The potential role of fosfomycin in neonatal sepsis caused by multidrug resistant bacteria

Grace Li1, Joseph F Standing1,2, Julia Bielicki1,4, William Hope3, John van den Anker4,5, Paul T. Heath1, Mike Sharland1

1Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George’s, University of London, Cranmer Terrace, London SW17 0RE

2UCL Great Ormond Street Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH

3Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, Sherrington Building, Liverpool L69 3GE

4Division of Paediatric Pharmacology and Pharmacometrics, University of Basel Children’s Hospital (UKBB), Spitalstrasse 33, Postfach, CH-4031 Basel

5Division of Clinical Pharmacology, Children’s National Health System, Washington, DC, USA

Corresponding author:

Professor Mike Sharland

Paediatric Infectious Diseases Research Group

Institute of Infection and Immunity

St George’s, University of London

Cranmer Terrace

London, SW17 0RE

UK

Email: mike.sharland@stgeorges.nhs.uk

Telephone: (+44) 207 725 5968

**Abstract**

Fosfomycin’s broad-spectrum activity, including against multi-drug resistance strains, has led to renewed interest in its use in recent years. Neonatal sepsis remains a substantial cause of morbidity and mortality at a global level, with evidence that multidrug resistant bacteria (MDR) play an increasing role.

The evidence for use of fosfomycin in neonatal subjects is limited. We summarise current knowledge of the pharmacokinetics and clinical outcomes for use of fosfomycin in neonatal sepsis and issues specific to neonatal physiology. Whilst fosfomycin has a broad range of coverage, we evaluate the extent to which it may be effective against MDR in a neonatal setting, in light of recent evidence suggesting it to be most effective when given in combination with other antibiotics. Given the urgency of clinical demand for treatment of MDR sepsis, we outline directions for further work including the need for future clinical trials in this at-risk population.

**Key points**

Availability of pharmacokinetic data for neonates is limited and does not permit dose adjustment taking into account prematurity <32 weeks corrected gestational age.

Further data are required to clarify the extent to which fosfomycin provides adequate antimicrobial coverage against the most common causative organisms of neonatal sepsis at a global level.

Pharmacokinetic trials, allowing stratification for prematurity <32 weeks, as well as postnatal age, are required.

**Introduction**

Intravenous fosfomycin has not been widely used across the world despite its discovery nearly fifty years ago and its broad-spectrum activity against Gram-positive and Gram-negative bacteria. The oral formulation as a single dose for urinary tract infection is more commonly used. This low usage may reflect both the introduction of newer compounds with which clinicians are now more familiar, including cephalosporins, as well as the perception amongst the same clinicians that resistance to fosfomycin may develop rapidly. However, the repurposing of older antimicrobials, such as fosfomycin, is likely to play an important part in addressing antimicrobial resistance (AMR). Ongoing programmes such as AIDA (www.aida-project.eu) aim to update the clinical outcome data for these antimicrobials and facilitate their reintroduction into mainstream clinical use. Fosfomycin has attracted particular interest as it also demonstrates synergistic effects with the newer antimicrobials against resistant organisms [1].

Recent studies have described significant morbidity and mortality associated with neonatal sepsis in countries where key multidrug resistant organisms are endemic [2]. However, there is currently no literature that addresses the utility of fosfomycin in this specific setting. This review article will describe why fosfomycin is an attractive option for the treatment of neonatal sepsis caused by multidrug resistant (MDR) bacteria, and will summarise current evidence regarding pharmacokinetics, dosing and clinical outcomes in this population.

1. **The burden of neonatal sepsis and AMR**

Despite significant progress in the reduction of child mortality (United Nations Millennium Development Goal 4), 23% of an estimated 2.9 million neonatal deaths a year are attributed to infection [3]. Sepsis of *any* cause in the neonatal period is significantly associated with adverse neurodevelopmental outcomes [4]. Neonatal sepsis in the first 72 hours of life is classified as early onset sepsis (EOS), thought to arise from transplacental pathogens, or those originating from the maternal urogenital tract. The most common causative organisms seen in EOS are Group B *streptococcus* (48-53%) [5] followed by *E.coli* (18%). EOS occurs in approximately 0.9 per 1000 live births. However, the risk of sepsis increases with prematurity – 26% of babies with birth weight <1000g will have at least 1 episode of sepsis during their stay in hospital [6]. There is evidence to suggest that the risk of Gram-negative EOS is higher in preterm infants [7].

Late-onset sepsis (LOS) is associated with the postnatal environment and nosocomial pathogens such as coagulase negative *Staphylococcus* and Gram-negative bacilli. LOS constitutes a larger number of cases; preterm infants have been shown to be at increased risk of LOS (36% of infants <28 weeks gestation develop one episode of LOS, 29.6% of moderately preterm (29-32 weeks), 17.5% of late preterm (33-36 weeks) and 16.5% of term infants [8] in the neonatal intensive care setting [9].

In high income countries (HIC), Gram-positive pathogens are the most common causative organisms of LOS (60-70%), and are commonly associated with the use of indwelling catheters and with tertiary neonatal units [10], whereas Gram-negative pathogens are associated with worse clinical outcomes and are more epidemiologically significant in LOS in the setting of low and middle- income countries (LMICs) [5].

