GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT (GARD) PARTNERSHIP

Developing new antibiotic treatments, promoting responsible use, and ensuring access for all

Addressing Antibiotic Treatment of Neonatal & Infant SBI in the Context of High Multidrug-Resistant Gram-negative Bacteria

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on behalf of PENTA-ID
Further progress in decreasing child mortality depends on reducing the 2.9 m neonatal deaths each year, around a quarter of which are directly due to infection.

- 6.9 m neonates required treatment for possible serious bacterial infection in 2012 in high-burden settings.

Neonatal Infection: “A major burden with minimal funding”

Lancet 2015
Burden of AMR in neonates

- Retrospective observational study, 4 years (2007 – 2010), Kolkata, India:
  - MDR in 50%; carbapenem resistance in 30% of Acinetobacter spp; pan-resistance in 5
  - MDRGN: a major cause of EO & LO neonatal sepsis in India & widespread in the community.

Arch Dis Child Fetal Neonatal Ed 2012;97:F182–7
ARPEC point prevalence survey in 2012 – 41 countries

**Neonatal prescriptions for HAIs**

- Africa (n=78)
- Asia (n=168)
- S-America (n=17)
- Europe (n=544)
- Australia (n=64)
- N-America (n=24)

Legend:
- Glycopeptides
- Aminoglycosides
- Carbapenems
- 3rd-gen. cephalosporins
- Broad-spectrum penicillins
- Combinations of penicillins
- Narrow-spectrum penicillins
- 2nd-gen. cephalosporins

**Resistance to last-resort antibiotic has now spread across globe**
Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO’s currently recommended antibiotics—systematic review and meta-analysis

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Arch Dis Child 2013;98:146–154

• only 57% of isolates susceptible to benzylpenicillin/ampicillin & gentamicin and only 56% susceptible to 3rd-gen cephalosporins

• main gaps in antibiotic coverage were due to enteric Gram-negative bacilli, particularly Klebsiella
Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC)

A global surveillance network focused on collection of data on neonatal and paediatric antimicrobial prescribing and resistance.

- Unique global surveillance system
- Uses customised online tool to collate information about neonatal and paediatric prescribing, including microbial culture data and AMR patterns
- Administrative base at St George’s, University of London
- 12 paediatric centres participating, covering 6 continents
- Full roll-out Q1 2016 following successful pilot in 2015
Optimising management of MDRGNB infections

- Neonatal studies generally show lower rates of toxicity for most antimicrobials
- Recent re-evaluation of dosing strategies e.g. targeting Cmax with gentamicin: use higher doses
- **Combination therapy** with 2 or more active drugs associated with increased efficacy: use new combinations
- Role for co-amoxiclav in neonatal infections: use new formulations

**Key issues**

- Aminoglycosides appear to have low rates of ototoxicity and nephrotoxicity in neonates.
- No studies are available that report vestibulotoxicity in neonates.
- Ototoxicity is more likely when aminoglycosides are given concomitantly with loop diuretics.
- Ototoxicity is more likely with prolonged courses of aminoglycosides.
- Genetic predisposition accounts for a small proportion of aminoglycoside-induced deafness; practical methods to identify such neonates before administering aminoglycosides are not yet available.
Review of “older agents”: Fosfomycin

**Pharmacokinetics**

- can be taken **orally as well as intravenously and intramuscularly**
- good penetration of tissues with favourable side effect profile
- *in vitro* susceptibility of MDRGNB is high:
  - MIC susceptibility breakpoint of 64 mg/L:
    - 97% of 1657 ESBL-producing *Escherichia coli* isolates susceptible
    - 81% of 748 ESBL-producing *Klebsiella pneumonias* isolates susceptible

  *Lancet Infect Dis. 2010 Jan;10(1):43-50*

- *in vitro* data suggests synergy with some antibiotic agents

**Access to Fosfomycin**

- Licensed for use IV in Europe
Pharmacodynamics of vancomycin for CoNS infection: experimental basis for optimal use of vancomycin in neonates

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Objectives: CoNS are the most common cause of neonatal late-onset sepsis. Information on the vancomycin pharmacokinetics/pharmacodynamics against CoNS is limited. The aim of this study was to characterize vancomycin pharmacokinetic/pharmacodynamic relationships for CoNS and investigate neonatal optimal dosage regimens.

Methods: A hollow fibre and a novel rabbit model of neonatal central line-associated bloodstream CoNS infections were developed. The results were then bridged to neonates by use of population pharmacokinetic techniques and Monte Carlo simulations.

Results: There was a dose-dependent reduction in the total bacterial population and C-reactive protein levels. The AUC/MIC and Cmax/MIC ratios were strongly linked with total and mutant resistant cell kill. Maximal amplification of resistance was observed in vitro at an fAUC/MIC of 200 mg·h/L. Simulations predicted that neonates <29 weeks post-menstrual age are underdosed with standard regimens with respect to older age groups.

Conclusions: The AUC/MIC and Cmax/MIC ratios are the pharmacodynamic indices that best explain total and resistant cell kill in CoNS infection. This suggests that less-fractionated regimens are appropriate for clinical use and continuous infusions may be associated with increased risk of emergence of antimicrobial resistance. This study has provided the pharmacodynamic evidence to inform an optimized neonatal dosage regimen to take into a randomized controlled trial.
Novel combinations: fosfomycin

Stage 1. Defining the extent and nature of the interaction against Gram negative pathogens
- 5 strains of: *Pseudomonas aeruginosa*, *Enterobacteriaceae* (*E. coli* and *Klebsiella pneumoniae*) and *Acinetobacter baumannii* (wild-type and defined mutants)
- fosfomycin-based combinations: (1) + amikacin; (2) + ciprofloxacin; (3) + aztreonam, (4) + meropenem
- study combinations against each of the 15 strains (60 experiments) in shaking flasks: estimate the temporal changes in total bacterial density and the resistant subpopulations
- The interactions will be classified as additive, synergistic or antagonistic and ranked in terms of magnitude and their ability to suppress the emergence of drug resistance
- The leading 3-4 regimens that result in killing and prevent the emergence of drug resistance will be studied in the Hollow Fibre Infection Model (HFIM)

Stage 2. HFIM to define PK-PD relationships of fosfomycin-based regimens
- Experimental models will be conducted for up to 14 days to provide a study duration that is clinically relevant and will provide a robust test of combination chemotherapy
- Human-like (neonatal) PK will be simulated in the HFIM.
- Relationship between drug exposure (i.e. PK) and the antimicrobial effect (bacterial killing and the emergence of drug resistance) will be described using mathematical models.
2. Clinical Trial stream

Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): An extension of the STROBE statement for neonatal infection research

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This proposal aims to develop a strategic pharmacometric, microbiological and clinical trial network for optimising existing antimicrobial options and rapidly and efficiently re-entering older antimicrobials into routine clinical practice. It recognises that currently a large number of neonates and infants cannot access appropriate antibiotic treatment for MDRGN serious bacterial infections.

- address key gaps in knowledge about current management of neonatal sepsis in the context of endemic rates of MDRGNB and in LMIC settings
- strengthen pre-clinical and clinical evidence base with regard to empirical regimes for treatment of neonatal sepsis
- support *in vitro* studies of novel antimicrobial combinations, with a focus on fosfomycin
- develop new standardised definitions for conducting neonatal antimicrobial trials and define the optimal design for neonatal sepsis clinical trials in the context of current regulatory requirements & LMIC settings
- conduct a phase 1 trial based on new pre-clinical data