

UTI Management in The Modern Era: Integrating Novel Therapies and Multifaceted Strategies

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Abstract-UTIs are a prevalent microbiological illness that can affect people of all ages and range from a mild case of cystitis to a life-threatening case of uroseptic shock. Multimodal UTI management is required due to the growing problem of antibiotic resistance (AMR) in pathogens such as *Escherichia coli* and *Klebsiella*. This review clarifies how the management of UTIs has changed in response to increased AMR and the introduction of new antimicrobial agents. Antibiotics are still essential treatments, but overuse and abuse are progressively reducing their effectiveness. Therefore, promising options for managing UTIs include alternative therapies like acupuncture, natural remedies, live-attenuated vaccinations, and hydration. Moreover, probiotics, natural polyphenols, and nutraceuticals show promise in the management and prevention of UTIs. Novel approaches to treating and preventing urinary tract infections (UTIs) include the use of antimicrobial catheters, antibiotic coatings, colistin, nanoparticles for targeted drug delivery, and nonsteroidal anti-inflammatory drugs (NSAIDs). The therapeutic arsenal against UTIs is further enhanced by the use of bacterial extracts in immunotherapy, estrogens that strengthen the uroepithelium, and the medicinal qualities of plants like black chokeberry and pomegranate. All these methods have different benefits when it comes to preventing UTIs, which emphasizes the need for a comprehensive plan to deal with this common and frequently recurring health issue. In the face of antibiotic resistance, healthcare professionals can improve patient outcomes, minimize treatment failures, and optimize UTI management by integrating diverse modalities.

Index Terms—UTI, antibiotics, resistance, microbial infection, pathogenesis, treatment

I. INTRODUCTION

Antibiotic resistance is the condition in which drugs that once killed bacteria now fail to do so. It is a serious and modern problem. Since resistant microbes can hinder the treatment of infections,

research on antibiotic resistance has focused primarily on these microbes' effects. It was thus demonstrated that the emergence of antibiotic resistance in bacteria was not the only cause of their resistance, but also a function of drug addiction and misuse as well as a dearth of novel therapeutic agents. As a result, patients infected with resistant bacteria will likely experience symptoms for a longer period of time and have a higher likelihood of their conditions worsening. In addition, there will be an increase in epidemics and a growing population at risk of infection. The primary causes of antibiotic resistance are improper use of the drugs: either too little, too quickly, or too frequently is administered; strong antibiotics are prescribed for infections that could be treated with milder antibiotics; or empirical treatment is carried out (without first conducting an antibiogram to test germ sensitivity)(1,2). *Escherichia coli* and the *Klebsiella* genus are the two species of the *Enterobacteriaceae* family that have the most concerning cases. The primary job of the urinary system, which is made up of the kidneys, ureters, bladder, and urethra, is to filter blood by eliminating waste materials and extra water. The elimination of metabolic waste products from the bloodstream is largely accomplished by the urinary system. The system also plays a key role in controlling blood pressure and volume, as well as normalizing the concentration of ions and other solutes in the blood. Urine is either sterile or contains very few microorganisms that can lead to an infection in healthy individuals(3)

A common microbial infection that affects people of all ages and genders, urinary tract infections. (UTIs) cause inflammation in the urinary tract. These infections can vary in severity, from mild cystitis (inflammation of the bladder) to life-threatening uroseptic shock.(3,4) Urinary tract infections (UTIs) are the most frequent bacterial infections seen in primary care, followed by respiratory tract infections. Any infection that affects the kidneys, ureters, bladder, or urethra is referred to as a urinary tract infection. The bladder, urethra, and lower urinary tract are all affected by the infection.(5)

SYMPTOMS OF UTI

Pain in the suprapubic area, pain during urination with or without frequency, or obvious haematuria are the typical symptoms of lower UTIs. Symptoms of an upper urinary tract infection (UTTI) can include fever ($>100^{\circ}\text{F}$), chills, nausea, vomiting, tenderness in the costovertebral angle, and nausea, with or without cystitis symptoms. Fever is typically linked to more complex types of UTIs and is infrequent in lower UTIs.(6)

PATHOGENESIS OF URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) start when certain adhesins in the gut harbor uropathogens that colonize the urethra and then the bladder. In the event that the inflammatory response of the host is unable to eradicate every bacterium, the bacteria start to grow and produce toxins and enzymes that help them survive. Bacteremia may develop from subsequent kidney colonization if the pathogen penetrates the kidney epithelial barrier(7). The urethra is typically the entry point for bacteria that cause urinary tract infections into the bladder. The lymphatic or blood systems, however, can also become infected. The bacteria are thought to typically enter the urethra

following a bowel movement. Once inside, organisms like E. Coli cling to the bladder wall to create a biofilm that thwarts the body's defenses against infection.(8) There is evidence that some people are genetically predisposed to developing urinary tract infections (UTIs). This is especially the case for premenopausal women who do not secrete ABH blood-group antigens. (8,9)

