Treating Resistant Gram-Negative Infections: Bedside to Bench and Back

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Organism

Six clinical isolates of *Acinetobacter baumannii*

- Opportunistic Gm-ve; Causes 20% nosocomial pneumonias
- Introduced by colonised patient, long-lived on hard surfaces
- Beta-lactam and increasing colistin resistance $\Longrightarrow$ combination therapy

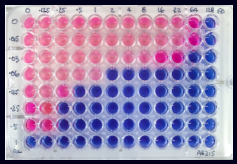
e.g. Colistin PLUS another antimicrobial

Antimicrobials

Screened colistin PLUS 10 agents with mainly Gm+ve activity

Colistin (polymixin E)

- Detergent-like effect
- Two-stage mechanism:
  - Outer Gm-ve outer membrane
  - Cytoplasmic membrane, osmotic disruption



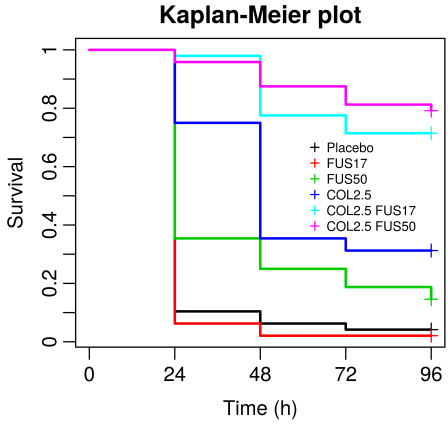
Fusidic acid

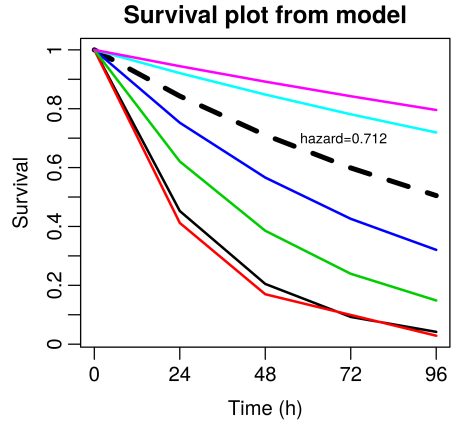
- Protein synthesis inhibition at ribosome

- $FICI = \frac{MIC_{C,comb}}{MIC_{C,alone}} + \frac{MIC_{F,comb}}{MIC_{F,alone}}$
- FICI < 0.25 for all strains


AB5075 10^5
200mg cor 2·5mg/kg
LP 2/1/15
AB5075 10^5
200mg cor 2·5/POT
LP 2/1/15


AB5075 LOT
200mg kg 2.5mg/kg
L.P. 2/1/15
AB5075 LOT
250mg kg 2.5/PO17
L.P. 2/1/15


Kaplan-Meier plot
Survival
Time (h)
0
0.2
0.4
0.6
0.8
1
0
24
48
72
96
Placebo
FUS17
FUS50
COL2.5
COL2.5 FUS17
COL2.5 FUS50


Survival plot from model
Survival
Time (h)
0
0.2
0.4
0.6
0.8
1
0
24
48
72
96
hazard=0.712

Overview

- Introduction (bedside to bench)
- Time-kill experiments
  - Method
  - Model development
  - Inference
- Case report (back to bedside)
- Conclusion

