Antifungal Pharmacodynamics
A Strategy to Optimize Efficacy

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Fungal infection and therapy

- Incidence of invasive fungal infections continues to rise
- Outcomes poor
  - Filamentous fungal infection survival 20%
  - Candidemia survival 50-70%
- Several new antifungal options
- Variable pharmacologic characteristics and treatment responses
- **Are there pharmacologic strategies to optimize outcome?**

1. Marr KA, et al. *Clin Infect Dis.* 2002;34:909-917.
2. Gudlaugsson O, et al. *Clin Infect Dis.*2003;37:1172-1177.
3. Morgan J, et al. *Infect Cont Hosp Epid.* 2005;26:540-547.

Antifungal pharmacology hypotheses

- Concentration matters
- We can determine the antifungal exposure that will optimize patient outcome
- The antifungal concentration should be considered relative to antifungal potency (the MIC)

1. Marr KA, et al. *Clin Infect Dis.* 2002;34:909-917.
2. Gudlaugsson O, et al. *Clin Infect Dis.*2003;37:1172-1177.
3. Morgan J, et al. *Infect Cont Hosp Epid.* 2005;26:540-547.

Antifungal therapy realities

- Patients who contract invasive fungal infections are complex
- Many host and other factors impact patient outcome (sometimes as much or more than the specific antifungal drug, dose, exposure)

1. Marr KA, et al. *Clin Infect Dis.* 2002;34:909-917.
2. Gudlaugsson O, et al. *Clin Infect Dis.*2003;37:1172-1177.
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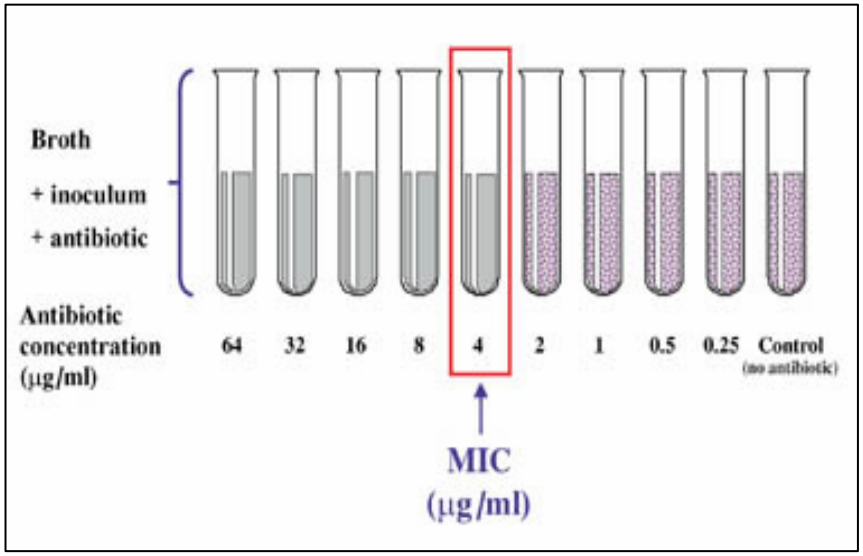
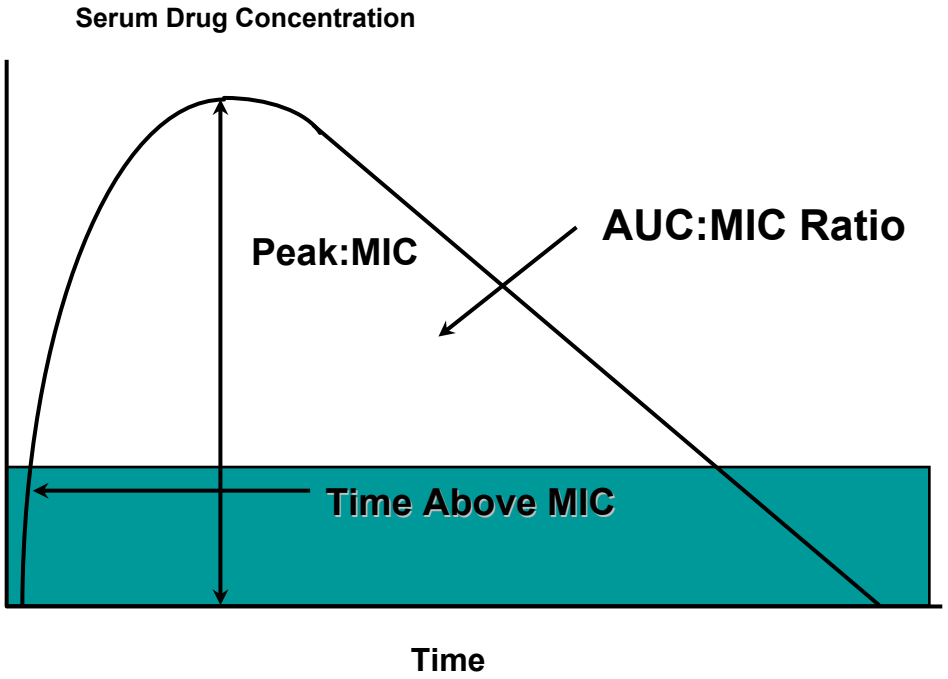
The concept and utility of pharmacodynamics

MIC

- Good indicator of potency



Pharmacodynamics



UTILITY

- Design optimal dosing regimen
- Guide therapeutic drug monitoring
- Development of susceptibility breakpoints

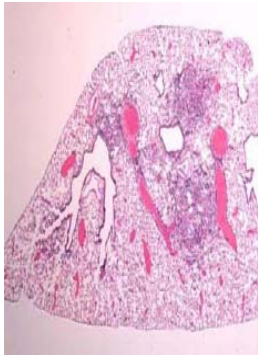
The MIC matters for fungi and antifungals

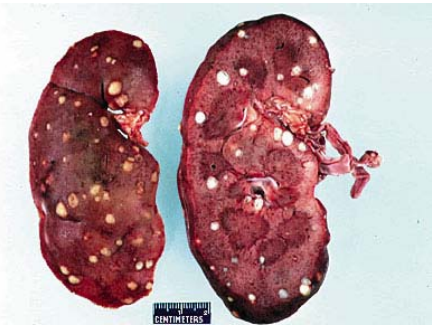
TABLE 5. Correlations of fluconazole susceptibility testing with clinical response for mucosal and invasive *Candida* infections treated with fluconazole[a]

Reference	Type of infection	Dose (mg/day)	MIC (μg/ml) used to determine susceptibility class			No. of events[b]	% Success (*n*/*N*)[f] by susceptibility class		
			S	SDD	R		S	SDD	R
84	Mucosal	100	≤8	16–32	≥64	302	98 (248/253)	78 (21/27)	73 (16/22)
6	Mucosal	100–200	≤8	16–32	≥64	48	80 (28/35)		46 (6/13)
15	Mucosal	100	≤8	16–32	≥64	66	96 (49/51)	0 (0/7)	0 (0/8)
88	Mucosal	100–400	≤32		≥64	21	88 (14/16)		0 (0/5)
37	Mucosal	100	≤0.39	1.56	≥3.12	27	93 (14/15)	0 (0/2)	30 (3/10)
14	Mucosal	NA[c]	≤8	16–32	≥64	73	75 (42/56)	50 (2/4)	23 (3/13)
80	Mucosal	100–800	≤8	16–32	≥64	155	87 (93/107)	72 (13/18)	43 (13/30)
Total mucosal						692	92 (488/533)	62 (36/58)	41 (41/101)
84	Invasive[d]	>100	≤8	16–32	≥64	217[e]	81 (122/150)	86 (24/28)	46 (18/39)
38	Invasive	400	≤8	16–32	≥64	32	79 (19/24)	67 (4/6)	0 (0/2)
5	Invasive	400	≤8	16–32	≥64	80	92 (54/59)	75 (6/8)	54 (7/13)
18	Invasive	50–400	≤8	16–32	≥64	32	67 (14/21)	20 (1/5)	0 (0/6)
100	Invasive	200	≤8	16–32	≥64	242	70 (144/206)	64 (16/25)	55 (6/11)
Total invasive						603	77 (353/460)	71 (51/72)	44 (31/71)
Total invasive plus mucosal						1,295	85 (841/993)	67 (87/130)	42 (72/172)

Pfaller et al CMR 2006;19:435

Disseminated fungal infection models





- Murine disseminated *Candida* and *Aspergillus* models
  - Mimics disseminated fungal infection
  - Organism burden primary endpoint (correlates well with animal survival)
  - Supports growth of most fungi
  - Can mimic multiple drug administration routes
  - Most high throughput *in vivo* fungal model
  - Large group of comparator antifungal compounds
  - Outcomes correlated with treatment success in patients

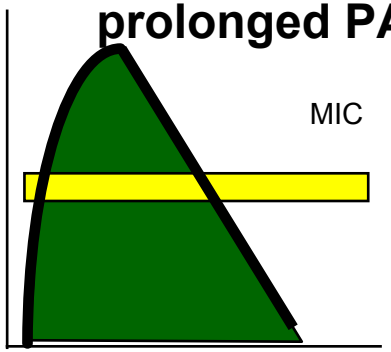
Pharmacodynamics questions and experiments

Predictive PD Parameter –
What PK characteristic do I optimize?

- What is the impact of concentration on rate and extent of antimicrobial activity?
- Are there antimicrobial effects that persist following exposure?
- What is the impact of the dosing interval (dose fractionation)?
- What is the impact of the pharmacodynamic parameter on efficacy?

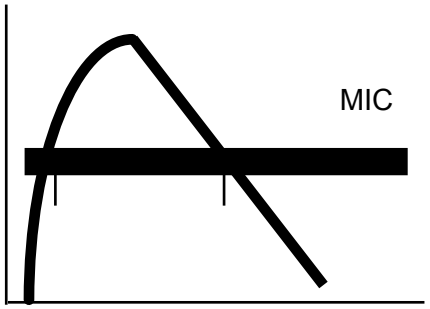
Pharmacokinetic/pharmacodynamic profiles

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



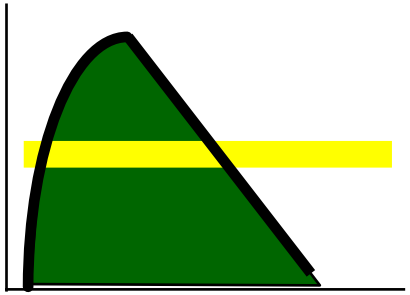
Amphotericin
Echinocandins

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



Flucytosine

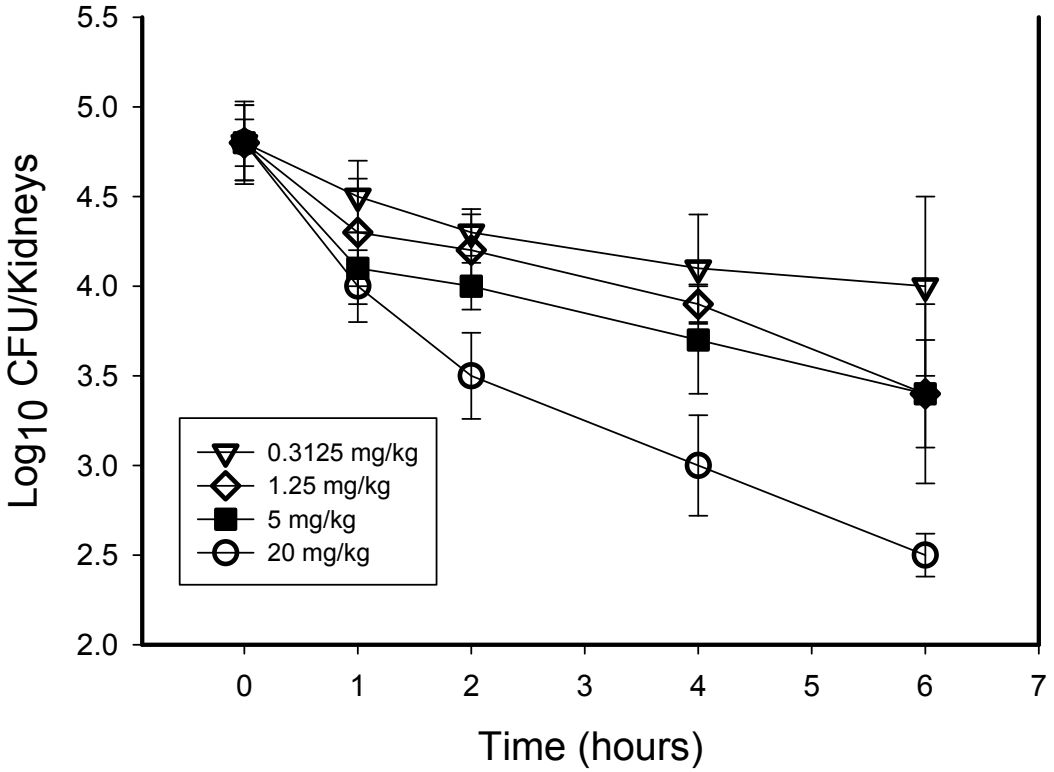
AUC_{24} /MIC
(time-dependent killing prolonged PAFE)



Triazoles

Andes D. *Antimicrob Agents Chemother.* 2003;47:1179-1186.

