



REVIEW ARTICLE

First-line therapeutic strategies for the management of recurrent urinary tract infections caused by *Escherichia coli*

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Received: December 30, 2025

Accepted: December 31, 2025

Published: December 31, 2025

Citar como: Guzmán-Ramos ED, Santamaria-Enríquez AD, Valencia-Herrera AR, Poveda-Paredes FX. Estrategias terapéuticas de primera línea para el manejo de infecciones urinarias recurrentes causadas por *Escherichia coli*. Rev Ciencias Médicas [Internet]. 2025 [citado: fecha de acceso]; 29(S2): e7060. Disponible en: <http://revcmpinar.sld.cu/index.php/publicaciones/article/view/7060>

ABSTRACT

Introduction: urinary tract infections represent a growing challenge for health systems, requiring comprehensive approaches based on updated scientific evidence.

Objective: to critically analyze recent scientific literature in order to identify first-line therapeutic strategies and preventive measures against recurrent urinary tract infections caused by *Escherichia coli*.

Methods: a systematic review of scientific literature was conducted across various databases. The search was performed using an algorithm with keywords and Boolean operators, allowing the identification of relevant sources. Selected studies, after applying inclusion and exclusion criteria, were critically analyzed considering timeliness, methodological quality, and thematic relevance, and integrated into the final synthesis of the review.

Development: the reviewed evidence indicates that first-line antibiotics include nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomicin trometamol, each with specific advantages and limitations. In pregnant women, nitrofurantoin is safe after the first trimester, while fosfomicin offers good adherence due to its single-dose administration. In cases of extended-spectrum beta-lactamase-producing strains, carbapenems and aminoglycosides are recommended, although they require monitoring due to toxicity. The most effective preventive measures include postcoital prophylaxis, vaginal estrogen use in postmenopausal women, adequate hydration, and hygiene practices.

Conclusions: the review confirms that the management of recurrent urinary tract infections requires combining safe antibiotic therapies with sustainable preventive strategies. Strengthening primary care, monitoring bacterial resistance, and fostering technological innovation are key elements to reduce recurrences and guide public health policies in community healthcare.

Keywords: Anti-Bacterial Agents; Drug Resistance, Microbial; Escherichia coli Infections; Urinary Tract Infections.

INTRODUCTION

Recurrent urinary tract infections (RUTIs) are defined as three episodes of UTIs within the last 12 months or two episodes within the last six months. They can occur in both men and women but predominantly affect young sexually active women, pregnant individuals, postmenopausal women, and patients with underlying urological conditions.⁽¹⁾ RUTIs may result from reinfection or relapse, both occurring more than two weeks after initial treatment. Reinfection accounts for approximately 95 % of cases and is caused by Gram-negative bacteria originating outside the urinary tract—primarily from the gut, with *Escherichia coli* (*E. coli*) responsible for 75–95 % of these infections.⁽²⁾

It is estimated that approximately 60 % of women experience at least one episode of acute bacterial cystitis in their lifetime. Of these, 20–40 % will have another episode, and 25–50 % will suffer multiple recurrences.⁽³⁾ In Ecuador, the annual incidence among women reaches up to 15 %, particularly in those with underlying conditions.⁽⁴⁾

RUTIs caused by *E. coli* are driven by virulence factors such as adhesins, toxins, and capsules that enable the bacterium to adhere to, invade, and persist in the urinary tract.⁽⁵⁾ Additionally, host-related factors—including alterations in vaginal microbiota, loss of normal acidic pH in secretions, anatomical abnormalities, immunological dysfunction, and use of urinary devices—contribute to susceptibility.⁽⁶⁾

Management of *E. coli*-related RUTIs relies on first-line antibiotics—nitrofurantoin, TMP-SMX, and fosfomycin trometamol—combined with preventive measures such as postcoital prophylaxis, vaginal estrogens in postmenopausal women, adequate hydration, and proper hygiene. Nitrofurantoin stands out for its efficacy and low resistance rates, although it may cause adverse effects in patients over 50 years of age. TMP-SMX acts synergistically by inhibiting folic acid synthesis, while fosfomycin offers high treatment adherence due to single-dose administration and a favorable safety profile. In pregnancy, nitrofurantoin is considered safe during the second and third trimesters, whereas fosfomycin serves as an effective alternative. These strategies aim to reduce recurrences while balancing therapeutic efficacy and safety.^(7,8,9,10)

