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A REVIEW ON FOSFOMYCIN RESISTANCE: A REVIVAL DRUG FACING MODERN THREATS

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ABSTRACT

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969. There are three forms of fosfomycin: fosfomycin tromethamine (a soluble salt) and fosfomycin calcium for oral use, and fosfomycin disodium for intravenous use. Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase. It has a broad spectrum of activity against a wide range of Gram_positive and Gram-negative bacteria. It is highly active against Gram-positive pathogens such as Staphylococcus aureus and Enterococcus, and against Gram-negative bacteria such as Pseudomonasaeruginosa and Klebsiella pneumoniae.

Fosfomycin is a broad-spectrum bactericidal antibiotic that inhibits cell wall biosynthesis in both Gram-negative and Gram-positive bacteria. This antibiotic has a unique mechanism of action and inhibits the initial step in peptidoglycan biosynthesis by blocking the enzyme, MurA. Fosfomycin has been used successfully for the treatment of urinary tract infections for a long time, but the increased emergence of antibiotic resistance has made fosfomycin a suitable candidate for the treatment of infections caused by multidrug-resistant pathogens, especially in combination with other therapeutic partners.

KEYWORDS: *Fosfomycin Resistance; Molecular Mechanisms ,Fosfomycin; Pharmacokinetics; Multidrug Resistance; Antimicrobial Activity.*

INTRODUCTION

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969.1 It is a phosphonic acid derivative, with an extremely low molecular weight, and shows almost no binding to proteins. Fosfomycin is a unique antibiotic that is chemically unrelated to any other known antibacterial agent. Its empirical formula is C3H7O4PC4H11NO3 and its chemical structure is shown In Figure 1.

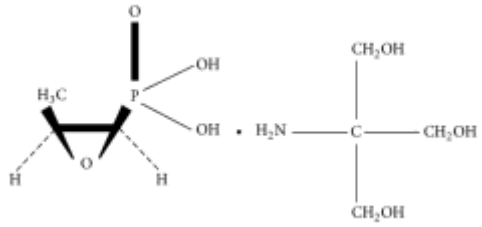

Figure 1. Chemical Structure of Fosfomycin

The discovery of antibiotics in the 1920s was one of the greates breakthroughs in the history of healthcare, leading to a marked decrease in both morbidity and mortality associated with bacterial infections [1]. However, the intensive and extensive use and misuse of antibiotics over the past 50 years has contributed to the emergence and spread of antibiotic-resistant bacterial strains [2–4]. This increase and global spread of multidrug-resistant (MDR) bacteria is particularly alarming [3,5]

In the current era of antimicrobial resistance, the family Enterobacteriaceae is one of the most problematic groups of pathogens. Many classes of antimicrobial agents used to be almost uniformly active against Enterobacteriaceae, including β-lactam-β-lactamase inhibitor combinations, cephalosporins, carbapenems, sulfonamides, fluoroquinolones and aminoglycosides.

Urinary tract infection (UTI) is an exceedingly common type of bacterial infection that affects healthy individuals as well as those with comorbidities around the world. It is estimated that one in every three women experience at least one episode of urinary tract infection (UTI) requiring treatment with antimicrobial agents by the age of 24 [6]. Given the increasing rates of resistance in urinary pathogens to agents commonly used to treat UTIs such as trimethoprim-sulfamethoxazole and ciprofloxacin, there has been a surging interest in identifying new treatment options or re-evaluate existing agents for the treatment of UTIs.

Forms of Fosfomycin

Fosfomycin is available in two oral formulations – fosfomycin tromethamine (synonym trometamol), a soluble salt with improved bioavailability over fosfomycin, which is synthetically prepared, and fosfomycin calcium. Fosfomycin tromethamine is the preferred formulation for oral administration of fosfomycin because it is more readily

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absorbed into the blood compared to fosfomycin calcium.2,3 There is also an intravenous f Fosfomycin is a broad-spectrum antibiotic that inhibits bacterial cell wall synthesis by targeting the enzyme MurA (UDP-N-acetylglucosamine enolpyruvyl transferase). Resistance to fosfomycin can occur through multiple mechanisms, and it has become increasingly relevant due to its use in treating multidrug-resistant infections.

