Long-acting Antimicrobial Agents: Current Status & Perspectives

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Disclosures

Consultant/Advisory Board/Speaker fees

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- Thermo Fisher, Biomiereuix
- BioTest, Nordic Pharma
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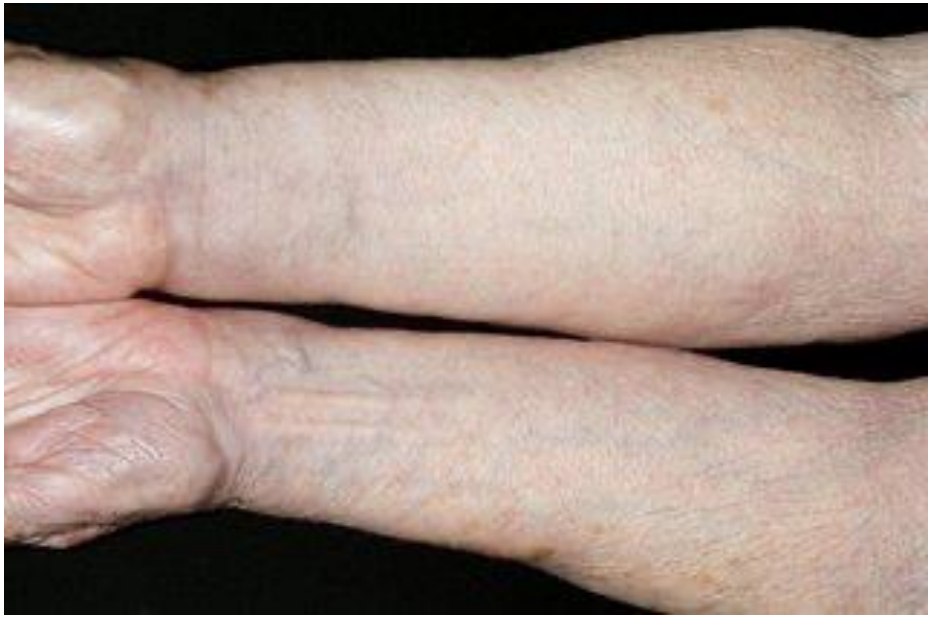
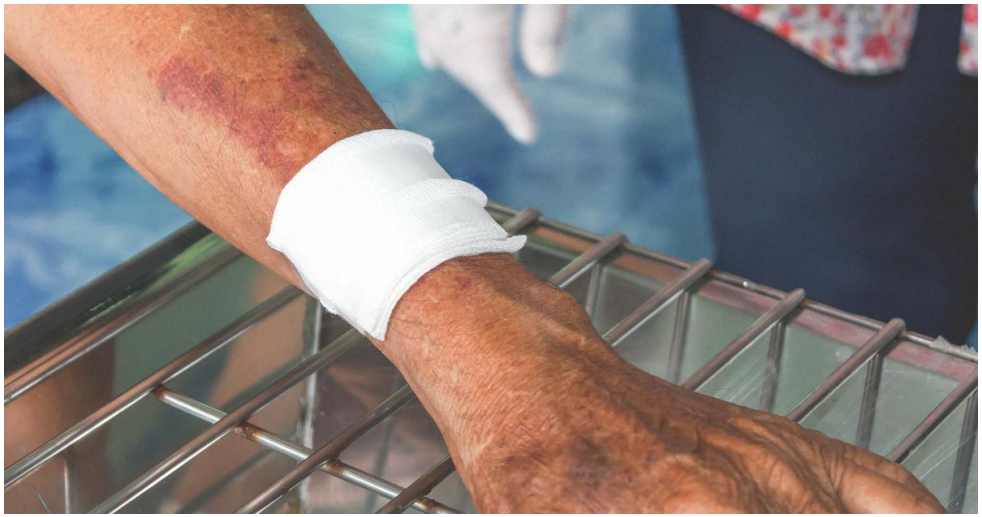
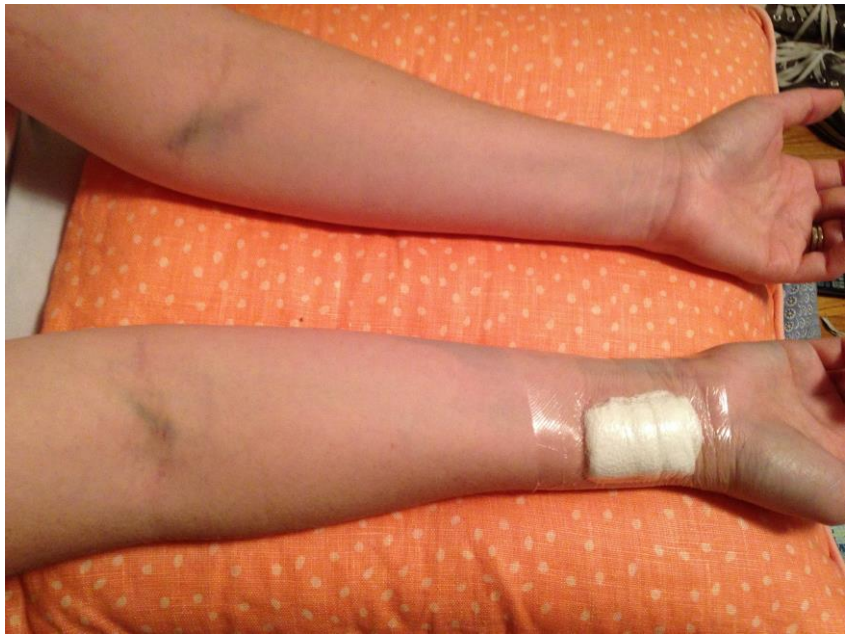






Current Status

- **«Lineless» Antibiotics**
  - Dalbavancin
  - Oritavancin
- **Long half-life**
  - (Tigecycline)
- **Prolonged half-life**
  - Liposomal amphotericin B

Lineless Antibiotics in Persons Who Use Drugs (PWUD)

Morrisette T et al Open Forum Infect Dis 2019

- **System-wide, retrospective analysis**
  - Adults admitted to University of Colorado Health from September 2015 to June 2018
  - Treated with dalbavancin or oritavancin based on clinical judgment
- **56 patients met inclusion criteria**
  - 17 **PWUD** vs 39 **non-PWUD**
- **PWUD group**
  - Younger, healthier by Charlson comorbidity index, more likely insured by Medicaid, and admitted for conditions requiring longer treatment
- **Clinical failure (with available follow-up)**
  - 1 **PWUD** patient (6%) and 6 **non-PWUD** patients (15%) (P = .413)
- **Median hospital length-of-stay reduction (P=.133)**
  - **PWUD** = 20 days (interquartile range [IQR], 10–30 days)
  - **Non-PWUD** = 11 days (IQR, 9–14 days)
- **Estimated median savings P = .065**
  - PWUD = $40 455.08 (IQR, $20 900.00–$62 700.00)
  - Non PWUD = $19 555.08 (IQR, $15 375.08–$23 735.08)

Lineless Antibiotics in Persons Who Use Drugs (PWUD)

Morrisette T et al Open Forum Infect Dis 2019

Table 2. Antimicrobial, Infection, and Microorganism Characteristics[a]