Current World Health Organisation (WHO) guidelines [11] recommend an aminopenicillin with gentamicin as first-line therapy in neonatal sepsis. Whilst the guidelines do not differentiate between EOS and LOS, treatment for the latter usually takes into account the source of infection suspected, e.g. addition of vancomycin if an indwelling catheter is present. Carbapenems such as meropenem or imipenem are increasingly being used as second-line therapy, especially in settings where infections caused by extended-spectrum beta-lactamase (ESBL)-producing organisms are endemic [12,13]. Increasing use of meropenem is associated with increasing rates of infection by carbapenem-resistant organisms (CRO). Hospitalised neonates are particularly vulnerable to resistant organisms as they undergo long inpatient stays, are exposed to multiple courses of antibiotic therapy for episodes of suspected sepsis and are often colonised with (multi)-resistant organisms. Historically, resistant Gram-positive bacteria (in particular methicillin-resistant *Staphylococcus aureus,* MRSA) were the most clinically troublesome [14]. Half of all childhood cases of MRSA bacteraemia, for example, occur in the neonatal period [15]. Studies describe the detection of multi-drug resistant (MDR) Gram-negative organisms on neonatal units (NNUs) and an association has been shown between species responsible for colonization and those causing fulminant sepsis, particularly with regards to *Klebsiella* and *Enterobacter* species [16]. Gram-negative sepsis is associated with especially high rates of morbidity and mortality in neonatal populations [17].

The most commonly isolated species from European neonatal and paediatric blood cultures are *S. aureus*, *E. coli*, *K. pneumoniae* and *Enterococcus faecalis* [18]. *E. coli* isolates show resistance rates as high as 65% to aminopenicillins and 14% to aminoglycosides, and *K. pneumoniae* were resistant to cephalosporins in nearly 30% of cases. Resistance to second-line antibiotics is also substantial – 26% of *Pseudomonas* species isolated are resistant to carbapenems, suggesting that genetic elements conferring resistance are widespread [16]. LMICs are particularly vulnerable to the effects of AMR as they face the challenges of access to medicines, weak health-care systems and limited resources [19]. Two recent systematic reviews suggest that MDRGN are increasingly clinically significant on a global scale. Downie et al. [20] reviewed the aetiology of community acquired sepsis in infants in developing country settings and found that *Staphylococcus aureus*, *Klebsiella species* and *Escherichia coli* accounted for the majority of isolates. Recommended WHO first line therapy provided only 43-44% coverage in neonates, and third-generation cephalosporins conferred no additional coverage. Le Doare et al. [21] reviewed data from confirmed Gram-negative blood stream infections in children in a LMIC setting and found that Gram-negative bacteria form the majority of isolates in this population (67%).

Both reviews were limited by the quality and quantity of the data available. However, emerging studies from individual LMIC settings [22] show that resistance to recommended first-line antibiotics is of clinical significance. Alternative therapies in areas with high rates of AMR are therefore sought after, and this is where fosfomycin might potentially play a role.

**Fosfomycin: Mechanism of action**

Fosfomycin, or phosphonomycin, was discovered in 1969 as a product of *Streptomycetes* and *Pseudomonas syringae* [23]. It is a low molecular weight (138 kDa) polar compound that has two unusual features in its configuration: an epoxy ring responsible for its antibiotic activity and a direct carbon-phosphorus link. It is available principally as a disodium salt for parenteral administration, or as a trometamine salt for oral consumption, and it has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. A small number of species are naturally resistant to fosfomycin, including *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Staphlococcus capitis*, *Staphlococcus saprophyticus*, M*ycobacterium tuberculosis*, *Vibrio sheri* and *Chlamydia trachomatis* [24].

Fosfomycin exerts its bactericidal effects by acting as an analog of phosphoenolpyruvate, binding and inhibiting the cytosolic enzyme MurA (UDP-N-acetylglucoasmine enolpyruvyl transferase) that is involved in the formation of the initial cell-wall peptidoglycan chain. Uptake into susceptible bacteria is mediated by the glycerol-3-phosphate and hexose phosphate uptake transport systems [25]. Resistance to fosfomycin may originate at a chromosomal level leading to the loss or reduction in the number of uptake transporters (insertional mutations or inactivating mutations [26], reduced affinity of the target enzyme MurA (single amino acid substitution [26] or production of fosfomycin-modifying enzymes that render the drug inactive [24].

Figure 1 shows a schematic outline of the mechanism of action and resistance mechanisms towards fosfomycin.

Figure 1: Mechanism of action of fosfomycin and resistance mechanisms

[insert Figure 1]

The production of fosfomycin-modifying enzymes is a resistance mechanism that can additionally be conferred by plasmids. The most well-characterized enzymes include FosA and FosX (commonly produced by Gram-negative bacteria), FosB (produced by Gram-positive bacteria), and FosC, which inactivates fosfomycin via ATP-dependent phosphorylation. The pre-existing epidemiology of fosfomycin resistance genes is likely to be of critical importance. The FosA3 gene, commonly found in *E. coli*, is known to reside on a conjugate plasmid that also confers resistance to cephalosporins via a mechanism similar to CTX-M [27].

There is evidence that polymorphisms of MurA contribute to heteroresistant bacterial subpopulations in *Streptococcus pneumoniae* [28], however, in an experimental setting, mutation of MurA alone is insufficient to confer resistance. More work remains to be done to understand the molecular and phenotypic interaction between resistance mechanisms, particularly in Gram-negative species.

