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Is it time to rethink echinocandin dosing?

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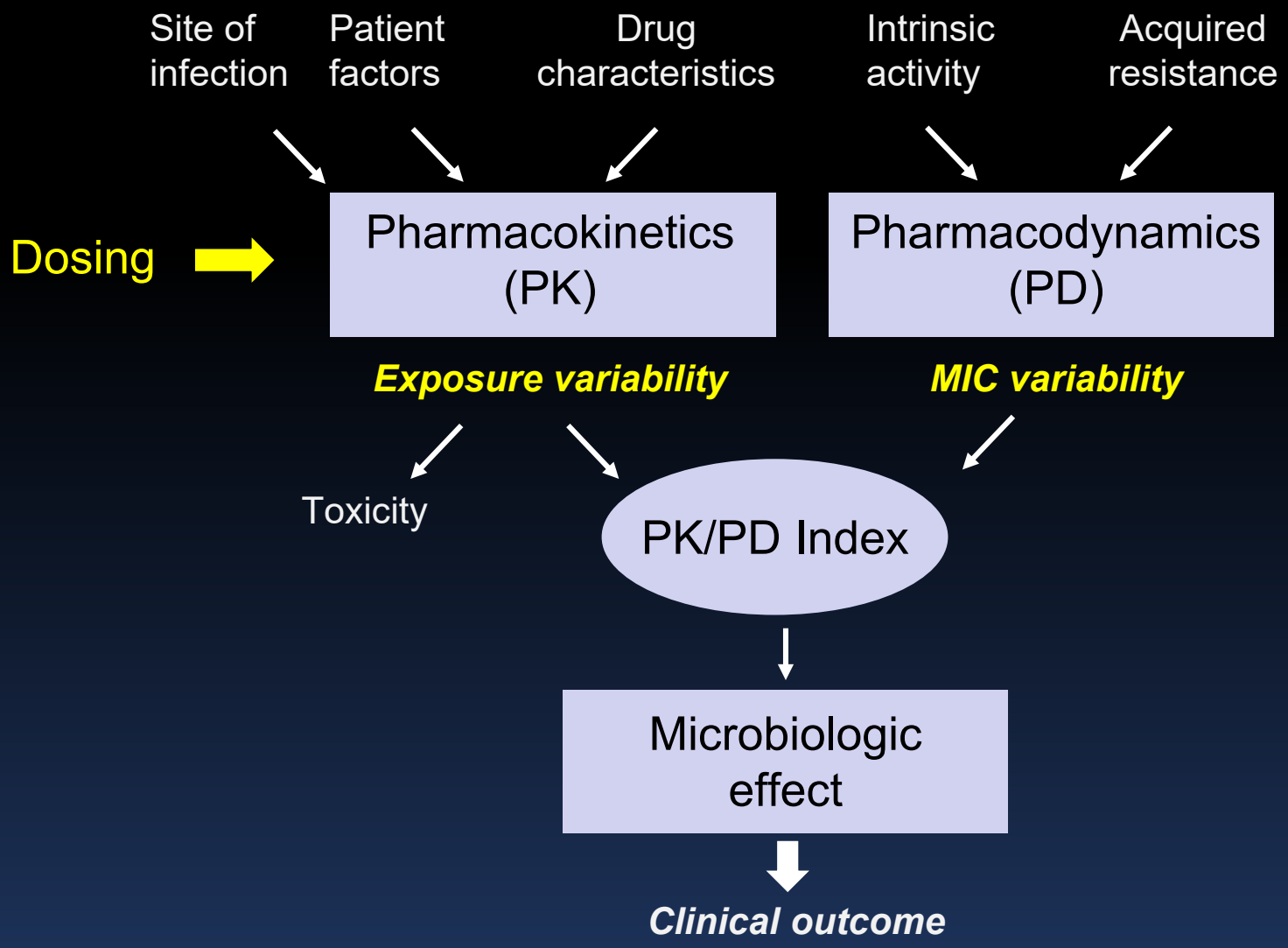
Disclosures

- Research support: Merck Inc.
- Advisory committees: Gilead, Cidara, F2G

“Medicine is a science of uncertainty, and an art of probability”

Sir William Osler, M.D.
(1849-1919)

The uncertain science of antibiotic dosing



Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792

Echinocandin exposures are variable in critically-ill patients

- **Pharmacokinetic point prevalence study (n=68 ICUs):[1]**
  - **Included patients receiving caspofungin/ anidulafungin**
    - **Cmax, AUC_{0-24}, Cmin** ~50% lower values than reported in healthy volunteers
    - **Cmax, AUC_{0-24}, Cmin** ~40% lower values than reported in previous ICU PK studies

- **Empirical micafungin in ICU patients with sepsis, organ failure and *Candida* colonization (EMPIRICUS trial):[2,3]**
  - **Empirical micafungin 100 mg/day was not associated with improved fungal-free survival vs. placebo by day 28**
  - **Measured micafungin blood concentrations were lower than expected → increased clearance (low albumin) and obesity[4]**

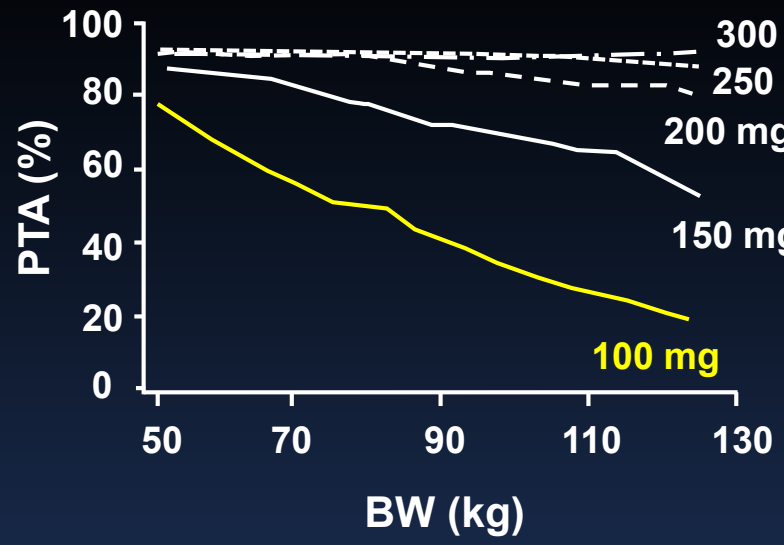
[1] Sinnollareddy M et al. *Crit Care* 2015;19(1):1.
[2] Timsit JF, et al. *JAMA* 2016;316(15):1555–64.
[3] Jullien V, et al. *J Antimicrob Chemother* 2017;72(1):181–9.
[4] Lempers et al. Antimicrob Agents Chemother 2015; 59: 4403 – 9

Micafungin 100 mg/day probability of target attainment (PTA)*

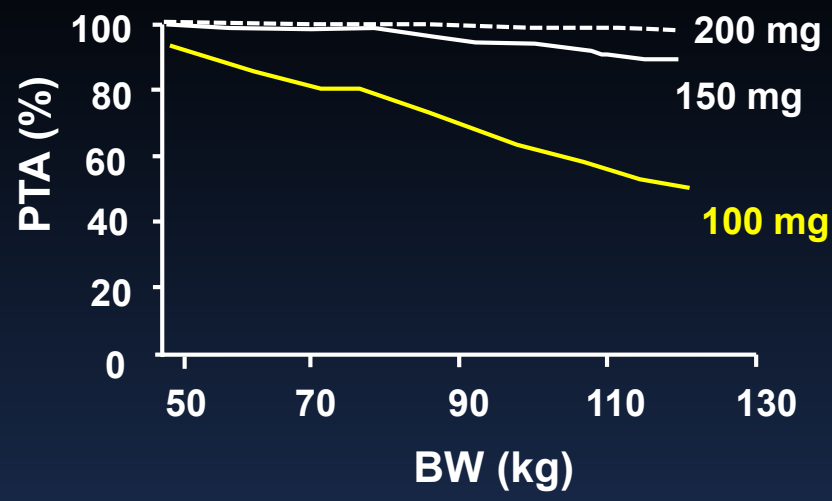
A PK/PD autopsy of the EMPIRICUS trial

PTA* was ≥ 90% in *Candida albicans* and *Candida glabrata* infections, except when the MIC was ≥0.015 mg/L

***C. albicans* MIC=0.016 mg/L; SOFA < 10**



***C. albicans* MIC=0.016 mg/L; SOFA ≥ 10 (25% decrease in clearance)**



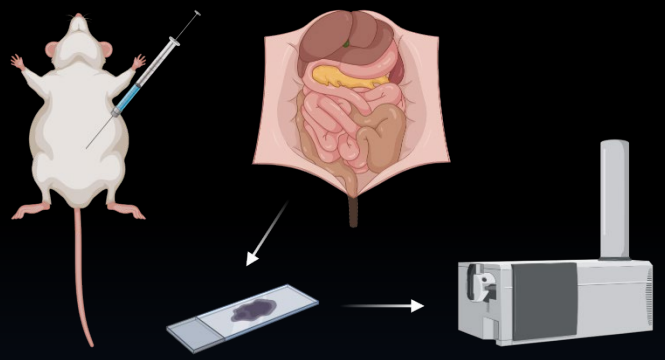
Median patient weight: 84.5 kg (48-141)

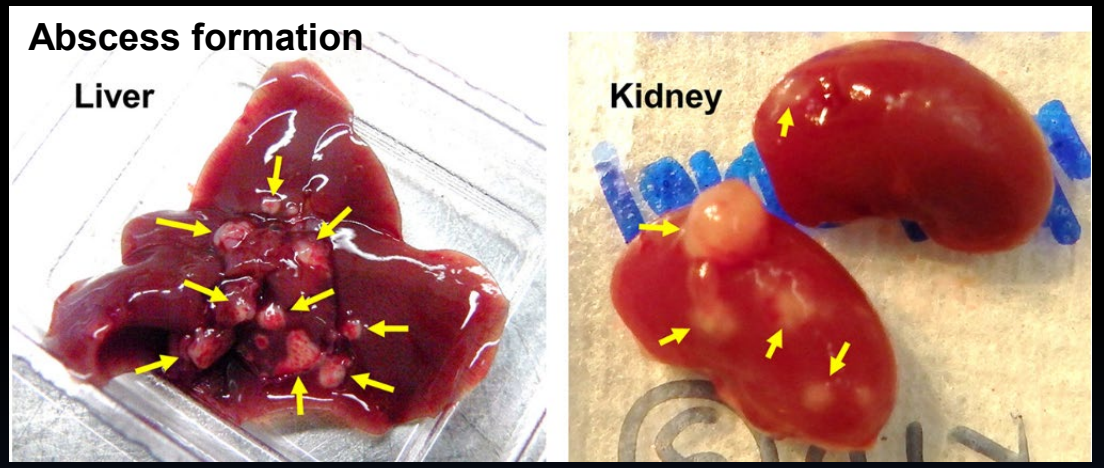
Jullien V, et al. *J Antimicrob Chemother* 2017;72(1):181–9.

