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Urinary Tract Infections Caused by ESBL Producing *E. coli* in Diabetes Mellitus: Alternative Approaches for Treatment and Management

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ABSTRACT

Diabetes Mellitus (DM) is associated with a higher risk of several infections, of which the most common is UTI. Multiple epidemiological studies show a 1.21 to 2.2 increase in the relative risk of UTI in diabetic patients compared to non-diabetic patients. UTIs in DM involves multiple causative factors, such as hyperglycemia, glucosuria, neurogenic bladder but more often bacteremi, mostly caused by ESBL producing *E. coli* worldwide and associated with rising health care costs. ESBLs are a group of enzymes that hydrolyze antibiotics, acquired resistance to β-lactamase, as broad-spectrum cephalosporin. The UTIs, caused by ESBL producing *E. coli* is often complicated in treatment due to the development of bacterial resistance to antibiotics. Some promising alternative is using to prevent and treat recurrent complicated and uncomplicated UTI, such as herbal remedies like cranberry, probiotics and effects of home remedies, food products. The aim of this study was to identify some alternative options for treatment and management of multidrug resistance *E. coli*.

INTRODUCTION

According to National Institutes of Health (NIH), the second most common type of infection affecting women, the elderly, and infants are urinary tract infections (UTIs) meaning one in three will have a UTI at least once in their lifetime. Acute UTI is one of the commonest acute bacterial infections among women(1-5) because urethra the tube is close to the anus (6). The bacteria as *E. coli* from the large intestine are in the perfect position to escape the anus and invade the urethra and trigger a recurrent infection (7). Having sex can also introduce bacteria into the urinary tract, and if the infection is not treated, an infection can continue to the kidneys (8). As many as 80% of UTIs are caused by *E. coli*in both the community-acquired and the hospitalized patients (9) with an estimated 150 million cases of community-acquired UTIs diagnosed worldwide annually (10) and increase of antimicrobial resistance for both gram positive and gram negative bacteria (11-13), *E. coli*, is a major concern worldwide (14-16).

The worldwide dissemination of extended-spectrum *β*-lactamases (ESBLs) in Enterobacteriaceae has become a major global public health problem since first reported in the 1980s in Europe (17-19). ESBLs are enzymes produced by Gram-negative bacilli, and they have the ability to inactivate*β*-lactamases such as ceftazidime, cefotaxime, ceftriaxone and monobactam and cause resistance to various types of antibiotics as penicillins, cephalosporins, and monobactams (20-21). Until more than 600 different types of *β*-lactamases have been illustrated (22) and can be divided into three major group of ESBL enzymes; TEM, SHV, and CTX-M can be divided into some subgroups, TEM and SHV have more than 200 members known (http://www.lahey.org/studies). ESBL producing bacteria are mostly isolated from the urine sample and most of these bacteria are *E. coli*. Patients with an infection caused by ESBL-producing *E. coli* are at risk for therapeutic failure or even death due to delay incorrect treatment is given.(23). Overtreatment and incorrect empiric choice in combination with the high prevalence of UTIs is a serious risk factor for the increase of antibiotic resistance and undertreatment of this infection also poses a threat of complications (24).

DM is associated with a higher risk of several infections, of which one of the most prevalent is UTIs as compared with patients without DM. Diabetic patients have been found to have a 5-fold frequency of acute pyelonephritis at autopsy than nondiabetics (25). Some multiple epidemiological studies have reported a 1.24 in 2017 to 1.53 in 2012, increase in the relative risk of UTI in various cohorts in individuals with diabetes compared to non-diabetes (26-27).

An observational study found that the incidence rate of UTI was 46.9 per 1,000 person-years among diabetic patients and 29.9 for patients without diabetes in general practice research database in United Kingdom (27). Multiple potential factors unique to diabetes may contribute to increased susceptibility to UTI, such as hyperglycemia, glucosuria, and neurogenic bladder and most UTIs infections in diabetic patients are relatively asymptomatic (28-31).

Alternative therapeutic strategies, to prevent the development of antibiotic-resistant, prevent and treat recurrent UTI, restore a balanced microbial flora and enhance the defense mechanisms of the human body. Herbal remedies and probiotics have been proposed as alternative treatments and recurrent of UTI. Proanthocyanidins (PACs) are polyphenolic metabolites widely distributed in a variety of plants, have been associated with potentially positive health benefits, including antibacterial and chemotherapeutic activities(32-33). Cranberry is widely known as a potential source of antioxidants and anti-adhesion activity which helps protect the body from harmful bacteria that cause UTIs, due to the natural compound PACs. Cranberry treatment is a safe, well-tolerated supplement that does not have significant drug interactions. (32, 34).

