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Fosfomycin in the Clinical Practice of Urinary Tract Infection

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Abstract

General Background: Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, affecting millions of individuals and occurring more frequently in women due to anatomical factors. **Specific Background:** The increasing prevalence of antimicrobial resistance among uropathogens, particularly *Escherichia coli*, has complicated conventional treatment approaches and renewed interest in alternative therapeutic agents. **Knowledge Gap:** Although fosfomycin has gained attention as a treatment option for UTIs, a comprehensive overview of its clinical applications, safety profile, and use in special populations remains important. **Aims:** This study reviews the role of fosfomycin in the clinical management of UTIs, including its mechanism of action, therapeutic applications, adverse effects, contraindications, and use in pregnant women and pediatric patients. **Results:** Fosfomycin exhibits broad-spectrum bactericidal activity against Gram-positive and Gram-negative bacteria, including multidrug-resistant pathogens, through inhibition of bacterial cell wall synthesis. Clinical evidence indicates that both single-dose and multiple-dose regimens are utilized according to infection severity and patient characteristics. The drug is generally well tolerated, although gastrointestinal disturbances, electrolyte abnormalities, hypersensitivity reactions, and specific contraindications have been reported. Fosfomycin is frequently recommended for UTIs during pregnancy and has demonstrated utility in pediatric patients, particularly in infections caused by resistant organisms. **Novelty:** This review consolidates current evidence regarding fosfomycin use across diverse UTI settings, including resistant infections and special patient populations. **Implications:** Fosfomycin represents a valuable therapeutic option for UTI management in the context of growing antimicrobial resistance and increasing demand for alternative antibacterial therapies.

Highlights:
• Fosfomycin demonstrates activity against Gram-positive, Gram-negative, and multidrug-resistant uropathogens.
• Treatment regimens vary from single-dose administration to repeated dosing based on infection complexity.
• Clinical applications include management of UTIs in pregnant women and pediatric populations.

Keywords: Fosfomycin, Urinary Tract Infection, Antimicrobial Resistance, Pregnancy, Pediatric Patients

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Introduction

Urinary tract infections (UTIs) are among the common bacterial infections, annually impacting nearly 150 million people worldwide [1]. These infections occur due to the existence and multiplication of bacteria in the urinary tract. While primary involved microorganisms are bacteria, however, fungi, viruses, and parasites can also occasionally cause UTIs.The term UTI refers to infections affecting any segment of the urinary tract, including the bladder (cystitis), urethra (urethritis), or kidneys (pyelonephritis) [2].Common pathogens responsible for UTIs include Escherichia coli (E. coli), Proteus mirabilis, Pseudomonas aeruginos ,Streptococcus faecalis,Staphylococcus aureus, and Klebsiella pneumoniae. Other less common causes include Mycobacterium tuberculosis, Actinomycetes, Nocardia, and Candida species [3].

Patients commonly presented with symptoms of a UTI include an persuasive need to urinate, frequent urination, a burning feeling during urination, foul-smelling urine, fever with chills, pain in the lower back or sides (loin pain), nighttime urination (nocturia), and blood in the urine (haematuria). To diagnose a UTI, healthcare providers typically take a detailed patient history and collect amidstream urine sample for analysis if an infection is suspected [4]. Women are significantly more affected by UTIs, with 50% of women experiencing a UTI at least once in their lives, compared to one in 20 men.However, UTIs also occur in babies, children, men, and older adults. It is widely believed that women are prone to UTIs due to the shorter length and positioning of their urethra, though strong evidence supporting this claim is limited [5]. UTIs are common in adult women though certain life stages and medical conditions can increase the risk. These include pregnancy, menopause, post-menopause, diabetes, immunosuppressive conditions, spinal or pelvic injuries, and the use of catheters [5]. Approximately 60% of women experience at least one symptomatic UTI in their lifetime, with around 10% of women in the United States experiencing one or more symptomatic episodes annually. Young, sexually active women aged 18–24 are most at risk, with about 25% experiencing spontaneous symptom resolution and a similar percentage developing infections. In contrast, UTIs are far less common in men, primarily affectingy those with structural abnormalities of the urinary tract or older men [6]. There are different type of UTI, which include uncomplicated, complicated, recurrent, relapse, catheter-associated (CAUTI’s). Uncomplicated UTIs occur in otherwise healthy individuals without any physical or functional abnormalities in their urinary tract. Complicated UTIs are linked to obstructions or blockages in the urinary tract. These may be caused by an distended prostate in men, neuronal disorders, such as, multiple sclerosis, epilepsy, cerebral palsy, and spinal conditions, immune system disorder, bladder or kidney stones, and diabetes. Recurrent UTIs are described as having at least tumors in the bladder or kidneys 2–3 uncomplicated or complicated infections within six-month period or 3 infections per annum. Relapse UTIs refer to infections that recur within 15 days of completing the antibiotic course for the first-time UTI. Catheter-associated UTIs (CAUTIs) occur in individuals with an indwelling urinary or suprapubic catheter or in those who have been catheterized within the last 48 hours [7].

