Long-acting Antimicrobial Agents:

Current Status & Perspectives

Turin, January 15, 2021

Francesco G. De Rosa
City of Health and Science, Turin
Cardinal Massaia Hospital, Asti
University of Turin, Italy

Disclosures

Consultant/Advisory Board/Speaker fees

- Pfizer, MSD, Angelini
- Basilea, Thermo Fisher
- BioTest, Nordic Pharma
- Gilead Sciences, Correvio
- Avir Pharma

"Long-acting"

- **Prolonged antimicrobial effect**
- **Not equal: "long-life" or "prolonged half-life"**
- **Physiology**
  - Protein binding & chemical structure
  - Enzymatic modifications
    - Rifampin-induced metabolism: timing and duration
  - Produgs
- **Pathology**
  - Renal failure
  - Liver failure

Historical Perspective

- **Evolution & Eras of anti-microbial drugs**
  - **Great antiquity**
    - Natural plant products
  - **Synthesis**
    - Prontosil (sulphonamido-chrysoidin)
    - 1932 by Klarer and Mietzsch
  - **Natural plant product and synthesis**
- **First discovered Long-acting antimicrobial**
- **G-benzatyn penicillin**

Penicillin: Tasks & Achievements

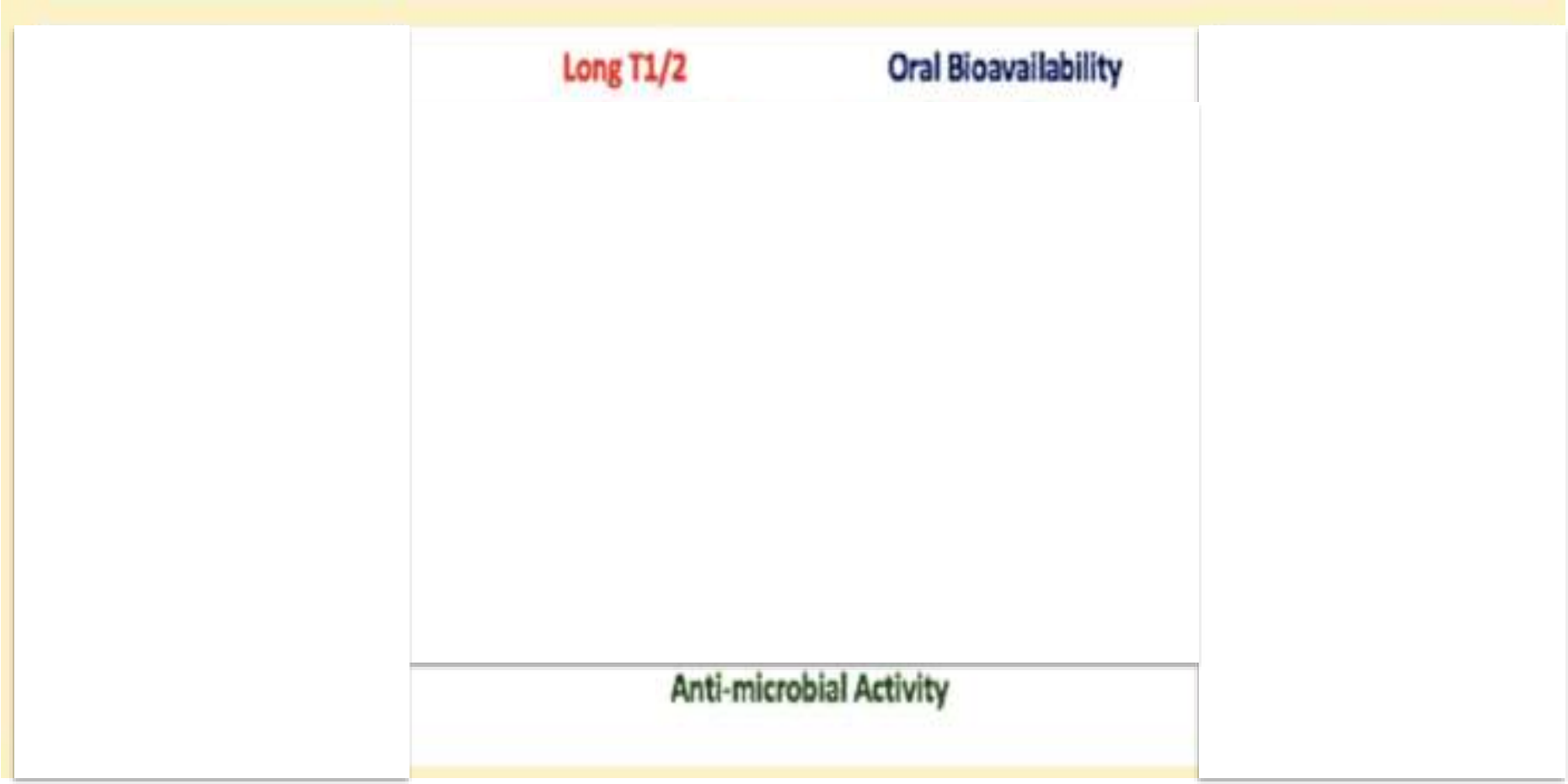
- **Extracting labile substance from culture fluids**
  - Examine its action and toxicity
  - Prove its systemic efficacy
- **Enough quantity of a substance**
  - Excreted with unexplained rapidity
- **Several years needed**
  - Penicillin fully purified
  - Structure ascertained
  - Large-scale production achieved

Adaptation of Existing Drugs

- **Alteration for better pharmacological properties**
  - Procaine penicillin → less soluble → longer acting
- **Synthetic manipulation of penicillin**
- **Question of changing anti-bacterial activity**
- **Properties of Beta-lactams for long half-life**
  - Ionization
  - Polarity
  - Flexibility
  - Increasing protein binding → decreased renal 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

