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

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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 gram negative bacteria (MDRGNB) 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 MDRGNB in a neonatal setting, in light of recent evidence suggesting it to be most effective as a combination chemotherapy. Given the urgency of clinical demand for treatment of MDRGNB sepsis, we outline directions for further work including the need for future clinical trials in this at-risk population.

Introduction

Intravenous fosfomycin has not been widely used across the world despite its discovery nearly fifty years ago and broad spectrum activity against Gram-positive and Gram-negative bacteria. The oral form as a single dose for urinary tract infection has been more commonly prescribed. This might have been the result of 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 trials such as the AIDA project (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 bacteria, and will summarise current evidence regarding pharmacokinetics, dosing and clinical outcomes in this population.

Neonatal sepsis

Despite significant progress in the reduction of child mortality (as identified in United Nations Millennium Development Goal 4), 23% of an estimated 2.9 million neonatal deaths a year are attributed to infection (3). Serious bacterial infections in neonates account for 3% of all disability-adjusted life years Sepsis of *any* cause in the neonatal period is significantly associated with adverse neurodevelopmental outcomes (4).

Neonatal sepsis can be categorised by time of occurrence to enable broad differentiation between causative organisms. For the purposes of this paper, 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 genital tract. The most common causative organisms seen in EOS are Group B *streptococcus* (48-53%) (5) followed by *E-coli* (18%). Late-onset sepsis (LOS) is associated with the postnatal environment and nosocomial pathogens such as coagulase negative *Staphylococcus* and Gram-negative bacilli.

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 pre-term infants (7).

LOS constitutes a larger number of cases; pre-term infants have been shown to be at increased risk of LOS (36% of infants <28 weeks gestation develop one episode of LOS vs. 16% of term infants in neonatal intensive care (8)). 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 (9), Gram-negative pathogens are associated with worse clinical outcomes and are more epidemiologically significant in LOS in LMIC settings (5). Continued improvements in neonatal care combined with these factors contribute towards an increasing burden of Gram-negative neonatal sepsis in LMIC settings.

Current World Health Organisation (WHO) guidelines recommend an aminopenicillin with

gentamicin as first-line therapy in neonatal sepsis. 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. The pharmacokinetic and safety profile of meropenem in neonates is now described (10,11). Increasing use of meropenem is associated with increasing rates of infection by carbapenem-resistant organisms (CRO). It is now vital to explore other treatment regimens to limit the development of carbapenem resistance and to provide therapeutic options if present.

AMR in neonates

Term but especially preterm infants treated at the neonatal unit (NNU) are particularly vulnerable to AMR as they have 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 and have been associated with both endemic and epidemic infections (12). Half of all childhood cases of MRSA bacteraemia, for example, occur in the neonatal period (13). Studies have shown that colonization of inpatient preterm neonates differs vastly from term neonates in the community. There are, however, increasing numbers of studies describing the detection of multi-drug resistant Gram-negative (MDRGN) organisms on 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(14). Gram-negative sepsis is associated with especially high rates of morbidity and mortality in neonatal populations (15).

The Antibiotic Resistance and Prescribing in European Children (ARPEC) project found that the most commonly isolated species from neonatal and paediatric blood cultures were *S. aureus*, *E. coli*, *K. pneumoniae* and *Enterococci faecalis* (16). Isolated *E. coli* showed 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 was also substantial – 26% of *Pseudomonas* species isolated were resistant to carbapenems.

These data are representative of a High Income Country (HIC) setting. Low and middle-income countries (LMIC) are particularly vulnerable to the effects of AMR as they face the challenges of access to medicines, weak health-care systems and limited resources, all of which compound the higher burden of infectious diseases that they share (17).

Microbiological data from LMICs are more limited. However, two recent systematic reviews suggest that MDRGN are increasingly clinically significant on a global scale. Downie et al. (18) 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. They found that the recommended WHO first line therapy provided only 43-44% coverage in neonates, and that third-generation cephalosporins conferred no additional coverage. Le Doare et al. (19) 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 all isolates in this population (67%). Again, *Klebsiella* species were the dominant Gram-negative pathogen to be isolated (50%), a concerning finding due to their intrinsic resistance to ampicillin.

Both reviews were limited by the quality and quantity of the data available. However, emerging studies from individual LMIC settings (20) suggest that resistance to recommended first-line antibiotics is of clinical significance.