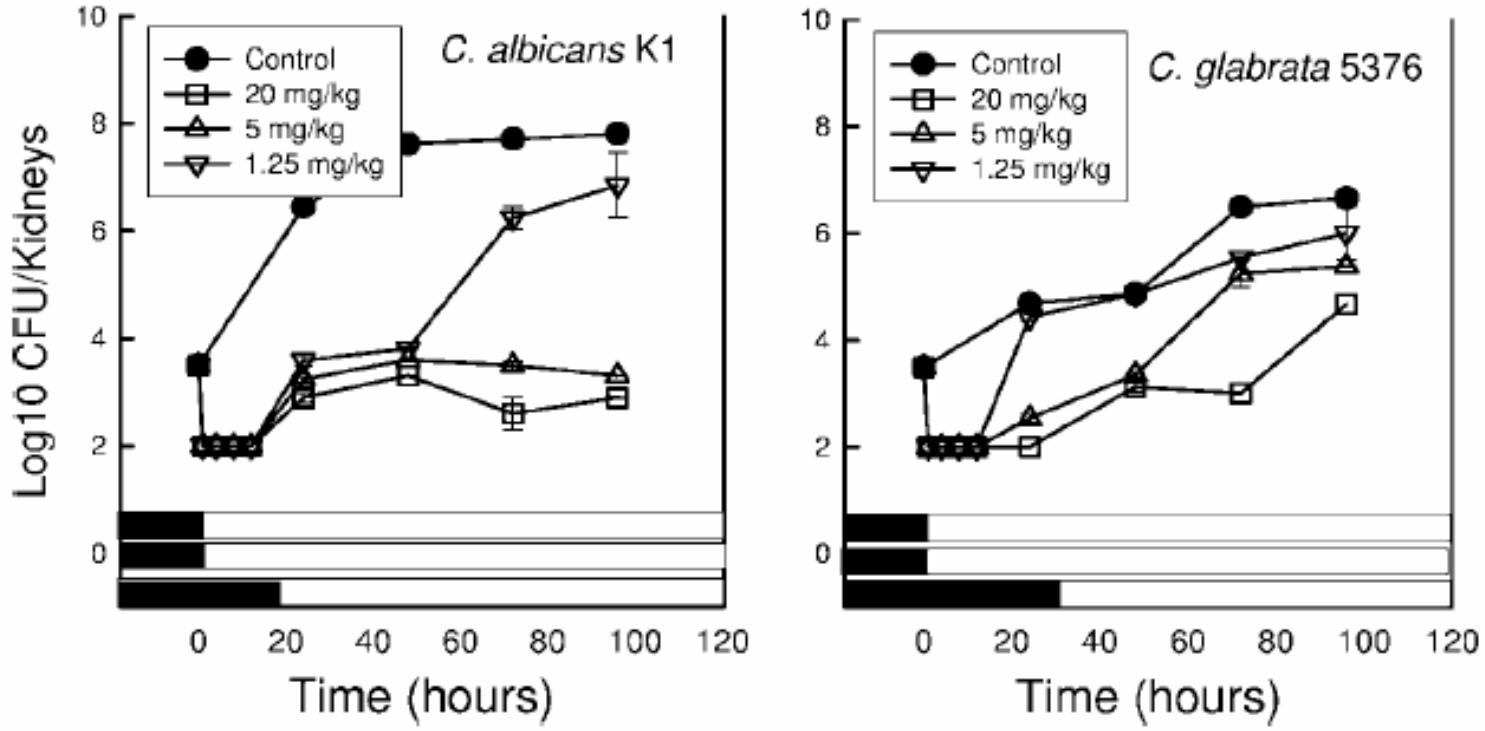
Impact of echinocandin concentration against *C. albicans*



- Aminocandin
- C. albicans
- Disseminated candidiasis
- Enhanced extent and rate of killing with increase in concentration

Andes D, et al. AAC. 2003;47:1187-1192.

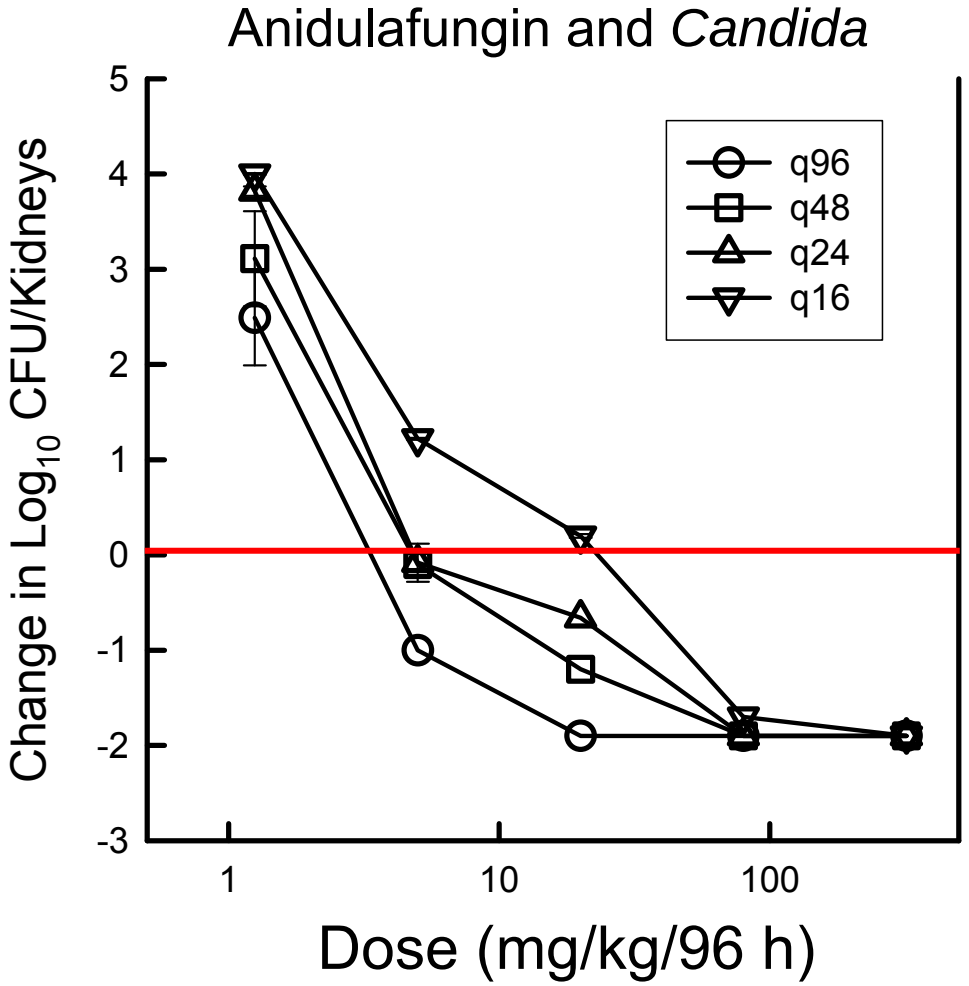
Impact of echinocandin concentration over time – persistent effects



Anidulafungin Post-antifungal effects ranging from 56 to 96 hours

Andes et al AAC 2008:52:539

Impact of echinocandin concentration and dosing interval

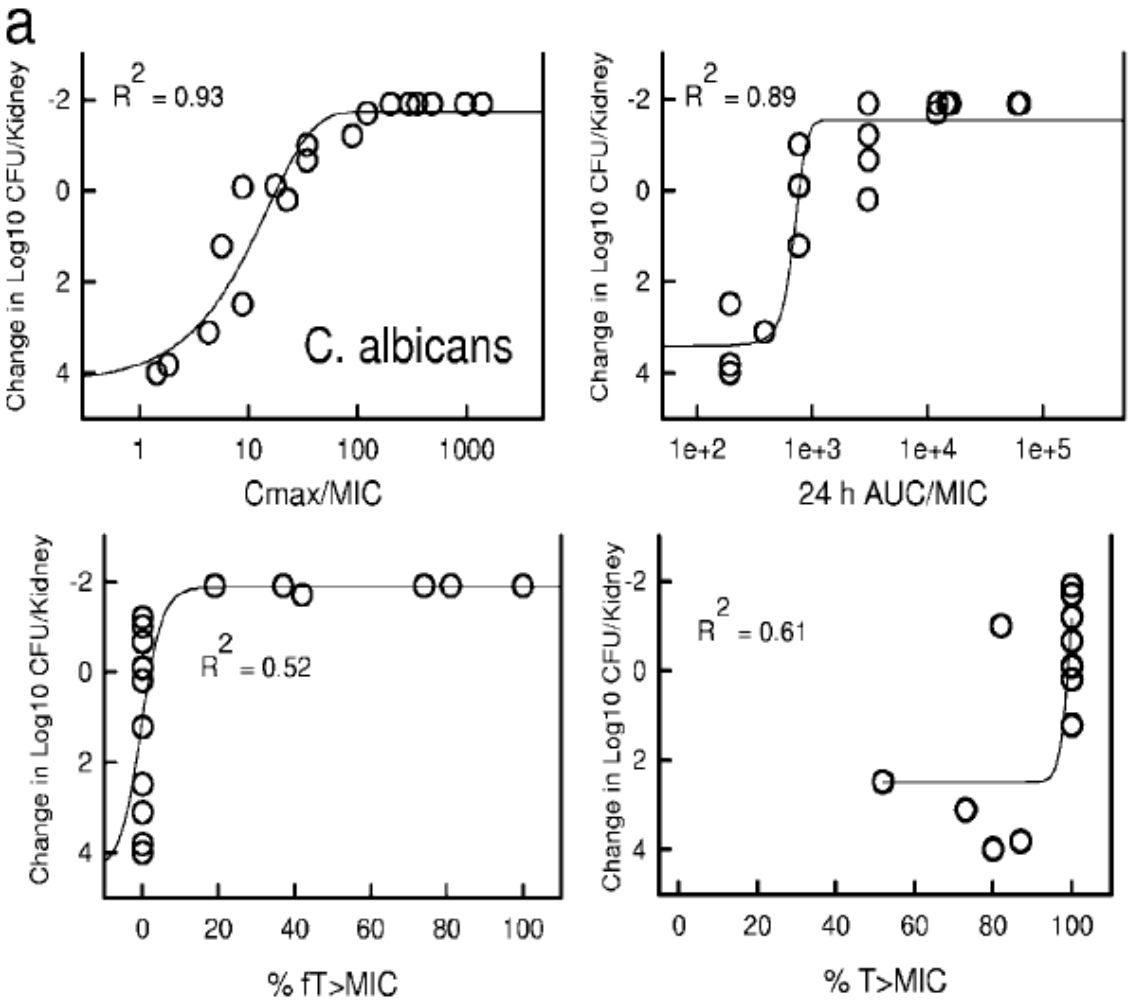


Large infrequent doses most effective

Andes D et al *Antimicrob Agents Chemother* 2008;52:539-50

Impact of pharmacodynamic indice:

