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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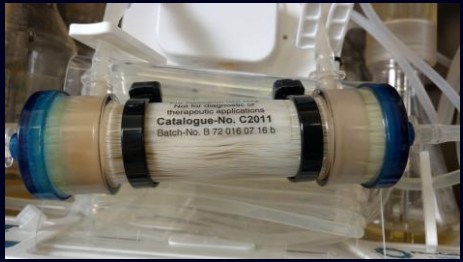
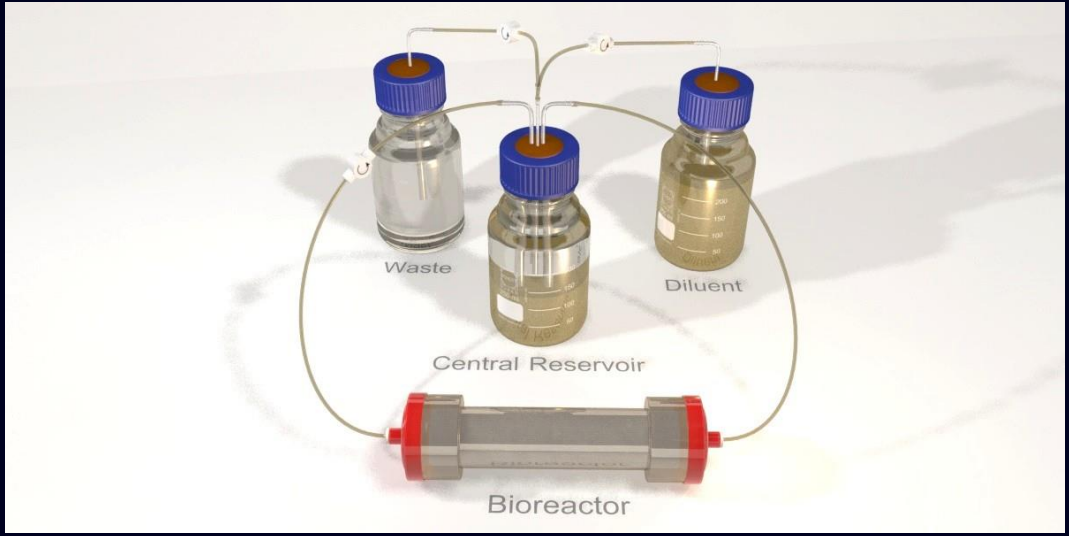
Precision AMR

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)

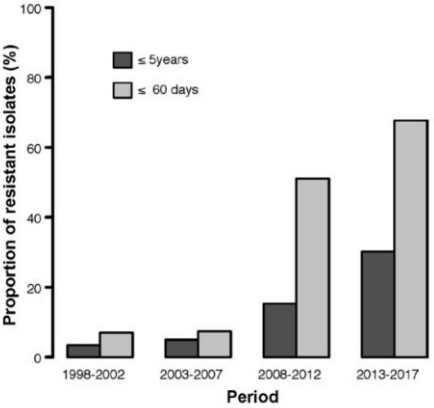


Figure 2. Proportion of culture-confirmed bloodstream pathogens resistant to empiric first-line antimicrobials by period, for children ≤5 years and ≤60 days. First-line antimicrobials in Malawi are ampicillin/penicillin with gentamicin, or ceftriaxone.

Tam *et al* 2018 CID

Neonatal sepsis

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

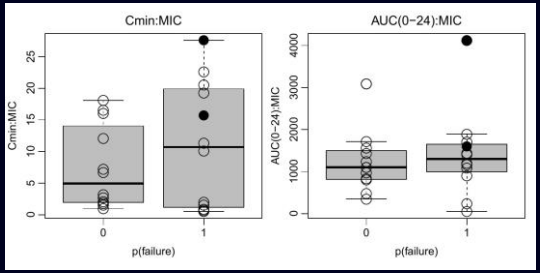

Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study

*Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration**

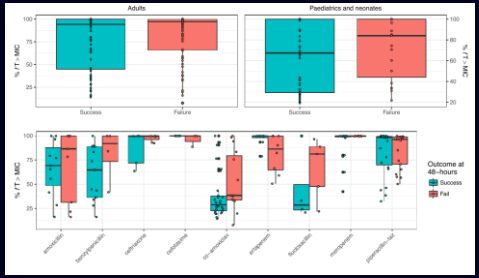
- Need to optimise use of current agents, and develop new antimicrobials
- Includes studying dose for efficacy and ?resistance suppression

Paediatric drug development

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



(Germovsek 2018 JAC)



(Lonsdale 2018 PhD thesis)

- 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**?