Azythromycin Example of Concentration-dependent

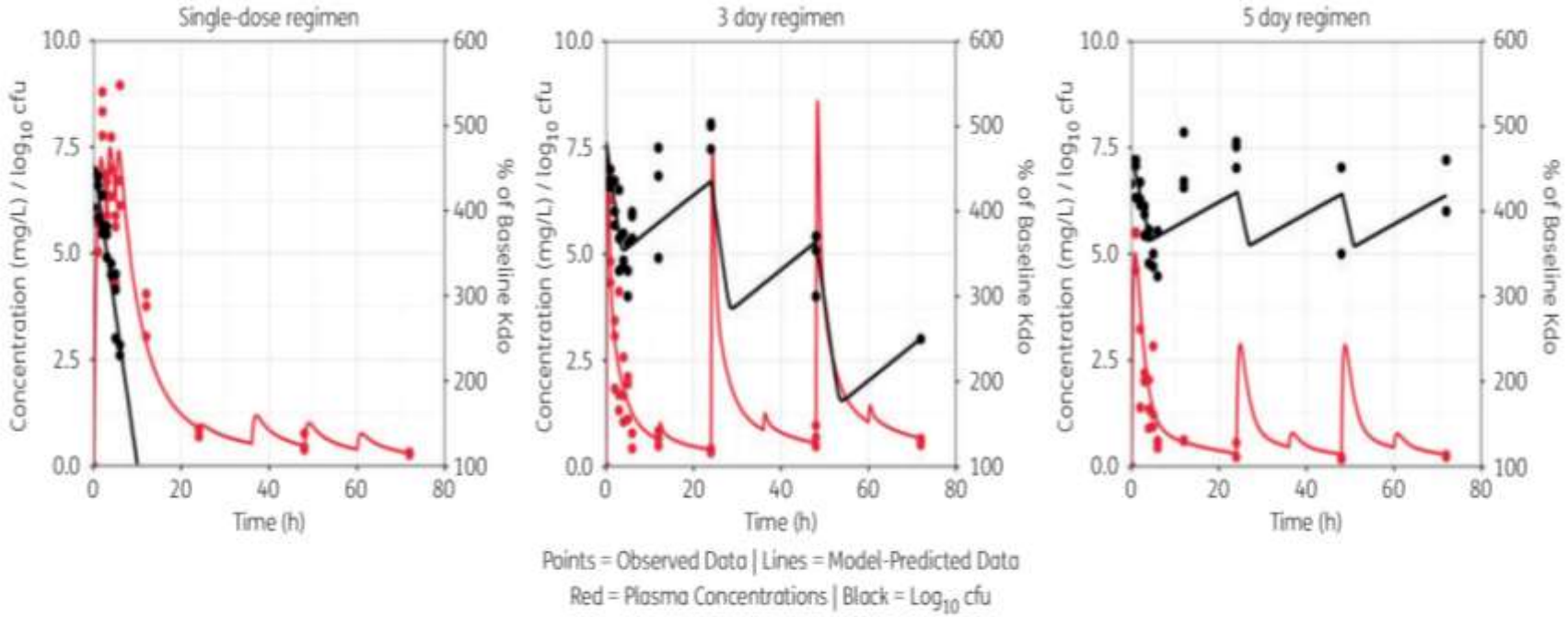
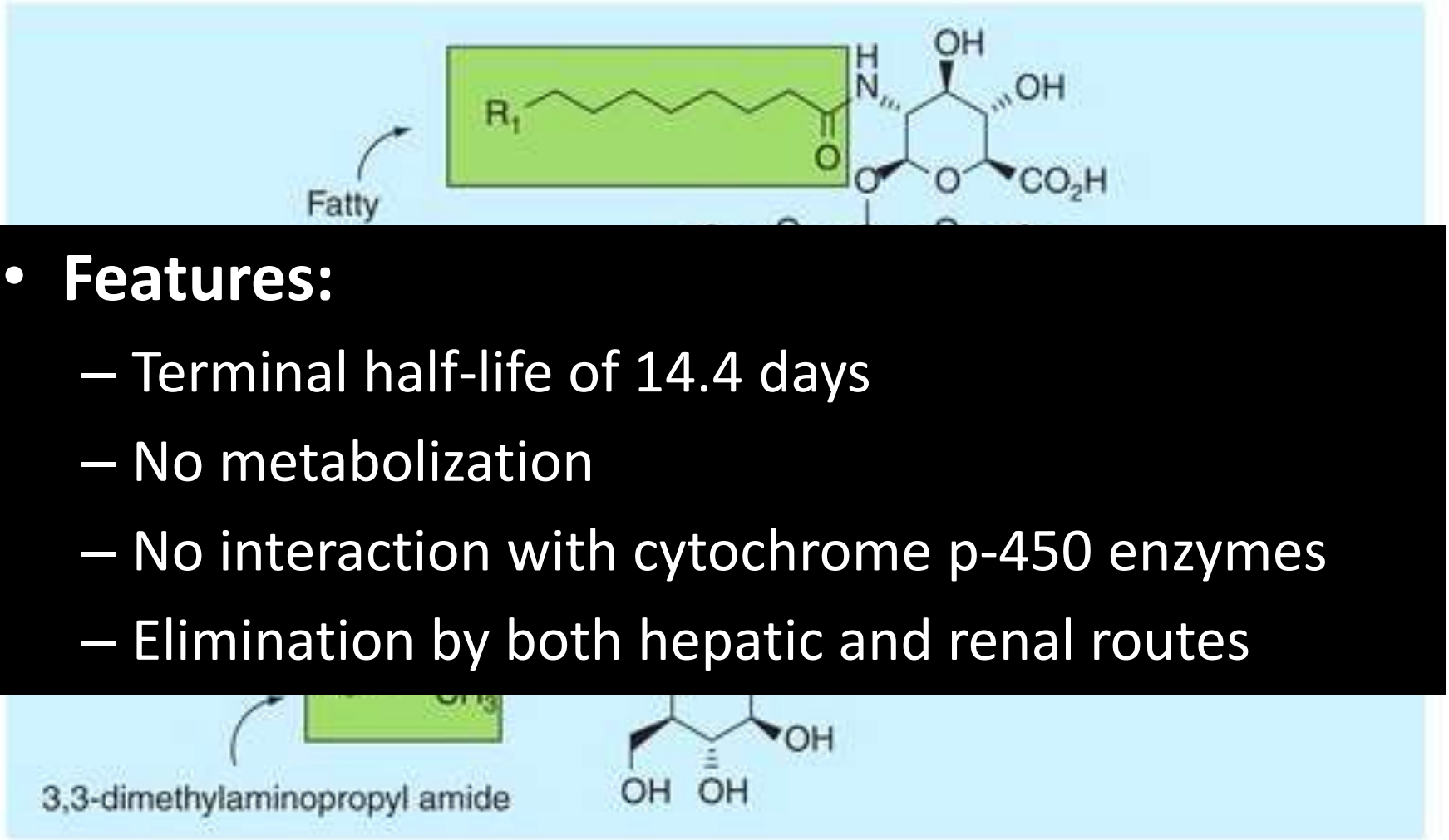


Figure 2. Plots of gerbil plasma concentration-time and changes in bacterial density superimposed over observed data and the model-predicted function for the rate of bacterial death.

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

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

Serum Bactericidal Activity Levels Monitor to Guide Intravenous Dalbavancin Chronic Suppressive Therapy of Inoperable Staphylococcal Prosthetic Valve Endocarditis: A Case Report

Martina Spaziante,[1] Cristiana Franchi,[2] Gloria Taliani,[2] Antonio D'Avolio,[3] Valeria Pietropaolo,[1] Elisa Biliotti,[2] Rozenn Esvan,[1] and Mario Venditti[1]

Table 1.

Dalbavancin Administration Schedule[a] Based on SBA Titers Against the *S. epidermidis* Blood Isolate

Day of Therapy	i.v. Dalbavancin, mg	SBA Titers	Dalbavancin Serum Concentration, mg/L
Day 1	1500	n.a.	n.a.
Day 7	1500	n.a.	n.a.
Day 42	1500	1:128[b]	n.a.
Day 63	Not administered	1:512	32.8[c]
Day 112	1500	1:8[b]	0.6[c] (410.5[d])
Day 133	Not administered	1:128	17.9[c]
Day 154	Not administered	1:16	n.a
Day 189	1500	1:2[b]	n.a.

Abbreviations: i.v., intravenous; SBA, serum bactericidal activity.

[a]After day 42, it was decided to administer dalbavancin whenever an SBA titer ≤1:8 was detected; these circumstances accounted for through SBA titers previously reported as resulting in bacteriological cure in infective endocarditis [5].