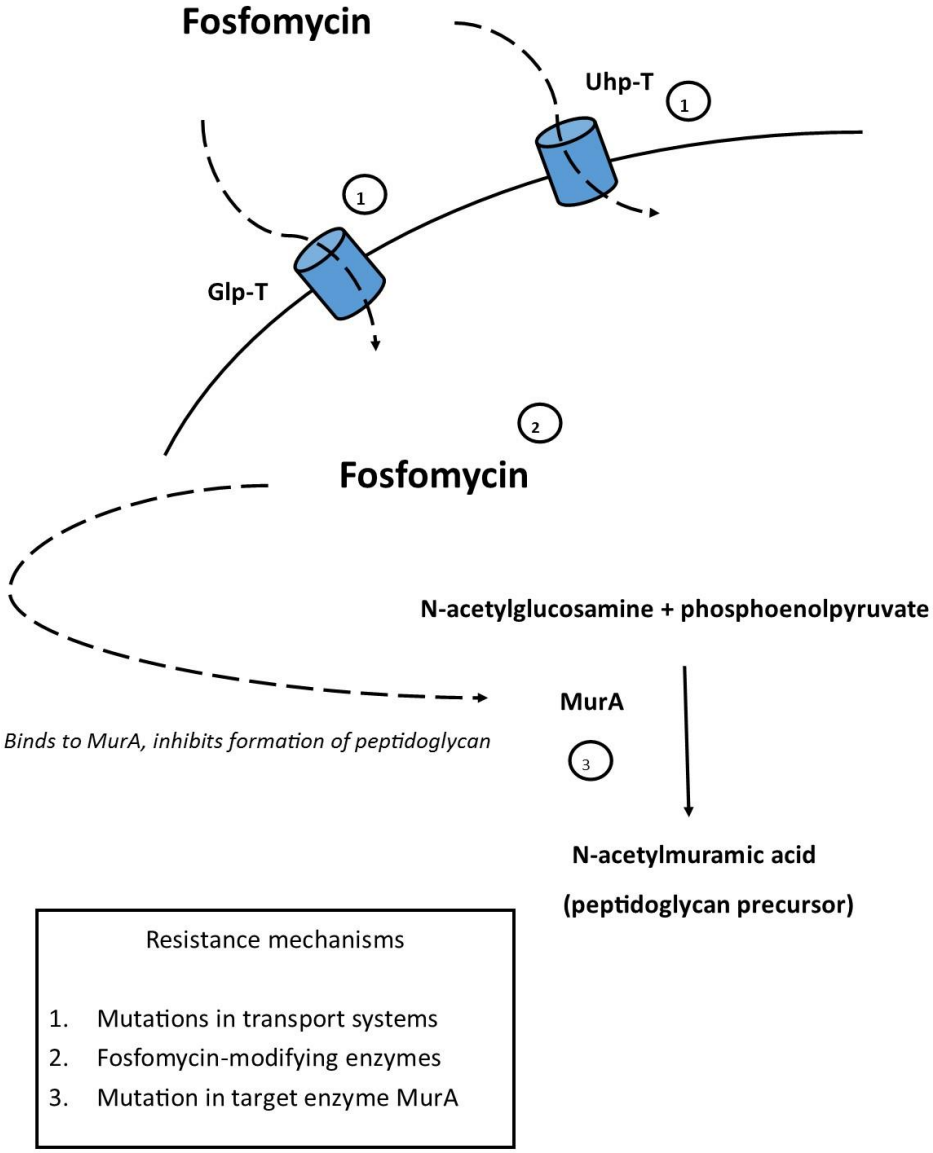
Mechanism of action

Fosfomycin, or phosphonomycin, was discovered in 1969 as a product of *Streptomycetes* and *Pseudomonas syringae* (21). 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 *M. tuberculosis*, *V. sheri* and *C. trachomatis* (22).

Fosfomycin exerts its bactericidal effects by acting as an analog of phosphoenolpyruvate, binding and inhibiting the cytosolic enzyme MurA (N-acetylglucoasmine enolpyruvate 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 update transport systems (23). 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,(24)), reduced affinity of the target enzyme MurA (single amino acid substitution,(24)) or production of fosfomycin-modifying enzymes that render the drug inactive (22).

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



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 (25).

There is evidence that polymorphisms of MurA contribute to heteroresistant bacterial subpopulations in *Streptococcus pneumoniae* (26), 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, and particularly in Gram-negative species.

