Antifungal PK/PD ‘Made Simple’

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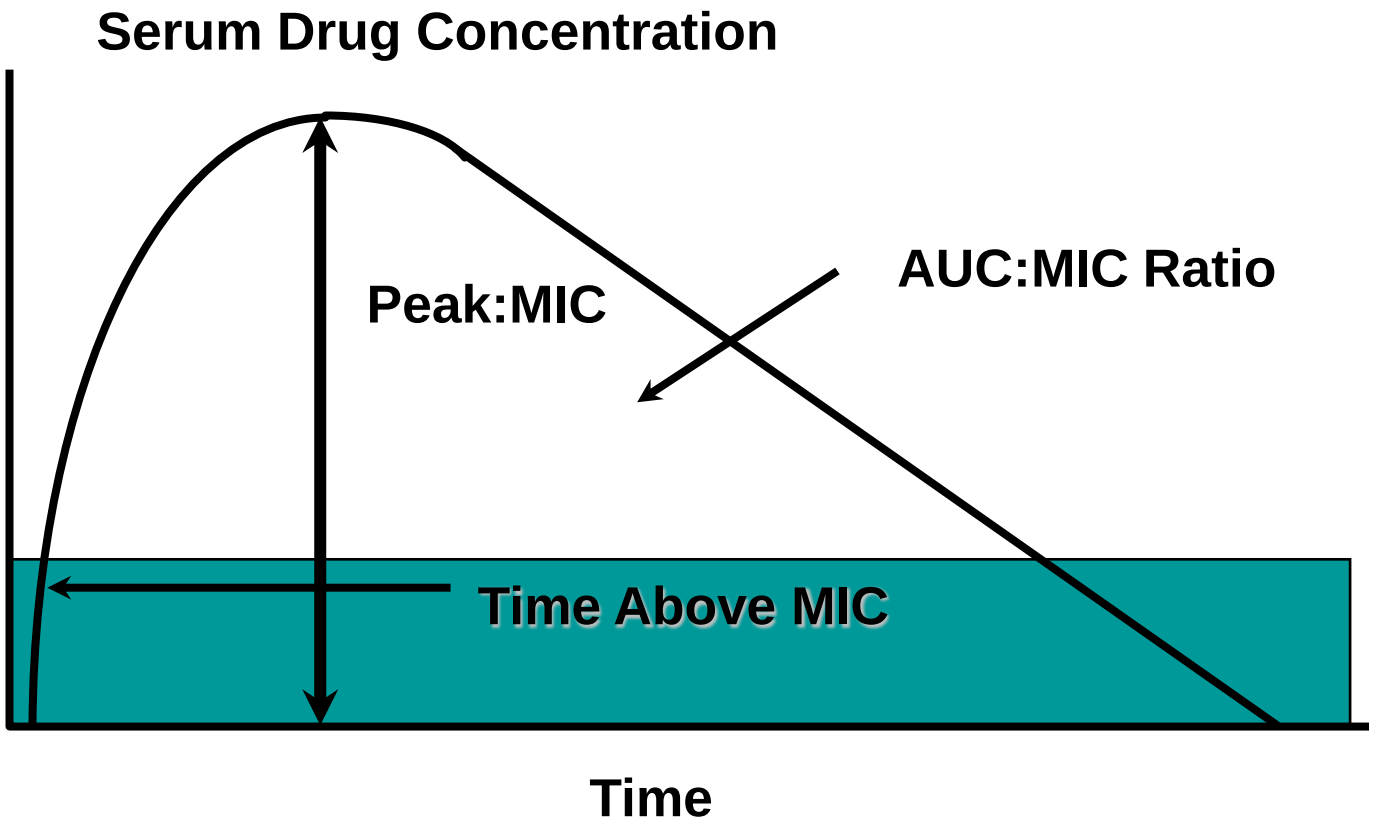
PK/PD Concept



Hypothesis and Concept

- There is an optimal drug exposure (concentration and time of exposure) for antifungal treatment efficacy
- Examination of relationship among antifungal pharmacokinetics, a measure of drug potency (MIC), and effect will define the optimal regimen and organism susceptibility limit.

Interest in PK/PD

- Occurs when there is narrow difference between MICs and obtainable drug concentrations

  - Early days of penicillin in 1940s (low doses used)

  - Appearance of *Pseudomonas* infections in 1960s and 1970s (high MICs)

  - Appearance of resistant *S. pneumoniae* and other resistance bacteria in 1990s (more recently ESBLs)

Antifungal PK/PD Interest

Historical

- Pre-HAART HIV OPC 20-30% resistant *Candida* (Martin et al CID 1997;25:843)

Current

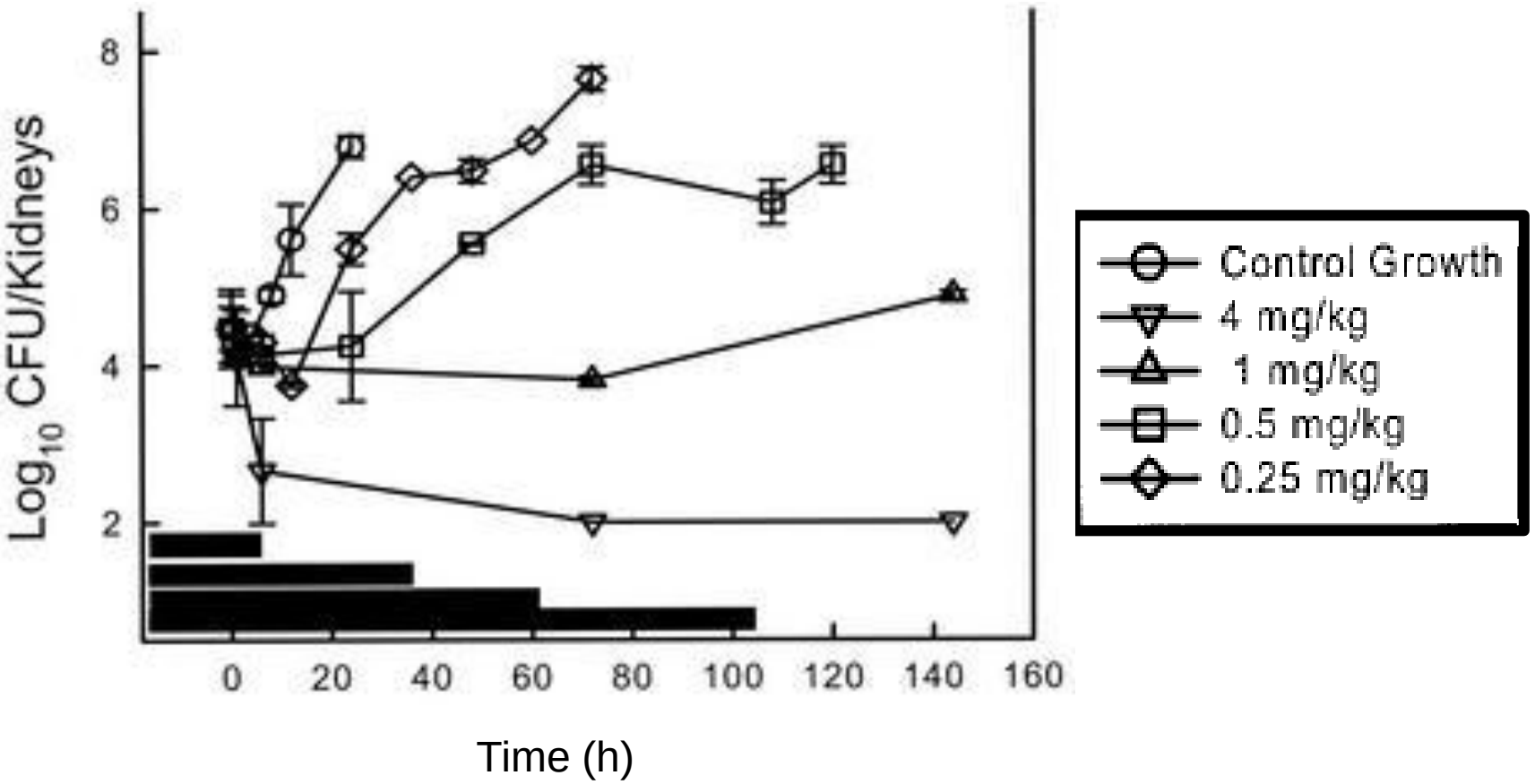
- MIC: Triazoles and *C. glabrata* (10-40%) (Arendrup et al JCM 2011;49:325, Pfaller et al JCM 2012;50:1199, Pfaller et al CMR 2006;19:435, Lockhart et al JCM 2011;49:2404)
- MIC: Triazoles and *Aspergillus* (0-20%) (Snelders et al PLoS Med 2008;11:e219)
- MIC: Echinocandins and *C. parapsilosis* (Andes et al CID 2012;54:1110)
- MIC: Echinocandins and *C. glabrata* (4-15%) (Pfeiffer et al JCM 2010;48:2373, Pfaller et al JCM 2012;50:1199)
- PK: Triazoles variability (Smith et al AAC 2006; 50:1570, Pascual et al CID 2008;46:201)

