Identifying carbapenem and amikacin-sparing first-line combination therapy for neonatal sepsis in high extended-spectrum beta-lactamase (ESBL) prevalence settings

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17 February 2020
Hollow fibre cartridge
Hollow Fibre Set-up
Hollow Fibre Uses

► Drug development:
  ► Dose ranging studies - human PK
  ► Optimising duration of treatment
  ► EMA TB guideline:

► Combinations
  ► Induction of resistance
  ► Multi-organism
  ► Intracellular pathogens
  ► Genotype-phenotype correlation
Paediatric blood stream infections (e.g. Malawi)

Tam et al 2018 CID

Figure 2. Proportion of culture-confirmed bloodstream pathogens resistant to empiric first-line antimicrobials by period, for children ≤5 years and ≤60 days. First-line antimicrobials in Malawi are ampicillin/penicillin with gentamicin, or ceftriaxone.
Neonatal sepsis

- ↑ infections with multi-drug resistant (MDR) organisms
- Culture positive neonatal sepsis mortality:
  - 12% for non-MDR pathogens
  - 15.7% for MDR pathogens

Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study

Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration

- Need to optimise use of current agents, and develop new antimicrobials
- Includes studying dose for efficacy and resistance suppression
Paediatric drug development

- Running pivotal phase III trials challenging
- Clinical PKPD not always straight-forward:

(Germovsek 2018 JAC)

- Legislation $\rightarrow$ $\uparrow$ paediatric trials, but 42% failures (Wharton 2014 Pediatrics)
- Regulators ready to accept PK and safety
- What is the PD target and duration?

(Lonsdale 2018 PhD thesis)
Study Summary

► **Problem:** We have clinical isolates of *E. coli* and *K. pneumoniae* which are: ampicillin/cefotaxime/gentamicin R/R/R (usual first-line agents)

► **Research question:** Using combinations of these agents, can we prevent need for first-line meropenem/amikacin use?
  - What is the activity of β-lactam PLUS gentamicin (additivity, synergy?)
  - Can phenotype be reversed with double β-lactam or adding β-lactamase inhibitor?
  - What is the optimal duration?

► **Aim:** Perform detailed *in vitro* characterisation of neonatal isolates, particular focus on hollow fibre method
Methods

► STEP 1:
  ► Take *E. coli* and *K. pneumoniae* isolated in neonates where clinical outcome is documented (Europe and Taiwan):
  ► Chose sulbactam (SUL) as β-lactamase inhibitor as available in combination with ampicillin and cefotaxime
  ► Identify isolates with multi-drug resistance, take forward to STEP 2

► STEP 2:
  ► Checkerboard test for synergy with 2 and 3 agents
  ► Checkerboard layout (concentrations informed by 2D experiments):
Fractional inhibitory concentration index (FICI):

If we have drug 1 and drug 2 recall:

\[
FICI = \frac{\text{MIC}_{1,\text{comb}}}{\text{MIC}_{1,\text{alone}}} + \frac{\text{MIC}_{2,\text{comb}}}{\text{MIC}_{2,\text{alone}}}
\]

If \( \text{MIC}_{1,\text{alone}} \) is halved in presence of drug 2 and vice versa = \( \Rightarrow \) additivity \((FICI = 1)\)

Synergy \( FICI < 0.5 \) Antagonism \( FICI > 2 \)

Assuming additivity = \( \Rightarrow \) n-fold reduction in MIC can extend to n drugs:

\[
FICI = \frac{\text{MIC}_{1,\text{comb}}}{\text{MIC}_{1,\text{alone}}} + \frac{\text{MIC}_{2,\text{comb}}}{\text{MIC}_{2,\text{alone}}} + \cdots + \frac{\text{MIC}_{n,\text{comb}}}{\text{MIC}_{n,\text{alone}}}
\]
Methods

► STEP 3:
  ► Time-kill experiments with most resistant (highest MIC) isolates and most promising combinations identified in STEP 2