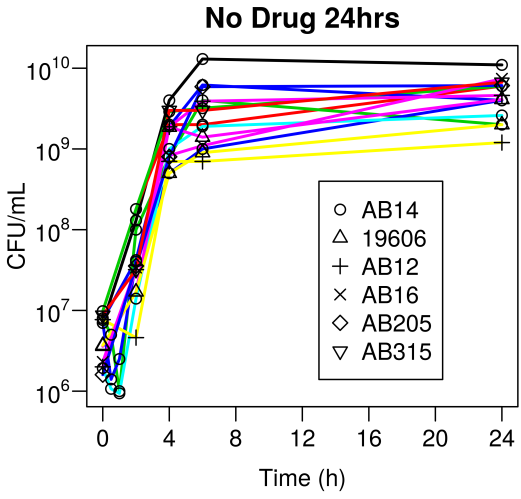
Time-Kill Experiments

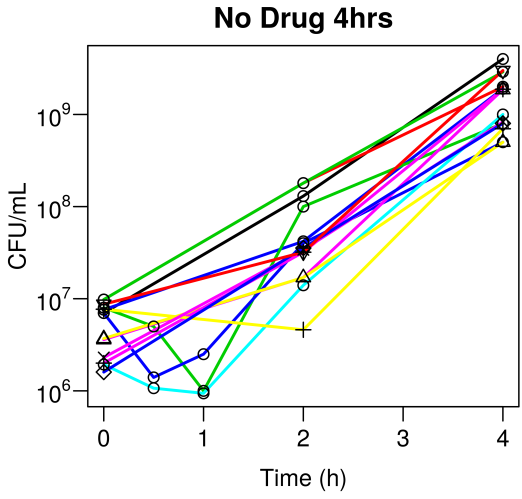
Experimental method:

- 10 mL broth +/- colistin sulfate (COL) and/or fusidic acid (FUS)
- COL 0-64 mg/L; FUS 0-512 mg/L; 46 combinations
- Viable CFU/mL measured over 24 h

Modelling:

- Model CFU/mL *versus* time for all strains and drug/dose combinations
- Extend time-dependent effect (resistance development) models to n$>$1 drugs
- Experiment and strain level random effects (population approach)


No Drug 24hrs
CFU/mL
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
0
4
8
12
16
20
24
Time (h)
AB14
19606
AB12
AB16
AB205
AB315


No Drug 4hrs
CFU/mL
10^{9}
10^{8}
10^{7}
10^{6}
0
1
2
3
4
Time (h)

System model

Basic model:

$$\frac{\mathrm{d}B}{\mathrm{d}t} = kB\left(1 - \frac{B}{B_{max}}\right) \tag{1}$$

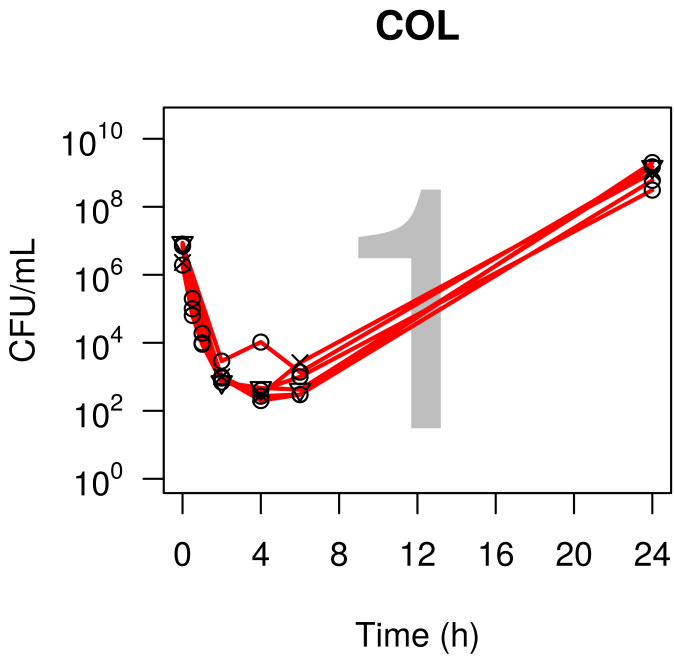
Parameters:

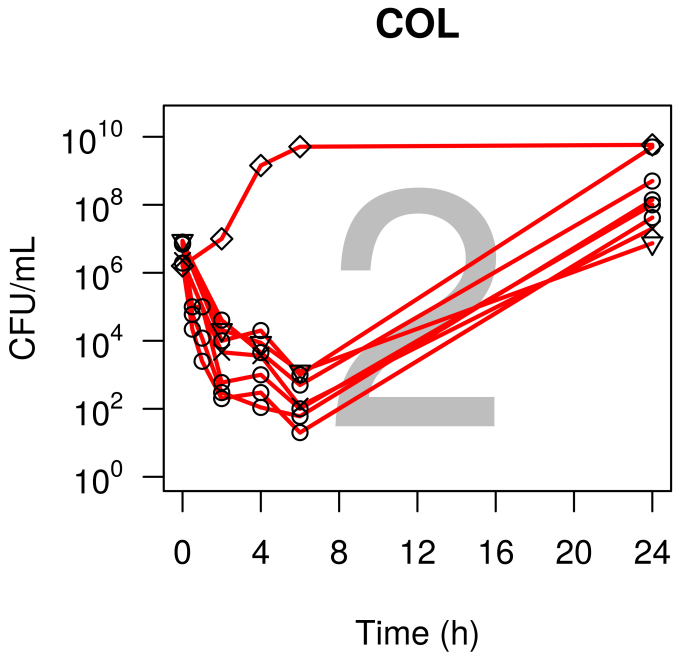
- $k = \lambda - \mu$, net growth/loss
- B_{max}, set point
- B_0, initial CFU/mL