One promising alternative is the use of live microorganisms (probiotics) to prevent and treat recurrent complicated and uncomplicated UTI as Lactobacillus species (35). Heavy growth of lactobacilli is associated with a lower frequency of vaginal colonization with *E. coli (*36). Lactobacillus species also live in the bowel, vagina, and periurethral; some Lactobacillus produces hydrogen peroxide, and modulate the local pH (37). Apple cider vinegar is a rich source of enzymes, potassium and other useful minerals that can prevent the bacteria that cause UTI as a natural antibiotic to treat the infection.

Table No. 1: Symptoms of UTI

The following symptoms for identification of a UTI:	
1.	Frequent or intense urge to urinate without passing much urine
2.	Increased urgency of urination
3.	Feeling as though patient is unable to empty bladder fully
4.	Burning with urination
5.	Pain or pressure in back and or side below the ribs
6.	Pelvic pain in women
7.	Rectal pain in men
8.	Women feel an uncomfortable pressure
9.	Milky, cloudy, dark, bloody or strange smelling urine
10.	Incontinence
11.	Fleeing tried, unwell, achy and lethargy
12.	Nausea and/or vomiting
13.	Fever of chill which may mean that the infection has reached the kidneys

The risk of UTI in Diabetes Mellitus

DM is evolving as one of the most serious diseases confronting humanity right behind cancer and cardiovascular diseases. About 4% population worldwide are dying from this deadly disease and this toll is likely to swell by 5.4% in the year 2025. Additionally, diabetes is known to be a risk factor for other diseases like the more frequent risk of UTIs, compared with and without DM. (38). The consequences of UTI in diabetic patients are serious and the risk of bacteremia is 4 times greater in diabetic patients than in non-diabetic patients (39). Higher glucose concentrations in urine may promote the growth of pathogenic bacteria and act as a culture medium and increased risk of bacteremia, enormous morbidity and mortality rising health care costs (40). Decreased immune function, such as impaired migration, intracellular killing, phagocytosis or chemotaxis in polymorphonuclear leukocytes in patients with diabetes, may weaken host defenses against UTI (25). Genitourinary neurological damage due to diabetes may result in dysfunctional bladder voiding and relative urinary retention, resulting in conditions favorable to UTI.

Pathogenesis and Complications

The common pathogens of UTIs are residents of the enteric or vaginal flora. *E. coli* is by far the most common cause of UTI, causing about 80% of infections in women and girls (41). Humans are normally able to eliminate foreign organisms from the urinary tract through high voiding frequency, bactericidal effects of bladder mucosa, secreted proteins that bind to fimbrial adhesins on the bacterial wall, inflammatory response mediated by cytokines and

antimicrobial factors in the urine, but some pathogens have developed mechanisms to escape such defences and successfully establish infection (42). The increased frequency of UTI in diabetic patients may be the result of differences in host responses between diabetic and non-diabetic patients. Many factors contribute to the complex pathogenesis of UTIs in diabetes include age, metabolic control, diabetic nephropathy, autonomic neuropathy and vascular complications. ESBL-producing *E. coli* not only are an indirect public health threat by being harmless common carriers of ESBL genes but also poses a direct threat upon exposure by actually carrying virulence factors representative for major pathogenic groups of *E. coli*(22). The most important of these are probably the adhesins that aid bacteria in the uroepithelium adherence process (43). *E. coli* adhere more to the uroepithelial cells of diabetic women compared to cells from non-diabetic (25), either because of substances excreted in the urine or because of a difference in the uroepithelial cells.

Overtreatment and antibiotic resistance are becoming increasingly common, and under treatment also poses a threat of complications. Moreover, there are several disadvantages to using antibiotics over long periods including adverse reactions, increasing the risk for bacterial resistance and costs. Antibiotics often eliminate lactobacilli, along with harmful bacteria that cause an overgrowth of *E. coli* in the vagina. Thus, it seems that taking antibiotics for a UTI increases the risk of a subsequent infection. According to the American Centers for Disease Control and Prevention (CDC), ESBL-producing bacteria are considered a serious threat in the U.S (44).

Epidemiology

UTIs have been reported to affect up to 150 million individuals annually worldwide (45), represent one of the most common diseases which are encountered in the medical practice today. UTI exists 9%–20% in female and 3%–11% in male patients with diabetes. As many as 80% of UTIs are caused by *E. coli*(46). DM is associated with a higher risk of several infections, UTI is most common of them. ESBL producing *E. coli* most frequently found bacteria in both the community-acquired and the hospitalized UTI patients and becoming more complex in both healthcare and community settings (47-48). In particular, ESBL-producing *E. coli* are emerging worldwide (49-51), ESBL-genes cause a high level of multi-drug resistance and virulence factors.

