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REVIEW ARTICLE

Fosfomycin: Antimicrobial and Clinical Efficacy Review

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ABSTRACT
The emergence of extensively drug-resistant (XDR) and multidrug-resistant (MDR) pathogens and the dearth of novel medicines that are effective against these bacteria provide two key challenges to the treatment of bacterial diseases. Consequently, physicians in present days have reverted to usingtraditional antibiotics such as aminoglycosides, tetracyclines, and polymyxins. Lately, due to the development of resistance to these agents as well, the broad-spectrum antibacterial agent, Fosfomycin has gained attention. It is a low-molecular-weight, bactericidal, broad-spectrum antibiotic, with activity against Gram-positive and Gram-negative multidrug-resistant bacteria. Fosfomycin, an older drug with well -established safety profile, has experienced a rise in application for various infections, such as chronic bacterial prostatitis (CBP) and chronic pelvic pain syndrome (CPPS). However, despite its broad application, there is a lack of well-designed clinical trials supporting various uses. As a result, there is a need for more robust data to validate its efficacy, optimal dosing, and treatment duration, particularly considering much of the current information comes from public domain sources rather than rigorous scientific research.In this review, we summarize the available susceptibility data on Fosfomycin, focusing on current trends in its clinical use, its pharmacokinetic and pharmacodynamic properties, its activity against susceptible and antibiotic-resistant bacteria, its synergistic effects with other antibiotics, and its overall clinical effectiveness in treating urinary tract infections. The dosing guidelines for Fosfomycin and adverse events caused by this agent are also presented in this review.

Keywords: Fosfomycin, Multidrug-resistant bacteria, Broad-spectrum antibiotic, Urinary tract infection

INTRODUCTION
Before the 20th century, infectious diseases caused significant illness and death globally. Even in industrialized nations, the average life expectancy at birth was around 47 years for both men and women. Diseases like smallpox, cholera, pneumonia, and tuberculosis were rampant during that period.[1] With the discovery of antibiotics in the 1920s, a substantial reduction in morbidity and mortality associated with bacterial infections was noted.[2] Between 1938 and 1952, the United States witnessed a significant decline of 8.2% per year in annual mortality due to infectious disease. This notable decrease was in disease states such a pneumonia, influenza, and tuberculosis.[3]
However, as the use of antibiotics increased, bacterial resistance became more prevalent globally and hence there has been a growing need to create novel antibiotics and instances of reuse of existing antibiotics in medical situations where there are not many sufficient alternatives.
Fosfomycin ($C_3H_7O_4P$) (originally phosphonomycin), is a broad-spectrum antibiotic first found in fermentation broths of *Streptomyces fradiae* (ATCC 21096) in Spain through a collaborative effort of Merck and Spain's Company Española de Penicilina

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de Antibióticos (CEPA) in a joint program.[4]This agent is in an antimicrobial class of its own and is structurally unrelated to other antibacterial agents.[5] It is hydrophilic with negligible serum protein binding, excreted unchanged in urine, and hence achieving high concentrations for a prolonged period.[6] It also has good distribution into other tissues, reaching clinically relevant concentrations in sites such as serum, soft tissue, lungs, bone, cerebrospinal fluid, and heart valves.

Fosfomycin is a molecule with a low molecular weight (MW) (138 g/mol).[7] The molecular structure of Fosfomycin differs with regard to the available drug formulations. The two oral formulations are Fosfomycin tromethamine (or Fosfomycin trometamol) ($C_3H_7O_4P \cdot C_4H_{11}NO_3$) (Fig. 1A) and Fosfomycin calcium ($C_3H_5CaO_4P$) (Fig. 1B). The third formulation is intended for intravenous administration, Fosfomycin disodium ($C_3H_5Na_2O_4P$) (Fig. 1C).

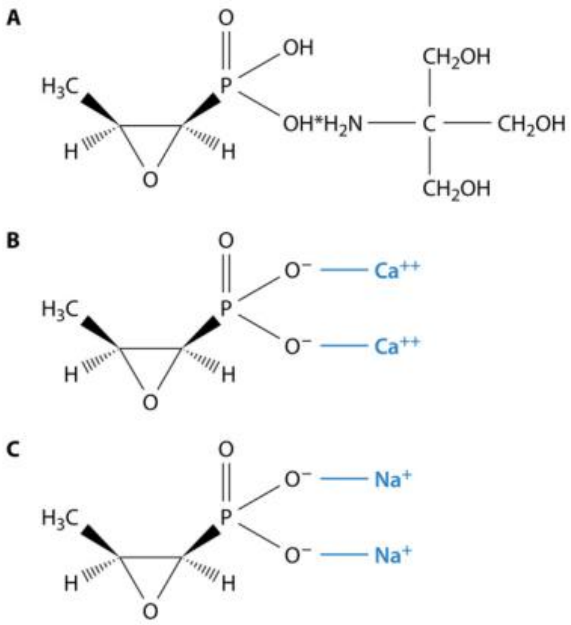

Fig 1 (A) Molecular structure of Fosfomycin trometamol. (B) Molecular structure of Fosfomycin calcium. (C) Molecular structure of Fosfomycin disodium.