Characteristic	PWUD (n = 17)	Non-PWUD (n = 39)	*P* Value
Dalbavancin	12 (71)	28 (72)	>.999
Oritavancin	4 (24)	10 (26)	>.999
Dalbavancin and oritavancin	1 (6)	1 (3)	.519
Lipoglycopeptide doses (number), median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	.769
Previous antibiotic received	15 (88)	36 (92)	.634
Concomitant antibiotics	5 (29)	12 (31)	.919
Empiric	2 (12)	4 (10)	>.999
Targeted therapy	15 (88)	32 (82)	.707
Suppression	0	2 (5)	>.999
Hospital length of stay, median (IQR)	6.0 (3.5–12.0)	6.0 (3.0–14.0)	>.999
Lipoglycopeptide Indication	—	—	—
ABSSSIs	6 (35)	14 (36)	.965
Osteomyelitis	6 (35)	9 (23)	.349
Endocarditis	3 (18)	2 (5)	.158
Catheter-related bacteremia	0	2 (5)	>.999
Pneumonia	0	2 (5)	>.999
Other	2 (12)	10 (26)	.309
Source control, if applicable	11 (65)	26 (67)	>.999
Concomitant bacteremia	8 (47)	14 (36)	.432
Isolated Microorganisms[b]	—	—	—
MSSA	8 (47)	8 (21)	.058
MRSA	5 (29)	7 (18)	.480
Enterococcus faecalis	1 (6)	6 (15)	.421
Coagulase-negative *Staphylococcus* spp	0	7 (18)	.088
VRE	1 (6)	4 (10)	>.999
Other organism	0	8 (21)	.090
Clinical success	13 (77)	27 (69)	.409
Clinical failure	1 (6)	6 (15)	.413
In-hospital mortality	0	2 (5)	>.999
Adverse effects	0	6 (15)	.163

Abbreviations: ABSSSIs, acute bacterial skin and skin-structure infections; IQR, interquartile range; PWUD, persons who use drugs; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; VRE, vancomycin-resistant *Enterococcus faecium*.

Lineless Antibiotics in Persons Who Use Drugs (PWUD)

Morrisette T et al Open Forum Infect Dis 2019

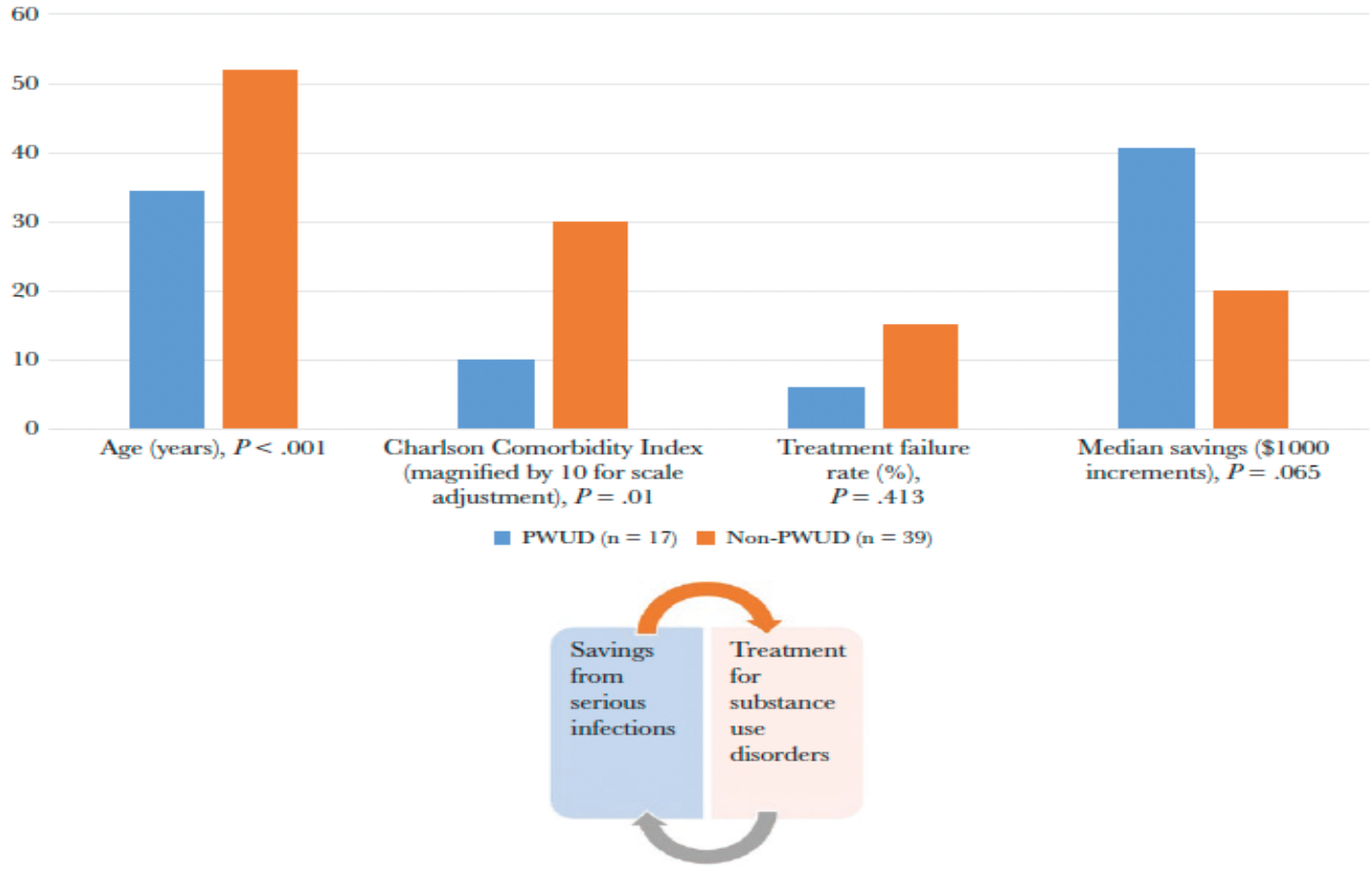
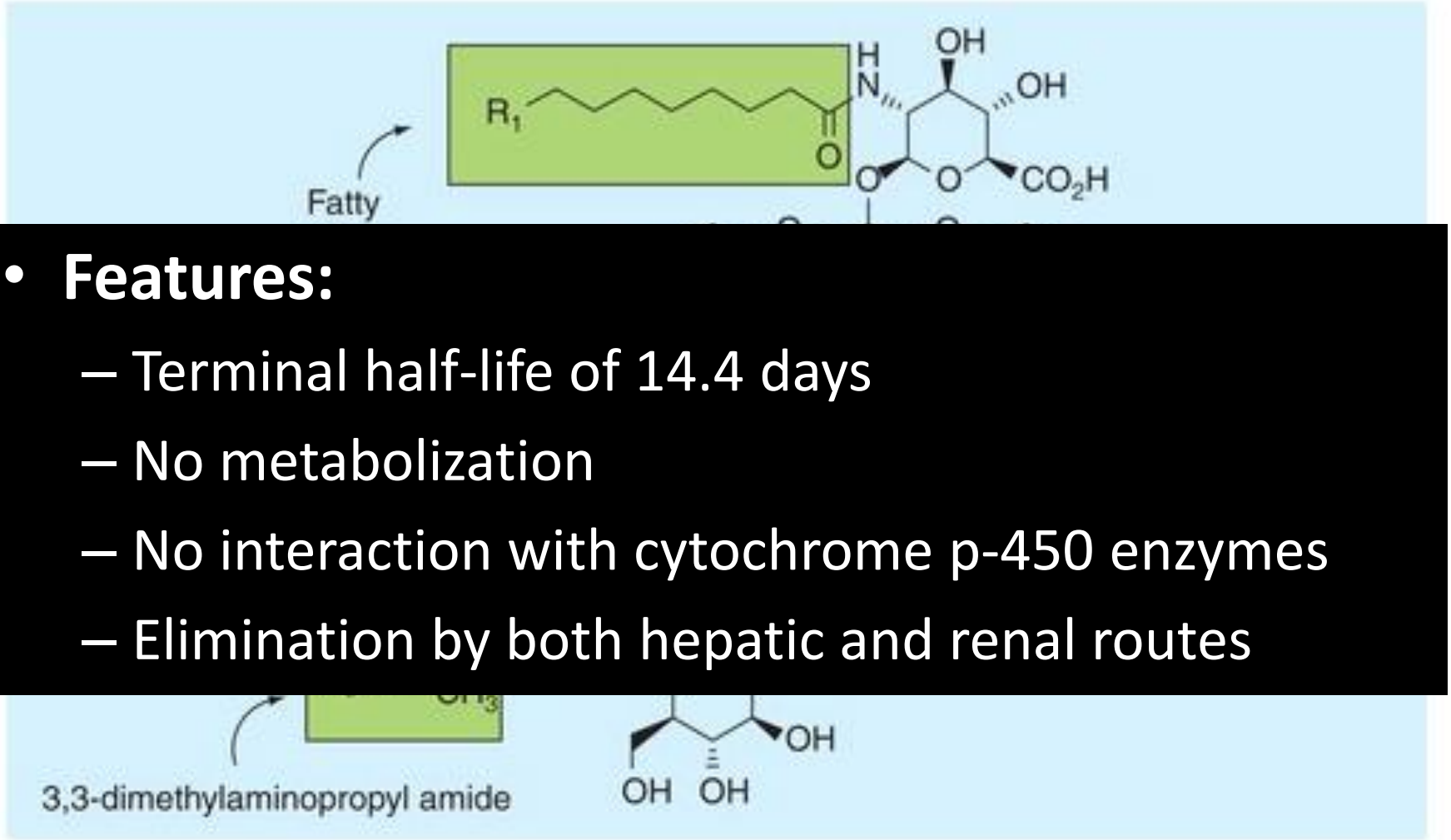