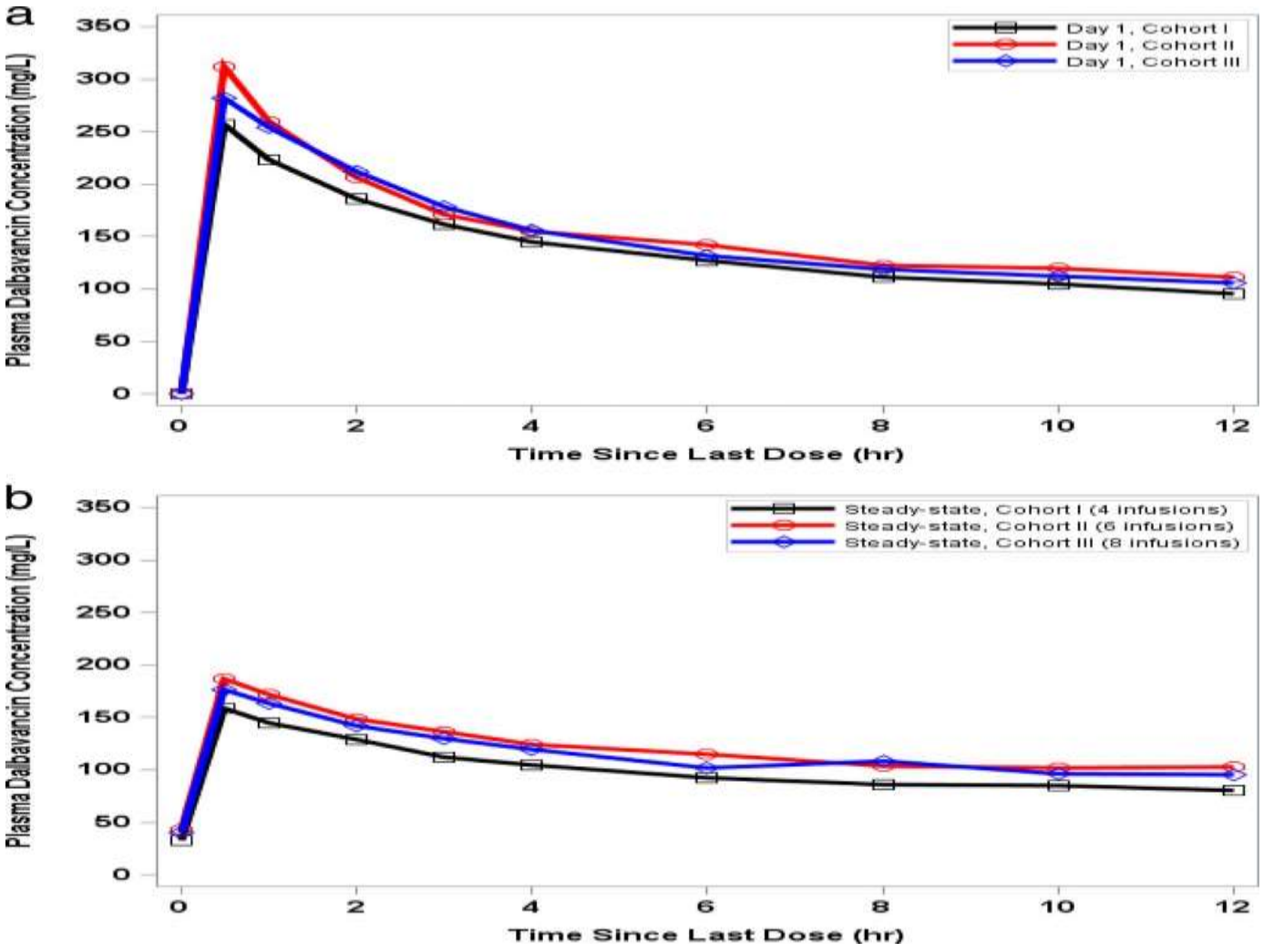
[b]SBA titer before i.v. dalbavancin administration.

[c]Through serum drug concentration.

[d]Peak serum drug concentration (measured 15 minutes after dalbavancin i.v. administration).

The 7-week daptomycin plus ceftriaxone regimen without valve replacement could not be a successful therapy for our inoperable case of MRCoNS PVE.

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



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

Dalbavancin & Oritavancin Pharmacology

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

- **New pharmacologic features**
  - Terminal half-lives for both are approximately 2 weeks
  - Serum free-drug concentrations exceed MICs for ≥1 week
- **Concentration-dependent killing**
  - AUC / MIC correlates with *in vivo* efficacy
- **Clinical trials designed accordingly**
  - Administration of one or two large, pulse doses
  - Not smaller, closely spaced, multiple doses

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

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

Liposomal antibiotic drug

Drugs (2020) 80:1309–1318
https://doi.org/10.1007/s40265-020-01359-z

REVIEW ARTICLE

Inhaled Liposomal Antimicrobial Delivery in Lung Infections

Matteo Bassetti[1,2] · Antonio Vena[1] · Alessandro Russo[3] · Maddalena Peghin[4]

Published online: 20 July 2020

Abstract
The management of difficult-to-treat acute and chronic respiratory infections (infections in cystic fibrosis, non-cystic fibrosis bronchiectasis, immunocompromised and mechanically ventilated patients) and difficult-to-treat pathogens (including multidrug-resistant strains) has become a challenge in clinical practice. The arsenal of conventional antibiotic drugs can be limited by tissue penetration, toxicities, or increasing antibiotic resistance. Inhaled antimicrobials are an interesting therapeutic approach for optimizing the management of respiratory infections. Due to extensive developments in liposome technology, a number of inhaled liposome-based antibiotic and antifungal formulations are available for human use and many products are undergoing clinical trials. Liposomes are biocompatible, biodegradable, and nontoxic vesicles able to encapsulate and carry antimicrobials, enhancing the therapeutic index of various agents and retention at the desired target within the lung. Liposomes reduce drug toxicity and improve tolerability, leading to better compliance and to decreased respiratory side effects. The aim of this article was to provide an up-to-date overview of nebulized liposomal antimicrobials for lung infections (with a special focus on liposomal amikacin, tobramycin, ciprofloxacin, and amphotericin B for inhalation), discussing the feasibility and therapeutic potential of these new strategies of preventing and treating bacteria, mycobacterial and fungal infections.

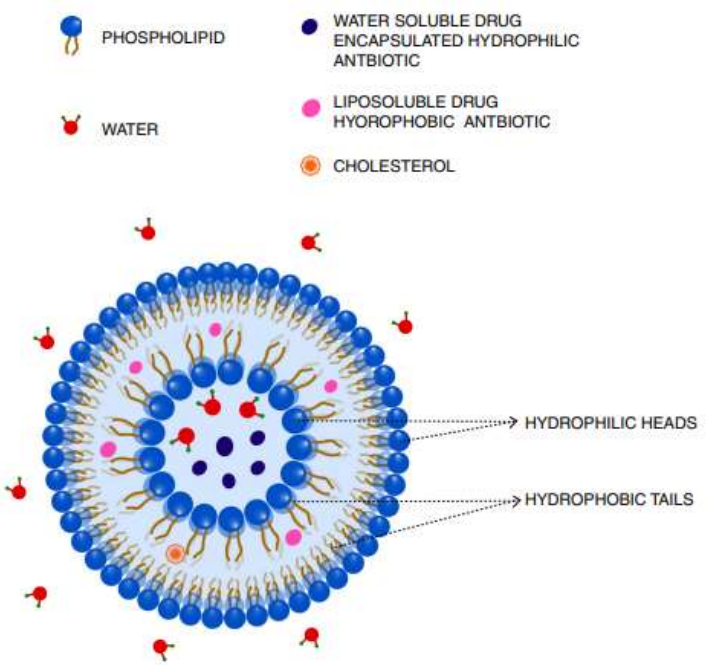


Fig. 1 Liposomal antibiotic drug delivery

Review

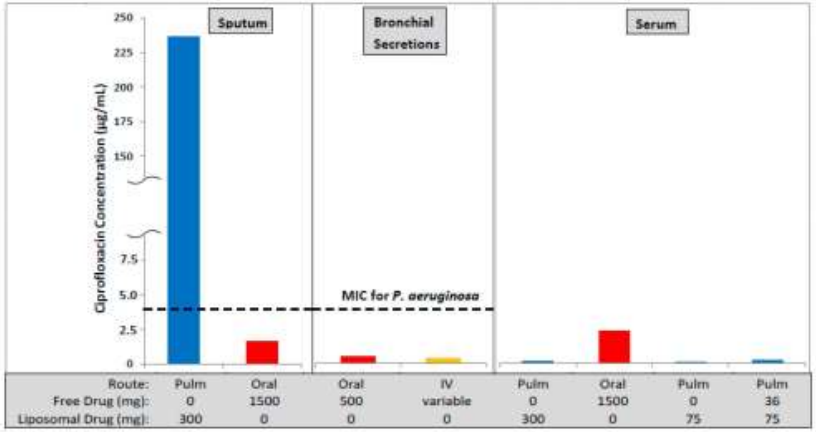
Development of Liposomal Ciprofloxacin to Treat Lung Infections