For many years, individuals suffering from severe infections, such as meningitis, have been administered parenteral injections of Fosfomycin disodium.[8] More recently, it has been produced in an oral form, Fosfomycin trometamol, which is a monobasic hydrosoluble Fosfomycin salt used specifically in the treatment of UTIs.[9]

In 1996, the United States approved the use of Fosfomycin (marketed under the names Monurol® and Fosfomycin tromethamine) for the single-dose oral treatment of uncomplicated urinary tract infections (uUTI) (acute cystitis) in women caused by *Escherichia coli (E. coli) and Enterococcus faecalis*. With the problem of increasing resistance to other antibiotics, parenteral use of Fosfomycin has also been investigated in the treatment of range of diseases because it has been found effective against many multidrug-resistant (MDR) pathogens.[10]

SYNTHESIS OF FOSFOMYCIN

Natural

Fosfomycin, the only phosphonate antibiotic, has been prescribed for over two decades in countries like the USA, Japan, and Germany to treat urinary tract infections (UTIs).[11]Phosphonates, characterized by the presence of covalent carbon-phosphorus linkages, are a diverse group of organic compounds with fascinating biological characteristics. Despite the discovery of their synthesis in protozoa more than 50 years ago, the full scope and diversity of phosphonate production in nature remain inadequately understood.[12] Biosynthesis involves the rearrangement of phosphoenol pyruvate into phosphono pyruvate, catalyzed by phosphoenol pyruvate mutase.[13]

Fosfomycin is produced by various *Streptomyces* species**, and its purification from broth involves ion-**exchange chromatography, gel filtration, and adsorption chromatography.[4,14-15]

Synthetic

The first chemical synthesis of Fosfomycin, reported in 1969,[16] involved the epoxidation of (Z)-1-propenylphosphonic acid. First, (Z)-1-propenylphosphonic acid was obtained by reducing dibutyl 1-propynylphosphonate to dibutyl (Z)-1-propenylphosphonate. Then, the protecting groups were removed using concentrated hydrochloric acid, resulting in racemic (S)-(Z)-1,2-

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epoxypropylphosphonic acid. The enantiomerically pure Fosfomycin was finally generated using the quinine salt.

Another approach of synthesis involves(Z)-1-propenyl-phosphonate treated with sodium hypochlorite, to form threo-1-chloro-2-hydroxypropylphosphonic acid, resolved with (S)-α-phenylethylamine, and treated with aqueous NaOH to yield Fosfomycin. This process produced (+)-chlorohydrin in an 80% yield. Finally, Fosfomycin (1a) was obtained by treating the chlorohydrin with aqueous NaOH, resulting in an 85–90% yield.[17]

A third method involved the addition of Trimethylsilyl dibenzyl phosphite to (S)-tri isopropyl silyloxyl acetaldehyde, followed by deprotection and ring closure, yielding Fosfomycin with a 76% yield.[18]

Mechanism of Action

The usual mechanism of action of antibiotics, in general involves the important physiological and/or metabolic processes of the microorganism, such as protein, DNA, RNA, cell wall synthesis, and cell membrane organization of the bacterial cell, in order to present their bactericidal or bacteriostatic effects. Fosfomycin inhibits the bacterial cell wall synthesis at an early stage. This is a unique mode of action. Fosfomycin utilises the active transport proteins Glycerol-3-phosphate transporter (GlpT) and Hexose phosphate uptake transporter (UhpT) to enter the cell by mimicking both glucose-6-P (G6P) and glycerol-3-P (G3P). Thus, Fosfomycin gets imported into the bacterial cell via the hexose monophosphate transport system (which is induced by G6P) and via the L-a-glycerophosphate transport system (which is induced by G3P) (Fig 2).[5,9]

Once within the bacterial cell, Fosfomycin disrupts the synthesis of the peptidoglycan precursor UDP N-acetylmuramic acid (UDP-MurNAc), which is the first cytoplasmic step of bacterial cell wall biosynthesis.[19]The enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) plays a specific role in the biosynthesis of peptidoglycan. It catalyzes the transfer of the enolpyruvyl moiety from phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-N-acetylglucosamine (UNAG).[20] Fosfomycin covalently binds to the thiol group of a cysteine (position 115 in*E. coli*numbering: target Cys^{115}) in the active site of MurA and consequently inactivates it and it hinders the synthesis of peptidoglycan which in turn weaken the cell walls and affects the structural integrity and shape of the cell wall, leading to bactericidal effect.[5,20-22]

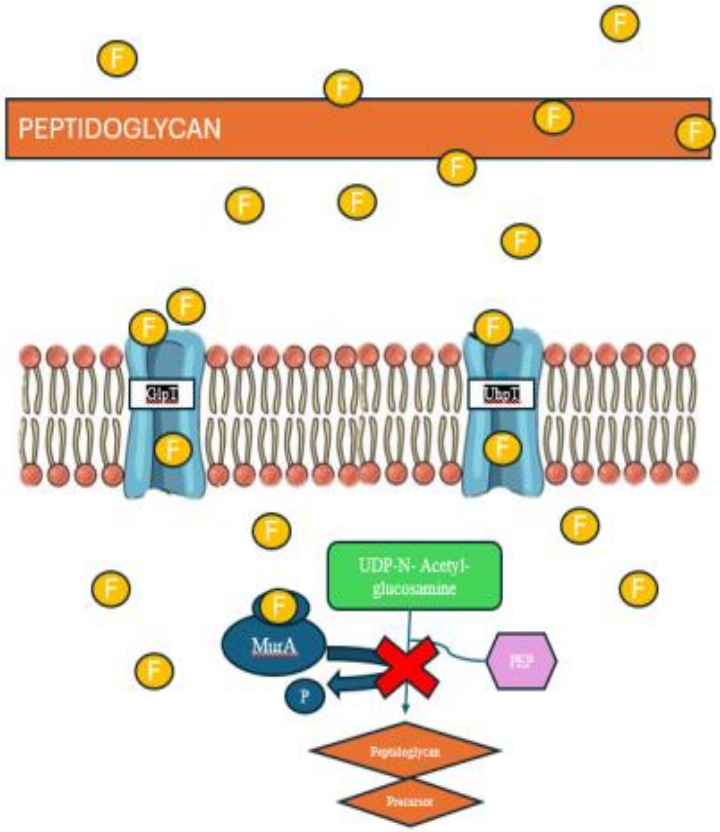

Fig 2: Diagrammatic Illustration of the Mechanism of Action of Fosfomycin

UDP-N-acetylglucosamine enol pyruvyl transferase (MurA) is an enzyme that facilitates the production of UDP-GlcNAc-3-O-enolpyruvate (uridine diphosphate N-acetylglucosamine-3-O-enolpyruvyl), an intermediate compound in the biosynthesis of peptidoglycan, a critical component of bacterial cell walls. This compound is formed during the first step of peptidoglycan biosynthesis, where MurA catalyzes

