Influence of therapy duration on suppression of emergence of resistance and influence of granulocytes on cell kill

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Ordway Research Institute
Short Course Therapy
Short Course Therapy

What are the Two Great Chemotherapy Questions?

Can We Delineate Exposure-Response i.e.
What is the Right Therapy Intensity?

For How Long Should We Treat?
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Indeed, in a paraphrase of the late, great Louie Weinstein:

“There are only two things we do not understand about antimicrobial therapy: How much drug to give and for how long to give it”
P. aeruginosa outcome studies

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What about Intensity to Suppress Resistance?
Levofloxacin and Pseudomonas

Can a drug exposure be identified that will prevent the resistant subpopulation from taking over the total population?
Levofloxacin and Pseudomonas

Levofloxacin Effect: Mouse Thigh Infection Model
Preventing Emergence of the Resistant Mutant Population

AUC/MIC ratio of 157 Shuts Off Growth of Resistant Mutants
How Long is Long Enough?
PK/PD – How Long is Long Enough?

• We examined the quinolone garenoxacin against a strain of *Staphylococcus aureus*

• One question to be addressed was the impact of therapy duration upon emergence of resistance

• Another was to examine the relationship (or lack thereof) between kill rate and emergence of resistance
PK/PD – How Long is Long Enough?

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PK/PD – How Long is Long Enough?

Modeling first 2 days of therapy

PK/PD – How Long is Long Enough?

Modeling all 10 days of therapy

PK/PD – How Long is Long Enough?

• When the first 2 days are modeled and simulation is performed, it is estimated that an AUC/MIC ratio of 100 is necessary to suppress mutant amplification for 2 days. Breakthrough is expected after day 4. Maximal kill rate is achieved at this AUC/MIC ratio.

• When all 10 days are modeled, we expect an AUC/MIC ratio of 280 is required for suppression of resistance for all 10 days.
Garenoxacin Prospective Validation Study

- Hypotheses to be tested in a prospective validation experiment:

1) The higher-intensity regimen will drive the colony counts down by circa 5-6 \( \log_{10} \) (CFU/ml) by 5 days of therapy

2) The lower-intensity regimen will be similar to the intense regimen for 5 days as regards total colony counts

3) The higher-intensity regimen will suppress resistance for the full 10 days of therapy

4) The lower-intensity regimen will allow resistant organism amplification after day 4
• We studied the quinolone garenoxacin against *S. aureus*
• We studied and modeled 7 regimens
• We performed a prospective validation with 4 hypotheses
• All were validated
• Resistance suppression requires more drug exposure than that for maximal rate of kill

PK/PD – How Long is Long Enough?

• Clearly, stopping early prevents mutant amplification because we are limiting the number of rounds of replication (importance of error-prone replication?)
• When therapy goes longer, more intense drug exposure is required to suppress mutant amplification
• The two regimens had the SAME initial kill rate. One failed (100) and one succeeded (280)
Resistance Suppression and Outcome Optimization

• Here, the pathogen is *Staphylococcus aureus*, not *Pseudomonas aeruginosa*, where we had previously shown the first resistance mechanism was pump over-expression (JCI 2003;112:275-285; J Infect Dis. 2005;192:420-428.)

• As previously, there were NO target site mutations

• All the resistance was efflux pump mediated, as shown by Dr. Fritsche from Ron Jones Lab

• What happens when therapy stops? Does the resistant population gain the upper hand?
We performed an experiment where 4, 5 or 6 daily doses (AUC/MIC ratio=100) were administered; outcomes monitored out to day 13.

We fit an expanded mathematical model to all the data simultaneously.

We included a natural death rate term for sensitive and resistant populations.

This allows us to look at relative biofitness in conjunction with the growth terms for the two populations.
Garenoxacin – Short Therapy

• The model fit the data well for all three system outputs
  1. Garenoxacin Concentrations
  2. Total S. *aureus* Counts
  3. Resistant S. *aureus* Counts

• But, to gain an idea of the individual fits for the four regimens, each is presented next
Garenoxacin – Short Therapy

• Of interest, in each of the garenoxacin-treated arms, there is a final downturn in the number of resistant mutants before or after day 10, depending on the number of garenoxacin doses administered.

• Model parameters indicate that resistant mutants have an intrinsically higher rate of natural death and slower growth relative to sensitive clones.