II. TREATMENT OF UTIS

(1) ANTIBIOTIC TREATMENT

Antibiotics are substances that possess antibacterial properties. They are effective against bacteria even at low concentrations and follow the principle of selective toxicity. They work at the molecular level, targeting a crucial metabolic pathway for bacteria, which is either not present in eukaryotic cells or, if it is, is not impacted by the antibiotic.(10)

Antibiotics used to treat UTIs

Traditionally, amoxicillin has been the first-line treatment for UTIs. However, due to the rising rate of E. coli resistance, studies have shown that trimethoprim/sulfamethoxazole is an antibiotic that has higher cure rates. In addition to amoxicillin/clavulanate, cefixime, cefprozil, levofloxacin, nitrofurantoin, fosfomycin, and nalidixic acid, these antibiotics are frequently used to treat bacterial UTIs. Understanding the mechanism of action of antibiotics is necessary for the development of effective antibiotics. The mechanisms of action of antimicrobial medications are primarily five.

1. suppression of the synthesis of bacterial cell walls.
2. The production of bacterial nucleic acids is inhibited.
3. Reduction of the synthesis of bacterial proteins.
4. The inhibition of the metabolism.
5. Membrane function inhibition.(11)

First-Line Antibiotic

Sulfamethoxazole or trimethoprim in areas where E. Coli resistance is less than 20%. Women who have received treatment within the last six months should not use this antibiotic because their organisms are more likely to be resistant.

Second-Line Antibiotic or First-Line in Resistant Communities

Fluroquinolones- Ciprofloxacin, Levofloxacin, Norfloxacin, Ofloxacin.(12)

(2) NON-ANTIBIOTIC TREATMENTS

Antibiotic treatment for UTIs is a useful approach, but in most cases, the body heals itself from minor, uncomplicated infections. Instead of using antibiotics in such minor cases, people can try other strategies to expedite their recovery. UTIs can be prevented and treated by staying

hydrated, which is consuming lots of water and avoiding beverages that irritate the bladder (like alcohol and caffeinated drinks). Water retains the vital nutrients and electrolytes that the body needs while aiding in the removal of waste from the body. By accelerating the urine's passage through the system and diluting it, drinking enough water makes it more difficult for bacteria to enter the urinary system and cause an infection.(13)

(3) LIVE-ATTENUATED VACCINE TO TREAT E. COLI INFECTION OF THE URINARY TRACT

The goal of vaccine research on recurrent urinary tract infections is to prime the immune system to respond to uropathogens, not to eradicate infectious pathogens and shield the host from infection. As a preventive measure against recurrent UTIs, various vaccine strategies have taken into consideration the use of both surface antigen and inactivated whole bacteria from uropathogens to generate protective antibodies. At present, four vaccines are in circulation that have been shown to yield positive outcomes in randomized control trials (RCTs): Uro-Vaxom R, Urovac R, ExPEC4V, and Uromune R (24).Uropathogenic Escherichia coli is the primary cause of urinary tract infections. It was recently shown that the uropathogenic E. Coli isolate NU14, when its O antigen ligase gene, *waaL*, was deleted, produced a strain that induced increased urothelial cytokine secretion. They looked at NU14 Dwaal's therapeutic potential as a urinary tract infection vaccine because improved innate immune responses were desirable for vaccine development. (9,14)

(4) NATURAL REMEDIES

(4.1) Cranberry (*Vaccinium Macrocarpon*)

North America is home to the cranberry (*Vaccinium macrocarpon* Ait.). Cranberries have become more popular in the prophylactic treatment of recurrent UTIs in recent years (Howell et al., 2005). Cranberry has multiple potential targets, though its exact mode of action is unknown.(33) Urinary tract disorders have long been treated with cranberries. For the treatment of urinary tract infections, cranberry extracts in capsule form, cranberry juice, and cranberry tincture—an alcohol-based mixture of cranberries—are advised. An abundance of anthocyanidin flavonoids, including cyanidin, peonidin, and quercetin, can be found in raw cranberries and cranberry juice(15).