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; this 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 (27)	11 neonates	50mg/kg IV, comparing infants 1-3d old and 3-4 weeks old	Elimination slower at earlier CGA
Guggenbichler et al., 1978 (28)	5 term, 5 pre-term	25mg/kg IV	95-98% recovered in the urine, 1 compartment model
Guibert et al., 1987 (29)	10 neonates	200mg/kg BD, comparing 30m or 2hr infusion schedules	No difference between schedules, serum concentrations are above MIC of common pathogens at 12h post dose
Suzuki et al., 2009 (30)		Dose estimation for renally excreted drugs	Dose estimation validated with GFR, tubular secretion clearance and fraction of unbound drug in plasma

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)(27,28). However, gestational age was only described in one study (36.3 weeks ± 0.7) and both studies included low birth weight infants (mean 1.9 kg ± 0.1/0.4). Longer fosfomycin half-life in neonates compared to children (5-13 years) is likely to be largely due to lower clearance associated with maturation of glomerular filtration (31), but also to a lesser extent possibly due to greater volume of distribution (0.41 L/Kgin neonates versus 0.35 L/Kg children). 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.

A neonatal C_{max} at 60-90mg/L is comparable with adult populations (32). Whilst there is evidence demonstrating oral bioavailability of fosfomycin in adults (33), no data are available for paediatric populations. Fosfomycin is not available in a rectal formulation, and its contribution 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 (34). However, no pharmacokinetic data are available.

Serum protein binding is estimated to be below 3% (35). 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 (of which 1 neonatal subject) following treatment with IV fosfomycin were too low to justify fosfomycin monotherapy (36) 80%–95% of the dose is recovered unchanged in urine within 24 hours (35).

Dosing

In anticipation of its reintroduction into clinical use and given the discrepancy between dosing recommendations between European countries, Traunmü et al (37) remodeled the limited existing paediatric pharmacokinetic data for parenteral administration using a two-compartment model with Kinetica open-source software (Innaphase, 2001). Fosfomycin has traditionally thought to exhibit time-dependent antibacterial activity as fosfomycin bacterial killing correlates well with T>MIC. Use of G6PD supplementation *in vitro* makes it challenging to compare studies describing fosfomycin MICs.

Based upon this, their target attainment was T>MIC 40-70% with an MIC of 32mg/L. Whilst their source of data was limited, they found that the lowest current recommended paediatric doses (100mg/kg/d) only achieved target T>MIC for preterm infants. Their study confirmed that corrected gestation 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 SPC for Fomicyt in the UK).

However, only one pre-existing pharmacokinetic study explores the range of doses upon which these recommendations are based. The broad categorisation of pre-term infants as <40 weeks signals the need for future pharmacokinetic modelling of fosfomycin in pre-term infants as there is evidence to suggest that the difference in renal maturation between 26 and 36 weeks gestation can influence recommended dosing schedules (38).

Table 2: Fosfomycin neonatal dosing recommendations, taken from Nordic Pharma 2016

Age/weight	**Daily dose**
Premature neonates (corrected gestational age <40 weeks)	100mg/kg in 2 divided doses
Neonates (corrected gestational age 40-44 weeks)	200mg/kg in 3 divided doses
Infants 1-12 months (up to 10kg)	200-300mg/kg in 3 divided doses
Infants and children aged 1-12 years (10-40kg)	200-400mg/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 were reviewed recently

(39). 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 pergram), 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 (40). There is evidence that excessive early fluid administration and sodium supplementation of >4mmol/k/g in infants <30 weeks corrected gestational age can lead to adverse outcomes (41) and has been linked to the development of CLD. The current dosing recommendations for fosfomycin would lead to sodium administration of 1.4mmol/kg/d and 2.8mmol/kg/d for preterm (1kg) and term (2kg) infants, respectively, highlighting the need for dosing regimes taking into account the physiology of extremely preterm infants.

Hypernatremic dehydration would also 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 8 hourly, 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).

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 (42). 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 (43), combination therapy with tobramycin/gentamicin (44) one case report of meropenem combination therapy for successful treatment of intracranial *Citrobacter* infection.