Figure 1. Notable differences observed and their potential for improved healthcare delivery. PWUD, persons who use drugs.

Dalbavancin

Dunne MW et al Drug Saf 2015



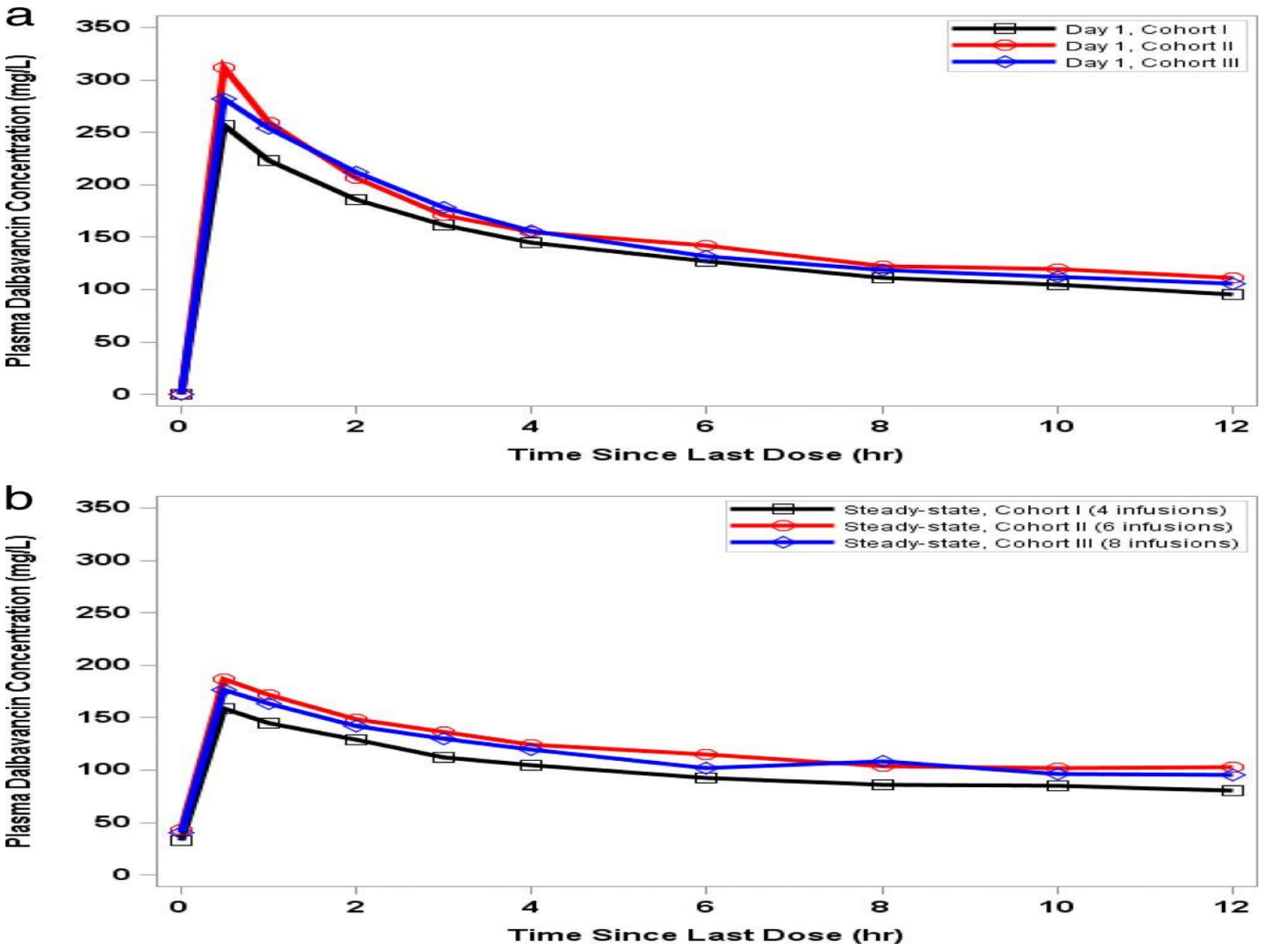
- **Features:**
  - Terminal half-life of 14.4 days
  - No metabolization
  - No interaction with cytochrome p-450 enzymes
  - Elimination by both hepatic and renal routes

Dalbavancin

Chambers HF et al, NEJM 2014; 370:2238-2239

- **Molecule**
  - Semisynthetic lipoglycopeptide analogue of teicoplanin
  - Bactericidal inhibition the transpeptidase and transglycosylase steps in bacterial cell-wall synthesis of gram-positive bacteria by binding to the terminal D-alanyl-D-alanine of the stem pentapeptide of the nascent peptidoglycan
- **Lipid moieties**
  - Binding & anchoring to the cell membrane and dimerization
- **New pharmacologic features**
  - Terminal half-life is approximately 2 weeks
  - Serum free-drug concentrations exceed MICs for $\geq$1 week

Mean Dalbavancin Plasma Concentrations
Day 1 (a) & Steady State (b)



Michael W. Dunne et al. AAC 2015;59:1849-1855

Perspectives

- «One Health» Approach
- Antibacterials
- Anti-malaria agents
- Antifungals

Pharmacokinetics of Short- and Long-acting Intramuscular Oxytetracycline in Chickens