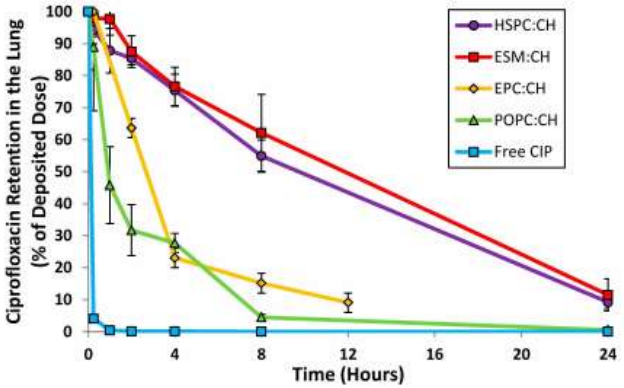
David Cipolla *, Jim Blanchard and Igor Gonda

Aradigm Corp., Hayward, CA 94545, USA; blanchardj@aradigm.com (J.B.); gondai@aradigm.com (I.G.)
* Correspondence: cipollad@aradigm.com; Tel.: +1-510-265-8849

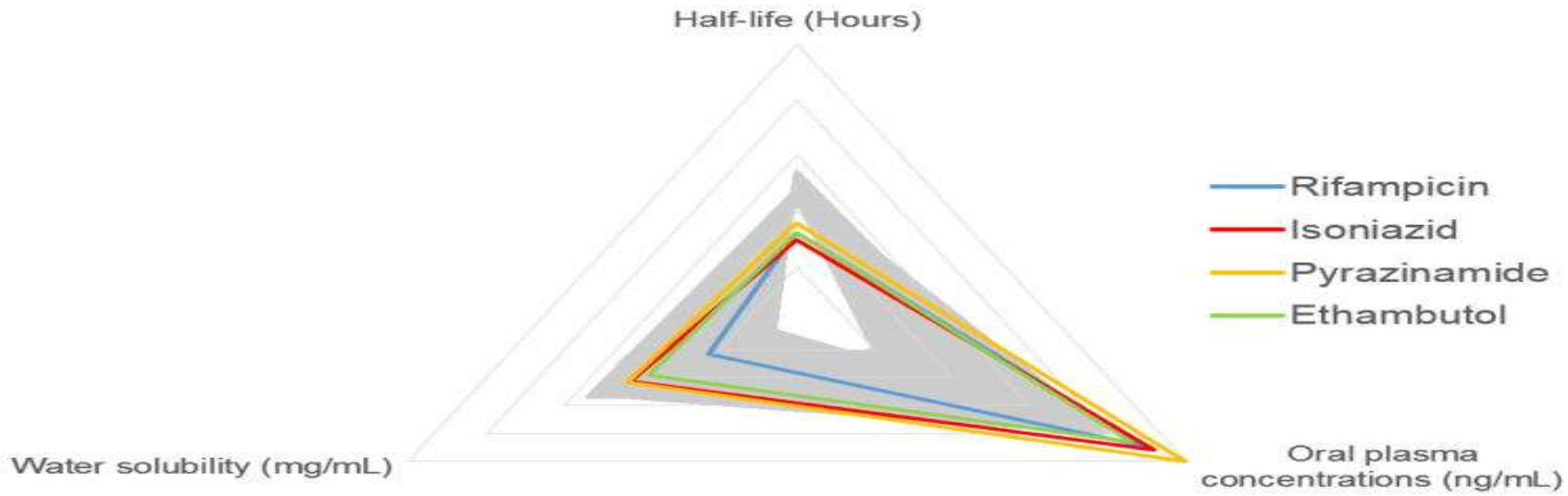
Academic Editor: Natasa Skalko-Basnet
Received: 2 January 2016; Accepted: 23 February 2016; Published: 1 March 2016

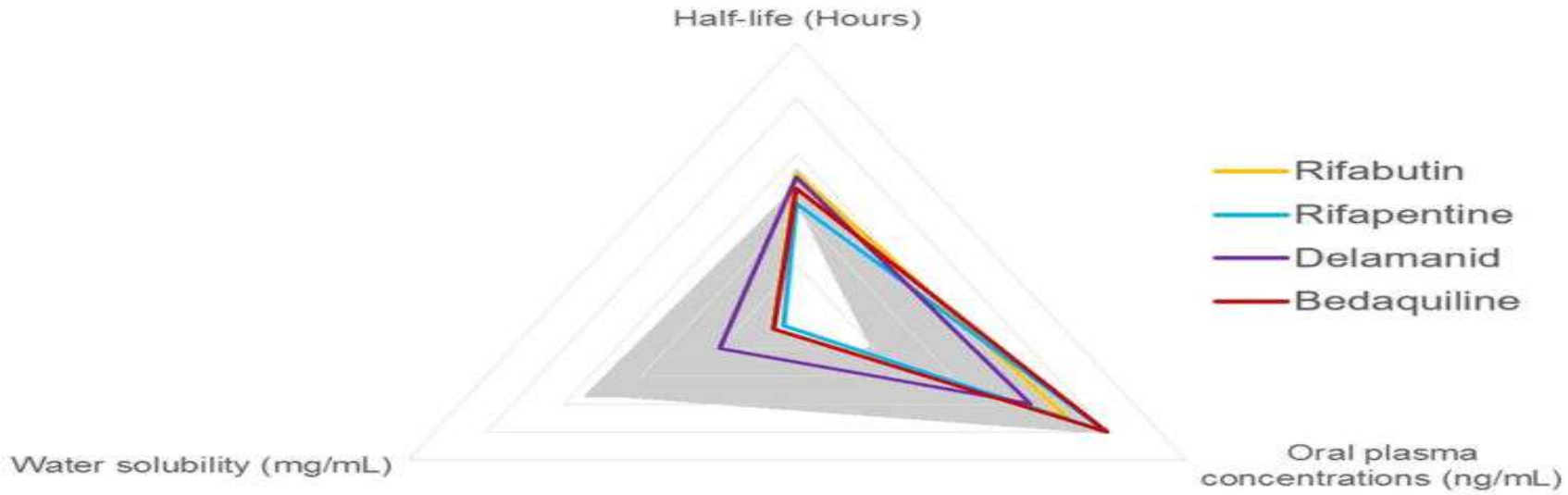
Abstract: Except for management of *Pseudomonas aeruginosa* (PA) in cystic fibrosis, there are no approved inhaled antibiotic treatments for any other diseases or for infections from other pathogenic microorganisms such as tuberculosis, non-tuberculous mycobacteria, fungal infections or potential inhaled biowarfare agents including *Francisella tularensis*, *Yersinia pestis* and *Coxiella burnetii* (which cause pneumonic tularemia, plague and Q fever, respectively). Delivery of an antibiotic formulation via the inhalation route has the potential to provide high concentrations at the site of infection with reduced systemic exposure to limit side effects. A liposomal formulation may improve tolerability, increase compliance by reducing the dosing frequency, and enhance penetration of biofilms and treatment of intracellular infections. Two liposomal ciprofloxacin formulations (Lipoquin® and Pulmaquin®) that are in development by Aradigm Corporation are described here.





