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THE MANAGEMENT OF RECURRENT URINARY TRACT INFECTION UTIS A COMPREHENSIVE REVIEW OF PREVENTION STRATEGIES ANTIBIOTIC STEWARDSHIP AND THE EMERGING ROLE OF NON-ANTIBIOTIC TREATMENT

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Abstract

Urinary tract infections (UTIs) are very frequent, contribute to substantial patient morbidity, entail large financial costs to health-care systems and are one of the most common causes for antibiotic usage globally. Two or more incidents during a six-month period, or three or more within a year, are considered recurrent urinary tract infections, or rUTIs. With the exception of the first year of life, women have urinary tract infections more frequently than males. rUTIs cause a large financial strain on the healthcare system and several missed workdays. Antibiotics were formerly the basis of acute therapy; now, due to rising resistance patterns, antibiotic overuse and abuse, and a move toward antimicrobial stewardship, we are increasingly relying more on non-antibiotic and preventive measures. It is crucial to find non-antibiotic solutions for rUTI treatment and prevention. Behavior modifications, dietary supplements (such as cranberry products and Chinese herbal medicines), probiotics, NSAIDs, D-mannose, methenamine hippurate, estrogens, intravesical glycosaminoglycans, immunostimulants, vaccinations, and inoculation with less-pathogenic bacteria are some non-antibiotic measures and treatments for rUTIs. Although some of the trial outcomes for these treatments are encouraging, more substantial data is needed before solid recommendations for their application can be made. Trials in certain demographic groups are needed to determine if a combination of these medications would be the best course of action to minimize recurrent UTI.

INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent bacterial diseases, impacting around 150 million individuals annually globally. UTIs are defined microbiologically as the inflammatory reaction of the urothelium to microbial pathogens (1). Due to variations in reporting procedures and diagnostic standards, it is challenging to determine the actual incidence; nonetheless, it is believed that half of all women will have a UTI at some point in their lives, and that up to 50% of them will return within the next six months (2,3). According to observational studies, women experience 2.6 infections on average each year for recurrences (4). Men are far less likely than women to get a UTI, with an estimated lifetime frequency of 13.7%.

In the USA alone, UTI recurrence caused 2-3 million ER visits and 10.5 million outpatient consultations in 2007 (5) Furthermore, 17.2% of all nosocomial infections in England (6) are caused by UTIs, making them the most frequent source of infection in hospitalized patients. Moreover, UTIs cause significant patient morbidity and missed work, which means that treating this illness comes with high financial costs—estimated to be $3.5 billion annually in the USA.(7, 8). Although there is no agreed-upon definition of recurrent UTI, it is generally understood to mean that there have been two or more episodes of symptomatic infection (dysuria, frequency, urgency, suprapubic pain, or haematuria) within the previous six months, or three infections within the previous year (9).

A research conducted on college-aged women using a questionnaire found that episodes of UTI typically lasted 6.1 days, 2.4 days of limited activity, and 1.2 days of time off work. This suggests that recurrent UTI is linked to short-term morbidity. UTIs are very common, the main cause of hospital-acquired infections and subsequent morbidity, and they account for a significant portion of outpatient and emergency department consultations. These factors highlight the public health burden of UTIs. Though about 25% of all antibiotic prescriptions are for UTIs, the increased danger of antimicrobial resistance resulting from our present manner of handling these patients is more significant than these factors (10). One of the biggest global challenges to patient safety today is antibiotic resistance (10). Antimicrobial resistance is thought to cost the European Union $1.5 billion in medical costs and lost productivity annually, according to the European Centre for Disease Prevention and Control (11). Antimicrobial-resistant bacteria infections can result in more serious infections, lengthier hospital stays, and higher mortality rates (12).

The goal of antimicrobial stewardship is to counteract the effects of these widespread prescribing patterns by ensuring cost-effective therapy, improving clinical outcomes, and minimizing the side effects of antibiotic use, such as toxicity, selection of virulent organisms, emergence of resistant bacterial strains, and healthcare-associated infections like Clostridium difficile. The World Health Organization (WHO) has declared antimicrobial resistance (AMR) as one of the top ten global public health threats facing humanity and has created a global action plan for AMR. Due to the adherence to these principles, there is now more interest in and use of non-antibiotic adjuncts in the treatment and prophylaxis of urinary tract infections.