* Total micafungin AUC/MIC > 5000

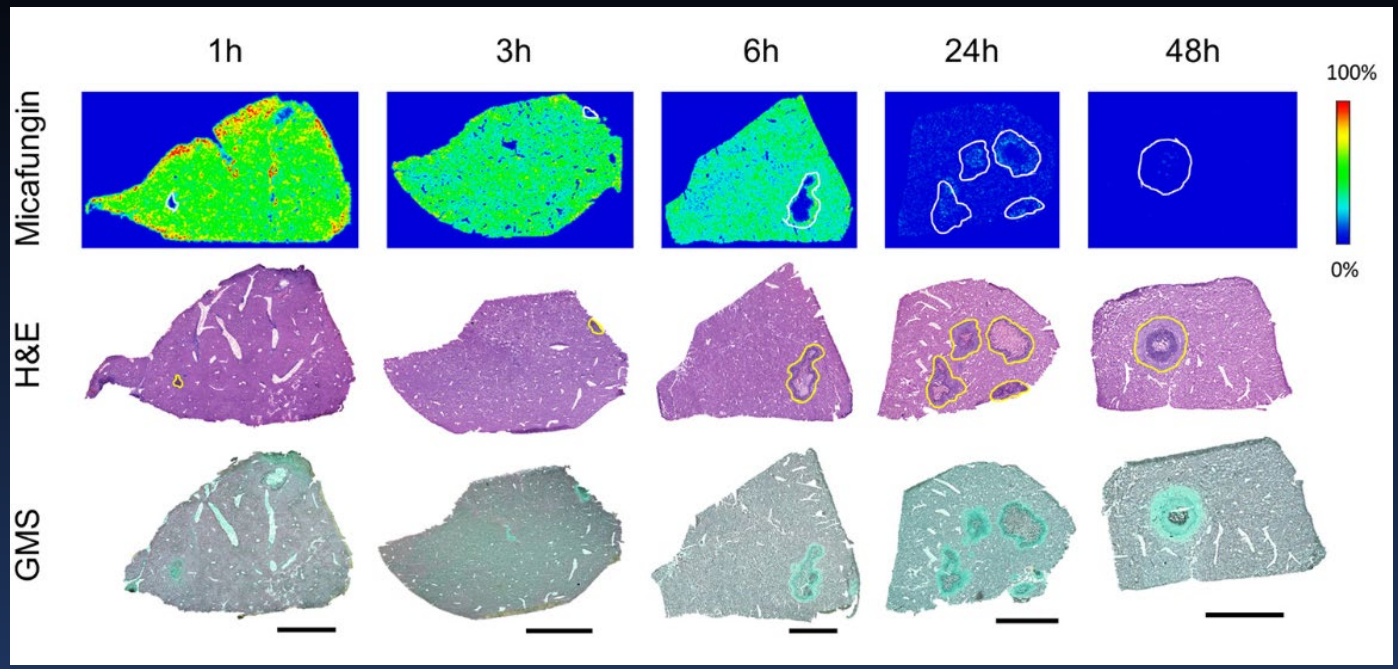
Echinocandin drug penetration at the site of infection
Intraabdominal abscess model

IP infection model: 1x10^7 *C. albicans* with sterile stool





Matrix-assisted desorption ionization mass spectrometry imaging technology

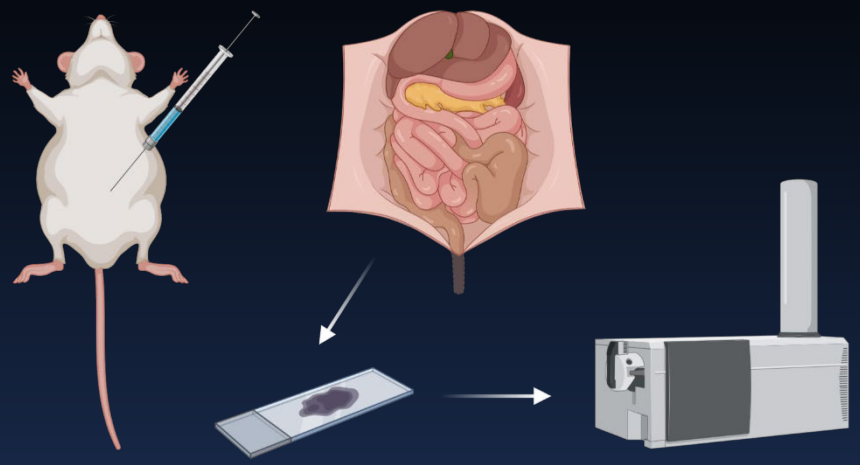


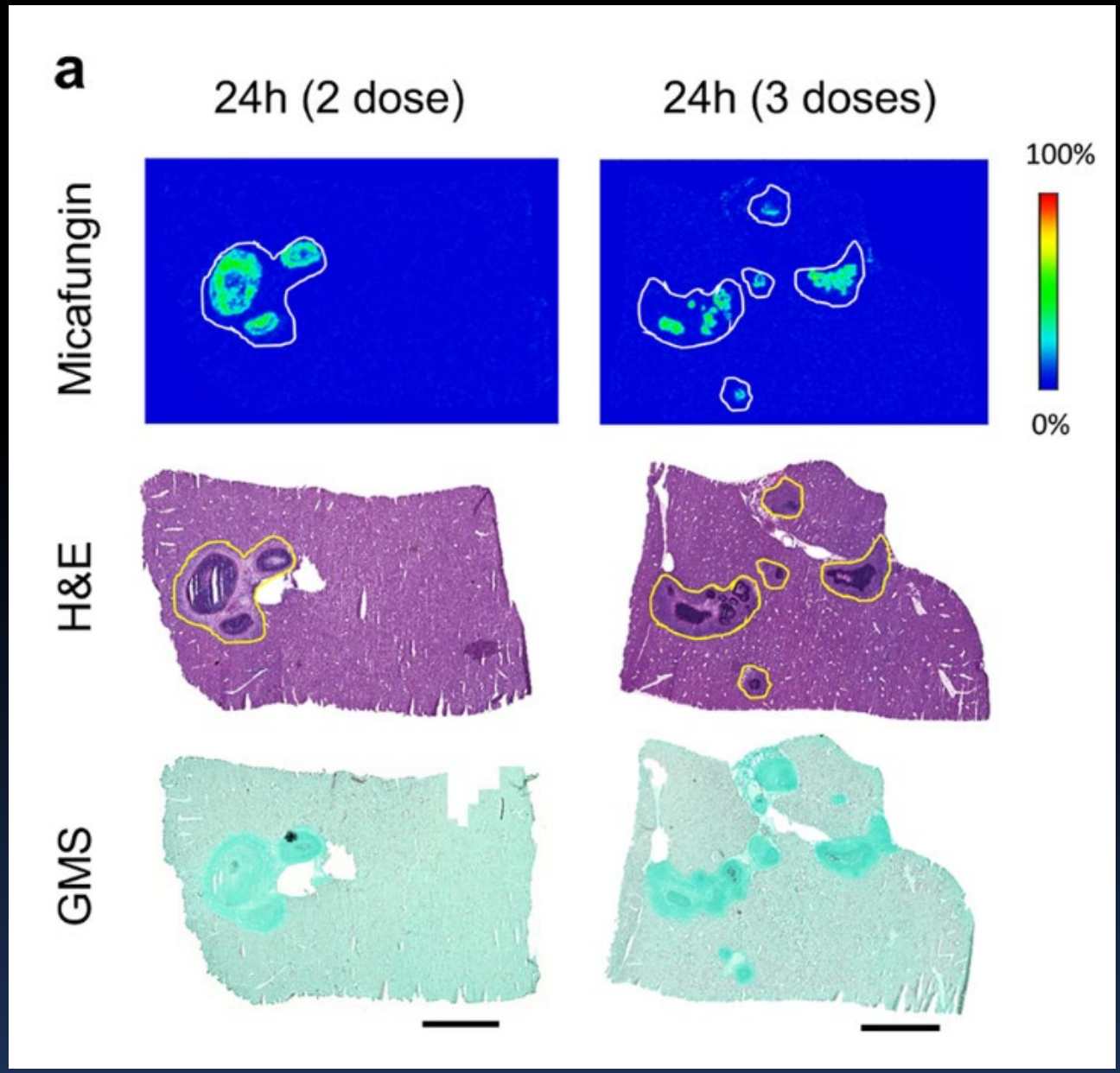
Liver lesions after single dose experiment

Zhao Y et al. Antimicrob Agents Chemother 2017;61(10).