Study Summary

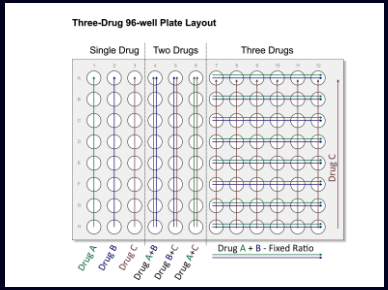
- **Problem:** We have clinical isolates of *E. coli* and *K. pneumoniae* which are: ampicillin/cefotaxime/gentamicin R/R/R (usual first-line agents)
- **Research question:** Using combinations of these agents, can we prevent need for first-line meropenem/amikacin use?
  - What is the activity of β lactam 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

Overview

- Introduction
- Aims
- Methods
- Results
- Discussion
- Conclusion

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:

$$FICI = \frac{MIC_{1,comb}}{MIC_{1,alone}} + \frac{MIC_{2,comb}}{MIC_{2,alone}}$$

If $MIC_{1,alone}$ is halved in presence of drug 2 and *vice versa* = $\Rightarrow$ additivity ($FICI = 1$)

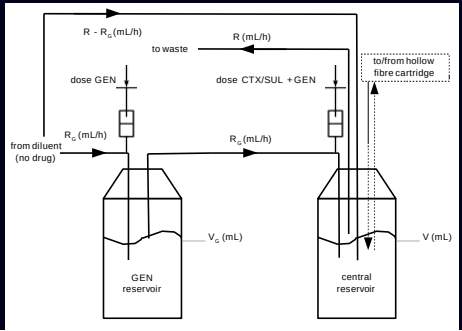
Synergy $FICI < 0.5$ Antagonism $FICI > 2$

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

$$FICI = \frac{MIC_{1,comb}}{MIC_{1,alone}} + \frac{MIC_{2,comb}}{MIC_{2,alone}} + \cdot \quad \frac{MIC_{n,comb}}{MIC_{n,alone}}$$

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)



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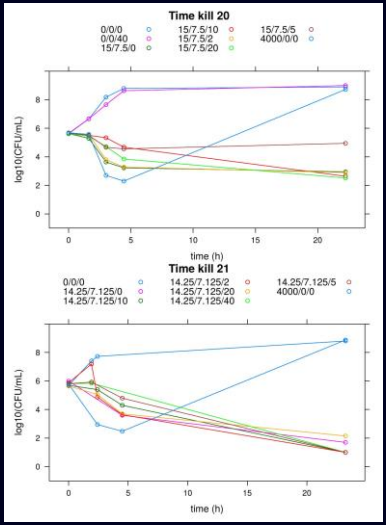
Results

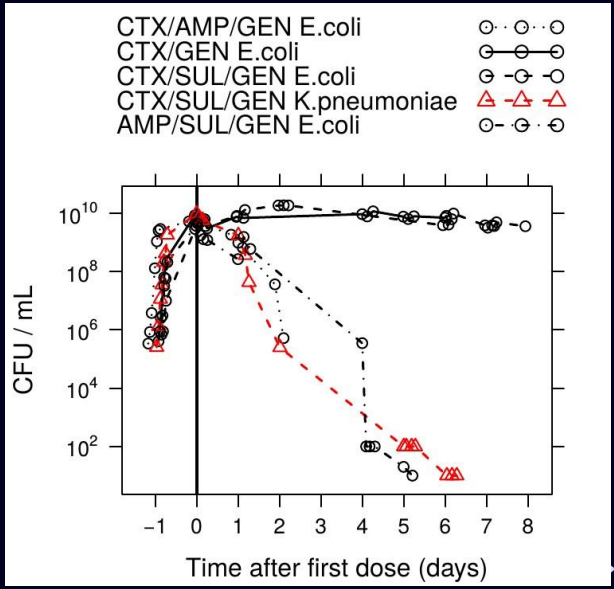
- Isolates:
  - 34 *E. coli*
  - 4 *K. pneumoniae*
- *E. coli*
  - 7 resistant to cefotaxime (CTX) AND ampicillin (AMP) AND gentamicin (GEN)
  - 26 resistant to at least one, all sensitive to amikacin and/or meropenem
- *K. pneumoniae*
  - 3/4 CTX/AMP/GEN R/R/R
  - 3 also resistant to amikacin (AMIK)
  - 1 resistant R/R/R/R/R to CTX/AMP/GEN/AMIK/Meropenem

Results - FICI median (range) & Time Kill (e.g. CTX/SUL/GEN)

Combinations	Median FICI (range)
CTX/GEN	0.25 (0.063-0.625)
AMP/GEN	0.75 (0.156-1)
CTX/AMP	0.38 (0.14-0.63)
CTX/SUL	**0.16 (0.09-0.36)**
AMP/SUL	0.42 (0.078-0.75)
CTX/SUL/GEN	**0.22 (0.11-0.41)**
AMP/SUL/GEN	0.51 (0.31-0.82)
AMP/CTX/GEN	0.32 (0.25-1.09)
AMP/CTX/SUL	0.28 (0.22-0.50)



Results - Hollow fibre



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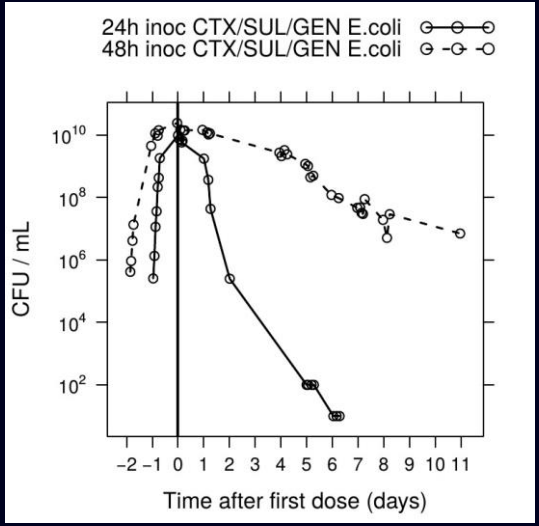
Hollow Fibre Discussion - “Internal control” and inferring duration?



- 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

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