Treatment of Lower UTI

Acute uncomplicated cystitis or urethritis, occurring as a first episode in young, healthy women, is typically managed with a 3-day course of antibiotics. This approach reduces the presence of Gram-negative bacteria in the rectum without increasing the risk of recurrence. Recommended oral antimicrobial options for treating acute uncomplicated cystitis include cotrimoxazole, trimethoprim, nitrofurantoin, and ampicillin. Cotrimoxazole is considered the best initial choice for empirical treatment in non-pregnant women due to its affordability and safety profile.In cases whereresistance to E. coli is low, a 5–7-day course of nitrofurantoin is equally effective.Fosfomycin is a more expensive alternative that can also be used as a first-line empirical treatment. However, fluoroquinolones are not advised for the management of uncomplicated cystitis [8].

Treatment of upper UTI

Acute pyelonephritis is often linked to underlying conditions such as obstructive uropathy or diabetes mellitus, classifying it as a complicated UTI. Patients may present with severe illness or sepsis. Urine and blood cultures are essential before initiating treatment, as they guide adjustments to the therapy once results are available. However, treatment is typically started immediately without waiting for culture reports. For mild cases, recommended medications include ampicillin, ciprofloxacin, cotrimoxazole, amoxicillin-clavulanate (especially for infections caused by Enterobacter), or a cephalosporin. In pregnant women, parenteral cephalosporins and/or extended-spectrum penicillins are the preferred choices. A follow-up urine culture-sensitivity test is advised 15 days after completing therapy [8]. Antimicrobial resistance connoted to the adeptness of bacteria to withstand and proliferate regardless of the presence of the drugs inferred to kill them or reduce their growth. This resistance arises when antimicrobial therapy targets susceptible bacteria,leaving a small fraction of naturally resistant microorganisms to thrive and expand their population under selective pressure [9]. UTIs are one of the commonest community-acquired infections, with fluoroquinolones and co-trimoxazole frequently used as treatments. However, the global rise in drug resistance has prompted increased efforts to explore new treatment options and reassess existing therapies. Alternatives like fosfomycin and nitrofurantoin have gained attention, with fosfomycin now being increasingly prescribed for oral treatment of UTIs in outpatient settings [10,11].

As one of the antibiotics, fosfomycin has a great efficacy in treatment of many bacterial infections. including those caused by organisms resistant to several drugs, because based on how it works differently from other drugs. You can both take it orally and intravenously, and there are both oral and intravenous forms of this drug.By using it the UTls which are very helpful in treating UTIs can be managed. The drug is bactericidal It inhibits these effects which stem from its capacity to prevent the manufacture of peptidoglycan, basic unit of bacterial cell walls. The beginning step in peptidoglycan synthesis is disrupted by fosfomycin, which targets the enzyme MurA. This effectively Strikes a blow at the integrity of the cell wall and causes bacterial cell lysis [12]. This action helps explain its broad-spectrum effectiveness against both Gram-positive and Gram-negative bacteria, including infections that are resistant to other antibiotics, like Enterobacterales that produce

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carbapenemase and ESBL [13]. Furthermore, when taken with different antibiotics, fosfomycin exhibits synergistic effects that enhance the treatment trajectory for severe infections [14]. In clinical In more serious infections, especially in immunocompromised individuals, but primarily used for uncomplicated UTIs. [15]. Its importance in the treatment of UTIs resistant to multiple drugs is growing.more widely recognized. Fosteromycin is administered in single and multiple doses, A dosing based on the features of the patients and the UTI three types. A single oral dose of 3 An example of the dosage that is used in this case describes a woman with an uncomplicated UTI thus grammes has shown similar efficacy to longer courses of antibiotics like cephalexin. For individuals with simple infections, in particular, this one-dose regimen offers a viable therapeutic option [16].