Host defense mechanisms;

The host defense to infection by UPEC are characterized by neutrophil migration into the tissue and production of pro-inflammatory cytokines such as Interleukin 6 and 8 (IL-6 and IL-8) (52). The bacterial attachment activates the mucosal cells which then orchestrate the subsequent host response by the release of cytokines and other mediators of inflammation and immunity (53). The IL-6 and IL-8 are produced by uroepithelial cells as part of the early immune response and play an important role in the regulation of the host defenses against local or systemic bacterial infections (54-55). In diabetic patients, hyperglycaemic environment has been observed to alter immune function. Lower urinary concentrations of IL-6 and IL-8 women with diabetes have been shown to correlate with a lower urinary leukocyte cell count, which may contribute to the increased incidence of UTIs in a patient with diabetes (56-57). Some mechanisms as regular bladder emptying, urine flow, including epithelial defensins, mucous production, barrier formation, inflammation and urine characteristics such as urinary osmolality and a high concentration of urea, which inhibits bacterial growth (58-59).

Treatment & Management

Infections of ESBL-producing *E. coli* present a major therapeutic dilemma as a very limited choice of antibiotics due to the broad-spectrum of the β-lactamases produced by these microbes. The multiple drug resistance significantly affects the course and outcomes of infections, both in the community and in the hospital setting. Patients with diabetes are at greater risk for complications from aminoglycosides. Treatment of UTI in diabetic patients depends on several factors as if the infection is localized in the lower UTI part or also involves the upper UTI part kidney, the presence of urologic abnormalities, accompanying metabolic alterations, and renal function (40). Treatment of UTI in diabetic patients is similar to UTI in non-diabetic patients, as a general rule. Herbal remedies, probiotic and D-mannose have been proposed as alternative treatments for recurrent UTI and some other options as potassium citrate or sodium bicarbonate (60), and vitamin C. The ingredients of cranberry counteracts the effects of *E. coli*: cranberry concentrate inhibits the ability of *E. coli* to adhere to the urinary tract wall.

Choice of antimicrobial agent

Antibiotic the first choice for treatment of UTI and same treatment use in diabetic and non-diabetic patients in general. First-line treatment options for various types of UTI are in detailed. The increasing prevalence of UTI caused by antibiotic-resistant bacteria makes any empirical treatment more difficult, especially in a high-risk population like elderly women, and frequent antibiotic usage, bacteria begin to develop a resistance to the antibiotic itself (61).

Herbal remedies for UITs

Medicinal plants differ greatly from other plant species by their peculiarities in secondary metabolism and in the composition of their unique biologically active substances. Traditional herbal medicines are currently serving the healthcare needs of the majority of the world's population (62), as herbs are generally a safe way. Herbal remedies may relieve UTIs by combating the bacteria, decreasing irritation and healing urinary tract tissues. Herbal remedies can provide an effective alternative option to prescription medications for UTIs like *Vaccinium* macrocarpon [cranberry], Hydrastis Canadensis [goldenseal], agathosmabetulina [buchu], Arctostaphylos uva-ursi [bearberry], echinacea purpura [cone flower] and Equisetum arvense [horse tail] that have been clinically proven for UTI cure as well as bladder infection treatment (34-36). The best-studied natural therapeutic and preventative for UTI is the American cranberry.

Cranberry (*Vaccinium macrocarpon*)

Cranberry fruit has a long history of herbal and medicinal use, documented as far back as the 17th century, contain 80% water and 10% carbohydrates (63), has been used widely to prevent and treat UTIs, known as a potent source of antioxidants and for their unique anti-adhesion activity which helps protect the body from harmful bacteria. The anti-adhesion activity is primarily due to natural flavonoids, proanthocyanidins (PACs) (64-65), specifically inhibit hemagglutination of *E. coli* by expression of types 1 and P adhesin, can prevent *E. coli* from adhering to uroepithelial cells in the urinary tract (66). Some other constituents of cranberry are anthocyanins, catechin, triterpenoids, organic acids, and a small amount of ascorbic acid (67). Some study also suggests that benefits of cranberry were due to its acidity (68), an acidic state by lowering the pH; the acidic environment kills and inhibits the growth of bacteria. The PACs in cranberry contain unique A-type PACs, rarely found elsewhere in

nature, target *E. coli* cells as alter the cell membranes, compress fimbriae, that makes it more difficult for certain types of bacteria to remain in place long enough to launch an infection and change in shape from rods to spheres, affecting its activity. All of these effects inhibit the ability to attach to cells lining the bladder wall, prevent the bacteria from making contact with cells, disrupt bacterial communication and can be flushed out in the urine instead of causing an infection.Cranberries can be processed into fresh fruit, concentrate, sauce products, and juice drinks (65). Therefore, the potential of cranberry products to act as a nonantibiotic alternative for preventing UTI caused by ESBL producing *E .coli*, especially in diabetic patients with decreased immune function.

