REVIEWS ARTICLE

Potential of fosfomycin in treating multidrug-resistant infections in children

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In an era of increasing antimicrobial resistance, there are limited treatment options available to treat multidrug-resistant organisms in paediatric patients. Fosfomycin is an antibiotic defined as ‘critically important’ by the World Health Organization due to its potential efficacy against multidrug-resistant bacteria and is increasingly cited in the international literature as a promising antimicrobial for combating sepsis in an era of increasing antimicrobial resistance. With broad-spectrum cover that includes both Gram-positive and Gram-negative organisms and both parenteral and oral formulations available, fosfomycin provides a promising treatment option for paediatric patients. This review summarises fosfomycin’s spectrum of activity, published efficacy in paediatric patients, safety considerations and pharmacokinetic data, as well as identifying current clinical trials delineating pharmacokinetic parameters and safety parameters in neonatal sepsis which will provide further information regarding the use of fosfomycin in neonatal and paediatric infections. Limitations regarding the current standards for fosfomycin susceptibility definitions, variations in dosing regimens and the potential mechanisms for resistance are also discussed.

Key words: antimicrobial resistance; carbapenem-resistant Enterobacteriaceae; extended spectrum $\beta$-lactamase; fosfomycin; legacy antibiotics; neonatal sepsis.

Antimicrobial resistance (AMR) is a global health challenge that transcends borders yet disproportionately impacts the most vulnerable. The extensive use and misuse of antibiotics since their discovery has resulted in a significant increase in the emergence and spread of multidrug-resistant (MDR) bacteria, and there is increasing morbidity and mortality caused by their invasive infection. In high-income settings, AMR is estimated to cause a similar disease burden to human immunodeficiency virus, tuberculosis and influenza combined. In low- and middle-income settings, neonates (born into crowded wards where infection control practices may be poorly resourced), are particularly vulnerable to AMR; and AMR has been estimated to cause 60,000 deaths in newborn babies alone each year.

The clinical impact of AMR began with the emergence of resistant strains of Gram-positive organisms such as Staphylococcus aureus in the 1940s, yet it is the arrival of carbapenem-resistant Enterobacteriaceae (CRE) that has heralded the dawn of a post-antibiotic era. Enterobacteriaceae are Gram-negative, non-spore forming facultative anaerobic bacteria that are predominantly enteric gastrointestinal commensals, yet have the potential to cause invasive bacteraemia. As AMR has evolved, Enterobacteriaceae and other Gram-negative bacilli have become the most clinically important microbes due to their diversity of resistance mechanisms and ability to produce powerful and highly mobile extended spectrum $\beta$-lactamases (ESBLs) and carbapenemases that can spread rapidly worldwide.

There are few agents currently available to treat ESBL-producing and CRE infections in children, due to limited safety and efficacy data and the toxicity profiles of many agents which are commonly used to treat these infections in adults. In resource-rich settings, critically ill children infected with ESBL-producing organisms are often prescribed carbapenems or other broad-spectrum agents that are associated with a high incidence of adverse events.

Key Points

1. In an era of increasing antimicrobial resistance, there are a limited number of antibiotics available to treat multidrug-resistant infections in children, particularly those caused by extended spectrum $\beta$-lactamase-producing and carbapenem-resistant bacteria.
2. Fosfomycin is a legacy antibiotic that exhibits low levels of resistance world-wide, and is a very promising treatment option for a wide range of Gram-positive and Gram-negative infections (including multidrug-resistant infections) in children.
3. Published data regarding fosfomycin’s safety in children is promising. Dosing regimens vary in countries in which it is licensed, and further delineation of pharmacokinetic parameters in children is required.

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later-generation cephalosporins; yet for CRE infections, a combination of two antimicrobials which ideally produce synergistic effects is often required, encompassing antimicrobials with more toxic profiles (such as polymixin, aminoglycosides, fluoroquinolones or tigecycline in adolescents). In low- and middle-income country settings, where the vast majority of AMR deaths occur each year, there are often no treatment options available.

The available options for treating MDR bacterial infections in children are therefore limited, and with a dearth of new antimicrobial agents in the discovery pipeline, legacy antimicrobials have recently been highlighted as a promising strategy for reintroduction to clinical practice despite a limited evidence base regarding their safety and pharmacokinetic profile. In 2017, the World Health Organization published a list of ‘priority pathogens’ that pose the greatest threat to human health (Table 1), to guide the research and development efforts of the scientific community in a focussed search for new antibiotic treatment regimens. Subsequently, research into carbapenem-sparing agents has increased over recent years, and older agents such as fosfomycin – an antibiotic defined as ‘critically important’ by the World Health Organization – have been highlighted as providing promise.

Fosfomycin is a broad-spectrum antibiotic that was discovered in 1969. Low international use since its discovery has resulted in retained susceptibility to a large number of organisms, and this antibiotic provides significant promise against MDR organisms in children, due to its comprehensive spectrum of activity and encouraging safety profile. There is increasing global interest regarding fosfomycin’s potential for the treatment of infections caused by many MDR organisms, particularly due to its synergistic effects when combined with aminoglycosides and carbapenem.