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the transfer of an enolpyruvyl group from phosphoenol pyruvate (PEP) to UDP-N-acetylglucosamine (UDP-GlcNAc). This reaction is essential to produce peptidoglycan precursors necessary for bacterial cell wall construction and overall cell growth. Fosfomycin enters the cell via the glucose-3-phosphate transporter (GlpT) and the glucose-6-phosphate transporter (UhpT). By mimicking PEP, the natural substrate of MurA, Fosfomycin inhibits the synthesis of UDP-GlcNAc-3-O-enolpyruvate. This inhibition disrupts cell wall synthesis and results in cell death.

Spectrum of Activity

Fosfomycin is effective against both Gram-positive and Gram-negative bacteria, inhibiting the formation of N-acetylmuramic acid necessary for peptidoglycan synthesis. This broad spectrum covers a variety of pathogens.

Gram-positive bacteria

Fosfomycin is effective against S. aureus (both methicillin-resistant and methicillin-sensitive S. aureus), S. epidermidis, Enterococcus faecalis, Enterococcus faecium, Listeria monocytogenes, Aerococcusurinae, Peptococcus, and Peptostreptococcus spp. ICMR reported the susceptibility of Enterococcus faecalis, and Enterococcus faeciumisolated from urine samples of patients to Fosfomycin was above 70.6% and 71.5% respectively.[23]A review article published in 2019 analyzed cases caused by Gram-positive bacteria treated with various Fosfomycin combinations and indicated that the Fosfomycin-daptomycin combination was the most effective.[24]**Xu-hong et al. (2014)**[25] investigated the in vitro effects of combining Fosfomycin with linezolid against methicillin-resistant S. aureus (MRSA). After analyzing 102 MRSA isolates from Chinese hospitals, they found that the Fosfomycin-linezolid combination exhibited synergism in 98.04% of cases. These findings suggest that this combination could be a promising option for treating difficult MRSA infections. In another in vitro study, **Simonetti et al. (2018)**[26] explored the synergistic and bactericidal effects of combining Fosfomycin with rifampicin and tigecycline against clinical isolates of E. faecalis, E. faecium, and MRSA. They found synergism rates for all enterococcal strains: 75% for E. faecalis and 73% and 67% for E. faecium isolates when combined with rifampicin and tigecycline, respectively. The Fosfomycin/rifampicin combination demonstrated synergistic action against all tested *S. aureus* strains, while the Fosfomycin and tigecycline combination was effective in 75% of cases. Notably, no antagonism was observed.

Tang et al. (2014)[27] investigated the in vitro effects of combining Fosfomycin with other antibiotics against clinical isolates of *E. faecium* and *E. faecalis*. They assessed the anti-VRE (vancomycin-resistant enterococci) activities of Fosfomycin alone and in combination with ampicillin, linezolid, minocycline, rifampicin, tigecycline, teicoplanin, and vancomycin. Notably, the Fosfomycin-teicoplanin combination demonstrated synergistic effects against
89% of VRE faecalis isolates. However, in a biofilm model, only linezolid alone reduced bacterial loads, while Fosfomycin-based combinations (excluding rifampicin) failed to enhance antibacterial activity against VR *E. faecium*. For *E. faecalis*, ampicillin alone or in combination with Fosfomycin plus rifampicin, tigecycline, or teicoplanin showed inhibitory effects. Interestingly, an antagonistic effect was observed for ampicillin plus Fosfomycin against some VR *E. faecalis* isolates.

Descourouez et al. (2013)[28] reported strong synergy and bactericidal effects against VRE when combining Fosfomycin with either daptomycin or amoxicillin.

Gram-negative bacteria

Fosfomycin is effective against a range of Gram-negative pathogens, including *Salmonella, Shigella, E. coli, Klebsiella, Enterobacter, Neisseria gonorrhoeae*, and *Helicobacter pylori*.[29-34]ICMR reported the susceptibility of *E. coli and K. pneumoniae* isolated from urine samples of patients to Fosfomycin was above 95.5% and 70.4% respectively.[23]Over the past decade, the resistance of Gram-negative bacteria has become one of the largest threats to public health worldwide. The severity of infections generated by these bacteria, their considerable capacity for transmission and dispersion through the environment, the difficulty in employing empiric treatment (and even appropriately targeted treatment), and the scarcity of new antibiotics against some Gram-negative bacilli with numerous mechanisms of resistance, have raised enormous concern in healthcare systems worldwide.[35]

In a comprehensive analysis of 1859 isolates of multidrug-resistant (MDR) Gram-negative bacteria revealed that 30.2% of *P. aeruginosa* isolates were susceptible to Fosfomycin, while 3.5% of *A. baumannii* and none of the MDR *Burkholderia spp*. isolates showed susceptibility. Fosfomycin demonstrated synergy when combined with other antibiotics, leading to a 91% improvement in patients with MDR-*P. aeruginosa* infections.[10]

In a systematic review, **Fagalas et al. (2010)**[36]found that among 5057 clinical isolates of *Enterobacteriaceae* with advanced resistance to antimicrobial drugs, at least 90% were susceptible to Fosfomycin. Specifically, 96.8% of *E. coli* isolates and 81.3% of *K. pneumoniae* isolates producing ESBL showed susceptibility. Clinical studies demonstrated that oral Fosfomycin trometamol effectively treated lower UTI caused by *ESBL-producing E. coli* in 93.8% of evaluated patients.