- **Injectable of short- and long-acting formulations**
  - Same pharmaceutical company were administered
  - Healthy 6-week-old broiler chickens
  - Short-acting: 10 mg/kg IM q24h for 4 days
  - Long-acting: 20mg/Kg im single dose
- **PK analysis by EIA:**
  - 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 24 hours & q24h up to 120 h
- **Both dosing**
  - Respectful of recommended dosing intervals

Gberindyer AF et al. J Avian Med Surg 2015;29(4):298-302

Pharmacokinetics of β-Lactam Antibiotics: Clues from the Past for the Future

- **Beta-lactams (BL) discovered in 1928 (penicillin)**
- **Historically:**
  - No utility against *M. tuberculosis (M. tb)*
    - Erroneous data on poor drug penetration through the outer wall of *M. tb*
    - *M. tb* also uses transpeptidases for cross-linking in cell wall synthesis
- **Nowadays:**
  - Clavulanic /& avibactam inhibit *bla*-C, class-A
    - Chromosomal beta-lactamases in *M. tb*
  - Meropenem & other new drugs have *in vitro* activity Vs. *M. tb*
  - *M. tb* mutants with *bla*-C deleted → increased susceptibility to BL

Smith PW ACS Infect Dis 2018; Hugonnet JET, Science 2009; Deshpande D Sci Adv 2017; Kaushik A AAC 205; Flores AR Microbiology 2005

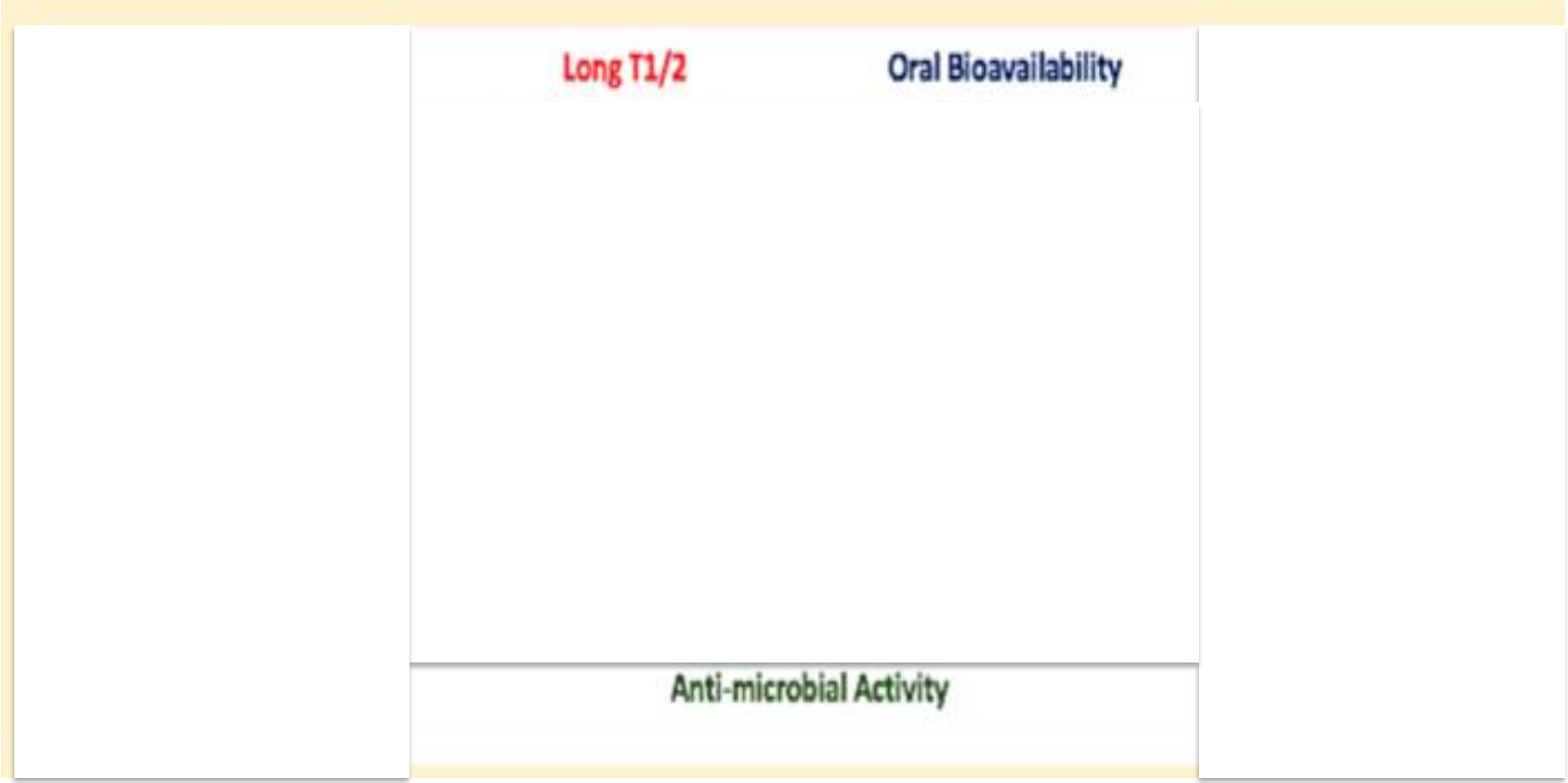
β-Lactam Antibiotics

- **122 compounds**
  - Many are monoacids
- **Properties associated with long half-life**
  - Ionization
  - Polarity
  - Flexibility
  - Increasing protein binding → decrease renal CL

Half life: 0.693 V_d/CL

Smith PW et al. ACS Infect Dis 2018;4(10):1439-1447

Pharmacokinetics of β-Lactam Antibiotics: Clues from the Past for the Future



Smith PW et al. ACS Infect Dis 2018;4(10):1439-1447

Aerosolized Liposomal Amikacin

- **Liposomal amikacin for inhalation (LAI; Arikayce™)**
  - Amikacin sulfate encapsulated in liposomes
  - Maximization of the dose and delivery to the lungs by a nebulizer
  - Infected patients by *P. aeruginosa* or *M. abscessus* (ongoing study)
- **Small liposome particles**
  - Penetration and diffusion through sputum into the bacterial biofilm
  - Deposit drug close to the bacterial colonies
    - Meers, et al., 2008; Clancy, et al., 2013
- **Clinically achievable local doses of LAI formulations:**
  - Can effectively increase the half-life of the drug in the lungs
  - Can decrease the potential for systemic toxicity

https://clinicaltrials.gov/ct2/show/NCT03905642?term=liposomal+amikacin&draw=2&rank=3

Tafenoquine: First Global Approval

- **Long-acting analogue of primaquine**
  - Orally-active 8-aminoquinoline anti-malarial drug
  - Activity against pre-erythrocytic (liver) and erythrocytic (asexual) forms &
  - Gametocytes of Plasmodium species that include *Plasmodium vivax* and *P. falciparum*
  - (Krintafel™, Arakoda™)
- **Developed by GlaxoSmithKline (formerly SmithKline Beecham)**
  - → Radical cure of *P. vivax* malaria
- **Developed by 60 Degrees Pharmaceuticals**
  - → Prophylaxis of malaria
- **Exact mechanism(s) of action unknown**
  - Possible effect by inhibiting haematin polymerization
  - Possible induction of mitochondrial dysfunction → apoptotic-like death