1. **Pharmacokinetic profile, dosing and toxicity in neonates**

***Pharmacokinetics***

Most data regarding the pharmacokinetic profile of fosfomycin in adults refer to intravenous administration. There is limited data regarding the pharmacokinetics of IV fosfomycin in neonates which is summarised in Table 1 below:

Table 1: Neonatal fosfomycin pharmacokinetic studies

|  |  |  |  |
| --- | --- | --- | --- |
| Study | N | Dose and study | Outcome |
| Molina, Olay and Quero et al., 1977 [29] | 11 neonates | 50 mg/kg IV, comparing infants 1-3d old and 3-4 weeks old | Elimination slower at younger CGA |
| Guggenbichler et al., 1978 [30] | 5 term, 5 preterm  | 25 mg/kg IV (CGA and PNA not specified) | 95-98% recovered in the urine, 1 compartment model  |
| Guibert et al., 1987 [31] | 10 neonates | 200 mg/kg BD, comparing 30 min or 2hr infusion schedules | No difference between schedules, serum concentrations are above MIC of common pathogens at 12 h post dose |
| Suzuki et al., 2009 [32] |  | Dose estimation for renally excreted drugs | Dose estimation validated with GFR, tubular secretion clearance and fraction of unbound drug in plasma |

Abbreviations: CGA, corrected gestational age; GFR, glomerular filtration rate; MIC, minimal inhibitory concentration; BD, twice a day; IV, intravenous

The elimination half-life of fosfomycin in neonates following IV bolus is described in two studies and ranges from 2.4-7.0 hours following a dose of 25-50 mg/kg) [29,30]. The variation in half-life values may be explained by difference in postnatal and gestational age between cohorts (gestational age was only described in one study (36.3 weeks ± 0.7), postnatal age was not described for the other study) and both studies included low birth weight infants. Therefore, there are potentially wide variations in renal maturation between the cohorts. Longer fosfomycin half-life in neonates compared to children (5-13 years) [33] is likely to be largely due to the lower clearance associated with maturation of glomerular filtration [34], but also to a lesser extent may be due to greater volume of distribution (0.41 l/kg in neonates versus 0.28 l/kg in children [30]. Due to the limited availability of data, it is difficult to accurately describe the effects of prematurity or weight on clearance of fosfomycin in neonates.

Few studies have explored the appropriate pharmacokinetics/pharmacodynamic (PK/PD) target for optimal systemic treatment with fosfomycin. The comparison of *in vitro*  fosfomycin studies is difficult due to the use of varying glucose-6-phosphate supplementation in agar which potentiates fosfomycin’s antimicrobial activity [35]. The first observational studies to measure fosfomycin concentration [36,37] produced equivocal results, partly due to limited exploration of PD parameters and measurement of fosfomycin in discrete physiological compartments (cerebrospinal fluid (CSF), abscess fluid). The first paper to explore the intrinsic PD characteristics of fosfomycin [38] presented *in vivo* data suggestive of concentration-dependent killing with a significant post-antibiotic effect. Recent hollow-fibre models provide evidence that area under the curve over the minimum inhibitory concentration (AUC/MIC) correlates with suppression of bacterial resistance [39]. However, time above minimum inhibitory concentration of 100% (T>MIC=100%) was simultaneously achieved, therefore PK/PD indices for future studies will need to be clarified. The most recent review of fosfomycin dosing in neonates is guided by T>MIC [45].

A neonatal Cmax (after IV administration) at 60-90 mg/l is comparable with that attained in adult populations [40]. Whilst there is evidence demonstrating oral bioavailability of fosfomycin in adults [41], no data are available for paediatric populations. Fosfomycin is not available in a rectal formulation, however the contribution of this mode of administration to the management of systemic neonatal sepsis is likely to be limited. One case report describes its successful use in a continuous subcutaneous infusion in combination with oral ciprofloxacin in a 14 year-old cystic fibrosis patient [42]. However, no pharmacokinetic data are available.

Serum protein binding is estimated to be below 3% [43]. Fosfomycin concentrations in the CSF are much greater during the acute phase of meningitis than in the absence of inflammation. However, CSF concentrations (3.7-11% of measured plasma values) measured in 22 paediatric samples (including 1 neonatal subject) following treatment with IV fosfomycin were too low to justify fosfomycin monotherapy [44]. 80%–95% of the dose is recovered unchanged in urine within 24 hours [43].

***Dosing***

In anticipation of its reintroduction into clinical use and given the discrepancy between dosing recommendations between European countries, Traunmüller et al. [45] remodeled the limited existing paediatric pharmacokinetic data for parenteral administration using a two-compartment model with Kinetica open-source software (Innaphase, 2001).The current European Committee on Antimicrobial Susceptibility Testing (EUCAST) fosfomycin breakpoint (32 mg/L) is set according to adult dosing schedules of 3-8g given three times a day, and can be applied in the context of urinary tract infection. Epidemiological cut-off data exist for two Gram-negative species: *E. coli and Proteus mirabilis* (8mg/L).

Based upon this, their target attainment was T>MIC of 40-70% for an MIC of 32 mg/L*.* Whilst their source of data was limited, they found that the lowest current recommended paediatric doses (100 mg/kg/d) only achieved target T>MIC for infants with a corrected gestational age of 37 weeks, of postnatal age 3-5 weeks. Their study confirmed that corrected gestational age and body weight comprised the most significant explanatory variables in fosfomycin PK.

They have refined the recommended neonatal dosing schedules, (Table 2, taken from the summary of product characteristics for Fomicyt in the UK). In particular, they recommend more frequent dosing (four times a day) to adjust for increased clearance due to renal maturation in the first few weeks of life.

The broad categorisation of preterm infants as <40 weeks signals the need for future pharmacokinetic modelling of fosfomycin in preterm infants as there is evidence to suggest that the difference in renal maturation between 26 and 36 weeks gestation can influence recommended dosing schedules [46].

