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Current key topics in fosfomycin

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Fosfomycin in the pediatric setting: Evidence and potential indications

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ABSTRACT

To date, there has been little experience in using fosfomycin in children. However, its broad spectrum of action and excellent safety profile have renewed interest in this antibiotic, especially for treating infections by multidrug-resistant bacteria. The main indication for fosfomycin in pediatrics is currently community-acquired lower urinary tract infection. Given its good activity against bacteria, fosfomycin can also be useful in urinary infections caused by extended-spectrum beta-lactamase-producing enterobacteria. Fosfomycin presents very good dissemination to tissues including bone and is therefore an option in the combined therapy of osteomyelitis, especially in cases produced by methicillin-resistant *Staphylococcus aureus* (MRSA) or in cases with beta-lactam allergies. Fosfomycin can also be employed in combination for multidrug-resistant Gram-negative bacteremia (especially carbapenemase-producing enterobacteria), *S. aureus* (if there is a high suspicion of MRSA or complicated infections) and vancomycin-resistant *Enterococcus* spp. Other infections in which fosfomycin could be part of a combined therapy include staphylococcal endocarditis (in case of beta-lactam allergy or MRSA), central nervous system infections (mainly by MRSA, *S. epidermidis*, *Listeria* and resistant pneumococcus), nosocomial pneumonia and infections associated with mechanical ventilation.

Keywords: Fosfomycin, Pediatrics, Children, Newborns, Beta-lactam resistance.

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BACKGROUND

Fosfomycin is a broad-spectrum bactericidal antibiotic, with activity against Gram-positive and Gram-negative microorganisms, including multidrug-resistant bacteria. Fosfomycin presents excellent dissemination to tissues (skin, soft tissue, muscle, bone, lungs, central nervous system) and has shown efficacy in experimental biofilm models [1]. Its unique mechanism of action leads to a synergistic effect with many antimicrobials and makes cross-resistance exceptional [1, 2]. Fosfomycin also presents an excellent safety profile in children [3], even in prolonged therapies [4]. These characteristics make the antibiotic a highly attractive option, especially for treating infections by multidrug-resistant bacteria, although the experience with children is still very limited.

DOSAGE OF FOSFOMYCIN FOR PEDIATRIC PATIENTS

The available formulations and pediatric doses for fosfomycin are shown in table 1 [5, 6]. The recommendations for its parenteral administration are based on highly limited data, especially regarding newborns. Although the datasheet indicates the possibility of intravenous administration every 12 h, pharmacokinetic studies conducted on children show that intervals of every 6-8 h are preferable, except for preterm newborns [7]. In premature infants, the recommendation is 100 mg/kg/day divided into 2 doses; for full-term newborns, 200 mg/kg/day in 3 doses is recommended. Starting at 12 years of age or 40 kg of weight, the dosage is the same as for adults [8]. In the case of infections by multidrug-resistant microorganisms, there are no specific recommendations for children, while for adults the recommendation is 8-12 g/day for Gram-positive microorganisms and 16-24 g/day for Gram-negative microorganisms [9].

For adults, the recommendation is to adjust the dosages for those with kidney failure and creatinine clearance lower

Table 1	Dosage of fosfomycin for pediatric patients
ORALLY	Calcium salt (suspension 250 mg/5 mL, 500-mg capsules)
	Younger than 1 year: 150-300 mg every 8 h
	Older than 1 year: 250-500 mg every 8 h
	Trometamol salt (granules for oral solution, 2 g or 3 g)
	6-11 years: 2 g single dose[a]
	≥12 years: 3 g single dose[a]
PARENTERALLY	Intramuscularly (starting at 2 and a half years): 500-1000 mg every 8 h[b]
	Intravenously: 200-400 mg/kg/day in 3 doses (maximum 4 g/dose[c])

[a]For recurrent infections or microorganisms susceptible to higher dosages, 2 doses might be necessary, with a 24-h interval.
[b]If a larger dose is needed, the intravenous route should be employed.
[c]For children older than 12 years (>40 kg), a dosage of up to 8 g every 8 h may be considered for treating severe Gram-negative infections with reduced susceptibility.

than 40 mL/min; for children, however, there are insufficient data to make dosage recommendations for those with nephropathy [8].