Types of Fosfomycin Resistance

1. **Reduced Drug Uptake** (Transport Mutations) Fosfomycin enters bacterial cells through specific transport systems: GlpT (glycerol-3-phosphate transporter)UhpT (hexose phosphate transporter) Resistance Mechanism: Mutations or downregulation in glpT or uhpT genes reduce or eliminate fosfomycin uptake. This is a common resistance mechanism in E. coli and other Enterobacteriaceae.
2. **Target Site Modification** Fosfomycin inhibits MurA, which catalyzes the first step of peptidoglycan biosynthesis. Resistance Mechanism: Point mutations in the murA gene (e.g., at the active site cysteine) can reduce fosfomycin binding. Overexpression of MurA can also confer resistance in some strains.
3. **Fosfomycin-Modifying Enzymes** (Fos Enzymes) These are plasmid-encoded enzymes that inactivate fosfomycin by catalyzing the addition of a glutathione molecule or similar modifications.

Key Enzymes
FosA (most common, especially in Gram-negative bacteria)
FosB (mainly in Gram-positive bacteria)
FosX (less common)
FosC (phosphorylates fosfomycin, found in some Pseudomonas species)
Notes: FosA is a metalloenzyme requiring Mn^{2+} or K^{+} and is often plasmid-borne, allowing horizontal gene transfer. FosB uses L-cysteine instead of glutathione.

4.Overexpression of Enzymes That Compete with Fosfomycin

Some bacteria can upregulate alternative pathways or enzymes that reduce fosfomycin's impact, although this is less common and less well-defined than the other mechanisms.

❖ **Mechanism of Action**

Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase. Fosfomycin enters the cells of fosfomycin-susceptible bacteria by means of two different transport uptake systems: a constitutively functional L-a-glycerophosphate transport system (GlpT) and the hexose–phosphate uptake system (UhpT).4 It inhibits the synthesis of peptidoglycan by blocking the formation of N-acetylmuramic acid.

Fosfomycin is in an antimicrobial class of its own and is structurally unrelated to any other agent currently approved for clinical use (Figure 1). Its mode of action is inactivation of the cytosolic N-acetylglucosamine enolpyruvyl transferase (MurA), thereby preventing the formation of N-acetylmuramic acid from N-acetylglucosamine and phosphoenolpyruvate, which is the initial step in peptidoglycan chain formation of the bacterial wall [7]. Hence, fosfomycin is bactericidal in nature. The mechanisms by which fosfomycin is transported across the bacterial permeability barrier have been well described. Fosfomycin primarily utilizes the glycerol-3-phosphate transport system (GlpT) as a method of entry in almost all susceptible bacteria [8].

Fosfomycin-modifying enzymes can be chromosomally encoded but are may also be encoded on transferable plasmids, especially in E. coli [9,10]. Three of the four known groups of fosfomycin modifying enzymes, namely FosA, FosB, and FosX, function by nucleophilic attack on carbon atom 1 of fosfomycin to open the epoxide ring thus rendering the drug inactive. The enzymes encoded by these genes differ by the identity of the nucleophile utilized in the reaction: glutathione for FosA [11], bacillithiol for FosB [12], and water for FosX [13]. In general, FosA and FosX enzymes are produced by Gram-negative bacteria, whereas FosB is produced by Gram-positive bacteria. Another group of plasmid_mediated fosfomycin modifying enzymes, FosC, utilizes ATP and adds a phosphate group to fosfomycin, thus altering its properties and inactivating the drug [14].