(4.2) Apple Cider Vinegar

It is rich in minerals, enzymes, and potassium, among other things. They prevent the bacteria that cause UTIs from growing and multiplying. It functions as a naturally occurring antibiotic to treat the infection. Acetic acid, which is present in it, is one of the best naturally occurring disinfecting agents that kills resistant bacteria (13). A glass of water containing one spoonful of honey and two spoonfuls of apple cider vinegar can aid in the removal of infection. It is recommended to take three times a day to get the effects faster. (16)

(4.3) Tea Tree Oil (*Melaleuca Alternifolia*)

It can be used to combat the bacteria that cause bladder infections because it has antibacterial properties. Since this cannot be taken orally, wash your urethra with bath water that has been diluted with ten drops of tea tree oil. This is a very good method of treating pain-related UTIs. To see good effects, it is advised to use it every day for three to four days.(17)

(4.4) Uva Ursi (*Arctostaphylos Uva-Ursi*)

This herb has been traditionally used to treat specific kinds of UTIs. It helps treat urinary tract infections (UTIs) because of its many chemicals and antiseptic qualities.(41). It has been demonstrated that employing UU as a first-line treatment can effectively relieve UTI symptoms and minimize the need for antibiotics. Arbutin, a glycoside found in its leaves, has mild diuretic and antibacterial properties. (18)

(4.5) Grapefruit (*Citrus Paradisi*)

The grape fruit pulp and seed are used to make grape fruit seed extract, or GSE. It has been discovered to have inherent antiviral, antifungal, and antiseptic qualities. Akin to synthetic antibacterial medications, grapefruit seed extract has antibacterial properties. Its wide range of activity affects the development of both gram-positive and gram-negative organisms. Strong components in it inhibit the growth of pathogenic organisms in urine, including *Pseudomonas aeruginosa*, *Klebsiella* species, and *Staphylococcus aureus*. After 15 minutes of contact with a diluted solution, the extract has been demonstrated to eradicate harmful bacteria.(19)

(4.6) Garlic (*Allium Sativum*)

Due to its capacity to reduce inflammation and boost the immune system, garlic has long been recognized to possess antibacterial qualities. It contains a lot of the sulfur compound allicin, which improves detoxification, and is a great source of glutathione, a potent antioxidant(47). Additionally, using it has been shown to lessen pain in the pubic area as well as the frequency and urge to urinate (20)

(4.7) Vitamin C

It is well known that vitamin C, or ascorbic acid, has antibacterial and antioxidant properties. Because phagocytes release reactive oxygen species (ROS) as a result of microbial infections, this deactivation of microorganism killing aids in the limitation of infection. Since ROS have the potential to harm host cells as well, phagocytes should immediately reduce their ROS production following infection (20,21). This nutrient works to combat infection by increasing the activity of biological agents. It improves the body's ability to absorb bioflavonoids from food and prepares it to deal with stress and tissue damage (21).

(4.8) VITAMIN D

Sunlight exposure has been scientifically shown to have a positive effect on the immune system and can help prevent infections like tuberculosis (51). One underlying mechanism that has been identified more recently is a direct correlation between the expression of CAMP and vitamin D(52). The hormonally active form 1,25-dihydroxyvitamin D3 is necessary for vitamin D to work. In the liver, vitamin D precursors from the diet or from exposure to sunshine are transformed into the primary storage form, 25-hydroxyvitamin D3(53).while the kidney is the principal organ to convert the inactive form into active 1,25-dihydroxyvitamin D3 by the 1α -hydroxylase (Cyp27B1)(22).

(5) NUTRACEUTICALS

(5.1) Hyaluronic Acid

Hyaluronic acid is a major mucopolysaccharide that is widely present in neural, connective, and epithelial tissue. It is a non-sulphated glycosaminoglycan and one of the main components of the extracellular matrix. As hyaluronic acid becomes permeable, it permits harmful substances and irritants to enter the bladder wall and cause a cascade of inflammatory reactions that worsen pain and damage the urothelium. Hyaluronic acid does, in fact, act as a protective compound for the urothelial lining. Urothelial cells, the first line of defense against pathogens, are the constituents of the urinary bladder epithelium. These cells possess particular properties and sensors(24). Sulfated polysaccharide glycosaminoglycan (GAG), which coats the epithelium and creates a non-specific anti-adherence factor, is produced by these cells in order to preserve their ability to fight infections. Hyaluronic acid (HA) and chondroitin sulfate (CS) make up a significant amount of the bladder's GAGlayer. To prepare for adhesion, virulence factors (secreted by *E. coli*, for example) cause damage to the GAG layer. Restoring the GAG layer of the bladder epithelium through intravesical instillations of HA, either alone or in conjunction with CS, is one method of managing UTIs. Numerous randomized and non-randomized investigations have been carried out. (23,25)

