitis, classic symptoms such as urgency, increased urinary frequency, dysuria, and suprapubic tenderness

may still be present. However, older individuals frequently exhibit nonspecific signs, including lower abdominal pain, back pain, chills, and constipation, which can obscure the underlying urinary origin of symptoms (57, 58). For pyelonephritis, typical manifestations include fever, chills, and flank pain. Yet, systemic signs such as fatigue, malaise, or a general decline in functional status may dominate the clinical picture in older patients (59).

In long-term care (LTC) residents or those with significant cognitive impairment, the symptom profile becomes even more challenging (60, 61). Traditional urinary symptoms are less common, and nonspecific presentations such as confusion, anorexia, falls, or a decrease in functional capacity often predominate (62). Fever, a hallmark of infection in younger adults, may be diminished or absent, further complicating the diagnosis. In cases of catheter-associated urinary tract infection (CAUTI), presentations may include fever, new or worsening suprapubic or costovertebral angle pain, changes in mental status, or purulent discharge from the catheter site (2, 5, 8). This divergence from classical presentations necessitates heightened clinical suspicion and comprehensive evaluation strategies to avoid underdiagnosis or overtreatment.

The diagnostic approach to UTIs in older adults involves distinguishing symptomatic infections from ASB, which is prevalent in this age group but typically does not require treatment. The diagnosis of ASB is established by the presence of $\geq 10^5$ CFU mL^{-1} of bacteria in two consecutive urine specimens for women or a single specimen for men, in the absence of urinary symptoms. In catheterised patients, a lower threshold of $\geq 10^2$ CFU mL^{-1} is used, but symptoms must be present to diagnose a UTI (2, 7). In cognitively intact, community-dwelling older adults, diagnosing UTI requires genitourinary symptoms or more generalised signs, as previously stated, combined with evidence of urinary tract inflammation, indicated by pyuria, and a positive microbiological culture. When these patients present with UTI-like symptoms, initial evaluation should include a dipstick test for nitrite and leukocyte esterase, followed by urinalysis to detect pyuria. Although not mandatory for uncomplicated UTIs, a urine culture remains the preferred method for confirming bacteriuria and assessing antimicrobial resistance (2, 7).

Various diagnostic frameworks have been developed to guide clinical decision-making in LTC facilities, and are detailed in Table I. In 1991, McGeer and colleagues first proposed a set of infection definitions for surveillance purposes in those places. Although it has been adopted for use by several regulatory agencies, these criteria were never validated (63). The Loeb criteria suggest that either isolated acute dysuria or a combination of fever (defined as > 37.9 °C or an increase of > 1.5 °C from baseline) with additional urinary symptoms, such as new or worsening urgency, frequency, suprapubic pain, gross hematuria, or incontinence, can be used to initiate treatment for UTI in residents without an indwelling urinary catheter. The SHEA/CDC revised McGeer criteria expand on these by incorporating changes in mental status or functional decline along with urinary symptoms and requiring a positive urine culture (2, 7). According to the Infectious Disease Society of America (IDSA), diagnostic testing for suspected UTI in LTC residents should be limited to those with a sudden onset of symptoms, such as fever, dysuria, visible hematuria, new or worsening urinary incontinence, or suspected bacteremia. The minimum recommended evaluation includes urinalysis and a urine dipstick test (7).

Despite these guidelines, diagnostic challenges persist due to the frequent absence of localised urinary symptoms in older populations, many of which are necessary components of the original Loeb and McGeer criteria (2, 4, 7). In a recent study of LTC residents

Table I. Diagnostic criteria in suspicion of UTIs in residents of LTC facilities without indwelling urinary catheters