• This indicates the resistant clones are likely less biofit.
Garenoxacin – Short Therapy

• This is seen graphically by the dramatic downturn in resistant clone number between days 10 and 13 for the garenoxacin-treated regimens
• So, the longer therapy continues, the more amplification goes on of the resistant population with a suboptimal regimen
• To prevent resistance, shorter is better
• BUT, we also have to clear the infection, so therapy needs to be long enough to accomplish this end
• How much effect do we need?
• Enough to allow the immune system to do its job!
Parameter  \( K_{\text{max-growth}} \)  POPMAX  \( V_{\text{max-kill}} \)  \( K_m \)

Units    \( h^{-1} \)  \( \text{CFU/g} \)  \( h^{-1} \)  \( \text{CFU/g} \)

Mean   0.622   0.916x10^{11}   0.00535  147660

SD      0.104   0.980x10^{10}   0.00400  203928

* Rate constant is multiplied by the granulocyte count
PK/PD – How Long is Long Enough?
Hollow Fiber System Data

**Moxifloxacin vs Spn 58 (wild type)**
Total Population [April 2004]

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Log cfu/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
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<td>4</td>
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<td>6</td>
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<td>7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**HFS: Moxifloxacin vs Spn RC2**
Total Population (June 2004)

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Log cfu/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
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<tr>
<td>2</td>
<td>8</td>
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<tr>
<td>3</td>
<td>7</td>
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<tr>
<td>4</td>
<td>6</td>
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<td>5</td>
<td>5</td>
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<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total Population: Moxifloxacin vs Spn RC4**
(efflux pump and ParC mutant) 6/04

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Log cfu</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

**Moxifloxacin MIC Values**
- Wild-Type: 0.125 mg/L
- RC2: 0.16 mg/L
- RC4: 0.25 mg/L
PK/PD – How Long is Long Enough?

Normal

Granulocytopenic

RC₂

RC₄

Stasis Line = 7.6 Log₁₀ (CFU/g)

Stasis Line = 7.25 Log₁₀ (CFU/g)

Stasis Line = 6.95 Log₁₀ (CFU/g)

Stasis Line = 7.38 Log₁₀ (CFU/g)

Log₁₀ (CFU/g)

Log₁₀ (CFU/g)

Moxifloxacin Dose (mg)

Moxifloxacin Dose (mg)
PK/PD – How Long is Long Enough?

Drug Plus WBC Effect
S. pneumoniae RC2

Remove Drug Effect
S. pneumoniae RC2

Difference from the hollow fiber system is determined by the PK of Moxi in mice and in man
PK/PD – How Long is Long Enough?

**Normal Mice**

Murine Thigh Infection with *Strep. pneumoniae* RC4
Non-Neutopenic Mice; Moxifloxacin 400 mg Dose-Equivalent

- Moxifloxacin Conc.
  - 400 mg Dose
- *S. pneumoniae* RC4 Colony Counts

**Neutropenic Mice**

Murine Thigh Infection with *Strep. pneumoniae* RC4
Neutropenic Mice; Moxifloxacin 400 mg-Equivalent

- Moxifloxacin Conc.
  - 400 mg Dose
- *S. pneumoniae* RC4 Colony Counts
PK/PD – How Long is Long Enough?

• Please note that in the hollow fiber system, which has NO immune function at all, moxifloxacin performed BETTER against RC2 than in the mouse model with or without granulocytes

• Why?

• We are in the midst of sorting this out, but fully believe it is because we did not “humanize” the dosing in the mice
Torezolid with and without WBC
Torezolid with and without WBC
### Table 1: Parameter Values for the Model Linking Torezolid Exposure to Kill of Staphylococcus aureus ATCC 33591

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_g$</td>
<td>h$^{-1}$</td>
<td>1.300</td>
<td>0.884</td>
<td>0.879</td>
</tr>
<tr>
<td>Popmax</td>
<td>CFU/g</td>
<td>1.36x10$^9$</td>
<td>1.72x10$^9$</td>
<td>6.48x10$^8$</td>
</tr>
<tr>
<td>$K_{k\text{-max}}$</td>
<td>h$^{-1}$</td>
<td>1.782</td>
<td>0.104</td>
<td>2.768</td>
</tr>
<tr>
<td>$C_{50k}$</td>
<td>mg/L</td>
<td>3.860</td>
<td>4.513</td>
<td>1.848</td>
</tr>
<tr>
<td>$H_k$</td>
<td>Unitless</td>
<td>8.056</td>
<td>7.895</td>
<td>0.431</td>
</tr>
<tr>
<td>WBCKill$N$</td>
<td>(CFU/g)/h</td>
<td>0.657</td>
<td>0.536</td>
<td>0.557</td>
</tr>
<tr>
<td>WBCKill$N_{50}$</td>
<td>CFU/g</td>
<td>3.47x10$^6$</td>
<td>2.41x10$^6$</td>
<td>3.02x10$^6$</td>
</tr>
<tr>
<td>WBCKill$N$</td>
<td>(CFU/g)/h</td>
<td>2.638</td>
<td>0.995</td>
<td>3.797</td>
</tr>
<tr>
<td>WBCKill$N_{50}$</td>
<td>CFU/g</td>
<td>1.58x10$^6$</td>
<td>1.80x10$^4$</td>
<td>3.22x10$^6$</td>
</tr>
</tbody>
</table>