### Mechanism of action and pharmacokinetics

Fosfomycin was first discovered from cultures of the *Streptomyces* spp. and as a phosphonic acid derivative (structurally unrelated to other antibiotics), forms its own unique antimicrobial class. Fosfomycin is bactericidal in its effect, targeting murepapptide synthesis by inhibiting phospho-ethyl-pyruvate transferase, which is the first enzyme involved in peptidoglycan synthesis. It therefore acts on the first stage of peptidoglycan synthesis, inhibiting bacterial cell wall production at an earlier stage than most antibiotic classes. Fosfomycin’s activity depends on transportation into the bacterial cell via two different membrane transport systems: (i) the glycerol-3-phosphate transport system (GilT); and (ii) the hexose phosphate uptake transport system (UlptT), in the presence of glucose-6-phosphate. Alongside its bactericidal effects, fosfomycin also exerts immunomodulatory actions by altering levels of TNF-α, interleukins and leukotrienes, as well as reducing bacterial adherence to the epithelia of the respiratory and urinary tracts.

Fosfomycin is a small, hydrophilic agent with negligible serum protein binding and is eliminated exclusively via glomerular filtration, with a large proportion of the dose excreted unchanged in the urine promptly after dosing. The intravenous (IV) formulation of fosfomycin (fosfomycin-disodium) achieves efficacious concentrations following administration into cerebrospinal fluid, soft tissues and bone. There are two oral fosfomycin formulations available – fosfomycin tromethamine and fosfomycin calcium – which are both rapidly absorbed, yet the bioavailability for fosfomycin tromethamine is thought to be greater than fosfomycin calcium (as the latter is rendered inactive by hydrolysis in the acidic gastrointestinal tract). Previous research investigating the oral bioavailability of fosfomycin in adults documented a range between 34 and 58%. Following oral administration, absorption is via the small intestine and is slightly reduced by concurrent administration with food, although pharmacokinetic parameters do not appear to be significantly impacted by food intake. In adults, peak plasma levels (of 22–32 mg/L) occur within 3 h of a single dose of oral fosfomycin, with peak urinary concentrations occurring within 4 h.

A current clinical trial is clarifying the pharmacokinetic parameters of both IV and oral fosfomycin in neonates, which...
will confirm the bioavailability and pharmacokinetics of fosfomycin in sick infants (https://clinicaltrials.gov/ct2/show/NCT03453177).

Fosfomycin has a serum half-life of 2.4–7.3 h and achieves very high urinary concentration (>128 mg/L) which persist for up to 48 h, resulting in its highly efficacious use for urinary tract infections (UTIs).\(^{18,21–25}\) In fact, a single dose of oral fosfomycin has been found to be clinically equitable to a three- or seven-day course of fluoroquinolones, cotrimoxazole, nitrofurantoin, amoxicillin-clavulanate or oral cephalosporins in the treatment of uncomplicated cystitis across all patient groups (including pregnant women and children).\(^{26}\) Oral fosfomycin is therefore currently used in the USA and Europe for treating UTIs (predominantly in adults) caused by *Escherichia coli* and *Enterococcus faecalis* and is licensed for use in Australia for MDR UTIs in females >12 years. As fosfomycin is renally excreted, reduced creatinine clearance impacts its excretion and its dose should be adjusted in these circumstances.

Fosfomycin’s high penetration results in favourable distribution into many tissue types, although it has variable abscess permeability.\(^ {27}\) Fosfomycin crosses the blood-brain barrier (and its concentration in the cerebrospinal fluid is increased with meningeal irritation) although it should be used as part of a combination regimen in meningitis to ensure adequate CNS penetration and to prevent the development of resistance.\(^ {28}\) Fosfomycin is also able to penetrate both cortical and cancellous bone and intra-abdominal sites, and has the ability to penetrate biofilms (either alone or in combination with other antibiotics).\(^ {17}\) The bactericidal effects of fosfomycin correlate with time above the minimum inhibitory concentration, MIC (t > MIC).\(^ {29}\)

### Spectrum of activity

Fosfomycin has a broad spectrum of activity against both Gram-positive and Gram-negative organisms, including MDR organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE) and ESBL-resistant *Enterobacteriaceae* and CRE.\(^ {30}\) An overview of the organisms susceptible to fosfomycin (and MIC data/susceptibility rates, where known) is outlined in Table 2.