In another study, **Zaman et al., (2021)**[37] evaluated the efficacy of different antibiotic combinations against *P. mirabilis* isolates and found that among the 500 samples, 70% were culture positive and out of these,

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10.57% were *P. mirabilis.* Among the isolated P. mirabilis, a resistance rate of 24.32% was observed towards Fosfomycin. In laboratory conditions, a synergism rate of 100% was documented for the combination of Imipenem-Amikacin, while Imipenem-Fosfomycin exhibited 75% synergism, resulting in complete bacterial clearance at a rate of 100%.

Activity in Biofilms: Fosfomycin can penetrate biofilms and, in combination with other antibiotics, reduce or eliminate bacteria in biofilm structures. Anderson et al. (2013),[38]Cai et al/. (2009),[14]Corvec et al. (2013),[39] Mihăilescu et al. (2014),[40] and Oliva et al. (2014)[41]demonstrated its efficacy in vitro and in biofilm infection models. Combination therapy with Vancomycin and Fosfomycin eliminated MRSA biofilm in a rat model.[42] Fosfomycin reduced *Staphylococcus epidermidis* biofilm density and combining it with Prulifloxacin destroyed *P. aeruginosa* biofilms.[43]

On polystyrene plates, Fosfomycin decreased E. coli biofilm formation, with enhanced activity when combined with N-acetylcysteine.[44] In urinary stent biofilms, Fosfomycin was bacteriostatic against VRE, with MIC90 increasing from 64 mg/L in planktonic cultures to 128 mg/L in biofilm cultures.[28]

PHARMACOKINETICS OF FOSFOMYCIN

Absorption

The two salts of this antibiotic, Fosfomycin calcium and Fosfomycin tromethamine can both be administered by oral route of administration. Upon oral intake, both salts are rapidly absorbed; however, the bioavailability is notably higher for Fosfomycin tromethamine (40%) compared to Fosfomycin calcium (12%), as the former undergo acid-catalyzed hydrolysis in the stomach before reaching the small intestine, where factors such as intragastric acidity and gastric emptying rate can impact the extent of Fosfomycin's hydrolytic degradation and, its overall bioavailability.[45-46] Bioavailability calculations based on urinary excretion data of Fosfomycin tromethamine after both oral and IV administration has shown values reaching up to 58%.[47]Both salts present a decrease in bioavailability when taken orally with food;[48-49]however, administration under fasting conditions results in approximately 2–4 times higher serum concentrations of the tromethamine salt than the calcium formulation. The third salt, Fosfomycin disodium is available only as the intravenous formulation.

Distribution and Tissue Penetration

Fosfomycin is a hydrophilic compound that exhibits minimal protein binding,[6] resulting in exclusive elimination through glomerular filtration, showing a strong correlation with the glomerular filtration rate.[50] The distribution of Fosfomycin is extensive, reaching various tissues besides serum, such as kidneys, bladder, prostate, lungs, bone, cerebrospinal fluid, inflamed tissues, and abscess fluid, where biologically significant concentrations have been detected.[51-59] Following a single 3-gram oral dose, the peak serum concentration (Cmax) ranges from 22 to 32 µg/ml within about 2 hours, with an elimination half-life of 2.4 to 7.3 hours and an area under the concentration-time curve of 145 to 228 µg/ml·h.[60] The apparent volume of distribution (Vd/F) after oral Fosfomycin tromethamine administration is around 100–170 L for a 70-kg individual.[49,61] In contrast, due to its enhanced bioavailability, IV-administered Fosfomycin disodium presents a Vd of 9–30 L at steady state, with reported values of 3–12 L for both the central (Vc) and peripheral (Vp) compartments.[47,51,55,62-65] Since it does not bind to plasma proteins, Fosfomycin is reported to undergo no metabolism.

Elimination

Elimination in healthy individuals

Approximately 90% of a 3 g IV dose of Fosfomycin disodium is excreted unchanged in the urine 36–48 hours after administration.[47,50,66] A high urine concentration (1,000 to 4,000 µg/ml) is attained and sustained above 100 µg/ml for 30 to 48 hours, forming the pharmacokinetic rationale for the single-dose oral regimen.[67] About 10% of the initial dose is found unchanged in the feces following an oral administration of the tromethamine salt.[49] Segre et al. (1986)[47] noted that the proportion of the original dose excreted in the urine declines with escalating oral doses, indicating reduced absorption with higher doses. Typically, the overall clearance rate varies from 5 to 10 L/h, while renal clearance ranges from 6 to 8 L/h.[47,51,54-55,62,64,68-69] In individuals without health issues, IV Fosfomycin is distributed in the serum and eliminated in a bi-exponential fashion; the serum half-life for Fosfomycin disposition (t1/2α) ranges from 0.18 to 0.38 hours,[63,69] while the terminal (or elimination) half-life (t1/2β) is between 1.9 and 3.9 hours.[47,50,51,54-55,62-63,66,69] Conversely, the t1/2β is extended after taking an oral dose of Fosfomycin tromethamine (3.6–8.28 hours),[50,61,66] which can be clarified by a prolonged absorption phase.

Elimination in patients with renal failure

Renal impairment leads to a significant reduction in the excretion of Fosfomycin as it mainly exits the body through the urinary system. Hence, dosage adjustments are necessary when the creatinine clearance falls below 50 ml/min.[61] Fosfomycin is removed during hemodialysis but remains in the body in between sessions; therefore, a suggested approach is to administer 2 grams post hemodialysis and continue with subsequent doses after each session.[70] For patients with renal failure or undergoing hemodialysis, the elimination half-life of Fosfomycin can extend up to 50 hours, depending on the individual's renal function.[66,69]

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Dosing guidelines for oral Fosfomycin and parenteral Fosfomycin are presented in Table 1 and Table 2, respectively.

