



## UTI prevalence among population with chronic conditions

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### Abstract

UTIs are a severe public health problem and are caused by a range of pathogens, but most commonly by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus*. High recurrence rates and increasing antimicrobial resistance among uro-pathogens threaten to greatly increase the economic burden of these infections. UTIs typically occur when bacteria enter the urinary tract through the urethra and begin to multiply in the bladder. Although the urinary system is designed to keep out such microscopic invaders, these defenses sometimes fail. If left untreated, a urinary tract infection can have serious consequences. Adult women are 30 times more likely than men to develop a UTI, with almost half of them experiencing at least one episode of UTI during their lifetime. Uncomplicated lower UTI remains one of the most commonly treated infections in primary care. A complicated UTI is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease. Diagnosis of a UTI is based on a focused history, with appropriate investigations depending on individual risk factors. The paper reviews several chronic conditions that are risk factors for UTIs in human being.

**Keywords:** complicated and uncomplicated UTIs; asymptomatic bacteriuria; UTIs among obese and heart patients; UTIs among renal and hepatic insufficiency; pregnancy induced complications; urinary infections among HIV and other STD

### Introduction

UTI is one of the most prevalent diseases with diverse etiological agents annually affecting 250 million and causes death of 150 million people worldwide. The disease can be developed in 40% - 50% of women and 5% of men. Financial burden of UTIs exceeds \$3.5 billion in US alone, while over half of the anti-infection agents prescribed for a suspected UTI in older adults being considered unnecessary [1]. Interestingly, nosocomial UTIs account for nearly 40% of all hospital acquired infections and around half of UTI in children are missed. UTI prevention is necessary as renal scarring, low birth weight, fetal growth restrictions, neonatal UTIs, premature labor, miscarriage, hypertension, preeclampsia, septic shock, malformation, anorectal malformation and increased incidence of death in the womb are reported in several studies [2]. The most common bacterial species that are implicated in UTIs are *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa* and *Proteus mirabilis* [3]. The association of UTI in diabetic females is more common than males because of their anatomical structure such as shorter urethra, the absence of prostatic secretion, and perineal contamination of the urinary tract with fecal flora [4]. Complicated UTIs occur most commonly in patients with abnormal genitourinary tract [5]. About 150 million people suffer from UTIs each year globally which results in greater than 6 billion dollars in direct health care [6]. UTIs are also common among many other chronic conditions like patients with diabetes, stroke, arthritis, obesity, alcohol use disorder, hypertension, HIV, liver cirrhosis, Hepatitis C, long-term care residents, immunocompromised, or pregnancy, history of/current catheterization, spinal cord dysfunction and a few cancers.

Classification	Definition
Uncomplicated UTI	A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk of developing serious complications
Acute uncomplicated cystitis	A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute uncomplicated pyelonephritis	An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C)
Asymptomatic bacteriuria	A positive urine culture (>10 <sup>5</sup> colony-forming units/ml) in the absence of urinary symptoms
Recurrent uncomplicated UTIs	A recurrent UTI refers to the occurrence of ≥2 symptomatic episodes within 6 months or ≥3 symptomatic episodes within 12 months

### Diabetes Mellitus

The International Diabetes Federation (IDF) estimated that, worldwide, approximately 425 million people had diabetes in 2017, projected to be 629 million by 2045. And surprisingly, 80% of people with this so called "Rich Man's Disease" live in LMICs. According to a recent study of American Medical Association, China and India collectively are home of nearly 110 million diabetic patients [8, 9]. Significant bacteriuria had an association with the consumption of alcohol, gender and glucose level [10]. Asymptomatic bacteriuria (ASB) is common in neonates,