With regard to Gram-positive cover, fosfomycin typically has good activity (>90% susceptibility) against *S. aureus*, including MRSA and coagulase-negative *Staphylococcus* spp.\(^ {30}\) Fosfomycin is also active against *Streptococcus* spp. including *Streptococcus pneumoniae*, *Streptococcus pyogenes*.\(^ {37}\) Fosfomycin exhibits good in vitro activity against most *E. faecalis* strains, as well as the majority of VRE strains.\(^ {41,42}\)

From a Gram-negative point of view, fosfomycin is highly active against *E. coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* with susceptibility rates against these species ranging from 86 to 100%,\(^ {30}\) *Enterobacter* spp., *Citrobacter* spp., *Serratia marcescens* and *Salmonella enterica* have all exhibited susceptibility to fosfomycin. However, *Acinetobacter baumannii* and *Morganella morgani* exhibit intrinsic resistance, although some synergistic bactericidal effects may occur when combined with other antimicrobials.\(^ {30}\) For example, fosfomycin has shown efficacy against carbapenem-resistant *A. baumannii* when combined with colistin, despite its intrinsically low activity when used as monotherapy.\(^ {43,44}\) Similarly, while microbiological efficacy against *Pseudomonas aeruginosa* as a monotherapy is limited (with higher in vitro MICs documented due to inactivation of the Gsp transport system in *P. aeruginosa*), there may be some clinical efficacy when combined with a second antibiotic.\(^ {28}\)

Fosfomycin’s unique mechanism of action and the high susceptibility exhibited by MDR-organisms has resulted in a number of in vitro assessments of its antimicrobial capacity, revealing synergy with amoxicillin, daptomycin, ceftiraxone (against MDR-*Neisseria gonorrhoeae* and linezolid (for MRSA or VRE infections).\(^ {45–47}\) In ESBL-producing *K. pneumoniae*, fosfomycin exhibits synergy with carbapenems and colistin.\(^ {28}\)

### The potential of fosfomycin in paediatric patients

There are several case reports documenting fosfomycin’s efficacy when administered for the treatment of neonatal and paediatric patients with invasive infections, including those due to MDR organisms\(^ {48}\) (Table 3). Fosfomycin has a number of beneficial properties with regards to its use in paediatric patients, including a broad-spectrum of cover (which may be helpful in empirical treatment) and synergistic effects when prescribed with other antibiotics (including β-lactams, aminoglycosides and fluoroquinolones).\(^ {56}\) Subsequently, IV fosfomycin is licensed in Europe and the USA as a second-line treatment for children with osteomyelitis, complicated UTI, nosocomial lower respiratory tract infections, bacterial meningitis or bacteraemia associated with any of these foci of infection.

However, one of the challenges currently limiting the uptake of fosfomycin in neonates and paediatric patients is a lack of clarity regarding its dosing regimen, particularly in infants and young children. The summary of product characteristics gives a neonatal IV dosing regimen, including for preterm and term infants, stratified by age and body weight (Table 4). However, parenteral dosing recommendations for neonates and children patients vary widely between countries in which it is licensed in Europe (Table 5), and there are currently divergent published oral dosing recommendations for children, although a current pharmacokinetic trial which has completed recruitment will soon provide clarity on dosing recommendations in neonates (https://clinicaltrials.gov/ct2/show/NCT03453177).

### Safety of fosfomycin in neonatal and paediatric patients

A 2015 review of adverse events (AE) with regard to fosfomycin as documented in the international literature, as well as those reported to the US Food and Drug Administration, concluded that fosfomycin exhibits low toxicity and there are minimal concerns regarding its safety profile (in both adult and paediatric patients).\(^ {57}\) This review included data assessing 254 paediatric patients across six trials (three trials of IV and three of oral fosfomycin; age range: neonates – 15.5 years), three of which were retrospective (*n* = 118)\(^ {30,54,56}\) and three prospective randomised trials (*n* = 134).\(^ {59–61}\) In the trials involving parenteral fosfomycin, the drug was administered for up to 4 weeks for the treatment of acute haematogenous osteomyelitis, bacteraemia and lung infection; while in those trials in which oral fosfomycin was prescribed, it was administered as a single dose for the treatment of UTI. Overall, no serious safety issues related to the use of fosfomycin in children were identified in this review. The most frequently reported AEs associated with (IV and oral)
administration across all age ranges identified were non-specific rash, peripheral phlebitis (with IV administration) and gastrointestinal symptoms, although these appear to occur less frequently than other antimicrobial agents. There have been no reported serious AE attributed to fosfomycin.

Fosfomycin susceptibility testing and published in vitro efficacy data

Due to a lack of preclinical and published data no universal MIC susceptibility values have been defined for fosfomycin, with ranges from ≤32 mg/mL to >256 mg/L documented in the literature. There are two published guidelines for the susceptibility testing of fosfomycin – the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. However, both these publications have significant limitations in their breakpoint data utility for fosfomycin (Table 6). Clinical and Laboratory Standards Institute have published breakpoints for fosfomycin susceptibility to E. coli and E. faecalis urinary tract isolates only, while the European Committee on Antimicrobial Susceptibility Testing guidelines define a susceptibility breakpoint of ≤32 mg/mL for Enterobacteriaceae and Staphylococcus spp. (IV formulation only) with no disk diffusion criteria validated.