$K_g$ is the first order growth rate constant; Popmax is the estimated maximal number of organisms in stationary phase; $K_{k\text{-max}}$ is the first order kill rate constant directly induced by torezolid; $C_{50k}$ is the torezolid concentration at which kill rate is half maximal; $H_k$ is the Hill constant; WBCKill$N$ is the maximal kill rate induced by granulocytes in the granulocytopenic cohort; WBCKill$N_{50}$ is the organism load at which the system is half saturated; WBCKill$N$ is the maximal kill rate induced by granulocytes in the normal cohort; WBCKill$N_{50}$ is the organism load at which the system is half saturated. In the Bayesian estimates, the WBCKill$N$ and WBCKill$N$ give the estimate of kill for the granulocytes alone (no-treatment control) or for the granulocytes plus torezolid killing effect (treated cohorts).

The pharmacokinetic parameter values for TR701/700 were fixed at values identified previously (2). $K_a = 66.4$; $K_{\text{hydrol}} = 1.48$; $CL_{701} = 0.0102$; $V_{701} = 0.384$; $CL_{700} = 0.0101$; $V_{700} = 0.0164$; $K_{34} = 12.7$; $K_{43} = 12.8$
Table 2: *Determination of the Effect of Torezolid Mediated Through Granulocytes*

Direct Effect of Torezolid =
Net Growth No Treatment – Net Growth 200 mg Equivalent Dose (Both Granulocytopenic)

<table>
<thead>
<tr>
<th>Time</th>
<th>Log (CFU/g) Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr</td>
<td>$3.26 - 2.81 = 0.45$</td>
</tr>
<tr>
<td>48 hr</td>
<td>$3.48 - 3.62 = -0.14$</td>
</tr>
</tbody>
</table>

Effect of Torezolid Mediated Through Granulocytes + Direct WBC Effect =
Total Effect (G-penic - Normal Cohort Treated) — Direct Effect of Torezolid

<table>
<thead>
<tr>
<th>Time</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr</td>
<td>$-3.12 + 0.45 = -2.67$</td>
</tr>
<tr>
<td>48 hr</td>
<td>$-5.12 - 0.14 = -5.26$</td>
</tr>
<tr>
<td>72 hr*</td>
<td>$-6.43 - 0.00 = -6.43$</td>
</tr>
</tbody>
</table>

Estimate of Torezolid Effect Mediated Through Granulocytes =

<table>
<thead>
<tr>
<th>Time</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr</td>
<td>$-2.67 + 1.51 = -1.16$</td>
</tr>
<tr>
<td>48 hr</td>
<td>$-5.26 + 1.73 = -3.53$</td>
</tr>
<tr>
<td>72 hr</td>
<td>$-6.43 + 1.73 = -4.70$</td>
</tr>
</tbody>
</table>

* The actual direct drug effect cannot be calculated for the 72 hr time point because all the animals in the granulocytopenic no-treatment control cohort had expired before that time. As the actual value for 48 hr was a negative, the direct effect was fixed to zero for this time point.

+ It is not a fair appraisal of direct granulocyte effect to examine amplification in the granulocytopenic no-treatment control versus the normal no-treatment control, because there were different starting inocula, but the upper bound is fixed in both instances because of stationary phase. We estimated the direct effect by assuming the granulocytopenic no-treatment control cohort started at 7.54 Log (CFU), which is the same as the normal no-treatment control cohort and the direct granulocyte effect would be the difference in organism amplification between the granulocytopenic and normal no-treatment control cohorts. Again, for the 72 hr time point, we use the value from 48 hr because all animals in the granulocytopenic cohort had expired.
Torezolid with and without WBC
Torezolid with and without WBC

TR701/700 200 mg Dose Equivalent
With Granulocytes

TR701 Concentrations
TR700 Concentration
S. aureus Colony Counts

Time (Hours)

TR701/700 200 mg Dose Equivalent
Without Granulocytes

TR701 Concentrations
TR700 Concentration
S. aureus Colony Counts

Time (Hours)
TR701/700 200 mg-Equivalent Dose With Granulocytes

- TR701 Concentrations
- TR700 Concentration
- Pred. S. aureus Colony Counts
- Obs. S. aureus Colony Counts
Granulocyte Effect

• Granulocytes kill substantially
• They are Michaelis-Menten, meaning they can be saturated
• Poor drugs may work if the burden is low enough so that the drug causes the burden to decline to the area of the Km
• In the case of moxifloxacin, both drug and granulocyte effect are substantial
• In the case of torezolid, the majority of the cell kill is effected through the granulocytes
PK/PD – How Long is Long Enough?