(5.2) Chondroitin Sulphate

Chondroitin sulphate has gained attention as a possible UTI prevention agent in recent years. A naturally occurring substance present in connective tissues, including those lining the urinary tract, is chondroitin sulphate. In fact, a thick layer of glycosaminoglycans (GAGs) coats the bladder's urothelium, serving as a general anti-adherence factor and protective barrier against irritants and infections. There are two kinds of glycosaminidase (GAGs) that have been found in the bladder urothelium: hyaluronic acid, which is a non-sulphated GAG, and heparan, chondroitin, and dermatan sulphates, which are sulphated GAGs. It is well recognized that chondroitin sulphate can preserve tissue integrity and offer structural support(26).

(5.3) Hyaluronic Acid and Chondroitin Sulphate

Damiano and associates assessed the safety and effectiveness of intravesical hyaluronic acid and chondroitin sulfate in order to restore the integrity of the bladder glycosaminoglycan layer. 57 women with a history of recurrent rUTI were randomized to receive either a 50-mL solution containing 1.6% hyaluronic acid and 2.0% chondroitin sulfate or 50 mL of intravesical placebo. Over the course of a year, serial bladder instillations with IALURIL significantly decreased UTI rates (286.6% 6 47.6 vs. 29.6% 6 24.6%) and enhanced quality of life and urinary symptoms. There were no serious side effects, and the instillations were well tolerated.(27)

(5.4) Chinese Herbal Medicine (Chm)

Chinese Herbal Medicine (CHM) is the age-old craft of creating intricate herbal formulas, often made up of fifteen or more herbs. UTIs have traditionally been treated with CHM. Significant diuretic, antibiotic, immune-boosting, antipyretic, anti-inflammatory, and pain-relieving properties are known to be associated with some commonly used Chinese herbs. Certain herbs have demonstrated inhibitory activity *in vitro* against multiple uropathogens, particularly *E. coli*, wherein they reduce the pathogen's adherence to bladder epithelial cells(75). Sanjin tablets, which are made up of five different types of CHM, were found to have significant bacteriostasis activity in an antibacterial test conducted on mice (28).

(6) PROBIOTICS

The primary rationale supporting the use of probiotics in the prevention and treatment of urinary tract infections is the possibility that the bacteria responsible for these infections may be found in the vagina. Reduced protective *Lactobacillus* spp. colonies in the vaginal microbiota are linked to alterations in the microbiota and a higher risk of UTI. (29)

(6.1) Vaginal Lactobacilli

The predominant microorganisms in the vaginal flora are often lactobacilli. It is possible to make several observations:

- (i) They can obstruct UPEC's adherence, growth, and colonization.
- (ii) It has been demonstrated that altering the normal vaginal flora can promote the recurrence of UTIs.
- (iii) The employment of commensal bacteria, like *Lactobacilli*, restores bacterial homeostasis by lowering the proportion of uropathogens(30).

(7) NATURAL POLYPHENOLS FOR PREVENTION AND TREATMENT OF URINARY TRACT INFECTIONS

(7.1) Resveratrol

One of the most researched stilbenes is resveratrol (RSV;3,40,5-trihydroxystilbene), which is primarily present in red wine, peanuts, grape skins, and a number of woody plants. There are two stereoisomeric forms of RSV: trans-resveratrol (t-RSV) and cis-resveratrol (c-RSV). Numerous

advantageous effects, including antimicrobial, antiviral, antioxidant, anti-inflammatory, anti-aging, anticarcinogenic, and neuroprotective qualities, have been demonstrated by RSV in humans. Furthermore, some research revealed that RSV has a strong inhibitory effect on the development of a few human pathogens(31).

(7.2) Caffeic Acid

The plant-derived chemical known as caffeic acid (CA) is categorized as hydroxycinnamic acid and has acrylic and phenolic functional groups. Most food sources, such as coffee, tea, almonds, olive oil, and beer, contain a significant amount of it(31). Most of its nutraceutical potential has been shown. The anti-inflammatory, antioxidant, anticancer, and antidiabetic properties of CA were investigated. To be more precise, CA has been used extensively as a substitute method to distinguish between microbial pathogenesis and persistent infection brought on by different etiological agents like bacteria, fungus, and viruses. The anti-inflammatory potential of CAPE (caffeic acid phenethyl ester) was assessed by Celik et al. in rats with pyelonephritis (PYN) caused by *E. coli*.