Table 2: Fosfomycin neonatal dosing recommendations, Fomicyt UK and from Traunmuller et al. pharmacokinetic study

|  |  |  |
| --- | --- | --- |
| **Age/weight** | **Daily dose** | Dose recommended by Traunmüller et al. [45] |
| Premature neonates (corrected gestational age <40 weeks) | 50 mg/kg twice a day | D1-3 of life (PMA 36-38 weeks) – 50 mg/kg twice a day3-5 weeks of age (PMA 36-43 weeks) – 25 mg/kg four times a day, doubled dose in severe infection |
| Neonates (corrected gestational age 40-44 weeks) | 200 mg/kg in 3 divided doses | 3-5 weeks of age (PMA 36-43 weeks) – 25 mg/kg four times a day, doubled dose in severe infection |
| Infants 1-12 months (up to 10kg) | 200-300 mg/kg in 3 divided doses | 300 mg/kg a day  |
| Infants and children aged 1-12 years (10-40kg) | 200-400 mg/kg in 3-4 divided doses |  |

***Toxicity***

IV administration of fosfomycin is generally associated with low toxicity. Adverse events reported to the FDA in association with fosfomycin administration in adults were reviewed recently (47). Serious side effects include heart failure (3%). and hypokalemia (particularly following shorter infusion times). These are attributable to the high sodium load of fosfomycin (14.4mmol of sodium per gram, compared with, for example, amoxicillin which contains 2.6 mmol of sodium per gram), and is linked to hypernatremic heart failure in adult cardiac patients. It is hypothesised that the body may attempt to compensate for the administered sodium load by increasing renal sodium excretion with concomitant potassium excretion and hypokalemia.

Sodium is important for growth in neonates but they paradoxically have low sodium requirements for the first 48-72 hours of life, followed by a physiological diuresis 8]. There is evidence that excessive early fluid administration and sodium supplementation of >4 mmol/kg/d in infants <30 weeks corrected gestational age can lead to adverse outcomes 9] and has been linked to the development of chronic lung disease (CLD). The current dosing recommendations for fosfomycin would lead to sodium administration of 1.4 mmol/kg/d and 2.8 mmol/kg/d for preterm (1kg) and term (2kg) infants, respectively. As sodium supplementation in preterm infants is routinely avoided in the first 48 hours of life, the potential risk of hypernatraemia would need to be carefully looked for in any future clinical trial. Whilst no specific study of fosfomycin toxicity has been carried out in neonates, no adverse events have so far been attributed to its use in neonatal sepsis (Table 3).

**Clinical outcomes in children and neonates**

The current EUCAST fosfomycin breakpoint (32mg/L) is set according to adult dosing schedules of 3-8g given three times a day, and can be applied in the context of urinary tract infection. Epidemiological cut-off data exist for two Gram-negative species: *E. coli and Proteus mirabilis* (8mg/L).

A Pubmed search was conducted using the search criterion “fosfomycin AND neonat\*” to review data on clinical outcomes using fosfomycin therapy in neonates.

Three studies were found which describe the successful use of fosfomycin in Gram-negative neonatal sepsis; its use as monotherapy for a cohort of 43 neonates with *E. coli* enterocolitis 50], combination therapy with tobramycin/gentamicin 1] and one case report of meropenem combination therapy for successful treatment of intracranial *Citrobacter* infection [54]. Whilst fosfomycin demonstrates a wide spectrum of activity, the limited existing literature describes the use of fosfomycin combination therapy primarily for Gram-positive neonatal sepsis (Table 3). In paediatric populations, fosfomycin is rarely administered and only occasionally prescribed to limit the empirical use of other broad-spectrum antibiotics such as teicoplanin, again for Gram-positive cover 2].

Table 3: Studies describing use of fosfomycin in neonatal sepsis

|  |  |  |  |
| --- | --- | --- | --- |
| Study  | N | Dose and clinical setting | Outcomes |
| Taylor et al., 1977[50] | 43 neonates | 150-200 mg/kg/d for enterocolitis caused by enteropathic *E-coli* | Favourable clinical outcome in 88% |
| Rossignol & Regnier, 1984 [51] | 21 neonates, 11 Gram- negative infections  | 200 mg/k/d, two divided doses, in combination with gentamicin/tobramycin for sepsis and UTI | Clinical recovery in 19/21  |
| Guillois et al., 1989 [53] | Case report n =1 | IV fosfomycin-vancomycin for MSSA septicaemia and liver abscesses, followed by oral pristinamycin | Full recovery |
| Gouyon et al., 1990 [54] | 16 neonates | IV fosfomycin-cefotaxime for Staphylococcal septicaemia including meningitis, osteomyelitis and congenital *varicella* superinfection | Full recovery n=15 |
| Algubaisi et al., 2015 [55] | Case report, 1 term infant | 120 mg/kg/d fosfomycin and meropenem used to treat multiple Citrobacter koseri intracerebral abscesses  | Clinical recovery  |

Abbreviations: MSSA, methicillin sensitive *Staphylococcus aureus*

Outcome data for the clinical efficacy of fosfomycin in adults is well-documented and was reviewed by Falagas et al. [56] for 1604 patients with Gram-positive and Gram-negative infections (including pneumonia, osteomyelitis, meningitis, and sepsis). Patients were treated with intravenous fosfomycin alone or in combination with other antibiotics and clinical cure was observed in 81% of patients. Michalopoulos et al. [57] examined the effectiveness and safety of fosfomycin in critically ill patients with ICU-acquired infections due to carbapenem-resistant *K. pneumoniae* and found that current sensitivity patterns may allow for wider use of fosfomycin in adult patients, especially in combination with other antibiotics.

1. **The role of fosfomycin in neonatal AMR**

The current WHO recommendation of aminopenicillin and gentamicin as first-line therapy aims to ensure adequate coverage of both Gram-negative and Gram-positive species. The potential applicability of fosfomycin to neonatal sepsis depends upon its activity against organisms responsible for neonatal sepsis, and the extent to which it is also effective against organisms resistant to aminopenicillins and gentamicin (as well as third generation cephalosporins, as these are increasingly recommended in an ambulatory care setting), i.e. where resistance is primarily ESBL mediated. The increased use of carbapenems as second line therapy is also thought to be driving increased resistance, and therefore the utility of fosfomycin in carbapenem resistant organisms (CRO) needs to be considered.