URINARY TRACT INFECTION

Urinary tract infection (UTI) is one of the most common childhood bacterial infections [10]. It is estimated that 7-8% of girls and 2% of boys will have at least one UTI before the age of 8 years. Febrile UTI mainly affects infants (of both sexes), while cystitis mainly occurs in girls older than 3 years [11, 12]. Acute pyelonephritis is especially severe in small infants, who have a greater risk of bacteremia and sepsis [13].

Escherichia coli is the main etiological agent in all age groups [14]. Since the introduction of conjugated vaccines against *Streptococcus pneumoniae*, *E. coli* has represented the most common cause of bacteremia in infants, and more than 90% occurr in children with UTI [15]. In Spain, various epidemiological studies have been conducted in recent years in the pediatric population, in which *E. coli* is the causal agent for 60-80% of UTIs, in patients from primary care, the emergency department and hospitals. Other Gram-negative microorganisms include *Klebsiella*, *Proteus*, *Enterobacter* and *Citrobacter*. Among the Gram-positive bacteria, we have *Enterococcus* (especially in small infants and children with previous nephro-urological conditions), *Staphylococcus saprophyticus* (adolescents) and, in rare cases, *Staphylococcus aureus* [16-18].

The enterobacteria's resistance profile varies due to numerous factors, such as the patient's characteristics and their geographical origin. We therefore need to determine the local resistance rates to make appropriate recommendations on empiric treatment for these microorganisms [19]. In Spain, the most recent studies on the pediatric population have shown that up to 50-60% of *E. coli* are ampicillin-resistant and that 20-30% are cotrimoxazole-resistant; these antibiotics should therefore not be employed in empiric therapy [16-18]. Resistances to amoxicillin-clavulanate appear to be increasing, although with significant local variations [16-18]; it is therefore advisable to employ this antibiotic with caution, especially in those areas where susceptibility is below 85-90%. In contrast, the resistance rates remain below 10% for aminoglycosides, fosfomycin and second and third-generation cephalosporins [16-18].

Treatment with fosfomycin has numerous advantages for use in children with UTI: 1) It is easy to dose, 2) it achieves high concentrations in urine, 3) adverse effects are uncommon, and 4) fosfomycin does not affect the intestinal flora. Due to the excellent susceptibility pattern of *E. coli* and other enterobacteria, fosfomycin is considered one of the treatments of choice for afebrile UTI, especially in its trometamol form [16]. In the case of febrile UTI, fosfomycin is not recommended for use in monotherapy at this time due to the potential development of resistances during therapy [20]. Although the rate at which resistant mutations appear *in vitro* is high, the rate is very low in clinical studies and especially in the case of UTI by *E. coli*, due to the high antibiotic concentration and acidic pH in the urinary tract. The development of resistances could entail a biologic cost for bacteria, with a lower growth rate and adherence to urinary epithelial cells. To establish the role of fosfomycin in severe UTI, data from the FOREST and ZEUS studies, recently conducted on adult patients, will be of considerable assistance. The FOREST study was conducted in Spain from 2014 to 2017 and compared the efficacy of fosfomycin versus meropenem in treating bacteremic UTI by extended-spectrum beta-lactamase (ESBL)-producing *E. coli* [21]. The ZEUS study began in the US in 2017 and compared the safety and efficacy of fosfomycin versus piperacillin-tazobactam in complicated UTI [22].

Although these conditions are still uncommon in children, an increase in infections by ESBL-producing *E. coli* has been

observed in recent years in patients in the community, many times in combination with other mechanisms of antibiotic resistance [19]. It is currently estimated that, in Spain, these bacteria appear in 1-4% of pediatric UTIs [16-18, 23] and are increasingly associated with recurrent UTI [23]. These patients could benefit from fosfomycin therapy [24], given that very high susceptibility to fosfomycin has been demonstrated in ESBL-producing enterobacteria in UTIs [25]. However, there are barely any available pediatric data on this issue [26].

In Spain, *Enterococcus faecalis* presents high susceptibility to fosfomycin [16-18], which would therefore make this antibiotic an excellent option for treating lower UTIs due to this microorganism.