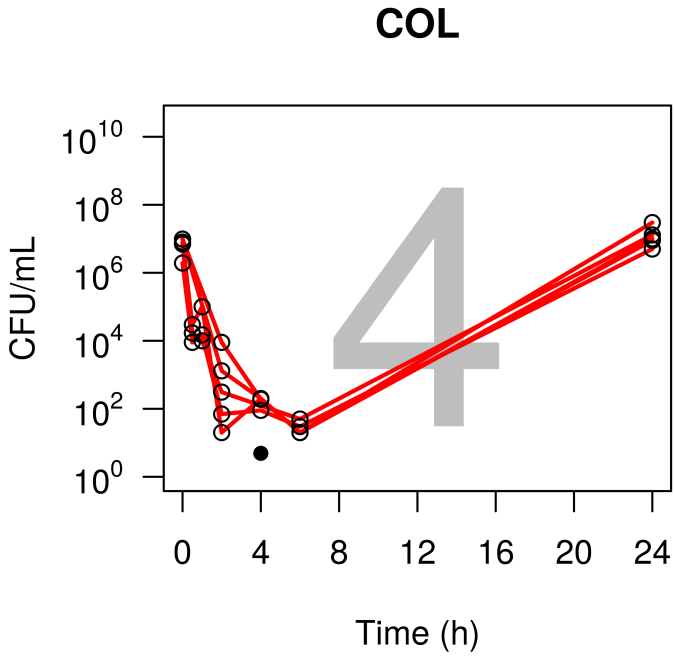
Accounting for lag:

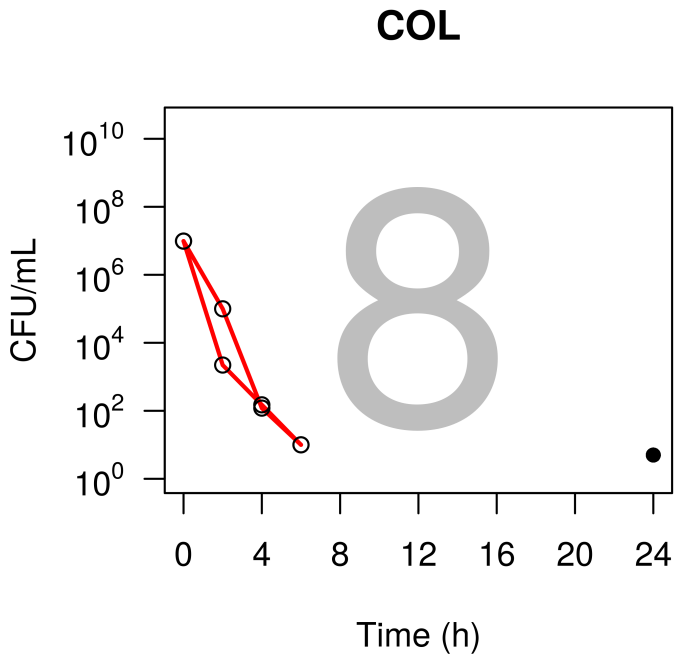
$$k = -\theta + 2\theta\frac{t^{20}}{L^{20} + t^{20}} \tag{2}$$