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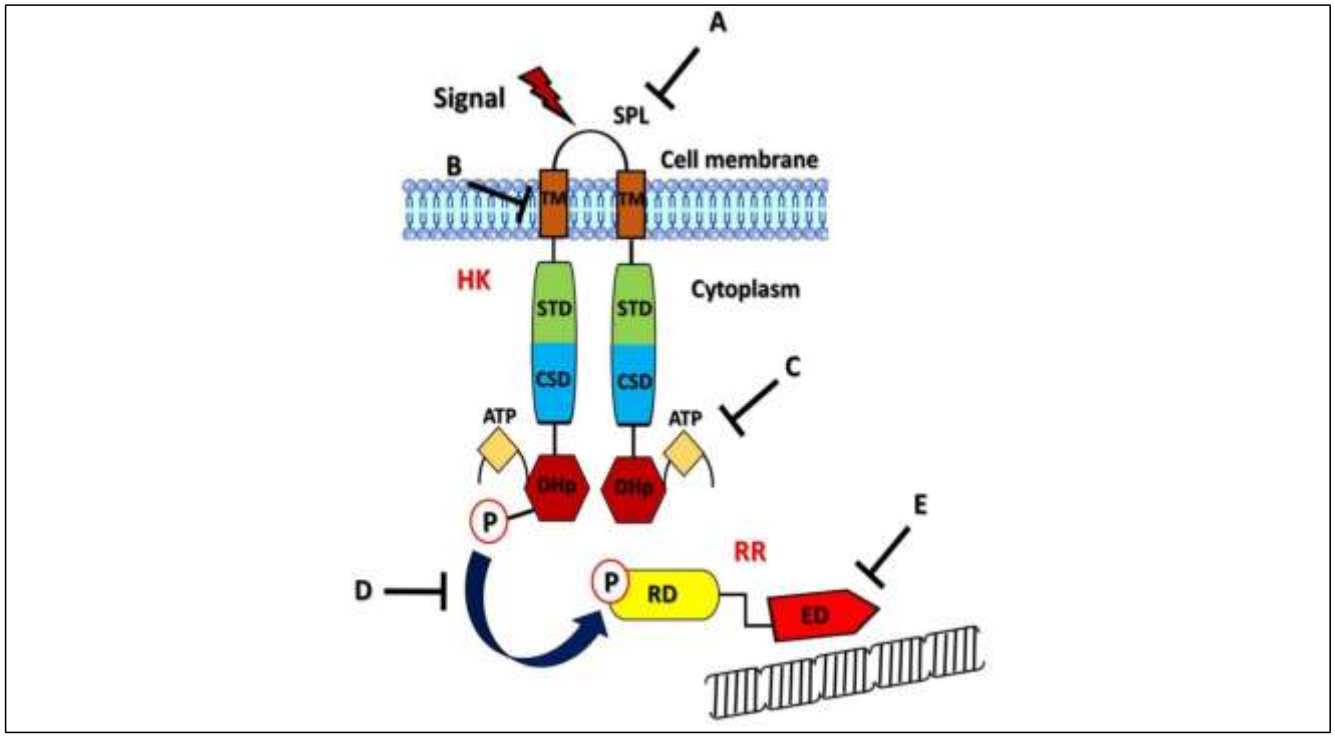

Figure 2. Mechanism of action of Fosfomycin Resistance

Fosfomycin is a bactericidal antibiotic agent. It inhibits an enzyme-catalyzed reaction in the first step of the synthesis of the bacterial cell wall (15). Fosfomycin interferes with the first cyto_plasmic step of bacterial cell wall biosynthesis, the formation of the peptidoglycan precursor UDP N-acetylmuramic acid (UDP_MurNAc) (16).

Specifically, the enzyme UDP-N-acetylgluco_samine enolpyruvyl transferase (MurA) is involved in peptidogly_can biosynthesis by catalyzing the transfer of the enolpyruvyl moiety of phosphoenolpyruvate (PEP) to the 3=-hydroxyl group of UDP-N-acetylglucosamine (UNAG) (17). Fosfomycin cova_lently binds to the thiol group of a cysteine (position 115 in Esch_erichia coli numbering; target Cys115) in the active site of MurA and consequently inactivates it (18–19). This inhibitory action takes place at an earlier step than the action of B-lactams or gly_copeptides. For the entry inside the bacterium, fosfomycin uses two differ_ent uptake pathways (identified at least for E. coli), the L-alpha_glycerophosphate and the hexose-6-phosphate transporter sys_tems (3). The activity of the second uptake system is induced by glucose-6-phosphate (G-6-P) (3).

- **Spectrum of Activity**

Fosfomycin is mainly used for the treatment of uncomplicated urinary tract infections (UTIs) [20], and various formulations are available. The form of the medication for intravenous use is fosfomycin disodium salt. For oral use, the antibiotic is combined in calcium salt or formulated with tromethamine. Fosfomycin tromethamine is primarily administered in a single dose, reaching a very high antibiotic concentration that is able to successfully kill the most common urinary pathogens [21]. It has also been used in combination with other antibiotics in the treatment of patients suffering serious infections, systemic infections with sepsis or nosocomial infections [22]. Fosfomycin shows a powerful bactericidal activity against enteric Gram-negative bacteria, such as Escherichia coli, although some of them have decreased susceptibility, as Klebsiella pneumoniae and Enterobacter cloacae. Fosfomycin is also very effective against Gram-positive cocci, like Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis and Enterococcus faecium [23].