(7.3) Quercetin

Quercetin is a flavonoid-class polyphenol that can exist as an aglycone (without linked sugars) or as a glycoside (with linked sugars). Onion, apples, berries, tea, red wine, and kales are rich natural sources of quercetin. Due to its antibacterial and immune-stimulating properties, this antioxidant molecule has been thoroughly studied recently.

(8) ANTI-MICROBIAL CATHETERS

The prevalent hospital-associated infections (HAIs) that can be avoided by taking the appropriate safety measures and utilizing antimicrobial urinary catheters (UCs) are catheter-associated urinary tract infections (CAUTIs). There is not much research on how well antimicrobial UCs work to prevent CAUTIs when compared to conventional catheters.(100) Almost 15% to 25% of hospitalized patients have catheters (UCs). For patients who have had surgery or have mobility issues, UCs are used in both male and female patients to treat urinary retention, incontinence, and drainage(32).

(8.1) Silver

The Food and Drug Administration (FDA) has approved the use of silver, one of the antimicrobial agents that are frequently used in medical devices to prevent microbial invasion, in UCs. The two most widely used and researched silver Foley catheters are Bardex® IC and DoverTM. The catheters' exterior and interior surfaces are coated with silver, which can also be used as an alloy with gold, platinum, nanoparticles, and polymers. Silver-coated catheters will still be taken into consideration for preventing CAUTI because of their broad-spectrum antimicrobial activity, ease of manufacture, lower cost, and fewer side effects when compared to those with nitrofural. Another benefit of the silver-impregnated catheter over the nitrofurazone

one was that it demonstrated greater comfort during the catheter's insertion, during its removal, and for three days afterward (31,33).

(8.2) Antibiotic coatings

Antibiotics are small molecules with antimicrobial or bacteriostatic qualities that are extracted from microorganisms. Once the catheters are impregnated with these antibiotics, the pathogens are directly affected. Through the gradual and regulated release of antibiotics to the colonization site, they prevent the formation of biofilms. The following antibiotics are used in UCs: vancomycin, norfloxacin, sparfloxacin, rifampin, nitrofurazone, and minocycline. By blocking various bacterial enzymes involved in the aerobic and anaerobic breakdown of glucose and pyruvate, nitrofurazone works against both gram-positive and gram-negative bacteria. The silicone catheter group experienced a higher frequency of catheter-associated bacteriuria and fungi Uri (CABF) at 24.7% compared to the nitrofurazone catheter group's 9.1%.

(9) NANOPARTICLES

Nanoparticles (NPs) are multifunctional, three-dimensional structures that can have a diameter of up to 1000 nm. NPs' characteristics are linked to their smaller size and the way their constituent parts interact with their surroundings. Since the excipient may have a variety of beneficial qualities in addition to the therapeutic effects of the active ingredient, NPs components in nanomedicine serve a variety of purposes (33).

(9.1) ORGANIC NANOPARTICLES

Stable particles known as organic nanoparticles (NPs) are made of organic substances such as lipids or polymers and have shown great promise in drug delivery. Consequently, because of their makeup, they are better suited for biological applications and are becoming more and more significant in the fields of nanomedicine and pharmaceuticals. For the most part, they are thought of as nanocarriers in the search for cutting-edge methods of treating UTIs(34). Because they prevent pathogens from forming biofilms, these nanocarriers continue to be very relevant.

(9.1.1) Nanodiamonds

Carbon-based nanoparticles known as nanodiamonds (ND) have been investigated as possible medication delivery agents. Typically, the way that carbon nanomaterials work against bacteria is through direct interaction between their chemical groups on the surface and the bacterial wall. This interaction results in both physical harm and suppression of metabolism. It's interesting to note that NDs' physical and chemical attributes—such as their tiny size, varied and adaptable surface functionalization, chemically inert core, and capacity to integrate into mammalian cells—improve these antibacterial qualities. Additionally, NDs are becoming more significant in biomedicine because they are less cytotoxic and more biocompatible than other carbon-based NPs(35).

(9.2) INORGANIC PARTICLES

The potential uses of inorganic nanocomposites in a multitude of domains, particularly biomedicine, has led to extensive research on them in the literature(130). In the field of biomedical research, numerous inorganic materials are investigated for their possible utility in the management of urinary tract infections. Copper, iron, gold, silver, and other elements are examples of these new nanocarriers or nano scaled materials.