Fosfomycin susceptibility testing currently requires agar dilution with Mueller-Hinton agar supplemented with glucose-6-phosphate to reduce the rates of false resistance (as this is required for the UhpT uptake system, as described above). Alternatively, disk diffusion methods (whereby the fosfomycin discs are supplemented with glucose-6-phosphate) may be used for urinary tract isolates (Table 6). The two testing methods appear to correlate quite closely among contemporary Gram-negative clinical isolates. The labour- and cost-intensive nature of agar dilution methods makes susceptibility testing a challenge to perform in laboratories, particularly in resource-limited settings.

Despite these challenges in susceptibility definitions, there is a vast body of literature documenting the microbiological efficacy of fosfomycin against multi- and extensively drug-resistant bacteria. A recent systematic review analysed 17 antimicrobial susceptibility studies with regard to fosfomycin (accounting for 5057 Enterobacteriaceae isolates, of which 4448 were ESBL-producing organisms) revealing that over 90% of MDR isolates were susceptible to fosfomycin.

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**Table 2** Spectrum of fosfomycin activity

| Class          | Organisms                                      | Susceptibility rates, where known | MIC breakpoint (if available) |
|----------------|-----------------------------------------------|-----------------------------------|-------------------------------|
| Gram-negative  | Escherichia coli                              | Very high susceptibility (98–100%), including ESBL producing isolates | ≤32 μg/mL or ≤64 mg/L (urinary isolates) |
|                | Klebsiella pneumoniae                         | Susceptibility rates 70–85%       | ≤32 μg/mL.                   |
|                | Pseudomonas spp.                              | Variable activity, high MIC       | ECOFF <128 μg/mL.            |
|                | Haemophilus species                           | Not available                     | Not available.               |
|                | Proteus mirabilis                             | Susceptibility rates 80–97%       | ≤32 μg/mL.                   |
|                | Enterobacter spp.                             | Susceptibility rates 75–99%       | ≤32 μg/mL.                   |
|                | Citrobacter spp.                              | Susceptibility rates 100%         | ≤32 μg/mL.                   |
|                | Serratia marcescens                           | Susceptibility rates 100%         | ≤32 μg/mL.                   |
|                | Salmonella enterica                           | Susceptibility rates 90–100%      | ≤32 μg/mL.                   |
| Gram-positive  | Staphylococcus aureus and coagulase-negative  | Susceptibility rates 68–99%       | ≤32 μg/mL.                   |
|                | Staphylococcus spp.                           |                                   |                               |
|                | Streptococcus pyogenes                        | Susceptibility rate of 41%        | Not available.               |
|                | Streptococcus agalactiae                      | Not reported                      | Not available.               |
|                | Streptococcus pneumoniae                     | Susceptibility rate 72%           | Not available.               |
|                | Enterococcus spp. (including VRE)            | 96–100%                          | ≤64 mg/L (urinary isolates)  |
|                | Listeria monocytogenes                        | Susceptibility rate of 52%        | Not available.               |
| Intrinsic resistance | Acinetobacter baumannii (however, may exhibit some activity when used synergistically with other agents) | | |
| Bacteroides spp. |                                               |                                   |                               |
| Stenotrophomonas maltophilia |                                              |                                   |                               |
| Burkholderia cepacia |                                              |                                   |                               |
| Staphylococcus capitis |                                              |                                   |                               |
| Staphylococcus saprophyticus |                                             |                                   |                               |
| Mycobacteria tuberculosis |                                            |                                   |                               |

ECOFF, Epidemiological cut off value; ESBL, extended spectrum β-lactamase; MIC, Minimum inhibitory concentration; MRSA, Methicillin-resistant Staphylococcus aureus.
Mechanisms of fosfomycin resistance

Resistance to fosfomycin is induced via one of three mechanisms: (i) reducing the production of functional transporters (impacting the GlpT or UhpT transport systems); (ii) reduced affinity to MurA, the target enzyme; or (iii) production of fosfomycin-modifying enzymes. The enzymes responsible for modifying fosfomycin can be chromosomally encoded or encoded on transferable plasmids, as occurs in E. coli. There are four known groups of fosfomycin modifying enzymes (FosA, FosB, FosC, and FosX); with FosA and FosX enzymes generally produced by Gram-positive bacteria, while FosB is commonly produced by Gram-negative bacteria.

The most epidemiologically-important Fos enzyme is the plasmid-mediated FosA3 found in E. coli, which is typically located on a conjugative plasmid that also carries the CTX-M-type ESBL. Transmission of this plasmid-mediated resistance therefore causes simultaneous resistance to both cephalosporins and fosfomycin simultaneously in E. coli; and a recent analysis of Klebsiella-producing carbapenemases (KPC)-producing K. pneumoniae isolates collected in China (where fosfomycin is produced and used in clinical practice) revealed 34% of isolates collected in China (where fosfomycin is produced and used in clinical practice) revealed 34% of isolates carried FosA (rendering fosfomycin ineffective for treating KPC-producing organisms).