ETIOLOGY

The majority of UTIs are caused by bacterial infections, however fungal and viral infections can occasionally happen, especially in immunocompromised people. Escherichia coli is the most prevalent kind of bacterial pathogen. Proteus mirabilis, enterococcus faecalis, Klebsiella pneumoniae, and pseudomonas aeruginosa are a few more prevalent pathogens. The urethra is

the pathway via which the majority of Gram-negative bacteria ascend from the digestive system. The occurrence of UTI due to hemorrhagic dissemination is less common.

Pathophysiology and Risk Factors

Because of the urethra's close proximity to the anus, which results in a unique microbiome in the periurethral area and gives pathogens from the faecal reservoir, like uropathogenic *Escherichia coli* (UPEC), easier access to the bladder and renal pelvises, women are thought to be more susceptible to UTIs than men. Furthermore, infections are able to enter the bladder more easily since the female urethra is shorter than the male urethra [13, 14]. Other host-related risk factors for rUTIs, such as urological, genetic, and behavioral variables, have been discovered in addition to being female. Sexual activity has been found to be a major risk factor, particularly in young, healthy women. The incidence of rUTIs is associated with certain behaviors, including frequent partner changes, frequency of sexual activity, and use of spermicides or diaphragms [15]. Having a mother with a history of UTIs and early commencement of UTI episodes are additional risk factors in addition to sexual activity [16]. The observation that specific blood types have been associated with an increased susceptibility to rUTIs further emphasizes the potential significance of genetics. A higher susceptibility to rUTIs has been linked to phenotypes other than Lewis-non-secretors. This is due to uropathogens' enhanced adherence to the urothelial membrane through the expression of specific globoseries-glycolipid receptors [17].

A decrease in estrogen causes a change in the microbiome that favors more pathogenic bacteria, and following menopause, anatomical and functional urological variables may be crucial. Controversial discussions have centered on post-voiding residual urine, urinary incontinence, and cystocele diagnosis as risk factors for recurrent urinary tract infections [18].

Management of UTIs

According to an independent analysis on antimicrobial resistance (AMR) commissioned in July 2014 by the UK Government to address the issue, if action is not done, it might result in 10 million deaths annually worldwide by 2050 and cost an estimated US$ 100 trillion (19). According to the World Health Organization's (WHO) AMR Collaborators' most recent prediction models, bacterial AMR-related fatalities worldwide were linked to 4.95 million deaths in 2019 (20). This comprises 3.57 million fatalities linked to AMR and 1.27 million deaths directly related to bacterial AMR. There were only six infections that were linked to or caused over 250,000 fatalities related to bacterial AMR:

Escherichia coli, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. 929,000 fatalities were caused by them together (21). After bloodstream infections, peritoneal and intra-abdominal infections, lower respiratory infections, and all related thoracic infections, UTIs were the fourth most common infectious syndrome linked to worldwide fatalities attributable to or associated with AMR (21).

Classification and diagnosis

While there are other categorization schemes for UTIs, the European Society for Infections in Urology (ESIU) and the EAU Section of Infections in Urology have created a useful method that the EAU has endorsed. The EAU/ESIU system categorizes UTIs based on the frequency of occurrence (rare and recurring), location (lower and upper UTIs), prevalence of risk factors (complex and complicated UTIs), relapse or reinfection, and in both genders (22). In other words, the system is predicated on the following: the clinical manifestation of the UTI, the anatomical level of the UTI, the infection's severity grade, the classification of risk factors, the frequency of recurrence, and the accessibility of suitable antimicrobial medication (23).

An example of an uncomplicated UTI would be a young, premenopausal, nonpregnant woman who presents with the typical symptoms of a urinary tract infection (UTI) but has no known significant anatomical and functional abnormalities within the urinary tract or comorbidities. All other UTIs are, by definition, complex UTIs with a greater potential for a convoluted path. Table I summarizes this UTI categorization scheme.