Frampton JE. Drugs. 2018;78(14):1517-1523

Tafenoquine: First Global Approval

Features and properties of tafenoquine	
Alternative names	60P 003; Arakoda; Etaquine; Krintafel; SB-252263; SB-252263-AAB; SB-252263-AX; tafenoquine maleate; tafenoquine succinate; WR 238605; WR 238605 succinate
Class	Aminoquinolines; antimalarials; antiprotozoals; small molecules
Mechanism of action	Electron transport complex III inhibitor; reactive oxygen species stimulant. Molecular target in malaria unknown
Route of administration	Oral
Pharmacodynamics	Active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. vivax* and *P. falciparum*. No clinically relevant effect on QT interval
Pharmacokinetics	Time to peak plasma concentration ≈ 12–15 h; drug exposure increased when coadministered with food; apparent oral volume of distribution ≈ 1600 L; average elimination half-life ≈ 15 days
Most frequent adverse events	Headache, dizziness, nausea, vomiting, decreased haemoglobin
ATC codes	
WHO ATC code	P01A-X (other agents against amoebiasis and other protozoal diseases); P01B-A (aminoquinolines)
EphMRA ATC code	P1D (anti-malarials); P1G (other anti-parasitic agents)
Chemical name	4-N-[2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinolin-8-yl]pentane-1,4-diamine

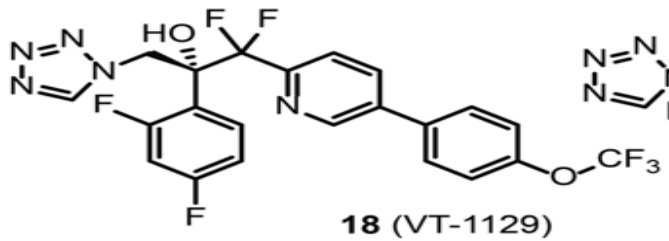
Frampton JE. Drugs. 2018;78(14):1517-1523

New Promising Targets for Antifungals

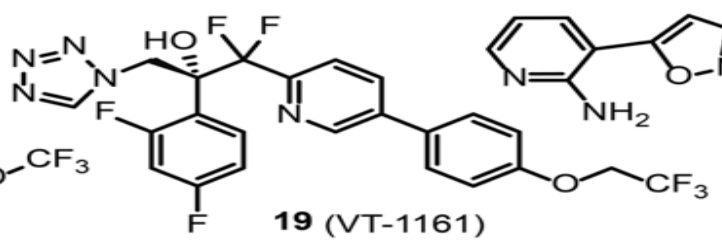
- Homoserine transacetylase
- Methionine synthase
- ATP sulfurylase
- Transcription factor protein (MET4)
- Homocysteine synthase
- Aspartate kinase
- Homoserine dehydrogenase
- Homoserine kinase
- Threonine synthase
- Acetolactate synthase
- ROS production
- Biofilm formation
- Sulfite transporter
- Phosphopantetheinyl transferase
- Mitochondrial phosphate carrier
- Bromodomain

Su H et al J Antibiot (Tokyo) 2018

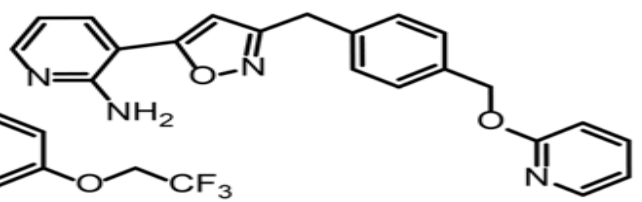
Potential Targets for the Development of New Antifungal Drugs



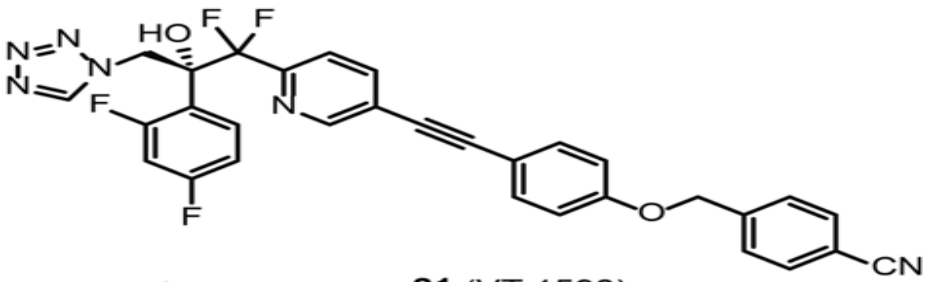
18 (VT-1129)



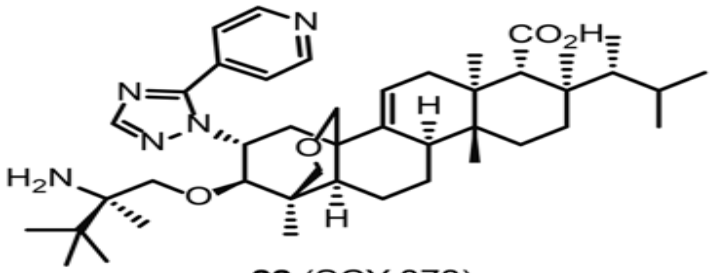
19 (VT-1161)



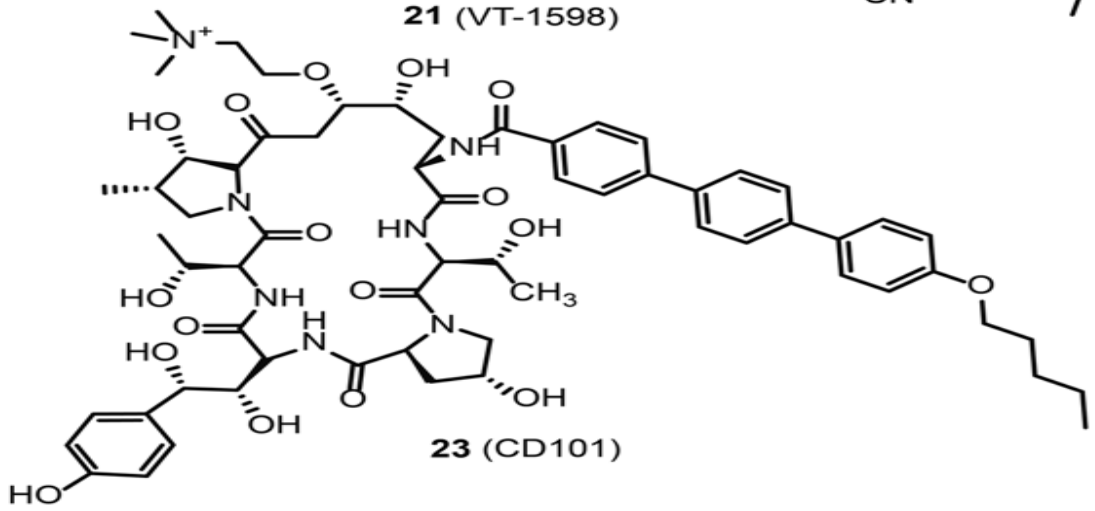
20 (AX001)



