



Aetiology of urinary tract infection: A review

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Abstract

Urinary tract infection is one of the common conditions all over the world, in this review the most important infections of urinary tract infection, as many people suffer from this infection continuously.

One of the most important causes of infection are fungal, viral and bacterial pathogens, including *Escherichia coli* bacteria, coliforms and enterococci, common bacterial causes of UTIs, which are present in numbers.

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1. Introduction

It is well-known that the short urethra of females spreads bacteria into the bladder to obstruct evacuation of urine. The bacteria also have lesser distance to cover to achieve the bladder than in men. Also, the urethra of the female lays in close proximity to the large intestine, hence accounting for bacterial presence. Pregnancy is an additional risk factor for urinary stasis and reflux of urine into the upper urinary tract. The purpose of the present review is to report on the role of *Enterococcus* species in ascending UTI and to also highlight some unique factors of Group B streptococci, which may account for its characteristic ascendant. (Czajkowski *et al.* 2021) ^[9] (Cai, 2021) ^[6].

Urinary tract infection (UTI) is a common infection encountered globally with a high rate of prevalence. Women are more prone to UTI than men because the female urethra is shorter and closer to the anus, putting women at risk. Menopausal changes in the vaginal epithelium make them susceptible to UTI. Urinary tract infections (UTIs) impact significantly upon individual patients and health services, generating a large workload for general practitioners and placing an extremely heavy burden on antibiotic drugs. The diagnosis of UTI is relatively easy and available; however, confounding patients consume much of our time and accounts for much of the cost in the management of these patients. Recurrent infection is a common problem in women. Within six months of an initial infection, one-third of the women will experience recurring acute postcoital infection. UTI forms an intrinsic part of gynecology and is a big concern during pregnancy. The causative organism for UTI belongs predominantly to both the gastrointestinal and vaginal flora such as *E. coli*, *Klebsiella* sp, *Proteus* sp, *Enterococcus* sp, and Group B streptococci. (Hegazy 2021) ^[16] (Ali *et al.* 2020) ^[1].

2. Anatomy and Physiology of the Urinary Tract

The kidneys are responsible for producing urine after filtering blood to exclude macromolecules and cells from capillary structures within the nephron of the kidney. Approximately 170 L of plasma is filtered daily in the human being, of which a variable percentage is reabsorbed by the body along the length of the tubule system.

Because the length of the nephron undulates as it travels into and out of the renal cortex, the excretory tubule is of variable length: from proximal tubule through the loop of Henle, distal tubule, connecting tubule, and collecting duct. Mitochondria within the tubular cells provide the energy for this transport, allowing for the control of Na⁺, K⁺, H⁺, and other electrolytes by a series of flow and voltage-driven ion channels. Osmotically driven water channels lie alongside these ion channels, and the urine produced by the collecting ducts is typically iso-osmotic to blood plasma, e.g., 300-600 mosmol/kg. Upon entering the bladder, urine can be either stored until appropriate or released via the urethra; these processes require normal contraction or relaxation of the detrusor muscle. However, control of the process may be disrupted by some agents, such as the toxins produced by *E. coli* during urinary tract infection. (Zhang & Mahler, 2021)^[54] (Cusumano *et al.* 2021)^[8].

An understanding of the anatomy and physiology of the human urinary tract is helpful in order to appreciate the way in which *Escherichia coli* and other pathogens colonize susceptible subsets of this structure and invade tissues, leading to infection of the host. Human urine is normally sterile because the urethra resides anterior to the external sphincter and because the urinary tract has numerous natural defenses that prevent infections. The production of urine, which depends upon the continued functioning nephron structure of the kidneys, serves the homeostatic role of balancing electrolytes within the body. Throughout life, humans excrete the solutes in urine necessary to maintain electrolyte balance. Furthermore, the kidneys balance the body's internal environment by regulating the pH and osmolality of the blood. (Munoz *et al.* 2022)^[31] (Neugent *et al.* 2020)^[33].

3. Epidemiology of Urinary Tract Infections

Financial implications are further increased in hospital patients. It is the most common nosocomial infection, accounting for up to 40% of infections in hospitalized patients. One large European ICU study found the absolute risk of developing bacteriuria in a group of 502 patients was 0.95 on day 1 and increased to 8.45 on day 10. This financial burden is further increased due to the increasing (mostly non-susceptible) organisms, such as Extended-Spectrum Beta-Lactamase (ESBL) producing Enterobacteriaceae. Therefore, there is a need to optimize therapy to reduce the emergence of resistant organisms while still assuring the cure of infection and relief from symptoms in patients. (Diaz *et al.* 2022)^[13] (Nouri *et al.* 2020)^[36].