However, the presence of extended-spectrum beta-lactamase (ESBL)-producing strains poses a clinical challenge, as they inactivate penicillins and cephalosporins, necessitating broad-spectrum antibiotics such as carbapenems, aminoglycosides, and newer-generation cephalosporins (e.g., ceftazidime/avibactam). Fosfomycin remains useful due to its safety and convenience—even in pregnant and lactating women—though aminoglycoside use requires monitoring for renal and auditory toxicity. Empirical treatment must consider expected resistance patterns, with options including meropenem, piperacillin/tazobactam, and amikacin,

pending antimicrobial susceptibility results. Overall, evidence underscores the need for protocols based on microbiological surveillance and rational antibiotic use to address rising bacterial resistance.^(11,12,13)

Given this context, the present review was conducted to critically analyze recent scientific literature and identify first-line therapeutic strategies and preventive measures for RUTIs caused by *E. coli*.

METHODS

A systematic and descriptive bibliographic review was conducted, restricted to English and Spanish languages. High-impact, academically relevant scientific articles were selected using rigorous Medical Subject Headings (MeSH) terms: "Urinary Tract Infections," "Therapeutics," "Anti-Bacterial Agents," "Prevention & Control," combined with Boolean operators (AND, OR) to refine the search strategy. The search period spanned May to July 2024.

Inclusion criteria comprised publications from 2019 to June 2024 addressing: "Confirmed Diagnosis of Urinary Tract Infection," "Recurrent Infections," "Antibiotic Resistance," and "Clinical Symptoms." Exclusion criteria included: "Medical Complications," "Adverse Effects or Allergies," "Recent Antibiotic Use," and "Severe Infections." Indexed, high-impact journal articles, systematic reviews, meta-analyses, updated textbooks, and relevant medical literature on first-line therapeutic management of *E. coli*-associated RUTIs were included.

The PICOT framework guided the research scope and evidence evaluation:

- P (Population): Women of all ages, including pregnant individuals, with recurrent UTIs
- I (Intervention): First-line therapeutic management
- C (Comparator): Available alternative treatments
- O (Outcome): Efficacy in reducing recurrences and improving symptoms
- T (Time): Follow-up period

PICOT Question: In women of all ages, including pregnant individuals, with recurrent urinary tract infections, what is the first-line therapeutic management compared to alternative treatments in terms of efficacy in reducing recurrences and improving symptoms?

Following PRISMA methodology (Figure 1), an exhaustive search was performed in electronic databases including SciELO, Elsevier, PubMed, Cochrane, Epistemonikos, and journals such as Medigraphic Artemisa, Medicrit, Science, and Recimundo. Approximately 80 records were identified; after duplicate removal, 54 remained. Following title/abstract screening and publication date verification, 26 were excluded, leaving 28 eligible articles. After applying inclusion/exclusion criteria, 19 were removed, and 35 articles were included in the final analysis and synthesis.