Table 3: Studies describing use of fosfomycin in neonatal sepsis

Study	N	Dose and clinical setting	Outcomes
Taylor et al., 1977 (43)	43 neonates	150-200mg/kg/d for enterocolitis caused by enteropathic E coli	Favourable clinical outcome in 88%
Rossignol & Regnier 1984 (44)	21 neonates, 11 gram negative infections	200mg/k/d, two divided doses, in combination with gentamicin/tobramycin for sepsis and UTI	Clinical recovery in 19/21
Guillois et al., 1989 (45)	Case report n =1	IV fosfomycin-vancomycin for MSSA septicaemia and liver abscesses, followed by oral pristinamycin	Full recovery
Gouyon et al., 1990 (46)	16 neonates	IV fosfomycin-cefotaxime for	Full recovery n=15

		staphylococcal septicaemia including meningitis, osteomyelitis and congenital varicella superinfection	
Algubaisi et al., 2015 (47)	Case report, 1 term infant	120mg/kg/d fosfomycin and meropenem used to treat multiple citrobacter koseri intracerebral abscesses	Clinical recovery

Outcome data for the clinical efficacy of fosfomycin in adults is well-documented and was reviewed by Falagas et al. (48) 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. (49) examined the effectiveness and safety of fosfomycin in critically ill patients suffering from 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.

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. (50) 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
Staphlococcus aureus Yu et al., Lu et al., Sultan et al., (51–53)	33.2-100%	MIC_{90} = 16-128
CoNS Chiquet et al., Sultan et al., (53,54)	77.5-100% MICs not available in the literature	Not documented
Group B *Streptococcus* Falagas et al.,(55)	40.6%	Not documented 0.32% resistance to fosfomycin reported in review of 131 strains responsible for EOS (56)

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

Gram negative	Susceptibility to fosfomycin	MIC
E - coli Matthews et al., Chen et al., (57,58)	78-98% >95% sensitivity reported in NDM producing species (59)	Not documented
Klebsiella spp. Sahni et al. (60)	40-94%	4-64
Enterobacter spp. Hsu et al., Pogue et al., (61,62)	76-98%	Variable

Preliminary evidence suggests fosfomycin may have generally good coverage of both common causative organisms in neonatal sepsis except for Group B Streptococcus, which requires further investigation.

The overall susceptibility of ESBL-producing *E. coli* strains to fosfomycin ranged from 81% - 100% (95% C.I. 94.3-95.9%), however MIC_{90} values for these organisms showed a wide range from <4mg/L up to 128mg/L in some Asian studies. The susceptibility in ESBL-producing *Klebsiella* strains was somewhat lower, ranging from 15%-100% (95% C.I. 78.7-89.4%) and higher MIC_{90} values (up to >1024mg/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 (63,64). Data on the activity of fosfomycin against CRO is mostly restricted to KPC-producing *Klebsiella pneumoniae*, and the review 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 mean that it will have to be considered for use in a combination regime. Nilsson et al.,(65) demonstrate that the development of fosfomycin resistance *in vitro* comes at a biological cost and concomitant reduction in growth rate of the bacterial population, explaining why resistance may not manifest clinically. Karageorgopoulos et al., (66) reviewed both *in vitro* and clinical evidence for the emergence of resistance to fosfomycin in Gram-negative species during treatment and found that resistance in *Pseudomonas aeruginosa* developed more readily than for *E coli* isolates. Again, the evidence for clinical sequelae of fosfomycin resistance was limited, and they did not make any recommendations to change current practice based on their findings. As with all antibiotics, increased use has been associated with increased resistance in clinical isolates (67).

Combination regimes will also have the added benefit of the additive or synergistic antimicrobial effects of more than one compound. Promisingly, fosfomycin has shown *in vitro* synergy with the aminoglycoside plasmocin against CRO (68). Walsh et al. (69) have

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 particularly with tobramycin, the rate of emergence of resistant subpopulations was not reduced. Amikacin is an aminoglycoside commonly used as an alternative to gentamicin and recent *in vitro* evidence suggests that amikacin improves the bacterial killing of fosfomycin whilst also suppressing the development of resistance (70).

One challenge will be to clarify the interaction between fosfomycin combination therapies and the potentiation of resistance. The introduction of fosfomycin into a setting of endemic MDRGN infection will have substantial effects on the selection of organisms and the choice of combination therapy will be crucial. For example, the intrinsic resistance of *Klebsiella* to ampicillin could be potentiated with a combination that does not adequately cover for resistance *Klebsiella* species (71) . Much work remains at both the in vitro and clinical level.

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 pre-term 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.

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