FosA3 was initially reported in Japan in 2006 but has now spread across Asia in both humans and animals. FosB3 is also of concern in E. faecium on self-transmissible plasmids, resulting in simultaneous resistance to fosfomycin and vancomycin (vanA).

### Table 3: Clinical studies describing the use of fosfomycin in invasive infections in children

| Study | n (total n = 131) | Dose (where published) and adjunctive agents used | Clinical setting | Outcomes |
|-------|-------------------|-------------------------------------------------|-----------------|----------|
| Taylor et al.59 | 43 neonates; both term and premature | 150–200 mg/kg/day fosfomycin calcium PO for 4 days | Enterocolitis due to Escherichia coli | Favourable clinical outcome in 38 (88%) of patients |
| Baquero et al.50 | 6 infants | Fosfomycin monotherapy 300–500 mg/kg/day IV for 2–4 weeks | Serratia marcescens septicaemia | Clinical cure in 3/6 patients |
| Rossignol and Regnier51 | 18 infants | Fosfomycin 300–500 mg/kg/day plus gentamicin 3–5 mg/kg/day IV for 2–4 weeks | S. marcescens septicaemia | Clinical cure in 16/18 patients |
| Guillous et al.52 | 2 infants | Fosfomycin 300–500 mg/kg/day plus carbenicillin 300–500 mg/kg/day IV for 2–4 weeks | S. marcescens septicaemia | Clinical cure in 2/2 patients |
| Guoyon et al.53 | 21 neonates | 200 mg/kg/day in two divided doses, in combination with gentamicin/tobramycin | Urosepsis | Clinical recovery in 19/21 (91%) |
| Corti et al.54 | 16 neonates | IV fosfomycin-vancomycin, followed by oral pristinamycin | Staphylococcus aureus septicaemia with a liver abscess | Full recovery |
| Algubai et al.55 | n = 5; 0–2 years | Fosfomycin monotherapy; 200 mg/kg/day | Acute haematogenous osteomyelitis | Full recovery in n = 5 (100%) |
| | n = 18; 2–15 years | Fosfomycin monotherapy; 200 mg/kg/day | Acute haematogenous osteomyelitis | Full recovery in n = 18 (100%) |

### Table 4: Parenteral fosfomycin neonatal dosing recommendations (Nordic Pharma, UK, 2016)

| Age/weight | Daily dose |
|------------|------------|
| Premature neonates (age† < 40 weeks) | 100 mg/kg/day in 2 divided doses |
| Neonates (age‡ 40–44 weeks) | 200 mg/kg/day in 3 divided doses |
| Infants 1–12 months (up to 10 kg birthweight) | 200–300‡ mg/kg/day in 3 divided doses |
| Infants and children aged 1–12 years (10–40 kg birthweight) | 200–400‡ mg/kg/day in 3–4 divided doses |

†Sum of gestational and post-natal age. ‡The high-dose regimen may be considered for severe infections and or serious infections (such as meningitis), in particular when known or suspected to be caused by organisms with moderate susceptibility.
There are also reports emerging of plasmids harbouring `bla-CTX-M-55 alongside FosA, rmtB and the mcr gene, encoding resistance to fosfomycin, aminoglycosides, colistin and cephalosporins simultaneously. This highlights the importance of fosfomycin being prescribed as part of a combination therapy when managing invasive infections due to MDR organisms. When fosfomycin is used as monotherapy, resistance will soon follow: for example, a study in

| Table 5 | Recommended total daily dosages for intravenous fosfomycin in paediatric patients with normal renal function across various European settings |
|---------|---------------------------------------------------------------------------------------------------------------|
| Country | Neonates (pre- and full-term; 0–1 months) | Infants (1–12 months, up to 10 kg) | Children (1–12 years, 10–40 kg) |
| Austria | 100–200/400† mg/kg/day in 2–3 doses | 100–200/400† mg/kg/day in 2–3 divided doses | 4–8 g/day, in 2–3 doses |
| Germany | 100 mg/kg/day in 2 doses | 200–250 mg/kg/day in 3 doses | 100–200/300† mg/kg/day in 3 doses |
| United Kingdom | Premature: 100 mg/kg/day in 2 doses | 200–300 mg/kg/day in 3 doses | 200–400 mg/kg/day in 3–4 doses |
| Spain | Not specified | Not specified | 100–200 (max 400) mg/kg/day in 2–3 doses |
| France | Not specified | Not specified | 100–200 mg/kg/day; number of daily doses not specified |

†Maximum dosage is listed for use in ‘severe infections’.

