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Fosfomycin in antimicrobial stewardship programs

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ABSTRACT

Due to the increase in antimicrobial resistance, strategies such as antimicrobial stewardship programs (ASP) have been developed to improve the clinical results, decrease the adverse effects and the development of resistances and ensure cost-effective therapies. Fosfomycin has a unique mechanism of action against Gram-positive and Gram-negative bacteria. Cross-resistance is uncommon; however, fosfomycin should be used in combination in severe infections to avoid selecting resistant mutations. Fosfomycin's oral formulation facilitates sequential treatment, has low toxicity and high tissue penetration, even in the central nervous system and bone. Fosfomycin is active against resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*, as well as against resistant Gram-negative bacteria such as extended-spectrum beta-lactamase-producing and carbapenemase-producing enterobacteria. Fosfomycin is therefore useful for cases of persistent bacteremia, skin and soft tissue infections, as a glycopeptide-sparing and carbapenem-sparing drug for healthcare-associated infections and for polymicrobial infections. Published studies have demonstrated the synergy between fosfomycin and beta-lactams, daptomycin and glycopeptides against MSSA and MRSA; with linezolid in biofilm-associated infections and with aminoglycosides and colistin against Gram-negative bacteria, providing a nephroprotective effect.

Keywords: Fosfomycin, ASP, Multidrug resistant microorganisms, Antibiotic synergy.

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The increase in infections caused by multidrug-resistant (MDR) microorganisms is currently one of our greater medical challenges. In fact, antimicrobial resistance is considered by the World Health Organization as one of the greater threats to worldwide health. The problem is aggravated by the lack of a parallel increase in new antibiotics, mainly of agents that offer relevant advantages in treating MDR bacteria [1]. While new compounds are being developed (a long and costly process), a number of "old" antibiotics developed decades ago and whose use was discontinued for various reasons are being repurposed for new indications [2]. This situation has prompted the design and implementation of various strategies to alleviate the problem. One of these strategies is the implementation of antimicrobial stewardship programs (ASP), whose objectives are to improve clinical results, reduce adverse effects related to the use of antibiotics (including resistance) and ensure a cost-effective therapy [3].

One of the lines of action in ASP is the selection of antibiotics that do not promote the emergence of MDR microorganisms. Cephalosporins, quinolones and carbapenems have been associated with the selection of extended-spectrum beta-lactamase (ESBL)-producing enterobacteria, *Clostridium difficile* and MDR *Pseudomonas* [3]. In addition, alternatives need to be found to treat these increasingly resistant microorganisms.

Fosfomycin has a unique mechanism of action against Gram-positive and Gram-negative bacteria, through peptidoglycan synthesis inhibition. This unique mechanism of action implies that cross-resistance is very rare [4]. However, fosfomycin in monotherapy selects resistant mutations and therefore needs to be employed in combination with other agents to treat severe infections. Fosfomycin offers the advantage of its low toxicity and ease of oral administration in sequential treatment (e.g., urinary tract infection), unlike other options such as colistin and tigecycline. Just as other old antibiotics, however, fosfomycin was not subject to a development program as strict as the current programs for authorization; thus,

the necessary pharmaceutical information for developing optimal dosage regimens (maximizing the efficacy and minimizing the toxicity) is limited [5]. Given fosfomycin's potential, studies need to be conducted to determine its efficacy in new contexts and to define its optimal pharmacokinetics/pharmacodynamics index [6, 7].

FOSFOMYCIN IN ANTIMICROBIAL STEWARDSHIP PROGRAMS FOR INFECTIONS BY GRAM-POSITIVE MICROORGANISMS

Fosfomycin can be useful for treating infections caused by drug-resistant Gram-positive bacteria because of fosfomycin's activity against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae* [8, 9]. Due to this spectrum of action, fosfomycin is useful for cases of persistent bacteremia, such as initial or sequential therapy of skin and soft tissue infections, as a glycopeptide-sparing drug for healthcare-related infections and for polymicrobial infections by enterococci, Gram-negative microorganisms and MRSA. Fosfomycin is also a treatment option for nosocomial infections caused by vancomycin-resistant enterococci such as bacteremia, pneumonia or intra-abdominal infections [6].