Long-acting Formulations & Latent Tuberculous Infection: Opportunities and Challenges





Swindells S et al Int J Tuberc Lung Dis. 2018;22(2):125-132

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* spp. 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

EXPERT OPINION ON DRUG SAFETY
https://doi.org/10.1080/14740338.2021.1859476

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REVIEW

OPEN ACCESS

Tafenoquine: a toxicity overview

Cindy S. Chu [a,b] and Jimee Hwang [c,d]

[a]Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Mae Sot, Thailand; [b]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, UK; [c]U.S. President's Malaria Initiative, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, GA, USA; [d]Global Health Group, University of California San Francisco, San Francisco, CA, USA

ABSTRACT

Introduction: A century-long history in 8-aminoquinolines, the only anti-malaria drug class preventing malaria relapse, has resulted in the approval of tafenoquine by the U.S. Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) and to date registration in Brazil and Thailand. Tafenoquine is an alternative anti-relapse treatment for vivax malaria and malaria prophylaxis. It should not be given in pregnancy, during lactation of infants with glucose-6-phosphate dehydrogenase (G6PD) unknown or deficient status, and in those with G6PD deficiency or psychiatric illness.

Areas covered: This systematic review assesses tafenoquine associated adverse events in English-language, human clinical trials. Meta-analysis of commonly reported adverse events was conducted and grouped by comparison arms.

Expert opinion: Tafenoquine, either for radical cure or prophylaxis, is generally well tolerated in adults. There is no convincing evidence for neurologic, ophthalmic, and cardiac toxicities. Psychotic disorder which has been attributed to higher doses is a contraindication for the chemoprophylaxis indication and psychiatric illness is a warning for the radical cure indication. Pregnancy assessment and quantitative G6PD testing are required. The optimal radical curative regimen including the tafenoquine dose along with its safety for parts of Southeast Asia, South America, and Oceania needs further assessment.

ARTICLE HISTORY
Received 3 September 2020
Accepted 1 December 2020

KEYWORDS
8-aminoquinoline; adverse effect; causal prophylaxis; chemoprophylaxis; radical cure; meta-analysis; plasmodium vivax; relapse prevention; drug safety; tafenoquine

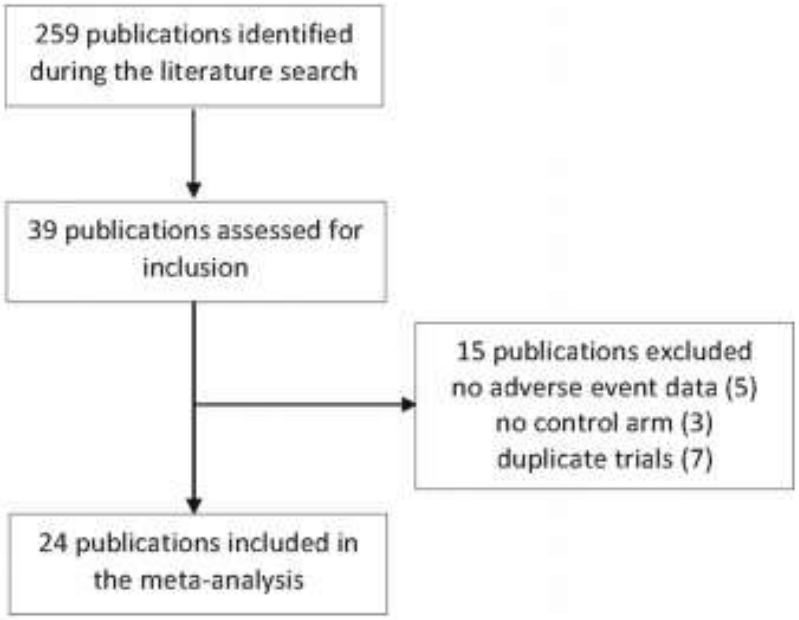


Figure 1. Selection of publications.

There is no evidence for neurologic, ophthalmic, and cardiac toxicities!