Criteria	Diagnostic requirements	Application	Comments
Original McGeer Criteria (1991)	At least 3 of the following signs/symptoms: 1. Fever (≥ 38 °C) or chills – new or increased burning pain on urination, urgency, or frequency 2. New flank or suprapubic pain – change in urine character 3. Worsening mental or functional status	Used for monitoring and reporting infections rather than guiding direct antibiotic use. Best for surveillance purposes.	Although the original McGeer criteria were adopted for use by several regulating agencies, these criteria were never validated. Used for infection surveillance in long-term care facilities.
Loeb Criteria (2001)	Acute dysuria OR fever (> 37.9 °C or 1.5 °C above baseline) PLUS at least 1 of the following: 1. New or worsening urgency or frequency – suprapubic pain 2. Gross hematuria – costovertebral angle tenderness 3. New urinary incontinence	Applied when making decisions about initiating antibiotic therapy. Provides minimum criteria to limit unnecessary treatment.	Developed to assist in determining when to start antibiotics. Simpler and more practical than McGeer criteria.
Revised McGeer Criteria (SHEA/CDC) (2012)	Both criteria 1 and 2 must be met: Criteria 1: At least one of the following: 1. Acute dysuria or pain/swelling/tenderness in the testes, epididymis, or prostate OR 2. Fever or leukocytosis PLUS one localizing symptom or at least two in absence of fever or leukocytosis: – Acute costovertebral angle pain – suprapubic pain – Gross hematuria – new or marked increase in incontinence/urgency/frequency Criteria 2: Microbiological findings: 1. $\geq 10^5$ CFU mL^{-1} of up to 2 microorganisms in a voided urine sample 2. $\geq 10^2$ CFU mL^{-1} in a specimen collected by in-and-out catheter	Used for diagnosis and treatment decisions in long-term care facilities to distinguish symptomatic UTI from asymptomatic bacteriuria.	More comprehensive, incorporating updated evidence and detailed microbiological criteria.
Infectious Diseases Society of America (IDSA) (2019)	Minimum laboratory evaluation: 1. Urinalysis for pyuria – dipstick for leukocyte esterase and nitrite THEN 2. Urine culture only if dipstick or pyuria is positive	Applied when considering laboratory testing for suspected UTI. Helps avoid unnecessary urine cultures and antibiotic use.	Urine culture is not recommended if both leukocyte esterase and nitrite are negative (100 % negative predictive value). Do not culture urine in asymptomatic patients.

with advanced dementia, the most common reason for suspected UTI was a change in mental status (44.3 %). Localised genitourinary symptoms such as dysuria, urgency, and suprapubic pain were infrequent or absent (7). This showed that in cognitively impaired patients, symptoms such as a change in mental status, like delirium, in behaviour, or the character of urine (*e.g.*, hematuria or new foul odour) may be the only indicators, and can lead to antibiotic treatment without a correct indication (64). Accurate application of these criteria is essential to balance appropriate antibiotic use with the prevention of overtreatment and the associated risks of antimicrobial resistance (2, 7).

Managing the spectrum of syndromes classified under UTIs presents significant challenges due to various key factors. These include:

– imprecise clinical criteria for diagnosis,
– overlapping, nonspecific, or age-related symptoms,
– reliance on laboratory findings rather than clinical signs to confirm infection,
– limited guidelines for the use and interpretation of diagnostic tests,
– difficulty selecting appropriate empirical antimicrobial therapy,
– difficulty distinguishing ASB from UTIs.

The last topic is particularly challenging in older adults with urinary catheters, where symptoms like frequency, urgency, or dysuria are often masked, in people who have baseline urological conditions, causing chronic urinary urgency or frequency, and in those who have cognitive impairments, such as dementia (8). UTIs in elderly patients also tend to manifest with atypical symptoms, delaying diagnosis. When finally identified, these infections pose management challenges that increase hospitalisation rates and mortality. Therefore, prompt clinical suspicion by general practitioners or specialists is crucial for accurate diagnosis (5). It is primarily important to consider the decline in immune function known as immunosenescence as a key point in the increasing incidence of UTIs with age (65). Present in varying degrees in all older adults, immunosenescence links frailty to reduced immune competence. As the immune system ages, its ability to fight infections, malignancies, and autoimmune conditions decreases, increasing vulnerability to illness. Many older adults also experience mild immunosuppression due to this decline, compounded by age-related organ dysfunction, chronic diseases, geriatric syndromes, frailty, malnutrition, functional impairments, and polypharmacy, all of which worsen the prognosis for infectious diseases (5).

Older adults also tend to have more comorbidities, such as hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD) and depression, often requiring multiple medications. This increases susceptibility to adverse drug interactions and healthcare-associated infections, including UTIs (1, 7). In individuals with diabetes, metabolic imbalances and neurological complications impair immune responses. Glucosuria and advanced glycation end products disrupt monocyte migration and cytokine production, further elevating UTI risk (5). Cognitive decline, reduced mobility, and conditions like dementia or cerebrovascular disease compromise hygiene, increasing susceptibility to bacteriuria, especially in older women (1, 4, 7).