Table1: Dosing guidelines for oral Fosfomycin

Oral Fosfomycin	
Medical Condition/ Patient Populations	Dose
Uncomplicated UTI (Cystitis)	3 gm dose of Fosfomycin trometamol Or 3gm of Fosfomycin trometamol every two to three days for a total of three doses.
For children and neonates	100-200 mg/kg/day split into 3-4 doses
Juvenile patients	1-2 gm

Table2: Dosing guidelines for Parenteral Fosfomycin

Parenteral Fosfomycin	
People with normal renal function (creatinine clearance ≥ 80 ml/min	12-16 gm in two or four divided doses
Patient receiving intermittent dialysis (every 48 hrs.)	2 gm following each session
Premature babies	100 mg/kg divided into two doses
Newborn to one year old (and up to 10 kg)	200-300 mg/kg divided into three doses
Children from one to twelve years old	200-400 mg/kg in three to four separate doses

Fosfomycin and Urinary tract infections(UTIs)

Urinary tract infections (UTIs) are the most common bacterial infection and thus contribute significantly to the cost of healthcare-associated with hospitalization.[71] Approximately 150 million people worldwide develop a UTI each year; by the time they are 24 years old, this number may increase to 75% among females, and 15% to 25% of these individuals may experience recurring UTIs.[72] UTIs result in 10 million office visits and 2 million emergency room trips in the US each year, with a cost of about $3.5 billion.[73]

Clinically, urinary tract infections are categorized as uncomplicated UTI (uUTI) and complicated UTI (cUTI).[74] Different techniques have been proposed to categorize UTIs, distinguishing between uUTIs and cUTIs depending on the host's anatomy, the site of the infection, and the presence of risk factors. Recurrent UTIs are regarded as complex as well. This distinction is crucial as cUTIs are often associated with bacteria other than *E. coli* and exhibit high drug resistance.[75]An estimated 38% of kidney transplant recipients (KTRs) get UTIs. These infections can be brought on by vesical-urethral reflux, underlying urologic conditions, urinary catheter use, immunosuppression, and comorbidities (such as diabetes mellitus).[76]**The presence** of underlying immunological or anatomical defects, high rates of comorbid disease and polypharmacy, allergies or intolerances to antimicrobial drugs, and the prevalence of MDR pathogens have made treatment of UTI more difficult.[77]

The range of uropathogens involved in cUTI can vary depending on a number of factors, including geographic pattern, time period, and patient type. It has generally been observed that while *E. coli* remains one of the most common uropathogens in cUTI, other Gram-negative microorganisms, including *Klebsiella spp., Enterobacter cloacae, Serratia marcescens, Proteus spp., and Pseudomonas aeruginosa*, are becoming increasingly important. Additionally, it is common to isolate gram-positive bacteria such as enterococci, *Staphylococcus* species, and *Candida* species.

The traditionally used antibiotics to treat UTIs, like fluoroquinolones and β-lactams, have a different susceptibility profile at present date because of the overuse of antibiotics in recent years. According to several studies, the percentage of *E. coli* and *K. pneumoniae* that are resistant to fluoroquinolones ranges from 7% to 56%. Additionally, there is a rise in the number of bacteria that produce AmpC and extended-spectrum β-lactamase (ESBL), which has further led to a decrease in their susceptibility to β-lactams. ESBL-producing enterobacteria were responsible for 13% of healthcare-related bacteremic UTIs, and 30% of these cases showed decreased sensitivity to Amoxicillin-Clavulanate, according to the multicenter Spanish study ITUBRAS-GEIH, which was published in 2013. Therefore, it should come as no surprise that so-called "old antibiotics" like Fosfomycin, Aminoglycosides, and Polymyxins have become more significant in clinical practice in recent years.[75]

The escalating antibiotic resistance rates observed among various pathogens have led to the exploration of alternative treatment strategies. Given the limited availability of novel antimicrobial drugs, reconsidering older antibiotic agents presents a promising option. Fosfomycin was previously used as an oral treatment for uUTIs.[78]Some appealing characteristics of Fosfomycinin treatment and management ofUTI include rapid absorption after oral administration; concentration for excretion in urine; biofilm activity; efficacy against many MDR organisms, including extended-spectrum beta-

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lactamase (ESBL); and AmpC-producing *Enterobacteriaceae*.[79]Prominent specialists advocate for the more frequent prescription of Fosfomycin in appropriate situations as one of the carbapenem-sparing techniques.[80]In clinical settings, Fosfomycin has proven to be safe and effective in treating acute, simple cystitis. It is also well-tolerated in older adults and pregnant women.[81]

Other Activities

In addition to its direct antimicrobial activity, Fosfomycin also modulates the immune system by reducing bacterial adhesion to the respiratory and urinary tract epithelia, modifying the levels of TNF-a, interleukins, and leukotrienes, and affecting the function of neutrophils, T cells, and B cells.[82]

With its broad spectrum of antibacterial activity that includes many resistant uropathogens (such as ESBL-producers) and low risk of allergic reactions, Fosfomycin tromethamine is an oral antibiotic that can potentially improve patient quality of life while lowering healthcare costs associated with outpatient UTI treatment.[73]