**Table 1:** Key classifications of UTIs [7]

Preschool children, pregnant women, elderly, diabetics, catheterized patients, and patients with abnormal urinary tracts or renal diseases. Diabetic patients have more than twice the tendency of developing genitourinary tract infections [11]. Bharti et.al, 2019 estimated that ASB was common among diabetics, as evident by a prevalence of 21% [12]. In patients with diabetes mellitus, infections caused by *Klebsiella*, *Enterobacter*, and *Candida* are more common [7]. According to Zubair et.al 2019, *E. coli* was the most frequent pathogen, followed by *Staphylococcus aureus* [13]. Urine cultures are not needed in uncomplicated UTI. Urine should be cultured in all men and patients with diabetes mellitus, who are immunosuppressed, and women who are pregnant [14]. The increased risk of infection in diabetics can be partially explained by a decreased T-cell-mediated immune response and impaired neutrophil function among diabetics. Other factors such as local complications related to neuropathy such as impaired bladder emptying and higher glucose concentrations in urine may also play a role in increased incidences of UTI in diabetics [15,16]. Non-drug-related mechanisms include autonomic neuropathy, glucose-dependent ICAM-1 expression, and immune system competence. Concerning drug-related mechanisms, there are currently over 40 different drugs in 12 distinct classes approved in the United States to treat patients with T2DM. Except for SGLT-2i, among the new drugs for the treatment of DM, no risk of UTIs or genital infections has been found [17].

### Stroke

Stroke is a leading cause for disability and morbidity associated with increased economic burden due to treatment and post-stroke care, which was found \$4850 per month in USA, \$883 in UK, \$752 in Australia and \$192 in Malaysia [18]. Stroke-related annual national spending was estimated to be \$34 billion in US, \$3.6 billion in Canada and 6\$ billion in China [19,20]. Stroke is the second largest cause of death in Australia and the total burden of disease cost for stroke in 2012 was AUD 49.3 billion [21]. Approximately one-third of all stroke patients have diabetes [22]. HbA1c  $\geq 7.2\%$  ( $>55$  mmol/mol) is an independent risk predictor for 1-year all-cause mortality after acute first-ever ischemic stroke [23]. The incidence of ischemic stroke is up to 2-fold higher in people with diabetes. The relative risk of stroke increases by 1.15 with each 1% increase in glycated hemoglobin (HbA1c) level [24]. Of interest, UTIs account for a majority of the infections, and are independently associated with 30-day readmission in stroke patients [25]. Unlike other infections such as pneumonia or invasive line infections, UTI are often present on admission, which complicates efforts at eradication [26]. Providers may reflexively prescribe antibiotics, without considering other reasons for a clinical change. This may delay appropriate interventions and lead to patient harm [27]. The incidence of infections varies, but previous studies have quoted the rate for UTI as ranging from 3% to up to 44% [26], [28]. Patients with stroke have different risks for, consequences of, and barriers to reducing UTI than other hospitalized patients [29]. The role of infection in ischemic stroke is likely to be complex and multifactorial. Infection may play a causal role in the immunological triggering of stroke, and a stroke itself may have untoward effects on the immune system. The concepts of CNS injury-induced immunodepression or stroke-induced

Immunodepression have even been used to describe the findings of secondary immunodeficiency after stroke. Also, stroke patients usually have comorbidities, which seem to make them more susceptible to infections [28]. Urinary catheterization is common after acute stroke and a well-known risk factor of UTI [30].

### Hypertension

Hypertension has been reported as one of the long-term complications of UTI with renal parenchymal damage [16]. Children with UTIs are at risk of renal scarring which may lead to impaired renal function and hypertension [31]. Long-term follow-up of these children has to be done for the identification of complications such as renal function deterioration and hypertension [32]. Again, UTI prevention is necessary to prevent spread to the kidneys or developing pyelonephritis, which can cause the destruction of the delicate structures in the nephrons and lead to hypertension [4]. Following a UTI there is concern with recurrences which can contribute to scarring which may lead to hypertension, pregnancy-induced hypertension and even renal failure in later years [33]. Each year 10 million women worldwide develop preeclampsia (PE) and approximately 76,000 die due to PE and related hypertension disorders, 2–13% or more are responsible for nearly 40% of premature birth delivered before 35th weeks of gestation [34]. A number of studies suggest that UTI during the course of gestation is associated with elevated risk for preeclampsia (along with premature birth and low birth weight), while others have failed to prove such an association [35-37]. However, Rasouli et.al, 2019 revealed that presence of UTI in the third trimester, is strongly associated with preeclampsia [38].