In addition, structural (chronic prostatitis, prolapses, cystocele, and urinary obstructions from stones or neoplasm) and functional (neurogenic bladder dysfunction) changes in the genitourinary tract, along with urinary and faecal incontinence, a condition that negatively affects both social and psychological well-being, further elevate the risk.

Sarcopenia, which affects all skeletal muscle groups, including the pelvic floor muscles, is an important disease that predisposes the condition (1). Sexual activity remains a recognised risk factor for UTIs, although its influence diminishes with age. Research shows that sexually active older women, especially those engaging in intercourse at least weekly, have a higher infection rate (1, 5). In postmenopausal women, reduced estrogen levels lower vaginal colonisation by protective lactobacilli, facilitating the growth of *Escherichia coli* and other pathogens. In elderly men, age-related prostate enlargement causes urethral obstruction and turbulent urine flow, increasing UTI risk (7). A history of recurrent UTIs is the strongest predictor of future infections in this population (1). A recent study stated that UTIs predispose depression in elderly men, and this is marked to be the most common psychological disorder in older adults, impairing functionality, reducing quality of life, and increasing mortality, justifying once again the importance of the proper management of suspected cases (1). In long-term care (LTC) residents, risk factors differ by gender. In women, urinary incontinence is a prominent factor, while in men, conditions such as dementia, urinary and faecal incontinence, and cerebrovascular disease are common.

Healthcare-associated factors also play a significant role in infection risk among older adults. Hospitalisation increases exposure due to catheterisation and other invasive procedures (7). Frequent transfers between facilities, fragmented care, and inconsistent infection control practices further raise the likelihood of acquiring infections. Additionally, poor hand hygiene among healthcare staff and inadequate sanitation exacerbate these risks (66). Improving communication during care transitions and adhering to strict infection control measures are essential strategies for reducing infection rates and enhancing outcomes in geriatric care.

Current therapeutic strategies and clinical challenges in managing urinary tract infections in older adults

The treatment of chronic urinary infections in elderly patients is a widely accepted approach, carefully individualised, considering the specific challenges of this population, such as asymptomatic bacteriuria, comorbidities, renal function, antibiotic resistance, and the need for personalised management strategies. Asymptomatic bacteriuria is common in the elderly and should not be treated with antibiotics except in specific situations, such as before invasive urological procedures (1, 2). Poorly indicated treatment can lead to increased antimicrobial resistance and does not prevent future symptomatic infections (4). For symptomatic UTIs, antibiotic choice should be guided by identification of the uropathogen and local rates of antibiotic resistance (Table II). Frequently recommended first-line antimicrobial agents include nitrofurantoin, fosfomycin, and trimethoprim-sulfamethoxazole, as long as local resistance to *E. coli* is less than 20 %. Nitrofurantoin is effective against *E. coli* and many Gram-negative species, but is ineffective against some *Proteus*, *Enterobacter* and *Klebsiella* (67–69). Fosfomycin is a useful option due to its low propensity to select resistance (4, 5, 7).

The selection of treatment duration and antimicrobial agents may vary due to the individual characteristics and constraints of the elderly population (70, 71). Acute cystitis, in the absence of limiting factors, can be treated with trimethoprim/sulfamethoxazole for a short duration of 3 days, nitrofurantoin for 5 days, or a single dose of fosfomycin (72, 73).

Table II. Relation of drug and clinical use indications

Drugs	Clinical use
Nitrofurantoin	Treatment of uncomplicated cystitis. Effective against *E. coli* and many Gram-negative species, but ineffective against *Proteus, Enterobacter* and *Klebsiella*. Not indicated for upper urinary tract infections.
	Fosfomycin treatment of lower urinary tract infections (*e.g.*, cystitis), with a single dose. Useful due to low propensity to select for resistance. Not indicated for upper urinary tract infections.
Fosfomycin	Treatment of lower urinary tract infections (*e.g.*, cystitis), with a single dose. Useful due to low propensity to select for resistance. Not indicated for upper urinary tract infections.
Aminoglycosides	Treatment of uncomplicated acute cystitis. Recommended for 3 days if *E. coli* resistance is less than 20 %.
	Aminoglycosides used in severe infections or sepsis. Monitor drug levels and renal function.
Aminoglycosides	Used in severe infections or sepsis. Monitor drug levels and renal function.
Tetracyclines Fluoroquinolones Beta-lactamase inhibitores Broad-spectrum cephalosporins	Second-line therapy, considered when first-line antibiotics are unavailable or not indicated

These medications are generally well-tolerated by the population in question due to their minimal side effects and lower cost compared to longer treatment regimens.