Even a mild UTI is more than simply an infection since it causes symptoms, limits activity, and even calls for bed rest or sick leave. A recurrent UTI is one that occurs at least twice in the preceding six months or three times annually. Nonetheless, it is highly advised against treating instances of asymptomatic bacteriuria, which occur when bacteria are discovered in a urine culture obtained during a normal clinical visit in a patient who is asymptomatic, in contrast to past practice (23). Evidence suggests that asymptomatic bacteriuria is a frequent commensal colonization that may protect against superinfection of symptomatic UTI, and in certain situations, treating it may be detrimental (23,24).

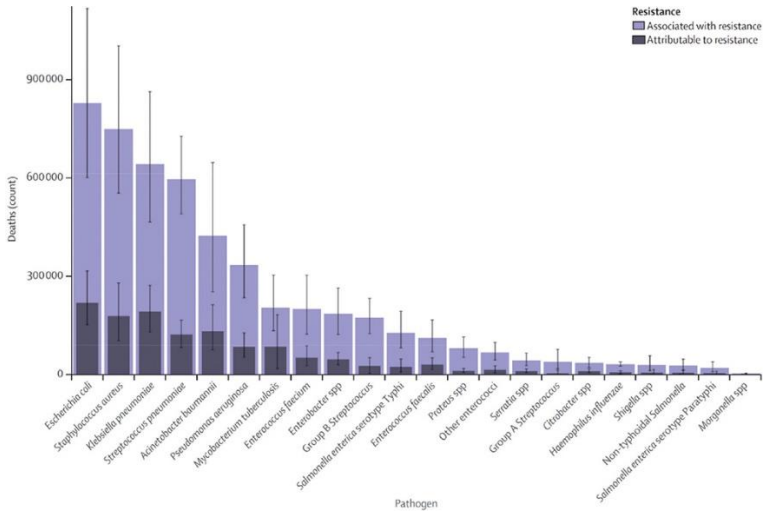

Fig. 1 - Global deaths attributable to or associated with antimicrobial resistance by pathogen in 2019.
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Table I -The classification of urinary tract infections according to the European Association of Urology (EAU) Urological Infections Guidelines.

Classification	
Uncomplicated UTIs	Acute, sporadic, or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to nonpregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs that are not defined as uncomplicated, meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course, that is, all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases, for example, diabetes.

Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last 6 months.
Catheter-associated UTIs	Catheter-associated UTI (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterized or has had a catheter in place within the past 48 hours.
Urosepsis	Urosepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs (54).

UTI = urinary tract infection.

Reproduced from EAU Guidelines on Urological Infections by Bonkat G, Bartoletti R, Bruyere F, et al. Edn. given in Milan, Italy in 2023 during the EAU Annual Congress. Published by uroweb.org as an Open Access paper under the CC BY 4.0 license, with an ISBN of 978-94-92671-19-6. Among all infectious disorders, UTIs have one of the most pronounced sex differences and are substantially gender biased. Compared to males of the same age, premenopausal women had a 20–40 times higher risk of UTIs (25–26). A portion of this discrepancy might be explained by anatomical variations. For example, the urethra is longer in men and shorter in women between the anus and the urethral opening.

However, the identical rates of rUTIs in young boys and females cannot be explained by anatomical differences, and in guys over 65, UTI rates rise significantly until they are almost equal to those in older women (27, 28). Alternatively, urodynamic alterations such prostatic hypertrophy or other variables, including aging-related biochemical or immunological changes, may be to blame for variations in the prevalence of UTIs in older men (29–30). In fact, postpubescent individuals under 50 years old have the greatest disparities in UTI susceptibility by gender during this period, when testosterone and estrogen levels in males and females, respectively, are at their maximum (30).

Antibiotic-sparing strategies can reduce antibiotic use by 60–70%, according to a recent systematic review of randomized controlled trials of analgesics (NSAIDs and NSARs), herbal formulations, delayed antibiotic prescription, and placebo therapy to prevent the overuse of antibiotics in women with uncomplicated UTIs (31). In contrast to early antibiotic treatment, they may, however, lead to greater rates of therapy failure or partial recovery, as well as a higher prevalence of secondary outcomes such febrile UTIs or pyelonephritis (31–32).

The EAU Guidelines for antimicrobial treatment in uncomplicated UTI suggest using pivmecillinam, various nitrofurantoin formulations, or fosfomycin trometamol as first-line therapy. The European Commission prohibited the use of fluoroquinolone and quinolone antibiotics in 2019 for the treatment of uncomplicated UTIs (32). It's critical to understand local resistance statistics before selecting an antibiotic for a simple UTI. For instance, a surveillance research on the epidemiology of antibiotic resistance in females with cystitis was carried out in Europe and Brazil.