Echinocandin drug penetration at the site of infection

Intraabdominal abscess model multiple micafungin doses



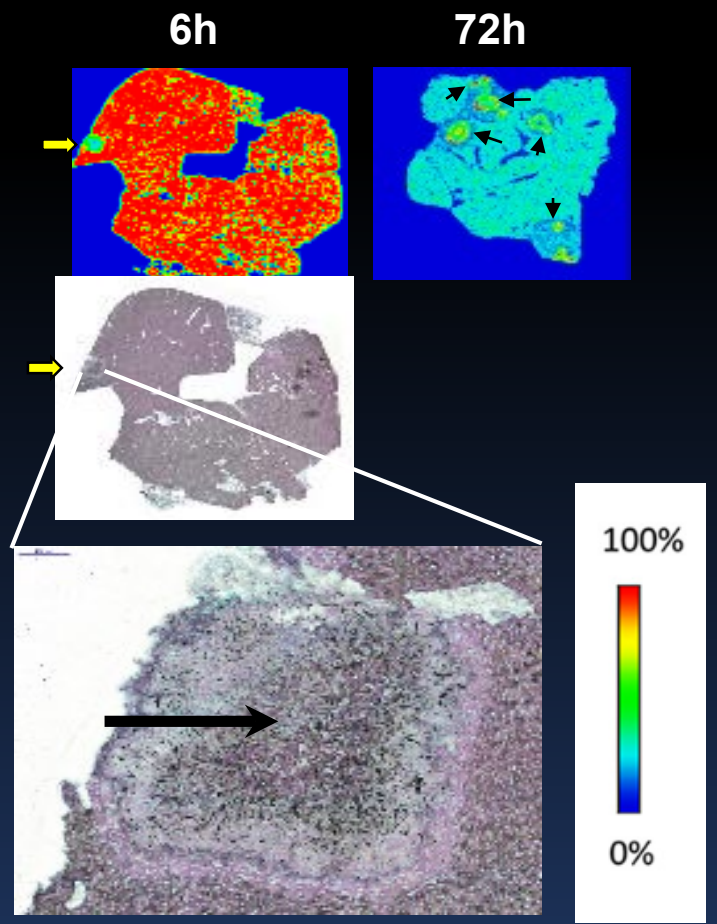


Liver lesions after 2-3 micafungin doses

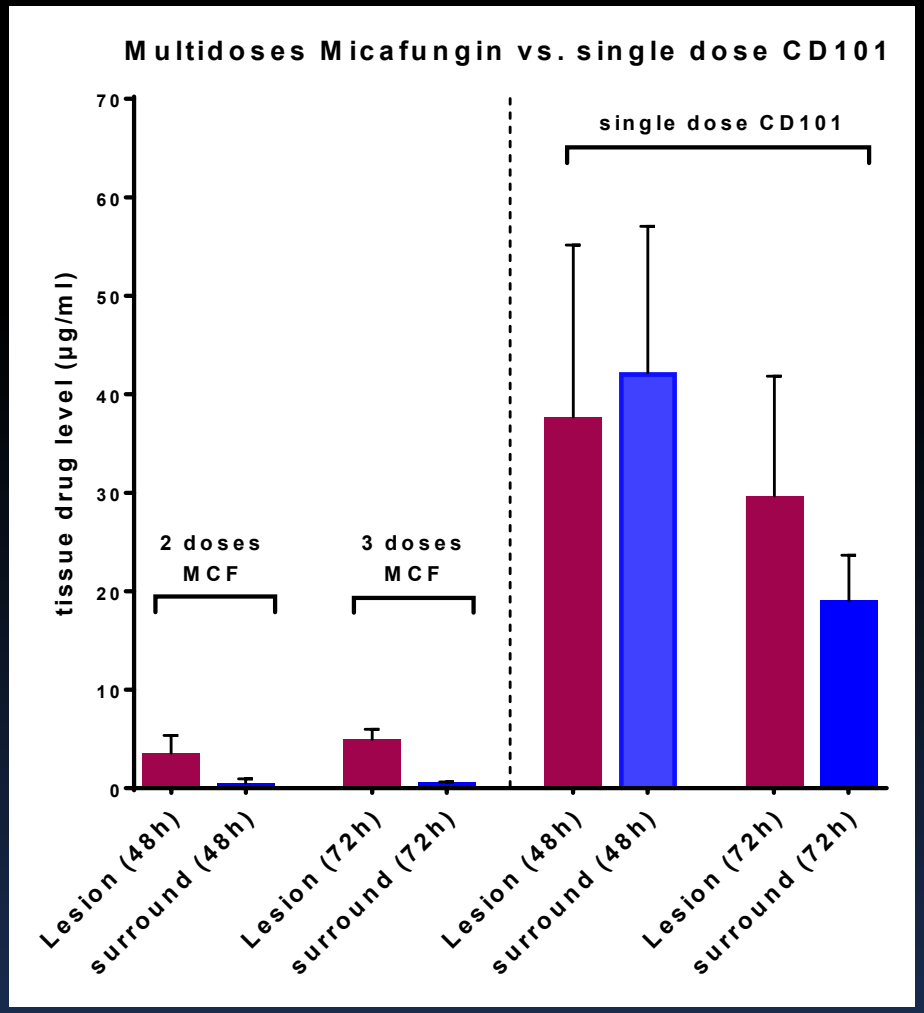
Zhao Y et al. *Antimicrob Agents Chemother* 2017;61(10).

Rezafungin penetration at the site of infection

Drug distribution in liver after single dose CD101 at 20 mg/kg determined by MALDI MS Imaging