Fosfomycin is a broad-spectrum agent which has been shown to have excellent bactericidal activity against a range of gram-positive as well as gram-negative organisms, including drug-resistant varieties [24]. Since the epidemiology of antimicrobial resistance is changing rapidly, the studies published in the 21st century are referenced below.Activity against Gram-positive organisms Fosfomycin is broadly active against methicillin-susceptible and -resistant S. aureus (MRSA) with a modal MIC of about 1 µg/ml [26], but there may be a subset of highly resistant strains among MRSA [27]. It is also active against the majority of coagulase_negative Staphylococcus spp., but not as predictably as with S. aureus [28].Sastry and Doi Page 4 J Infect Chemother. Author manuscript; available in PMC 2017 May 01.Author Manuscript Author Manuscript Author Manuscript Author Manuscript Fosfomycin is active in vitro against most E. faecalis strains and the majority of vancomycin-resistant E. faecium (VRE) strains with modal MICs of 32 to 64 µg/ml [29].

Unlike with S. aureus, high-level resistance in enterococci appears uncommon. Susceptibility of streptococcal species including Streptococcus pneumoniae, Streptococcus pyogenes and Streptococcus agalactiae are variable [30]Activity against Gram-negative organisms.Fosfomycin has excellent activity against E. coli, the primary UTI pathogen, based on in vitro data available from various countries including the U.S. with the susceptibility to fosfomycin ranging between 98 and 100% [31]. Fosfomycin has shown good in vitro activity against K.

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pneumoniae with susceptibility rates between 70 and 85% and slightly higher susceptibility rates of 80 to 97% against Proteus mirabilis [32].

Importantly, fosfomycin has excellent activity against extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [33]. For example, against ESBL-producing E. coli, fosfomycin had susceptibility rates of 86 to 100 % [34],

❖ **Pharmacokinetics and Pharmacodynamics**

Fosfomycin is rapidly absorbed following oral administrationand is converted to the free acid, fosfomycin. Bioavailability is around 40% for fosfomycin tromethamine vs. 12% for the calcium salt of fosfomycin; 30–60% of fosfomycin tromethamine is excreted unchanged in the urine vs. 9–18% for the calcium saltof fosfomycin.9 Fosfomycin has a renal elimination of 95%. No tubular secretion occurs. Fosfomycin has a relatively long elimination half-life, which varies between 4 and 8 h.10 In patients with chronic renal failure, the half-life of fosfomycin is increased significantly (up to 50 h) and is associated with a lower fosfomycin recovery in urine.

Two fosfomycin salts are available for oral administration: fosfomycin tromethimine and fosfomycin calcium. Both salts are rapidly absorbed following oral administration, but the bioavailability is significantly better for fosfomycin tromethamine (40%) than fosfomycin calcium (12%) since fosfomycin calcium is inactivated by hydrolysis in the acidic gastric environment [36]. Fosfomycin disodium is the only intravenous formulation available, marketed under different brand names and used extensively outside the U.S. This intravenous formulation is associated with a high sodium intake that could be a limitation in patients with heart failure or who are receiving hemodialysis [37].The high penetration of fosfomycin leads to favorable distribution into many tissue types, including interstitial fluid of muscle [38] and soft tissue [39], infected lung tissue[40], heart valves [41], urinary bladder wall [42], prostate [43] and cerebral spinal fluid (CSF) [44]. However, it has highly variable abscess permeability, possibly necessitating multiple doses of fosfomycin to assist in exceeding the MICs of the target bacteria at the site of infection [45].

There are 3 fosfomycin formulations: a disodium formu_lation for intravenous infusion and 2 oral presentations (one calcium and one trometamol). The first formulation consists of 1-8 g of fosfomycin disodium powder with succinic acid as the only excipient. The second formulation is fosfomycin in calci_um salt, marketed in a few countries as 500-mg hard gelatin capsules. The third, fosfomycin trometamol, is a derivative of phosphonic acid, available as (1R,2S)-(1,2-epoxypropyl) propane_diol. The formulation is presented in a 3-g packet with white granules of fosfomycin-trometamol.phos_phonic acid with 2-amino-2-(hydroxymethyl)-1,3-