Anidulafungin and *C. albicans*

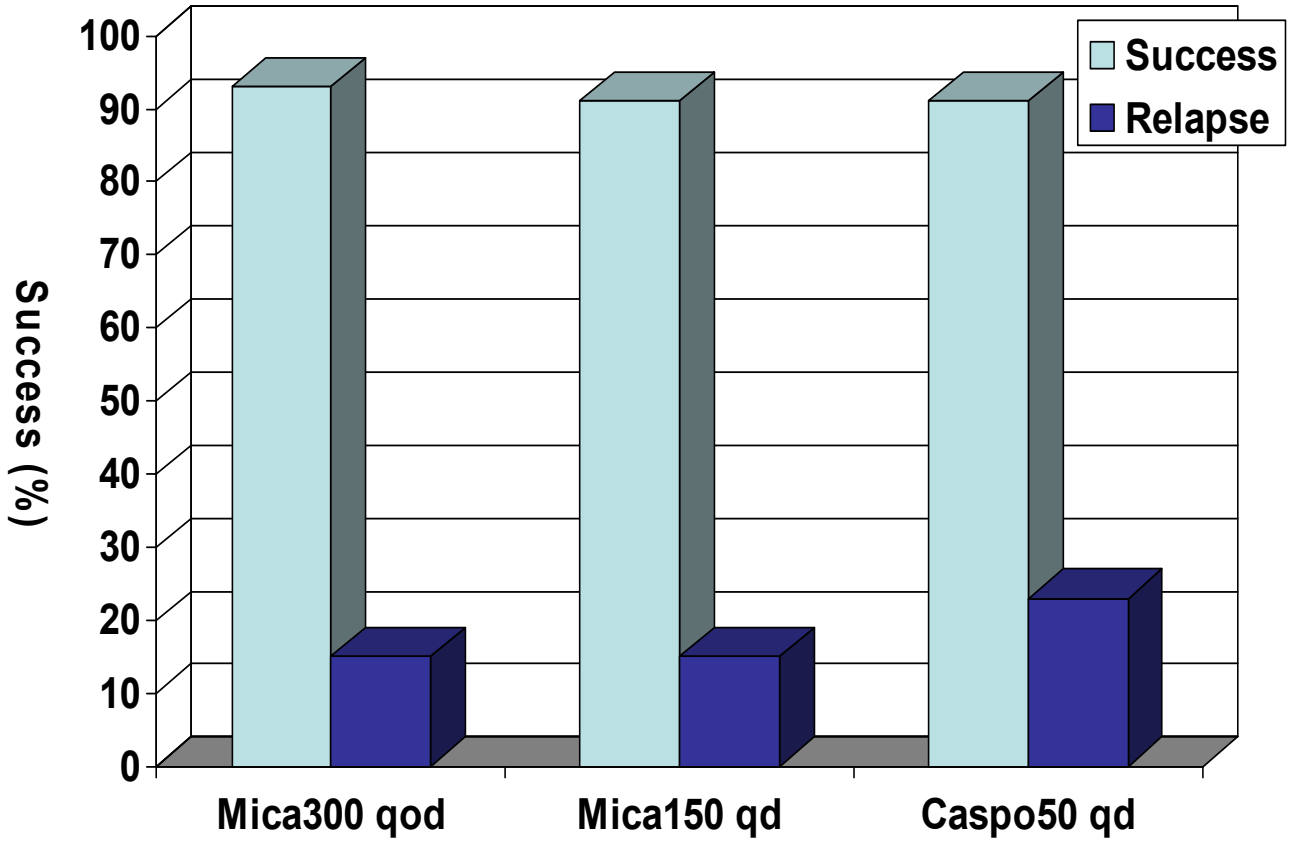


- Both Cmax and AUC indices most strongly associated with echinocandin efficacy

Andes et al AAC 2008:52:539

Echinocandin PK/PD Profile - Clinical

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



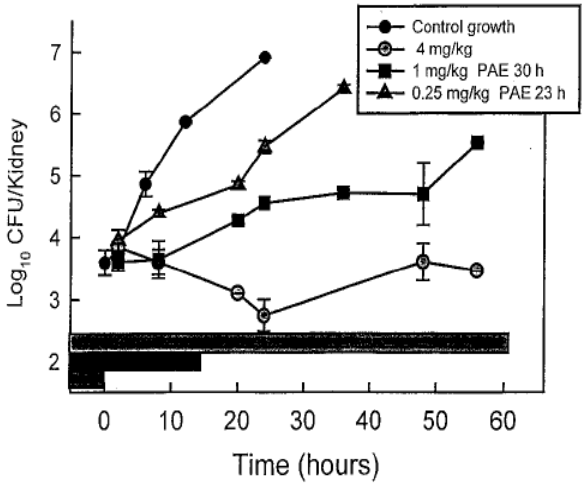
Increased dose, increased interval equivalent

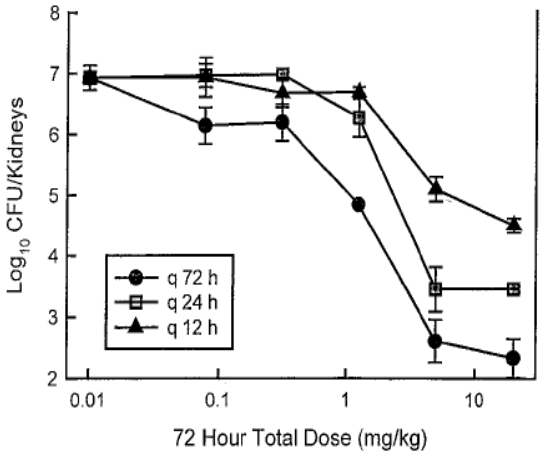
Mica regimens = Same AUC

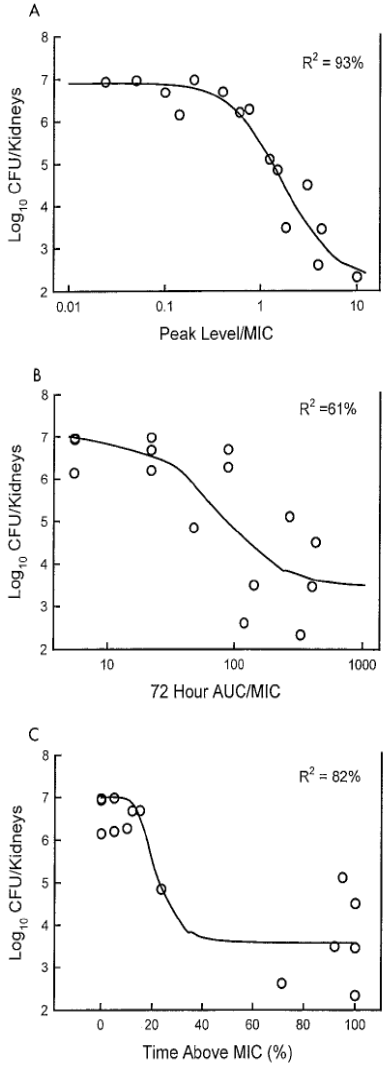
Outcome = Concentration dependent

Buell et al ICAAC 2005 Abst M719

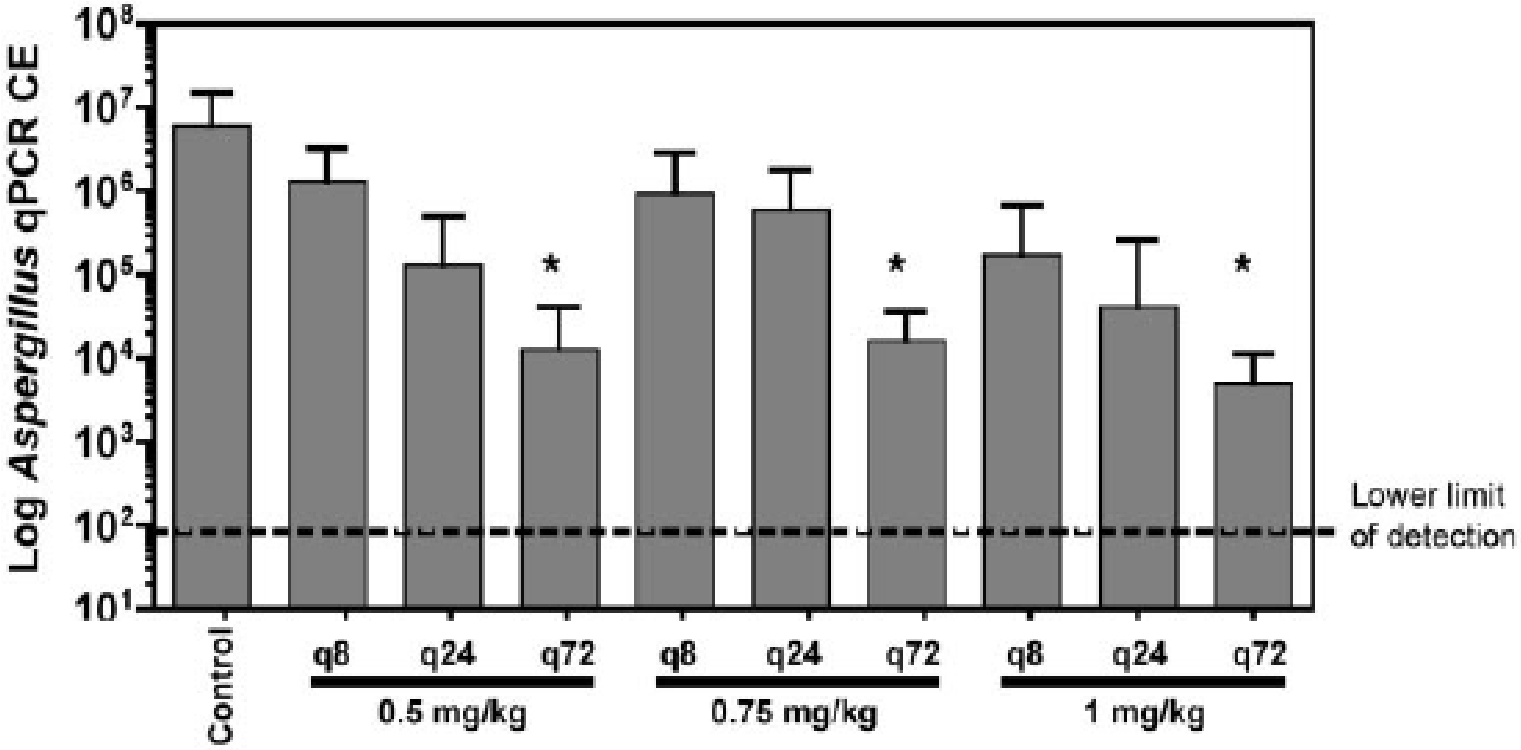
AmB - Impact of concentration and dosing interval







Impact of AmB dosing interval on *in vivo* efficacy against *A. fumigatus*

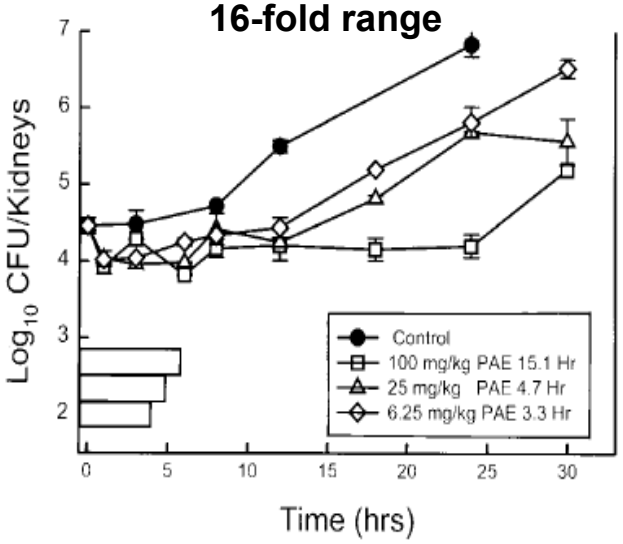


Wiederhold NP, et al. *Antimicrob Agents Chemother.* 2006;50:469-473.