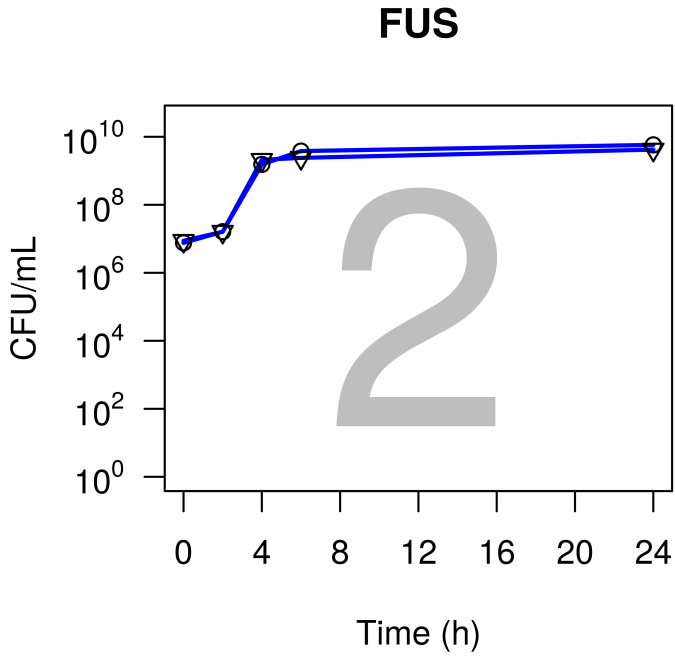
- L: growth lag
- Δ OFV -46; L estimate: 52 min
- k 1.8-fold higher

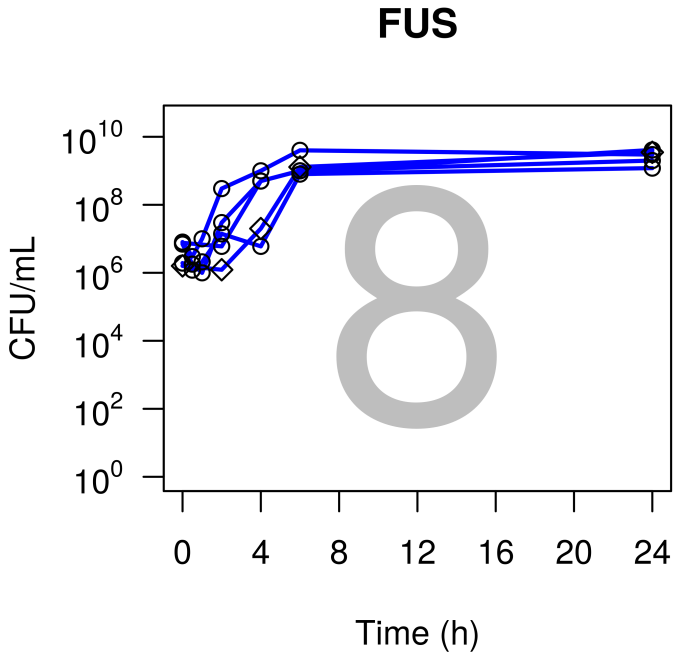

COL
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (h)
1

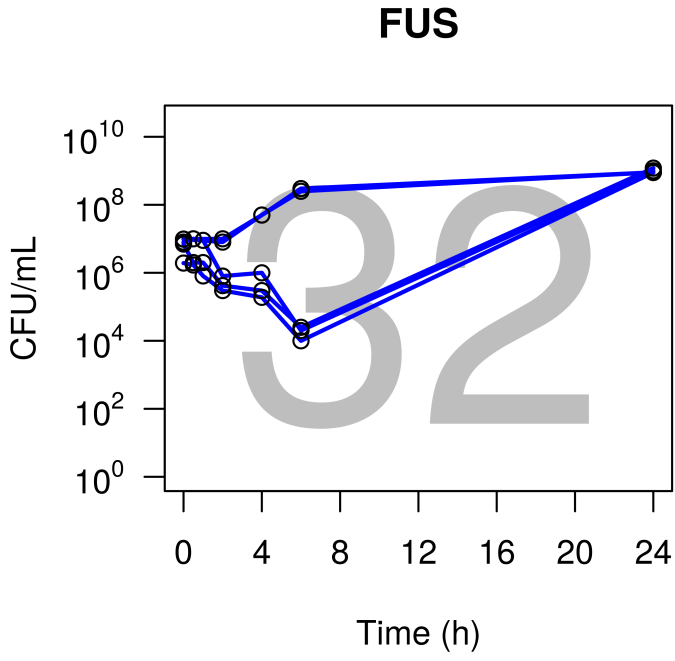

COL
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (h)