Its use in combination with other antibiotics reduces the risk of developing fosfomycin resistance during therapy. Several synergy studies have shown that fosfomycin can decrease the penicillin resistance level in pneumococci and methicillin resistance in staphylococci, altering the expression of penicillin-binding proteins. Studies have also been published that demonstrated the synergy *in vitro* between fosfomycin and beta-lactams against methicillin-susceptible *S. aureus* (MSSA) [10]. This combination can therefore be an option in cases of persistent bacteremia [11, 12], although randomized studies are needed to demonstrate the effect of this combination for treating bacteremia by MSSA. A number of experimental studies have demonstrated the synergy between fosfomycin and various antibiotics against MRSA strains. In experimental models of endocarditis (*in vitro* and *in vivo)* that have evaluated the synergy of fosfomycin combined with various beta-lactams against MRSA and strains of *S. aureus* with intermediate glycopeptide susceptibility, the combination of fosfomycin and imipenem was the most active. A multicenter study assessed the clinical efficacy and safety of treatment with fosfomycin and imipenem as salvage therapy for 16 patients with endocarditis or complicated bacteremia by MRSA. The blood cultures became negative within the first 72 h after the first dose, and the cure rate was 69%, with only 1 death attributable to the infection; the combination was shown to be safe in 94% of the patients [13]. Currently, there is an ongoing randomized clinical trial by the same team comparing vancomycin versus the combination of imipenem and fosfomycin in infectious endocarditis by MRSA with the minimum inhibitory concentration (MIC) of vancomycin <2 mg/L [14]. The results could demonstrate that this combination is effective and safe in patients with complicated bacteremia by MRSA and can be a therapeutic option that spares treatments with glycopeptides whose use has been associated with a poor response to new drugs (such as daptomycin).

The synergy between fosfomycin and daptomycin has been studied *in vitro*, and although the experience is limited, there are several reports of cases of bacteremia by MRSA successfully treated with this combination [15, 16]. To assess the safety and efficacy of this combination, an open, multicenter randomized study is underway in Spain comparing this combination versus daptomycin in monotherapy in patients with bacteremia by MRSA [17]. These combinations could therefore be considered in cases of persistent bacteremia or those with a higher risk of complication (e.g., advanced age, significant comorbidity, bacteremia of unknown focus) [18]. For severe infections caused by methicillin-resistant *S. epidermidis*, especially those with a large inoculum (such as endocarditis), the use of antibiotics in monotherapy, including vancomycin at suboptimal dosages, can promote the selection of resistant mutations. The recommendation is therefore to use combinations. The use of vancomycin plus fosfomycin is the best option [19].

The oral formulation of fosfomycin is an added value in treating community-acquired infections, such as skin and soft tissue infections by MRSA. Fosfomycin is also useful for improving sequential therapy in patients infected by resistant bacteria that would otherwise require maintaining intravenous administration, should other options be used. The reduction in hospital stay can be quite significant in some cases. The high concentrations in urine reached by fosfomycin allow for its use in monotherapy against infections by vancomycin-resistant enterococcus in this location [9]. Fosfomycin is a low-molecular-weight molecule with low protein binding, which favors its penetration into the interstitial fluid of subcutaneous cell tissue in healthy patients, patients with diabetes and critically ill patients. Due to its structural similarity to hydroxyapatite, fosfomycin penetrates the bone in adequate concentrations for treating MRSA and other pathogens. Fosfomycin is therefore an alternative for treating diabetic foot infections and osteomyelitis [20], even as salvage therapy in cases of clinical failure or the development of resistances [21]. The use of fosfomycin in combination has an immunomodulatory and nephroprotective effect when employed with nephrotoxic drugs such as aminoglycosides and vancomycin. Based on studies on animal models, this effect is apparently due to the inhibition of histamine release that occurs after the destruction of mast cells [7, 22]. There are even published cases of extended therapy with the combination of vancomycin, aminoglycoside and fosfomycin with no renal function impairment [23].

High dosages of antibiotics and extended durations are necessary for the treatment of infections associated with biofilms. The combination of linezolid and fosfomycin has shown synergy, which could help decrease the dosage of both drugs and reduce the risk of adverse effects such as the thrombopenia and peripheral neuropathy associated with linezolid [24].

FOSFOMYCIN IN ANTIMICROBIAL STEWARDSHIP PROGRAMS FOR INFECTIONS BY GRAM-NEGATIVE MICROORGANISMS

The main objectives of ASP for infections caused by Gram-negative microorganisms is to prevent the emergence of further resistance and to provide a more effective and efficient use of the available antibiotics. The lack of effective antibiotics in the face of increased resistance is especially important in infections caused by Gram-negative microorganisms.

The increase in infections by MDR microorganisms requires the use of very broad-spectrum empiric antibiotics such as carbapenems, often with no options for de-escalation. A number of old antibiotics repurposed in new indications have significant toxicities, which is not the case for fosfomycin. Let us see fosfomycin's potential role in this context.

1) Preventing the emergence of multidrug-resistant microorganisms

Fosfomycin, unlike carbapenems, has not been overused, so that its use can contribute towards decreasing the selective pressure of other broad-spectrum antibiotics, as it does not promote the emergence of MDR microorganisms, and reserving potent antibiotics such as carbapenems for the occasion when other options are lacking. In addition, fosfomycin does not appear to promote the selection of *C. difficil*e [25]. In some cases, penicillin allergies motivate the selection of a carbapenem for the treatment. An added value of fosfomycin is the possibility of employing it instead of carbapenems as an option for patients with penicillin allergies.