Non antibiotic management

The arsenal of potent antibiotics is dwindling quickly, and the severity of this issue cannot be emphasized (33). In many African nations, urinary *E. Coli* isolates are now 100% resistant to amoxicillin, and significant levels of resistance to numerous widely used antibiotics have been found globally (34). UTI epidemics are linked to resistant strains of *E. Coli*, including ST131 (O25:H4), and the widespread development and dissemination of carbapenem-resistant *Enterobacteriaceae* (CRE) poses a danger to global public health (35). *Enterobacteriaceae* are

currently developing transmissible resistance to colistin (via mcr-1), which has the potential to spread quickly (36).

Due to this change, the antibiotic we have been using as a last option to treat infections brought on by Gram-negative bacteria that are resistant to drugs is no longer effective. As a result, diseases caused by certain strains of bacteria may become incurable. A variety of resistance mechanisms have emerged, contributing to the rise in antibiotic resistance that is being driven by the growing use of antibiotics in both humans and animals (37,38). Mobile genetic elements (MGEs), emergent chromosomal mutations, sequential mutations, or a combination of these causes might result in resistance. MGEs, like transposons and plasmids, allow resistance in bacteria to spread quickly amongst them.

Resistance mechanisms have the ability to change the target of an antibiotic, change the concentration available at the moment of action, or render an antibiotic inactive (39). For generations, people have used plants or plant parts to heal medical ailments. The most research has been done on Chinese herbal medicine (CHM) and products that include cranberries in connection to the treatment and prevention of UTI.

Chinese herbal medicine

In randomized controlled studies, the plants utilized in CHM have been investigated for their potential to cure acute urinary tract infections as well as to prevent recurring infections. Chinese herbs, such as Huang Lian (Coptis chinensis Franch), have both anti-inflammatory and inhibitory efficacy against many uropathogenic bacteria, including E. coli, when cultured in vitro. It has been demonstrated that other herbs, like Compound Salvia Plebeia Granules (CSPG), lessen E. coli's adhesion to bladder urothelial cells. In an investigation involving male rats, intragastric delivery of 20–40 g/kg of CSPG was discovered to possess diuretic, antipyretic, and analgesic properties. Furthermore, it was discovered to suppress E. Coli growth, with a minimum inhibitory concentration of 0.25 g/ml (40).

The main active ingredient of C. chinensis Franch, berberine alkaloids, were the subject of an in vitro investigation assessing its antibacterial qualities. The results showed that all three berberine alkaloids—berberine, coptisine, and palmatine—reduced the growth rate constant of E. coli55. Er Xian Tang, Bai Tou Weng Tang, and San Jin Wan are the CHM that are most frequently researched in studies involving women who have recurrent UTIs. The effectiveness of CHM in treating and preventing recurrent UTIs was assessed in seven randomized controlled trials including 542 women, as part of a Cochrane review56. Two studies compared CHM plus antibiotics with antibiotics alone, two compared two distinct CHM regimes62,63, and three compared CHM with antibiotic treatments 41-43).

In trials comparing CHM with antibiotic prophylaxis, recurrent UTI rates were significantly lower in those receiving CHM (relative risk (RR) 0.28, 95% confidence interval (CI) 0.09–0.82) (44). Additionally, it was demonstrated that adding CHM to antibiotic prophylaxis reduced the incidence of recurrent UTIs more effectively than antibiotic prophylaxis alone (RR 0.53, 95% CI 0.35–0.80) (45). When evaluating these results, it is necessary to consider many significant limitations. Research had limited numbers of patients, were diverse, and were highly biased.

According to the GRADE Quality of Evidence criteria (46), all of the studies were rated as extremely low quality. The main causes of the high risk of bias were inadequate participant and staff blinding, ambiguous descriptions of allocation concealment, blinding of outcome assessment, and selective reporting.