### Arthritis

Recurrent UTI is significantly more common in women with RA and secondary Sjögren's syndrome [39]. RA is most probably caused or initiated by an upper UTIs with *Proteus* bacteria. Elevated levels of antibodies to *P. mirabilis* have been detected in patients with RA among many populations from 14 different countries including UK, USA, France, and Netherlands [40]. A positive correlation was found between high anti-*Proteus* antibody levels in sera of RA patients and the number of colony-forming units obtained from urine specimens of these patients [41]. Patients infected with *Proteus* microbes will produce not only antibodies against this microbe but also against the self-tissue molecules carrying the cross-reactive antigens [41,42]. These antibodies will bind to and be cytopathic to the joint tissues which carry *Proteus* cross-reactive antigens and this immune reaction will lead to the release of more self-tissue antigens with a consequent production of further autoantibodies, propagation of the pathological process and the development of classical RA, in the same way that *Streptococcus* causes rheumatic fever and valvular lesions in the heart [42]. Reactive arthritis following *Escherichia coli* UTI is very rare (and has a significant morbidity), with most presentations caused by *Staphylococcus aureus* [44-46]. However, Braga et.al, 2016 showed that highly diverse *E. coli* strains can be recovered from osteomyelitis and arthritis in broilers, even in the same flock. Most of these strains are multidrug resistant, with increasing rates of ceftiofur resistance, which is a public and animal health concern [47].

## Obesity

By 2025, the global obesity prevalence will reach 18% in men and exceed 21% in women [48]. It is now well-established that obesity (depending on the degree, duration, and distribution of the excess weight/adipose tissue) can progressively cause and/or exacerbate a wide spectrum of co-morbidities, including T2DM, hypertension, dyslipidemia, CVDs, NAFLD, reproductive dysfunction, respiratory abnormalities and psychiatric conditions [49]. Obesity-associated DNA damage can promote cancer growth by favoring cancer cell proliferation and migration, and resistance to apoptosis [50]. The aggregate national cost of overweight and obesity combined was \$113.9 billion in 2008 in US [51] and the global economic impact of obesity was estimated to be US \$2.0 trillion or 2.8% of the global GDP in 2014 [52]. Interestingly, chronic use of antibiotics during adulthood may have long-lasting impacts on BMI and weight gain in several populations [53]. Again, obesity may increase the risk of infection, but the association between obesity and febrile urinary tract infection (fUTI) is controversial [54]. However, elevated BMI appears to be associated with an increased risk for UTI and pyelonephritis [55, 56]. Semins *et al.* revealed a frequency of UTI 2.5 times higher in obese subjects than in non-obese children older than five years [55]. Also, obesity affects a greater proportion of women than men [57] and was found to be associated with RUTIs in premenopausal women [58]. Several studies have demonstrated that white adipose tissue is a crucial site of the formation of proinflammatory adipokines such as leptin, adiponectin, and resistin and classical cytokines such as IL-6 and TNF- $\alpha$  [59]. Altered leptin, adiponectin, resistin and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality [60]. Inflammation often accompanies UTIs and is associated with renal scarring and disease severity. TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8, are involved in the inflammation that accompanies UTIs [61]. Kennelly *et al.*, 2019 speculated that obese subjects (BMI > 50) have difficulty with bowel hygiene and as such are at increased risk of vulvovaginal symptoms and UTI [62]. Many health risks of obesity, including nephrolithiasis, will add more burden on urologists and nephrologists [63].

## Chronic Liver Diseases

a. **Non-alcoholic Fatty Liver Disease:** NAFLD is a leading cause of chronic liver disease and cirrhosis and is associated with metabolic syndrome, T2DM, CVDs, and 2-fold all-cause mortality among diabetics [64]. NAFLD prevails in 25% Americans, involves \$103 billion from direct medical care costs alone and another \$188 billion in societal costs annually [64, 65]. It is more prevalent in male gender, and with increasing age, obesity, and insulin resistance [66]. It is associated with bacterial infections. Nseir *et al.*, 2019 concluded that NAFLD is associated with RUTI in premenopausal women, independent of metabolic syndrome [67]. No significant associations were found between NAFLD and LUTS in middle-aged men [68]. SGLT2 inhibitors reduce hepatic steatosis, steatohepatitis, and fibrosis in patients with NAFLD [66]. Pioglitazone (SGLT-2 inhibitor) is the only drug recommended in diabetes patients with biopsy proven non-alcoholic steatohepatitis, improves the serum level of liver enzymes, decrease liver fat, and fibrosis with additional beneficial effects on various metabolic parameters in type 2 diabetes patients with NAFLD [69]. The most common

adverse effects of SGLT-2 inhibitors are genitourinary tract infections [69-72]. Although, Lega *et al.*, 2019 revealed that SGLT2 inhibitors among elderly is associated with increased risk of genital mycotic infections within 30 days but there is no associated increased risk of UTI [73].