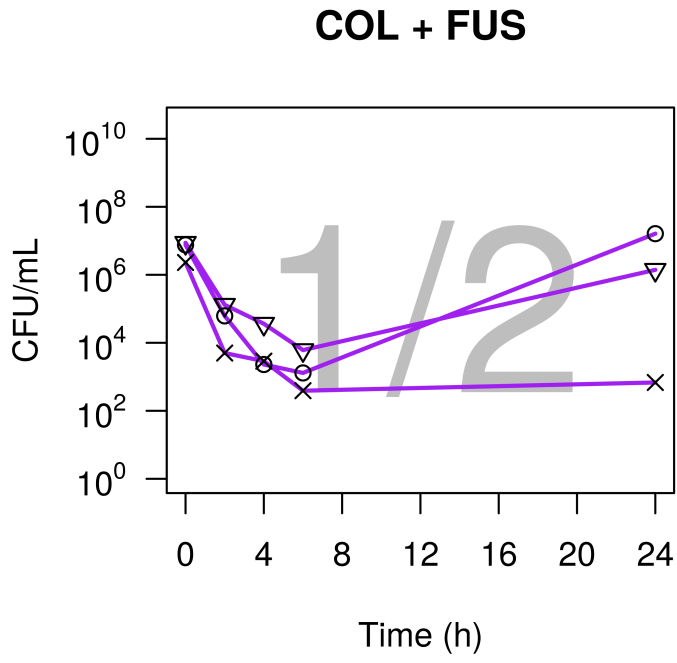

COL
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (h)

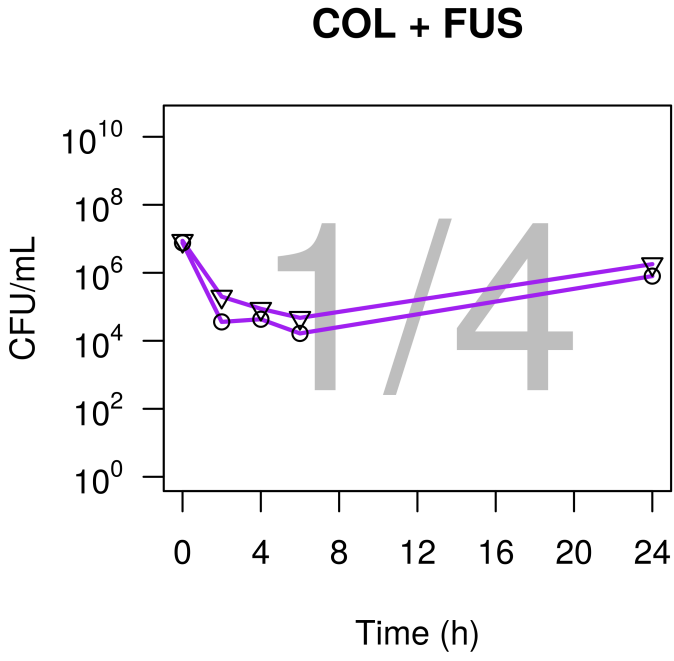

COL
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
8
0
4
8
12
16
20
24
Time (h)