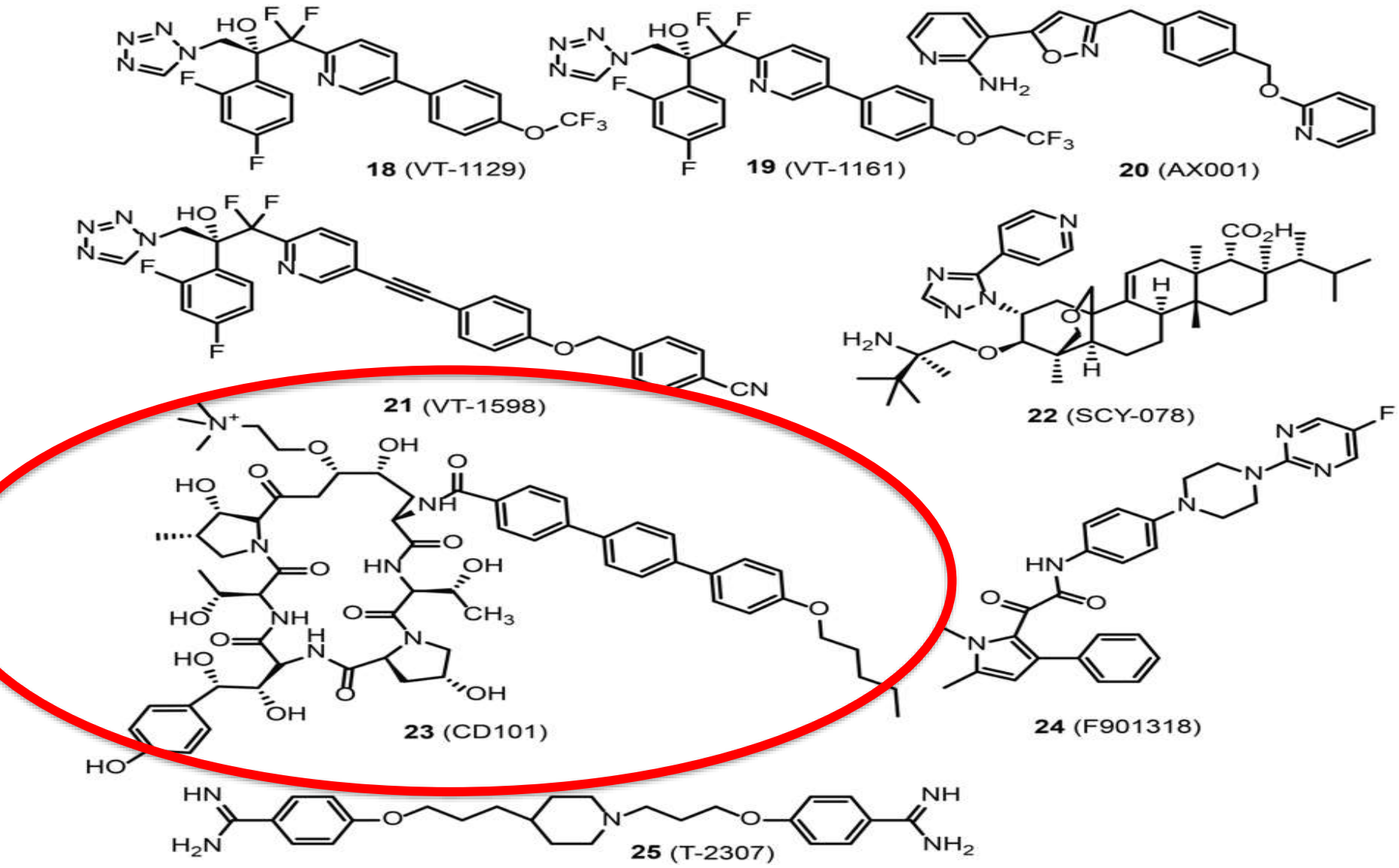
Long-acting Antifungal Drugs…

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



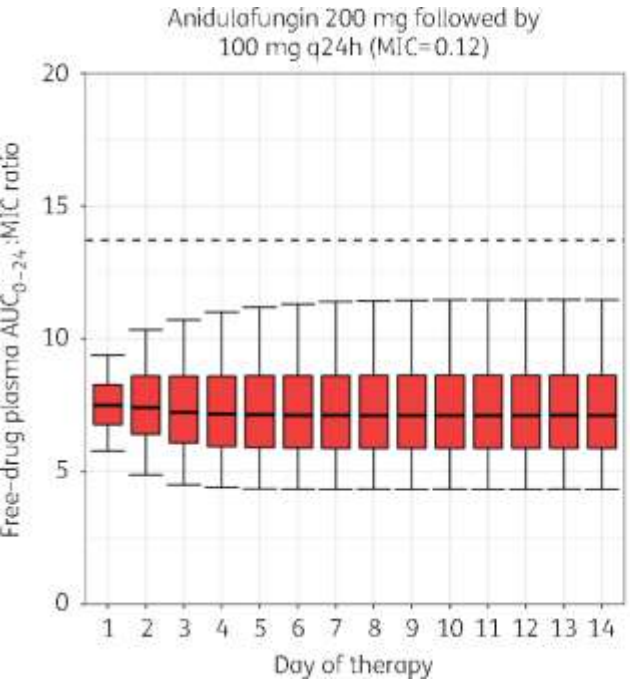
Su H et al J Antibiot (Tokyo) 2018

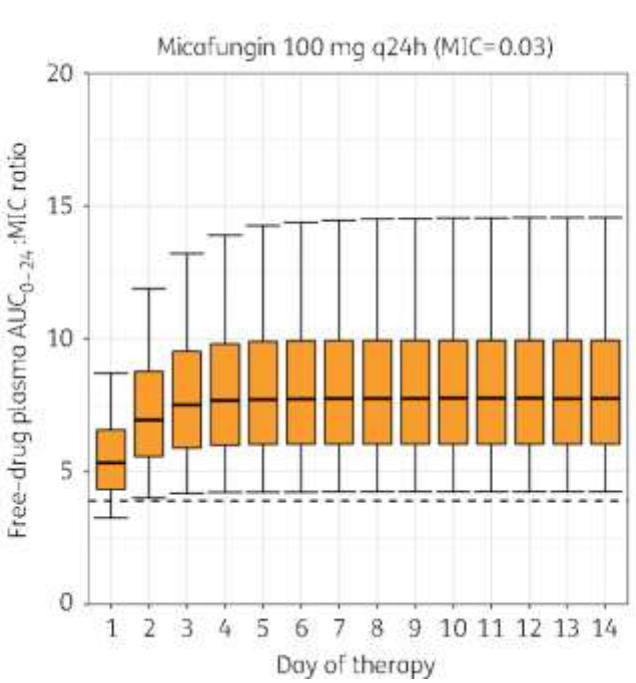
CD 101: Long Acting Echinocandin

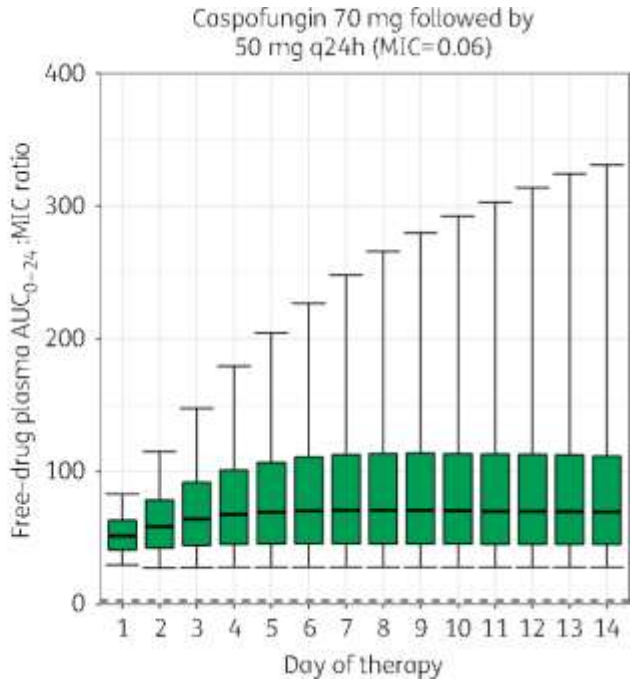
- **Echinocandins:**
  - Long half-lives that allow for once-daily dosing
  - Low toxicity profile (Denning, 2003)
- **CD 101 = Rezafungin**
  - Further improvement of this drug class
- **Advantages:**
  - Enhanced pharmacokinetic properties
  - Once-weekly intravenous therapy
  - Improved safety profile 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