Vardakas et al. [58] conducted a recent systematic review evaluating the coverage of fosfomycin with regards to resistant Gram-positive and Gram-negative species. Selected results from this review for pathogens relevant to neonatal sepsis are shown in Tables 4 and 5.

Table 4: Activity of fosfomycin against Gram-positive species responsible for neonatal sepsis

|  |  |  |
| --- | --- | --- |
| **Gram positive** | Susceptibility to fosfomycin | MIC (mg/l) |
| *Staphylococcus aureus* Yu et al., Lu et al., Sultan et al., [59–61] | 33.2-100% | MIC90 = 16-128 |
| CoNSChiquet et al., Sultan et al., [61,62] | 77.5-100%MICs not available in the literature | Not documented |
| Group B *Streptococcus*Falagas et al.,[63]  | 40.6%  | Not documented0.32% resistance to fosfomycin reported in review of 131 strains responsible for EOS [64] |

Abbreviations: CoNS, coagulase-negative Staphylococcal species

Table 5: Activity of fosfomycin against Gram-negative species responsible for neonatal sepsis

|  |  |  |
| --- | --- | --- |
| **Gram negative** | Susceptibility to fosfomycin | MIC (mg/l) |
| *E. coli*Matthews et al., Chen et al., [65,66] | 78-98%>95% sensitivity reported in NDM producing species [67] | Not documented |
| *Klebsiella spp.*Sahni et al*.,* [68] | 40-94% | 4-64 |
| *Enterobacter spp.*Hsu et al., Pogue et al., [69,70] | 76-98% | Variable |

Preliminary evidence suggests fosfomycin has varying activity against the pathogens most commonly causative of neonatal sepsis, such as *Staphylococcal spp.*, CoNS , *Klebsiella spp.* and *E. coli*. a. There is significant variation in the described sensitivities for *Klebsiella spp.* and *Staphylococcus aureus.* Methodological disparities, including G6P agar supplementation, as well as geographical variation in bacterial phenotypes may partly explain these differences and reinforce the need for local susceptibility testing. The overall susceptibility of ESBL-producing *E. coli* strains to fosfomycin ranged from 81% -100%, however MIC90 values for these organisms showed a wide range from <4mg/L up to 128 mg/L in Asian studies. The susceptibility in ESBL-producing *Klebsiella* strains was somewhat lower, ranging from 15%-100% and higher MIC90 values (up to >1024 mg/L) were again reported. Both ESBL *E. coli* and *Klebsiella* species consistently showed greater susceptibility to fosfomycin than gentamicin. There is evidence from *in vitro* hollow-fibre studies that lower dosing schedules of fosfomycin (administered 8 hourly to mimic the dosing schedule likely to be implemented clinically) are potentially associated with amplified development of resistant *E. coli* populations [39,71]. Data on the activity of fosfomycin against CRO is mostly restricted to Klebsiella pneumoniae carbapenemase -producing *Klebsiella pneumoniae*, and the review [57] found that susceptibility ranged from 39.2%-100% (95% C.I. 66.4-81.4%), the lower levels of susceptibility due in part to the co-existence of FosA in some isolates. Regardless of the resistance profile, *E. coli* appeared to be generally more susceptible to fosfomycin than *Klebsiella* species.

Whilst fosfomycin has broad coverage of both Gram-positive and Gram-negative organisms, rapid development of resistance *in vitro* together with the existence of single-point mutation resistance genes means it will have to be used in a combination regimen. Nilsson et al.,2] demonstrate that fosfomycin resistance *in vitro* is biologically costly and results in reduced growth of the bacterial population, so resistance may not manifest clinically. Karageorgopoulos et al., 73] reviewed *in vitro* and clinical evidence of resistance to fosfomycin in Gram-negative species during treatment and found resistance in *Pseudomonas aeruginosa* developed quicker than in *E. coli*. The evidence for clinical sequelae of fosfomycin resistance was limited, and they did not recommend changes to current practice based on their findings.  As may be expected, increased use of fosfomycin is linked to increased levels of fosfomycin resistance in clinical isolates [74].

Combination regimens have the benefit of additive or synergistic antimicrobial effects of more than one compound. Promisingly, fosfomycin has shown *in vitro* synergy with the aminoglycoside plasmocin against CRO [75]. Walsh et al. [76] published one of the first studies to explore the development of combination fosfomycin therapy (with tobramycin, polymyxin B or ciprofloxacin) for clinically isolated *Pseudomonas* species and found that whilst synergy could be demonstrated with tobramycin, the emergence of resistant subpopulations was not reduced. Amikacin is a commonly used alternative to gentamicin and *in vitro* evidence suggests that amikacin improves the bacterial killing of fosfomycin whilst suppressing the development of resistance [77].

Because some of the most common causative organisms in neonatal sepsis have a degree of intrinsic resistance to fosfomycin, it is important to ensure that whichever antibiotic is chosen to be paired with fosfomycin adequately covers for these organisms. It has been shown that inadequate coverage for intrinsically resistant *Klebsiella species* in empirical treatment of neonatal sepsis can increase levels of resistance [78].

**Conclusion**

Emerging evidence supports the validity of combination fosfomycin therapy in the management of MDRGNB sepsis in neonates. However, there remain substantial gaps in the current literature which need to be addressed. *In vitro* work is needed to assess the combinations of antimicrobials which optimise fosfomycin synergy in the treatment of MDRGNB, minimise the emergence of resistance, and that can be safely and reliably administered in neonates. Up-to-date pharmacokinetic data in preterm and term infants across a range of doses is needed, which will then require validation in a clinical trial setting. Lastly, appropriate formulations of the antimicrobials (fosfomycin and other agents to be used in combination with it) will be required. Fosfomycin licensing is currently geographically limited, and any global policy recommendations made for the empirical management of MDRGNB sepsis in infants will require affordable access to fosfomycin, including expedited local licensing. Whilst this represents a substantial amount of progress to be made, the global risk to neonates of untreatable MDRGNB sepsis cannot be ignored.