RESISTANCE OF FOSFOMYCIN

Fosfomycin, used to treat UTI, faces resistance from various bacteria. One of three ways by which resistance to Fosfomycin may be induced: (i) decreasing the amount of functional transporters produced, which affects the GlpT or UhpT transport systems; (ii) decreasing the target enzyme's affinity; or (iii) producing Fosfomycin-modifying enzymes. The enzymes that alter Fosfomycin can be transmitted on transferable plasmids, as in *E. coli,* or chromosomally encoded. FosA, FosX, FosC, and FosB are the four categories of known Fosfomycin-modifying enzymes. Gram-positive bacteria often make FosB, whereas Gram-negative bacteria typically produce FosA and FosX. Understanding Fosfomycin resistance will greatly help combat multidrug-resistant pathogens.[83]

In combination

It is suggested that the synergistic impact of β-lactam and Fosfomycin antibiotics stems from their inhibition of cell wall synthesis at different stages; β-lactam antibiotics inhibit the last stage of the cell wall synthesis process, while Fosfomycin inhibits the first enzymatic step. Furthermore, it is possible that Fosfomycin alters the function of penicillin-binding proteins, which could explain the synergistic relationship between Fosfomycin and β-lactam antibiotics.[2]Fosfomycin is not recommended for individuals with bacteremia or upper urinary tract infections, such as pyelonephritis, because low serum concentrations can result in treatment failures. The dosing approaches for Fosfomycin exhibits variation. According to NICE guidelines, women are recommended to take a single 3 g dose, while men are advised to take two 3 g doses with a 3-day interval. However, the UK product license permits only a single dose, and European guidelines from the European Association of Urology do not endorse Fosfomycin use in men at all. It is essential to consider these differing recommendations when prescribing this antibiotic.[79] Longer courses have occasionally been used to treat complex UTIs as a last resort when oral antibiotics are not an option in addition to intravenous antibiotics. Additionally, perioperative prophylaxis for urological procedures in males and prostatitis are developing fields.[84]

Clinical Studies

Some clinical studies have been summarized here that highlight the benefits of Fosfomycin administration in UTI.

The FOCUS study was a multicenter, randomized, open-label pragmatic superiority clinical trial that compared the efficacy of oral Levofloxacin with Fosfomycin in treating community-onset UTIs. After receiving parenteral antibiotic therapy for 0–48 hours, the trial examined two approaches for starting or tapering down oral medication for cUTI without bacteremia. Clinical cure rates at the test of cure were comparable (84% and 86% for the Levofloxacin and Fosfomycin strategies, respectively); however, the microbiological success rate for the Fosfomycin strategy was much lower (69% compared to 84% for the Levofloxacin strategy). These sparse findings imply that Fosfomycin might be an oral substitute for cUTI treatment as a step-down therapy.[85]

In a Phase IV multi-centre trial, researchers compared the effectiveness of Fosfomycin (administered as a single 3g oral dose) with Nitrofurantoin (given as 100 mg orally every 12 hours for 7 days) in treating acute uncomplicated lower UTIs in ambulatory females aged ≥12 years. 94% of pre-treatment isolates were susceptible to Fosfomycin, and 83% of pre-treatment isolates were susceptible to Nitrofurantoin. Both treatment groups had an overall similar clinical success rate of 80%. The clinical cure rates were not different between Fosfomycin and Nitrofurantoin. The study excluded patients with pyelonephritis, pregnancy, lactation, structural or functional abnormalities, recurrent UTIs, renal or hepatic dysfunction, and recent antibiotic treatment. Follow-up visits occurred at specific intervals after treatment initiation. While Fosfomycin did not demonstrate non-inferiority, it may still be considered for selected patients.[86]

In a double-blind randomized controlled trial, researchers compared the efficacy of single-dose Fosfomycin (3g oral dose) with Ciprofloxacin (500 mg orally every 12 hours for 3 days) in treating uUTIs in 100 adult non-pregnant women. The clinical cure rate for Fosfomycin was 96%, while Ciprofloxacin achieved a 94% cure rate. Notably, single dose Fosfomycin was found to be more tolerable and with similar efficacy than Ciprofloxacin treatment. No AEs were seen in the Fosfomycin group. The study

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provides valuable insights for managing UTIs in women.[87]

A study conducted in the Czech Republic examined 3295 unique isolates of gram-negative bacteria causing urinary tract infections. They studied the *in vitro* susceptibility of Fosfomycin in gram-negative urinary isolates. Fosfomycin demonstrated significantly higher *in vitro* susceptibility compared to other tested per-oral antibiotics against all tested Gram-negative rod isolates (excluding *Morganellamorgani and Acinetobacter spp*.). It also remained highly active against isolates with extended spectrum β-lactamase (ESBL) production (95.8% in *E. coli* and 85.3% in *K. pneumoniae),* rendering Fosfomycin highly effective against gram-negative rod isolates in urinary tract infections**.** The Czech Republic showed a very high susceptibility of Fosfomycin trometamoltoUTI pathogens**.**[88]

A retrospective study was conducted with 75 adult patients with UTI whoreceived Fosfomycin as their treatment course. Over the course study,there wasa significant difference in Fosfomycin treatment.Co-morbidities were seen in 71% of patients. The majority (69%) were infected with *E. coli*, and 59% of those infections produced extended-spectrum beta-lactamases (ESBLs). *Klebsiella* infections were more likely to be resistant to Fosfomycin. Five patients who received continuous Fosfomycin treatment did not have any adverse events. Of all the urine isolates that were gathered throughout the year, only 1% of *E. coli* and 19% of *Klebsiella spp.* showed evidence of Fosfomycin resistance. The research indicates that Fosfomycin is both safe and effective in individuals with complex comorbidities and over prolonged time periods. There was no significant effect seen in *E. coli* and *Klebsiella spp***.**[79]