The oral bioavailability of fosfomycin trometamol ranges between34 and 58% . Absorption occurs in the small intestine,and evidence suggests that coadministration of fosfomycin tro_metamol with food may reduce absorption of the drug (37% fast_ing versus 30% with food) The maximum concentration in serum (Cmax) was also higher under fasting conditions (12.1 _0.6 mg/liter and 7.8 _ 1.6 mg/liter, respectively), but urinary re_covery rates were similar (58% versus 52%) . Age does not seem to affect absorption . Metoclopramide increases gastro_intestinal motility and results in lower absorption and lower se_rum concentrations. The rate and extent of absorption of fosfo_mycin trometamol were approximately 6 times greater than those of fosfomycin calcium during the first 2 h postdose and approxi_mately 3 to 4 times greater during the 12-h postdose period . In a study comparing the pharmacokinetic (PK) properties of fosfo_mycin trometamol and fosfomycin calcium, mean peak serum concentrations following a single 2-g dose of fosfomycin trometa_mol were found to be 2- to 4-fold higher than those obtained after a single 3-g dose of fosfomycin calcium .

The reason for this observation is that fosfomycin calcium is hydrolyzed and thus inactivated by gastric acid .copeptides, rifampin, or daptomycin against MRSA infections as well as in monotherapy against infections with ESBL-producing Enterobacteriaceae. Although the current microbiological data fa_vor its use, there are few clinical data regarding both effectiveness and safety. The currently available data derive from case series or small cohorts, in which fosfomycin was administered mainly in combination with other antibiotics. In addition, it may prove to be useful for the treatment of other infections, such as H. pylori in_fection, when first-line antibiotic regimens fail. Also, there is a lack of data comparing the trometamol and calcium salt oral prepara_tions. Finally, its safety profile should be better studied in order to avoid serious adverse events such as hypokalemia and congestive heart failure.There is insufficient evidence for widely accepted breakpoints for all bacteria besides Enterobacteriaceae, Staphylococcusspp., and E. faecalis.

Thus, most studies extrapolate these breakpoints to other bacteria, such as P. aeruginosa, which is classified by the CLSI as inherently resistant to fosfomycin but for which several studies reported variable susceptibility rates. Accordingly, discor_dance between susceptibility to fosfomycin and effectiveness of fosfomycin monotherapy against UTIs due to P. aeruginosa was reported. In the same time, synergy and

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higher effectiveness was reported when combination treatment with other antibiotics was employed. In addition, there is a discrepancy between EUCAST and CLSI criteria for susceptibility, making interpretation and comparison of results from different studies difficult. Concerns over the potential development of resistance should prompt clinicians to use it judiciously in order to prevent the development of resistance inside hospitals and to prevent the dissemination of resistant strains from outpatients to inpatients.

In an era of antibiotic resistance and limited new treatment options, interest in fosfomycin is expected to culminate in the next decade. Several issues regarding effectiveness, safety, and resistance need to be addressed, namely, the susceptibility breakpoints, the appropriate dose and duration of administration for both oral and intravenous formulations, the effectiveness of oral fosfomycin for the treatment of complicated UTIs or non-UTIs, the everlast_ing question of the effectiveness of monotherapy and combination regimens (including existing [e.g., polymyxins, aminoglyco_sides, and glycopeptides] or forthcoming [e.g., combinations of-lactams and new B-lactamase inhibitors, new aminoglycosides, or polypeptide antibiotics] antibiotics), and the concerns over in_creased probability of development of resistance during treat_ment. Finally, the intravenous formulation is not available in sev_eral countries, including the United States. In a recent case report,the oral formulation was used successfully for a bacteremic MDR infection .

❖ **Adverse Effects**

1. Fosfomycin has a favorable safety profile in general, with the most common adverse event being mild gastrointestinal distress.
2. The rate of these adverse events reported in the literature related to the use of oral fosfomycin vary between 2 and 6%, with the higher rates associated with patients treated with more than one doses [46].
3. 3)A recent report indicated a high rate of mild hypokalemia (26%), suggesting that potassium monitoring may be prudent particularly when using prolonged courses of intravenous fosfomycin [47].
4. The effect on the intestinal flora after intake of a single 3-gram dose has not been well established.
5. However, longer intravenous treatment (5 grams twice daily for 5 days) alters the intestinal flora significantly, mainly with a reduction of Enterobacteriaceae as noted in an older study conducted over two decades ago [48].