- b. **Liver Cirrhosis:** The worldwide prevalence rate for CLD is 4.5% to 9%, causing over 6.3 million cases of liver cirrhosis per year [74]. Liver cirrhosis (LC) is the end stage of multiple processes that lead to hepatic failure and is the 10th most common cause of death in the Western world. It represents the main indication for liver transplantation in both United States and Europe. Common primary etiologies for liver cirrhosis were chronic hepatitis B cirrhosis (37.3%), ALD cirrhosis (24.1%), chronic hepatitis C cirrhosis (22.3%) and NAFLD cirrhosis (16.4%) [75]. Bacterial infections increase mortality four-fold in patients with decompensated cirrhosis. The presence of UTI indicates an increased risk of 90-day mortality in patients with advanced cirrhosis. Renal dysfunction and comorbidities are predictors of death in these patients [76]. UTIs found in 20% of cirrhotic patients [77]. UTI in this population does not correlate with the severity of liver disease but is associated with sex (females have a higher risk) and DM [78]. UTIs are also more frequent in patients with Primary Biliary Cirrhosis (PBC) [79]. The prevalence of increased aminotransferase levels in UTI patients without pre-existing liver disease was approximately 20%. In most cases, this change is mild and self-limiting in children [80].
- c. **Chronic Hepatitis C:** It is a major cause of CLD worldwide with an estimated 71 million people infected and a 20-year risk for developing cirrhosis of up to 30% leading to 400,000 deaths annually from hepatocellular carcinoma and end-stage liver disease [81]. From 2010 until 2019, HCV cause the loss of 1.83 million years of life in people younger than 65 with cost of \$21.3 and \$54.2 billion, respectively [82]. First diagnosed in 1989, HCV is a major public health problem affecting 185 million people worldwide [83]. An estimated 80 million people live with active HCV infection worldwide, with approximately 1.75 million new infections and 400,000 related deaths annually [84]. Most children are infected by hepatitis C at birth. The most common infections among these patients are spontaneous bacterial peritonitis, pneumonia, skin infections and UTIs [85].

## Alcohol Use Disorder

The WHO estimated that there are 2 billion alcohol users in the world and prevalence of alcohol use disorder is highest in Europe (7.5%) [86]. Alcohol causes over 3 million deaths worldwide each year and contributes to more than 5% of the global burden of disease. In the US, alcohol use is the fourth leading cause of preventable death with approximately 88,000 people dying each year due to alcohol-related causes [87]. In 2010, alcohol misuse cost the US \$350 billion [88]. An enhanced frequency and morbidity of UTIs have been observed in association with alcoholism and liver disease [89]. Alcohol increases the acidity of urine and can irritate the lining of the bladder [90]. Alcohol consumption is known to increase the urine output, which could interfere with normal hydration [91]. A person who drinks alcohol can become dehydrated, increasing the risk of a UTI [92]. Women with alcohol use disorders undergoing cesarean delivery have increased risk of hospital-acquired infections including UTIs [93].

A separate study shows that alcohol induced immune suppression increases risks of UTIs <sup>[94]</sup>.