In a prospective, uncontrolled, open label study took place in two tertiary hospitals within three years. Out of the total 304 urinary isolates major were Gram-negative *Enterobacteriaceae* family. Bacterial eradication, bacterial persistence, and bacterial reinfection were 96.3%, 3.9%, and 3.9%, respectively, following oral single or multiple doses of Fosfomycin. This demonstrated superior tolerability and safety in pregnant women and other female age groups, as well as greater eradication of bacteria after 48 hours. Upon receiving the medication, 23.5% of patients developed diarrhoea, and 19.7% of patients developed genital itching. Fosfomycin Trometamol is advised for mild daycare endourological interventions as well as for patients who fail to maintain compliance well with the prescribed medication**.**[89]

The study conducted a systematic review and meta-analysis to examine the effectiveness and safety of single-dose Fosfomycin tromethamine in comparison to other antibiotic treatments for women experiencing lower uUTIs and pregnant women with uUTIs or asymptomatic bacteriuria (ASB). It was shown that there was no notable distinction between pregnant and non-pregnant women in terms of overall microbiological resolution. Other than the gastrointestinal symptoms, no major adverse events were reported. Thus, in terms of both clinical and microbiological efficacy, a single dosage of Fosfomycin tromethamine yields clinical results, unlike the comparators. As a result, it has higher patient compliance and is clinically efficacious, safe, and suitable for women with uUTI and pregnant women with uUTI or ASB**.**[90]

A prospective study was conducted to investigate the efficacy of Fosfomycin tromethamine to prevent UTI in pregnant women that have undergone lower urinary tract endoscopic surgical treatment. There were 31 women included who had undergone DJ ureteric insertions for hydronephrosis, urinary bladder stones, and cystoscopy. Adverse events reported by the patients were diarrhoea, nausea, and vomiting. Some patients also reported asymptomatic bacteriuria and were given oral antibiotic therapy. Fosfomycin tromethamine reduces the requirement for postoperative parenteral antibiotics and is safe in avoiding urinary tract infections, in pregnant women who need lower urinary tract endoscopic procedures. [91]

The study with 200 female patients was examined to check the Fosfomycin efficacy on those that previously had lower UTI. Group one (100) received Fosfomycin and group two (100) received Cephalexin and later underwent urine culture test at one week and one month post treatment. *E. coli., Staphylococcus saprophyticus, Proteus spp and Klebsiella* were identified in urine samples collected from patients. Post one month treatment, 98% positive results were observed in patients treated with Fosfomycin and 95% in patients with cephalexin. As an alternative to Cephalexin, Fosfomycin can be used to treat uUTIs in women who have a substantial amount of tolerance**.**[92]

The retrospective study investigated the effectiveness of Fosfomycin in the management of *Enterobacteriaceae* that produce extended-spectrum beta-lactamases (ESBLs) and cause complex urinary tract infections (cUTIs). In the urine cultures, 43 Fosfomycin-susceptible urinary pathogens were identified, including 34 *E. Coli* ESBL isolates, seven *K. pneumoniae* ESBL isolates, and two *C. freundii* ESBL isolates. The overall microbiological cure rate reached 50%, with a clinical cure rate of 71% and an ESBL eradication rate of 74%. Patients with between zero and one complicating/clinical factors received significantly fewer Fosfomycin doses than patients with two or more complicating/clinical factors. Three kidney transplant patients achieved microbiological cure following prolonged Fosfomycin administration. No statistically significant correlation was found between the presence of individual complicating/clinical factors and treatment outcome. Fosfomycin may be a valid option for oral treatment of cUTIs caused by ESBL producing pathogens. The optimal duration of Fosfomycin treatment for cUTIs remains to be determined**.**[80]

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Adult female participants in a prospective open-labelled uncontrolled trial had clinical signs of UTIs, which were verified by microscopy and culture of midstream urine samples. The bacterial eradication rates were 86% (38/44), 91% (20/22), 100% (4/4), and 60% (3/5) for all bacteria, *E. coli* (ESBL-producing strains), and *Klebsiella*, respectively, 48 hours after treatment with Fosfomycin. Nineteen percent (19%) of the patients had diarrhea. In comparison to a one-week course of other antibiotics, our preliminary investigation indicates that a single dose of Fosfomycin had a high incidence of bacterial eradication after 48 hours, but it was also linked to a high frequency of diarrhea. It is needed to do more research with a bigger sample size and longer follow-up.[93]

In single centre observational retrospective study to access rate of recovery and microbiological cure in patients with UTIs administering oral Fosfomycin trometamol. There were sixteen male patients in total who reported twenty-one UTI instances. Four acute UTI episodes and seventeen cases of chronic bacterial prostatitis were reported. Sixteen of the *Enterobacterales* were makers of ESBLs. All patients showed clinical and microbiological improvement, and showed no recurrence, after 5.3 months of follow-up. In chronic bacterial prostatitis, the treatment plan included one oral dosage of Fosfomycin every 24- 48 hour, with a mean of 5.5 weeks between UTI episodes. In 16 instances, clinical and microbiological recovery was observed. After an average follow-up of 5.8 months, 7 patients with chronic bacterial prostatitis had relapsed of which 3 had experienced a second infection episode. Merely 6 participants experienced mild to moderate side effects, like digestive issues. When treating male UTIs with multidrug-resistant *Enterobacterales* infections, Fosfomycin trometamol may be a better option than carbapenems.[94]

In another prospective study, the in vitro activity of Fosfomycin against uropathogenic *E. coli* is evaluated, and comparison of its activity with other anti-microbial agents. For the duration of the study, 564 urine samples from suspected UTI cases were processed, and 170 *E. coli* isolates were found in those samples. The organisms were identified using standard biochemical tests, and Kirby-Bauer disc diffusion Test was used to screen for antibiotic sensitivity. Out of 170 isolates, 60 (35.30%) were isolated from males and 110 (64.70%) from females. Antibiotics having the highest sensitivity included Fosfomycin, imipenem, and methenamine mandelate, which were effective against 100% of the isolates. Compared to many other antibiotics, Fosfomycin has demonstrated very good in-vitro action against all of the studied isolates. Because of its distinct mode of action and low rate of resistance, Fosfomycin presents itself as a viable therapeutic option for the treatment of UTIs.[95]

In summary, clinical trials have demonstrated the efficacy of Fosfomycin in treating MDR UTIs caused by *E. coli*. Further research and real-world evidence are essential to refine its use and optimize patient outcomes.