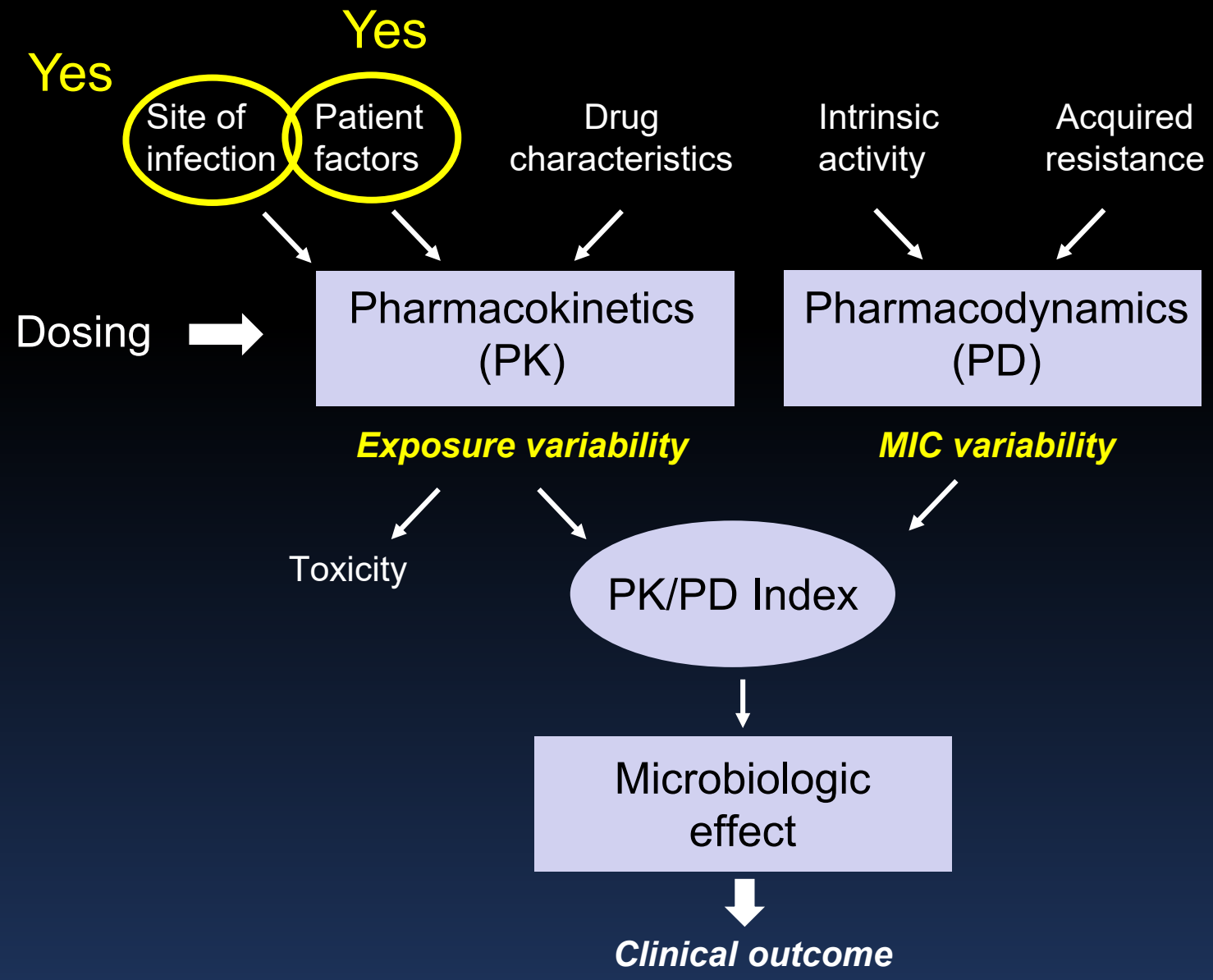


Fungi location stained by GMS



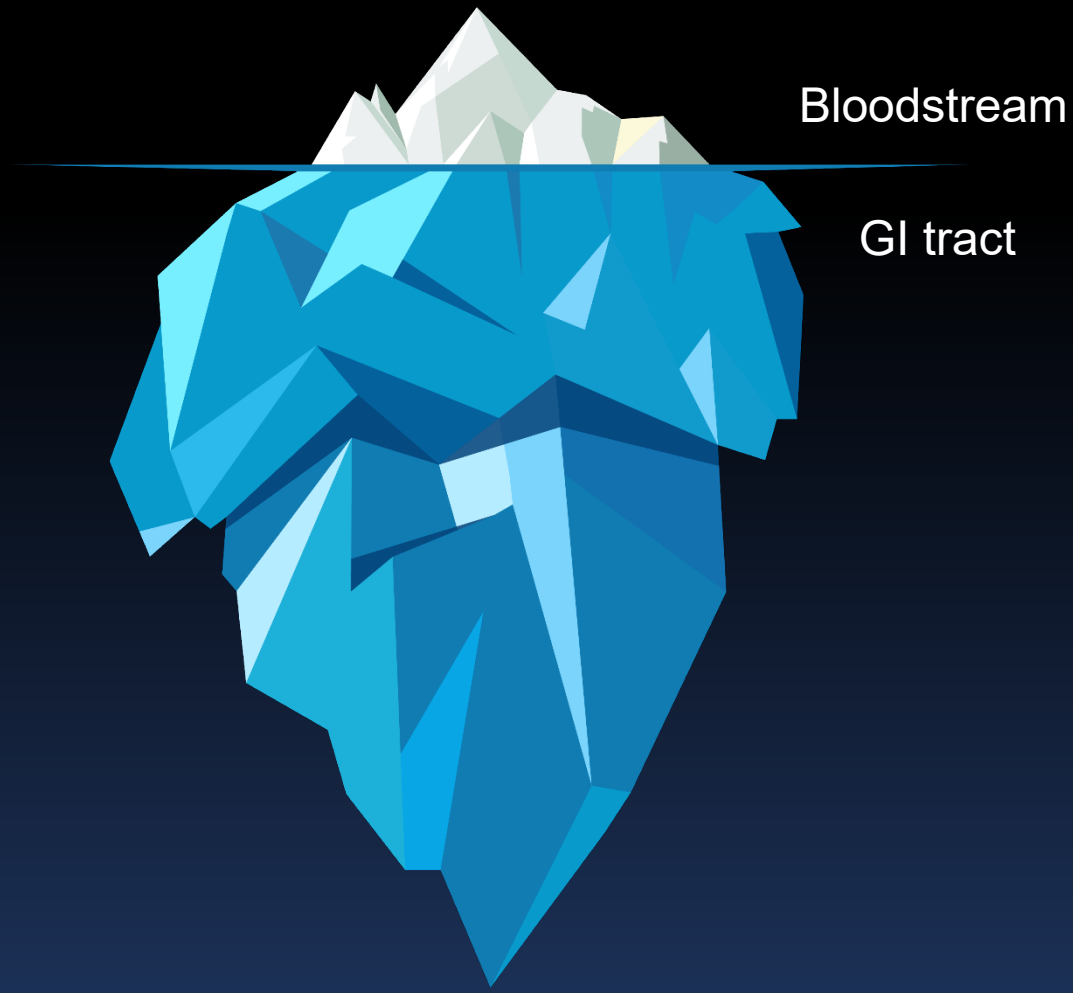
Zhao, Perlin et al, AAC July 2017

Time to rethink dosing?

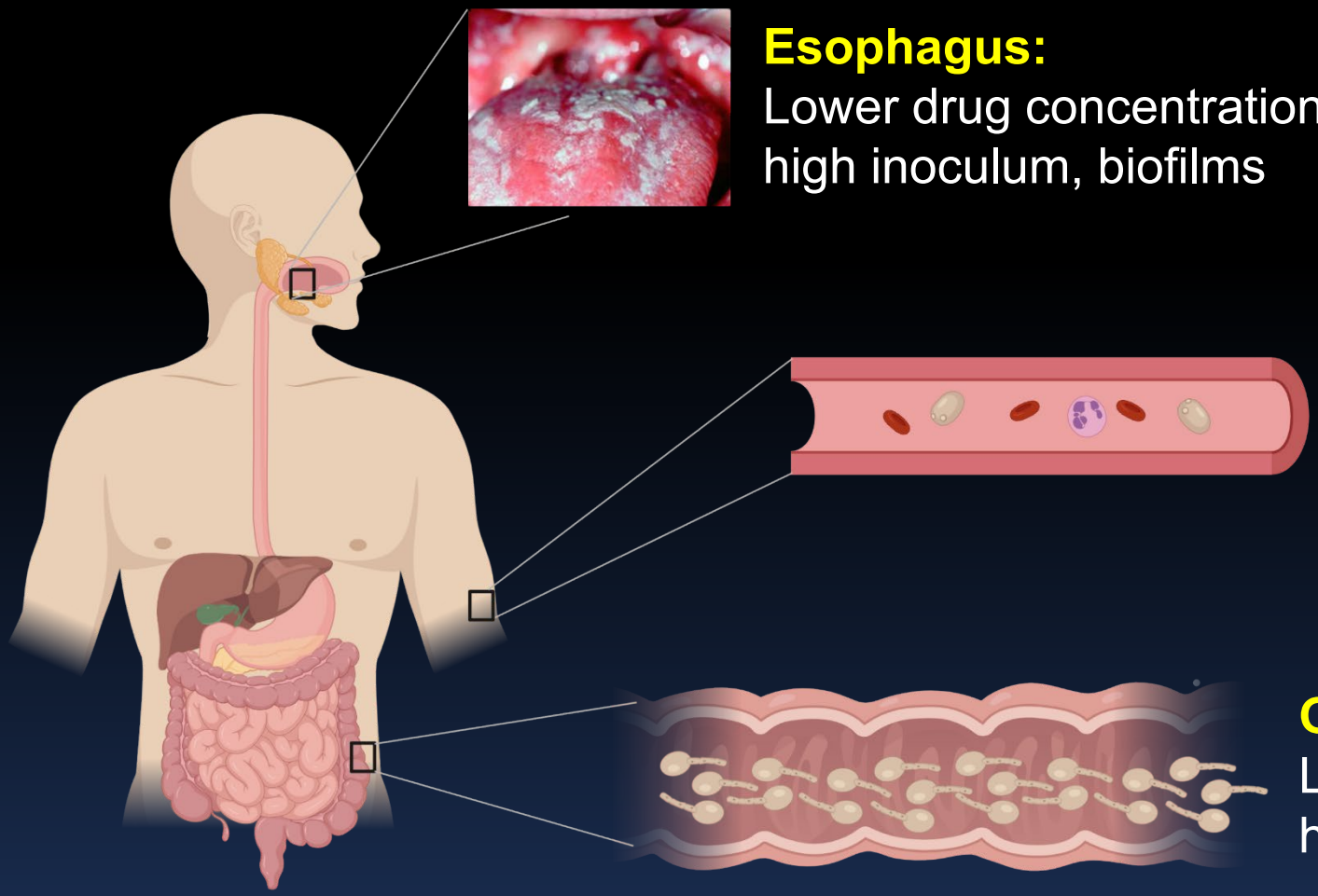


Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792

Where do we find echinocandin resistance?



Where do we look for echinocandin resistance?



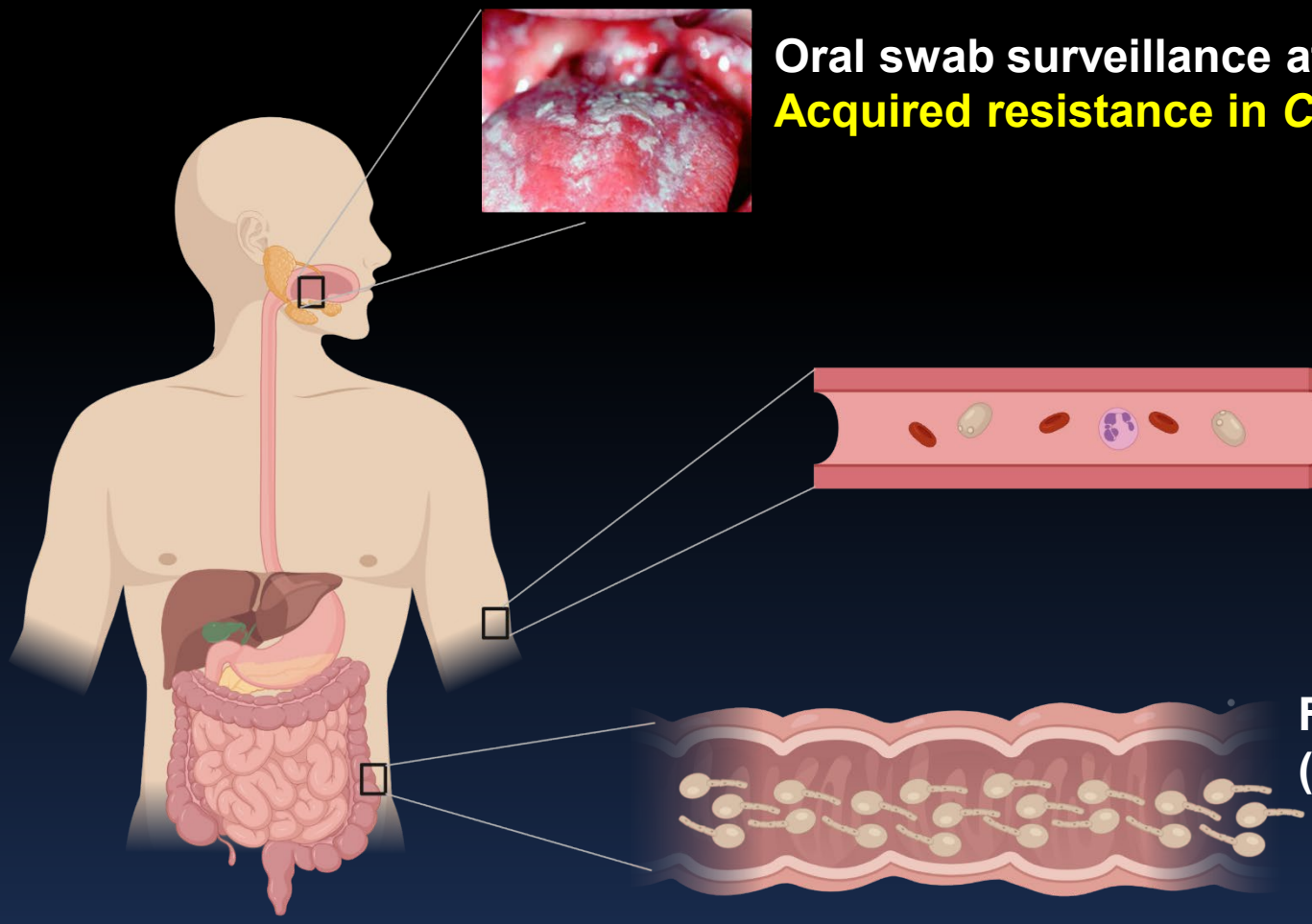
Esophagus:
Lower drug concentrations,
high inoculum, biofilms

Bloodstream:
High drug concentrations,
low inoculum

Gut:
Low drug concentrations,
high inoculum, biofilms?

Healey et al. *Antimicrob Agents Chemother* 2017;61(12).