| Table 6 | Published fosfomycin susceptibility testing guidelines33,62 |
|---------|---------------------------------------------------------------------------------------------------------------|
| **MIC** | Susceptible, mg/mL | Intermediate, mg/mL | Resistant, mg/mL |
| **Zone diameter** | Susceptible, mm | Intermediate, mm | Resistant, mm |

| CLSI | Escherichia coli and Enterococcus faecalis (urinary isolates only) | ≤64 | 128 | ≥256 |
| EUCAST | Enterobacteriaceae and Staphylococcus spp. (IV formulation only) | ≤32 | — | >32 |

EUCAST, European Committee on Antimicrobial Susceptibility Testing; IV, intravenous; NA, not available.

vancomycin.68 There are also reports emerging of plasmids harbouring `bla-CTX-M-55 alongside FosA, rmtB and the mcr gene, encoding resistance to fosfomycin, aminoglycosides, colistin and cephalosporins simultaneously.70 This highlights the importance of fosfomycin being prescribed as part of a combination therapy when managing invasive infections due to MDR organisms. When fosfomycin is used as monotherapy, resistance will soon follow: for example, a study in

| Table 7 | Mechanisms of fosfomycin resistance30 |
|---------|---------------------------------------------------------------------------------------------------------------|
| **Mechanism** | **Protein involved** | **Action** | **Bacteria often implicated** | **Mechanism of transfer** |
| Decreased permeability | GltP | Modifications or reduced expression of glycerol-3-phosphate transporter | MRSA | Chromosomally encoded |
| | UhpT | Modifications or reduced expression of the hexose-phosphate transporter | MRSA | Chromosomally encoded |
| Modification of bacterial cell wall target | MurA | Modification or over-expression of UDP-N-acetylglucosamine 1-carboxy-vinyl-transferase | Gram-negative organisms | Chromosomally encoded |
| Fosfomycin inactivation | FosA | Manganese-dependent glutathione-S-transferase | Gram-negative organisms | Plasmid-mediated |
| | FosB | Manganese/Magnesium-dependent bacillithiol-S-transferase | Gram-positive organisms | Plasmid-mediated |
| | FosX | Manganese-dependent epoxide hydrolase | Gram-negative organisms | Plasmid-mediated |
| | FosC (FomA) | Utilises ATP-dependent phosphorylation of fosfomycin to add a phosphate group to fosfomycin, rendering it inactive | Gram-negative organisms | Plasmid-mediated |

MRSA, Methicillin-resistant staphylococcus aureus.
Spain revealed a strongly positive correlation between the prescription of fosfomycin and fosfomycin resistance emerging in ESBL-producing *E. coli* UTIs among female adult outpatients treated for UTIs (from 4.4% in 2005 to 11.4% in 2009). However, there is little evidence to suggest resistance emerges when fosfomycin is used as part of a combination treatment regimen.

**Conclusion**

Fosfomycin is an old antibiotic which has been used sparingly since its discovery, and subsequently exhibits high-susceptibility rates world-wide. Fosfomycin’s broad-spectrum of activity against Gram-positive, Gram-negative and MDR organisms (particularly when used in combination with other antimicrobials) has increased interest in its use against infections caused by MDR organisms, including ESBL-producing and CRE. Fosfomycin’s unique mechanism of action allows for synergistic action with other antibiotics and makes cross-resistance uncommon, particularly when used as combination therapy.

Fosfomycin has the potential to develop rapid resistance if used in isolation, so its use needs to be explored as a clinical therapeutic option cautiously (and in combination with a second antibiotic), in order to preserve its susceptibility. In settings where fosfomycin is introduced into clinical practice, this should be coupled with close monitoring of susceptibility patterns through the systematic collection of microbiological data; yet it is worth considering that this is often unaffordable or unavailable in resource-poor health settings, where the burden of antimicrobial resistance is greatest. Future research should clarify the dosing regimens for fosfomycin in the paediatric population and define pharmacokinetic and safety parameters, to enhance the licensing and prescription of this affordable antibiotic in all health settings affected by the growing burden of antimicrobial resistance.