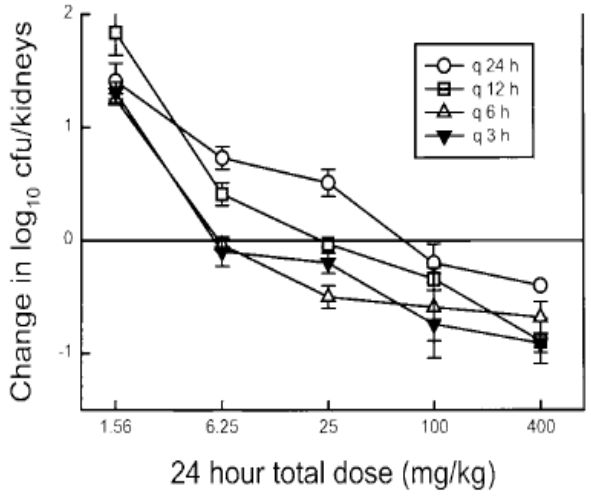
5FC - Impact of concentration and dosing interval

5-FC *in vivo* time kill[1]

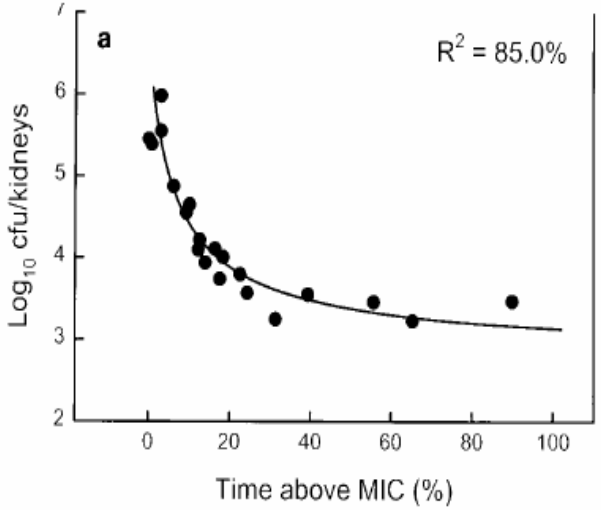
16-fold range



5-FC *in vivo* dose fractionation[2]



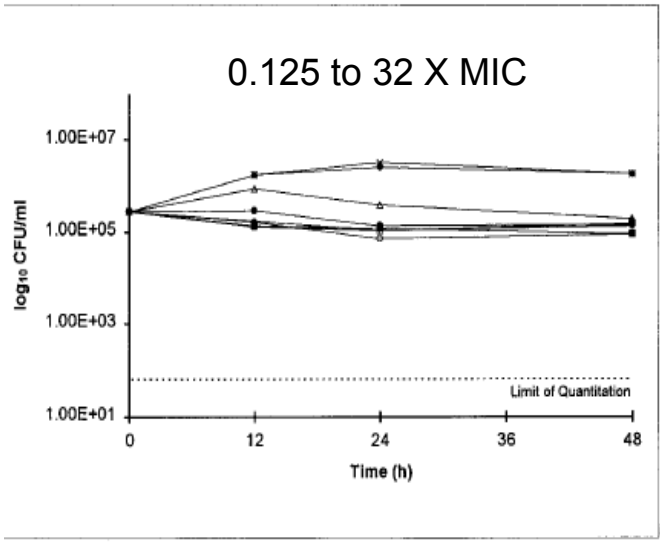
5-FC time above *C. albicans* MIC[1]



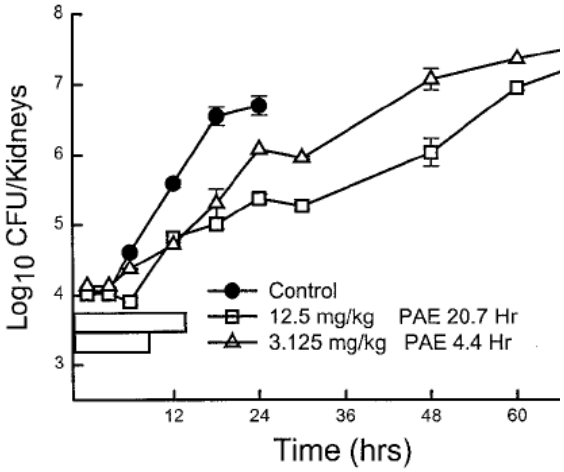
1. Andes D, van Ogtrop M. *Antimicrob Agents Chemother.* 2000;44:938-942.
2. 2. Andes D. *Antimicrob Agents Chemother.* 2003;47:1179-1186.

Triazole concentration effects and dosing intervals

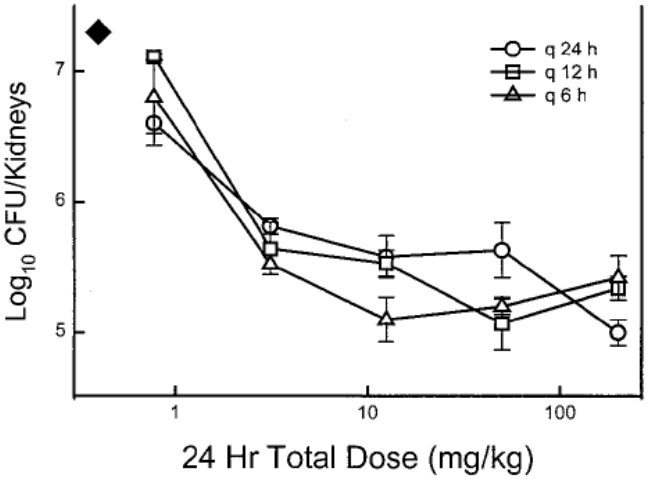
Fluconazole *in vitro* time kill[1]



Fluconazole *in vivo* persistent effect[2]



Fluconazole dosing interval variation[2]



1. Ernst EJ, et al. *Antimicrob Agents Chemother.* 2000;44:1108-1111.
2. Andes D, van Ogtrop M. *Antimicrob Agents Chemother.* 1999;43:2116-2120.

Pharmacodynamic questions - 2

What is the PD target?
(aka How much drug do I need?)

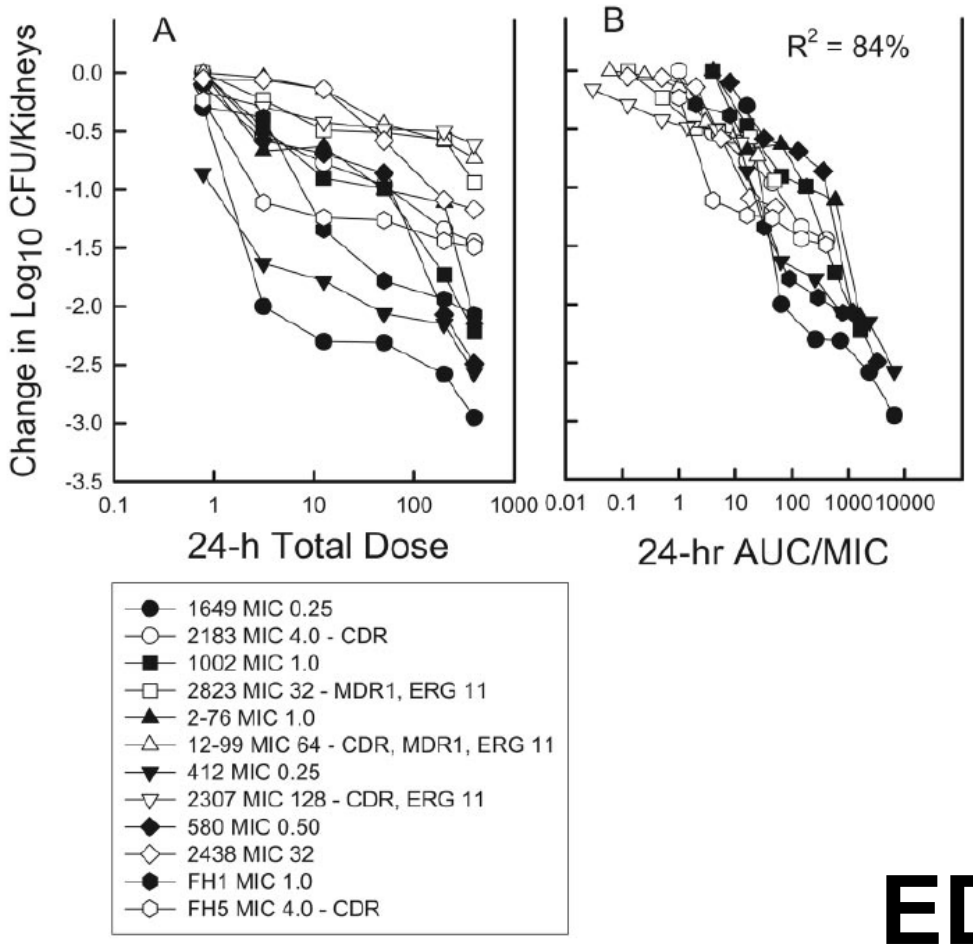
What factors impact how much drug I need?

- Protein binding
- Drug class
- Infecting pathogen
- Resistance in the infecting pathogen
- Animal species

Study PD correlation in humans?

Does this predict outcome in clinical disease?

Triazole pharmacodynamic target in mice: Impact of drug resistance



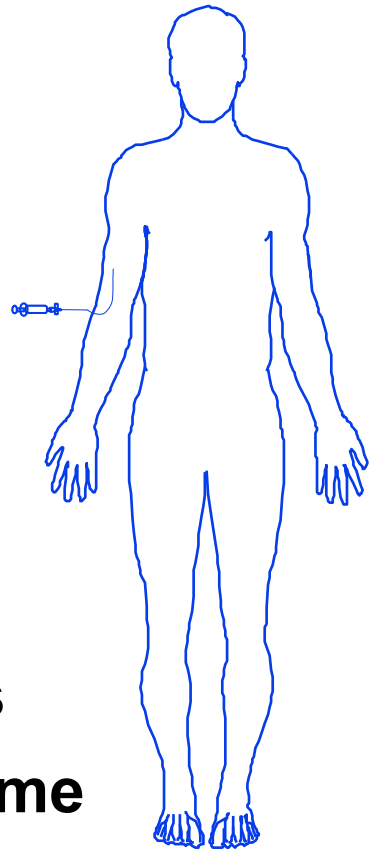
>500-fold MIC range and all resistance mechanisms

ED 50 = AUC/MIC 25

Andes D, et al *Antimicrob Agents Chemother* 2006;50:2374-83

How can experimental pharmacodynamic studies predict outcome in patients ?

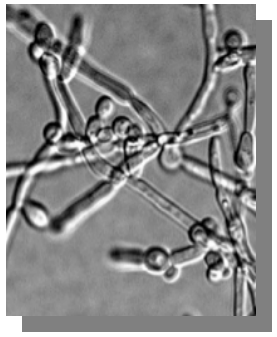
?

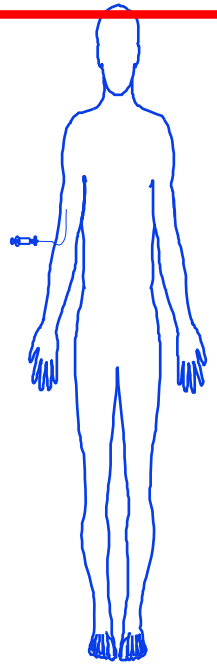


- **Different doses (mg/kg)**
- **Faster half-life in small animals**
- **Different drug exposure over time**

How can experimental pharmacodynamic studies predict outcome in patients ?