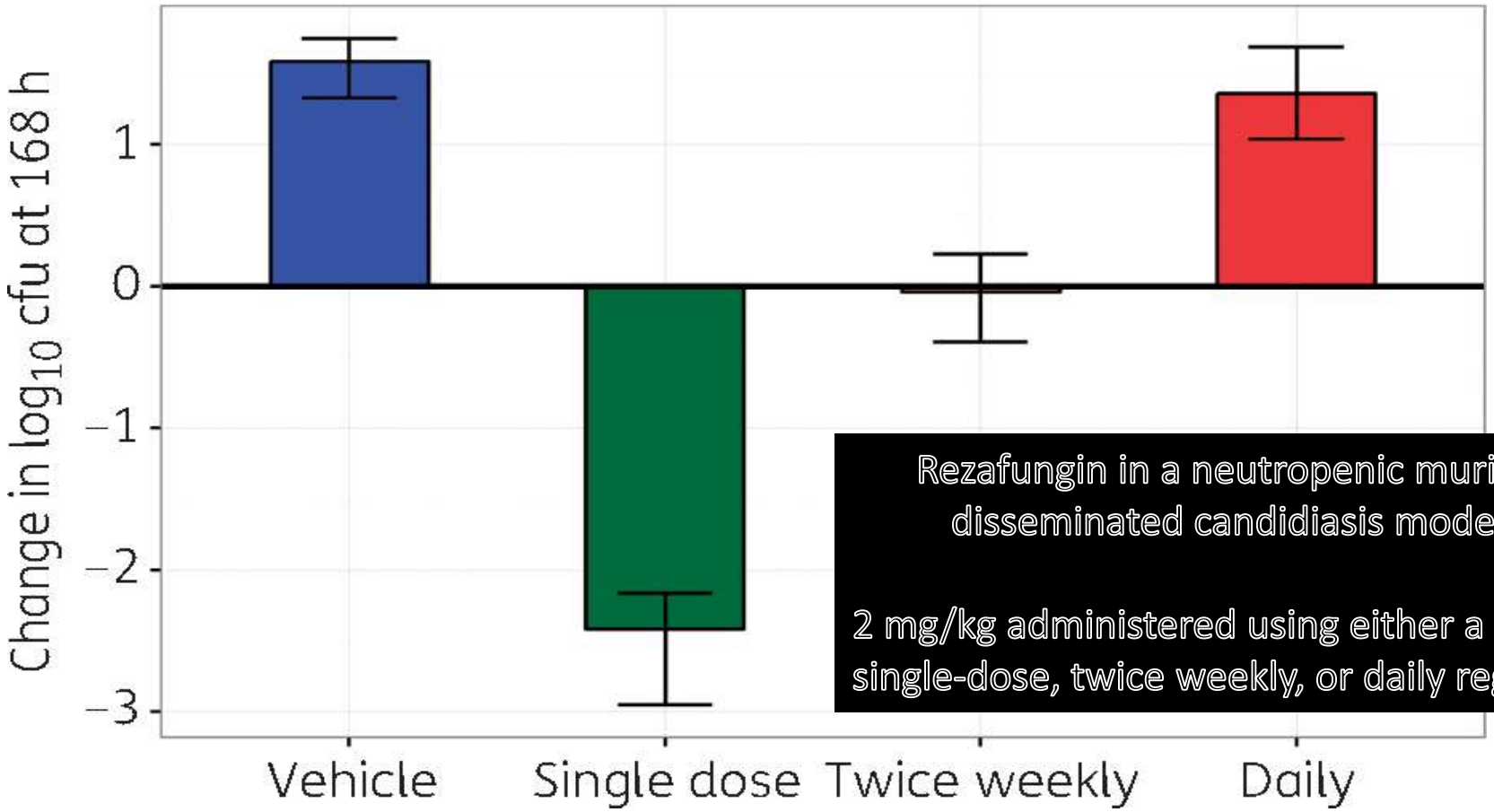






Bader JC et al JAC 2018;73(S1):i44-i50

We Can Do Better:
A Fresh Look at Echinocandin Dosing



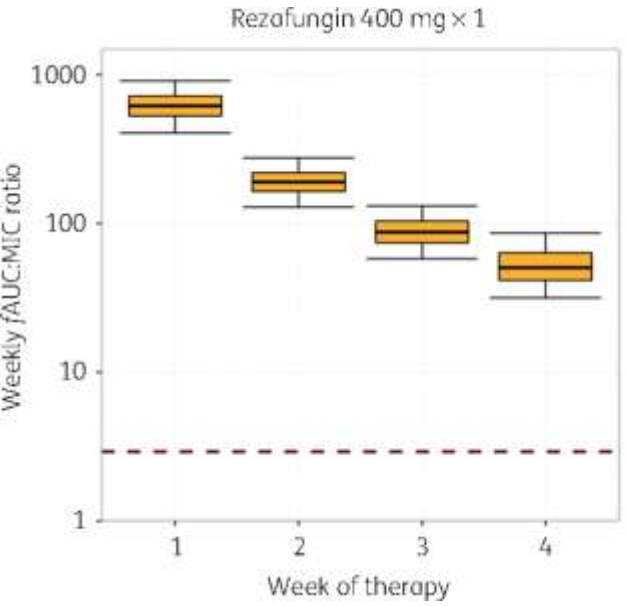
Bader JC et al JAC 2018;73(S1):i44-i50

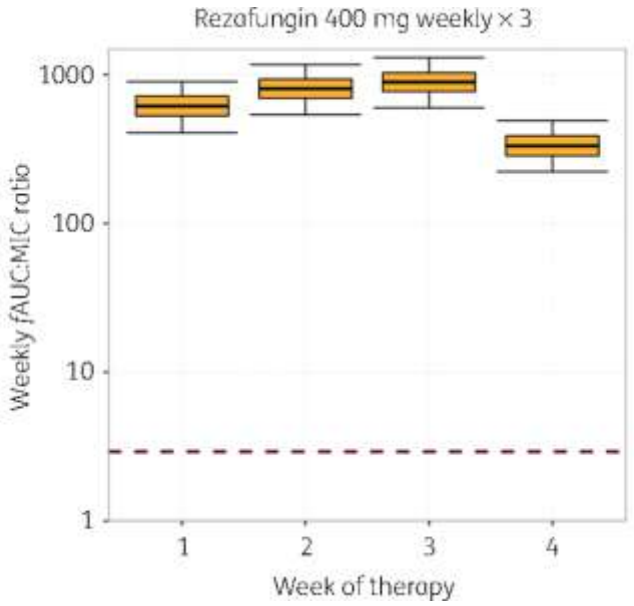
We Can Do Better: A Fresh Look at Echinocandin Dosing

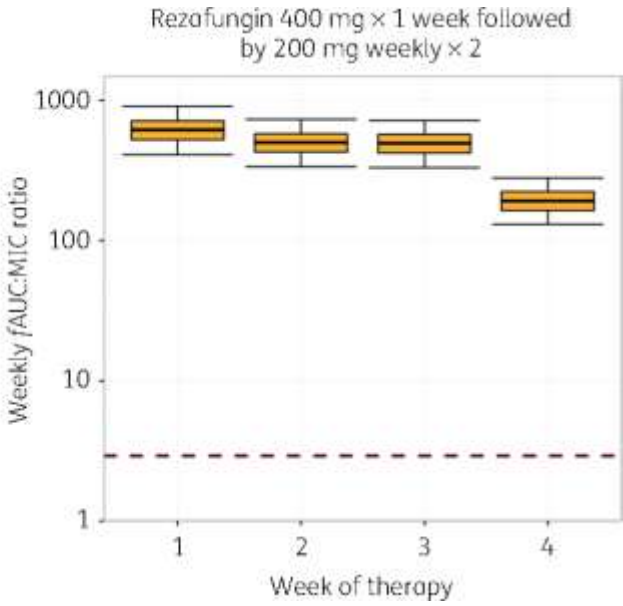
- **Anidulafungin and micafungin**
  - Unlikely therapeutic exposures sufficient to treat highly resistant isolates
- **Day 1 probabilities of PK/PD target attainment**
  - 5.2% and 85.1%, respectively, at the *C. glabrata* MIC90 (0.12 mg/L) and MIC97 (0.06 mg/L)
- **Rezafungin**
  - High probabilities 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