Urinary tract infections (UTI) are one of the most common infections in the general population as well as in hospital patients. The incidence varies from 0.7 to more than 20 episodes per 1,000 person-years in young men. The incidence is higher in young women with a range of 23-108 episodes per 1,000 person-years. Risks in elderly men and women are similar at about 36 infections per 1,000 person-years. In Europe, lower tract infections account for a great number of primary care visits (roughly 8.6%), with cystitis occurring in 5% of women below age 65 and 14% of women above 65 years of age, respectively. (Rosenthal *et al.* 2021)^[40] (Merali, 2021)^[29].

4. Microorganisms Involved in UTIs

Treatment for a symptomatic urinary tract infection should be considered only for patients with clear clinical symptoms.

(Wagenlehner *et al.* 2020)^[48].

Infection begins with colonization of the periurethral area by bacteria originating from the rectum. The microbes ascend the urethra, adhere to the urothelial cells via pili and fimbriae, and multiply. Virulence factors of the microorganisms and host defense mechanisms are critical to the establishment of an active infection. If the urinary tract infection is not treated with specific antimicrobial therapy, it can produce serious complications, including progression to acute pyelonephritis, irreversible kidney damage, renal abscess formation, sepsis, shock, and death. (Neugent *et al.* 2020)^[33] (Stepanova, 2022)^[44].

Bacteria are among the most common microorganisms causing UTIs, particularly in compromised patients, but other infectious agents such as mycobacteria, yeasts, algae, and viruses are capable of causing these infections as well. Middle-aged women have an important risk of urinary infections, lowering the risk after menopause since the estrogen level decreases during menopause, the mucosal changes outcome and decrease the risk of UTIs. (Amin *et al.* 2020)^[2] (Bitew *et al.*, 2022)^[4].

In general, UTI is a severe problem, as many organisms have the ability to colonize or infect different structures of the urinary tract. In normal conditions, the urinary tract is free of microorganisms; however, the urethra is frequently colonized by different microorganisms without producing signs of infection. Infection, when it occurs, is normally the result of the invasion by bacterial contamination coming from the gastrointestinal or urogenital tract. (Meštrović *et al.* 2020)^[30] (Lewis & Gilbert, 2020)^[26].

Urinary tract infections are amongst the most frequent infectious diseases of humans and equally affect community dwellers or hospitalized patients. Females of all ages are at greater risk of acquiring infections, as the female urethra is shorter than the male one, and the distance from the urethral opening to the anus is shorter, making fecal contamination reach the urethral opening more easily. Overall, age and female gender are definitely major predisposing factors, and the incidence of UTI increases from adolescence to menopause. (Kaur & Kaur, 2021)^[23] (Huang *et al.*, 2022)^[17].

4.1. Bacterial Pathogens

It is very important to perform the dry-dim of the catheter, tubing, and the collection bag. It is proven that the infection usually develops when microorganisms are present in the bag and drain tube, and they move from one to the other during drainage. Around 5% of catheterized men and 22% of catheterized women have a history of microbiologically confirmed urinary infection. The frequency of infection occurrence is a result of catheter maintenance during the time of application. The daily occurrence is 1-3% for sterile catheters. For clean-gate catheters, it is 1.7% and 1.9%, and for small, lifetime-used catheters, it is 16% and 0.8%. The short-term catheter, which is wider than the long-term catheter and is worn for a period longer than 28 days, prevents infection development. With the insertion of the prophylactic cemented catheter, the infection is also held back. It is necessary to point out the significance of the insertion technique and the hygienic procedure of self-catheterization in the early period. (Ndomba *et al.* 2022)^[32] (Gunardi *et al.* 2021)^[14] (Karthikeya *et al.* 2022)^[22].

The most common pathogen is *Escherichia coli*. Studies have shown that *E. coli* is responsible for about 85 to 90% of urinary infections. Other bacteria are responsible for the