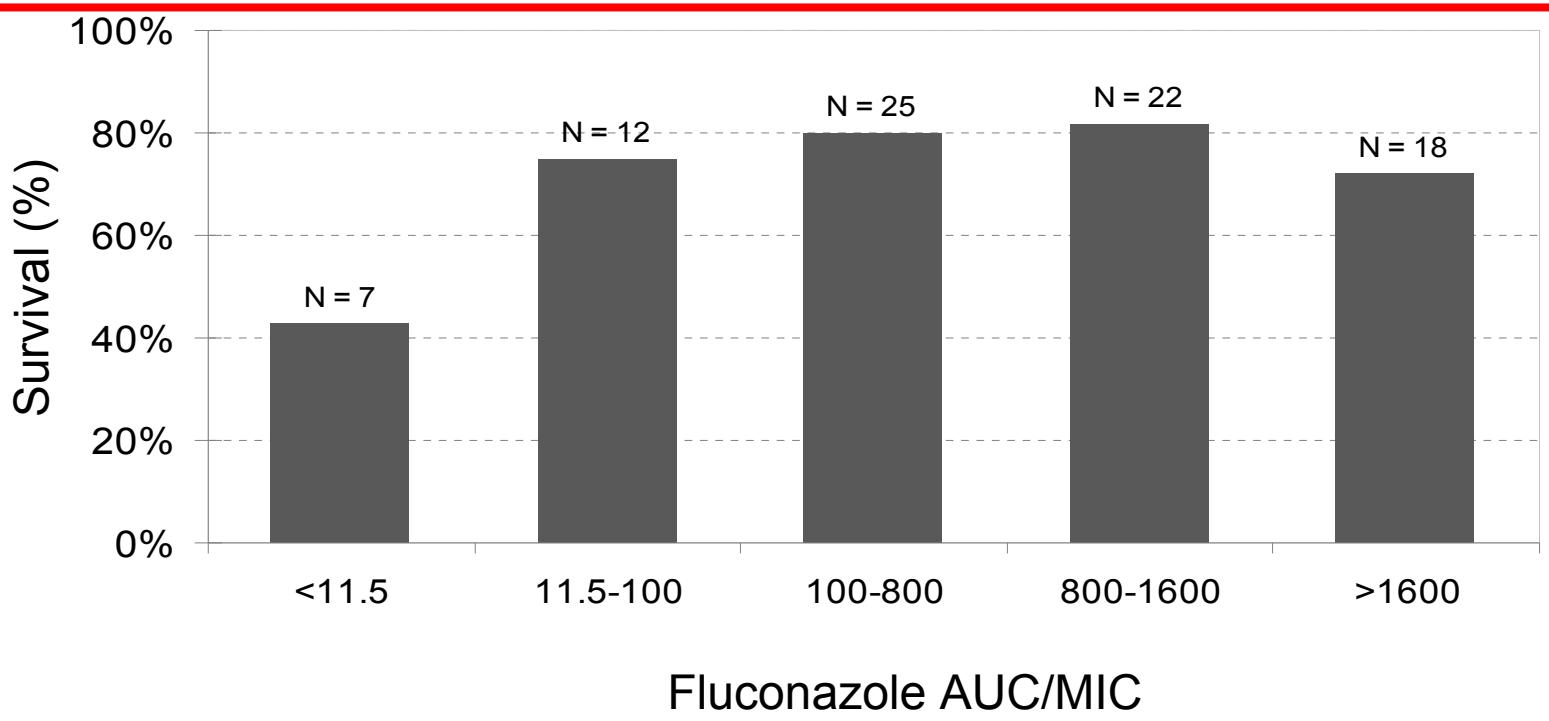
Yes





- **Drug target is in the organism and independent of the host**
- **Exposure relative to the MIC that the organism sees is the critical drug exposure/outcome determinant**
- **For example, AUC/MIC needed for efficacy in a mouse is the same as a human**

Fluconazole Pharmacodynamic Target Patients with Candidemia



Rex et al CID 1997;24:235 (n=108)
Lee et al AAC 2000;44:2715 (n=38)
Takakura et al Eur J Clin Microbiol Infect Dis 2004;23:380 (n=95)
Clancy et al AAC 2006;50:3496 (n=18)
Pai et al. AAC 2007;51:35 (n=77)
Rodriguez-Tudela et al AAC 2007;51:3599 (n=126)
Baddley AAC 2009

Maximal Survival = AUC/MIC 25

N>600

Pharmacodynamic target: clinical validation

- 12 published clinical databases
- 1,295 patient-episode-isolate events
- 7 mucosal studies (692 events)
- 5 invasive studies (602 events)

MIC	Mucosal	Invasive	Success
< 8	533 (77%)	460 (76%)	85%
16-32	58 (8%)	72 (12%)	67%
>64	101 (15%)	71(12%)	42%

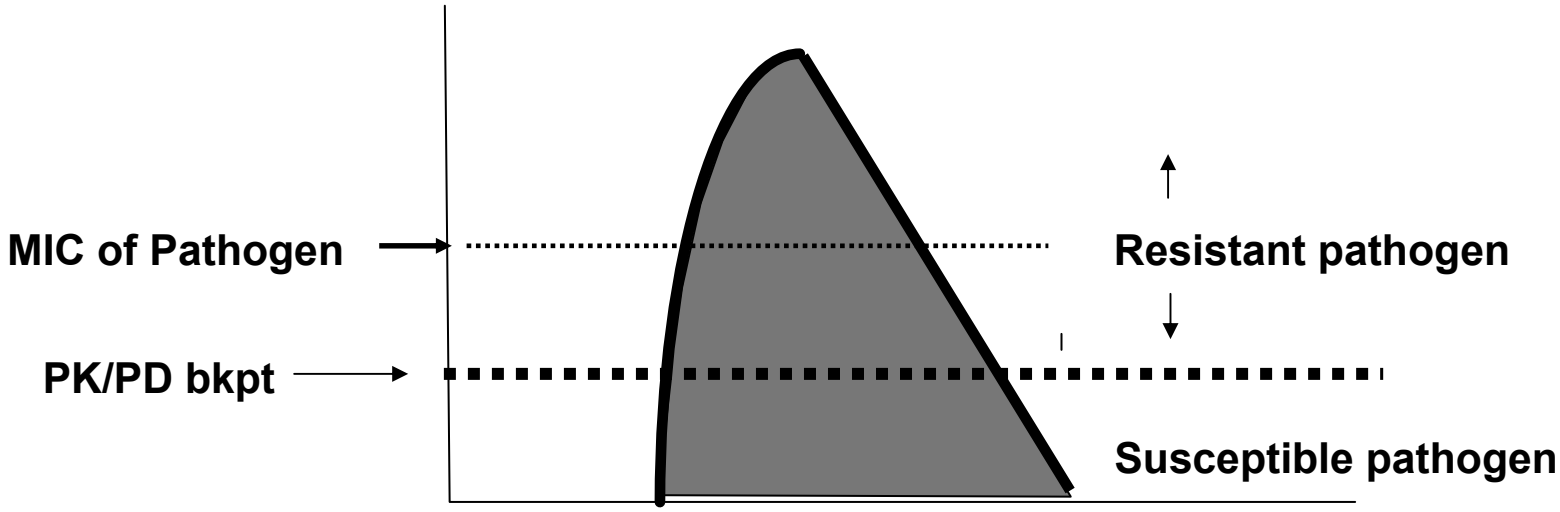
AUC/MIC >25	70% success
AUC/MIC <25	47% success

Fluconazole

Andes D. *Infect Dis Clin North Am.* 2006;;20:679-97

Clinical PK/PD breakpoints

- The MIC at which the pathogen is considered susceptible or resistant (e.g. AUC:MIC of 25 is met with an azole)
- Given the pharmacokinetics of an azole, how low does the MIC have to be in order to be considered susceptible (where the goals AUC:MIC are met)?



Impact of fluconazole pharmacodynamics

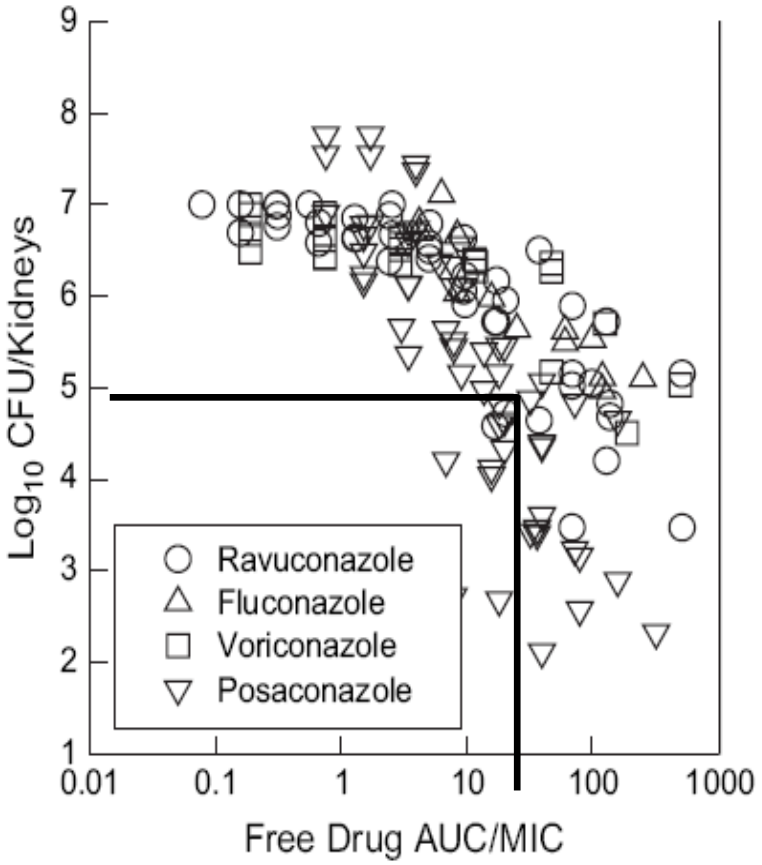
- 24 hr AUC/MIC PK/PD target of 25 for efficacy in animal models
- Choose the optimal dose or define resistance

- Similar target suggested in humans
  - If we use a target of 25, then
    - Loosely:1x above MIC for 24 hr = required dose
    - 100 mg/day should treat up to ≈ 4 mg/l
    - 400 mg/day should treat up to ≈ 16 mg/l
    - 800 mg/day should treat up to ≈ 32 mg/l

Impact of drug class and protein binding

Triazoles	**Protein Binding**
Itraconazole	99.8%
Fluconazole	12%
Voriconazole	58%
Ravuconazole	98%
Posaconazole	98%

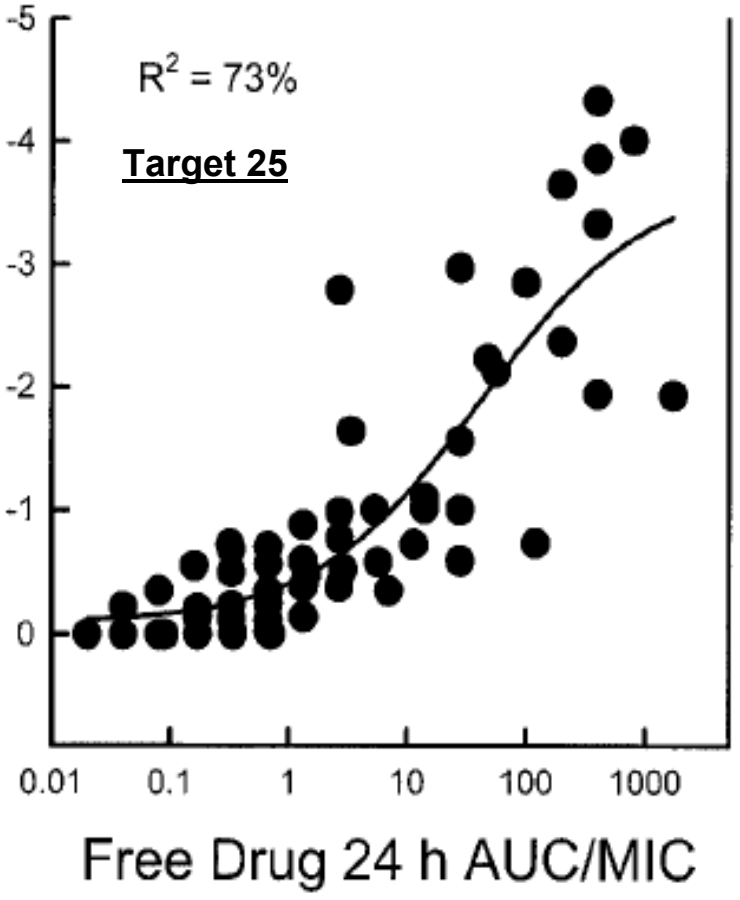
Target 24 h AUC/MIC 25



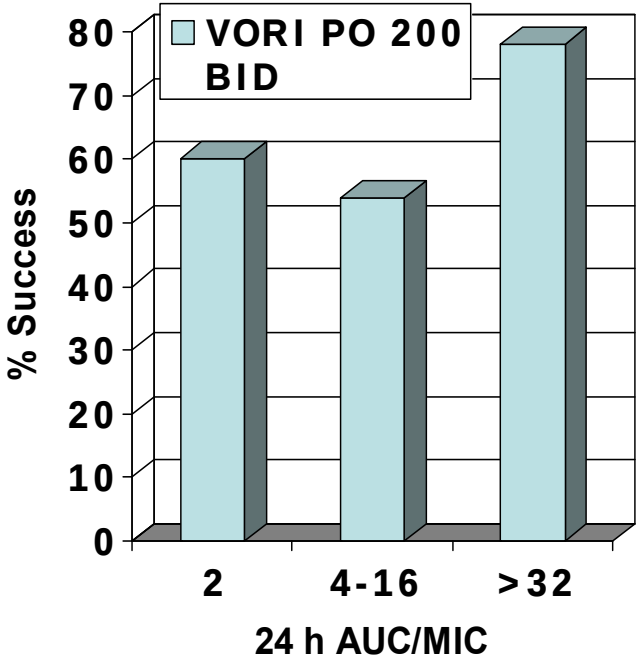
Andes D. *Infect Dis Clin N Amer.* 2003;17:635-649.