Where do we look for echinocandin resistance?



Oral swab surveillance after ≥ 7 days of echinocandins[2]
Acquired resistance in *C. glabrata* 21.6%

SENTRY 2006-2016, single center studies[1,2]
Echinocandin resistance rate: 3-12%

FKS mutant *Candida* isolates detected in 24% (6/25) patients exposed to echinocandins[4,5]
- ***C. glabrata* 29%**
- ***C. albicans* 14%**

[1]Pfaller M et al. *Open Forum Infect Dis* 2019;6 (Supplement_1):S79–94.
[2]Alexander et al. Clin Infect Dis 56:1724-32.
[3]Jensen RH, Johansen HK, Soes LM, et al. *Antimicrob Agents Chemother.* 2016;60(3):1500-1508.
[4]Shields RK, Nguyen MH, Press EG, Clancy CJ. *Antimicrob. Agents Chemother.* 2014;58(12):7601-7605.
[5]Prigent et. al. *Antimicrobial Agents Chemother.* 2016; Nov 15, 2016.

The GI tract as the major source of echinocandin resistance

1.5x10^{8}CFU *C. glabrata* → PIP/Tazo → Dexamethasome immunosuppression

Caspofungin 5 mg/kg
(humanized dose)

Caspofungin 20 mg/kg
(4x humanized dose)

↔ CFU in stool vs. control
(FKS mutants in 10% mice)

10^7-10^8 CFU/stool

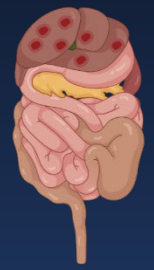
Transient ↓ then ↑
(100% mice with FKS mutants)

No positive BC
during caspofungin treatment

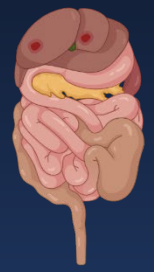
Controls 50%

No positive BC
during caspofungin treatment

Organ dissemination in 60% of mice
(No FKS mutants)
Mean small intestine-3.8 µg/mL
Mean large intestine-9.1 µg/mL



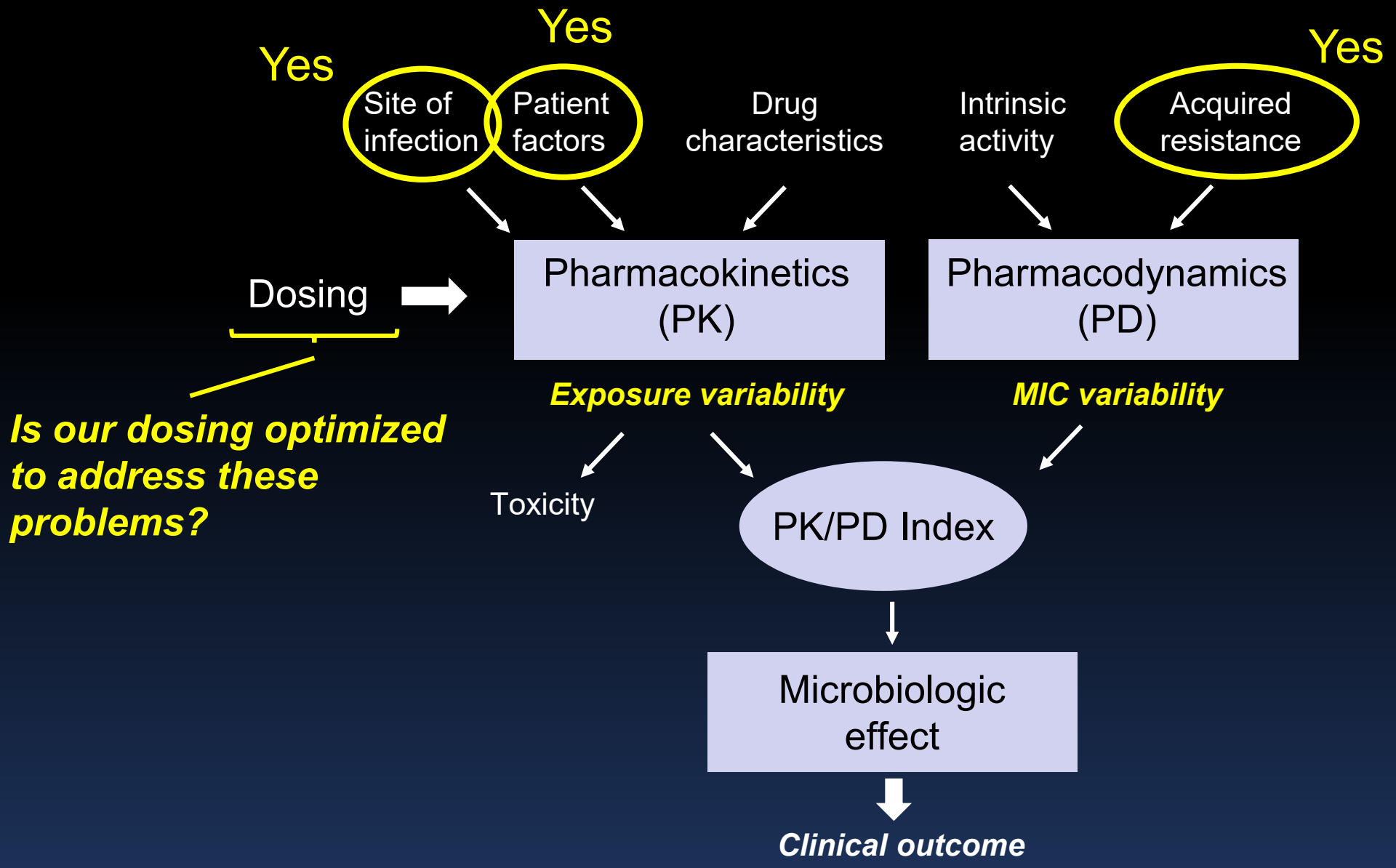
Controls 70%
(No FKS mutants)



Organ dissemination in 30% of mice
(ALL FKS mutants)
Mean small intestine-36.2 µg/mL
Mean large intestine-22.2 µg/mL

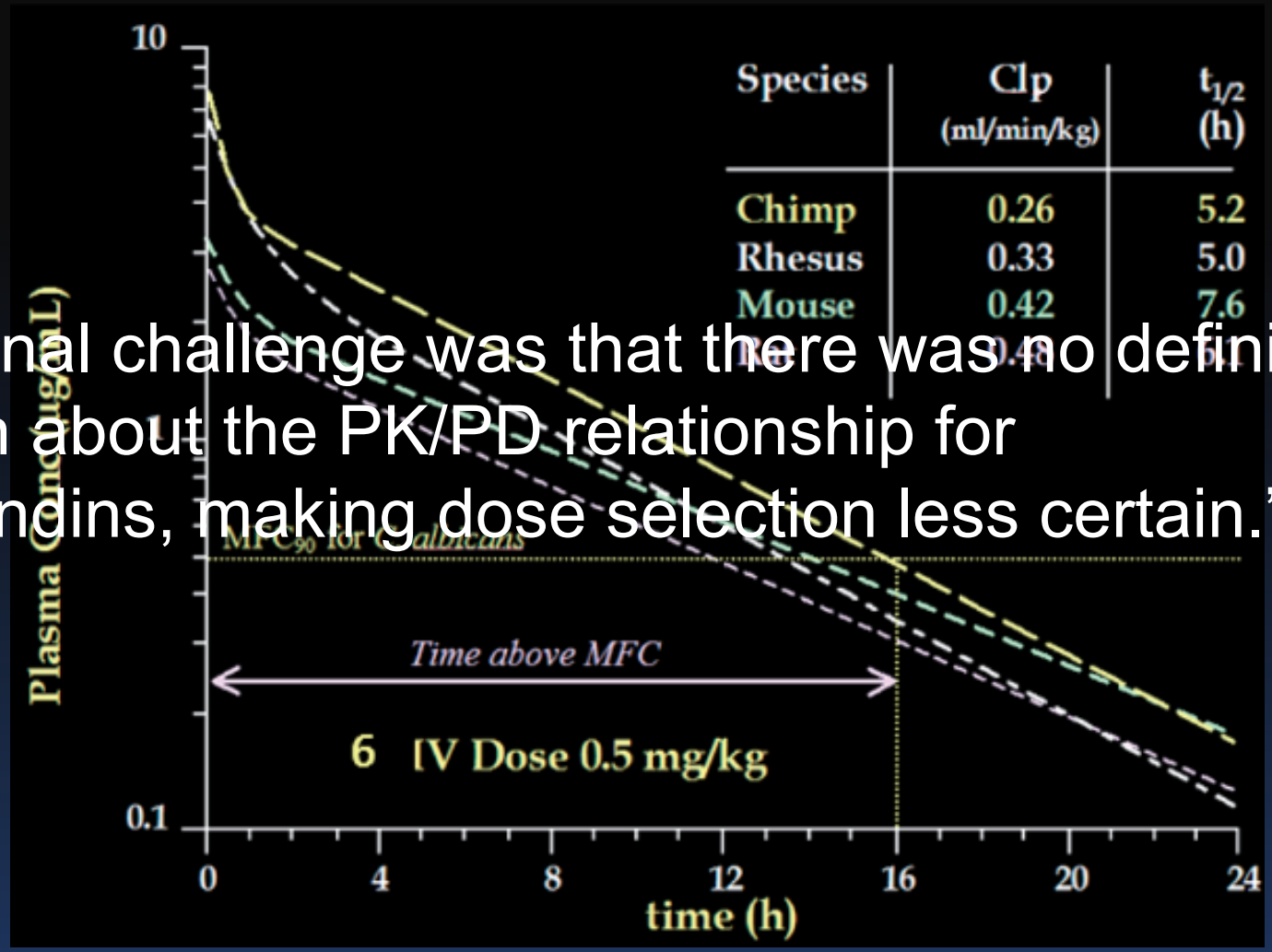
Healey et al. *Antimicrob Agents Chemother* 2017;61(12).

Time to rethink dosing?