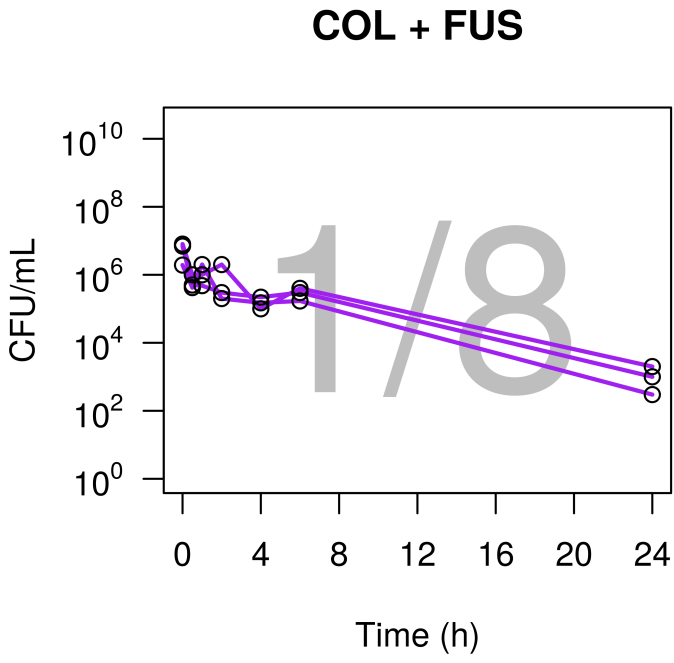

FUS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
2
0
4
8
12
16
20
24
Time (h)


FUS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (h)
8


FUS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (h)
32


COL + FUS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (h)
1/2


COL + FUS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
1/4
0
4
8
12
16
20
24
Time (h)


COL + FUS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
1/8
0
4
8
12
16
20
24
Time (h)

Drug model - similar to Bhagunde 2011

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \left(k\left(1 - \frac{B}{B_{max}}\right) - E_D\right) B \tag{3}$$

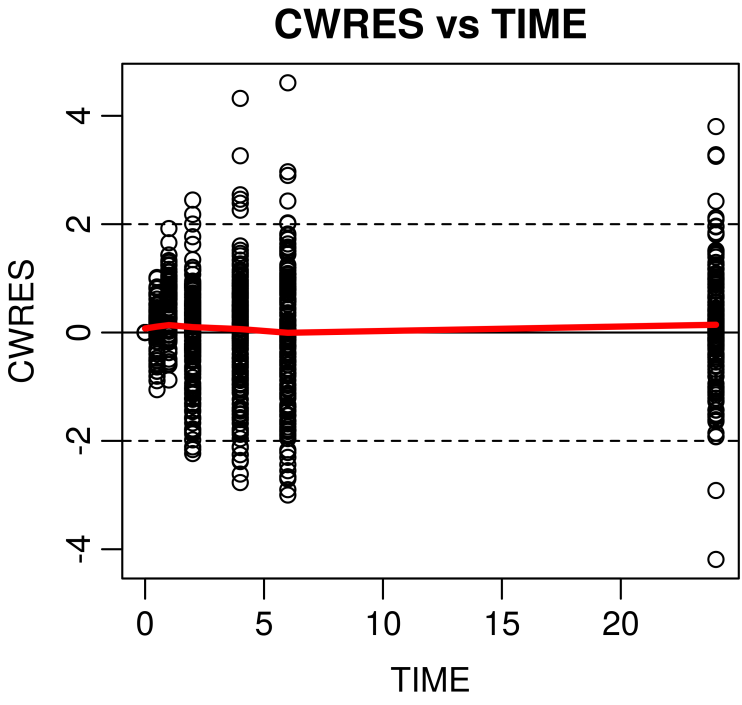
Assume additive effect:

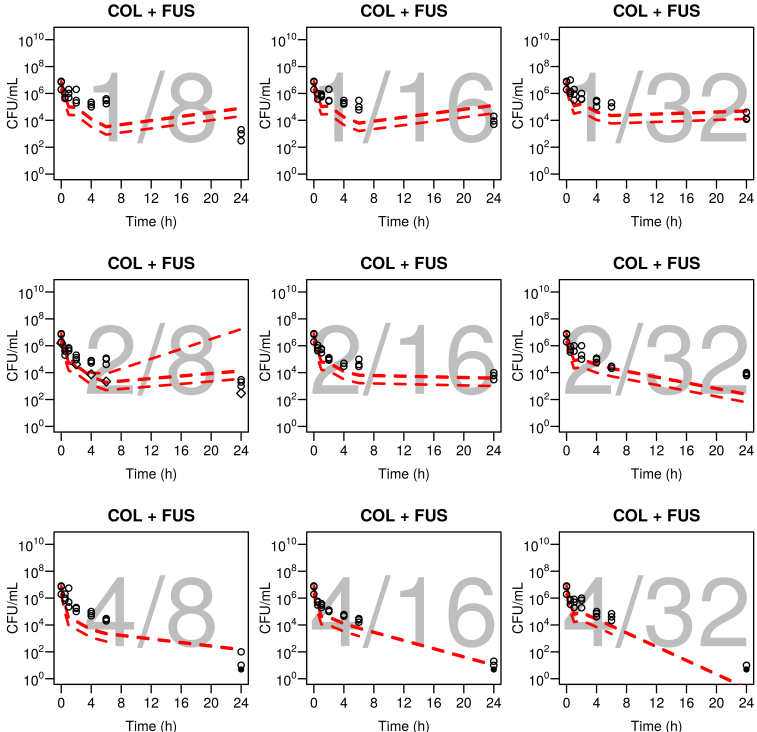
$$E_D = \alpha\left(\frac{E_{m,c} C_c^{\gamma_c}}{E_{C50,c}^{\gamma_c} + C_c^{\gamma_c}} + \frac{E_{m,f} C_f^{\gamma_f}}{E_{C50,f}^{\gamma_f} + C_f^{\gamma_f}}\right) \tag{4}$$

Time-dependent drug effect:

$$\alpha = 1 - \beta(1 - \exp\{-t(\tau_c C_c + \tau_f C_f + \tau_i C_c C_f)\}) \tag{5}$$

- $\beta \in [0, 1]$
- $\tau_i \rightarrow \Delta$ OFV -118
- No further improvement in fit with synergy terms (i.e. C_c affecting E_{C50_f})
- Strain differences on $E_{C50,c}$ 2.9-8.4 mg/L


CWRES vs TIME
CWRES
TIME
4
2
0
-2
-4
0
5
10
15
20


COL + FUS
1/8
1/16
1/32
2/8
2/16
2/32
4/8
4/16
4/32
CFU/mL
Time (h)

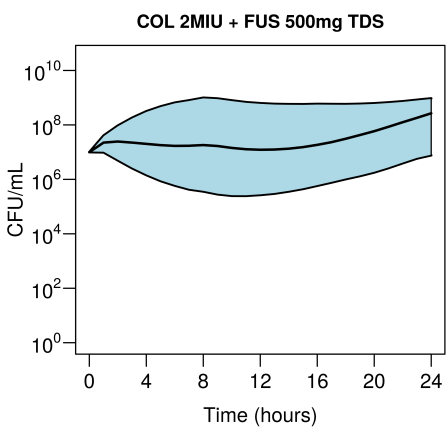
Simulations

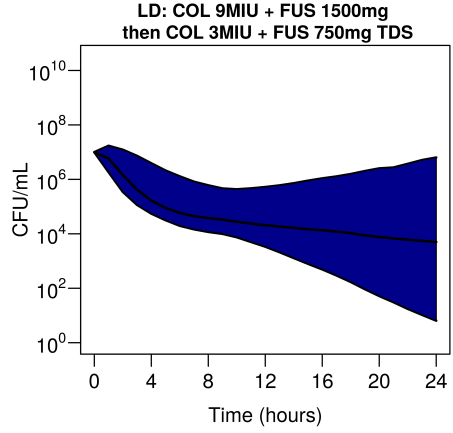
PK models:

- Colistin: Plachouras 2009, assume f_u 64%
- Fusidic acid: Bulitta 2012; use 'low' CL value; assume f_u 10%

Simulations:

- Evaluate current dose recommendations
- Identify potential improved dosing


COL 2MIU + FUS 500mg TDS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (hours)


LD: COL 9MIU + FUS 1500mg
then COL 3MIU + FUS 750mg TDS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (hours)

Overview

- Introduction (bedside to bench)
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Case Report

Patient:

- Female, 19 yrs, previously fit and well
- Admitted to ICU following RTA, multiple traumatic injuries
- Day 15: clinical diagnosis of VAP

Organism:

- *A. baumannii* from tracheal aspirate
- Multi-drug resistant:
  - Quinolones, aminoglycosides and carbapenems
  - Tigecycline MIC 0.5 mg/L (resistant)

Treatment:

- Colistimethane 2MIU PLUS fusidic acid 500 mg 8 hourly (suboptimal?)