infection, such as *Haemophilus influenzae* b, *Staphylococcus saprophyticus*, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Streptococcus faecalis*. *S. saprophyticus* and *H. influenzae* b cause an infection only in the case of young girls in the age group of 0-10 years, during their prepubertal period. *Ureaplasma urealyticum* and *Chlamydia trachomatis* are responsible for the infection in men, especially in cases of sexual activity. Chlamydial infection is common among users of diaphragms for contraception. *Enterobacter agglomerans*, *Proteus mirabilis*, *Acinetobacter calcoaceticus*, *Burkholderia cepacia*, and *Flavimonas oryzihabitans* are responsible for infectious complications in patients with urinary polytraumas. Infections are mostly recorded in patients who have a urinary tract with two ends. The development also depends on the time of immobilization. Applied prophylaxis for infection development does not give positive results. Studies confirm that there is a dominant role of bacterial skin flora and endogenous bacterial contamination of the urinary tract. In the category of more common exogenous factors, there are catheterizations, in which the number of microorganisms from the skin grows, and they contaminate the lower urethras and the bladder. Further factors for the development of catheter-associated infection are local catheter design and materials, and the duration of the used catheter. Other factors that reduce bacterial colonization resistance in urine are the use of corticosteroids, and inulin-inducing diuretics which increase the volume of diuresis, atonic that affect the evacuation of urine and reduce the muscular tone of the urinary bladder, and incontinence which reduces normal urination. (Lin *et al.* 2021) [28] (Dadi *et al.* 2020) [10] (Iqbal *et al.* 2021) [19].

4.2. Viral Pathogens

Viral infection alone may not be entirely responsible for the pathology observed in this infection, but the symptoms mimic bacterial cystitis so closely that treatment with antibiotics may be instigated. Cytomegalovirus has been found in catheterized urine from elderly subjects with acute confusion. The presence of such a virus in urine is significant because this urine is often handled by healthcare workers unaware of its unique infective potential. The resemblance of viral symptoms to urinary tract infection also has a bearing on the importance of specimen collection and bacteriological diagnosis of suspected infection of any etiology. Careful consideration of the mode of viral collection is essential. Swabs of the conjunctiva, the nasopharynx, and swabs of urine preserved in viral media; all to be tested for virus by specific culture, can provide diagnostic information and avoid unnecessary courses of antibiotics. (Leber, 2024) [25] (Saad *et al.* 2020) [41].

Currently reported viruses isolated from urine to date include Herpes Simplex Virus (HSV) 1 and 2, polyomavirus (BK and JC), Cytomegalovirus, adenovirus, and coxsackie virus. The ubiquitous nature of viruses has complicated studies into their presence in urine from patients with urinary tract infection (UTI) as controls not suffering from UTI may still excrete viral particles in urine. Also, the range of uncontaminated specimens that are found in routine urines and processed for viral cultures is limited, often to small numbers. Children appear to be susceptible to viral-associated UTI. Preschool children are more susceptible to renal infection with concomitant risk of long-term sequelae. Descriptions of virally-associated UTI are often case studies presented in journals with a pediatric interest. The clinical syndrome

presented by virally-associated UTI in preschool children is known as bacterial cystitis syndrome. (Park *et al.*, 2021) [39] (Jung *et al.* 2022) [21].

4.3. Fungal Pathogens

The frequent isolation of yeasts from various abiotic substrates implies that new knowledge regarding the genotypic, phenotypic and ecological characteristics of yeasts is needed so as to understand the distribution mechanisms of yeasts from various abiotic substrates excreted from human body surfaces. Among these, *Candida* spp. are considered to be the most frequent agents of infection and the frequency of its isolation has increased in recent years. Their principal condition is to find the niche or another site where they can become established. Various transition forms among pathogenic strains exist. Infections with these organisms may involve two types of transition form, the formation of true iron-involved ferments, which are able to modify the pH, and the production of adhesins. The basic adherence mechanism is the production of specific amylolytic fimbriae on the cell wall. These structures provide a specific recognition mechanism among different fimbriated strains. (Odabasi & Mert, 2020) [37] (Dias, 2020) [12].

Fungal infections are usually confined to immunocompromised patients, who may suffer from systemic candidiasis and also from genital and urinary infections. However, there is increasing awareness of the need to study the role of yeast among the causes of bacteriuria among elderly people, particularly among those requiring long-term care. Dimorphic pathogenic fungi are common environmental contaminants and may survive for long periods in untreated water supplies. Although commonly considered to be harmless commensal organisms, yeasts may emerge as an ever more serious problem in health care. Resistance to antimycotic agents increases as a consequence of subinhibitory exposure and two families of organisms in particular, *Candida* spp. and *Cryptococcus neoformans*, readily acquire resistance to conventional drugs. (Sabino *et al.*, 2020) [42] (Hata *et al.* 2020) [15].