PK/PD Question 1

Predictive PD Parameter – What PK characteristic do I optimize?

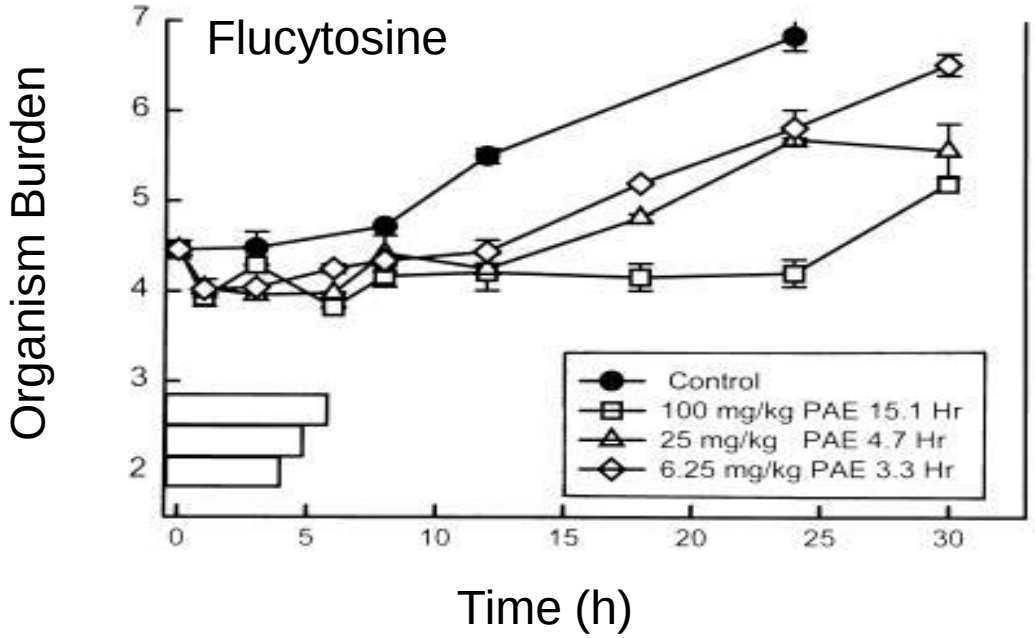
- What is the impact of concentration on rate, extent, and persistence of antimicrobial activity?

Echinocandin Concentration and Time



Andes AAC 2003;47:1187

Concentration and Time Characteristics



- Static vs Cidal
- AmB and Echinocandins concentration dependent
- Fluconazole and 5FC concentration independent

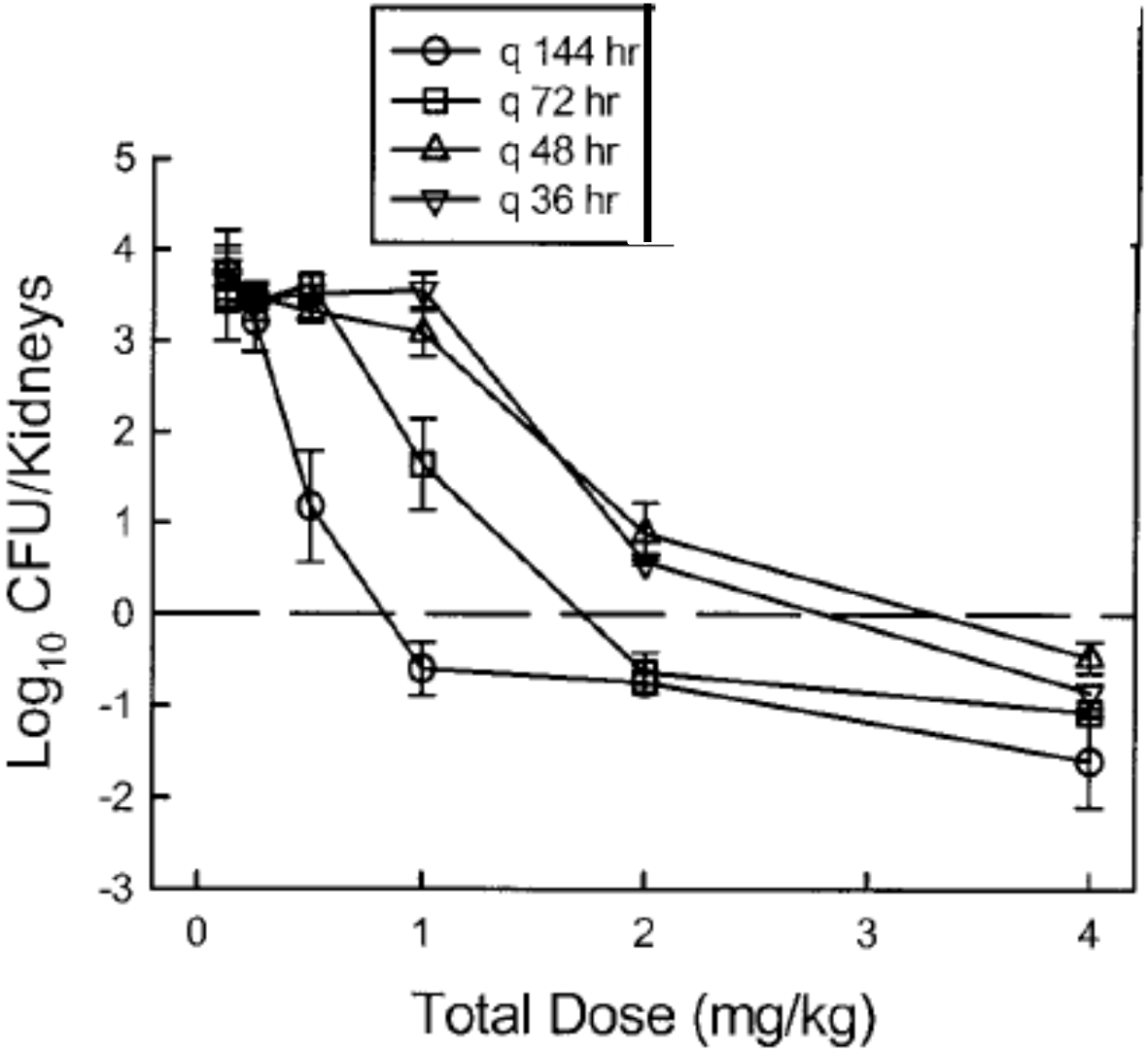
Klepser et al AAC 1999;41:1392
Ernst et al Diagn Microbiol Infect Dis 1999;33:75