### Renal Insufficiency & Compromised Immunity

In patients with chronic renal failure, UTIs occur most frequently after kidney transplantation when graft pyelonephritis is a life-threatening complication, with a reported rate of 45-72% <sup>[95,96]</sup>. CKD affects more than 10% of US adults. It is the 18th leading cause of death globally, an 82% increase in absolute number of deaths in two decades. Medicare expenditures with recognized CKD is \$45.5 billion and \$34.3 billion with ESRD, according to Ozieh et.al, 2017 <sup>[97]</sup>. CKD affects 12.5% of adults in Canada <sup>[98]</sup>, around 15% in US <sup>[99]</sup>, 10-16% of the adult in Australia <sup>[100]</sup> and 13.4% around the world <sup>[101]</sup>. Around 20% of adults aged  $\geq 65$  present to primary care at least once with a UTI, and around 20% have renal impairment <sup>[102]</sup>. Females and elderly patients with CKD are more prone to have more bacteriuria and upper UTIs than males <sup>[103]</sup>. Again, women with diabetes are more prone to severe cystitis, ascending pyelonephritis, and severe forms of pyelonephritis (e.g., perinephric abscess, papillary necrosis) <sup>[104]</sup>. Repeat UTIs may cause kidney disease and structural kidney disease may be identified through investigation of repeat UTIs <sup>[105]</sup>. In more severe renal impairment, uremic toxins impair the function of T-lymphocyte and antigen-presenting cells, which play important roles in cellular and humoral immunity <sup>[102]</sup>. These patients have a higher risk of urinary infection, but the signs of infection may be different to those in the general population <sup>[96]</sup>.

### Urogenital Conditions

- a. **Catheterization:** Healthcare-associated UTIs are the fourth most common type of healthcare-associated infection and approximately 80% of healthcare-associated UTIs are related to the use of indwelling urinary catheters <sup>[2]</sup>. CA-UTIs can lead to more serious complications such as sepsis and endocarditis, and it is estimated that over 13,000 deaths each year are associated with healthcare-associated UTIs <sup>[106]</sup>. Incidence of bacteriuria and UTIs are a function of the duration of catheterization. After 3 days, 100% of patients with an open-drain system will have ASB, and 3-6% of patients will develop ASB per day of closed-drain catheterization <sup>[107]</sup>. The use of chlorhexidine solution for meatal cleaning before catheter insertion decreased the incidence of catheter-associated asymptomatic bacteriuria and UTI and has the potential to improve patient safety <sup>[108]</sup>.
- b. **Neurogenic Bladder Dysfunction:** Lesions to the nervous system commonly cause bladder dysfunction. UTIs remain one of the most prevalent and frustrating morbidities for neurogenic bladder patients, and death attributed to urosepsis in the spinal cord injury patient is higher when compared to the general population. Risk factors include urinary stasis, high bladder pressures, bladder stones, and catheter use <sup>[109]</sup>. The management of neurogenic dysfunction through urethral catheter, suprapubic catheter, or nephrostomy also increase the risk of colonization and UTIs <sup>[107]</sup>.
- c. **Stress Urinary Incontinence:** Stress urinary incontinence (SUI) is the involuntary leakage of urine during periods of increased intra-abdominal pressure, including exertion such as laughing, coughing, sneezing, coughing, and jumping. Coexistence of UTIs and SUI is very common and UTIs

resolved in 82% of patients with previous RUTIs after surgical correction of SUI with transobturator suburethral tape (TOT) <sup>[110]</sup>. Synthetic mid-urethral slings are the most common procedures currently performed for stress urinary incontinence in women and preoperative antibiotic prophylaxis may not be needed for UTI prevention <sup>[111]</sup>.

- d. **Genital Prolapse:** Approximately 40% of patients with prolapse have voiding issues, resulting in increased risk of UTI. The USA alone performs approximately 200,000 pelvic prolapse surgical procedures per year. <sup>[112]</sup> Studies have shown that the presence of residual urine reflects a high risk of UTIs in women with urinary incontinence. Interestingly, data indicate that residual urine volumes as low as 30 ml can increase the risk for UTIs <sup>[107]</sup>.

### Long-Term Care Residents

Dehydration has been highlighted as a common cause of admission to hospital in nursing home residents, and there is evidence that many older residents living in care homes do not receive enough fluids. Inadequate staffing, including high turnover and understaffed care homes, increases the risk of dehydration in residents <sup>[92]</sup>. The prevalence of asymptomatic bacteriuria in long-term care residents is high: it is estimated that 15%-30% of men and 25%-50% of women have the condition <sup>[113]</sup>. The major reasons for this high prevalence are chronic comorbid illnesses with neurogenic bladder and interventions to manage incontinence. Chronic degenerative neurological diseases, such as Alzheimer's disease and Parkinson's disease, and cerebrovascular accidents are associated with a neurogenic bladder. These conditions cause impaired bladder emptying and ureteric reflux, which contribute to the high frequency of bacteriuria. Interventions to manage incontinence may also promote infection <sup>[114]</sup>. 30% to 50% of antibiotics prescribed in long-term care are for urinary indications <sup>[115]</sup>. The Infectious Diseases Society of America and the Association of Medical Microbiology and Infectious Disease Canada both discourage this practice. Also, Urinary catheters are still frequently used in nursing homes, with catheter prevalence ranging from 5% to 22% of all residents <sup>[116]</sup>, 30% of long-stay residents were suggested a bi-modal pattern in urinary catheter use according to another study of the same author <sup>[117]</sup>.