• Are there clinical data that short is good? YES!
  1) Ambrose Gatifloxacin Sinus Study
  2) Levofloxacin CAP Study
  3) Chastre Study for VAP
  4) Meropenem VAP Study (Not shown)
Ambrose Gatifloxacin Study

Demography & Patient Disposition

- 12 Patients enrolled, 6 male and 6 female Caucasians
  - Aged $48.3 \pm 15.3$ years
  - Height $172.6 \pm 7.9$ cm
  - Weight $73.6 \pm 11.2$ kg

- 10 Patients were clinically evaluable
  - 1 patient did not return for the TOC visit
  - 1 patient had only 2 days of antimicrobial therapy

- 7 Patients had sufficient pharmacokinetic data for analysis
## RESULTS

**Gatifloxacin Exposure: Plasma vs. Sinus Aspirate**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma</th>
<th>Sinus aspirate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>3.77 (2.52-4.80)</td>
<td>3.14 (2.18-4.32)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hrs.)</td>
<td>1.00 (0.3-1.5)</td>
<td>5.50 (2.2 – 7.8)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24\text{hr}}$ (mg*hr/L)</td>
<td>30.1 (22.6-38.4)</td>
<td>54.7 (27.2-67.6)</td>
</tr>
<tr>
<td>Ratio of $C_{\text{max}}$ (sinus:plasma)</td>
<td>0.90 (0.56-1.32)</td>
<td></td>
</tr>
<tr>
<td>Ratio of $\text{AUC}_{0-24\text{hr}}$ (sinus:plasma)</td>
<td>1.51 (0.88-2.23)</td>
<td></td>
</tr>
</tbody>
</table>

## RESULTS

**Microbiologic Outcome at End of Therapy**

<table>
<thead>
<tr>
<th>Organism Group &amp; Organism</th>
<th>Number of Isolates (Eradicated/Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-Positive</strong></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>4/4</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>2/2</td>
</tr>
<tr>
<td><strong>Gram-Negative</strong></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
<td>1/1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>7/7</td>
</tr>
</tbody>
</table>

RESULTS

Time to Eradication

- Number of pathogens = 7
- 75th percentile time to eradication = 91 hours
- Median time to eradication = 53 hours

Levo Short Course CAP Study

2521 Patients Screened

530 Patients Enrolled and Randomized

528 Patients Treated (ITT Population)

256 Patients Received Levofloxacin 750 mg/day IV/PO for 5 days

34 (13.3%) Discontinued Prematurely
3 (1.2%) Lost to Follow-Up

219 (85.5%) Patients Completed Therapy

198 (77.3%) Patients were Clinically Evaluable

103 (40.2%) Patients were Microbiologically Evaluable

272 Patients Received Levofloxacin 500 mg/day IV/PO for 10 days

48 (17.6%) Discontinued Prematurely
6 (2.2%) Lost to Follow-Up

218 (80.1%) Patients Completed Therapy

192 (70.6%) Patients were Clinically Evaluable

92 (33.8%) Patients were Microbiologically Evaluable
## Table 5. Clinical success rates for the clinically evaluable population at the 7–14-day posttherapy visit, according to the Pneumonia Severity Index (PSI) score.

<table>
<thead>
<tr>
<th>Patient category</th>
<th>750-mg group (n = 198)</th>
<th>500-mg group (n = 192)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratum I&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>183/198 (92.4)</td>
<td>175/192 (91.1)</td>
<td>–7.0 to 4.4</td>
</tr>
<tr>
<td>PSI class III&lt;sup&gt;f&lt;/sup&gt;</td>
<td>69/76 (90.8)</td>
<td>73/86 (84.9)</td>
<td>–16.5 to 4.7</td>
</tr>
<tr>
<td>PSI class IV&lt;sup&gt;g&lt;/sup&gt;</td>
<td>44/49 (89.8)</td>
<td>44/51 (86.3)</td>
<td>–17.2 to 10.2</td>
</tr>
<tr>
<td>PSI class V&lt;sup&gt;h&lt;/sup&gt;</td>
<td>25/27 (92.6)</td>
<td>27/32 (84.4)</td>
<td>–26.1 to 9.6</td>
</tr>
<tr>
<td>Stratum II&lt;sup&gt;i&lt;/sup&gt;</td>
<td>0/0 (0.0)</td>
<td>2/3 (66.7)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Stratum I = PSI classes III+IV+V