(9.2.1) Silver-Based Nanoparticles

Due to its ability to disrupt both cell walls and metabolic pathways, silver is acknowledged as a potentially effective strategy against microorganisms(131). Both alone and in conjunction with other materials, the application of silver-based nano systems for the treatment of UTIs has been investigated. For instance, Syed et al. evaluated the antibacterial activity of silver nanoparticles (AgNPs) against *S. aureus* and *E. coli* that were isolated from CAUTI patients. The present study employed the method of direct colony count to evaluate the bactericidal potential of AgNPs. Following a 24-hour incubation period, the number of viable bacteria was counted when 105 CFU/mL were exposed to varying concentrations of AgNPs suspension (0, 10, 50, and 100 mg/mL). AgNPs decrease the number of viable cells for *S. aureus* and *E. coli* in a concentration-dependent manner, according to the results(36).

(9.2.2) Copper-Based Nanoparticles

Another common metal that is frequently used for the synthesis of nanoparticles as nano antibiotics is copper (Cu), which has the advantage of being less expensive than silver (36). Cu is primarily useful as an antibiofilm agent to prevent CAUTI when fighting uropathogens.

(9.2.3) Zinc-Based Nanoparticles

Zinc is another metal that has antibacterial qualities and is utilized to synthesize NPs, which may lead to more successful UTI treatments. There are two ways to create zinc oxide nanoparticles (ZnO NPs): conventional chemical synthesis and green synthesis. The carbapenem-resistant RS307 strain of *Acinetobacter baumannii*, an opportunistic urinary tract pathogen, was used to test these NPs' antibacterial activity. (37)

(9.2.4) Gold-Based Nanoparticles

Strong bactericidal effects have been demonstrated by gold-based NPs (AuNPs) through a variety of mechanisms, such as membrane damage, protein inactivation, and inhibition of DNA replication. (38)

(9.3) Mixed Nanoparticle

The goal of developing veritable high-yielding solutions to combat UTIs was to combine the benefits of both organic and inorganic NPs while avoiding the disadvantages of each category. Using fluoroquinolone antibiotics, for example, Gupta et al.(138) produced Au-NPs that

functionalized the antibiotics and reduced the minimum inhibitory concentration of the drug by up to 16 times for both Gram-positive and Gram-negative bacteria. Analogously, Saha et al.(39) generated Au-NPs conjugated with Streptomycin, Kanamycin, and Ampicillin (AMP) and examined their effectiveness and durability on *Escherichia coli*, *Micrococcus luteus*, and *Staphylococcus aureus*. *Micrococcus luteus* was more susceptible to the inhibitory effects of streptomycin and Kanamycin Au-NPs than *Escherichia coli* or *Staphylococcus aureus*. However, because Streptomycin could not kill *Staphylococcus aureus*, neither its free form nor its Au-NP form could stop the growth of bacteria. In comparison to their classic counterparts, functionalized NPs generally exhibited greater activity following exposure to heat shocks or room temperature storage(40,41).

II.CONCLUSION

Urinary tract infections (UTIs) are a common microbial infection that cause urinary tract inflammation and can affect people of all ages and genders. Cystitis, a common form of urinary tract infection, can progress to severe cases of uroseptic shock. UTIs and respiratory tract infections are the most frequent bacterial infections seen in primary care settings. Due to the emergence of new antimicrobial agents and the increase in antimicrobial resistance (AMR), the treatment of urinary tract infections (UTIs) has changed significantly. Treatment of urinary tract infections is significantly hampered by antibiotic resistance, especially in bacteria like *Escherichia coli* and *Klebsiella*. Antibiotics are still the main treatment, but misuse and overuse are decreasing their efficacy. Alternative approaches to managing UTIs include non-antibiotic treatments like herbal therapies, live-attenuated vaccines, acupuncture, and cranberry and apple cider vinegar natural remedies. Probiotics, natural polyphenols, and nutraceuticals such as chondroitin sulphate and hyaluronic acid have all shown promise in the prevention and treatment of urinary tract infections. Furthermore, preventing catheter-associated UTIs is greatly aided by antimicrobial catheters, especially those coated with metals like silver. Antibiotic coatings on urinary catheters, the use of colistin and nanoparticles for targeted drug delivery, the potential of nonsteroidal anti-inflammatory drugs (NSAIDs) and D-mannose in symptom alleviation and prevention, the role of estrogens in strengthening uroepithelium, immunotherapy using bacterial extracts, and the promising medicinal properties of certain plants like pomegranate, black chokeberry, and cornelian cherry. It is clear from these approaches that using a variety of approaches is essential to effectively combating UTIs, which are a common and frequently recurring health concern. All things considered, the future of UTI management is a multidisciplinary strategy that incorporates developments in immunology, pharmacology, microbiology, and nanotechnology to create individualized, focused, and efficient preventative, diagnostic, and treatment plans. Translating these developments into clinical practice and improving UTI patient outcomes will require cooperation between researchers, clinicians, industry partners, and regulatory agencies.

