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Epidemiology, pathophysiology, diagnosis and treatment of urinary tract infections caused by bacteria

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Abstract
Urinary tract infections (UTIs) are among the most frequent diseases in hospital and outpatient clinical practice and can affect patients of all ages. UTIs can be of bacterial, fungal or parasitic origin, with bacteria being responsible for around 90% of cases. UTIs are caused in most cases by *E. coli*, a microorganism naturally present at the large intestine and perianal region. The diagnosis of UTIs is based on the patient's clinical picture, symptoms and laboratory diagnosis with urine samples. This paper briefly reviews the pathophysiology, diagnosis and treatment of UTIs, considering the most recent literature.

Keywords: Urinary tract infections, antimicrobials, *Escherichia coli*, epidemiology

Introduction
Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, affecting millions of people annually. It has a higher incidence in children, women sexually active women, pregnant or menopausal, and elderly and hospitalized patients. The main pathogenic bacterial species include *Escherichia coli*, *Klebsiella sp.*, *Enterococcus sp.* and *Acinetobacter baummanii.* The main clinical symptoms are polyuria, dysuria, back pain, urinary urgency, fever, changes in color and odor of urine. UTI is one of the most common infections requiring hospitalization and an important cause of sepsis, with a mortality rate ranging from 10% to 30% [1-3].
UTI is one of the most frequent diseases in outpatient clinical practice, as well as in hospitals. It is a common disease that can affect patients of all ages but has a higher incidence among women (pregnant or not), elderly, diabetic, and coronary artery disease patients. The disease can lead to severe complications that cause functional impairment if not treated properly UTIs can be of bacterial, fungal or parasitic origin, with bacteria being responsible for at least 90% of infections. *E. coli*, which belongs to the enterobacteria family, is the most detected species (prevalence ranging from 70% to 85%), followed by *Proteus*, *Klebsiella*, and *Enterococcus* [4-6].
Fungi have a decreased prevalence when compared to bacteria, the *Candida* family is the most relevant species, with *Candida albicans* as the most relevant fungus in UTIs that gets the name candiduria, being associated with individuals who have undergone recent surgery or are immunosuppressed [7, 8].

Epidemiology of UTIS
UTIs have an increased number of cases in men who practice anal sex without protection, diabetic patients, women (pregnant or not), children up to 2 years old, elderly and HIV positive patients, individuals with renal abnormalities and/or transplanted. These patients are more vulnerable to the disease, whilst the risk for males is lower. Children under 2 years of age present a high risk because they use diapers, have occlusive foreskin, and may have congenital malformations. In this sense, women are also more likely to have the disease because they have a shorter and closer to the anus urethra, what increases the risk of developing the disease at least once in life [9-11].
The predominance of UTI in pregnant women is around 20%, affecting mostly during the first trimester of pregnancy. Among the diseases that affect pregnant women, UTIs are the third most recurrent, being responsible for complications during the prenatal period, such as hypertension, chorioamnionitis and endometritis.

During pregnancy, due to changes in the body's physiology, such as mechanical and hormonal factors, changes related to the female urinary tract may occur, making them more susceptible to infections, which can present bacteriuria, cystitis, and pyelonephritis, or even be asymptomatic [12, 13].

Elderly patients are at risk of contracting infections for several reasons, some of them being the use of bladder catheter, prostate enlargement, use of diapers and physiological changes related to the increase of age, which may cause a decrease in functional capacity resulting in an increase of chronic and/or debilitating dysfunctions. In this sense, urinary tract infection represents a major problem for the elderly, regardless of whether they inhabit the community, hospitals or long-stay institutions. With aging, especially after 55 years of age, the chance of recurrence of urinary tract infection in women rises. The prevalence of recurrent UTIs in females older than 60 years represents about 10%, which is due to the fact that there is a lower production of estrogen at the end of reproductive life and the increased prevalence of urinary incontinence [14, 15].

Male individuals who practice anal sex without protection have a high risk of UTIs, due to exposition to the anus and contact with *E. coli* and other species related to the disease. Men from 2 years old to old age present a decreased risk of developing UTIs due to the larger urethra compared to women. This anatomical difference is useful to prevent UTIs [16-18].