Voriconazole PK/PD – Mice and Humans

Animals and *Candida*[1]



***Candida* and patients (n=267)[2]**

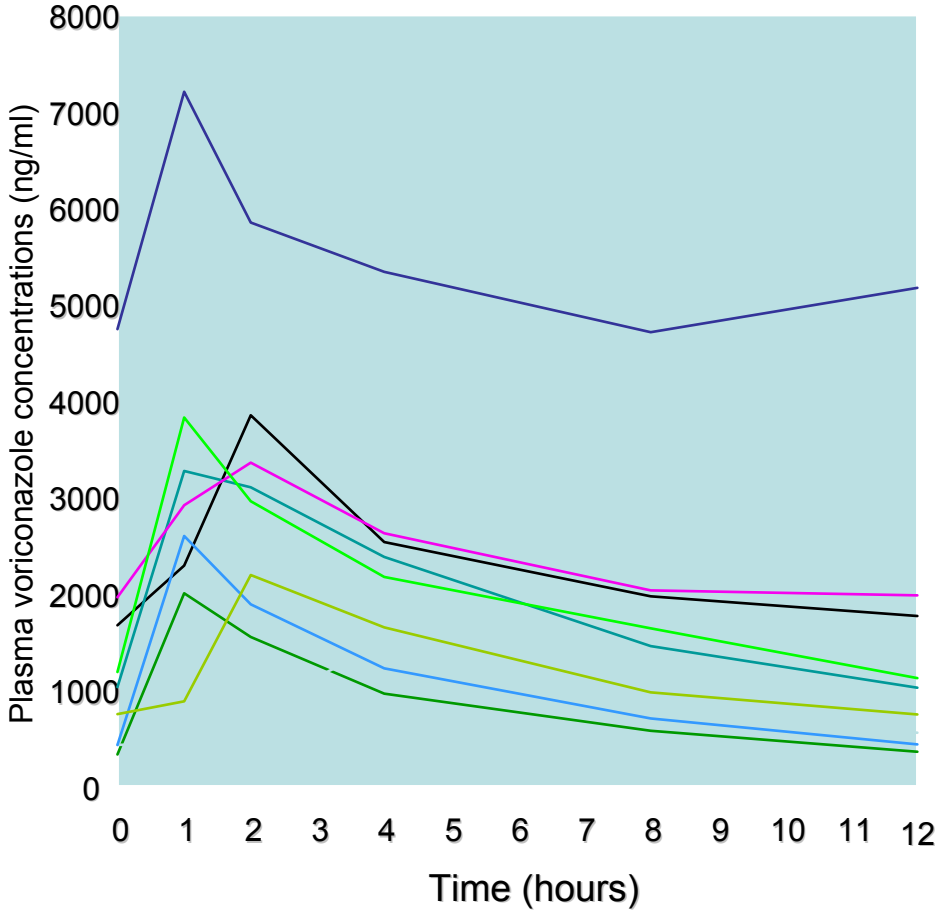


Free drug AUC
200 mg bid 8.4 mg*h/L
4 mg/kg q12h 21 mg*h/L

Candida spp MIC_{90}: 0.25 µg/mL
Aspergillus spp $MIC_{90:}$ 0.50 µg/mL

1. Andes D, et al. *Antimicrob Agents Chemother*. 2003;47:3165-3169.
2. Pfaller MA, et al. *J Clin Microbiol.* 2006;44:819-826.

Voriconazole PK *variability*



Individual pharmacokinetic profiles of voriconazole in patients receiving 200 mg q12h x 14 Days

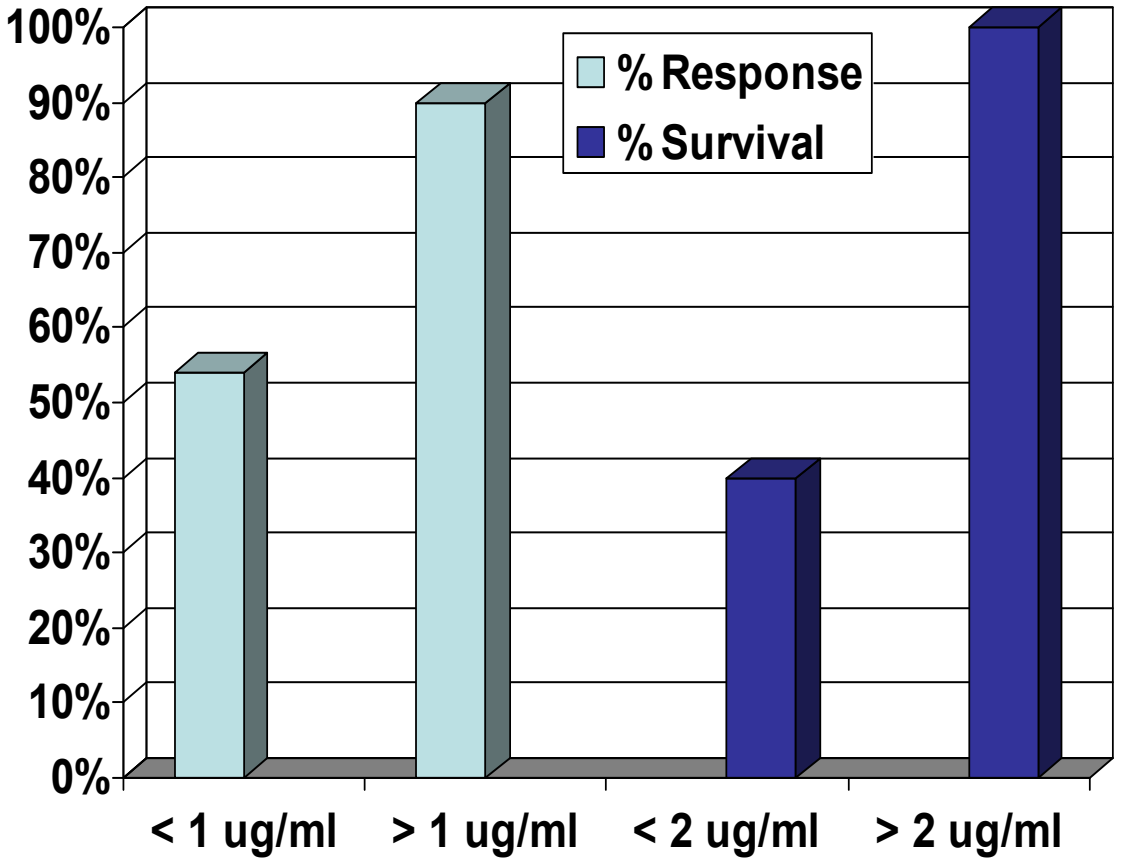
- Healthy volunteers
- Hematologic malignancy
- BMT
- Lung transplant
- ICU

Trifilio et al Cancer 2007;109:1532–5.
Mohammedi et al Eur J Clin Microbiol Infect Dis (2005) 24:358–360
Trifilio et al Bone Marrow Transplantation (2005) 35, 509–513
Berge M et al Transpl Infect Dis. 2009 Mar 17. [Epub ahead of print]

Voriconazole concentration effect

- Smith et al
  N = 28 patient with Aspergillosis

- Pascual et al
  N = 52 patients with Invasive fungal infections

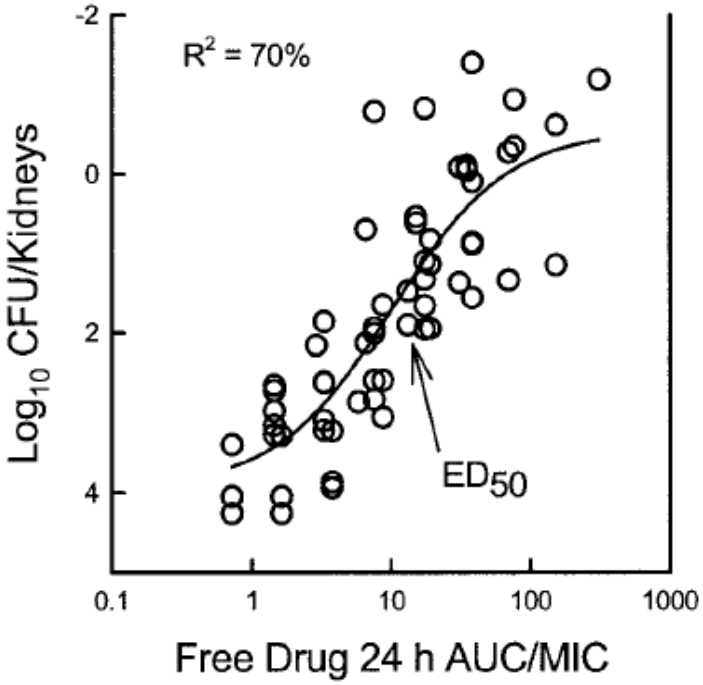


Voriconazole dose increased in 11 patients with concentration < 2.0, 8 of 11 survived

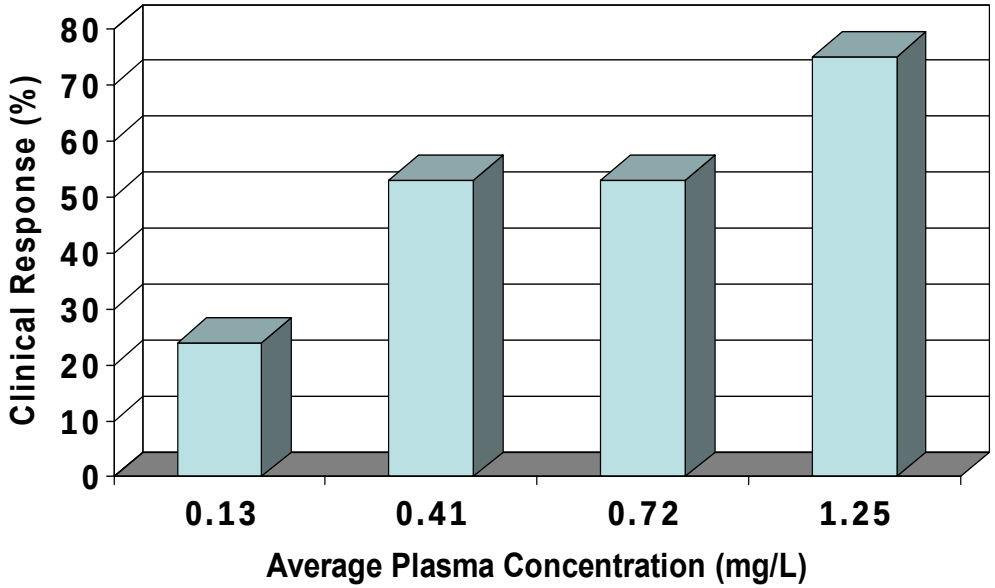
Smith et al Antimicrob Agents Chemother 2006;50:1570–1572
Pascual et al Clin Infect Dis 2008;46:201