1. Compliance with ethical standards

No funding was received for this article. No conflicts of interest are declared for GL JS, JB, JVDA, MS. WH has consulted for Nordic Pharma. PTH acts as an investigator for clinical trials conducted on behalf of St George’s University London sponsored by vaccine manufacturers and has participated in advisory boards but receives no personal payments from these activities.

Bibliography

1. Falagas ME, Vouloumanou EK, Samonis G, et al. Fosfomycin. *Clin Microbiol Rev*. 2016;29(2):321–47.

2. Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet.* 2016;387:168-75.

3. Seale AC, Head MG, Fitchett EJA, et al. Neonatal infection: a major burden with minimal funding. *Lancet Glob Health.* 2015;3(11):e669-80.

4. Synnes A, Luu TM, Moddemann D, et al. Determinants of developmental outcomes in a very preterm Canadian cohort. *Arch Dis Child Fetal Neonatal Ed.* 2016: doi: 10.1136/archdischild-2016-311228.

5. Dong Y, Speer CP. Late-onset neonatal sepsis : recent developments. *Arch Dis Child Fetal Neonatal Ed.* 2015: doi: 10.1136/archdischild-2014-306213.

6. Russell ARB, Kumar R. Early onset neonatal sepsis : diagnostic dilemmas and practical management. Arch Dis Child Fetal Neonatal Ed. 2015: doi: 10.1136/archdischild-2014-306193.

7. Stoll ABJ, Hansen NI, Watterberg KL, et al. Early Onset Neonatal Sepsis : The Burden of Group B Streptococcal and E . coli Disease Continues. *Pediatrics*. 2011; 127(5):817-26.

8. Tsai M, Hsu J, Chu S, et al. . Incidence , Clinical Characteristics and Risk Factors for Adverse Outcome in Neonates With Late-onset Sepsis. Paediatr Infect Dis J. 2014;33(1):7–13.

9. Tsai L, Chen Y, Tsou K. The impact of small-for-gestational-age on neonatal outcome among very-low-birth-weight infants. *Pediatr Neonatol*. 2015;56(2):101–7.

10. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England : the NeonIN surveillance network. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(1):F9-F14.

11. Pocket book of Hospital care for children. World Health Organisation. 2005. Accessed 7th April 2017: http://apps.who.int/iris/bitstream/10665/43206/1/9241546700.pdf

12. Lutsar I, Trafojer UMT, Heath PT, et al. Meropenem vs standard of care for treatment of late onset sepsis in children of less than 90 days of age : study protocol for a randomised controlled trial. *Trials*. 2011;12(1):215.

13. Hornik CP, Herring AH, Benjamin DK, et al. Adverse Events Associated with Meropenem versus Imipenem/ Cilastatin Therapy in a Large Retrospective Cohort of Hospitalized Infants. *Pediatr Infect Dis J*. 2013;32(7):748-53.

14. Cailes B, Vergnano S, Kortsalioudaki C, et al. The current and future roles of neonatal infection surveillance programmes in combating antimicrobial resistance. *Early Hum Dev*. 2015;91(11):613–8.

15. Russell AB, Sharland M, Heath PT. Improving antibiotic prescribing in neonatal units : time to act . A*rch Dis Child Fetal Neonatal Ed*. 2012;97(2):F141-6.

16. Simon A, Tenenbaum T. Surveillance of Multidrug-resistant Gram-negative Pathogens in High-risk Neonates — Does it Make a Difference? *Pediatr Infect Dis J*. 2013;32(4):407-9.

17. Folgori L, Livadiotti S, Carletti M, et al. Epidemiology and Clinical Outcomes of Multidrug-resistant , Gram-negative Bloodstream Infections in a European Tertiary Pediatric Hospital During a 12-month Period. *Pediatr Infect Dis J*. 2014;33(9):929–32.

18. Bielicki JA, Lundin R, Sharland M et al. Antibiotic Resistance Prevalence in Routine Bloodstream Isolates from Children’s Hospitals Varies Substantially from Adult Surveillance Data in Europe. *Pediatr Infect Dis J*. 2015;34(7):734–41.

19. Abdula N, Macharia J, Motsoaledi A, et al.National action for global gains in antimicrobial resistance. Lancet. 2016;387(10014):e3-5.

20. Downie L, Armiento R, Subhi R, et al. Community-acquired neonatal and infant sepsis in developing countries : efficacy of WHO’s currently recommended antibiotics — systematic review and meta-analysis. *Arch Dis Child.* 2013;98(2):146-54.

21. Doare K Le, Bielicki J, Heath PT, et al. Systematic Review of Antibiotic Resistance Rates Among Gram-Negative Bacteria in Children With Sepsis in Resource-Limited Countries. *J Pediatric Infect Dis Soc.* 2015;4(1):11–20.

22. Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *Lancet Glob Health.* 2016;4(10):e752-60.

23. Hendlin D, Stapley EO, Jackson M, et al. Phosphonomycin, a new antibiotic produced by strains of streptomyces. *Science*. 1969;(166):122–3.

24. Castañeda-García A, Blázquez J, Rodríguez-Rojas A. Molecular Mechanisms and Clinical Impact of Acquired and Intrinsic Fosfomycin Resistance. Antibiotics. 2013;16(2):217-36.