Pathophysiology

Contamination of the periurethral space by an intestinal Ur pathogen is considered the initial step of the pathophysiology of the disease, followed by colonization of the urethra and bladder. Elegant studies illuminating the colonization stages have elucidated the role of pili and flagella in the successful spread of uropathogens during UTIs development, as for *Acinetobacter* and *E. coli* [19, 54]. UTIs are mostly caused by *E. coli*, and women are more predisposed to colonization of the vaginal and urethral vestibule, what may cause elevation of this uropathogen to the bladder and/or kidneys. *Klebsiella pneumoniae, Proteus mirabilis, Enterobacter, Staphylococcus saprophyticus*, *Staphylococcus aureus* and *Streptococcus agalactiae* are also associated to UTIs [12, 19, 54].

The bacterial etiological agents that cause UTIs found in hospitalized patients are diverse, with a predominance of Enterobacteriaceae, but lower detection of *E. coli*, which is the most common pathogen that leads UTIs to cystitis. It has the ability to evade host immunity and develop resistance to the most common antimicrobials. During the infection process, positive selection on the two-domain FimH type 1 pilus adhesin increases the fitness for UTI. Bacterial pathogens adhere and establish fulcrums in favorable habitats within their host. Adhesion often confers fitness advantages for bacterial pathogens by promoting access to essential nutrients, resistance to displacement by fluid flow, or evasion of responses [21-23].

Bacterial pathogens have evolved in various ways to achieve specific or nonspecific adhesion through extracellular structures that include capsules, extracellular polymeric substances, pili/ fimbriae, flagella, and other various adhesins. Many of these adhesive virulence mechanisms figure prominently in bladder colonization by uropathogenic *E. coli* (UPEC), which are responsible for approximately 85% of all UTIs [24, 25]. Mouse models showed that adhesive hair-like surface appendages called pili type 1 allow UPEC to colonize the bladder epithelium during UTIs by binding to dansylated receptors on the urothelial surface via the adhesin FimH. Clinical observations and mouse UTI models have shown that FimH mediates the invasion of UPEC into bladder surface umbrella cells via endocytosis. Escape from the endocytic vesicle allows UPEC to replicate within the cytosol to form intracellular bacterial communities (IBCs), which is a mechanism used by UPEC to subvert neutrophil attack, thus facilitating survival and dissemination during UTI [26-28].

FimH evolved within human Ur pathogenic strains of *E. coli* by positive selection. FimH is composed of an N-terminal lectin domain (FimHLD) that binds to mannose through a pocket formed by three loops, a C-terminal pilin domain (FimHPD) that non-covalently binds FimH to the pilus tip, and a five amino acid ligand that connects the two domains. Three positively selected residues, which lie outside the mannose binding pocket, have been shown to modulate conformational changes in FimH. Crystal structures of FimH at various stages of pilus assembly revealed that FimHPDexists in one conformation, but FimHLD has at least two conformational states that show distinct affinities for mannose [29-31].

Diagnosis

The diagnosis of UTIs is based on the patient's clinical picture, being the laboratory diagnosis more precise, and also in some cases the imaging exams corroborate for the evaluation of the urinary tract status. The atypical presentation of the infection represents one of the causes of delays in diagnosis, since characteristic symptoms such as dysuria, frequency and tenderness at the costovertebral angle, are routinely found in patients with a late diagnosis of UTIs. One of the risk factors associated with the absence of urinary tract symptoms and signs in patients with UTIs is advanced age. The diagnosis of UTIs should also be laboratory-based, with the request for sedimentation and normal and abnormal elements. Urine culture is a more objective test, which is usually requested after confirmation of a clinical picture compatible with UTIs, and laboratory tests such as blood count also contribute to identify asymptomatic bacteriuria [32-35].

Bacterial urinary tract infection is established if the individual has symptoms such as fever or chills, indications of cystitis such as dysuria, polyuria, urgency, suprapubic pain, or lower abdominal tenderness on physical examination, or any indications of pyelonephritis such as flank pain, back pain, or tenderness at the costovertebral angle; if a bacterium was isolated in more than one urine and blood culture, and there were no other sources of infection; and the pathogen was present in ≥ 100,000 CFU/mL of urine. UTIs in patients presenting with indwelling catheter, neurogenic bladder, obstructive uropathy, or urinary retention due to benign prostatic hypertrophy was defined as complicated bacteremic UTIs [36-38].