❖ **Advantages of Fosfomycin Resistance**

1. Survival in the Presence of Fosfomycin
   The primary advantage: bacteria can survive and grow despite exposure to fosfomycin.
   This allows resistant strains to persist during antibiotic treatment, especially in environments like hospitals where fosfomycinis used to treat multidrug-resistant (MDR) infections.
2. Selective Advantage Under Antibiotic Pressure
   In settings with fosfomycin use (e.g., urinary tract infections, MDR infections), resistant strains can outcompete susceptible strains.
   This selective pressure promotes the expansion and dissemination of resistant clones.
3. Horizontal Gene Transfer of Resistance Genes
   Genes like fosA, fosB, etc., are often carried on mobile genetic elements (e.g., plasmids, transposons).
   Bacteria with these plasmids can transfer resistance to other species, gaining a competitive edge in mixed microbial communities.
4. Co-selection with Other Resistance Genes
   Plasmids carrying fosfomycin resistance often carry other resistance genes (e.g., for β-lactams, aminoglycosides).
   Use of other antibiotics can co-select for fosfomycin resistance even if fosfomycin is not used — a process known as co-resistance.
5. Persistence in Clinical and Environmental Reservoirs
   Resistance enables bacteria to persist in hospital environments, urinary catheters, or wastewater systems. This increases the chance of infecting new hosts or re-emerging in previously treated patients.

❖ **Disadvantages of Fosfomycin Resistance (for Bacteria)**

While fosfomycin resistance helps bacteria survive antibiotic treatment, it also comes with some disadvantages, especially in environments without the antibiotic.

1. Fitness Cost

Mutations that block fosfomycin entry (e.g., in glpT or uhpT) can slow down bacterial growth.
These transporters are also used for importing important nutrients — their loss affects overall metabolism and energy use.

2. Reduced Virulence

Some resistant strains may become less able to cause infection.
Example: E. coli with transporter mutations may colonize the urinary tract less effectively.

3. Increased Metabolic Burden

Producing resistance enzymes (like FosA, FosB) consumes resources and energy.
Carrying resistance plasmids can slow bacterial replication, especially without antibiotic pressure.

4. Loss of Competitiveness

In antibiotic-free environments, resistant bacteria may be outcompeted by non-resistant strains that grow faster or use nutrients more efficiently.

5. Instability of Resistance Genes

Some resistance genes (especially on plasmids) can be lost over time if they're no longer useful, meaning resistance is not always permanent.

6. Immune System Detection

Certain resistance changes can lead to altered surface proteins or metabolism, potentially making bacteria more visible to the host's immune systemS

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❖ Uses in Studying fosfomycin Resistance Mechanisms

1. Understanding resistance genes (e.g., fosA, fosB, fosC) helps scientists: Understand how bacteria evolve to resist antibiotics.
   Track resistance in hospital or community settings.
   Develop inhibitors or modifications to fosfomycin that overcome resistance.
2. Diagnostic & Surveillance Use Testing for fosfomycin resistance is important to:
   Choose appropriate antibiotics for urinary tract infections (UTIs), where fosfomycin is often used. Guide empirical therapy, especially for multi-drug-resistant (MDR) organisms.
   Monitor the emergence of resistance in clinical settings (e.g., in E. coli, Klebsiella, Pseudomonas).
3. Use in Molecular Cloning and Selection (Experimental)
   In biotechnology, fosfomycin resistance genes (e.g., fosA) can be used as selectable markers in genetic engineering, especially in non-pathogenic bacterial systems
4. Clinical Epidemiology Studying patterns of fosfomycin resistance helps in: Predicting treatment outcomes.
   Adjusting antibiotic stewardship programs.
   Identifying clones of bacteria associated with resistance.
5. Cross-Resistance and Combination Therapy Studies Researchers use fosfomycin resistance data to: Design combination therapies (e.g., fosfomycin + other drugs) that overcome resistance.
   Understand collateral resistance or sensitivity patterns