Patients who are unable to receive the antimicrobial orally or those who are septic should be administered the medication intravenously (74). When feasible, the route of administration may be transitioned to oral once the patient demonstrates clinical improvement and favourable progression based on laboratory results. Complicated urinary tract infections (UTIs) typically require extended treatment durations, depending on the specific pathogen, the clinical condition of the patient, and the severity of the infection (75).

When indicated, the use of aminoglycosides is essential and should be monitored through laboratory assessments to evaluate drug levels and renal function (76, 77). Nitrofurantoin is well tolerated, and its efficacy against the primary pathogens remains high in the elderly population (78). However, its concentrations in tissues and serum are relatively low, making it suitable exclusively for the treatment of cystitis (79). Fosfomycin, administered as a single dose, is effective for the management of lower UTIs but is limited by its availability and cost. Furthermore, like nitrofurantoin, fosfomycin exhibits low tissue penetration and should not be considered for the treatment of upper urinary tract infections (80).

Second-line therapies include tetracyclines, fluoroquinolones, aminoglycosides, beta-lactamase inhibitors, and broad-spectrum cephalosporins (81). The use of these

classes of antimicrobials should be evaluated on an individual basis and considered only when first-line agents are unavailable or their use is not indicated. In cases of severe infections or bacteremia, the empirical use of these medications may be deemed reasonable (82). In such instances, the duration of treatment typically extends beyond 7 to 14 days. The importance of starting antibiotic treatment immediately after a UTI diagnosis in the elderly, as delays or lack of treatment are associated with a significant increase in bloodstream infection and mortality (83). Therefore, early administration of antibicrobial agens seems to be crucial to avoid serious complications.

Additionally, it is important to consider the adverse effects of antibiotics, especially those that may impact cognitive function, and adjust dosage based on the patient's renal function (2, 84). Appropriate management of comorbidities, such as diabetes, and judicious use of urinary catheters are also essential to reduce the risk of UTIs (2). In summary, treatment of UTIs in the elderly should be based on an accurate diagnosis, appropriate choice of antibiotics considering local resistance, and careful monitoring of adverse effects, with special attention to patients' underlying health conditions.

Antimicrobial resistance in recurrent urinary tract infections: mechanisms, clinical impact, and epidemiological trends

Bacterial antibiotic resistance has been a subject of great attention to scientists ever since its discovery, since the logical implications of such bacterial populations could lead to the arrival of a global crisis, similar to a new pre-penicillin era (1, 2). Although logical scenarios, empirical evidence and adagios such as “necessity is the mother of invention” try to shed light upon future perspectives, little is still known concerning general impacts and approaches for antibiotic resistance.

Concerning our review, our most prevalent pathogen, *E. coli,* has been the subject of many breakthroughs on its resistance mechanisms. Firstly, it is worth mentioning that *E. coli* is not found among the so-called ‘ESKAPE bacteria’, species identified as responsible for the large majority of resistant bacterial nosocomial infections (4). However, its resistance mechanisms are surely important, as previously shown, and populations are especially susceptible to resistance in developing countries due to the lack of new-generation antibiotics (5).

The main mechanisms by which bacteria become antibiotic resistant are four: antibiotic modification or destruction, antibiotic influx inhibition, antibiotic efflux pumps and molecular drug target modifications (7). As these mechanisms are usually drug-dependent, all four have been reported for *E. coli*, concerning its worldwide first-line drug nitrofurantoin, and vary accordingly (5). Additionally, bacterial biofilm formation is considered an advantage against antibiotics, since it acts as an immune and drug physical barrier (8), while these species are also usually capable of entering a dormant state, another resistance mechanism (10). However ingenious these drug resistance mechanisms might be, one cannot be sure of their real clinical impact. Great population studies’ data on resistant uropathogenic *E. coli* are unreliable due to their overwhelmingly wide range and erratic distribution.