The UTIs is usually accompanied by inflammation, and increased number of red and white blood cells (RBC/WBC), and bacteria in the urine. Besides UTIs, urinary WBC can also come from the female genital tract, while some patients with low immunity may have normal urinary WBCs, and bacteria can also come from contamination of specimens with periurethral, epidermal, perianal and vaginal flora, so the clinical diagnosis of UTI still depends mainly on quantitative culture of bacteria in urine. In addition, the discovery of the female urinary microbiota makes the paradigm of sterile urine no longer valid. Unfortunately, culture-dependent techniques are limited as most of bacteria cannot be cultured using

standard laboratory techniques. Thus, UTIs are confirmed using the results of routine urinalysis [40-42].

Treatment

Women with symptoms of uncomplicated urinary tract infection (UTI) are commonly treated with empirical antimicrobials, resulting in overuse, which promotes antimicrobial resistance. The available diagnostic tools are not cost-effective or optimal for diagnosis. Most guidelines for uncomplicated UTI recommend treatment with empirical antimicrobials. However, when urine is analyzed, only one in three women with UTI symptoms has a culture on average. Therefore, prescribing empirically may result in overuse of antibiotics and contribute to the development of antimicrobial resistance. Exploratory approaches to aid UTI diagnosis have been based on serum and urinary biomarkers. The specificity of blood immunological markers is limited by the possibility of cross-reactivity due to other infections or inflammatory responses. Urinary biomarkers that may reflect local immune responses by the bladder epithelium include nerve growth factor, chemokines including IL-8/CXCL8 and antimicrobial peptides, human α-defensin, and lipocalin-associated neutrophil gelatinase [43-46].

For the treatment of UTI, different antimicrobials can be used orally, such as cephalosporins, which prevent cell wall synthesis by blocking peptidoglycan transpeptidation and subsequently activate autolytic enzymes in the cell wall leading to pathogen death. Uncomplicated lower urinary tract infection should be treated with sulfamethoxazole-trimethoprim, ampicillin, or cephalexin as a single dose or over three days without further risk, with the exception of sulfonamides which need to be avoided because of the danger of causing Kernicterus. Fluoroquinolones can affect the cartilage development of the fetus, so they should be avoided. A major challenge for therapy is the increase in antimicrobial resistance [47-49].

Empirical antibiotic therapy should be started soon after adequate urine culture collection, since its result takes 1 to 5 days. For the treatment of urinary infection caused by *E. coli* in patients who do not have immunodeficiencies, anatomical alterations, or aggravating factors, nitrofurantoin monohydrate is used twice daily for 5-7 days because of minimal induction of resistance and few side effects. The phosphamide trometamol should be used as a single dose for minimal induction of resistance and few side effects, but this appears to have less effectiveness compared to nitrofurantoin monohydrate, fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin, which are highly effective if used for three days. *E. coli* is the major cause of UTIs in pregnant women, and the most commonly used antibiotics for treating these are ampicillin and cefazolin. Currently, β-lactams such as amoxicillin, cefaclor, and cephalexin, have a lower efficacy associated with a higher frequency of adverse effects. In Brazil, the current resistance of *E. coli* is estimated at 45.4%, which makes it unfeasible to use in the treatment of cystitis [50-53].

Conclusion

UTI is one of the most prevalent bacterial infections worldwide and its incidence is increased in women due to the morphology of the urinary system. Considering the classical presentation, the clinical diagnosis is the most widely used, but less assertive than the laboratory evidence, which is more costly and requires more time to complete. Cases of atypical presentation are not rare, which also makes early diagnosis more difficult. Due to the impact of this disease on national and international public health, it is relevant to carry out new research exploring UTIs management and preventive alternatives, such as vaccines. Furthermore, antimicrobial resistance remains as a critical problem, which should be addressed by health education and regulatory measures.

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