PK/PD Question 2

Predictive PD Parameter –
What PK characteristic do I optimize?

- Dosing interval validation. What is the impact of the dose and dosing interval?

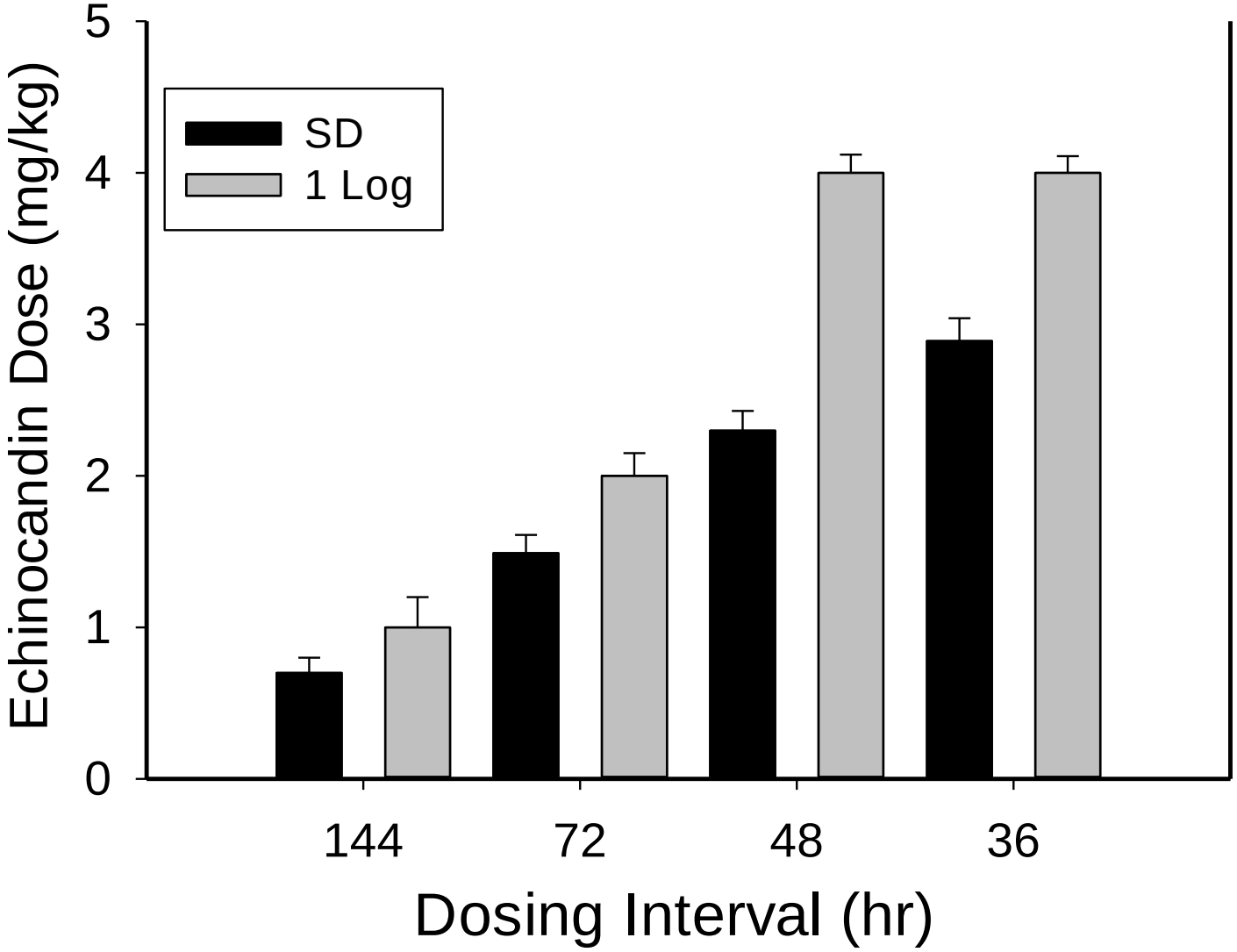
Echinocandin Dosing Interval and C. albicans



