Invidualised dosing: what about the immune status?

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The Goldilocks Principle and Antibiotic Resistance in Bacteria

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Located a microecology within the stress gradient, now that it is possible to identify type Escherichia coli resistant in microecology if the population at the stationary phase...
Current Antimicrobial Resistance Landscape

• Prescription of antibiotics can influence the selection and spread of drug resistance.
• Design and optimization of antibiotic treatments
  • conserve the effective life span of existing antibiotics
  • reducing both the probability of resistance evolution and treatment related adverse effects
• Antimicrobial stewardship programs
• Adjuvant Therapy
  • Efflux pump inhibitors, immunomodulators, checkpoint inhibitors
• For the rational design of these therapies we need to understand the disease pathogenesis with respect to the time course of immune response
Systems-based Approach

• Design and optimize treatment regimens - integrate host immune response with the traditional bacteria-drug data³

• Perform quantitative analysis – using systems pharmacology approach to bring the two parallel universes of systems biology and PK/PD together¹,²

• An approach to translational medicine that combines computational and experimental methods to apply new pharmacological concepts to the development and use of drugs

*Systems-based approach is a key for precision medicine to be able to develop and deliver individualized care*

1. Sorger PK AS, Abernethy DR et al. (2011). QSP Workshop Group, NIH, Bethesda
Example 1: Dynamics of Viral Infection
Treatment of within Host Influenza Viral Infection – Pharmacodynamics/Immune response

Neuraminidase inhibitors - an effective strategy as prophylaxis and treatment of influenza A virus

- Oseltamivir helps inhibit the spread of the virus within the host and clearance of the virus

Interaction between the virus, host immune system and the drug is the classic complex triad

Systems based approach for optimization includes

- PK of drug
- PD activity against virus within the host
- Dynamics of the viral infection

Within Host Drug Scheduling using Influenza A Immune Model

- Adaptive treatment of influenza A virus infections
- Determine the optimal dose of oseltamivir taking the measured viral concentration/load and the number of effector cells at each time of the drug administration
- Combined a mathematical Influenza A virus model that captures the viral dynamics & the immune effector response with oseltamivir PK model

Boianelli et al., Viruses. (2015)
Tailoring Oseltamivir Dose

**Black line:** no treatment

**Green dashed line:** Low dose common clinical practice

**Blue dotted line** – control based treatment

**Red line:** limiting the control based treatment

Γ : Virological efficacy index

$S_D$: Area under the drug exposure curve

<table>
<thead>
<tr>
<th>Treatment strategies</th>
<th>Γ</th>
<th>$S_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common clinical practice</td>
<td>71%</td>
<td>316</td>
</tr>
<tr>
<td>Control-based treatment</td>
<td>79%</td>
<td>349</td>
</tr>
<tr>
<td>Fixed dose treatment with 83 mg</td>
<td>72%</td>
<td>349</td>
</tr>
<tr>
<td>Safe control-based treatment</td>
<td>71%</td>
<td>155</td>
</tr>
<tr>
<td>Fixed dose treatment with 37 mg</td>
<td>56%</td>
<td>155</td>
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</tbody>
</table>

A Systems Based Approach to Model the Time Course of Influenza Virus

- Single center, randomized, placebo controlled, double-blind
- Healthy adult volunteer challenge study A/Texas/36/91 (H1N1)
- **Five dosing regimens** (placebo, 20mg bid, 100mg bid, 200mg qd, 200mg bid)
- Dosing initiated 28 hours after virus inoculation and continuing for 5 days

- **VL**: quantitative viral cultures of nasal lavage fluid collected once or twice daily for a period of 8 days
- **IL-6**: from nasal washing, collected on days 0, 3, 4, 7
- **CSS**: (feeling feverish, headache, muscle ache, sore throat, cough, overall discomfort, nasal symptoms)
- **PK**: Days 3, 4, and 7 prior to the morning dose

Rao GG, Forrest A. Submitted to J. Virology (2018)  
A Systems Based Approach to Model the Time Course of Influenza Virus

Rao GG, Forrest A. Submitted to J. Virology (2018)
Example 2: Within Host Dynamics of Bacterial Infection
A Dysregulated Balance of Proinflammatory and Anti-Inflammatory Host Cytokine Response in Staphylococcus aureus Bacteremia (SAB)

- Patient’s immune response is a significant predictor of both persistence of infection and outcomes.
- “Immunoparalysis”-Increased interleukin (IL)-10 levels at onset of infection, resulting in increased mortality especially in SAB [Rose et al.]
- Elevated IL-10/tissue necrosis factor (TNF) ratio at 48 hours post infection was predictive of mortality in a cohort of 65 patients [bacterial sepsis: 58 patients SA infections: 7 patients]. (Gong et al.)
- Establish a quantitative marker of host immune response to SAB that can identify patients at risk of poor outcomes, early during treatment. [Minejima, Wong-Beringer, et al.]
- Assessed individual host immune response by measuring serum levels of proinflammatory (TNF, IL-6, IL-8, and IL-17A) and anti-inflammatory (IL-10) cytokines at onset of infection and at 72 hours after treatment.
- Primary outcome was persistent bacteremia after 4 days of effective therapy. Secondary outcomes were 30-day mortality and 30-day recurrence.