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IV. REFERENCES

- [1] Schenone, M.; Dančík, V.; Wagner, B.K.; Clemons, P.A. Target identification and mechanism of action in chemical biology and drug discovery. *Nat. Chem. Biol.* 2013, 9, 232–240.
- [2] Frieri M, Kumar K, Boutin A. Antibiotic resistance. *J Infect Public Health.* 2017 Jul 1;10(4):369–78.
- [3] Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health.* 2015 Oct 3;109(7):309–18.
- [4] Ventola CL. The Antibiotic Resistance Crisis. *Pharm Ther.* 2015 Apr;40(4):277–83.
- [5] Davies J, Davies D. Origins and Evolution of Antibiotic Resistance. *Microbiol Mol Biol Rev MMBR.* 2010 Sep;74(3):417–33.
- [6] Aghapour Z, Gholizadeh P, Ganbarov K, Bialvaei AZ, Mahmood SS, Tanomand A, et al. Molecular mechanisms related to colistin resistance in Enterobacteriaceae. *Infect Drug Resist.* 2019 Apr; Volume 12:965–75.
- [7] Codjoe, F.; Donkor, E. Carbapenem Resistance: A Review. *Med. Sci.* 2017, 6, 1.
- [8] Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf.* 2014 Dec 1;5(6):229–41.
- [9] the JPIAMR AMR-RDT Working Group on Antimicrobial Resistance and Rapid Diagnostic Testing, Van Belkum A, Bachmann TT, Lüdke G, Lisby JG, Kahlmeter G, et al. Developmental roadmap for antimicrobial susceptibility testing systems. *Nat Rev Microbiol.* 2019 Jan;17(1):51–62.
- [10] Tenover FC. Mechanisms of Antimicrobial Resistance in Bacteria. *Am J Med.* 2006 Jun 1;119(6, Supplement 1): S3–10.
- [11] Mancuso G, Midiri A, Gerace E, Marra M, Zummo S, Biondo C. Urinary Tract Infections: The Current Scenario and Future Prospects. *Pathogens.* 2023 Apr;12(4):623.
- [12] Kaur R, Kaur R. Symptoms, risk factors, diagnosis and treatment of urinary tract infections. *Postgrad Med J.* 2021 Dec 1;97(1154):803–12.
- [13] Pulipati S, Babu PS, Narasu ML, Anusha N. An overview on urinary tract infections and effective natural remedies.
- [14] Hooton TM. Uncomplicated Urinary Tract Infection. *N Engl J Med.* 2012 Mar 15;366(11):1028–37.
- [15] Salvatore S, Salvatore S, Cattoni E, Siesto G, Serati M, Sorice P, et al. Urinary tract infections in women. *Eur J Obstet Gynecol Reprod Biol.* 2011 Jun 1;156(2):131–6.

- [16] John AS, Mboto CI, Agbo B. A review on the prevalence and predisposing factors responsible for urinary tract infection among adults. 2016;
- [17] Hooton TM. Pathogenesis of urinary tract infections: an update. *J Antimicrob Chemother*. 2000 Aug 1;46(90001):1–7.
- [18] Bader MS, Loeb M, Leto D, Brooks AA. Treatment of urinary tract infections in the era of antimicrobial resistance and new antimicrobial agents. *Postgrad Med*. 2020 Apr 2;132(3):234–50.
- [19] Egorov, A.M.; Ulyashova, M.M.; Rubtsova, M.Y. Bacterial enzymes and antibiotic resistance. *Acta Naturae* 2018, 10, 33–48.
- [20] Pham JV, Yilma MA, Feliz A, Majid MT, Maffetone N, Walker JR, et al. A Review of the Microbial Production of Bioactive Natural Products and Biologics. *Front Microbiol* [Internet]. 2019 Jun 20 [cited 2024 Apr 26];10. Available from: <https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2019.01404/full>
- [21] Purssell E. Antimicrobials. *Underst Pharmacol Nurs Pract*. 2019 Sep 4;147–65.
- [22] Brubaker L, Carberry C, Nardos R, Carter-Brooks C, Lowder JL. American Urogynecologic Society Best-Practice Statement: Recurrent Urinary Tract Infection in Adult Women. *Female Pelvic Med Reconstr Surg*. 2018 Sep;24(5):321–35.
- [23] Billips BK, Yaggie RE, Cashy JP, Schaeffer AJ, Klumpp DJ. A Live-Attenuated Vaccine for the Treatment of Urinary Tract Infection by Uropathogenic *Escherichia coli*. *J Infect Dis*. 2009 Jul 15;200(2):263–72.
- [24] Howell AB, Reed JD, Krueger CG, Winterbottom R, Cunningham DG, Leahy M. A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. *Phytochemistry*. 2005 Sep;66(18):2281–91.
- [25] Wang SM. Acupuncture. In: Vadivelu N, Urman RD, Hines RL, editors. *Essentials of Pain Management* [Internet]. New York, NY: Springer; 2011 [cited 2024 Apr 26]. p. 337–65. Available from: https://doi.org/10.1007/978-0-387-87579-8_16
- [26] Nation RL, Li J, Cars O, Couet W, Dudley MN, Kaye KS, et al. Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. *Lancet Infect Dis*. 2015 Feb;15(2):225–34.
- [27] Zheng W, Wang SY. Oxygen Radical Absorbing Capacity of Phenolics in Blueberries, Cranberries, Chokeberries, and Lingonberries. *J Agric Food Chem*. 2003 Jan 1;51(2):502–9.
- [28] Duthie SJ, Jenkinson AMcE, Crozier A, Mullen W, Pirie L, Kyle J, et al. The effects of cranberry juice consumption on antioxidant status and biomarkers relating to heart disease and cancer in healthy human volunteers. *Eur J Nutr*. 2006 Mar;45(2):113–22.
- [29] Spencer JFT, Gorin P a. J. Mannose-containing polysaccharides of yeasts. *Biotechnol Bioeng*. 1973;15(1):1–12.
- [30] Howell AB, D’Souza DH. The Pomegranate: Effects on Bacteria and Viruses That Influence Human Health. *Evid Based Complement Alternat Med*. 2013 May 20;2013: e606212.