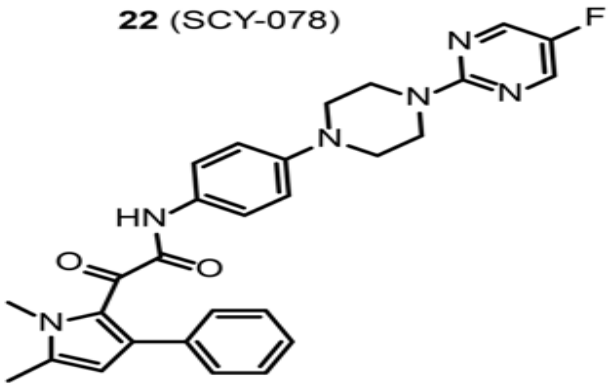
21 (VT-1598)



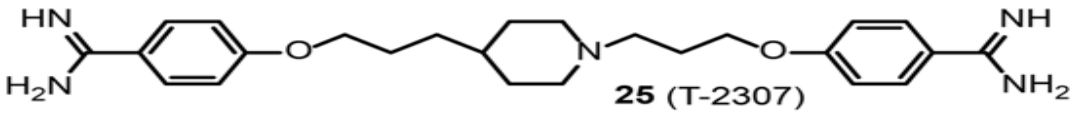
22 (SCY-078)



23 (CD101)



24 (F901318)



25 (T-2307)

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CD 101: Long Acting Echinocandin

- **Echinocandins:**
  - Long half-lives that allow for once-daily dosing
  - Low toxicity profile (Denning, 2003)
- **CD101 = Rezafungin**
  - Further improvement of this drug class
- **Advantages:**
  - Enhanced pharmacokinetic properties
  - Once-weekly intravenous therapy
  - Improved safety profile relative to other echinocandins (Ong et al., 2016; Ong et al., 2017; Sandison et al., 2017)

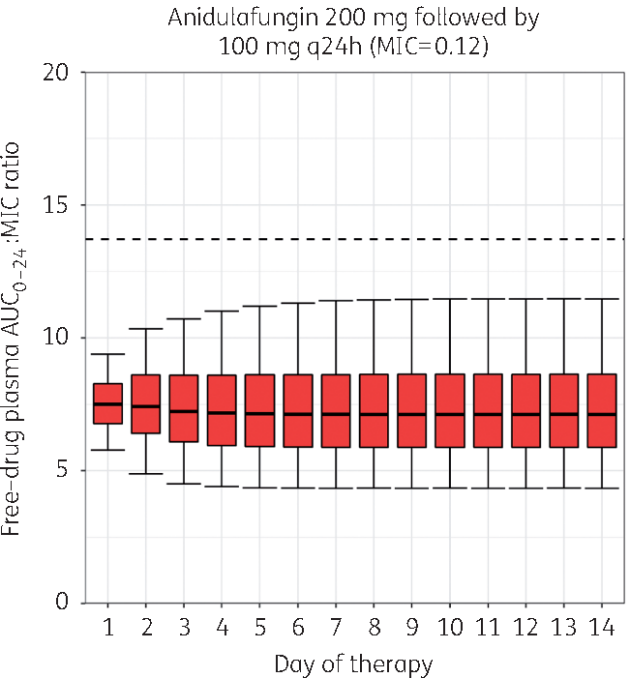
Berkow EL DMID 2018; Denning DW Lancet 2003; Ong V AAC 2017; Sandison AAC 2017

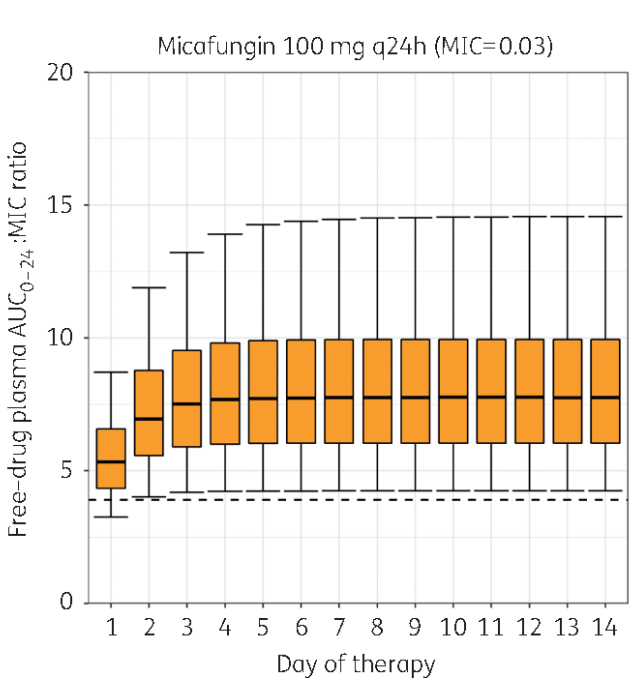
We Can Do Better:
A Fresh Look at Echinocandin Dosing

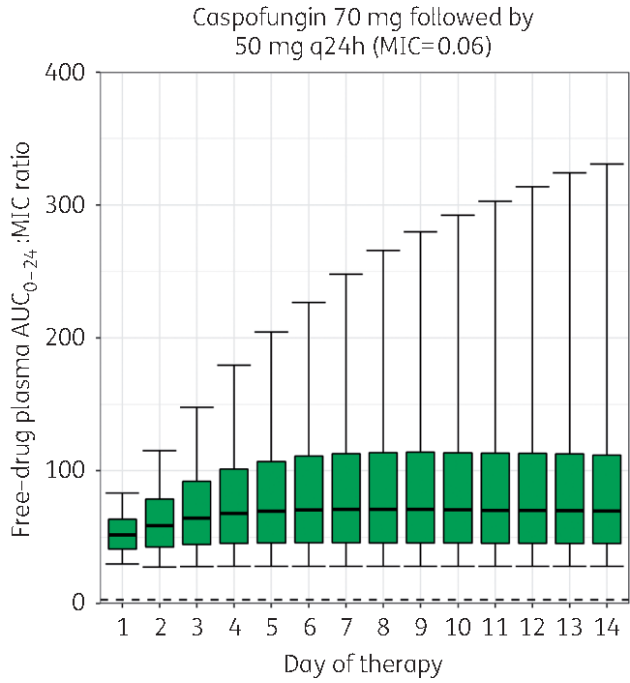
- **Anidulafungin and micafungin**
  - Unlikely to provide therapeutic exposures sufficient to treat highly resistant isolates
- **Day 1 probabilities of PK/PD target attainment**
  - 5.2% and 85.1%, respectively, at the C. glabrata MIC90 (0.12 mg/L) and MIC97 (0.06 mg/L)
- **Rezafungin**
  - High probabilities of target attainment over 4 weeks of therapy (100%) after administration of a single-dose regimen at the MIC90 of 0.06 mg/L
- **Conclusions on achievable drug exposure:**
  - Existing therapies are not optimal to treat resistant organisms
  - More potent new echinocandins may be on the horizon