Adapted from: Theuretzbacher U. Clin Infect Dis 2012;54:1785-1792

Currently-recommended echinocandin dosing schemes were not developed from PK/PD principles



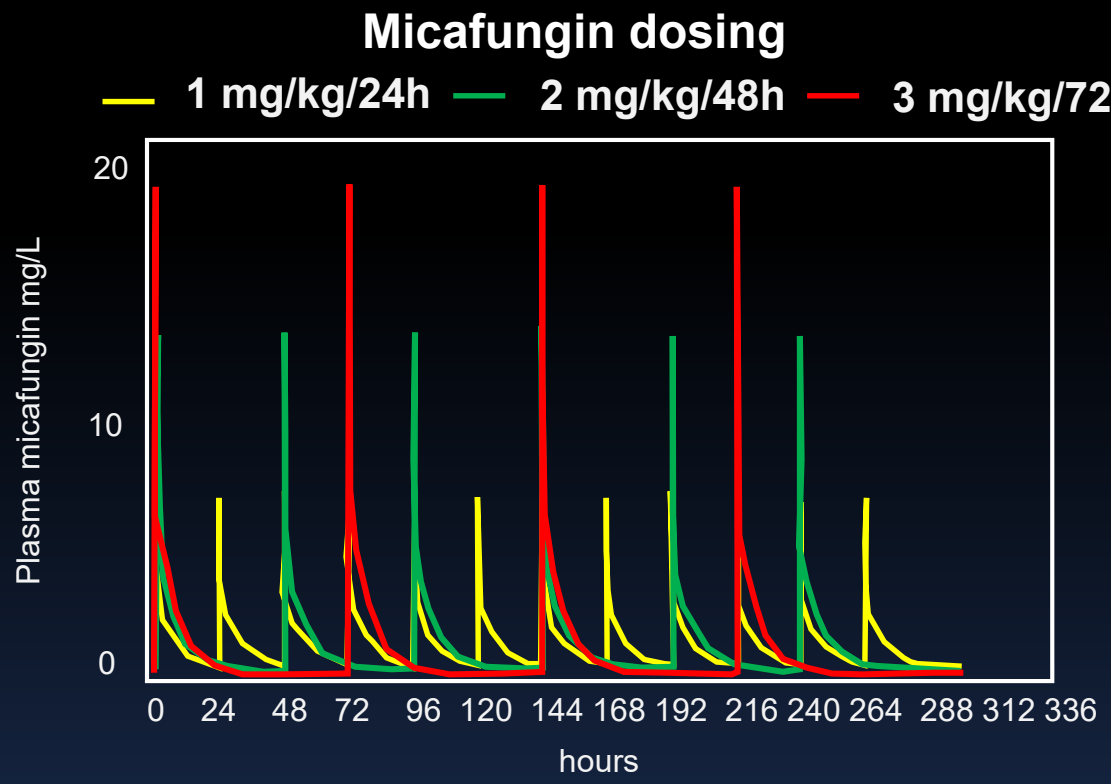
"An additional challenge was that there was no definitive information about the PK/PD relationship for pneumocandins, making dose selection less certain."

Balkovec JM. *Nat Prod Rep* 2014;**31**(1):15–34.

What have we learned about echinocandin PK/PD from animal models?

Rabbit model of invasive candidiasas

Micafungin Cmax/MIC and AUC/MIC correate with efficacy

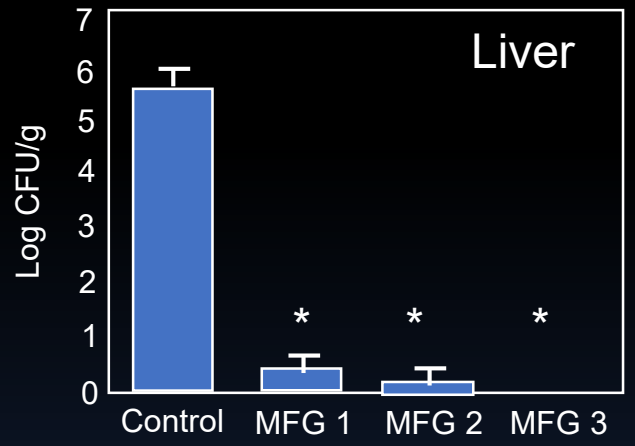


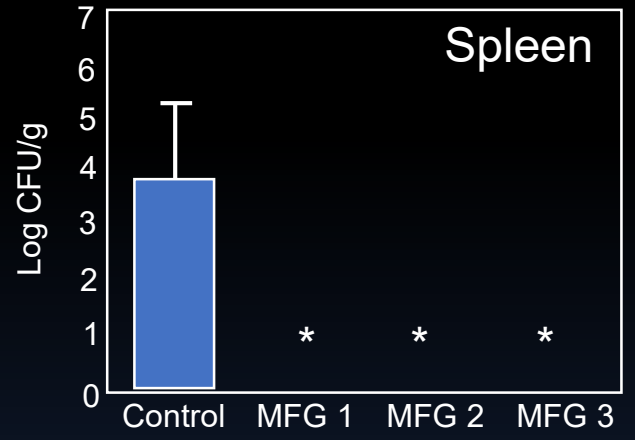
Mean AUC $_{0\text{-}312}$ similar for all three regimens

Petraitiene R, Petraitis V, Hope WW, Walsh TJ. Clin Infect Dis 2015;61:S643–51.

Larger infrequent doses maximize echinocandin antifungal activity

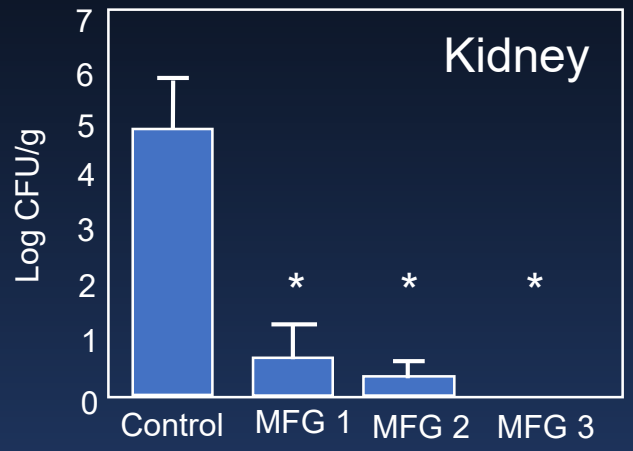
Neutropenic rabbit model of invasive candidiasis





C. albicans MIC 0.125 mg/L (CLSI)

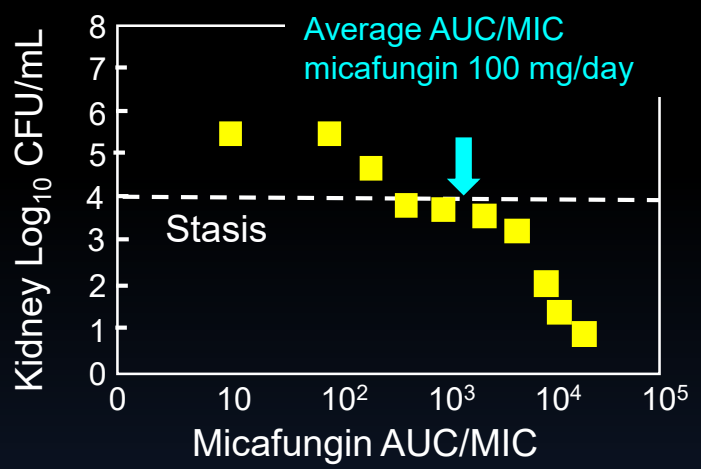
When AUC/MIC is equivalent, dosing regimens that acheive a higher Cmax/MIC exhibit improved killing



* P< 0.05 vs. control

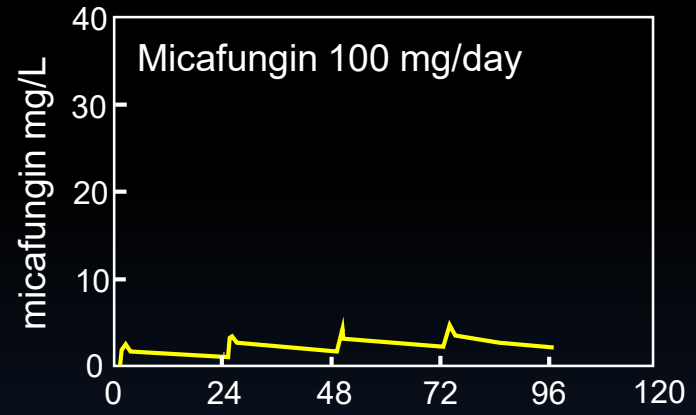
Petraitiene R, Petraitis V, Hope WW, Walsh TJ. Clin Infect Dis 2015;61:S643–51.