25. Kahan FM, Kahan JS, Cassidy PJ, et al. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci*. 1974;235(0):364-86.

26. Takahata S, Ida T, Hiraishi T, et al. Molecular mechanisms of fosfomycin resistance in clinical isolates of Escherichia coli. *Int J Antimicrob Agents.* 2010;35(4):333–7.

27. Cao XL, Shen H, Xu YY, et al. High prevalence of fosfomycin resistance gene fosA3 in bla CTX-M-harbouring Escherichia coli from urine in a Chinese tertiary hospital during 2010-2014. *Epidemiol Infect.* 2016;12:1–7.

28. Engel H, Gutiérrez-Fernández J, Flückiger C, et al. Heteroresistance to fosfomycin is predominant in Streptococcus pneumoniae and depends on the murA1 gene. *Antimicrob Agents Chemother.* 2013;57(6):2801–8.

29. Molina MA, Olay T QJ. Pharmacodynamic data on fosfomycin in underweight infants during the neonatal period. *Chemotherapy*. 1977;23:217–22.

30. Guggenbichler JP, Kienel G. Fosfomycin, a new antibiotic drug. *Padiatr Padol*. 1978;13(4):429–36.

31. Guibert M, Magny JF, Poudenx F, et al. Comparative pharmacokinetics of fosfomycin in the neonate: 2 modes of administration. *Pathol Biol*. 1987;35(5):750–2.

32. Suzuki S1, Murayama Y, Sugiyama E, et al. Dose estimation for renal-excretion drugs in neonates and infants based on physiological development of renal function. *Yakugaku Zasshi*. 2009;129(7):829–42.

33. Iwai N1, Nakamura H, Miyazu M, et al. A study of the absorption and excretion of fosfomycin sodium in children. Jpn J Antibiot. 1991;44(3):345-56.

34. Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation : a quantitative description using weight and postmenstrual age. *Pediatr Nephrol.* 2009;24(1):67-76.

35. Andrews JM, Baquero F, Beltran JM, et al. International collaborative study on standardization of bacterial sensitivity to fosfomycin. J Antimicrob Chemother. 1983;12(4):357-61.

36. Pfausler B, Spiss H, Dittrich P, et al. Concentrations of fosfomycin in the cerebrospinal fluid of neurointensive care patients with ventriculostomy-associated ventriculitis. J Antimicrob Chemother. 2004;53(5):848–52.

37. Sauermann R, Karch R, Langenberger H, et al. Antibiotic abscess penetration : fosfomycin levels measured in pus and simulated concentration-time profiles. Antimicrob Agents Chemother. 2005;49(11):4448–54.

38. Mazzei T, Cassetta MI, Fallani S, et al. Pharmacokinetic and pharmacodynamic aspects of antimicrobial agents for the treatment of uncomplicated urinary tract infections. Int J Antimicrob Agents. 2006 Aug;28 Suppl 1:S35-41.

39. Docobo-Pérez F, Drusano GL, Johnson A, et al. Pharmacodynamics of fosfomycin: insights into clinical use for antimicrobial resistance.Antimicrob Agents Chemother. 2015;59(9):5602-10.

40. Bergan T. Degree of absorption, pharmacokinetics of fosfomycin trometamol and duration of urinary antibacterial activity. *Infection.* 1990;18:S65-9.41. 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 Clin Pharmacol Ther Toxicol. 1989;27(8):411–7.

42. Cree M, Stacey S, Graham N, et al. Fosfomycin-investigation of a possible new route of administration of an old drug. A case study. J Cyst Fibros. 2007;6(3):244-6.

43. Bergan T. Degree of absorption, pharmacokinetics of fosfomycin trometamol and duration of urinary antibacterial activity. Infection. 1990;18:S65-9.

44. Llorens J, Lobato A, Olay T. The passage of fosfomycin into the cerebrospinal fluid in children’s meningitis. *Chemotherapy.* 1977;23(S1):189–95

45. Traunmüller F, Popovic M, Konz KH, et al. A reappraisal of current dosing strategies for intravenous fosfomycin in children and neonates. Clin Pharmacokinet. 2011;50(8):493-503.

46. De Cock RFW, Allegaert K, Schreuder MF, et al. Maturation of the Glomerular Filtration Rate in Neonates, as Reflected by Amikacin Clearance. Clin Pharmacokinet. 2012;51(2):105–17.

47. Iarikov D, Wassel R, Farley J, et al. 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(4):433–58.

48. O'Brien F, Walker IA. Fluid homeostasis in the neonate. *Paediatr Anaesth*. 2014;24(1):49-59.

49. Hartnoll G, Bétrémieux P, Modi N. Body water content of extremely preterm infants at birth. 2000;56–9. *Arch Dis Child Fetal Neonatal Ed*. 2000;83(1):F56-9.

450. Taylor CG, Mascarós E, Román J, et al. Enteropathogenic E. coli gastroenterocolitis in neonates treated with fosfomycin. *Chemother*. 1977;23(1):310–4.

51. Rossignol S, Regnier C. Fosfomycin in severe infection in neonatology. *Ann Pediatr.* 1984;31(5):437–44.

52. Hepping N, Simon A. Fosfomycin in paediatric cancer patients: a feasible alternative to glycopeptides? *Int J Antimicrob Agents.* 2009;33(4):389.

53. Guillois B, Guillemin MG, Thoma M, et al. Neonatal pleuropulmonary staphylococcal infection with multiple abscesses of the liver. Ann Pediatr.1989;36(10):681–4.

54. Gouyon JB, François C, Semama D, et al. Nosocomial Staphylococcus epidermidis and Staphylococcus aureus septicemias in neonates. *Ann Pediatr.*1990;37(1):21–5.

55. Algubaisi S, Buhrer C, Thomale UW, et al. Favorable outcome in cerebral abscesses caused by Citrobacter koseri in a newborn infant. *IDCases.* 2014;2(1):22–4.