- Outcome better with large doses given less frequently

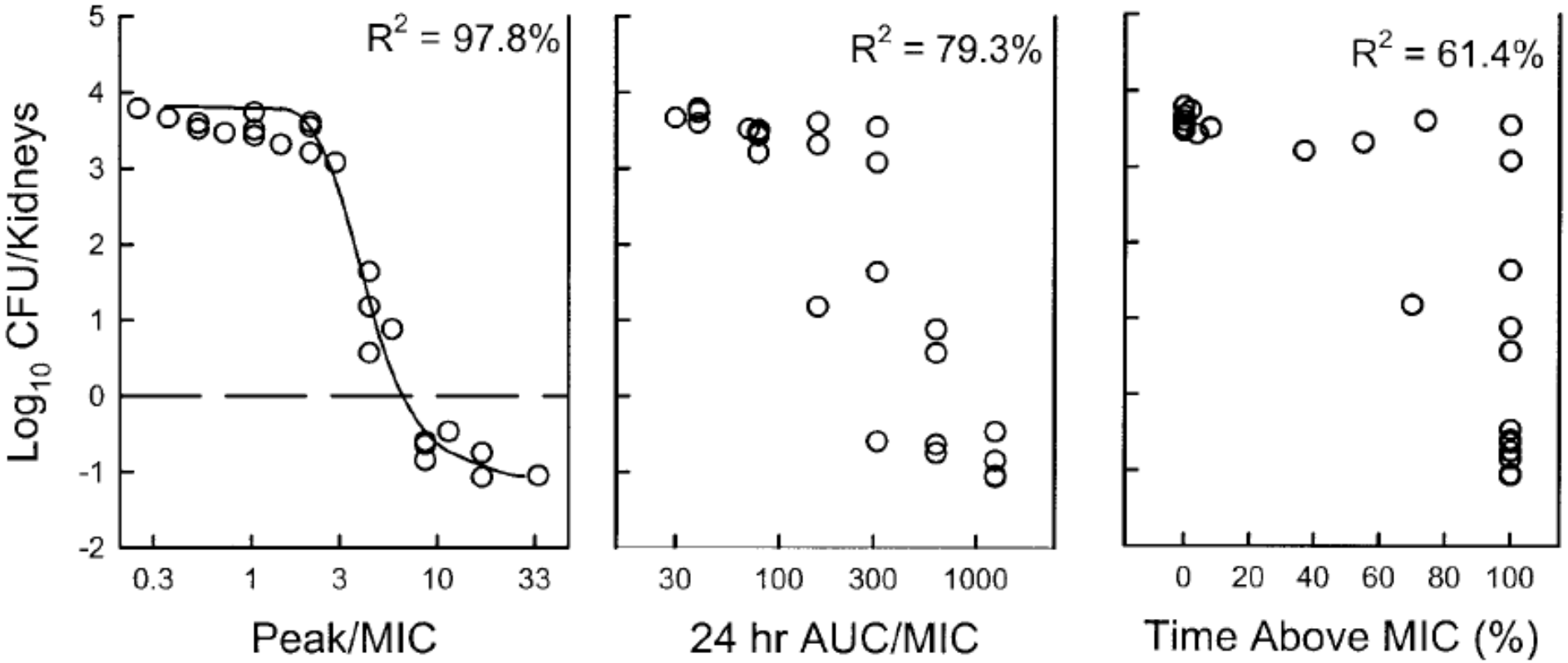
Andes AAC 2003;47:1187

Echinocandin Dosing Interval and C. albicans



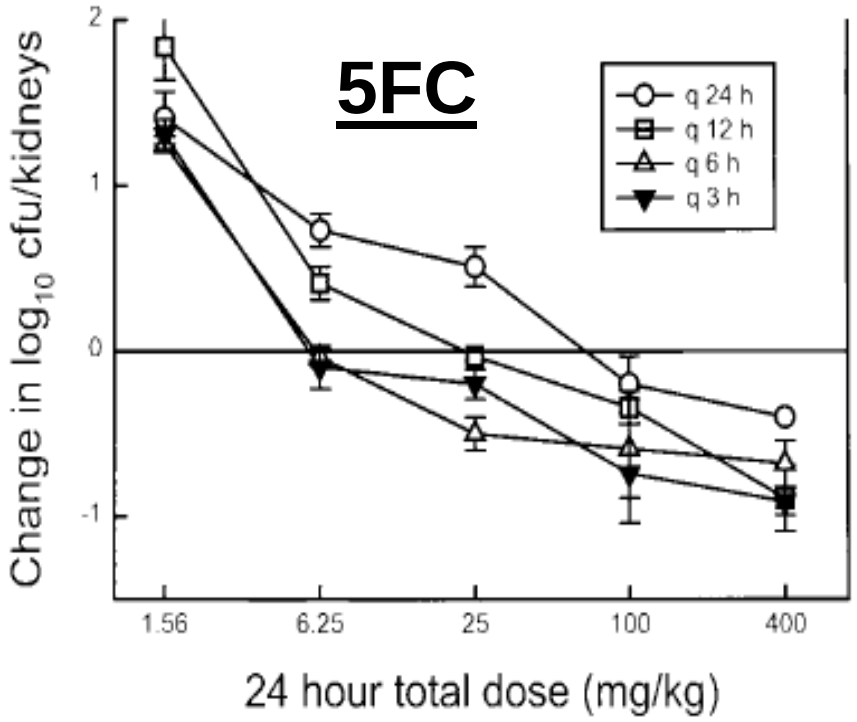
Andes AAC 2003;47:1187

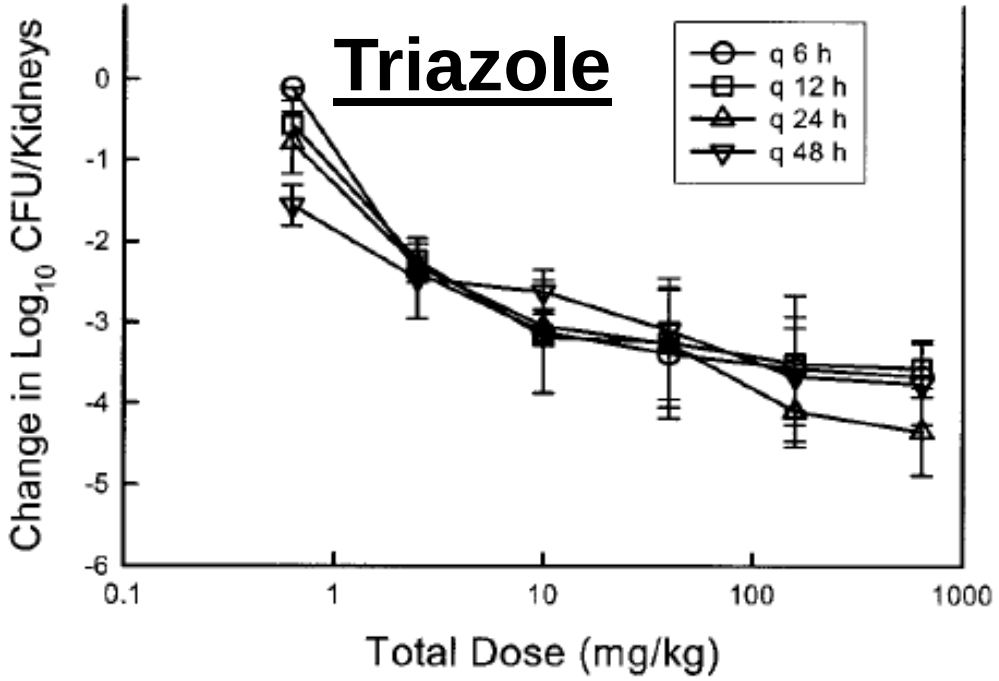
Echinocandin PK/PD Linked Index



Andes et al AAC 2003;47:1187

PK/PD Dosing Interval Patterns





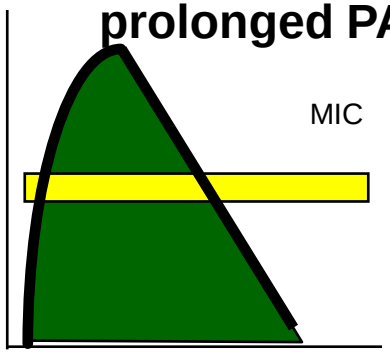
- Outcome better with small frequent administration

- Outcome independent of dosing interval

Andes et al AAC 2004;48:137, Andes et al AAC. 2000;44:938-942

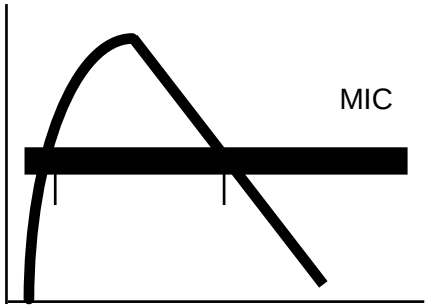
Distinct PK/PD Profiles

Peak/MIC or AUC/MIC (concentration-dependent prolonged PAFE)



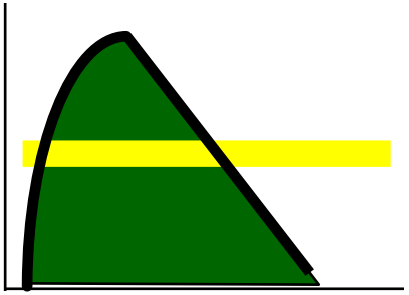
Amphotericin
Echinocandins

Time >MIC
(time-dependent killing short or not PAFE)