5. Risk Factors for UTIs

Urinary tract infections are caused by a variety of organisms, predominantly strains of the *Escherichia coli* group, but fungi, viruses, herpes simplex, and indeed several other organisms, namely *Klebsiella*, *Pseudomonas*, or *Proteus* group and *Streptococci* may cause the disease. On the other hand, certain strains of *Lactobacillus acidophilus* generally suppress the multiplication and perhaps settlement of several infecting *E. coli* group. The etiological agents of UTI are located in the perineum or rectum, which are influential in the magnitude of the infection and point to the necessity of the constitution of several predisposing factors. Such factors may be a structural or functional abnormality within the urinary tract or systemic factors such as immunosuppression or the administration of certain antimicrobials or cytotoxic drugs. These factors affect any part of the urinary system so that clinical syndromes of UTIs are detailed under several anatomical headings: pyelonephritis, renal abscess, renal carbuncle, renal papillary necrosis, renal and ureteral obstruction, urethritis and cystitis, urethral diverticulum, urethral stricture, urethrovaginal and urethrocystovaginal fistulae, hydronephrosis, cystitis due to bacterial prostatitis, and urinary tract infection during pregnancy and labor. The incidence of UTI related to the use of indwelling catheters is

emphasized frequently. (Yılmaz and Aslantaş2020) ^[52] (Kim *et al.*, 2022) ^[24] (Nielsen *et al.* 2021) ^[34].

Urinary tract infection (UTI) is a common bacterial infection in humans and can occur in any part of the urinary system, from the kidneys to the bladder through the urethra. Usually, UTI is classified according to site and causal organisms. A bladder infection is called cystitis. With such a definition, over ten million physician's service contacts are made each year in both Europe and America for this element of morbidity. However, no exact incidence of the disease can be estimated as all UTIs are not reported and only limited information is available from any survey. In the UK, it is the commonest bacterial infection of all, with over fifty percent of all women having at least one bout of UTI; in at least twenty-five percent, it is a recurrent problem. It is more common in females, since the normal urethra is anatomically and physiologically adapted in such a way to prevent the diseases, but the urethra of the male does not possess such protective mechanisms. The disease, usually ascending in nature, causes cystitis, pyelonephritis, which may be acute or chronic, and, albeit rarely, general infection. (Shallcross *et al.* 2020) ^[43] (Czajkowski *et al.* 2021) ^[9] (Tullus & Shaikh, 2020) ^[45].

5.1. Anatomical Factors

In light of the noticeable increase in infections after parturition, conspicuous in comparison to cows which were not pregnant, waiting for calving to commence at pasture is not delaying the rise in infection incidence in all cases. After calving, there is a pronounced distribution of infection's etiological agents which, though not linked to infectious spread between the cows, is closely bound to the hormonal system. The cow itself is the cause of the more than fivefold increased risk of introducing gland infection into the mammary gland directly following parturition. Induction of quarter inflammation through administration of a *Streptococcus* strain which is unable to multiply leads to an increase in the amount of the pathogen isolated. (Verdon & Tilbrook, 2021) ^[46] (Nitz *et al.* 2021) ^[35].

It has been estimated that one to three percent of all children suffer from repeat urinary tract infections, with a slight dominance among girls aged between the ages of six months and five years. This may give rise to scarring and kidney failure. Today, we understand the causes behind excess urine discharge in connection with stress and protracted diseases, which may give rise to difficult voiding. In addition to this, we understand that mammary gland hypoplasia and very high prolactin levels play a significant role in the etiology of both the development and progression of mammary gland inflammation symptoms. Raised levels of estrogen furthermore lead to an imbalance in the host mucous properties. (Yang *et al.* 2021) ^[50] (Boon *et al.* 2021) ^[5].

5.2. Behavioral Factors

These two adhesion patterns are due to the most virulent serotypes. These unique strains are usually responsible for simpler upper urinary infections. The internalization of *E. coli* in the vesicular cells is another important motif for the development of urinary infections. Persistence plays a role in the severity and recurrence of *E. coli* strains of urinary infections. Finally, *E. coli* has three storage mechanisms where *E. coli* can reproduce. The urinary system itself can cause an upward infection in the urinary tract. The physical and chemical changes of urine help transport and reproduce

pathogens. Hormones are important factors in female lower and lower urinary infections. The activities of bacterial and environmental bacteria are favored by the following reproductive hormone levels: low estrogen levels, contraceptive hormones, and estrogen levels in testosterone, dihydroepiandrosterone sulfate, female congenital hypothyroidism, sterile women, pregnancy, and surgery. Furthermore, urinary damage after the operation serves as a prerequisite for infection. Finally, female patients or patients who have undergone surgical treatment are more likely to be hospitalized with urinary infections. (Pang *et al.* 2022) ^[38] (Zhou *et al.* 2023) ^[55] (Dauros-Singorenko *et al.* 2020) ^[11].