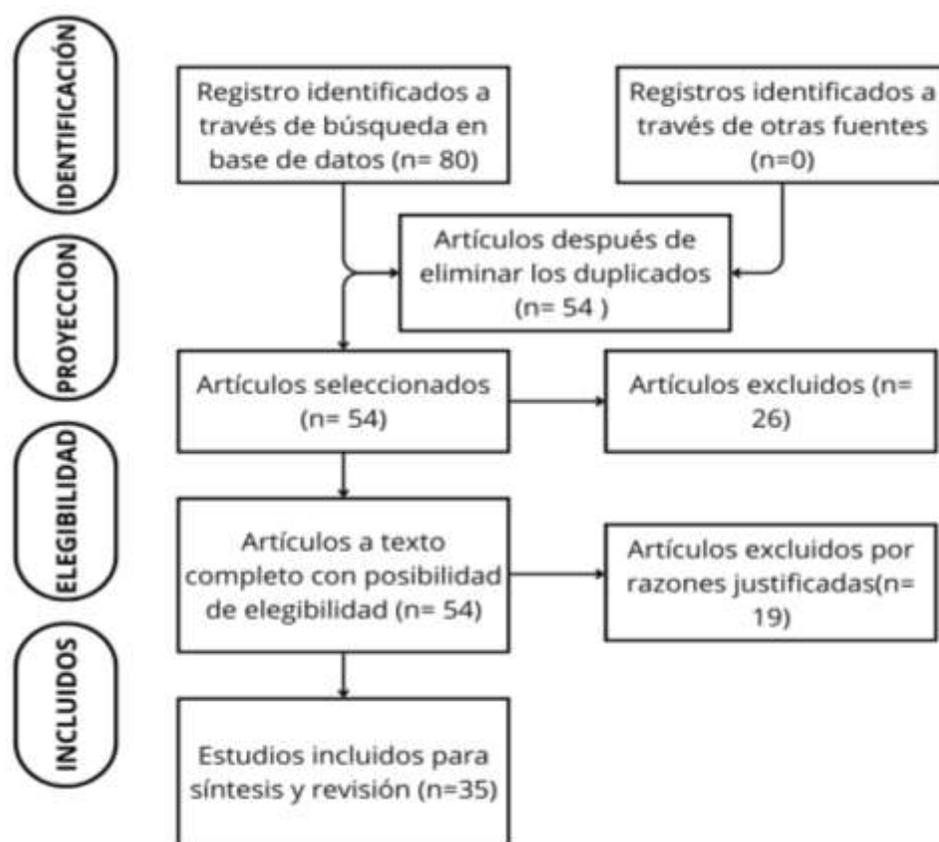


Fig. 1 PRISMA flow diagram.

RESULTS

First-line treatment for *E. coli*-related RUTIs includes antibiotics such as nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX), and fosfomicin trometamol, combined with postcoital prophylaxis and preventive measures to reduce recurrence risk.⁽⁷⁾

Nitrofurantoin, administered at 50–100 mg doses, is preferred for its ability to inhibit bacterial DNA and RNA synthesis, effectively eliminating pathogens without disrupting intestinal or vaginal microbiota and exhibiting low resistance rates. However, it may cause adverse effects in patients over 50 years, including acute pulmonary reactions and severe cutaneous allergic reactions, which can be life-threatening in rare cases.⁽⁸⁾

TMP-SMX's efficacy stems from the synergistic action of two antimicrobials that inhibit folic acid synthesis. At doses of 400 mg and 200 mg, respectively, it effectively eradicates *E. coli*. Prolonged use has not been linked to increased recurrence rates. Despite its effectiveness, it may cause allergic reactions and gastrointestinal disturbances.⁽⁹⁾

Fosfomicin trometamol inhibits bacterial cell wall synthesis, leading to rapid pathogen clearance. Its main advantage is single-dose administration (3 g), which improves treatment adherence. It has minimal side effects and lower bacterial resistance rates compared to other common

antibiotics, achieving high urinary concentrations and maintaining therapeutic levels for extended periods.⁽¹⁰⁾

Management of *E. coli* RUTIs in pregnant women requires special attention due to risks to both mother and fetus. Nitrofurantoin is the antibiotic of choice during the second and third trimesters but is avoided in the first trimester due to potential teratogenic effects.⁽¹¹⁾

Vaginal estrogen therapy can reduce RUTIs in postmenopausal women by restoring vaginal epithelium and microbiota, which are compromised by declining estrogen levels after menopause. This creates a healthier vaginal and urethral environment less susceptible to pathogenic colonization.⁽¹²⁾

Postcoital antimicrobial prophylaxis is an effective preventive strategy, particularly in women prone to UTIs after sexual activity. This approach involves taking a single antibiotic dose immediately after intercourse—commonly nitrofurantoin—to prevent infection development.⁽¹³⁾