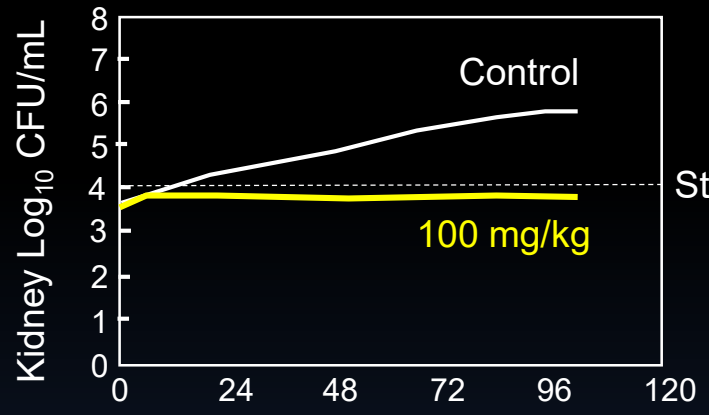
Echinocandins are not fungicidal against *C. glabrata* in neutropenic models at currently recommended doses

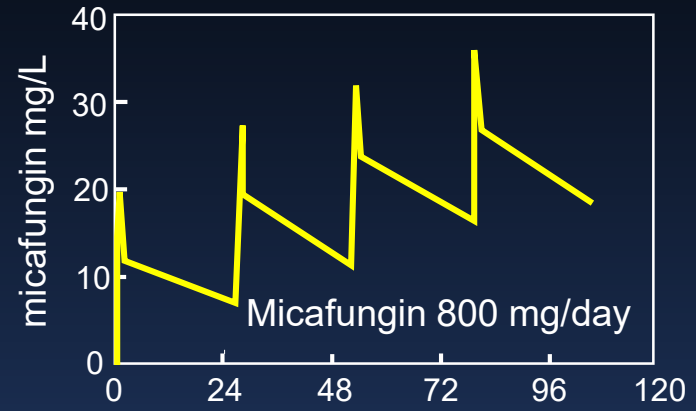


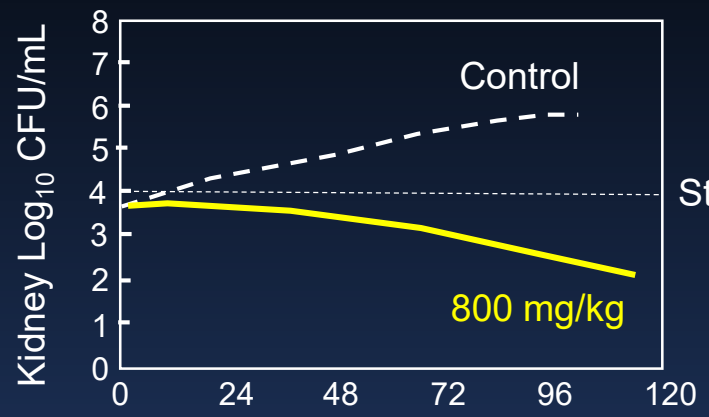
Humanized dosing, neutropenic murine model of *C. glabrata* fungemia (MIC 0.06 mg/L)

Model predictions





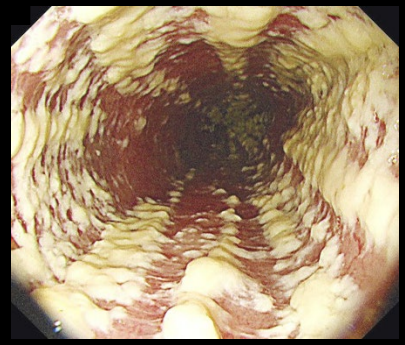




Time (hrs)

Howard S et al. *Antimicrob Agents Chemother* 2011;55(10):4880–7.

Clinical pharmacodynamic index identification for micafungin in esophageal candidiasis: Dosing strategy optimization



% of patients with indicated result

	Mycological response at EOT?*			Clinical relapse at 2 weeks?**		
Micafungin dosing regimen	Success (n=260)	Failure (n=56)	Total (n=316)	Yes (n=29)	No (n=278)	Total (n=307)
150 mg QD	145 (78.8)	39 (21.2)	184	22 (12.2)	159 (87.9)	181
300 mg QOD	115 (87.1)	17 (12.9)	132	7 (5.6)	119 (94.4)	126

P=0.056

P=0.051

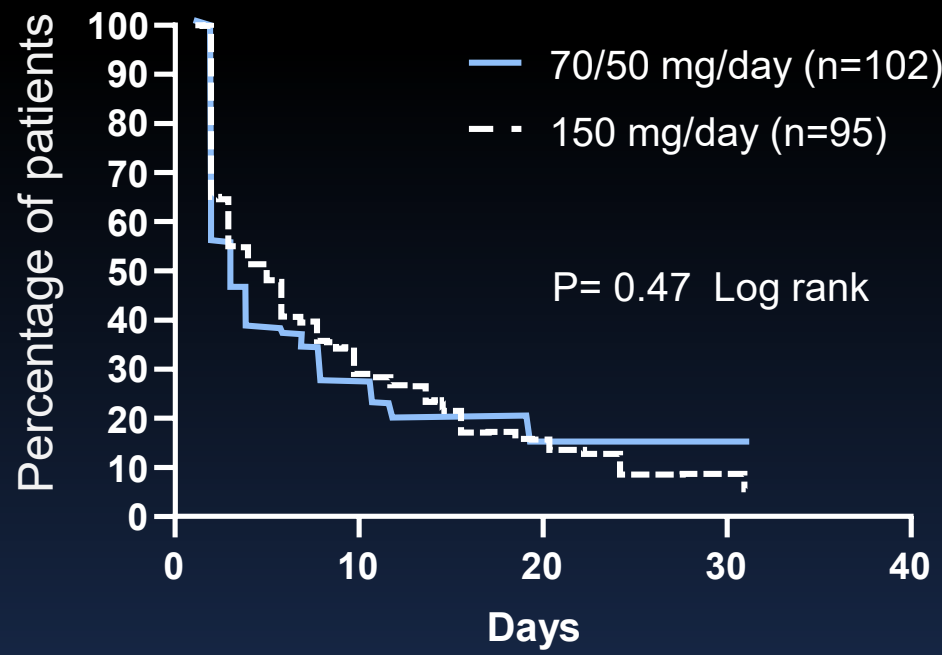
The dosing regimen that acheives a higher Cmax/MIC was assocaited with improved clinical success and lower relapse rates

de Wet et al. Aliment. Pharmacol. Ther. 21:899–907.
Andes DR, et al. *Antimicrob Agents Chemother* 2013;57(11):5714–6.

Caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

Conclusion: Both dosing regimens were equivalent and safe

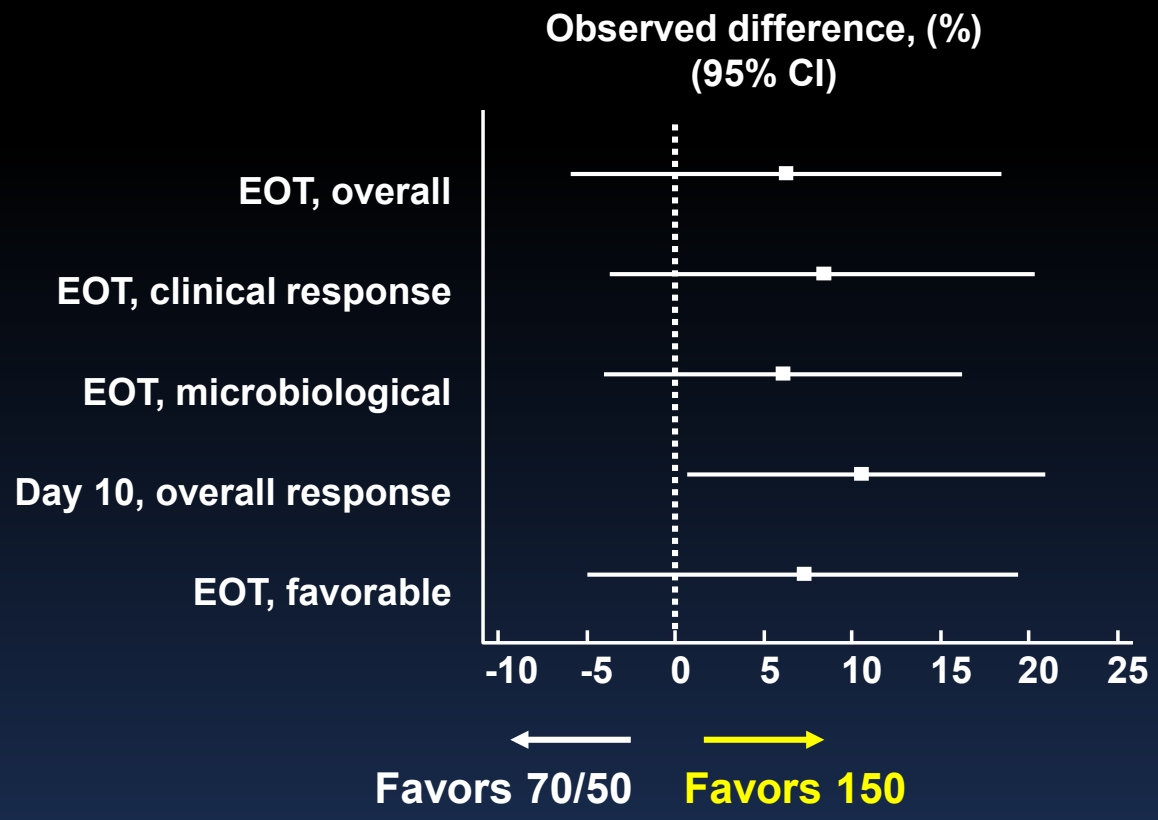
Time to clearance of blood cultures

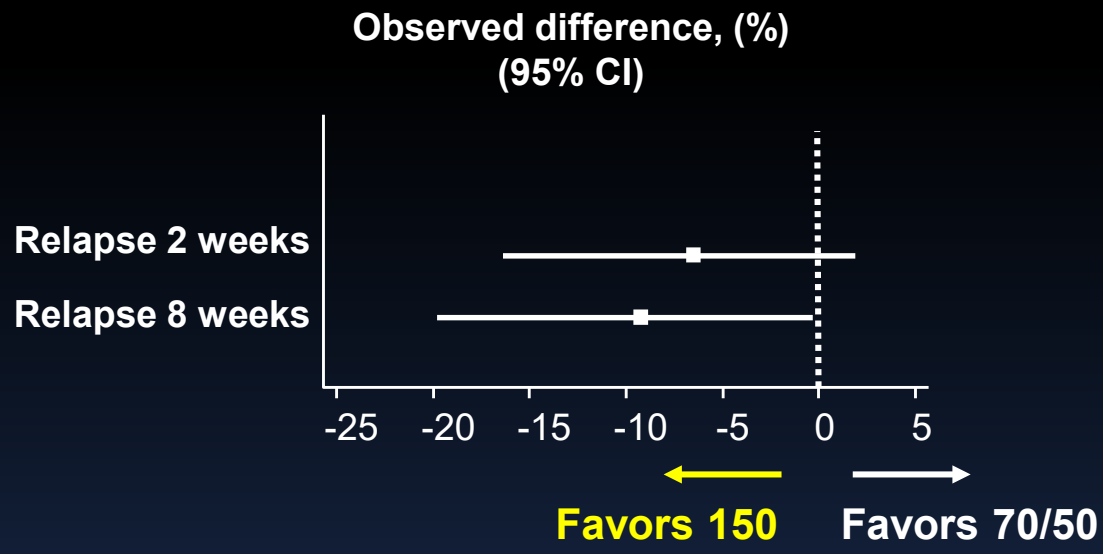


Design hypothesis: Higher caspofungin dose is safe and non-inferior Δ <15%.
Study was not powered to evaluate superiority of caspofungin higher dose

Betts RF et al. *Clin Infect Dis* 2009;48(12):1676–84.
Pea F, Lewis RE. *J Antimicrob Chemother* 2018;73(suppl_1):i33–43.