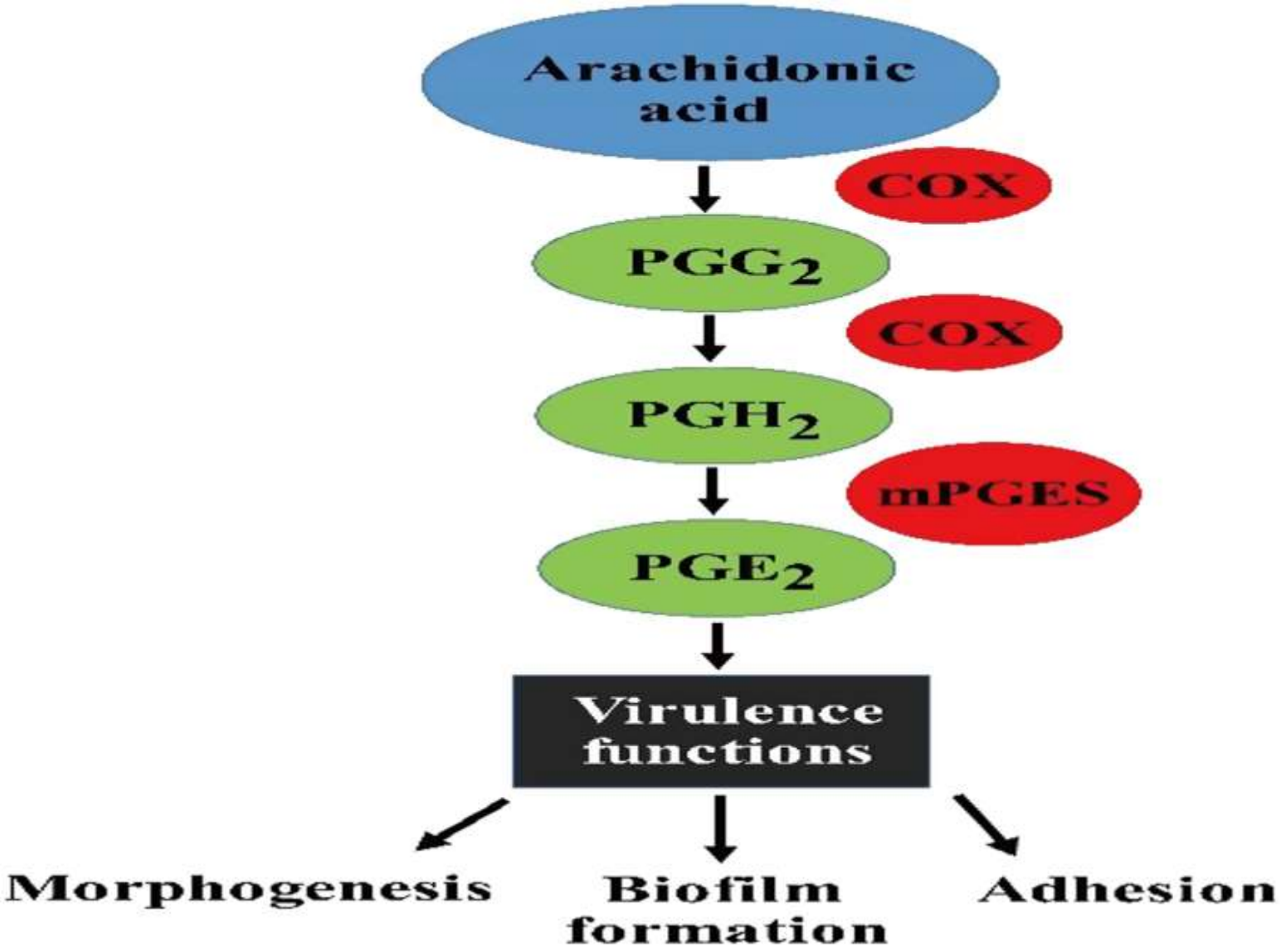


Bader JC et al JAC 2018;73(S1):i44-i50

Long-acting "Pan-Infective Agents"

- **Current Status:**
  - Clinical needs
    - Lineless Antimicrobials
    - Stewarship interventions
  - Pharmacoeconomic approaches
- **Perspectives:**
  - Chemistry vs. modality of administration
  - q24h or q7d definition of concentration-dependent?
  - Effect on microbiome
- **Future challenges:**
  - Long-acting anti-biofilm efficacy

Anti-Biofilm Strategies



Su H et al J Antibiot (Tokyo) 2018

ORIGINAL ARTICLE

MicrobiologyOpen WILEY

Drug repurposing: Antimicrobial and antibiofilm effects of penfluridol against *Enterococcus faecalis*

Xianghai Zeng | Pengfei She | Linying Zhou | Shijia Li | Zubair Hussain | Lihua Chen | Yong Wu

Department of Clinical Laboratory, The Third Xiangya Hospital of Central South University, Changsha, China

Correspondence
Yong Wu, Department of Clinical Laboratory, The Third Xiangya Hospital of Central South University. Changsha, 410013, Hunan, China.
Email: wuyong_zn@csu.edu.cn

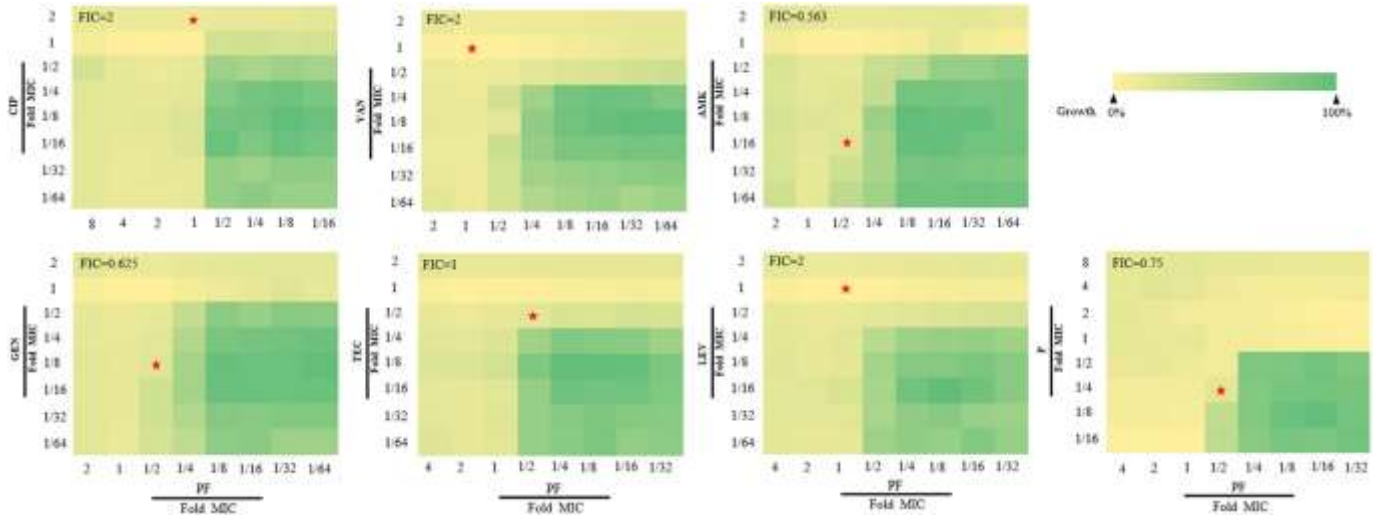
Funding information
National Natural Science Foundation of China, Grant/Award Number: 82072350; Graduate Student Innovation Project of the Central South University, Grant/Award Number: 2020zzts889

Abstract

The bacterium *Enterococcus faecalis* has increasingly attracted global attention as an important opportunistic pathogen due to its ability to form biofilms that are known to increase drug resistance. However, there are still no effective antibiofilm drugs in clinical settings. Here, by drug repurposing, we investigated the antibacterial activity of penfluridol (PF), an oral long-acting antipsychotic approved by the FDA, against *E. faecalis* type strain and its clinical isolates. It was found that PF inhibited the growth of *E. faecalis* planktonic cells with the MIC and MBC of 7.81 μg/ml and 15.63 ~ 62.50 μg/ml, respectively. Moreover, PF could significantly prevent the biofilm formation of *E. faecalis* at the concentration of 1 × MIC. Furthermore, PF significantly eradicated 24 h pre-formed biofilms of *E. faecalis* in a dose-dependent manner, with a concentration range of 1 × MIC to 8 × MIC. Here, through the checkerboard method with other tested conventional antibiotics, we also determined that gentamycin, penicillin G, and amikacin showed partial synergistic antibacterial effects with PF. Also, PF showed almost no hemolysis on human erythrocytes. In a mouse peritonitis model, a single dose of 20 mg/kg of PF treatment could significantly reduce the bacterial colonization in the liver (~5-fold reduction) and spleen (~3-fold reduction). In conclusion, these findings indicated that after structural optimization, PF has the potential as a new antibacterial agent against *E. faecalis*.

KEYWORDS
antibiofilm, *Enterococcus faecalis*, *in vivo*, penfluridol, repurposing

Future Perspectives with Past Drugs…



Drug Repurposing: Antimicrobial and Antibiofilm Effects of Penfluridol against *Enterococcus faecalis*

Zeng X et al Microbiologyopen. 2020 Dec 20:e1148

- **Penfluridol (PF): oral long-acting antipsychotic FDA-approved**
  - *E. faecalis* growth inhibition of planktonic cells with the MIC and MBC of 7.81 μg/ml and 15.63 ~ 62.50 μg/ml, respectively
  - Significant prevention of the biofilm formation of *E. faecalis* at the concentration of 1 × MIC
  - Significant eradication of 24 h pre-formed biofilms of *E. faecalis* in a dose-dependent manner: concentration range, 1 - 8 × MIC
- **Partial synergistic antibacterial effects with PF**
  - Through the checkerboard method
  - Genta, amika, penicillin