OSTEOARTICULAR INFECTION

Osteoarticular infection is more common in children than in adults, with 50% of cases occurring in children younger than 5 years, with *S. aureus* the most common microorganism in all ages. In newborns and infants younger than 3 months, other significant pathogens are *Streptococcus agalactiae* and enterobacteria; in those younger than 2 years, *Kingella kingae* is a significant pathogen. The fundamental importance of these infections lies in the potential involvement of cartilage and epiphysis, which can alter bone growth and lead to sequelae [27]. In Spain, more than 90% of infections in children are caused by methicillin-susceptible *S. aureus* (MSSA) [27]. In recent years, however, the emergence of community-acquired MRSA has been observed in various countries around the world [28, 29]. Community-acquired MRSA is typically susceptible to other non-beta-lactam antibiotics, and there are various options for their use in pediatrics: clindamycin, cotrimoxazole, glycopeptides, rifampicin, linezolid and daptomycin [30]. In terms of the fosfomycin susceptibility of *S. aureus*, 9 studies have been published between 2010 and 2015, with 7 of the studies showing sensitivities greater than 90%, with similar data in MSSA and MRSA [31]. Fosfomycin also presents excellent penetration in tissues including bone [32].

In France, one of the most widely used empiric treatment regimens in pediatric osteomyelitis is the combination of third-generation cephalosporin and fosfomycin [33, 34]. The results of treating acute hematogenous osteomyelitis with fosfomycin are highly favorable, and fosfomycin could therefore be considered an option for combined therapy, especially in cases produced by MRSA and for patients with allergies [35].

BACTEREMIA AND SEPSIS

Infants. Neonatal sepsis is still a significant cause of morbidity and mortality. Based on the time of onset, the condition is divided into early and late sepsis. Early sepsis typically occurs in the first 72 h of life and is caused by vertical transmission, before or during childbirth. The most common microorganisms involved are *S. agalactiae* and *E. coli*. Late infections occur starting from the third day of life, in most cases by horizontal transmission. In addition to the previously mentioned microorganisms, coagulase-negative staphylococci (the most common cause of sepsis in neonatal intensive care patients), *S. aureus* and Gram-negative bacilli are involved, among others [36]. Prematurity and low birth weight are the main risk factors for neonatal sepsis. Preterm newborns present immune system dysfunction and usually require extended hospitalization, venous accesses and mechanical ventilation, which contribute to a greater risk of infection [36]. Exposure to multiple antibiotic cycles during their hospitalization increases the risk of colonization and infection by multidrug-resistant bacteria [37]. Coagulase-negative staphylococci are still the most common bacteria in late nosocomial sepsis in premature newborns and have high resistance rates. In recent years, however, resistant Gram-negative bacteria have emerged, especially ESBL-producing enterobacteria [37, 38]. These infections present greater severity and are associated with higher morbidity and mortality than those caused by coagulase-negative staphylococci.

Various studies have confirmed the relationship between pathogens isolated in colonization detection programs and subsequent isolates in blood cultures, especially in children with colonization by *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae* and *Serratia marcescens* [39]. Selecting an inadequate empiric antibiotic therapy for a patient with colonization by multidrug-resistant Gram-negative bacteria can result in longer hospitalizations, higher mortality and poorer neurological outcomes [39]. Due to the limited therapeutic arsenal in these cases, a number of authors have proposed assessing the use of fosfomycin in combined therapy [40]. There are currently few data on the pharmacokinetics in newborns, and studies with premature infants are needed to assess the effect of kidney maturation in the clearance of the drug, which could change the administration interval. Specific studies on the drug's toxicity in infants have not been conducted either, although no adverse effects have been reported in patients treated for neonatal sepsis. Future studies should assess the risk of hypernatremia, given the sodium intake that the administration of fosfomycin entails [40].

To date, 2 series have been published on the use of fosfomycin in neonatal sepsis by Gram-negative microorganisms: one with 11 newborns (from a total of 24 patients) with sepsis by *S. marcescens*, most of whom were treated with fosfomycin and gentamicin [4], and another series of 21 patients with combined therapy with aminoglycoside in neonatal sepsis and UTI [41]. In both studies, 90% of the patients had favorable outcomes.

Infants and children. Pediatric sepsis is associated with a significant consumption of healthcare resources. The incidence of pediatric sepsis is higher in infants and children with underlying diseases, especially with immune, hematologic and oncologic diseases [42]. The overall mortality is 6%, increasing to 23% in cases produced by multidrug-resistant Gram-negative microorganisms [43, 44]. The most common causes of bacter-

emia in hospitalized children are coagulase-negative staphylococci, Gram-negative bacilli and *S. aureus* [45].