For complicated urinary tract in some infections (UTIs), an approach of multiple-dose fosfomycin may have superior efficacy than a single dose.Normally patients who have failed to respond to earlier treatment or who have multidrug -resistant organisms in their bodies are administered 3 grams every 48 to 72 hours for a total of three doses [17]. In the last study, clinical evidence was seen in 67.3% of cases.remission when one dose was administered every three days for an average of six days [18]. Despite its generally good tolerance, fosfomycin can have some adverse effects, especially when using oral preparations, gastrointestinal issues as nausea, diarrhoea, and abdominal discomfort are frequent[19]. Electrolyte abnormalities, such as hypokalaemia and hypernatraemia, might result with parenteral dosing [20]. Agranulocytosis is an uncommon but severe adverse event characterized by significant reduction of neutrophil doses may be associated with severe infections [20]. Reports after the first dose administration indicated that of immediate hypersensitivity reactions, including anaphylaxis, have also been made; symptoms include hives and hypotension [21]. Jaundice and increased liver Enzyme levels may indicate liver damage due to fosfomycin, but even then, they are rare. withdrawal when the drug is discontinued [22]. Although these potential risks, some Research suggests that fosfomycin may be more effective than its associated harm.for infections resistant to treatment, especially in seriously ill patients [23]. Concerns about the safety and effectiveness of fosfomycin make it contraindicated in a number of clinical settings. Patients who are hypersensitive to fosfomycin or any of its constituents should not use it because allergic responses, which can range from minor rashes to severe anaphylaxis, can happen [24].Additionally, because fosfomycin is primarily eliminated through the kidneys and individuals with severe renal impairment—especially those with a creatinine clearance <10 mL/min— should not take it, as this raises the risk of drug buildup and toxicity [25]. Additionally, aspartame, which is converted to phenylalanine, is present in fosfomycin oral granules. This means that patients with phenylketonuria(PKU), a hereditary condition that affects phenylalanine metabolism and may have negative consequences, should not take fosfomycin [26]. The medication may worsen gastrointestinal symptoms, hence it should be avoided in people with serious gastrointestinal disorders, such as diarrhoea linked to Clostridium difficile [27].Early in development, the foetus is particularly vulnerable and fosfomycin is contraindicated during the first trimester except when the benefit is greater than the risk given its pregnancy classification (FDA B) [28], even though it is generally considered safe during pregnancy [29]. Fosfomycin may increase fluid imbalances,thus dehydration or hypovolemia (severe) are also contraindication [28]. Continuing the use of fosfomycin in children younger than 12 years should be used with caution,because there are limited safety and efficacy data specifically in this age group [29]. Finally, since use of fosfomycin may contribute to renal failure fosinopril should be given with caution in patients who are also receiving nephrotoxic agents (e.g.NSAIDs or aminoglycosides [25]. In general, fosfomycin use should be assessed on a case-by-case basis in patients with renal function and allergy status or underlying conditions.

