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

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Abstract The broad-spectrum activity of fosfomycin, including against multidrug-resistant (MDR) 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 MDR bacteria 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 the use of fosfomycin in neonatal sepsis and issues specific to neonatal physiology. While fosfomycin has a broad range of coverage, we evaluate the extent to which it may be effective against MDR bacteria in a neonatal setting, in light of recent evidence suggesting it to be most effective when administered in combination with other antibiotics. Given the urgency of clinical demand for treatment of MDR bacterial sepsis, we outline directions for further work, including the need for future clinical trials in this at-risk population.

1 Introduction

Intravenous fosfomycin has not been widely used across the world despite its discovery nearly 50 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 among 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-
Recent studies have described significant morbidity and mortality associated with neonatal sepsis in countries where key multidrug-resistant (MDR) organisms are endemic [2]; however, there is currently no literature that addresses the utility of fosfomycin in this specific setting. This review will describe why fosfomycin is an attractive option for the treatment of neonatal sepsis caused by MDR bacteria, and will summarise current evidence regarding pharmacokinetics, dosing and clinical outcomes in this population.

2 The Burden of Neonatal Sepsis and Antimicrobial Resistance (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 h 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 Escherichia coli (18%). EOS occurs in approximately 0.9 per 1000 live births. However, the risk of sepsis increases with prematurity; 26% of babies with a birth weight <1000 g will have at least one 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 infants [29–32 weeks], 17.5% of late preterm infants [33–36 weeks] and 16.5% of term infants [8]) in the neonatal intensive care setting [9].

In high-income countries (HICs), Gram-positive pathogens are the most common causative organisms of LOS (60–70%), and are commonly associated with the use of indwelling catheters and tertiary neonatal units (NNUs) [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 Organization (WHO) guidelines [11] recommend an aminopenicillin with gentamicin as first-line therapy in neonatal sepsis. While the guidelines do not differentiate between EOS and LOS, treatment for the latter usually takes into account the source of infection suspected, e.g. the 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 β-lactamase (ESBL)-producing organisms are endemic [12, 13]. Increasing use of meropenem is associated with increasing rates of infection by carbapenem-resistant organisms (CROs). 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 MDR Gram-negative organisms in NNUs, and an association has been shown between species responsible for colonisation and those causing fulminant sepsis, particularly with regard to Klebsiella and Enterobacter species [16]. Gram-negative sepsis is associated with particularly 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, while K. pneumoniae were resistant to cephalosporins in nearly 30% of cases. Resistance to second-line antibiotics is also substantial; 26% of isolated Pseudomonas species 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 healthcare systems and limited resources [19]. Two recent systematic reviews suggest that MDR Gram-negative organisms 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 S. aureus, Klebsiella species and E. 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 an 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.

3 Fosfomycin: Mechanism of Action

Fosfomycin, or phosphonomycin, was discovered in 1969 as a product of Streptomyces 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 tromethamine salt for oral consumption, and 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, Staphylococcus capitis, Staphylococcus saprophyticus, Mycobacterium tuberculosis, Vibrio sheri and Chlamydia trachomatis [24].

Fosfomycin exerts its bactericidal effects by acting as an analogue of phosphoenolpyruvate, binding and inhibiting the cytosolic enzyme MurA (UDP-N-acetylglucosamine 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 glucose-6-phosphate (G6P) supplementation in agar, which potentiates fosfomycin’s antimicrobial activity [35]. 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.

4 Pharmacokinetic Profile, Dosing and Toxicity in Neonates

4.1 Pharmacokinetics

Most data regarding the pharmacokinetic profile of fosfomycin in adults refer to intravenous administration. Limited data are available regarding the pharmacokinetics of intravenous fosfomycin in neonates (summarised in Table 1).

The elimination half-life of fosfomycin in neonates following an intravenous bolus is described in two studies, and ranges from 2.4 to 7.0 h following a dose of 25–50 mg/kg [29, 30]. The variation in half-life values may be explained by the 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 with children (5–13 years) [33], is likely to be largely due to the lower clearance associated with maturation of glomerular filtration [34], but may also, to a lesser extent, be due to greater volume of distribution (0.41 L/kg in neonates vs. 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 pharmacokinetic/pharmacodynamic 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 (G6P) 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 pharmacodynamic parameters and measurement of fosfomycin in discrete physiological compartments (cerebrospinal fluid [CSF], abscess fluid).