Stratum II = PSI classes I+II

Chastre J et al. JAMA 2003;290:2588-2598

Patients with non-fermenting GNB did have a higher recurrence rate in the 8-d group, implying that eradication had not occurred (40.6% vs 25.4%)
How Long Is Long Enough?

• In general, go in hard and stop early
• Limit the number of rounds of replication under pressure
• Limit emergence of resistance!
• Granulocytes are central for our ability to succeed at antimicrobial chemotherapy!
Short Course Therapy

I have been trying to interest the anti-infective community in antimicrobial pharmacodynamics for almost a quarter of a century, certainly without notable success.

WELL!
"Hey, bucko ... I'm through begging."
Thanks for Your Attention!
Drusano VAP Study Design

**VAP**
- Initiate trial therapy
- BAL
  - Meropenem 2 g IV Q8h
  - Vancomycin 1 g IV Q12h
  - Tobramycin 5 mg/kg Q24h
- Low MIC pathogens

**C/S result**
- MRSA
  - Off study
- + Pseudomonas
- Meropenem + Tobramycin
- 1° End point
- Clinical end points

**Day 7 BAL**
- Meropenem 1 g IV Q8h
  - 30-min infusion
- Clinical end points
- Meropenem 500 mg IV Q8h
  - 3-h infusion
- Clinical end points
Drusano VAP Study Design

So, what were the hypotheses tested?

• High-dose meropenem plus an aminoglycoside would have a salutary effect on the emergence of resistance in *P. aeruginosa*

• No other resistance would emerge in other Gram-negative bacilli, except for *Acinetobacter* spp.

• Organism clearance would occur by day 7

• For organisms other than nonfermentors (and MRSA), low-dose (500 mg) meropenem would be as effective as 1000 mg Q8h
# Drusano VAP Study Design

<table>
<thead>
<tr>
<th></th>
<th>Meropenem 2 g Plus Tobramycin</th>
<th>Meropenem 1 g 30-min Infusion</th>
<th>Meropenem 0.5 g 3-h Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All pathogens/patients</strong></td>
<td>1/14 (7.1%) / 1/9 (11.1%)</td>
<td>0/28 (0%) / 0/14 (0%)</td>
<td>1/22 (4.5%) / 1/13 (7.7%)</td>
</tr>
<tr>
<td><strong>P. aeruginosa</strong></td>
<td>1/9 (11.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Acinetobacter</strong></td>
<td>—</td>
<td>—</td>
<td>1/2 (50%)</td>
</tr>
</tbody>
</table>
Hypothesis 3: Except for non-fermentative GNB, there was a high rate of documented eradication at day 7

Non-Pseudomonas/Non-Acinetobacter

Group 1 | Group 2 | Group 3
--- | --- | ---
5/5 (100%) | 20/22 (90.9%) | 13/15 (86.7%)
Overall Clearance 38/42 (90.5%)

Pseudomonas/Acinetobacter

Groups 1 and 3

3/11 (27.3%)
Peripheral (thigh) Compartment (C_p)

Central Blood Compartment (C_c)

Bacteria (X_{T/R})

\[ \frac{dC_a}{dt} = -k_a C_a \]  

\[ \frac{dC_c}{dt} = k_a C_a + k_{pc} C_p - k_{cp} C_c - k_e C_c \]  

\[ \frac{dC_p}{dt} = k_{cp} C_c - k_{pc} C_p \]  

\[ \frac{dX_S}{dt} = K_{GS} X_S L - f_{KS}(C_c^{H,\xi}) X_S \]  

\[ \frac{dX_R}{dt} = K_{GR} X_R L - f_{KR}(C_c^{H,\xi}) X_R \]  

\[ L = (1 - (X_R + X_S)/POPMAX) \]  

\[ f_{\psi,\xi}(C_c^{H,\xi}) = \frac{K_{max} \xi \cdot C_c^{H,\xi}}{C_c^{H,50} + C_c^{H,\xi}} \]  

\[ Y_1 = X_T = X_S + X_R \]  

\[ Y_2 = X_R \]
RESULTS

Gatifloxacin Exposure: Plasma vs. Sinus Aspirate