Bader JC et al JAC 2018;73(S1):i44-i50

We Can Do Better:
A Fresh Look at Echinocandin Dosing







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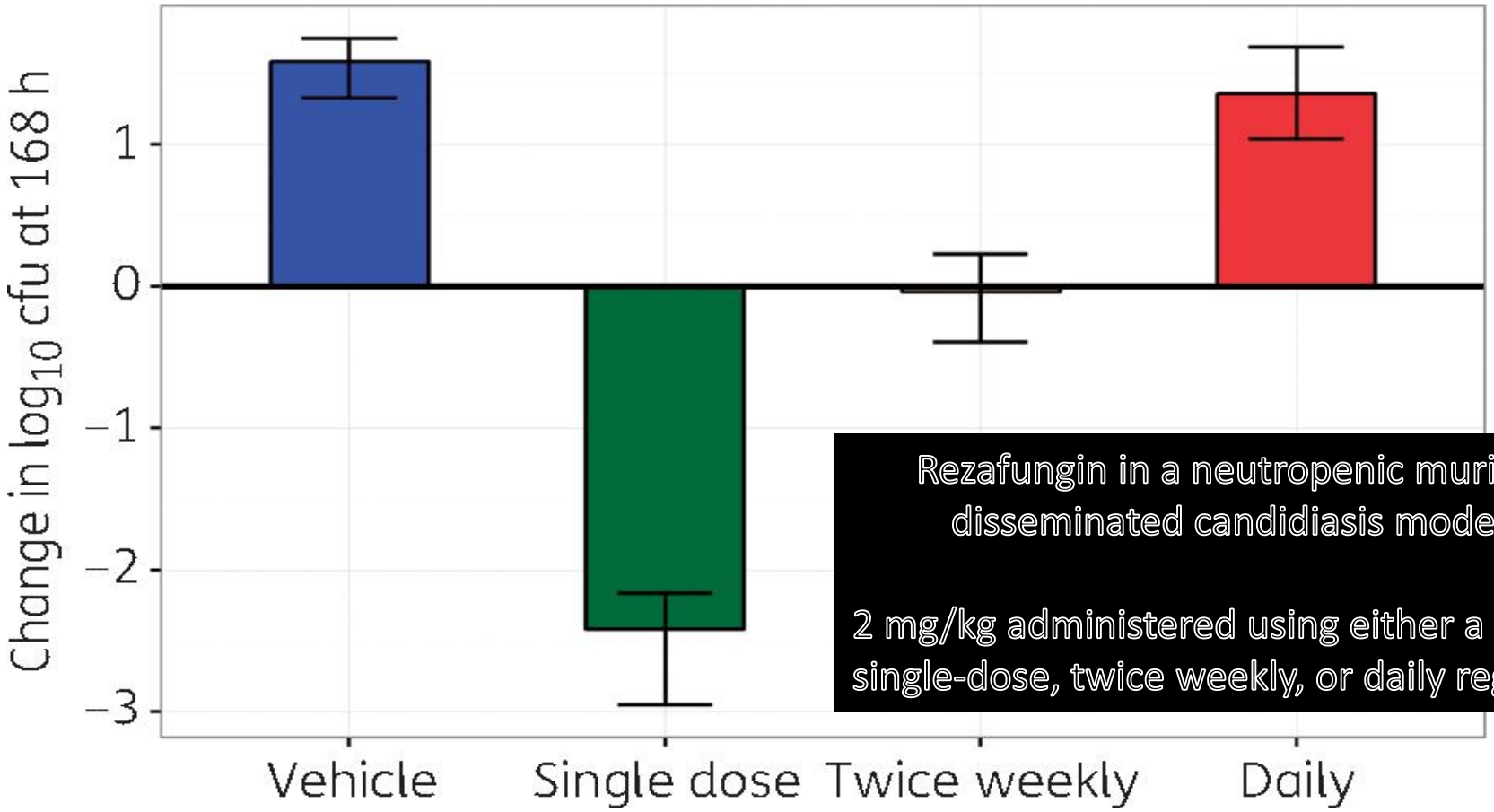

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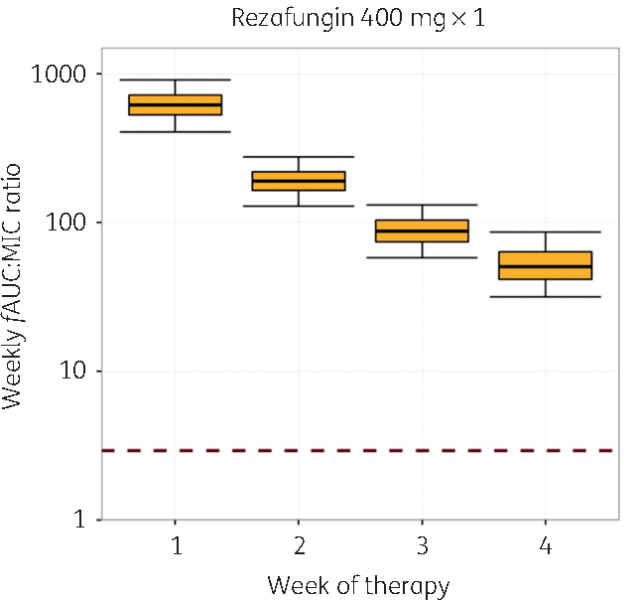
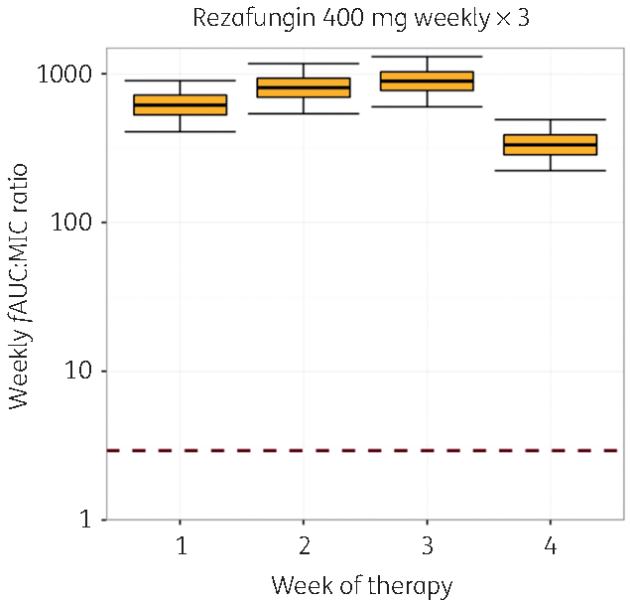
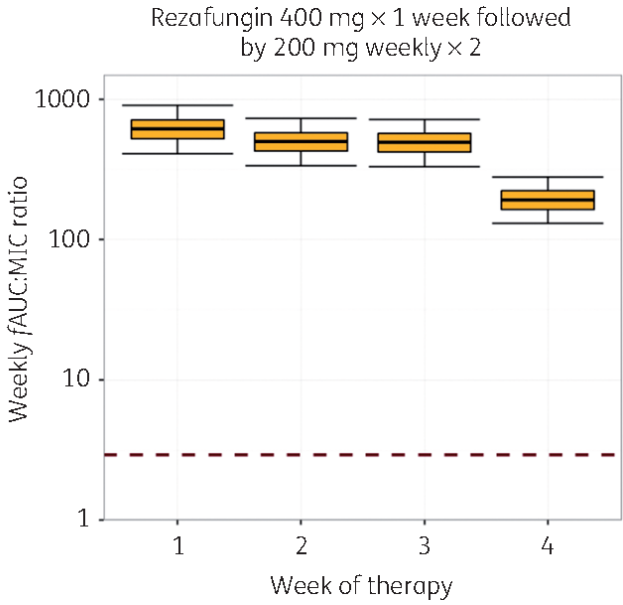