► STEP 4:
  ► Investigate dose and duration in hollow fibre
  ► PK parameters for GEN, CTX, AMP and SUL simulated for typical neonate receiving:
    GEN 5 mg/kg q24h, CTX 50mg/kg q12h, AMP 100 mg/kg q12h (SUL in ratio according to commercially available formulations)

![Diagram of hollow fibre system]

- \( R \cdot R_u (\text{mL/h}) \) from diluent (no drug)
- \( R (\text{mL/h}) \) to waste
- \( V_u (\text{mL}) \) GEN reservoir
- \( V (\text{mL}) \) central reservoir
- \( R_u (\text{mL/h}) \) to/from hollow fibre cartridge
- \( R_g (\text{mL/h}) \) dose CTX/SUL + GEN
Overview

► Introduction
► Aims
► Methods
► Results
► Discussion
► Conclusion
Results

- **Isolates:**
  - 34 *E. coli*
  - 4 *K. pneumoniae*

- **E. coli**
  - 7 resistant to cefotaxime (CTX) AND ampicillin (AMP) AND gentamicin (GEN)
  - 26 resistant to at least one, all sensitive to amikacin and/or meropenem

- **K. pneumoniae**
  - 3/4 CTX/AMP/GEN R/R/R
  - 3 also resistant to amikacin (AMIK)
  - 1 resistant R/R/R/R/R to CTX/AMP/GEN/AMIK/Meropenem
Results - FICI median (range) & Time Kill (e.g. CTX/SUL/GEN)

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Median FICI (range)</th>
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<tbody>
<tr>
<td>CTX/GEN</td>
<td>0.25 (0.063-0.625)</td>
</tr>
<tr>
<td>AMP/GEN</td>
<td>0.75 (0.156-1)</td>
</tr>
<tr>
<td>CTX/AMP</td>
<td>0.38 (0.14-0.63)</td>
</tr>
<tr>
<td>CTX/SUL</td>
<td>0.16 (0.09-0.36)</td>
</tr>
<tr>
<td>AMP/SUL</td>
<td>0.42 (0.078-0.75)</td>
</tr>
<tr>
<td>CTX/SUL/GEN</td>
<td>0.22 (0.11-0.41)</td>
</tr>
<tr>
<td>AMP/SUL/GEN</td>
<td>0.51 (0.31-0.82)</td>
</tr>
<tr>
<td>AMP/CTX/GEN</td>
<td>0.32 (0.25-1.09)</td>
</tr>
<tr>
<td>AMP/CTX/SUL</td>
<td>0.28 (0.22-0.50)</td>
</tr>
</tbody>
</table>
Results - Hollow fibre

- CTX/AMP/GEN E.coli
- CTX/GEN E.coli
- CTX/SUL/GEN E.coli
- CTX/SUL/GEN K.pneumoniae
- AMP/SUL/GEN E.coli

![Graph showing CFU/mL over time after first dose (days)](image-url)
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Hollow Fibre Discussion - “Internal control” and inferring duration?

Bacterial loads in neonatal sepsis of *E. coli* and *K. pneumoniae* around 10^4 cfu/mL

(van den Brand 2018 Critical Care)
Conclusions

This project:
- Sulbactam addition to ampicillin or cefotaxime promising for first-line neonatal sepsis
- Future work:
  - Attempt to replicate clinical cases in hollow fibre
  - Broader range of isolates
  - Need for optimising ratio of sulbactam

HFIM general:
- Complimentary to *in vitro* and *in vivo* data
- May replace some animal work
- Need to agree on/standardise hollow fibre methods
  - Ongoing systematic literature review: Zahra Sadouki
Acknowledgements

Main collaborators on work presented here: Mike Sharland (SGUL), Jodi Lindsay (SGUL), Cheng-Hsun Chiu (CGMH)  
London Pharmacometrics Interest Group

Student/Postdoc work presented here: John Readman, Aveen Hamawandi

Funding: MRC (Clinician Scientist Fellowship); NIHR