56. Falagas ME, Giannopoulou KP, Kokolakis GN, et al. Fosfomycin : Use Beyond Urinary Tract and Gastrointestinal Infections. *Clin Infect Dis*. 2008;46(7):1069-77.

57. Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. Int J Infect Dis. 2011;15:e732–9.

58. Vardakas KZ, Legakis NJ, Triarides N, et al. Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature. *Int J Antimicrob Agents.* 2016;47(4):269–85.

59. Yu X, Song X, Cai Y, et al. In vitro activity of two old antibiotics against clinical isolates of methicillin-resistant Staphylococcus aureus. *J Antibiot*. 2010;63(11):657–9.

60. Lu C, Liu C, Huang Y, et al. Antimicrobial Susceptibilities of Commonly Encountered Bacterial Isolates to Fosfomycin Determined by Agar Dilution and Disk Diffusion Methods. *Antimicrob Agents Chemother.* 2011;55(9):4295-301.

61. Sultan A, Rizvi M, Khan F, et al. Increasing antimicrobial resistance among uropathogens: Is fosfomycin the answer? Urol Ann. 2015;7(1):26–30.

62. Chiquet C, Maurin M, Altayrac J, et al. Correlation between clinical data and antibiotic resistance in coagulase- negative Staphylococcus species isolated from 68 patients with acute post- cataract endophthalmitis. Clin Microbiol Infect. 2015: doi: http://dx.doi.org/10.1016/j.cmi.2015.01.028

63. Falagas ME, Maraki S, Karageorgopoulos DE, et al. Antimicrobial susceptibility of Gram-positive non-urinary isolates to Fosfomycin. *Int J Antimicrob Agents.* 2010;35(5):497–9.

64. González JJ, Andreu A; Grupo de Estudio de Infección Perinatal, Sociedad Espanola de Enfermedades Infecciosas y Microbiologia Clinica. Susceptibility of vertically transmitted Group B streptococci to antimicrobial agents. *Enferm Infecc Microbiol Clin*. 2004;22(5):286–91.

65. Matthews PC, Barrett LK, Warren S, et al. Oral fosfomycin for treatment of urinary tract infection : a retrospective cohort study. *BMC Infect Dis*. 2016;16(1):556.

66. Chen YT, Ahmad Murad K, Ng LS, et al. In Vitro Efficacy of Six Alternative Antibiotics against Multidrug Resistant Escherichia Coli and Klebsiella Pneumoniae from Urinary Tract Infections. *Ann Acad Med Singapore.* 2016;45(6):245-50.

67. Ranjan A, Shaik S, Mondal A, et al. Molecular Epidemiology and Genome Dynamics of New Delhi Metallo-β-Lactamase-Producing Extraintestinal Pathogenic Escherichia coli Strains from India. *Antimicrob Agents Chemother.* 2016;60(11):6795-6805.

68. Sahni RD, Balaji V, Varghese R, et al. Evaluation of fosfomycin activity against uropathogens in a fosfomycin-naive population in South India: a prospective study. *Futur Microbiol*. 2013;8(5):67580.

69. Cheng A, Liu C, Tsai H, et al. Bacteremia caused by Pantoea agglomerans at a medical center in Taiwan, 2000-2010. *J Microbiol Immunol Infect.* 2013;46(3):187–94.

70. Pogue JM, Marchaim D, Abreu-Lanfranco O, et al. Fosfomycin activity versus carbapenem-resistant Enterobacteriaceae and vancomycin-resistant Enterococcus, Detroit, 2008-10. *J Antibiot.* 2013;66(10):625–7.

71. Vanscoy B, Mccauley J, Bhavnani SM, et al. Relationship between Fosfomycin Exposure and Amplification of Escherichia coli Subpopulations with Reduced Susceptibility in a Hollow-Fiber Infection Model. *Antimicrob Agents Chemother.* 2016;60(9):5141-5.

72. Nilsson AI, Berg OG, Aspevall O, et al. Biological Costs and Mechanisms of Fosfomycin Resistance in Escherichia coli. *Antimicrob Agents Chemother*. 2003;47(9):2850-8.

73. Karageorgopoulos DE, Wang R, Yu XH et al. Fosfomycin: Evaluation of the published evidence on the emergence of antimicrobial resistance in gram-negative pathogens. *J Antimicrob Chemother*. 2012;67(2):255–68.

74. Lara N, Cuevas O, Arroyo M,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(11):2459-63.

75. Rodríguez-Avial I, Pena I, Picazo JJ, et al. In vitro activity of the next-generation aminoglycoside plazomicin alone and in combination with colistin, meropenem, fosfomycin or tigecycline against carbapenemase-producing Enterobacteriaceae strains. *Int J Antimicrob Agents*. 2015;46(6):616–21..

76. Walsh CC, Landersdorfer CB, McIntosh MP, et al. Clinically relevant concentrations of fosfomycin combined with polymyxin B, tobramycin or ciprofloxacin enhance bacterial killing of Pseudomonas aeruginosa, but do not suppress the emergence of fosfomycin resistance. *J Antimicrob Chemother.* 2016;71(8):2218–29..

77. Sime FB, Johnson A, Whalley S, et al. Pharmacodynamics of Aerosolized Fosfomycin and Amikacin against Resistant Clinical Isolates of Pseudomonas aeruginosa and Klebsiella pneumoniae in a Hollow-Fiber Infection Model: Experimental Basis for Combination Therapy. *Antimicrob Agents Chemother*. 2016: doi: 10.1128/AAC.01763-16.

78. De Man P, Verhoeven BA, Verbrugh HA, et al. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet.* 2000;355(9208):973-8.