Most studies on fosfomycin efficacy have been conducted on urinary tract infection, because despite fosfomycin's suboptimal oral bioavailability (which is improved in the trometamol formulation), it reaches high concentrations in urine. However, fosfomycin presents good penetration in tissues such as the central nervous system, lung, abscesses, bone and soft tissue, as well as in urine. Although the intravenous formulation has been available in Europe and Japan, it is not available in the US, and therefore the publications that document its efficacy are case-series or case-reports [26]. A clinical trial (ZEUS) is currently ongoing to assess the efficacy of intravenous fosfomycin versus piperacillin/tazobactam in complicated urinary tract infection (Available at https://clinicaltrials.gov/ct2/show/NCT02753946).

There is increasing evidence in favor of the safety and efficacy of intravenous fosfomycin for treating other systemic infections, even in critically ill and immunocompromised patients [27-29].

2) Treating multidrug-resistant microorganisms

The scarcity of new drugs for treating MDR microorganisms is a public health problem, and it is imperative that we find options. The use of old drugs such as fosfomycin can offer a short-term solution [7]. Fosfomycin is frequently active against multidrug-resistant enterobacteria and even extremely drug-resistant enterobacteria, with greater activity against *E. coli* than against *Klebsiella, Enterobacter* and *Pseudomonas*.

To assess fosfomycin's potential as a carbapenem-sparing drug, a clinical trial [30] is currently underway that is attempting to remedy the lack of data regarding the development of fosfomycin resistance during therapy and its impact on colonization by MDR Gram-negative bacilli. This study will compare the efficacy of intravenous fosfomycin versus meropenem for treating bacteremic urinary tract infection by ESBL *E. coli*. There is also the option of oral sequential therapy with fosfomycin trometamol (once the source has been controlled and the bacteremia has been eliminated), providing a basis for using fosfomycin as an alternative to meropenem for this type of infection.

The data on fosfomycin's clinical efficacy for treating infections by carbapenemase-producing bacteria are limited [28, 31]. Fosfomycin susceptibility varies by geographical region [32], although the fact that the MIC cutoff is not universally accepted contributes to the confusion. Fosfomycin resistance is still scarce in Europe but is remarkable in a number of Asian countries [33]. It is interesting to note that up to 94% of New Delhi metallo-beta-lactamase carbapenemase-producing strains (for which the therapeutic arsenal is especially scarce) are susceptible to fosfomycin [34, 35]. Fosfomycin has also been shown to be effective against strains that produce mcr-1, the plasmid that encodes the colistin resistance gene. Fosfomycin's susceptibility is greater in *E. coli* than in *Klebsiella* [36]. To treat urinary tract infections by carbapenemase-producing bacteria, oral fosfomycin trometamol has been employed at high dosages (3 g/48 h x 3 d) [37].

Due to the risk of resistance appearing during treatment, fosfomycin's use in monotherapy is not generally recommended; however, fosfomycin's synergy with antibiotics from other families enables the administration of these antibiotics at lower and less toxic dosages (especially aminoglycosides, glycopeptides and polymyxin B) [5]. Furthermore, fosfomycin represents an alternative to nonnephrotoxic antibiotics, given that fosfomycin also presents synergy with carbapenems (even in some carbapenem-resistant strains). As has been stated earlier for Gram-positive microorganisms, fosfomycin provides protection from the renal toxicity of aminoglycosides in animal models [38]. In any case, when the use of fosfomycin in combination is planned, a synergy test should be performed, given that cases of unpredictable antagonism have been reported [39].

The emergence of fosfomycin resistance in *Pseudomonas aeruginosa* is more common than in *E. coli*, even in combined therapies, and, unlike *E. coli*, does not entail a reduction in bacterial fitness [40]. A number of authors therefore do not recommend using fosfomycin for infections by *Pseudomonas aeruginosa*. However, the O12 serotype, which is usually associated with a resistant phenotype, is more susceptible than others to fosfomycin. There are favorable clinical experiences

in treating respiratory infections by MDR *Pseudomonas*, especially in patients with respiratory exacerbations of cystic fibrosis, in which fosfomycin's efficacy in biofilms contributes [41], as well as in ventilator-associated pneumonia, although there are no randomized clinical trials on this issue [42].

In summary, fosfomycin is an antibiotic with potential for use in ASP given its bactericidal activity, good tolerance, good tissue penetration, absence of induction of MDR microorganisms and its activity against ESBL-producing and carbapenemase-producing enterobacteria. Fosfomycin even has activity against some types with no other available effective antibiotics and can act synergistically with other antibiotics.

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