Posaconazole pharmacodynamics

Animals and *Candida*



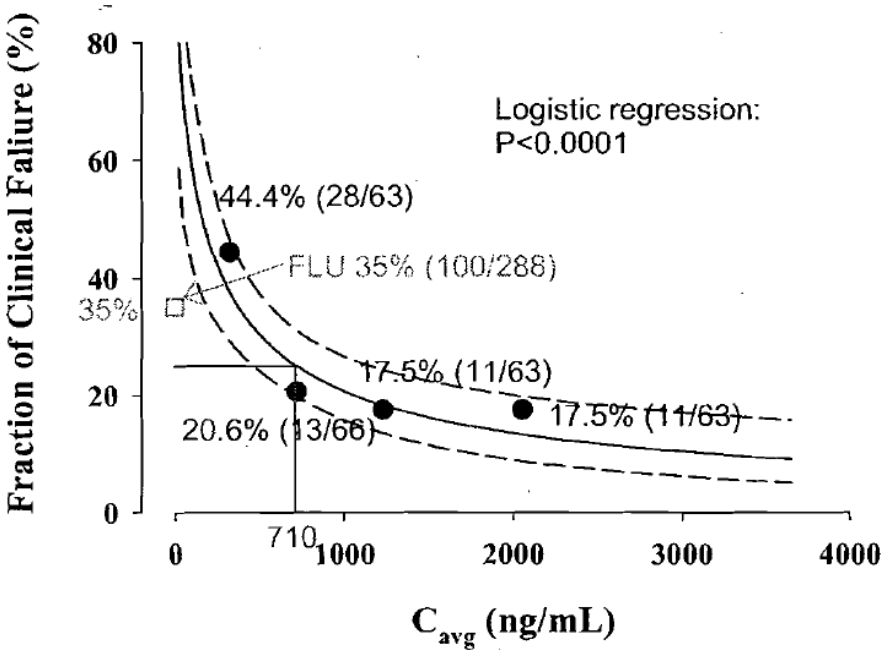
***Aspergillus* and patients**



Candida spp $MIC_{50/90}$: 0.12/0.5 µg/ml
Aspergillus spp $MIC_{50/90}$: 0.25/0.5 µg/ml

1. Andes D, et al. *Antimicrobial Agents Chemother.* 2004;48:137-142.
2. Walsh TJ, et al. *Clin Infect Dis.* 2007;44:2-12.
3. Diekema DJ, et al. *J Clin Microbiol.* 2003;41:3623-3626.
4. Pfaller MA, et al. *Diagn Microbiol Infect Dis.* 2004;48:201-205.

Posaconazole concentration effect



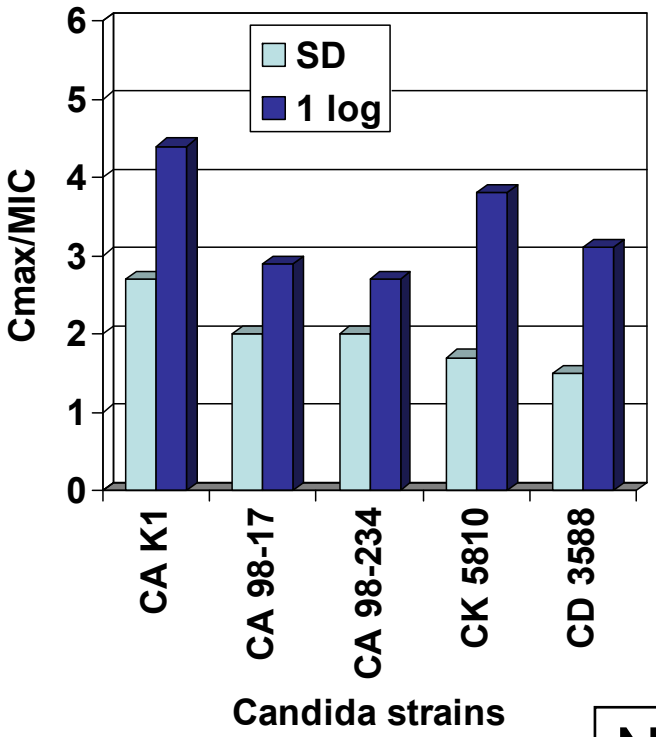
- IFI Prophylaxis in GVHD
  - Average level in those with IFI 0.611 ug/ml
  - Average level in those without IFI 0.922 ug/ml
- FDA Guidance
  - Goal = average concentration > 0.700 ug/ml

Krishna et al Pharmacotherapy 2009;53:958

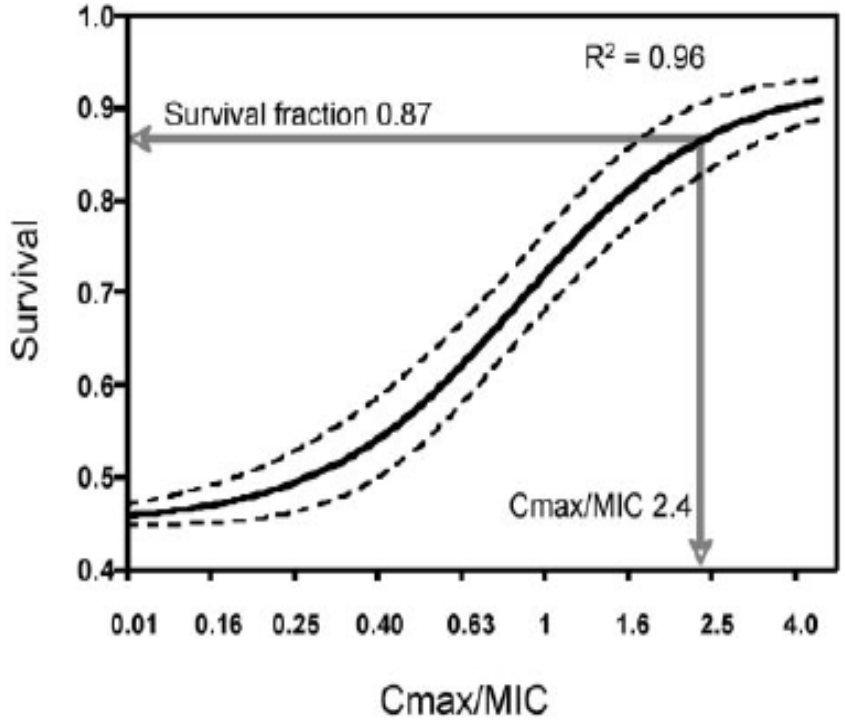
FDA. http://www.fda.gov/cder/foi/nda/2006/022003s333_NovafilTOC.htm

Pharmacodynamic target: AmB in animals

***Candida* spp**[1]



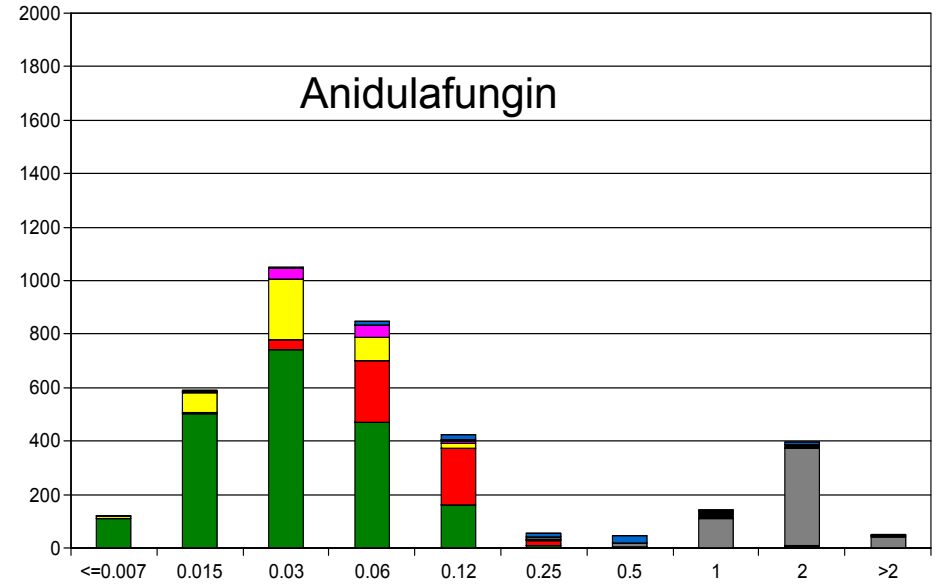
***Aspergillus* spp**[2]

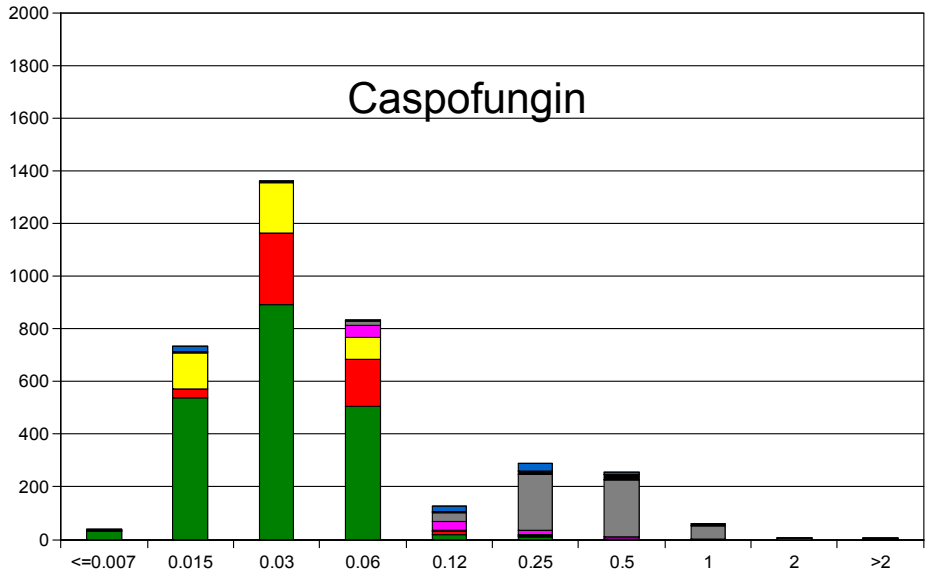


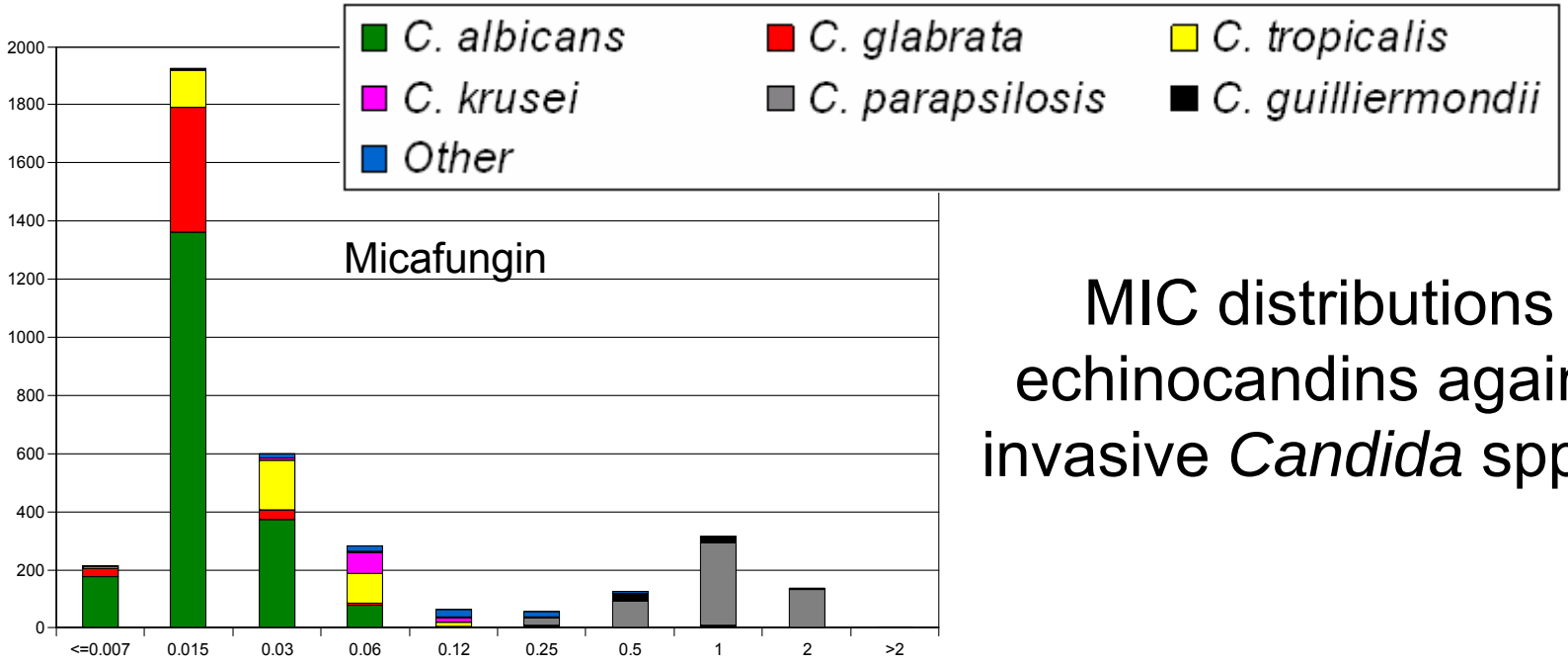
No clinical validation

1. Andes D, et al. *Antimicrob Agents Chemother.* 2001;45:922-926.
2. Wiederhold NP, et al. *Antimicrob Agents Chemother.* 2006;50:469-473.