Urinary tract infections caused by *E. coli* are the most common hospital- or community-acquired renal infections. When this microorganism emerges in large UTI outbreaks, the direction of the upward infection in the urinary tract is stronger, especially in hospital conditions. Uropathogenic *E. coli* strains have been cloned with different mechanisms. Two genes, group 1 and group 2, in *E. coli* adhesion play a role in this adhesion. They act on adhesin Dr and P pili. Dr and fimbrial pili are folded after binding to digalactoside units of N, N'-biscarbosimedo lisoma in R1. The former, in particular, are linked to the construction of a large number of determined *E. coli* strains. Small proteins, Omp and Lps, are also responsible for the adhesion of *E. coli*. (Whelan *et al.*, 2023) ^[49] (Yousefipour *et al.*2023) ^[53].

5.3. Medical Conditions

(v) Patients with urinary tract obstruction caused by tumors or stones can cause local tissue congestion, ureteral ischemia, glomerular perfusion reduction, and increased permeability of the glomerulae, making it easy to facilitate bacterial growth and proliferation in the surrounding environment and leading to the development of infection. In addition, menopause, genital and urinary tract biological environment changes, and its physiological and physiological function are reduced, mainly in the decrease in the immune function of the genital and urinary tract, the reduction of estrogen secretion or the postmenopausal obstruction-free bacteria (*E. coli* and enterococci), and passive spread to the urinary tract. (Yang *et al.* 2022) ^[51] (Vestby *et al.*, 2020) ^[47].

(iv) Men with benign prostatic hyperplasia can cause urinary tract obstruction, prostatitis, urethritis, and secondary urinary tract infections. The self-sufficiency cavity, the pathogen enters the reproductive tract, and spreads to the bladder, and then enters the upper urinary tract to become infected by local spread of the urinary bladder. (Choi & Min, 2021) ^[7].

(iii) Pregnant women have mechanical changes in the urinary tract caused by the gradual relaxation of the muscles of the uterus. The pressure of the uterus on the bladder and urethral dilatation, the anterior sagging of the uterus causes the posterior displacement of the bladder base, and the position of the pregnant woman leads to the occurrence of urinary stasis, while the decrease in the secretion of antibacterial substances in the urinary tract, antipeptidases, Na, e, inhibits metabolic factors and enhances the adhesion of bacteria, increasing the risk of urinary tract infections. (Johnson *et al.* 2021) ^[20].

(ii) Elderly with more frequent genitourinary tract dilation, detrusor muscle trabecular atony, urinary incontinence incompetence, often incontinence, unable to promptly remove residual urine and so on, causing residual urine pool. The elderly cystometry often shows bladder pressure straight and flat with sharp waves and decreased voiding obstruction

force, resulting in incomplete emptying of urine, which is easy to clear the foreign bacteria leading to the occurrence of urinary tract infection. It is also related to the loss of estrogen in postmenopausal women and chronic diseases. (Ioannou *et al.* 2020) ^[18].

(i) Female children have a short and widely open urinary tract and rectum, making it easier for bacteria to migrate into the child's urinary tract from other contamination sites. (Barola *et al.*, 2024) ^[3].

6. Conclusion and Future Directions

After invasion of the renal parenchyma by UPEC, the infiltrated polymorphonuclear leukocytes cause tissue damage. Moreover, the overexpressed pro-inflammatory genes recruit more leukocytes to bypass the expression of anti-inflammatory genes, exacerbating the acute injury. Meanwhile, the UPEC can also impact cellular autophagy, apoptosis, and cytokines of renal cells to affect the immune system as survival strategies. Taken together, understanding the mechanisms of bacterial and host pathogenesis in the pathogenesis of UTI may lead to the identification of potential therapeutic targets through reducing damage caused by bacterial activities and inflammatory invasion. More studies are required to analyze which regulators are necessary at each phase of response to UPEC in order to cure UTI and pyelonephritis.

Urinary tract infection (UTI) is a common bacterial disease suffered by people. Uropathogenic *Escherichia coli* (UPEC) has been reported to be the most prevalent pathogen, although the etiology of UTI is not fully understood. In this review, we summarized the known mechanisms and the roles of UPEC and host factors that contribute to the pathogenesis of UTI. Acute cystitis is associated with epithelial damage and inflammatory host immune response to protect the host against UPEC. However, recurrent cystitis results in severe symptoms and persistent bacteriuria, which are related to the formation of quiescent intracellular reservoirs—a newly discovered UPEC survival mechanism—and the abnormal host immune response. Another severe consequence of UTI is pyelonephritis. Local host defense and the dysregulated immune response generally induce renal cortical abscess formation.

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