### HIV and Other STDs

UTI prevalence is fueled by HIV infection. The frequency of UTI is gradually increasing amongst HIV-infected patients as an opportunistic infection. This is due to the unique pathogenesis of the virus, which decreases the CD4+ cells, and as such, the individual's immune system can no longer fight against invading commensal organisms. *E. coli*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas aeruginosa*, *Enterococcus* spp., and *S. aureus* are the most causative agent of UTI in people living with HIV <sup>[118]</sup>. Of approximately 20 million new STDs each year in the US, half of cases occur among adolescents age 15-24 years. It is estimated that 1 out of 4 sexually active adolescent females have an STD, most commonly *Chlamydia trachomatis* infection and human papillomavirus infection <sup>[119]</sup>. *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* can cause adverse birth outcomes and infertility. Syphilis (*Treponema pallidum*) can cause neurological, cardiovascular and dermatological disease in adults, and stillbirth, neonatal death, premature delivery or severe

disability in infants. All four infections are implicated in increasing the risk of HIV acquisition and transmission [120]. Atypical UTIs are commonly caused by *C. trachomatis* and *N. gonorrhoeae* [107]. The clinical presentations for STDs and UTIs may overlap, and symptoms of dysuria and urinary frequency/urgency occur with both STDs and UTIs [121]. Complications in urinary tract nervous routes due to *Herpes simplex virus type 2* and *Varicella-zoster virus* (unique members of the *Herpesviridae* family) are well known. Acute urinary retention and chronic neuropathic pain are not rare when sacral dermatomes are involved by these viruses [122]. When acute urinary retention occurs several neurological and gynecological disorders must be considered. Unusually, benign inflammatory nervous diseases also cause acute urinary retention that can be divided into CNS disorders such as the meningitis-retention syndrome, a combination of aseptic meningitis and acute urinary retention, and PNS disorders such as sacral herpes [123].

### Pregnancy

During pregnancy, urinary tract changes predispose women to infection. The prevalence of UTI among pregnant women was estimated to be 12.5% [124]. If asymptomatic bacteriuria is untreated in pregnancy, the rate of subsequent UTI is approximately 25% [125]. Pregnancy UTI is classified into two categories of symptomatic and asymptomatic: a) The involvement of the lower urinary tract, leading to asymptomatic bacteriuria is the most common cause of UTI during pregnancy b) The involvement of the upper urinary tract can lead to symptomatic bacteriuria and is characterized by acute Pyelonephritis. Based on performed researches, the prevalence of symptomatic urinary tract infection in pregnant women has been 18% and asymptomatic form in 13%. If asymptomatic infection is not treated, it leads to some clinical manifestations in mother and newborn [126]. Women face dual risks when they experience UTIs; the risk from the infection and the risk from antibiotic treatment. Pre-natal attachment to the fetus is highlighted in the decision-making process. The focus is on the shorter-term risk from UTIs while undermining the longer-term risks from antibiotic use, especially the risk of AMR. Although AMR is a global public health threat to everyone, in pregnancy it can be particularly concerning due to the risk of resistant bacteria passing on to the neonate during birth which can be a vulnerable stage of life with regards to contracting infections. In addition to this, antibiotic use in pregnancy may also carry the risk of potentially teratogenic effects including spontaneous abortion [127].