Echinocandin in vitro potency

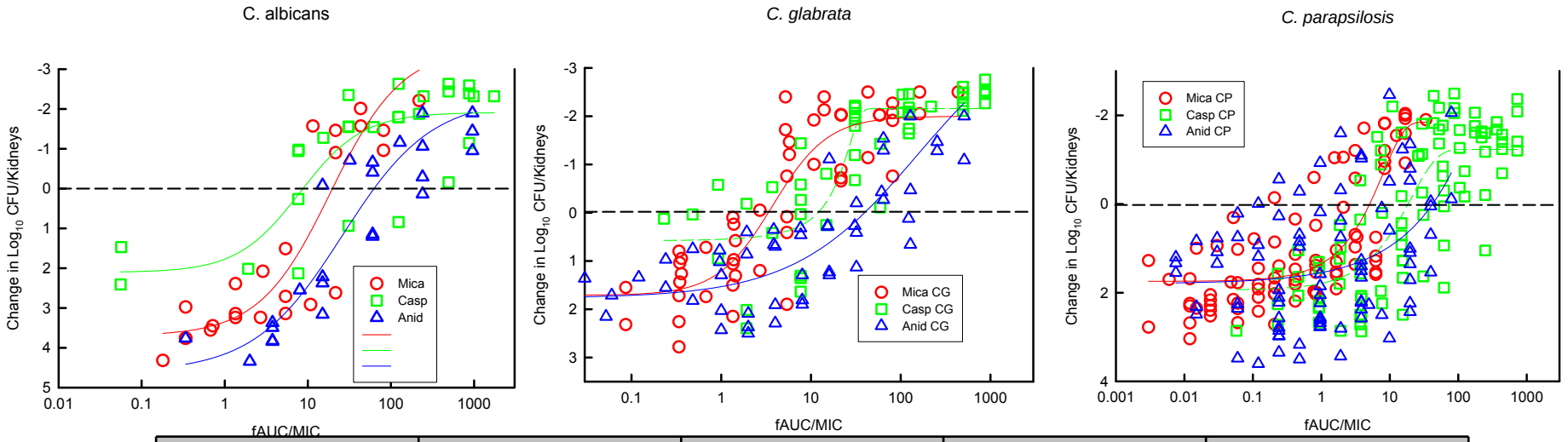






MIC distributions of the echinocandins against 3717 invasive *Candida* spp. isolates

Echinocandin PK/PD target in mice



Drug	Organism Group (n)	MIC range (ug/ml)	Static Dose (mg/kg/24h)	f24h AUC/MIC
Anidulafungin	C. albicans (6)	0.015-0.03	2.08 ± 1.23	23.3 ± 17.8
	C. glabrata (9)	0.03-1.0	4.24 ± 2.38	13.3 ± 12.4
	C.parapsilosis (15)	0.25-4.0	17.9 ± 22.1	4.27 ± 5.72
Caspofungin	C. albicans (4)	0.015-0.12	0.72 ± 1.51	5.47 ± 5.43
	C. glabrata (9)	0.03-0.25	0.33 ± 0.71	8.50 ± 8.78
	C.parapsilosis (15)	0.06-4.0	3.56 ± 3.08	73.0 ± 112
Micafungin	C. albicans (6)	0.008-0.03	2.54 ± 0.41	12.2 ± 5.73
	C. glabrata (9)	0.008-0.25	2.47 ± 2.79	3.87 ± 3.14
	C.parapsilosis (15)	0.12-1.0	25.0 ± 15.3	4.91 ± 3.82

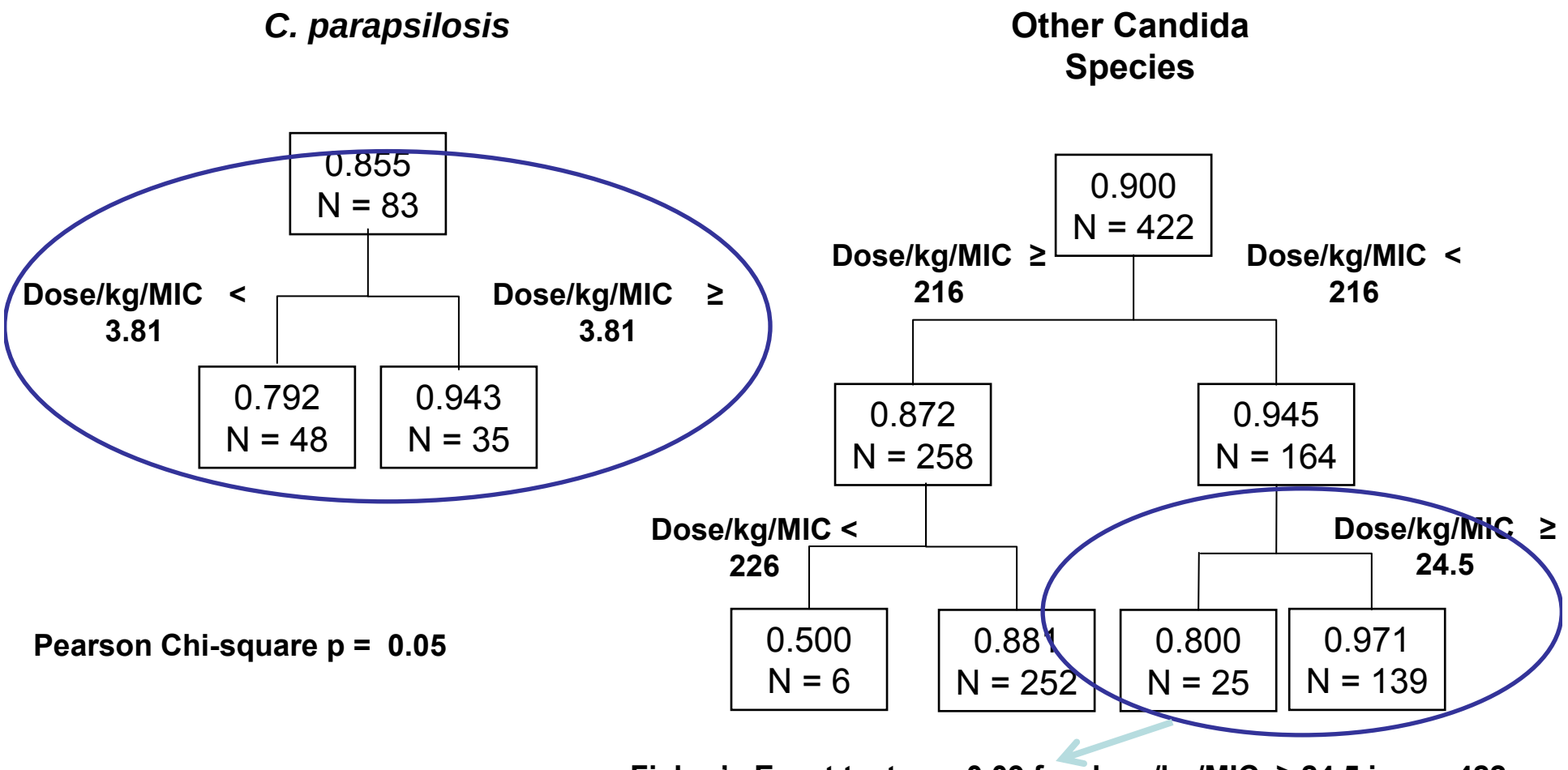
Echinocandin vs *C. parapsilosis:* animal pharmacodynamic summary

- More echinocandin was need to treat these CP isolates than the CA and CG isolates (i.e. MIC matters)
- BUT, the PD exposure (i.e. amount relative to the MIC) needed for CP efficacy was less than for CA or CG
- Suggests that species specific echinocandin difference
- FUTURE – Is the CP PD target from clinical trials lower than the PD target for other *Candida* species?

Clinical PK/PD breakpoint predictions - echinocandins

	Anidulafungin	Caspofungin	Micafungin
AUC (total)	112	98	126
Protein Binding	99%	97%	99.5%
AUC (free)	1.12	2.94	0.38
MIC Max for AUC/MIC 10-20 CA/CG	0.12-0.25	0.25-0.5	0.06-0.12
MIC90 CA/CG	0.12	0.06	0.03
MIC Max for AUC/MIC 3-5 CP	0.25-0.5	0.5-1.0	0.25-0.5
MIC90 Cp	1.0	1.0	1.0

Clinical micafungin breakpoints in candidemia



[1]Boxes within tree model show proportion of mycological success and sample size

Slide 38

smb1 Kim, to cut tree off after seond set of breakpoints for Other Candida and first set of breaks for C. parasiolis
sbhavnani-icpd, 20/04/2009

Back of the Napkin Calculations

- Micafungin Dose/Wt/MIC 3.81

100/70/x = 3.81
x=0.38

150/70/x = 3.81
x=0.56

200/70/x = 3.81
x=0.75

- Micafungin Dose/Wt/MIC 24.5

100/70/x = 24.5
x=0.06

150/70/x = 24.5
x=0.09

200/70/x = 24.5
x=0.12

Clinical trial echinocandin pharmacodynamics

- **Preliminary Pharmacodynamic Insights**
  - Dose/Weight/MIC vs Outcome
    - Classification and regression tree (CART) analysis revealed a dose/weight/MIC breakpoint of 3.8 predictive of mycological response
    - Mycological response: 91.6% ≥ 3.8; 78.4% < 3.8 (p =0.007)
  - *C. parapsilosis* vs Other *Candida* species
    - A stratified CART analysis suggested that the breakpoint of 3.8 was driven by those patients with *C. parapsilosis*
      - A breakpoint of 3.8 was found to be predictive of mycological response among patients with *C. parapsilosis* (n=83, p=0.053) while a breakpoint of 24.5 was predictive of response among patients with other Candida species (n=182, p=0.045)
  - These findings are consistent with animal model pharmacodynamic Candida species discrepancy

Antifungal pharmacokinetics/ pharmacodynamics: animals + people

Drug	Pattern	PAE	PK/PD	Magnitude
Azoles	Static	Long	AUC/MIC	**25**
5-FC	Static	Modest	T>MIC	25-50
AmB	Cidal	Long	Peak/MIC	2-4
Echinocandin	Cidal	Long	Peak/MIC	1-2
			AUC/MIC	**10-20/3-6**

Andes D. *Antimicrob Agents Chemother.* 2003;47:1179-1186.

What can pharmacodynamics do for you?

- Clinicians
  - Choose most potent and safe drug
  - Choose most potent and safe dosing regimen
  - Guide therapeutic drug monitoring
- Laboratory
  - Development of susceptibility breakpoints

Limitations and Needed Investigation

- More Aspergillus
- Incorporation of host factors
- Incorporation of infection site factors
- Consideration of prophylaxis
- Consideration of timing of therapy
- Additional clinical studies

It all started with a mouse.

- Walt Disney

THANK YOU