[31] Fahmy H, Hegazi N, El-Shamy S, Farag MA. Pomegranate juice as a functional food: a comprehensive review of its polyphenols, therapeutic merits, and recent patents. *Food Funct.* 2020 Jul 22;11(7):5768–81.

[32] Pirzadeh M, Caporaso N, Rauf A, Shariati MA, Yessimbekov Z, Khan MU, et al. Pomegranate as a source of bioactive constituents: a review on their characterization, properties and applications. *Crit Rev Food Sci Nutr.* 2021 Mar 26;61(6):982–99.

[33] Das S, Panigrahi S, Panda P. Antiurobacterial Activity of *Punica granatum* L. Seed Extract. *Eur J Med Plants.* 2018 Feb 10;22(2):1–12.

[34] AlFadel F, Al laham S, Alkhateb R. The Anti-Bacterial Activity of Various Parts of *Punica granatum* on Antibiotics Resistance *Escherichia coli*. *Int J Pharmacogn Phytochem Res.* 2014 Feb 15; 6:79–85.

[35] Bakkiyaraj D, Nandhini JR, Malathy B, Pandian SK. The anti-biofilm potential of pomegranate (*Punica granatum* L.) extract against human bacterial and fungal pathogens. *Biofouling.* 2013 Sep 1;29(8):929–37.

[36] Howell AB, Foxman B. Cranberry Juice and Adhesion of Antibiotic-Resistant Uropathogens. *JAMA.* 2002 Jun 19;287(23):3082–3.

[37] Kokotkiewicz A, Jaremicz Z, Luczkiewicz M. Aronia Plants: A Review of Traditional Use, Biological Activities, and Perspectives for Modern Medicine. *J Med Food.* 2010 Apr;13(2):255–69.

[38] Valcheva-Kuzmanova SV, Belcheva A. Current knowledge of *Aronia melanocarpa* as a medicinal plant. *Folia Med (Plovdiv).* 2006 Jan 1;48(2):11–7.

[39] Bayram HM, Arda Ozturkcan S. Bioactive components and biological properties of cornelian cherry (*Cornu's mas* L.): A comprehensive review. *J Funct Foods.* 2020 Dec 1; 75:104252.

[40] 182. Dinda B, Kyriakopoulos AM, Dinda S, Zoumpourlis V, Thomaidis NS, Velegraki A, et al. *Cornu's mas* L. (cornelian cherry), an important European and Asian traditional food and medicine: Ethnomedicine, phytochemistry and pharmacology for its commercial utilization in drug industry. *J Ethnopharmacol.* 2016 Dec 4; 193:670–90.

[41] 183. Efenberger-Szmechtyk M, Nowak A, Czyżowska A, Kucharska AZ, Fecka I. Composition and Antibacterial Activity of *Aronia melanocarpa* (Michx.) Elliot, *Cornu's mas* L. and *Chaenomeles superba* Lindl. Leaf Extracts. *Molecules.* 2020 Jan;25(9):2011.