### Cancer

In immunocompromised cancer patients, UTI is one of the major causes of fever and morbidity. *E. coli* was the most common organism isolated in cancer patients with UTI. There is trend of increasing resistance to aminoglycosides, cephalosporins and fluoroquinolones among Gram negative bacilli [128]. UTI is significantly related to GUC and may serve as an early sign of genitourinary cancers (GUC), especially in the male genital organs, prostate, kidney, and urinary bladder. The symptoms of overactive bladder (OAB) have overlap with other common conditions, most notably UTI, BPH, and bladder cancer/carcinoma in situ [129]. An elevated prostate-specific antigen (PSA) level is well known in the diagnosis of prostate

cancer, but it also might have a potential protective role in recurrent UTI [130]. In UTI treatment, especially when multiple pathogenic factors are entailed, antibiotics must be used cautiously, and the time and dose of antibiotics should be minimized. Because UTI may increase the incidence of genital organ, bladder, kidney, male colorectal, prostate, and female liver cancer, knowledge about preventing UTI such as proper drinking water, exercise, and toilet habits should be enhanced in educating the general public [131].

### Pre- and Post- Menopausal Women

Risk factors in premenopausal women include sexual intercourse, changes in bacterial flora, history of UTIs during childhood or family history of UTIs, and blood group [132]. Specific risk factors related to sexual intercourse include frequency (four or more times per week), the use of spermicides that may alter vaginal pH and thus affect its flora (particularly the *Lactobacilli* component), and engagement with a new sexual partner within the last year [133]. Lack of postcoital urination, vaginal douches, use of hot tubs, restrictive underwear, and the hygiene and circumcision status of male partners have been proposed as risk factors, but lack an evidence base [2]. For postmenopausal women, the most significant risk factor is estrogen deficiency. Sexual intercourse and estrogen deficiency in postmenopausal women might have the strongest association with recurrent UTI. Lack of estrogen could cause thinning of the vaginal epithelium and decreased amounts of glycogen, predisposing women to introital colonization with *E. coli* [134]. The main vaginal flora usually changes from *Lactobacilli* to uropathogen such as *E. coli* after estrogen loss at menopause, leading to UTI recurrence [130], [135]. Urobiome research for bladder health and disease is a young field of investigation with significant potential to improve care for postmenopausal women affected by rUTI through novel, evidence-based prevention and treatment strategies [136].

### Conclusion

UTIs cause both anxiety and depression in significant number of patients, with a significant improvement in the QoL after proper treatment and prophylaxis. Treating UTI might not be difficult, but preventing UTI recurrence sometimes might be very troublesome for both patients and physicians. Treatment of asymptomatic bacteriuria in the general population is highly discouraged due to the risk of increased AMR. Diagnosing and managing upper and lower UTI have always been a challenge to physicians, given its high prevalence, risk of recurrence and improper treatment, and the fact of worldwide increase in antibiotic resistance, necessitating implementation of a proper antibiotic stewardship. Effective UTI management should provide established guidance for the RUTI evaluation and management to prevent inappropriate use of antibiotics, decrease the risk of antibiotic resistance, reduce adverse effects of antibiotic use, provide guidance on antibiotic and non-antibiotic strategies for prevention, and improve clinical outcomes and quality of life by reducing recurrence of UTI events.

### Abbreviations

International Diabetes Federation (IDF); Low-and Middle-Income Countries (LMICs); Asymptomatic bacteriuria (ASB); Intercellular Adhesion Molecule-1 (ICAM-1); Sodium-glucose co-transporter-2 inhibitors (SGLT-2i); Type 2 Diabetes Mellitus

(T2DM); Hemoglobin A1C (HbA1c); Preeclampsia (PE); Non-Alcoholic Fatty Liver Disease (NAFLD); Gross Domestic Product (GDP); febrile Urinary Tract Infection (fUTI); Tumor Necrosis Factor Alpha (TNF- $\alpha$ ); Interleukin-1  $\beta$  (IL-1 $\beta$ ); Body Mass Index (BMI); Alcoholic Liver Disease (ALD); Chronic Liver Disease (CLD); Primary Biliary Cirrhosis (PBC); Hepatitis C Virus (HCV); End Stage Renal Disease (ESRD); Chronic Kidney Disease (CKD); Stress Urinary Incontinence (SUI); Transoburator Suburethral Tape (TOT); Recurrent UTIs (rUTIs); Sexually Transmitted Diseases (STDs); Central Nervous System (CNS); Peripheral Nervous System (PNS); Antimicrobial Resistance (AMR)

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