Nevertheless, we may draw safer conclusions concerning our main drug, nitrofurantoin. It is universally reported to retain a high level of antimicrobial activity, despite its frequent use. In Europe, levels of reported resistance in 2013–2014 were below 1.5 % (85).

More recent surveillance studies continue to demonstrate very low resistance rates, generally ranging from 0–3 % between 2019 and 2024, supporting the sustained efficacy of nitrofurantoin in the treatment of lower urinary tract infections. So, although new therapies, strategies to overcome drug resistance, and the promising outlook for our first-line treatment do not eliminate antibiotic resistance as a challenge for GrUTI, they present it as a challenge that can be effectively managed. Clinically, local resistance patterns should remain the main guide for antibiotic prescription.

Emerging and innovative therapeutic strategies for recurrent urinary tract infections

Urinary tract infections (UTIs) remain a significant public health concern, particularly due to the rise of antimicrobial resistance. In recent years, innovative approaches such as faecal transplantation, bacteriophages, probiotics and proanthocyanidins have emerged as alternatives or complements to conventional therapies. Faecal microbiota transplantation (FMT) is being explored as a promising strategy to prevent recurrent UTIs. Restoring a healthy gut microbiota may positively influence the urogenital microbiota, reducing colonisation by resistant pathogens (4, 86). Preliminary studies have shown that FMT can decrease the incidence of recurrent UTIs in patients with persistent dysbiosis, especially with *Clostridium difficile* infection. Still more research is needed to validate its efficacy and safety on a larger scale (87).

Probiotics, particularly strains of *Lactobacillus*, play a crucial role in maintaining a healthy urogenital environment. They compete with pathogens for nutrients and space while strengthening the mucosal barrier and modulating the local immune response. Clinical trials have demonstrated benefits in women with recurrent UTIs, suggesting their potential as a preventive measure (2, 4). A systematic review with 9 articles suggests that probiotics may help reduce the risk of recurrent UTIs, though evidence is limited and inconclusive. Despite this, their minimal side effects and good tolerance make them a promising treatment option, pending further randomised studies (88).

Proanthocyanidins (PACs) are a class of plant-derived molecules contained in various phytocomplexes, such as cranberry, which have demonstrated clinical benefit in the treatment of UTIs. A new intestinal mucosal protective agent, formed from a combination of cranberry extract, chondroitin sulfate, NAC, and hyaluronic acid in a specific mass ratio, was shown to reduce biofilm production in UTI pathogens. This mixture offers a potential new approach for treating recurrent cystitis and UTIs linked to intestinal dysfunction (1, 10). Recent products combining cranberry extracts and *Lactobacillus* probiotic preparations have been introduced to the market as potential preventive solutions for UTIs, available to the public without a prescription. While many of these products lack scientific backing, some human studies have explored the effects of cranberry-probiotic combinations. Notably, Montorsi *et al*. (89) conducted a pilot study demonstrating the effectiveness of a combined regimen of *Lactobacillus rhamnosus* SGL06, cranberry, and vitamin C in preventing recurrent UTIs.

Complementing this, bacteriophage therapy, using viruses that specifically infect and destroy bacteria, has emerged as a personalised approach to combating UTIs, particularly those caused by multidrug-resistant pathogens such as *Escherichia coli*. The ability of bacteriophages to prevent cross-resistance positions them as a promising alternative to conventional antibiotics (2, 4). Beyond UTIs, bacteriophage therapy has been explored for

nearly a century, targeting various bacterial infections through personalised phage cocktails designed to enhance antimicrobial activity and minimise resistance. Interestingly, like probiotics, bacteriophages can also be used prophylactically, eliminating gastrointestinal pathogens and modulating microbiota composition, further expanding their therapeutic and preventive potential (90). Competitive inoculation involves instilling *E. coli* strains (83972 or HU2117) into the bladder to prevent symptomatic UTIs by leveraging asymptomatic bacteriuria (ABU). While evidence suggests it may reduce rUTI recurrence in patients with incomplete bladder emptying, its safety, efficacy, and low colonisation rates remain concerns. Cai *et al*. (91) demonstrated ABU's protective effects against rUTI recurrence in young women, highlighting its potential. However, the method requires frequent reapplications, limiting its clinical feasibility. Further research is necessary before recommending its broader use as an alternative to antibiotics.