Bader JC et al JAC 2018;73(S1):i44-i50

Azythromycin Example of Concentration-dependent

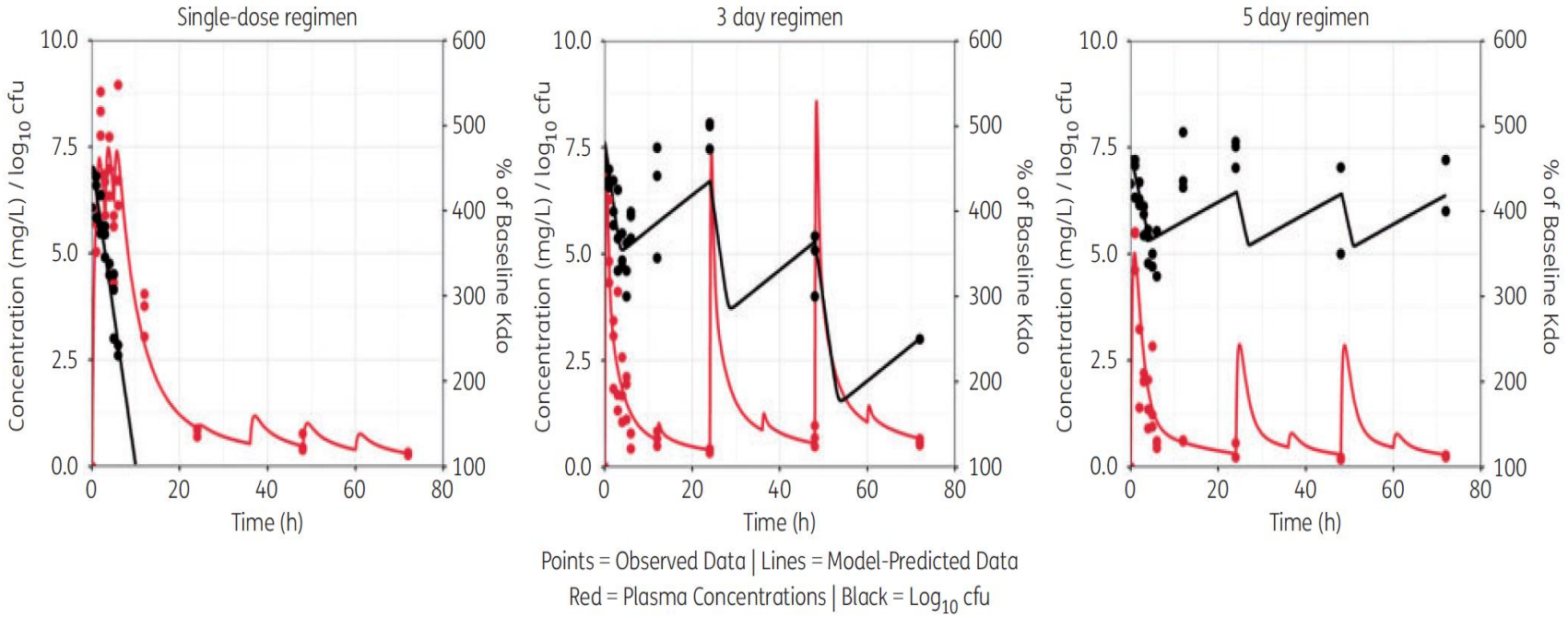


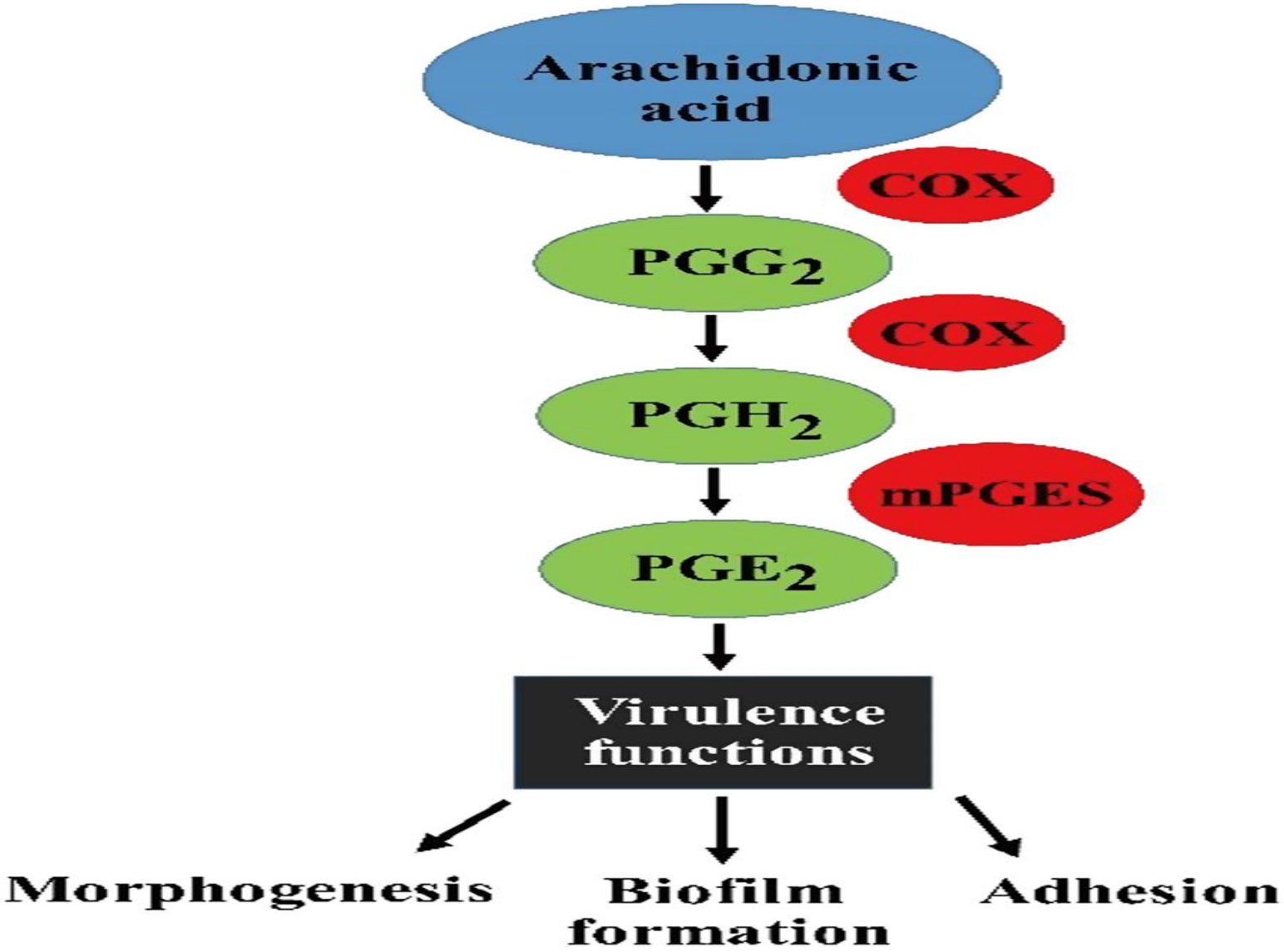
Figure 2. Plots of gerbil plasma concentration–time and changes in bacterial density superimposed over observed data and the model-predicted function for the rate of bacterial death.

Bader JC et al JAC 2018;73(S1):i44-i50

Long-acting

- **Current Status:**
  - Clinical needs
  - Stewarship interventions
  - Pharmacoeconomic approaches
- **Perspectives:**
  - Variety of antimicrobials
  - Variety of administrations
  - q24h or q7d definition of concentration-dependent?
- **Future challenges:**
  - Long-acting reduction of microbiome perturbations
  - Long-acting anti-biofilm efficacy

Anti-Biofilm Strategies



Su H et al J Antibiot (Tokyo) 2018