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**References**

1. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: Efficacy of WHO’s currently recommended antibiotics-systematic review and meta-analysis. *Arch. Dis. Childhood*. 2013; 98: 146–54.
2. Laxminarayan R, Duse A, Watral C et al. Antibiotic resistance—the need for global solutions. *Lancet Infect. Dis*. 2013; 13: 1057–98.
3. Cassini A, Högborg LD, Plachouras D et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: A population-level modelling analysis. *Lancet Infect. Dis*. 2019; 19: 56–66.
4. Laxminarayan R, Bhutta ZA. Antimicrobial resistance: A threat to neonate survival. *Lancet Glob. Heal*. 2017; 4: e676–7.
5. Centres for Disease Control and Prevention. Vital signs: Carbapenem-resistant Enterobacteriaceae. *MMWR Morb. Mortal. Wkly Rep*. 2013; 62: 165–170.
6. Moxon CA, Paulus S. Beta-lactamases in Enterobacteriaceae infections in children. *J. Infect*. 2016; 72: 541–9.
7. World Health Organization. WHO Publishes List of Bacteria for Which New Antibiotics Are Urgently Needed. Geneva: The Organization; 2017. Available from: https://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed [accessed 10 January 2019].
8. World Health Organization. Critically Important Antimicrobials for Human Medicine. 3rd revision. Geneva, Switzerland: The World Health Organization; 2011.
9. Hendlin D, Stapley EO, Jackson M et al. Phosphomycin. A new antibiotic produced by strains of Streptomyces. *Science* 1969; 166: 122–3.
10. Souli M, Galani I, Boukouvalas S et al. In vitro interactions of antimicrobial combinations with fosfomycin against KPC-2 producing Klebsiella pneumoniae and protection of resistance development. *Antimicrob. Agents Chemother*. 2011; 55: 2395–7.
11. Raz R. Fosfomycin: An old-new antibiotic. *Clin. Microbiol. Infect.* 2012; 18: 4–7.
12. Kahan F, Kahan J, Cassidy P, Kropp H. The mechanism of action of fosfomycin (phosphomycin). *Ann. N. Y. Acad. Sci*. 1974; 10: 364–86.
13. Kadner R, Winkler H. Isolation and characterisation of mutations affecting the transport of hexose phosphates in *Escherichia coli*. *J. Bacteriol*. 1973; 113: 895–900.
14. Falagas ME, Athanasaki F, Voulgaris GL, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *Int. J. Antimicrob. Agents* 2009; 34: 506–15.
15. Bergan T. Degree of absorption, pharmacokinetics of fosfomycin trometamol and duration of urinary antibacterial activity. *Infection* 1990; 18 (Suppl. 2): 565–9.
16. Falagas M, Vouloumanou E, Samonis G, Vardakas K. Fosfomycin. *Clin. Microbiol. Rev.* 2016; 29: 321–47.
17. Patel S, Balfour J, Bryson H. Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997; 53: 457–56.
18. Duzé J, Mousson C, Siebor E et al. Fosfomycin and its application in the treatment of multidrug-resistant Enterobacteriaceae infections. *Clin. Med. Rev. Ther.* 2011; 3: 123–42.
19. Borgia M, Longo A, Lodola E. Relative bioavailability of fosfomycin and of trometamol after administration of single dose by oral route of fosfomycin trometamol in fasting conditions and after a meal. *Int. J. Pharmacol. Ther. Toxicol.* 1989; 27: 411–7.
20. Falagas ME, Kastoris AC, Karageorgopoulos DE, Rafailidis PI. Fosfomycin for the treatment of infections caused by multidrug-resistant nonfermenting Gram-negative bacilli: A systematic review of microbiological, animal and clinical studies. *Int. J. Antimicrob. Agents* 2009; 34: 111–20.
21. Shrestha NK, Tomford JW. Fosfomycin: A review. *Infet. Dis. Clin. Pract.* 2001; 10: 255–60.
22. Mazzac T, Bosetti M, Fallani S, Arrigucci S, Novelli A. Pharmacokinetic and pharmacodynamic aspects of antimicrobial agents for the treatment of uncomplicated urinary tract infections. *Int. J. Antimicrob. Agents* 2006; 28: 535–41.
23. Guggenbichler JP, Kienel G, Frisch H. Fosfomycin, a new antibiotic drug. *Pediatr. Padiatr*. 1978; 13: 429–36.
24. Molina MA, Olay T, Quero J. Pharmacodynamic data on fosfomycin in underweight infants during the neonatal period. *Chemotherapy* 1977; 23 (Suppl. 1): 217–22.
25. Falagas M, Vouloumanou EK, Togias AG, Karadima M et al. Fosfomycin versus other antibiotics for the treatment of cystitis: A meta-analysis of randomised controlled trials. *J. Antimicrob. Chemother*. 2010; 65: 1862–77.

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producing OXA-23 carbapenemases. Southeast Asian J. Trop. Med. Public Health 2011; 42: 890–900.

45 Xu-hong Y, Falagas ME, Dong W, Karageorgopoulos DE, de-feng L, Rui W. In vitro activity of fosfomycin in combination with linezolid against clinical isolates of methillin-resistant Staphylococcus aureus. J. Antibiот. 2014; 67: 369–71.

46 Descourclev JL, Jorgensen MR, Wergin JE, Rose WE. Fosfomycin synergy in vitro with amoxicillin, daptomycin, and linezolid against vancomycin-resistant Enterococcus faecium from renal transplant patients with infected urinary stents. Antimicrob. Agents Chemother. 2013; 57: 1518–20.

47 Hauser C, Hirzberger L, Unemo M, Furrer H, Endimiani A. In vitro activity of fosfomycin alone and in combination with ceftriaxone or azithromycin against clinical Neisseria gonorrhoeae isolates. Antimicrob. Agents Chemother. 2015; 59: 1605–11.