Response:

- Clinical response within 48 hours
- Clinical cure and microbiological eradication achieved by day 16

Conclusions

- Combination therapy requited for MDR organisms - we need to develop methods
- Colistin PLUS fusidic acid promising for *A. baumanii*
- Model extension to two drugs achieved
- Synergy empirically handled in τ_i?
- Framework developed for identifying combination therapy
- To do:
  - Utility method for defining dose
  - Extension to other organisms
  - Further clinical evaluation

Acknowledgements

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- EU FP-7 (YC)
- MRC Methodology Fellowship (G1002305) (JS)

References

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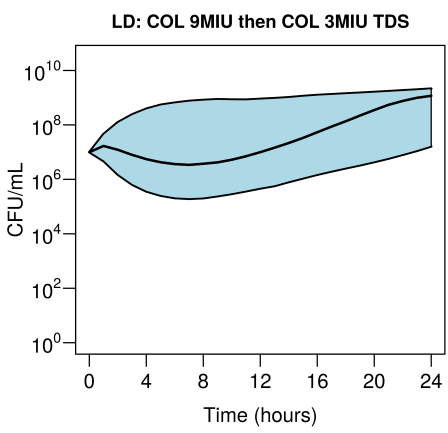
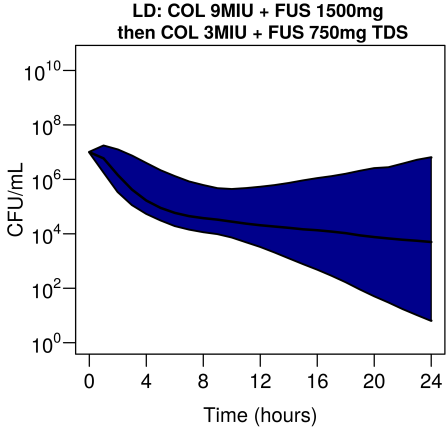
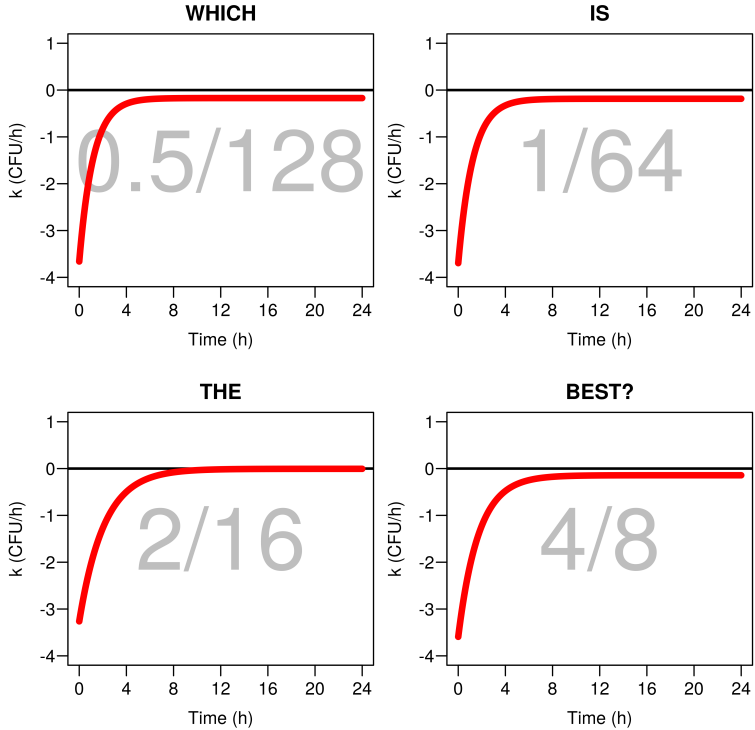

LD: COL 9MIU then COL 3MIU TDS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (hours)


LD: COL 9MIU + FUS 1500mg
then COL 3MIU + FUS 750mg TDS
CFU/mL
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
0
4
8
12
16
20
24
Time (hours)


WHICH
IS
THE
BEST?
0.5/128
1/64
2/16
4/8
k (CFU/h)
Time (h)
1
0
-1
-2
-3
-4
0
4
8
12
16
20
24