Flucytosine

AUC_{24} /MIC
(time-dependent killing prolonged PAFE)

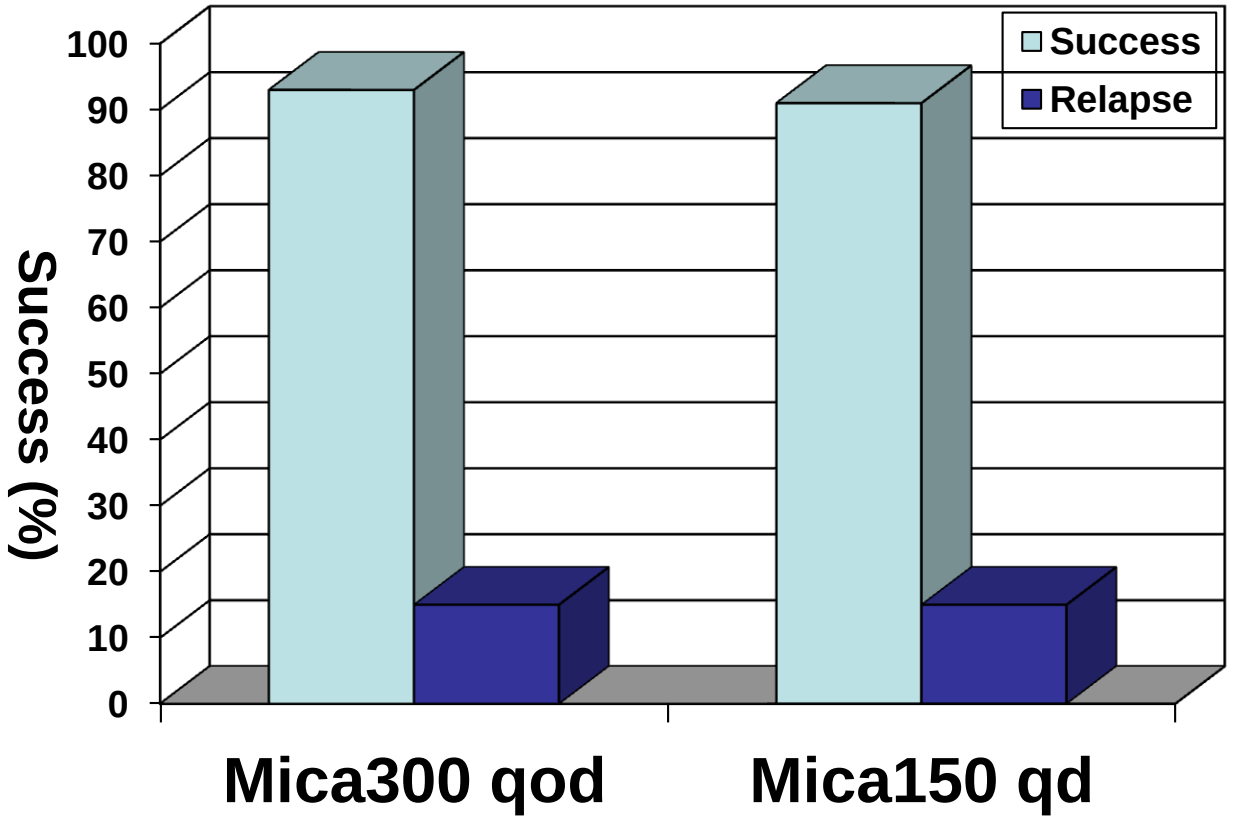


Triazoles

Andes D. AAC. 2003;47:1179-1186.

Dosing Frequency – Clinical Translation

- n = 453
- Esophageal candidiasis
- Impact of dosing regimen



- Increased dose, **extended interval** equivalent
- Mica regimens = Same AUC
- Outcome = **Concentration dependent**

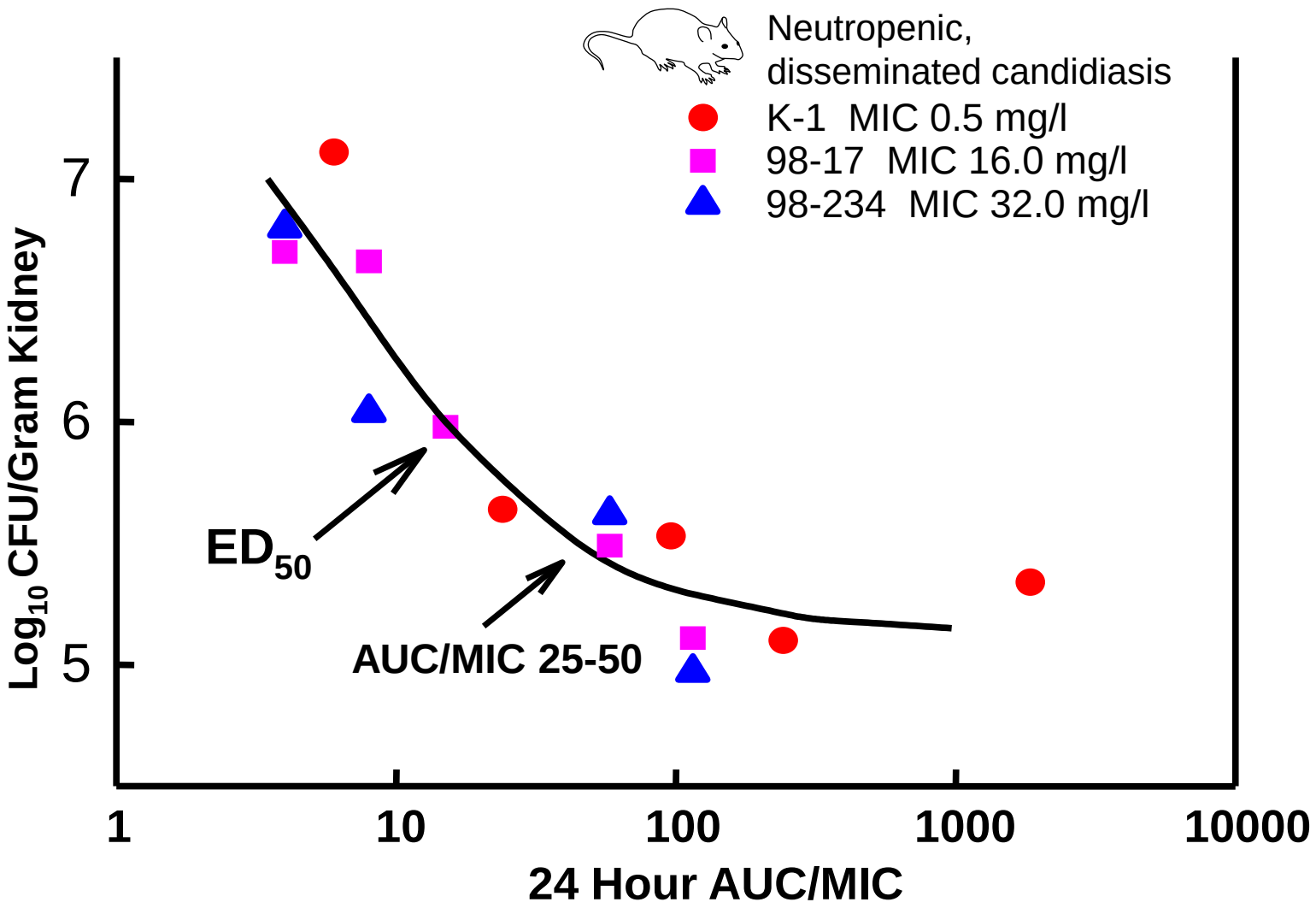
Andes et al Antimicrob Agents Chemother 2013; Aug 19. [Epub ahead of print]

PK/PD Question 3

What is the PK/PD target?