Special cases treated by fosfomycin

The use in pregnancy

UTIs is one of the common consequences during pregnancy. Between 20-40% of pregnant women demonstrated asymptomatic bacteriuria are likely to progress to pyelonephritis[30]. Due to the anatomical characteristic of a shorter urethra, women exhibit a heightened vulnerability to UTIs [31]. This susceptibility is further exacerbated by the influence of inadequate hygiene practices and urine discharge, which can facilitate the infection course. A systematic review indicated that approximately five percent of pregnant individuals required hospitalization due to a UTI [32]. UTIs associated with pregnancy are a predominant factor contributing to both maternal and neonatal morbidity and mortality. Furthermore, it has been documented that UTI correlates with an elevated risk of preterm birth. Fetal dealth is a possible, with higher incidence of neonates presenting with low birth weight [33]. Anemia, thrombocytopenia, gestational hypertension, transient renal inadequacy, and postpartum endometritis constitute significant risk factors for the development of pyelonephritis among pregnant individuals [34]. UTIs are a frequently observed complication during gestation. Typically, the uropathogen most often isolated in pregnant women is E. coli. In addition to the Enterobacteriaceae family (Klebsiella, Enterobacter, and Proteus), other potential pathogens include Staphylococcus, Staphylococcus, and Enterococcus. Asymptomatic bacteriuria is reported in 2-13% of pregnant individuals, whereas symptomatic infection impacts 1-2% of this population, based on investigations conducted in the USA, Europe, and Australia [35]. Hormonal fluctuations and the effect of mechanical variables during gestation may precipitate UTIs and bacteriuria [36,37]. UTIs are widespread and represent a significant rationale for the prescription of antibiotics [38]. Misuse of antibiotics in outpatient environments may exacerbate the emergence of antibacterial resistance within the broader residents [39]. Fosfomycin has recently attracted considerable attention due to its sustained effectiveness against multidrug-resistant and extremely resistant Gram-positive and Gram-negative bacteria, particularly in light of the rising resistance to these pharmaceutical agents [40]. Fosfomycin is commonly recommended as a first-line treatment for UTIs in pregnant women, particularly in cases of asymptomatic bacteriuria and symptomatic infections[41]. Studies show that a single 3 g oral dose of fosfomycin is highly effective in achieving bacterial eradication. However, it is crucial for patients treated with this antibiotic to undergo follow-up urine cultures to confirm that the infection has been fully cleared. This step is especially important in pregnant women to avoid complications like pyelonephritis[41].

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The use in pediatric

UTI is common childhood bacterial infections [42], 7-8% of females and 2% of males will be infected with UTI before the age of 8 years at least once. Infants UTI mainly of both sexes mainly associated with fever, while cystitis is common in girls older than 3 years [43,44]. Acute pyelonephritis is serious condition in small infants, who are prone to bacteremia and sepsis [45]. E. coli is the causative agent in all age groups [46]. Since the application of conjugated vaccines against S. pneumoniae, E. coli has become the commonest causative agent in infants, and up to 90% occur in children with UTI [47]. In the other hand, Gram-negative bacteria (Klebsiella, Proteus, Enterobacter, and Citrobacter). Gram-positive bacteria like Enterococcus (in infants and children), Staphylococcus saprophyticus (in adolescents), and Staphylococcus aureus (rare)[48-49]. There are many benefits of using fosfomycin to treat children with UTIs. It's simple to administer, highly excreted in urine, gut flora is unaffected by fosfomycin, and side effects are rare [48]. Fosfomycin is primarily used to treat community-acquired lower UTIs in children, particularly those caused by antibiotic-resistant bacteria, such as extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. Its broad-spectrum activity allows it to target a wide range of pathogens, including multidrug-resistant organisms[50-51]. Fosfomycin have safety profile in pediatric patients, although limited research exists on its use in children under 12 years old, necessitating caution in this age group[52]. Due to the lack of standardized dosing guidelines, healthcare providers must determine the appropriate dosage on a case-by-case basis. Clinical studies have shown that fosfomycin can be effective in reducing recurrent UTIs, especially in infants with complex urinary tract abnormalities[53], by lowering the incidence of infections caused by resistant strains. Additionally, research on the pharmacokinetics of fosfomycin in neonates indicates that it reaches sufficient urinary concentrations to combat common uropathogens, but further studies are needed to optimize dosing for this vulnerable population[54].

Conclusion

UTIs is common mainly affecting women because of anatomical and physiological differences. Treating UTIs based on causative microorganisms, mostly E. coli, with pregnancy, diabetes, and catheter use are risk factors. Simple antibiotics course could be enough for most cases with more complex infections requiring more treatments approaches. Antibiotic resistance are challenging the therapy raising the need for fosfomycin particularly for resistant infections, due to its broad-spectrum nature and distinct mode of action. Fosfomycin is safe and effective against bacteria that are resistant to many drugs, it has showed promise in specific populations, including children and pregnant women.

Conflict of Interest

The author declares no conflict of interests.

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