The first paper to explore the intrinsic pharmacodynamic characteristics of fosfomycin [38] presented in vivo data suggestive of concentration-dependent killing, with a significant post-antibiotic effect. Recent hollow-fibre models

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Fig. 1 Mechanism of action of fosfomycin and resistance mechanisms. Glp-T glycerol-3-phosphate transport system, Uhp-T hexose-phosphate transport system

Table 1 Neonatal fosfomycin pharmacokinetic studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N</th>
<th>Dose and study</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Molina et al., 1977</td>
<td>11</td>
<td>50 mg/kg IV, comparing infants aged 1–3 days and 3–4 weeks</td>
<td>Elimination slower at younger CGA</td>
</tr>
<tr>
<td>Guggenbichler and Kienel, 1978</td>
<td>5 term, 5 preterm</td>
<td>25 mg/kg IV (CGA and PNA not specified)</td>
<td>95–98% recovered in the urine, one-compartment model</td>
</tr>
<tr>
<td>Guibert et al., 1987</td>
<td>10</td>
<td>200 mg/kg bid, comparing 30-min or 2-h infusion schedules</td>
<td>No difference between schedules, serum concentrations are above the MIC of common pathogens at 12 h postdose</td>
</tr>
<tr>
<td>Suzuki et al., 2009</td>
<td></td>
<td>Dose estimation for renally excreted drugs</td>
<td>Dose estimation validated with GFR, tubular secretion clearance and fraction of unbound drug in plasma</td>
</tr>
</tbody>
</table>

CGA corrected gestational age, PNA postnatal age, GFR glomerular filtration rate, MIC minimal inhibitory concentration, bid twice daily, IV intravenously
provide evidence that area under the curve over the minimum inhibitory concentration (AUC/MIC) correlates with suppression of bacterial resistance [39]. However, time above MIC of 100% (T > MIC = 100%) was simultaneously achieved, therefore pharmacokinetic/pharmacodynamic indices for future studies will need to be clarified. The most recent review of fosfomycin dosing in neonates is guided by T > MIC [44].

A neonatal Cmax (after intravenous administration) at 60–90 mg/L is comparable with that attained in adult populations [40]. While 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 the successful use of fosfomycin 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% [40]. 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 one neonatal subject) following treatment with intravenous fosfomycin were too low to justify fosfomycin monotherapy [43]. Eighty to 95% of the dose is recovered unchanged in urine within 24 h [40].

4.2 Dosing

In anticipation of its reintroduction into clinical use, and given the discrepancy between dosing recommendations between European countries, Traumüller et al. [44] remodelled the limited existing paediatric pharmacokinetic data for parenteral administration using a two-compartment model with Kinetica open-source software (Innaphase Corporation, 2001). The current European Committee on Antimicrobial Susceptibility Testing (EUCAST) fosfomycin breakpoint (32 mg/L) is set according to adult dosing schedules of 3–8 g administered three times daily, 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 (8 mg/L). Based on this, their target attainment was a T > MIC of 40–70% for an MIC of 32 mg/L. While their source of data was limited, they found that the lowest current recommended paediatric doses (100 mg/kg/day) only achieved target T > MIC for infants with a corrected gestational age of 37 weeks and postnatal age of 3–5 weeks. Their study confirmed that corrected gestational age and body weight comprised the most significant explanatory variables in fosfomycin pharmacokinetics.

Traumüller et al. 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 daily) 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 [45].

4.3 Toxicity

Intravenous administration of fosfomycin is generally associated with low toxicity. Adverse events reported to the US FDA in association with fosfomycin administration in adults have recently been reviewed [46]. Serious side effects include heart failure (3%) and hypokalemia (particularly following shorter infusion times). These are attributable to the high sodium load of fosfomycin (14.4 mmol 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 and concomitant potassium excretion and hypokalemia.

Sodium is important for growth in neonates but, paradoxically, they have low sodium requirements for the first 48–72 h of life, followed by a physiological diuresis [47]. There is evidence that excessive early fluid administration and sodium supplementation of >4 mmol/kg/day in infants <30 weeks corrected gestational age can lead to adverse outcomes [48] 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 and 2.8 mmol/kg/day for preterm (1 kg) and term (2 kg) infants, respectively. As sodium supplementation in preterm infants is routinely avoided in the first 48 h of life, the potential risk of hypernatremia would need to be carefully looked for in any future clinical trial. While 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).