- How much drug do I need for efficacy?

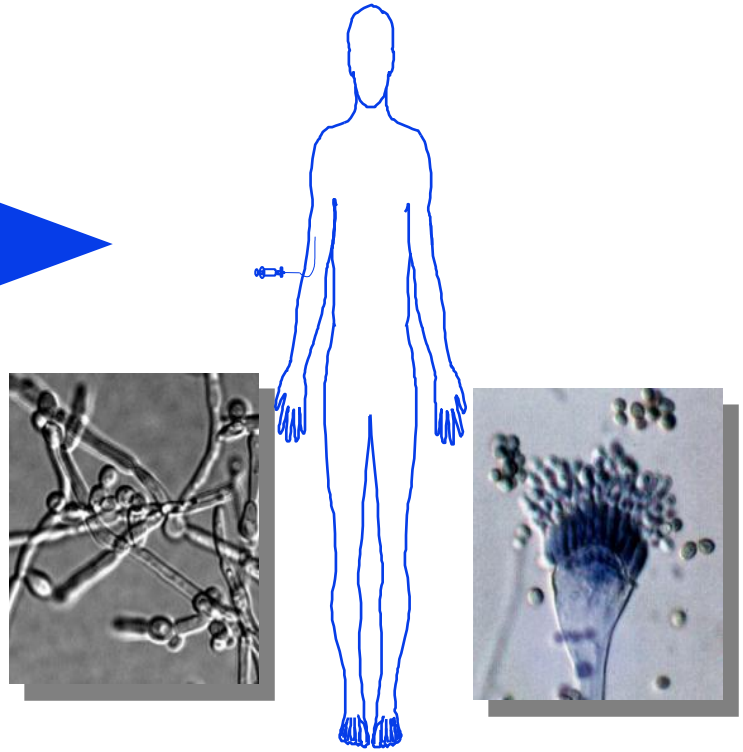
PK/PD Target Identification



Andes D, van Ogtrop M. AAC 1999;43:2116-2120.

PK/PD Target in Mice to Men

?

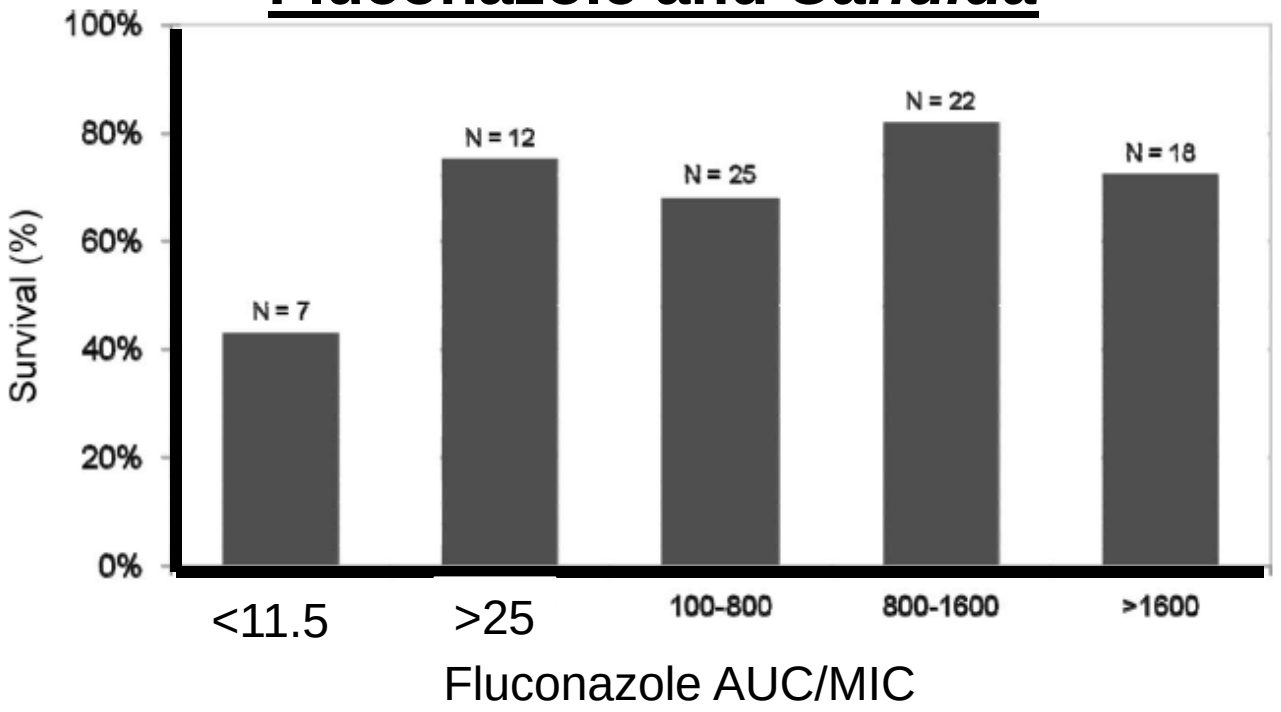


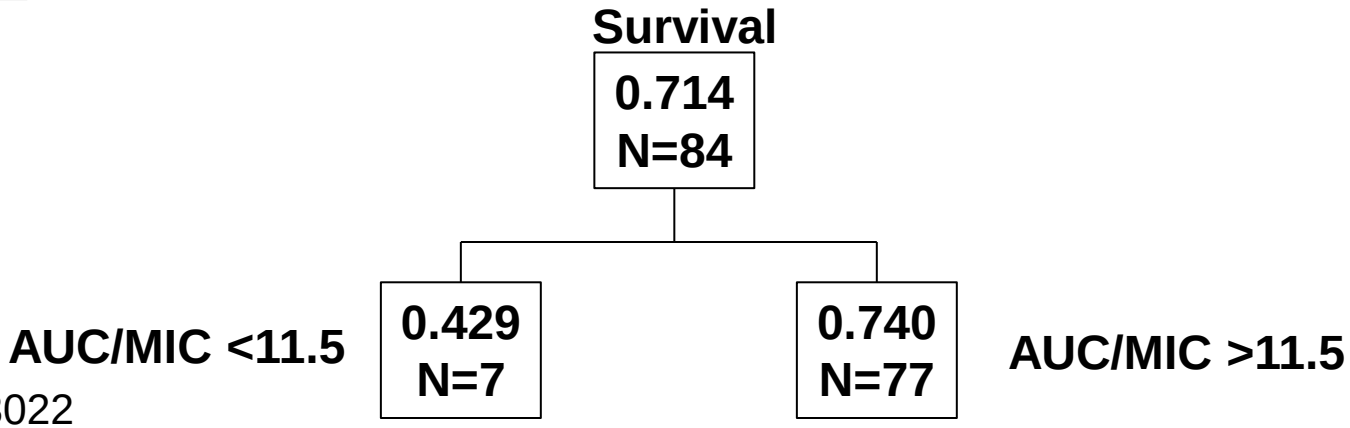
- Different doses (mg/kg)
- Faster half-life in small animals
- Different drug exposure over time
- **BUT:**
- Drug target is in the organism and independent of the host
- Exposure relative to MIC is the critical PK/PD determinant