Cranberry

There is conflicting data supporting the use of cranberries and products derived from them for the prevention of urinary tract infections (UTIs), and less research supports its use in the management of acute UTIs. The plant Vaccinium macrocarpon, Vaccinium oxycoccos, and Vaccinium erythrocarpum are all members of the Ericaceae family. Water makes up 88% of the berries, with organic acids, fructose, ascorbic acid, flavonoids, anthocyanidins, proanthocyanidins, catechins, and triterpenoids making up the remaining complex mixture (47,48). The tannins (polyphenols) anthocyanidins and proanthocyanidins serve as a natural plant defense mechanism against microbial infection and are believed to be the most therapeutically significant in reducing urinary tract infections (UTTIs) in women (49).

Cranberry has been a well-liked treatment for urinary tract infections (UTTIs) for almost a century, especially prior to the development of antibiotics. It was first employed in the 17th century for a variety of therapeutic reasons, such as stomach and hepatic illnesses, scurvy, and cancer (50,51) suggested action mechanism Cranberries have a preventive effect in preventing recurrent UTIs, although no clear mechanism of action has been shown to far. With a pH of less than 2.5, pure cranberry juice is very acidic (52). It was once thought that urine acidification contributed to the antibacterial activity of cranberries because to their acidity (52). Nevertheless, this theory was disproved more than 20 years ago when in vitro research revealed the significance of one of its essential elements (51). Proanthocyanidins have an antiadherence impact and an inhibitory effect on the motility of Pseudomonas aeruginosa, E. coli, and Proteus mirabilis, it is believed that their presence is the most significant mechanism mediating the therapeutic benefit of cranberries in UTI prevention (50,53).

Non-steroidal anti-inflammatory drugs

There are no trials assessing NSAIDs as a preventative measure to stop UTIs from coming back Ibuprofen, an NSAID, has been tested in two randomized controlled studies to treat women's acute, uncomplicated UTIs. A double-blind experiment comparing ibuprofen and ciprofloxacin, both given for three days, was conducted by Bleidorn and colleagues (54) on 79 women who presented with an acute urinary tract infection. Day 4 symptom-free rates were 58% in the ibuprofen group and 52% in the ciprofloxacin group ($P = 0.744$). As a result, findings of NSAIDs' efficacy for UTIs should be read cautiously but also call for larger, randomized trials to be conducted.

Probiotics

Bacteria in probiotics are believed to provide health advantages when ingested. Probiotic supplementation of the human natural bacterial flora is an appealing way to avoid illness since it is believed to be a major defense mechanism against infection.

The vagina is a balanced environment in healthy women, and the natural flora there plays a vital role in preventing the colonization of harmful organisms that can lead to urinary tract infections. The majority of commensal organisms in the periurethral and vaginal regions are Lactobacillus species, which are in charge of stopping pathogen adhesion and migration to the bladder urothelium (55). Vaginal lactobacilli levels have been shown to be significantly lower after sexual activity, spermicide use, and in postmenopausal women, all of which have been linked to an increased rate of vaginal E. coli colonization

In a study of 70 women receiving antibiotics for a UTI, a vaginal swab taken 4-6 hours after therapy revealed lactobacilli colonization in just 14% of the women (56). It is believed that lactobacilli work through a variety of methods to provide protection by competing with uropathogens for vaginal epithelial adhesion receptors, these organisms inhibit the colonization of the vagina by uropathogenic organisms (57). Adhesion can be prevented by displacement

(moving uropathogens that have already bound to vaginal epithelial cells), competition (directly competing with uropathogens for available adhesion receptors on vaginal epithelial cells), or exclusion (occupying binding sites so that uropathogens cannot initially bind).

D-mannose

One of glucose's monosaccharide isomers, D-mannose, is involved in the glycosylation of several proteins, including monoclonal antibodies. When taken orally, D-mannose is rapidly absorbed, appears in the plasma around 30 minutes after ingestion, and is eventually eliminated by the urinary tract (58). Enteric bacteria, including E. coli, include virulence factors such as type 1 fimbriae or pili, which are essential for attachment and are proteinaceous projections protruding from the bacterial cell (59).

When D-mannose reaches a high enough quantity in urine, it can saturate FimH adhesins and inhibit bacteria from attaching to urothelial glycoprotein receptors (60). This is because D-mannose shares a structure with the binding site of urothelial glycoprotein receptors, such as uroplakin.