5 Clinical Outcomes in Children and Neonates

The current EUCAST fosfomycin breakpoint (32 mg/L) is set according to adult dosing schedules of 3–8 g administered three times daily, 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* \((8 \text{ mg/L})\).

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 identified that 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 [49], combination therapy with tobramycin/gentamicin [50], and one case report of meropenem combination therapy for successful treatment of intracranial *Citrobacter* infection [51]. While 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 is only occasionally prescribed to limit the empirical use of other broad-spectrum antibiotics such as teicoplanin, again for Gram-positive cover [54].

Outcome data for the clinical efficacy of fosfomycin in adults is well-documented and has been reviewed by Falagas et al. [55] 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. [56] examined the effectiveness and safety of fosfomycin in critically ill patients with intensive care unit-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.

### 6 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 on 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 CROs needs to be considered.

Vardakas et al. [57] conducted a recent systematic review evaluating the coverage of fosfomycin with regard 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.

Preliminary evidence suggests fosfomycin has varying activity against the pathogens most commonly causative of neonatal sepsis, such as Staphylococcal spp., coagulase-negative Staphylococcal species, Klebsiella spp. and E. coli. Furthermore, there is significant variation in the described sensitivities for Klebsiella spp. and S. 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 to 100%; however, the MIC\textsubscript{90} values for these organisms showed a wide range, from <4 up to 128 mg/L, in Asian studies. Susceptibility in ESBL-producing Klebsiella strains was somewhat lower, ranging from 15 to 100%, and higher MIC\textsubscript{90} 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, 70]. Data on the activity of fosfomycin against CROs is mostly restricted to Klebsiella pneumoniae carbapenemase-producing Klebsiella pneumoniae, and the review by Michalopoulos et al. [56] found that susceptibility ranged from 39.2 to 100%, 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.

While 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. [71]

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Susceptibility to fosfomycin</th>
<th>MIC (mg/L)</th>
</tr>
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<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Yu et al., Lu et al., Sultan et al. [58–60]</td>
<td>33.2–100%</td>
</tr>
<tr>
<td>CoNS</td>
<td>Sultan et al., Chiquet et al. [60, 61]</td>
<td>77.5–100%</td>
</tr>
<tr>
<td>Group B Streptococcus</td>
<td>Falagas et al. [62]</td>
<td>40.6%</td>
</tr>
</tbody>
</table>

CoNS coagulase-negative Staphylococcal species, MIC minimum inhibitory concentration, MIC\textsubscript{90} MIC required to inhibit the growth of 90% of organisms, EOS early-onset sepsis

<table>
<thead>
<tr>
<th>Gram-negative</th>
<th>Susceptibility to fosfomycin</th>
<th>MIC (mg/L)</th>
</tr>
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<tbody>
<tr>
<td>E. coli</td>
<td>Matthews et al., Chen et al. [64, 65]</td>
<td>78–98%</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>Sahni et al. [67]</td>
<td>40–94%</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>Cheng et al., Pogue et al. [68, 69]</td>
<td>76–98%</td>
</tr>
</tbody>
</table>

MIC minimum inhibitory concentration, NDM New Delhi metallo-beta-lactamase, Glp-T glycerol-3-phosphate transporter protein, Uhp-T hexose phosphate transporter protein

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demonstrated that fosfomycin resistance in vitro is biologically costly and results in reduced growth of the bacterial population, therefore resistance may not manifest clinically. Karageorgopoulos et al. [72] 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 Karageorgopoulos et al. 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 [73].

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 CROs [74]. Walsh et al. [75] 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 while 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 while suppressing the development of resistance [76].

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 [77].

7 Conclusions

Emerging evidence supports the validity of combination fosfomycin therapy in the management of MDR Gram-negative sepsis in neonates. However, there remain substantial gaps in the current literature that need to be addressed. In vitro work is needed to assess the combinations of antimicrobials that optimise fosfomycin synergy in the treatment of MDR Gram-negative bacteria and 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 are 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 fosfomycin) will be required. Fosfomycin licensing is currently geographically limited, and any global policy recommendations made for the empirical management of MDR Gram-negative sepsis in infants will require affordable access to fosfomycin, including expedited local licensing. While this represents a substantial amount of progress to be made, the global risk to neonates of untreatable MDR Gram-negative sepsis cannot be ignored.

Compliance with Ethical Standards

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References


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