Rose WE et al: J Infect Dis 2012; 206:1604–1611
Host Immune Response in SAB

TNF-α

Initial

72 hours

IL-17A

Initial

72 hours

IL-10

Initial

72 hours

IL-8

Initial

72 hours

IL-6

Initial

72 hours

IL-10/TNF-α

Initial

72 hours

Host Immune Response in SAB [Contd]

- Large prospective, observational study of 884 patients with SAB
- Longer durations of bacteremia were associated with worse clinical outcomes.
- Duration of persistence adversely affects outcomes of SAB with higher rates of mortality, metastatic complications, and prolonged hospitalization.
- As each day of positive blood cultures increases mortality risk by 16%
- Prompt achievement of source control was strongly associated with earlier bacterial clearance and better clinical outcomes.
- Persistent SAB can be defined as positive cultures ≥ 3 days at which mortality significantly increased.
- Need for prospective interventional studies to evaluate whether early recognition of persistence at 3d to prompt a change in management could improve outcomes.
Example 3: Incorporating Host Immune Response: Preclinical Bacterial Pneumonia Rat Model
Measurement of Disease progression biomarkers

- Bacterial dynamics (BALF + lung homogenate)
  - $7.00 \times 10^6$, $5.76 \times 10^7$, $3.50 \times 10^8$, $4.32 \times 10^8$, and $7.65 \times 10^9$ CFU/mL initial inoculum
  - Total lung A. baumannii titers
- Pulmonary host immune response (BALF)
  - IL-1β, TNF-α, and CINC-1
  - Neutrophil counts
- Lung injury (BALF)
  - Albumin concentrations
- ADAPT$^2$ was used for model development and simulation
  - Pooled approach with maximum likelihood estimation

Model Structure

Macrophage

Cytokines: IL-1β, IL-1α, IL-18, TNFα, IL-6

LPS

TLR4

CD14

MD2

MyD88

NF-κB

ESCMID eLibrary

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30 co-modeled outputs: 5 inocula each with 6 biomarkers
Model Prediction – AI

i) $7.00 \times 10^6$

ii) $5.76 \times 10^7$

iii) $3.50 \times 10^8$

iv) $4.32 \times 10^8$


Growth Control with/without Immune Response

Inoculum 10^6 CFU/mL

Inoculum 10^4 CFU/mL

Polymyxin B (PMB) Monotherapy

**Low Inoculum**

- Polymyxin B resistant
- Susceptible
- Total CFU

**High Inoculum**

- Polymyxin B resistant
- Susceptible
- Total CFU

**Time (h)**

- 0 4 8 12 16 20 24 28 32 36 40 44 48

**PMB Concentration (mg/L)**

- 0.0
- 0.4
- 0.8
- 1.2
- 1.6
- 2.0
- 2.4
- 2.8

**Log_{10} CFU/mL**

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
PMB in (additive) combination with Mero

Low Inoculum

High Inoculum

Low Inoculum with Immune Response

High Inoculum with Immune Response
We believe that mechanism-based models, embedded in a systems biology framework, is the future.


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- ‘Quantitative analysis of the dynamic interactions between drug(s) and a biological system that aims to understand the behavior of the system as a whole’

The challenge – ‘translate this data into knowledge and knowledge into understanding’ of the system - Sydney Brenner

Meropenem (Mero) Monotherapy

Low Inoculum

High Inoculum

Low Inoculum with Immune Response

High Inoculum with Immune Response

Mero Concentration (mg/L)

Time (h)

log_{10} CFU/mL

Total CFU

Meropenem resistant
Susceptible
The concept of PD front-loading (FL)

• At T=0, for a serious infection, total bacterial burden is high (too much for the host defenses, alone) and the percent of bacteria in resistant sub-populations, is low

• At the start of therapy (6-48 hours?), maximize rate and extent of killing of drug-susceptible bacteria, leaving the smallest possible residual (of more resistant bacteria) to be killed by the capacity-limited immune system

• For “concentration-dependent” drugs, with high maximum rate of kill and with a good safety margin, FL with monotherapy should be feasible

• For drugs with slower rates of kill, consider combinations
PMB Front Loaded Monotherapy

Low Inoculum

High Inoculum

Low Inoculum with Immune Response

High Inoculum with Immune Response

Polymyxin B resistant
Susceptible
Total CFU
PMB Front-loaded in combination with Mero

**Low Inoculum**

- Polymyxin B resistant
- Meropenem resistant
- Susceptible
- Total CFU

**High Inoculum**

- Polymyxin B resistant
- Meropenem resistant
- Susceptible
- Total CFU

**Low Inoculum with Immune Response**

**High Inoculum with Immune Response**