PK/PD Humans

- Case series
- MIC and Dose and Outcome
- Pop PK
- CART
- Logistic regression

Fluconazole and *Candida*

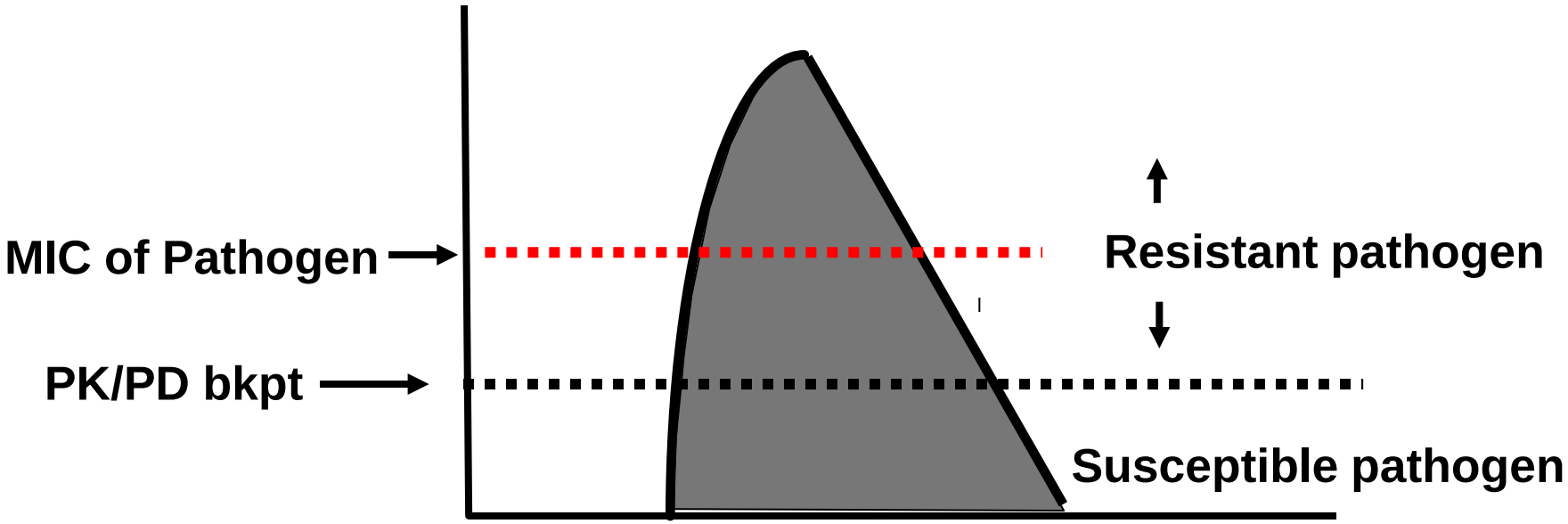




Baddley et al AAC 2008;52:3022

Clinical PK/PD Utility

- Consider the PK/PD numerator and denominator
- Define the dosing regimen that produces an exposure relative to MIC to achieve the PD target
- The MIC for a drug and dosing regimen for which the PD target is achieved (i.e. the MIC ceiling)



PK/PD Questions - Advanced

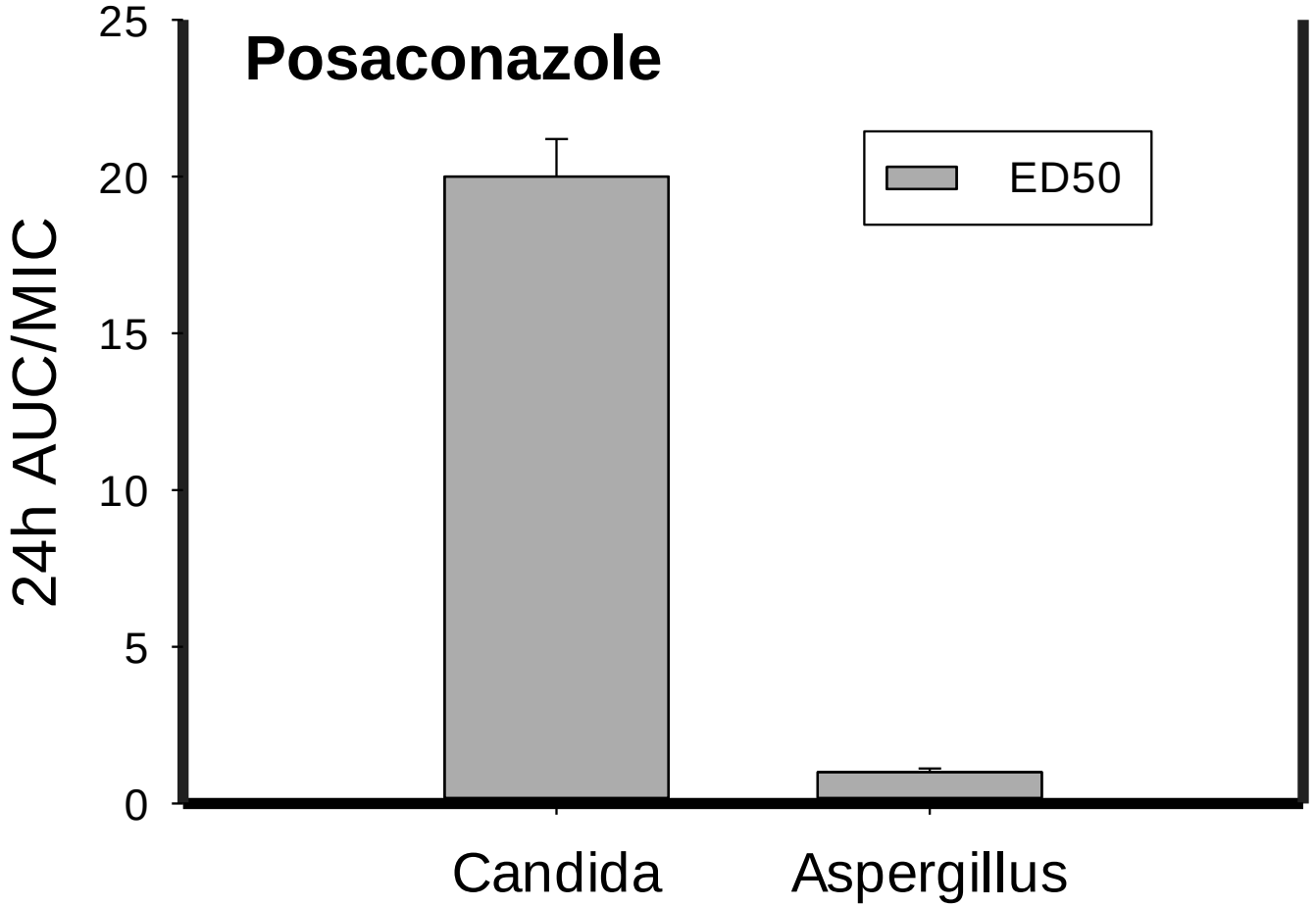
THINGS GET "LESS EASY"

PD Magnitude Variables?