Probiotics (*Lactobacillus* preparations)

Probiotics can be considered as safe according to a report of the Health Protection Agency Centre for Infections, London (69) and defined as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' by the WHO (70). Probiotics have various beneficial effects such as maintaining the acidic pH, bacteriocins, production of hydrogen peroxide, antimicrobial activity, prevention of colonization of pathogen, degrading the toxins and stimulation of immunity of the host (71). Lactobacilli are Gram-positive rods, primarily facultative or strict anaerobes that generally have a fastidious growth requirement and have effective therapeutics properties against the urogenital tract infections, use as probiotic (72). Uropathogenic *E. coli* can live in the bowel and vaginal cavities, around the urethral opening and in the urinary tract, during sexual activity bacteria moved into the bladder (73). Lactobacillus species also live in the bowel, vagina and produce hydrogen peroxide, may modulate host immune response, limit adhesion of *E. coli* to tissue or disrupt *E. coli* biofilm formation (74). These characteristics and some others anti-microbial role help the vagina and periurethral resist attack by pathogens such as *E. coli*. Lactobacillus bacteria have been used to treat or prevent infections of the intestinal and urinary tracts with different degrees of success (75-76).

Home remedies and preventative strategies for UTIs

Though UTIs traditionally treated with antibiotics, some home remedies have been suggested that provide an effective alternative approach to treat UTI and reduce the risk of recurrence, for which there is some scientific evidence. Garlic is a very common spice used in most food, allicin, one of the active compound, have a variety of antimicrobial properties and block the

growth of bacteria to prevent UTIs (77-78). The pure form of allicin has been found to exhibit antibacterial activity against a wide range of bacteria, including multi-drug-resistant strains of *E. Coli* (79). Some evidence shows that increasing intake of vitamin C could inhibit the growth of bacteria in the urinary tract since it makes urine more acidic, thereby killing off the bacteria that cause infection (80). Although it is usually advised that vitamin C intake is increased via a varied diet, supplements as Indian gooseberry is a rich source of vitamin C, inhibits the growth of *E. Coli* the urinary tract.

Adequate hydration status has been linked to the risk of UTI, important and may improve the results of antimicrobial therapy in UTI because regular urination can help flush bacteria from the urinary tract and a reduction in the incidence of UTIs (81). The basis on some clinical studies, advice given by expert committees to patients with UTI to drink large volumes of fluid, void frequently, and completely empty the bladder because low urine output associated with an increased risk of UTI (82).One study in 2003 showed that low fluid intake and infrequent urination were both linked to recurrent UTIs (83). Apple cider vinegar has some enzymes, potassium and other useful minerals that can prevent the UTIs, as a natural antibiotic to treat the infection. Wash before and after sexual intercourse, and urinate immediately to eliminate any new bacteria introduced. The inflammation and irritation can cause a constant, nagging discomfort that makes you feel painfully cramped up, applying heat over your bladder can bring some serious relief.

CONCLUSIONS

Patients with DM have a higher incidence of symptomatic UTIs, which is more severe, caused by more resistant pathogens, and carry worse outcomes than in patients without diabetes. Therefore these UTIs with diabetes are considered as more complicated; which leads to various impairments in the immune system, poor metabolic control, hyperglycemia, ketoacidosis, deregulated endocrine system and incomplete urinary bladder emptying due to autonomic neuropathy (40). The antibiotic treatment in such cases serves mostly to increase multidrug resistance and chance of possible drug interactions between antibiotics and anti-diabetics in patients with DM (84). Host response is different in ESBL producing or non-ESBL producing *E. coli*strains and close relationship between ESBL productions. Patients with an infection caused by ESBL-producing bacteria are at risk for therapeutic failure or even death because there is often a delay before the correct antibiotic treatment is given (58-59). Multidrug resistance leaves only a few treatment options for UTIs, therefore, alternative

prophylactic agents have been explored. Herbal medicines and probiotic medicines are most common alternative treatment options, many researchers proved that people are utilizing alternative treatment options for taking care of their UTI. Some increase the production of urine, others fight against the bacteria and soothe the discomfort caused by them.Cranberries have long been advocated as a possible intervention for the problem. The possible role of cranberries in managing UTIs is widely recognized and it is estimated that 48% of American consumers are aware of the link (85). Therefore, the potential of cranberry products to act as a non-antibiotic alternative for preventing UTI. Probiotics have various beneficial effects and stimulation of immunity of the host (68), show promise in becoming the potential alternative or complementary treatment strategy in UTI. Lactobacillus have effective therapeutics properties against the UTI, use as probiotic (69), have been used to treat or prevent infections of the intestinal and urinary tracts with different degrees of success (72-73). One of the simplest home remedies is to drink plenty of fluids for a UTI, flush the bacteria out of the body(76). Some hygienic measures are helpful, including proper wiping techniques and voiding after intercourse, women should wipe from front to back, wash before and after intimacy and urinate immediately after sexual intercourse to eliminate any new bacteria introduced (77).

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