48 Baylan O. Fosfomycin: past, present and future. Mikrobiyol. Bul. 2010; 44: 311–21.

49 Taylor CG, Mascaro E, Román J et al. Enteropathogenic E. coli gastroenterocolitis in neonates treated with fosfomycin. Chemotherapy 1977; 23 (Suppl. 1): 310–4.

50 Baquero F, Hortelano JG, Navarro M et al. Antibiotherapy of Serratia marcescens septicemia in children. Chemotherapy 1977; 23 (Suppl. 1): 416–22.

51 Rossignol S, Regnier C. Fosfomycin in severe infection in neonatology. Ann. Pediatr. 1984; 31: 437–44.

52 Guillois B, Guillemin MG, Thoma M, Sizun J, Monnery JL, Alix D. Neonatal pleuropulmonary staphylococcal infection with multiple abscesses of the liver. Ann. Pediatr.; 1989; 36: 681–4.

53 Gouyon JB, François C, Semama D, Sandre D, Duez JM, Portier H. Nosocomial Staphylococcus epidermidis and Staphylococcus aureus septicemias in neonates. Ann. Pediatr.; 1990; 37: 21–5.

54 Corti N, Sennhauser FH, Stauffer UG, Nadal D. Fosfomycin for the initial treatment of acute haematogenous osteomyelitis. Arch. Dis. Child. 2003; 88: 512–6.

55 Algubaishi S, Bahrer C, Thomale UW, Spors B. Favorable outcome in cerebral abscesses caused by Citrobacter koseri in a newborn infant. IDCases 2015; 2: 22–4.

56 Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. Int. J. Infect. Dis. 2007; 11: e732–9.

57 Iankov D, Wasseil R, Farley J, Nambiar S. Adverse events associated with fosfomycin use: Review of the literature and analyses of the FDA adverse event reporting system database. Infect. Dis. Ther. 2015; 4: 433–58.

58 Llorens J, Lobato A, Olav T. The passage of fosfomycin into the cerebrospinal fluid in children’s meningitis. Chemotherapy 1977; 23 (Suppl. 1): 189–95.

59 Careddu P, Borzani M, Scotti L, Varotto F, Garlaschi L, Fontana P. Treatment of lower urinary tract infections in children: Single dose fosfomycin trometamol versus pipemidic acid. Chemioterapia 1987; 6: 290–4.

60 Principi N, Corda R, Bassetti D, Varese LA, Peratoner L. Fosfomycin trometamol versus netilmicin in children’s lower urinary tract infections. Chemotherapy 1990; 36 (Suppl. 1): 41–5.

61 Varese LA. Trometamol salt of fosfomycin versus netilmicin: Randomized multicenter study in children’s lower urinary tract infections. Eur. Urol. 1987; 13 (Suppl. 1): 119–21.

62 Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 27th edition, CLSI supplement M100. Wayne, PA: The Institute; 2017.

63 Diez-Aguilar M, Morosini MI, del Campo R, Garcia-Castillo M, Zamora J, Cantón R. In vitro activity of fosfomycin against a collection of clinical Pseudomonas aeruginosa isolates from 16 Spanish hospitals: Establishing the validity of standard broth microdilution as
susceptibility testing method. Antimicrob. Agents Chemother. 2013; 57: 5701–3.

64 Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: A systematic review. Lancet Infect. Dis. 2010; 10: 43–50.

65 Jiang Y, Shen P, Wei Z et al. Dissemination of a clone carrying a fosA3-harbouring plasmid mediates high fosfomycin resistance rate of KPC-producing Klebsiella pneumoniae in China. Int. J. Antimicrob. Agents 2015; 45: 66–70.

66 Wachino J, Yamane K, Suzuki S, Kimura K, Arakawa Y. Prevalence of fosfomycin resistance among CTX-M-producing Escherichia coli clinical isolates in Japan and identification of novel plasmid-mediated fosfomycin-modifying enzymes. Antimicrob. Agents Chemother. 2010; 54: 3061–4.

67 Ho P, Chan J, Lo WU et al. Dissemination of plasmid-mediated fosfomycin resistance fosA3 among multidrug-resistant Escherichia coli from livestock and other animals. J. Appl. Microbiol. 2013; 114: 695–702.

68 Ho P, Chan J, Lo WU et al. Prevalence and molecular epidemiology of plasmid-mediated fosfomycin resistance genes among blood and urinary E. coli isolates. J. Med. Microbiol. 2013; 62: 1707–13.

69 Xu X, Chen C, Lin D et al. The fosfomycin resistance gene fosB3 is located on a transferable, extrachromosomal circular intermediate in clinical Enterococcus faecium isolates. PLoS One 2013; 8: e78106.

70 Lupo A, Saras E, Madec J-Y, Haenni M. Emergence of blaCTX-M-55 associated with fosA, mtrB and mcr gene variants in Escherichia coli from various animal species in France. J. Antimicrob. Chemother. 2018; 73: 867–72.

71 Oteo J, Bautista V, Lara N et al. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli. J. Antimicrob. Chemother. 2010; 65: 2459–63.