ADVERSE EVENTS OF FOSFOMYCIN

According to the literature, the most common side effects of Fosfomycin given intravenously are gastrointestinal irritation and localized phlebitis; otherwise, the drug is usually well tolerated and does not need to be stopped.[6]The most frequent side effects of oral Fosfomycin tromethamine therapy are usually mild and include headache and dizziness (noticed in 1-4%), vaginitis (reported in 6% of patients), and gastrointestinal irritation (occurring in 1-9% of cases).[60]Serious adverse events have, however, occasionally been reported during post-marketing surveillance. These include ailments including angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, liver necrosis, and toxic megacolon.[46]According to a comprehensive study conducted by Fagalas et al. (2008),[11] adverse events associated with Fosfomycin were mostly related to the skin and gastrointestinal systems and were rare. Treatment did not need to be stopped for mild gastrointestinal problems.[96] Of the total 1604 patients included in the review, two experienced severe nausea and neutropenia. Other patients reported local phlebitis,[97]pain at the injection site (more common with intramuscular administration), and transient eosinophil count changes.[98] In another review of adverse events from the analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) and published literature, it was reported that the common adverse events linked to parenteral Fosfomycin included rash, peripheral phlebitis, hypokalemia, and gastrointestinal issues. Serious adverse events like aplastic anemia, anaphylaxis, and liver toxicity were rarely reported.[99]

In a randomized clinical trial involving 143 adults with MDR bacteremic urinary tract infections caused by *E. coli*, the study found that 68.6% of patients treated with Fosfomycin achieved clinical and microbiological cures. In comparison, 78.1% of patients treated with other comparators achieved similar outcomes. However, Fosfomycin did not meet the criteria for noninferiority due to a higher rate of adverse event-related discontinuations (8.5% vs. 0%) associated with its use. Adverse events were noted in 56.2% of patients in the comparator groups and 62.9% of patients receiving Fosfomycin during the study. In the Fosfomycin treatment group, 18.6% of patients had major adverse events;in the comparison group, this percentage was 13.7%. It is noteworthy that 6 patients (8.6%) in the Fosfomycin group experienced heart failure, with one patient having two episodes (the second after stopping the medication).[100]

A total of 128 studies involving 5527 participants were assessed in a systemic review and meta-analysis

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on intravenous Fosfomycin. Of these 128 studies, 56% submitted safety information, including 480 adverse events affecting 2672 patients who received treatment (18.0%). The most common adverse events were abnormal laboratory findings (mostly temporary increase of liver enzymes), which accounted for 92 occurrences (3.4%), and gastrointestinal distress (such as nausea, vomiting, taste abnormalities, and diarrhea), which accounted for 140 events (5.2%). Furthermore, 86 individuals (3.6%) had hypernatremia or hypokalemia, which were important adverse effects. Merely 18 instances (<0.01%) met the seriousness criteria, with leukopenias accounting for six of these and neutropenias for three.[101]

A summary of key findings from clinical trials on Fosfomycin can be presented as below:

1. UTIs: Fosfomycin has shown effectiveness in treating uncomplicated UTIs caused by both Gram-positive and Gram-negative bacteria. It has been particularly useful in cases where other antibiotics have failed due to resistance.
2. Single-Dose Regimen: One of the significant advantages of Fosfomycin is its ability to be administered as a single oral dose, making it convenient for both patients and healthcare providers. This single dose regimen has found to be as effective as longer courses of antibiotics in many cases.
3. Safety profile: Fosfomycin is generally well-tolerated, with most adverse effects being mild and transient. Common side effects include gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain. Serious adverse reactions are rare.
4. Resistance: While Fosfomycin has demonstrated efficacy against many bacteria, there are concerns about the emergence of resistance. However, it is still considered an important antibiotic in the treatment arsenal, especially for infections where other options are limited.
5. Combination therapy: In some cases, Fosfomycin has been used in combination with other antibiotics to enhance efficacy, particularly in treating complicated UTIs or infections caused by multidrug-resistant organisms. Clinical trials have shown promising results with combination therapies.

Overall, Fosfomycin remains a valuable option for the treatment of UTIs, especially in cases where other antibiotics may not be effective due to resistance. However, continued surveillance for antibiotic resistance and judicious use of Fosfomycin are essential to preserve its efficacy for future generations.

CONCLUSIONS

Antibacterial drug resistance is one of the major threats that the global public health is facing, particularly given the reduction in the number of clinically effective antibiotics. In this regard, re-evaluating, and re-assessing "ancient" antibiotics like Fosfomycin has been suggested as a potential approach to treat drug resistant bacterial infections. Fosfomycin can be considered to be employed in infections affecting wide range of tissues and targets, such as the central nervous system, soft tissue, bone, lungs, and abscess fluid, because of its strong tissue penetration. Oral Fosfomycin in a multiple-dose regimen has become a viable treatment option for complex UTIs and prostatitis; further exhaustive research isneeded, though, because the pharmacological characteristics and causes of resistance to Fosfomycin are still largely unknown.

Associated Content

Author Contributions: All authors actively participated in the data collection and critical revision of the manuscript, ensuring the inclusion of key intellectual insights. Each author collectively approved the final version of this manuscript.

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