Multicenter double-blind trial of caspofungin 70/50 vs. 150 mg/day for adult patients with invasive candidiasis

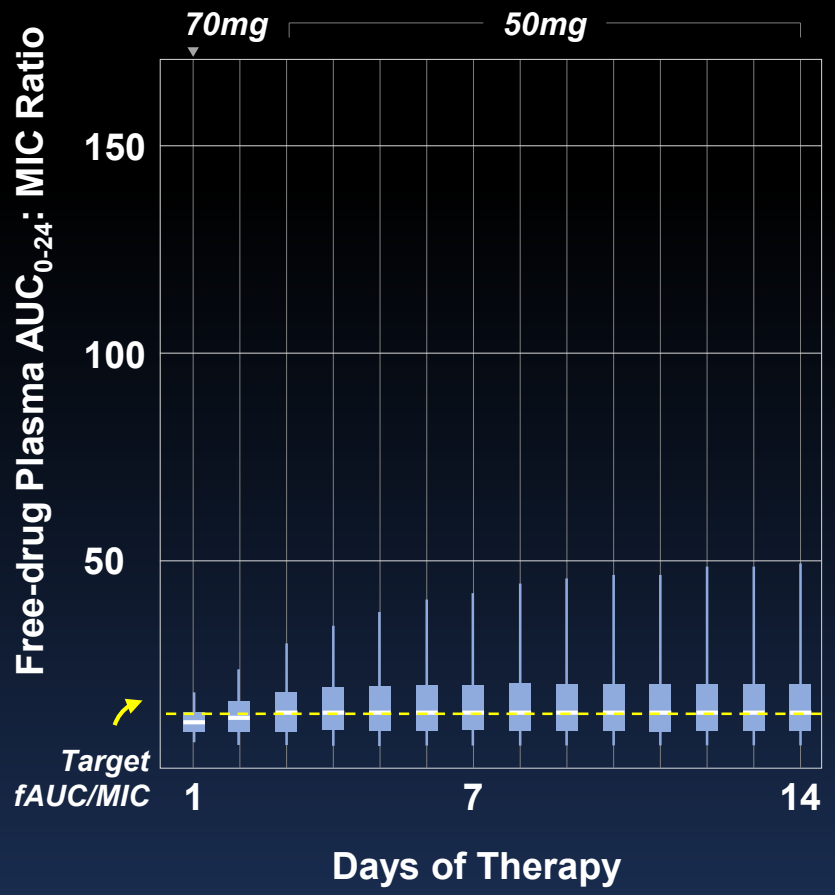




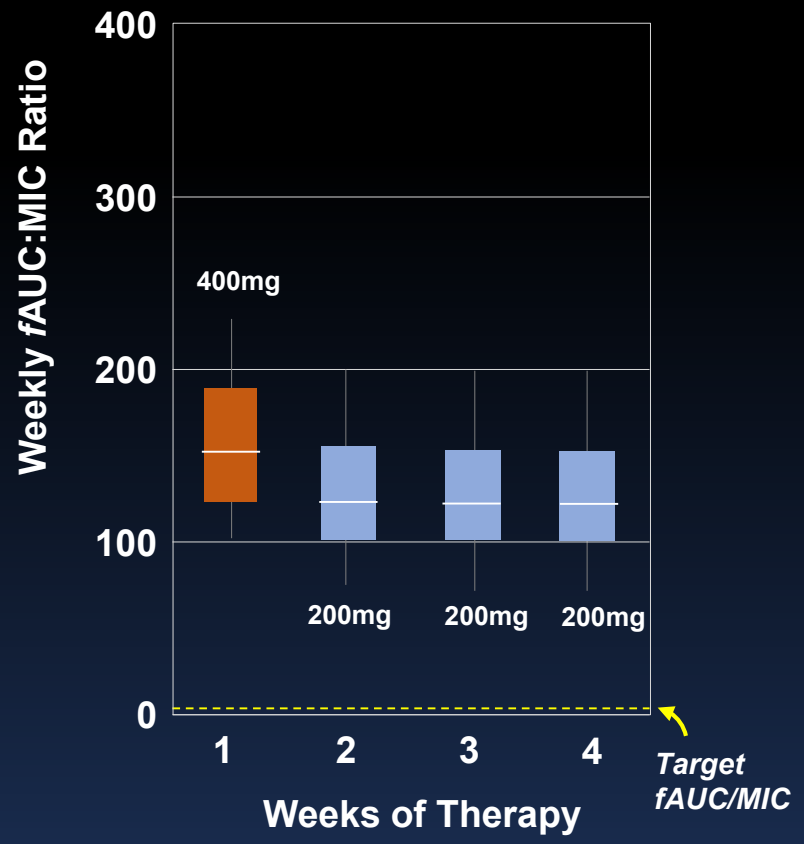
Betts RF et al. *Clin Infect Dis* 2009;48(12):1676–84.
Pea F, Lewis RE. *J Antimicrob Chemother* 2018;73(suppl_1):i33–43.

Comparison of caspofungin vs. rezafungin PK/PD target attainment (C. glabrata MIC 0.25 mg/L)

Caspofungin (14 daily doses)



Rezafungin (4 weekly doses)



MIC=0.25 for caspofungin. MIC=0.12 for CD101

Bader et al. Emerging Candida glabrata Resistance and Echinocandin Dosing: A Call to Arms! IDWeek 2016

Bader et al. Overcoming the Resistance Hurdle: PK-PD Target Attainment Analyses of Rezafungin (CD101) for Candida albicans and Candida glabrata. Submitted AAC 2018; revised with Phase 2 results.

Novel echinocandin dosing approaches during micafungin prophylaxis

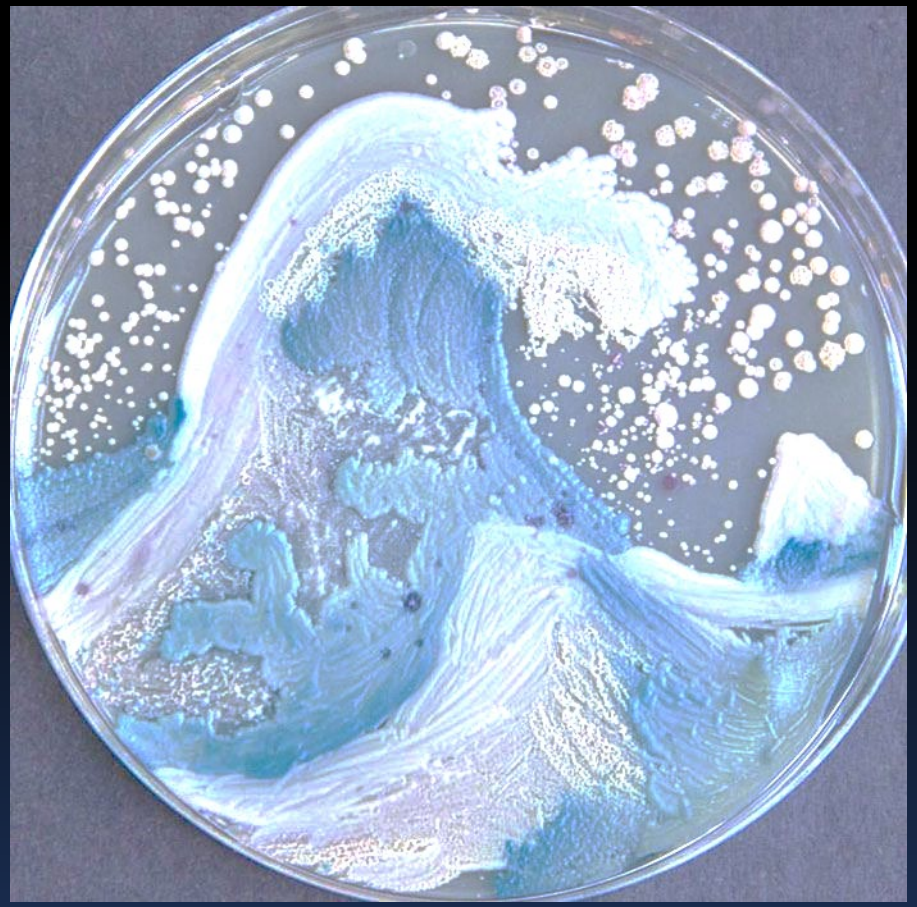
- Intermittent administration of higher-dose micafungin (≥ 5 doses of 300 mg 2-3 times weekly) was well tolerated in patients with acute leukemia and allogeneic SCT recipients[1]
- Intermittent higher-dose micafungin was safe in children[2,3]
- Equivalent weekly AUCs have been confirmed for 300 mg twice weekly dosing of micafungin (3hr infusion) → possible 700 mg once weekly? [4]

[1] Neofytos et al. Clin Infect Dis 2015;61:S652-61.
[2] Mehta et al. Biol Blood Marrow Transplant 2010; 16:1458-62.
[3] Bochennek et al. J Antimicrob Chemother 2015;70:1527-30.
[4] Muilwijk EJ et al. J Antimicrob Chemolther 2018;73:3095-3101

Summary

- Preclinical and clinical evidence suggest current echinocandin dosing approaches need revision for some patient groups
- Acquired echinocandin resistance can be detected at much higher frequency in the GI tract than bloodstream, and likely serves as a reservoir for future breakthrough infection
- Evidence that PK/PD optimization of echinocandin dosing might improve clinical efficacy, reduce relapse, and enhance dosing convenience

Thank you!



"The Great Wave of *Candida*"
Cristina Marcos

The Great Wave off Kanagawa
Katsushika Hokusai