What factors impact how much drug I need?

- Protein binding
- Drug class
- Infecting pathogen
- Resistance in the infecting pathogen
- Host immune system
- Tissue site (on Sunday)

PK/PD and Fungal Genera

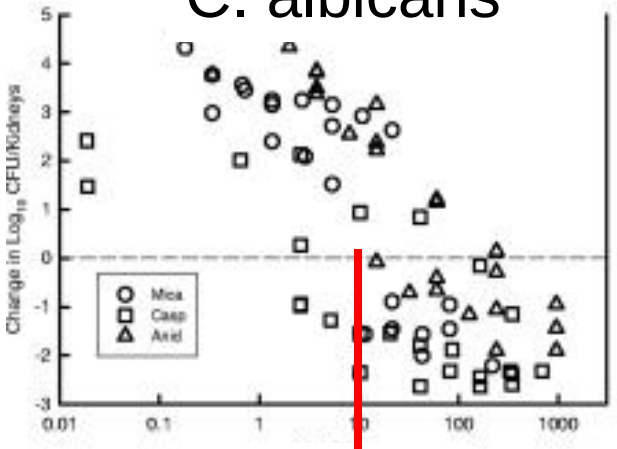


Andes et al AAC 2004, Lepak et al. AAC 2013, Mavridou et al. AAC 2010, Howard et al. JID 2011, Mavridou et al. AAC 2010

PK/PD and Fungal Species

Echinocandins

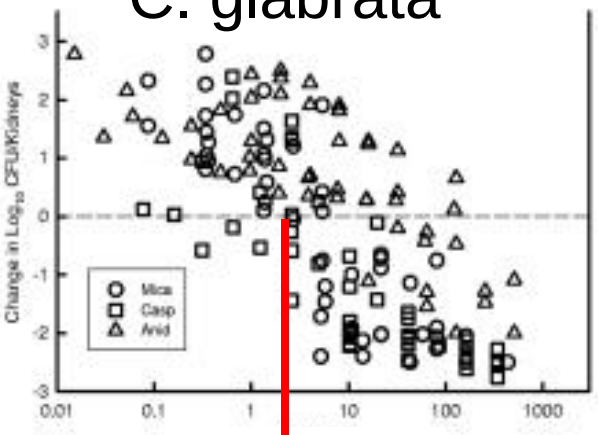
C. albicans



fAUC/MIC

10

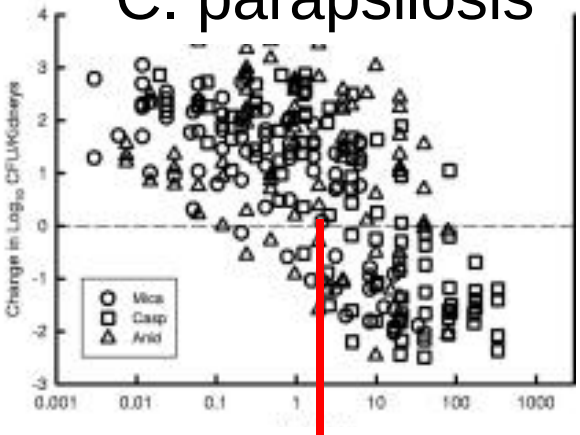
C. glabrata



fAUC/MIC

5

C. parapsilosis



fAUC/MIC

1-5

fAUC/MIC Stasis Target

C albicans ~ 10-20 (N=8 isolates)

C glabrata ~ 5 (N=9 isolates)

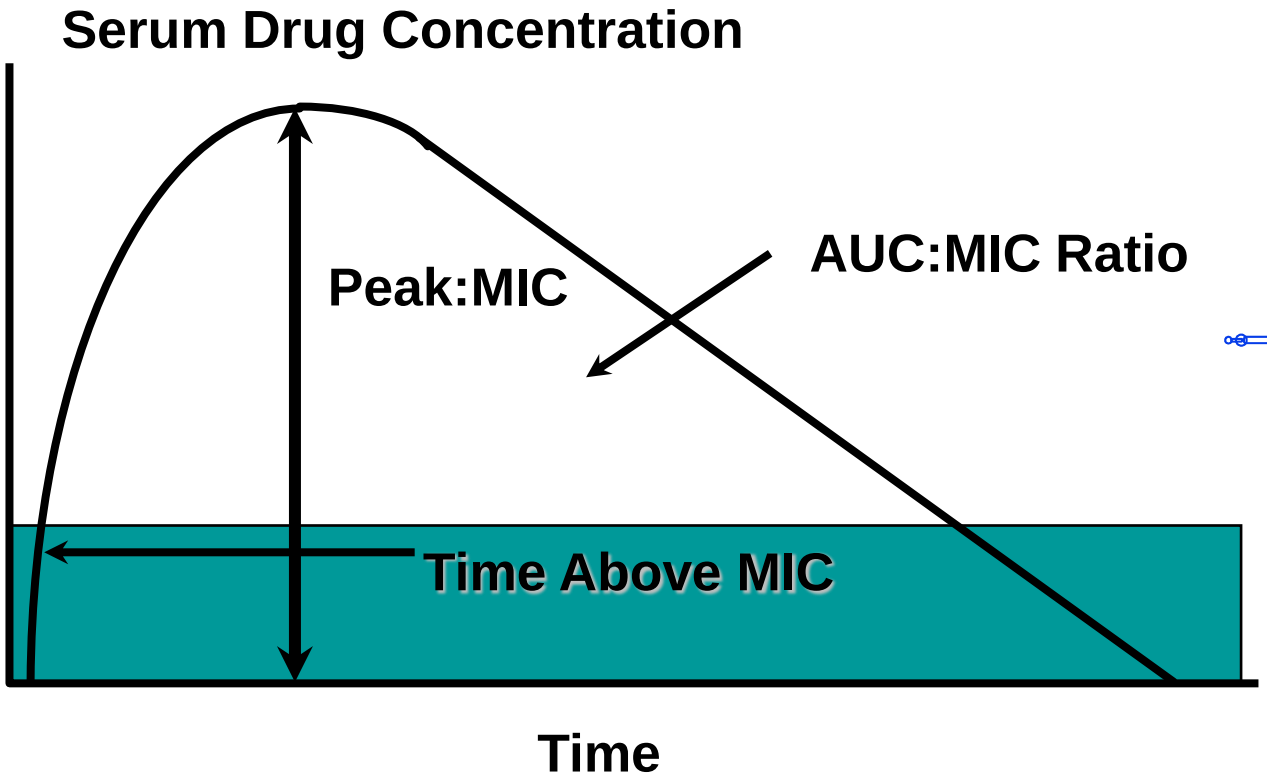
C parapsilosis ~ 1-5 (N=15 isolates)

Andes et al AAC 54:2497, 2010

Concluding Thoughts

- Individual antifungal drugs vary in their PK/PD characteristics
- Preclinical PK/PD models can predict clinical PK/PD relationships.
- Antifungal PK/PD can discern the optimal frequency and dose of administration.
- Antifungal PK/PD can define the susceptibility limit for relevant dosing regimens
- There are numerous PK/PD patient and disease state co-factors in need of further study.

THANK YOU


Serum Drug Concentration
Peak:MIC
AUC:MIC Ratio
Time Above MIC
Time