Methenamine hippurate

Methenamine hippurate has the benefits of being bacteriostatic without causing the emergence of antibiotic resistance, it has been used for decades as a urinary tract antiseptic in the treatment of UTIs. The following reaction indicates that methenamine, a cyclic hydrocarbon, hydrolyzes in an acidic environment to produce formaldehyde and ammonia: Because acidic urine contains hexamine, which is converted to formaldehyde by methenamine salts, the mechanism of action of these drugs in UTIs is believed to be bacteriostatic (61). By preventing cell division and causing the creation of 1,3-thiazane-4-carboxylic acid, which obstructs the synthesis of methionine, a necessary metabolite involved in cytoplasmic synthesis, formaldehyde is believed to have bacteriostatic properties. Therefore, formaldehyde causes bacteriostasis (62) by blocking nuclear and cytoplasmic production.

Ascorbic acid has been suggested by some research as a urinary acidifier in addition to methenamine hippurate because, in vitro, a urine pH of less than 5.85 is necessary to create the ideal bacteriostatic concentration of formaldehyde from methenamine.(63); it's uncertain if this acidity is required or helps its method of action (64,65,66)

Estrogen

Premenopausal women with circulating oestrogens promote lactobacilli (67) vaginal colonization. It has also been demonstrated that higher vaginal oestrogen levels increase the percentage of glycogen-producing vaginal epithelial cells, and that treatment with depot medroxyprogesterone acetate reduces the thickness of the layers of epithelial cells that bear glycogen. These findings suggest that oestrogens play a role in promoting glycogen storage within the vaginal epithelium (68) which in turn promotes lactobacilli growth. Glycogen is converted by lactobacilli into lactic acid, hydrogen peroxide, and antimicrobial peptides (like bacteriocin), which helps to keep the pH of the vagina low (acidic) and prevents the growth of uropathogens (69). After menopause, the vaginal pH rises (above pH 4.5), which causes a decrease in lactobacilli and an increase in gut microorganisms (such *E.coli*)

Intravesical Glycosaminoglycans

More research is being done on the intravesical delivery of glycosaminoglycans as a treatment for chronic types of cystitis, such as recurrent bacterial cystitis. A number of factors, including the diversity of pathogens, the lack of natural protective immunity in humans following UTIs, the induction of antibodies in the bladder, and the desire to avoid inducing a pathological immune response to colonizing bacteria in the gut, limit the effectiveness of developing vaccines

against UTIs. Antibodies may develop in response to kidney infection, but bladder infections do not appear to elicit this adaptive response (70).

Competitive Inoculation

To stop recurring UTI, colonization with less-pathogenic strains of UPEC is also being studied. One such strain is E. coli 83972, which does not exhibit virulence markers linked to symptomatic UTI. This strategy appears to be especially helpful for those who are vulnerable because of outside variables, such as chronic catheter usage, and people in whom colonization can successfully be established because of insufficient bladder emptying (71,72). In this trial, 65 patients with a history of recurrent UTI and neurogenic bladder following spinal cord injury were randomized in a 3:1 ratio to receive sterile saline or intravesical instillation with E. coli (71,72).

CONCLUSIONS

Most likely, preventing rUTIs is an impossible task. Rather, we ought to concentrate on lowering the frequency of recurring UTIs and the morbidity connected to them. Our toolkit has grown rapidly, and the old-fashioned method of treating infections with antibiotic doses is no longer effective. Today, there are a number of approaches available to patients and doctors to lessen the likelihood that UTIs will reoccur, including behavioral changes, non-antibiotic therapies, and alternative antibiotic treatment plans. The nonantibiotic treatments for UTI included in this Review are promising, but further research is required to determine the best nonantibiotic course of therapy and preventive measures for recurrent UTI.

Again, more research is needed on this strategy, but combining two medicines may be the most efficient method to lower the risk of recurring UTIs without using antibiotics. To best target these treatments, studies of combination medicines in certain patient populations (e.g., men, women, and women going through menopause) are also required. Numerous possible treatments are in preclinical development, and research into the underlying molecular processes of bacterial adhesion and invasion appears to be the most promising. This research may provide fresh targets for therapeutic development. Reducing the antibiotic resistance issue and laying the groundwork for a new era in the treatment of recurring UTIs are the objectives of these methods.

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