There are very few data on bacteremia by multidrug-resistant Gram-negative bacilli in the pediatric population. A recent study conducted in Italy within the Antibiotic Resistance and Prescribing in European Children (ARPEC) project analyzed more than 1000 episodes of bacteremia, 26% of which were caused by Gram-negative microorganisms, 39% of which were multidrug-resistant [44]. In these infections, there was synergy in the combination of fosfomycin and carbapenems or colistin [1]; therefore, the use of fosfomycin was proposed within a combined therapy and is the first choice in the case of carbapenemase-producing enterobacteria [46].

There are no pediatric guidelines on treating bacteremia by *S. aureus*. However, the guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) recommend combined therapy with fosfomycin and daptomycin as a possible option for suspected bacteremia by *S. aureus* with a high probability of MRSA and/or patient instability, secondary bacteremia or complicated infection [47].

In recent years, there has been an increase in nosocomial bacteremia by *Enterococcus* spp., especially in intensive care units (neonatal and pediatric) and hemato-oncological patients [48]. In severe infections by vancomycin-resistant strains, the use of fosfomycin in combination with daptomycin or linezolid may be considered [49].

ENDOCARDITIS

Endocarditis is uncommon in children and mainly affects infants, older children and adolescents with heart disease. The most commonly involved bacteria are streptococci of the *viridans* group in children with heart disease and *S. aureus* in children with no prior heart disease [50]. The mortality of endocarditis in children is 5-10% [51]. The guidelines of the European Society of Cardiology recommend similar treatment regimens for adults and children and list the indication for fosfomycin (in combination with daptomycin) as a treatment option for staphylococcal endocarditis on native valves in patients with allergies to beta-lactams or MRSA infection [52]. The SEIMC guidelines recommend the combination of daptomycin and fosfomycin as the empiric treatment of choice for all cases of endocarditis (native and prosthetic valve) in patients with beta-lactam allergies and as the definitive treatment in native valve endocarditis in cases of beta-lactam allergy or MRSA [47]; the use of this combination could therefore be assessed for children in the same situations.

CENTRAL NERVOUS SYSTEM INFECTIONS

Due to its low molecular weight and low protein binding, fosfomycin's cerebrospinal fluid penetration is high [53] and could therefore also be employed in central nervous system infections. The use of fosfomycin has been reported in infections by MRSA and *S. epidermidis*, typically within combined therapy [54]. In terms of pneumococcus, monotherapy with fosfomycin has failed in experimental meningitis models [55], while combined therapy can be useful in strains with high cephalosporin resistance [56]. In pediatrics, the use of fosfomycin in combination with third-generation cephalosporins has been reported in 2 patients with meningitis by pneumococcus with intermediate cephalosporin susceptibility [57]. The case of an infant with multiple brain abscesses by *Citrobacter koseri* was recently published, which was resolved with surgical drainage and combined therapy with meropenem and fosfomycin [58]. *Listeria monocytogenes* is resistant *in vitro* but susceptible *in vivo* to fosfomycin; the use of fosfomycin in combination with beta-lactams could therefore be assessed for complicated meningoencephalitis by these bacteria [59].

OTHER INFECTIONS

The use of fosfomycin in respiratory infections is poorly documented, despite its good lung dissemination. Currently, the use of fosfomycin in community-acquired pneumonia is not justified given the high susceptibility of pneumococcus to penicillin and cefotaxime [60]. Fosfomycin could be useful within combined therapy in nosocomial pneumonia and infections associated with mechanical ventilation. Fosfomycin has also been employed by inhalation in cystic fibrosis, in combination with tobramycin [61].

In acute gastroenteritis, especially in premature infants, fosfomycin has also been employed with good tolerance [62, 63]. Currently, the antibiotic therapy for these infections is reserved for selected cases (small infants, immunosuppression, severe symptoms), and a number of authors have also proposed antibiotic therapy for conditions in which the transmission of the infection needs to be prevented, such as hospitalized patients and in closed institutions [64]. Given the good fosfomycin susceptibility pattern of the main bacteria that cause gastroenteritis, fosfomycin could also be assessed for use in this indication.

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