To prevent UTIs caused by *E. coli*, it is crucial to maintain adequate hydration and good personal hygiene, such as wiping from front to back and fully emptying the bladder when urinating, which is also fundamental.⁽¹⁴⁾ Avoiding irritants such as tobacco and alcohol, and opting for cotton underwear to allow better ventilation, may reduce the risk of UTIs.⁽¹⁵⁾

Of particular concern are antibiotic-resistant strains, such as ESBL-producing *E. coli*. RUTIs caused by these bacteria present a significant therapeutic challenge due to their resistance to beta-lactam antibiotics.⁽¹⁶⁾

ESBL-producing *E. coli* are common and require broad-spectrum antibiotics. These resistant strains inactivate penicillins and cephalosporins via beta-lactamase enzymes, often resulting from inappropriate antibiotic use.⁽¹⁷⁾

Preferred agents for ESBL-producing *E. coli* RUTIs include carbapenems such as ertapenem (1 g IV/IM daily for 3–14 days), which are highly effective but require monitoring to prevent selection of resistant strains. Aminoglycosides are also effective but necessitate careful blood level and renal function monitoring due to high toxicity.⁽¹⁸⁾

Newer-generation cephalosporins like ceftazidime/avibactam (2,5 g IV infusion over 2 hours every 8 hours for 5–14 days) are effective against ESBL-producing *E. coli*, especially in severe infections. Fosfomicin trometamol (3 g oral single dose dissolved in water) offers a favorable safety profile and convenient administration.⁽¹⁹⁾

In pregnant women with ESBL-producing *E. coli* RUTIs, treatment options include ertapenem (1 g IV daily), fosfomicin trometamol (3 g oral single dose), and nitrofurantoin (100 mg every 6–12 hours for 5–7 days)—the latter avoided in the first trimester due to potential congenital defects and in late pregnancy due to risk of neonatal hemolytic anemia.⁽²⁰⁾

In lactating infants, carbapenems and aminoglycosides (e.g., amikacin 15 mg/kg/day IV in one or two divided doses; gentamicin 5–7,5 mg/kg/day in two–three divided doses for 7–10 days) are preferred, with careful monitoring due to ongoing renal and auditory system development. Fosfomicin may be used cautiously.⁽²¹⁾

Empirical treatment of ESBL-producing *E. coli* UTIs is complex due to multidrug resistance. Initial therapy must account for expected resistance patterns while awaiting culture and susceptibility results.⁽²²⁾

Empirical treatment options include carbapenems such as meropenem 1 g intravenously every 8 hours, fosfomicin trometamol as a single 3 g oral dose, piperacillin/tazobactam 3,37 g intravenously every 6 hours, and amikacin 15 mg/kg per day administered intravenously.⁽²³⁾

RUTIs are defined as three UTI episodes in the past 12 months or two in the past six months. While affecting both sexes, they are especially prevalent in young sexually active women, pregnant individuals, postmenopausal women, and those with underlying urological conditions.⁽²⁴⁾

Reinfection (95 % of cases) is typically caused by gut-derived Gram-negative bacteria like *E. coli*, responsible for 75–95 % of RUTIs.⁽²⁵⁾

In terms of incidence and prevalence, approximately 60 % of women experience at least one episode of acute bacterial cystitis during their lifetime. Of these, between 20 % and 40 % will have another episode, and between 25 % and 50 % experience multiple recurrences.⁽³⁾ In Ecuador, the annual incidence in women is up to 15 %, being higher among those with underlying conditions.⁽²⁶⁾

First-line treatment for UTIs caused by *E. coli* includes antibiotics such as nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomicin trometamol, along with postcoital prophylaxis and preventive measures. Nitrofurantoin, at doses of 50 or 100 mg, is preferred for its efficacy in inhibiting bacterial DNA and RNA synthesis without altering intestinal or vaginal microbiota, and for its low resistance rate. However, it may cause severe adverse effects in patients over 50 years of age. Trimethoprim-sulfamethoxazole combines two antimicrobial agents that inhibit folic acid synthesis, effectively eradicating *E. coli* at doses of 400 mg and 200 mg respectively. Despite its effectiveness, it may cause allergic reactions and gastrointestinal disorders.⁽²⁶⁾