Building on these innovative approaches, targeting bacterial virulence factors and utilising advanced nanomaterials have also emerged as promising strategies for UTI management. The bacterial endopeptidase MepM, essential for *E. coli* virulence, has been identified as a potential target, with evidence showing that MepM deficiency significantly reduces bacterial survival, motility, and infection-causing capacity (7). Furthermore, nanoparticles are being explored for their antibacterial and anti-biofilm properties, with silver, copper, zinc oxide, and copper sulfide nanoparticles demonstrating effectiveness against UTI-causing pathogens. These advancements include enhanced catheter coatings to prevent infections and the use of magnetic iron oxide nanoparticles conjugated with antibiotics, highlighting their potential to combat multidrug-resistant pathogens and catheter-associated UTIs (92).

Prevention strategies for recurrent urinary tract infections: antibiotic and non-antibiotic approaches

Antibiotic prevention. – There are two main types of antibiotic prophylaxis for rUTI: continuous and postcoital. Postcoital prophylaxis is recommended for women whose rUTIs are frequently triggered by sexual intercourse, with a single dose of an antimicrobial drug, such as trimethoprim-sulfamethoxazole (93, 94). Continuous prophylaxis has shown efficacy in preventing rUTI, with a significant reduction in episodes, but the benefits do not persist after stopping the treatment. A meta-analysis shows that long-term prophylactic use of antibiotics is clinically the most effective preventive measure (RR 0.15; 95 % CI 0.08–0.29), indicating a significant reduction in recurrent UTI risk compared with placebo or no prophylaxis, but carries risks of side effects and should be avoided in patients with urinary catheters due to the risk of bacterial resistance (95). The ideal duration of prophylaxis is still uncertain, but an initial treatment period of 3 to 6 months is recommended to assess individual response (96).

The options include nitrofurantoin, fosfomycin trometamol, and trimethoprim, with doses adjusted according to the regimen chosen (97). When other options fail, or during pregnancy, cephalosporins like cephalexin or cefaclor may be used. Studies show that continuous prophylaxis reduces rUTI frequency, but the benefits do not persist after treatment ends (98). Regarding bacterial resistance and preventive forms, the effectiveness of rapid drug rotation in limiting resistance evolution is presented as a safer and more cost-effective alternative to combination therapy (99, 100). Frequent shifts in selective pres-

sures reduce bacterial adaptation, aligning with evolutionary rescue theories. Clinical studies have demonstrated its efficacy, particularly with rotation intervals of 5–7 days. However, factors such as drug sequence, interactions, and pharmacokinetics significantly influence its effectiveness. Further research is needed to optimise this approach and address challenges such as resistance reversion and adaptation costs.

Non-antibiotic prevention. – Behavioural modifications may prevent rUTIs (4). Increased fluid intake can help flush out pathogens from the bladder and urethra, with evidence supporting its effectiveness in premenopausal women consuming less than 1.5 litres daily, though excessive consumption might dilute natural antibacterial agents (4). Sexual activity, particularly anal intercourse, and contraceptive methods involving spermicides, such as condoms or diaphragms, are associated with a higher risk of rUTIs, suggesting the need for alternative practices (101). Additionally, avoiding hypothermia is crucial, as exposure to cold conditions, such as cooling the feet, has been linked to symptomatic UTIs in susceptible individuals (4).

Complementary approaches, such as cranberry usage, show preventive potential. Cranberry-derived products contain proanthocyanidins, which inhibit the adhesion of uropathogenic bacteria to the urinary epithelium, especially *E. coli* (4). A meta-analysis demonstrated 30 % reduction in the UTI recurrence rate by treatment with cranberry preparations (RR 0.70; 95% CI 0.60–0.80; $p < 0.01$) (102). However, a recent systematic review with 50 articles shows that cranberry products effectively reduce the risk of symptomatic UTIs in women with recurrent infections, children, and post-intervention patients, but show no benefit for the elderly, those with bladder emptying issues, or pregnant women. This is related to this other systematic review, which shows that cranberry is promise as a prophylactic option for recurrent urinary tract infections (UTIs) in women by preventing bacterial adhesion, with potential to reduce antibiotic resistance, though further research is needed to establish proper dosage and clinical protocols.