❖ Challenges of Fosfomycin Resistance

1.Reduced Treatment Options
Fosfomycin is often used as a last-line agent against MDR pathogens such as extended-spectrum β-lactamase (ESBL) or carbapenem-resistant Enterobacterales (CRE). Resistance significantly limits its utility, especially in settings with few alternative antibiotics.
2.Emergence of Resistance During Therapy
Bacteria can rapidly develop resistance during fosfomycin treatment, particularly when used as monotherapy. This is due to mutations affecting:
Drug transporters (e.g., glpT, uhpT) Target enzymes (e.g., MurA) This leads to treatment failure, even when initial susceptibility is observed.
3.Horizontal Gene Transfer and Rapid Spread
Many fosfomycin resistance genes (e.g., fosA, fosB, fosC) are located on mobile genetic elements such as plasmids. This allows horizontal transfer between different bacterial species, accelerating the global spread of resistance in both community and healthcare settings.
4.Complex and Multifactorial Resistance Mechanisms
Resistance can arise via: Enzymatic inactivation (e.g., FosA enzymes) Reduced intracellular accumulation (due to transporter mutations)
Target modification (via MurA mutations) These multifactorial mechanisms complicate both detection and treatment planning.
5.Challenges in Laboratory Testing
Standardized methods for fosfomycin susceptibility testing (especially for non-urinary isolates) are limited. Some commonly used methods (e.g., disk diffusion, automated systems) may produce inaccurate results, increasing the risk of misguided therapy.
6.Limited Surveillance and Monitoring
Global surveillance for fosfomycin resistance is inadequate compared to other major antibiotics. This limits the ability to track resistance trends, implement control measures, and guide empirical therapy based on local epidemiology.
7.Dependence on Combination Therapy
As monotherapy becomes less effective, clinicians increasingly rely on fosfomycin-based combination regimens. This increases: Treatment complexity ,Cost, Risk of drug interactions or adverse effect

❖ Future of Fosfomycin Resistance

1.Increasing Resistance Rates
Continued overuse or misuse of fosfomycin—particularly as monotherapy—is likely to accelerate resistance, especially in high-burden settings.
Resistance is expected to rise among: ESBL-producing Enterobacterales Carbapenem-resistant organisms Pseudomonas aeruginosa and other non-fermenters.
2.Global Spread via Mobile Resistance Genes
Plasmid-mediated genes such as fosA3 are increasingly reported across continents.
The horizontal transfer of these genes between species will likely: Broaden the range of resistant pathogens Make infections harder to treat in both hospitals and communities
3.Need for Enhanced Surveillance
Future control depends on global antimicrobial resistance (AMR) monitoring programs that include fosfomycin. Improved surveillance can: Identify emerging resistance hotspots Inform local and global treatment guidelines
4.Development of Diagnostic Tools
Innovations in rapid and reliable fosfomycin susceptibility testing are critical. Wider adoption of molecular diagnostics could allow: Quick detection of fos genes Personalized antibiotic selection to avoid resistance-driven failure
5.New Therapeutic Strategies The future may include:
Fosfomycin combination therapies (e.g., with β-lactams or aminoglycosides) Adjuvants or resistance inhibitors targeting enzymes like FosA
Modified fosfomycin derivatives with improved pharmacodynamics
6.Regulatory and Stewardship Interventions
Greater focus on antimicrobial stewardship is essential to: Prevent overuse
Preserve fosfomycin's effectiveness
Guidelines may evolve to limit use to cases with proven susceptibility or as part of combination regimens
7.Potential for Regional Disparities
High-income countries may implement stricter stewardship and monitoring. Low- and middle-income countries may face higher resistance due to: Unregulated antibiotic use
Limited access to diagnostics and surveilla.

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CONCLUSIONS AND FUTURE OUTLOOK

The data presented here lead to the conclusion that fosfomycin has comparable clinical efficacy with other antibiotic classes and has retained activity against MDR organisms. Fosfomycin therefore has a place in the armamentarium of substances to combat chal_lenging indications in the multidrug resistance era. Moreover, it shows an overall favourable safety profile. Sepsis/bacteraemia, and respiratory tract, urinary tract, CNS, and bone and joint infections were identified as the most important indications, combined with a more recent trend towards the treatment of MDR Gram-negative bacteria.

Fosfomycin is a bactericidal antibiotic with a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. It presents good distribution into several tissues. It has a unique mechanism of action that may provide a synergistic effect to other antibiotics, including beta-lactams, aminoglycosides, and fluoroquinolones. Oral fosfomycin is used in the treatment of UTIs, mainly those caused by E. coli and E. faecalis. Intravenous fosfomycin has been administered in combination with other antibiotics for the treatment of nosocomial infections due to MDR Gram-positive and Gram-negative bacteria in daily doses ranging from 12 to 20 g. The intravenous administration of fosfomycin is associated with a low incidence of adverse effects.

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