Fosfomicin trometamol inhibits bacterial cell wall synthesis and is administered as a single 3 g dose, improving treatment adherence. It has minimal side effects and a low bacterial resistance rate, reaching high urinary concentrations and maintaining prolonged therapeutic levels. In pregnant women, treatment of UTIs caused by *E. coli* requires special attention. Nitrofurantoin is the antibiotic of choice during the second and third trimesters but is avoided in the first trimester due to potential teratogenic effects.⁽²⁷⁾

Vaginal estrogen therapy can reduce UTIs in postmenopausal women by restoring the vaginal epithelium and microbiota, creating an environment less susceptible to bacterial colonization.⁽¹²⁾ In addition to antibiotic therapy, postcoital microbial prophylaxis is effective in preventing UTIs, especially in women susceptible after sexual activity, using nitrofurantoin.⁽²⁸⁾

To prevent UTIs caused by *E. coli*, it is crucial to maintain good hydration, personal hygiene (wiping from front to back and fully emptying the bladder when urinating), avoid irritants such as tobacco and alcohol, and opt for cotton underwear to improve ventilation.

Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* resistance to beta-lactam antibiotics such as penicillins and cephalosporins represents a significant challenge in UTI treatment. This resistance is due to the bacterium's ability to inactivate these antibiotics through the production of specific beta-lactamases.⁽²⁹⁾

To address this resistance, several antibiotics of choice have been identified: carbapenems such as ertapenem and meropenem are highly effective against ESBL-producing *E. coli*, but prolonged use requires careful monitoring to avoid the selection of resistant strains.⁽²⁹⁾

Aminoglycosides such as amikacin and gentamicin are also effective, although their use must be accompanied by strict monitoring due to potential toxicity, which may manifest as nephrotoxicity and ototoxicity. Fosfomicin trometamol stands out for its safety profile and convenience, as it is administered as a single oral dose and is effective in severe infections.⁽³⁰⁾

In pregnant women, carbapenems and fosfomicin trometamol are safe options, although nitrofurantoin should be avoided in the first trimester and in the last weeks of pregnancy due to potential risks to the fetus, such as congenital defects and neonatal hemolytic anemia.⁽³¹⁾ In infants, carbapenems and aminoglycosides are preferred, with special attention to monitoring due to the risk of toxicity in developing systems, and fosfomicin may be used cautiously.⁽²¹⁾

Empirical treatment for urinary tract infections caused by ESBL-producing *Escherichia coli* is challenging due to resistance to multiple antibiotics. Empirical options include carbapenems such as meropenem (1 g intravenously every 8 hours) and ertapenem (1 g intravenously every 24 hours), which are effective against these resistant strains. Fosfomicin trometamol (3 g orally as a single dose) may be considered in uncomplicated infections.⁽³²⁾

Although piperacillin/tazobactam (3,37 g intravenously every 6 hours) may be useful in some strains, its efficacy is not guaranteed in the presence of ESBLs. Amikacin (15 mg/kg/day intravenously) is another effective alternative for complicated infections. Treatment selection must be tailored to the severity of the infection and antimicrobial susceptibility results.⁽³³⁾

CONCLUSIONS

Recurrent urinary tract infections constitute a significant clinical challenge due to their high prevalence and impact on quality of life—particularly in young women, pregnant individuals, postmenopausal women, and those with urological comorbidities. First-line treatment includes nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomicin trometamol, selected based on safety and resistance profiles. Preventive strategies—postcoital prophylaxis, vaginal estrogens, adequate hydration, and proper hygiene—are essential to reduce recurrences. In cases of ESBL-producing *Escherichia coli*, empirical management is complex and requires broad-spectrum antibiotics such as carbapenems, fosfomicin, piperacillin/tazobactam, or amikacin, enabling early intervention and improved clinical outcomes despite the challenge of bacterial resistance. These findings highlight the importance of integrating antimicrobial stewardship, resistance surveillance, and patient-centered prevention into community health strategies.

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