Another promising approach involves topical estrogen therapy in postmenopausal women, which has proven effective in reducing recurrent UTIs by restoring a *Lactobacillus*--dominated vaginal flora and improving urogenital mucosal integrity (4). A meta-analysis revealed that vaginal estrogen may reduce the rate of rUTI (RR 0.42), with two small trials confirming its efficacy in postmenopausal women (103). In the largest study, 108 patients were randomised to receive a vaginal ring or placebo, with a lower incidence of rUTI in the treated group (51 *vs*. 80 %) (104).

Additionally, D-mannose, a simple sugar that prevents *E. coli* adhesion to urothelial cells, has shown promise (105). Recent clinical trials suggest its efficacy may be comparable to certain antibiotics, with the added advantage of a superior safety profile (106). However, a systematic review evaluating eight randomised studies highlights persistent uncertainty regarding its efficacy in the prevention or treatment of urinary tract infections (UTIs) in any population (107).

Oral immunostimulants, such as OM-89 and MV140, have shown potential in reducing rUTIs in women, although with certain limitations (108). A meta-analysis indicated that OM-89 reduces the frequency of reinfections in the short term. Meanwhile, MV140, evaluated in an RCT, demonstrated a significant reduction in rUTIs, with 58 % of women remaining infection-free at six months compared to 25 % in the placebo group (109). On the other hand, the parenteral vaccine StroVac showed response rates of 86.8 %, lower than

nitrofurantoin (91.8 %), but with fewer adverse effects (110). Despite these advances, factors such as high costs and the lack of data for specific populations, such as the elderly, limit their widespread clinical application.

Additionally, intravesical administration of glycosaminoglycans, such as hyaluronic acid and chondroitin sulfate, aims to restore the urothelial protective layer, reducing bacterial adherence and promoting tissue regeneration (111). This approach has demonstrated benefits in patients with interstitial cystitis and recurrent UTIs. Lastly, urinary antiseptics, such as methenamine, offer an alternative to antibiotics, particularly in long-term prophylaxis. These agents acidify the urine and create an inhospitable environment for bacterial growth, making them useful for patients with contraindications to antibiotic use (112, 113).

CONCLUSIONS AND FUTURE PROJECTIONS

The management of chronic urinary tract infections in the elderly population presents multifaceted challenges, involving not only microbiological factors but also diagnostic, clinical, and antimicrobial resistance-related issues. The prevalence of *Escherichia coli* as the primary pathogen, combined with its ability to form biofilms and advanced immune evasion strategies, highlights the need for targeted therapeutic approaches. In parallel, the complexity of clinical presentations in the elderly, often marked by nonspecific symptoms or functional changes, emphasises the importance of improved diagnostic criteria, especially in long-term care facility residents and individuals with cognitive impairment.

The future of treating and preventing these infections depends on progress in several areas. First, the development of new antimicrobials and therapies based on specific targets, such as bacterial virulence factors (*e.g.*, siderophores and adhesion mechanisms), may offer more effective alternatives with less impact on the resident microbiota. Additionally, vaccines against uropathogenic pathogens, particularly against *E. coli*, represent a promising preventive strategy. Emerging technologies, such as inflammation biomarkers and advanced imaging techniques, may also improve diagnostic accuracy, reducing cases of inadequate treatment.

Finally, it is crucial to adopt an integrated approach that combines medical, educational, and structural interventions. The implementation of individualised care protocols, coupled with the training of healthcare professionals and the rational use of antimicrobials, will help minimise the impact of urinary tract infections on the quality of life of vulnerable populations.

List of acronyms, abbreviations, and symbols. – ABU – asymptomatic bacteriuria; ASB – asymptomatic bacteriuria; CAUTI – catheter-associated urinary tract infection; cAMP – cyclic adenosine monophosphate; CDC – Centers for Disease Control and Prevention; CFU – colony-forming units; COPD – chronic obstructive pulmonary disease; CUP – chaperone-usher pathway; *E. coli* – *Escherichia coli*; FMT – fecal microbiota transplantation; GBS – group B *Streptococcus*; HAUTI – healthcare-associated urinary tract infection; IDSA – Infectious Diseases Society of America; IBC – intracellular bacterial community; LTC – long-term care; PACs – proanthocyanidins; rLUTI – recurrent lower urinary tract infection; rUTI – recurrent urinary tract infection; SHEA – Society for Healthcare Epidemiology of America; TLR4 – toll-like receptor 4; UPEC – uropathogenic *Escherichia coli*; UTI – urinary tract infection.

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