Which Antifungal for Which Site of Infection?

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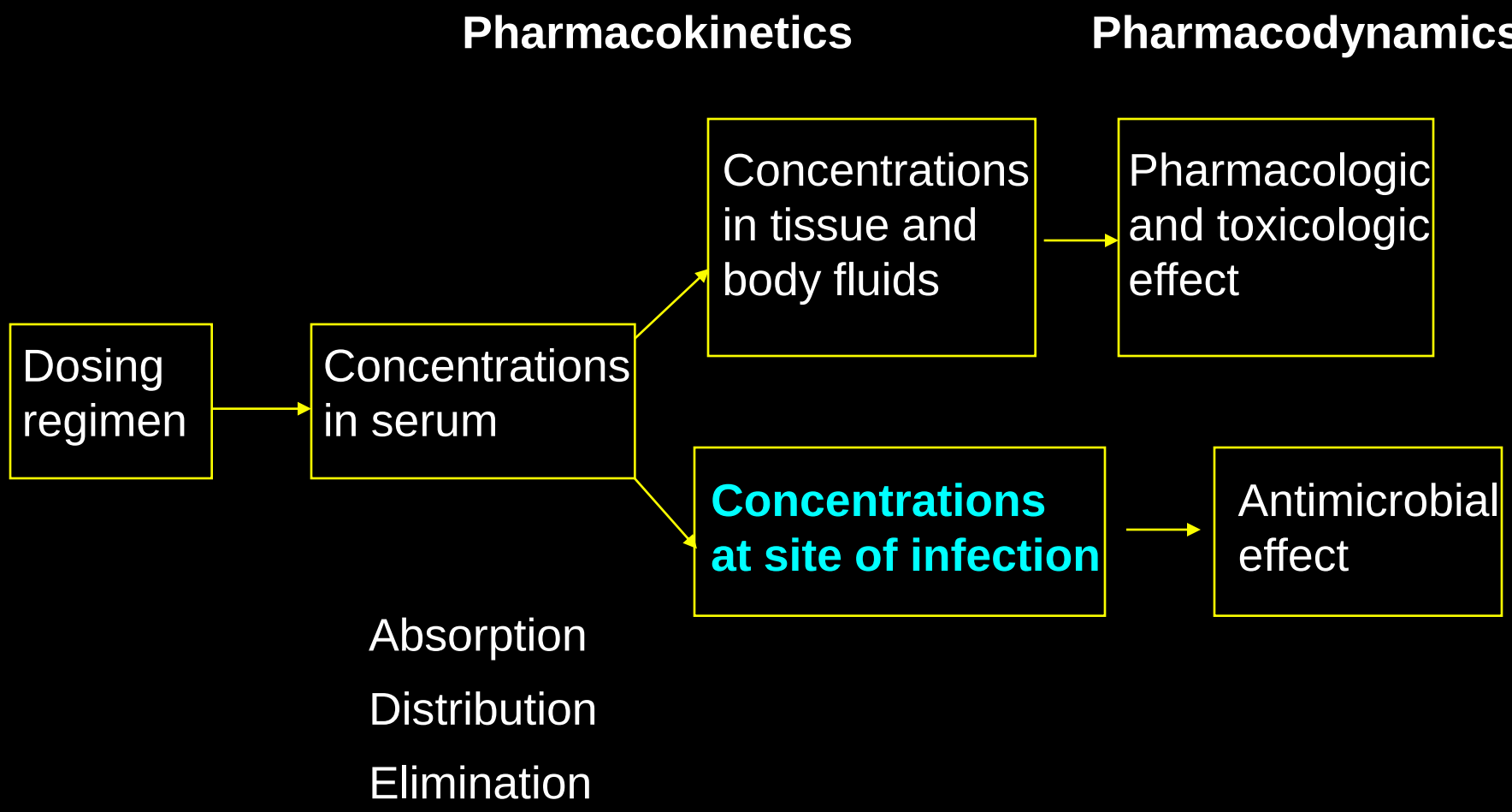
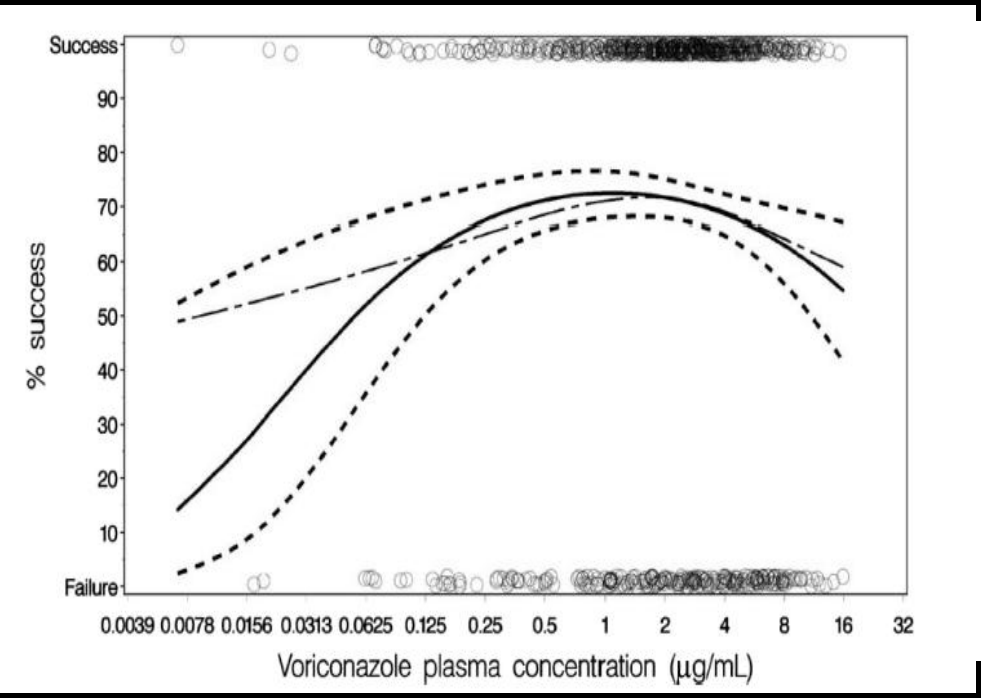
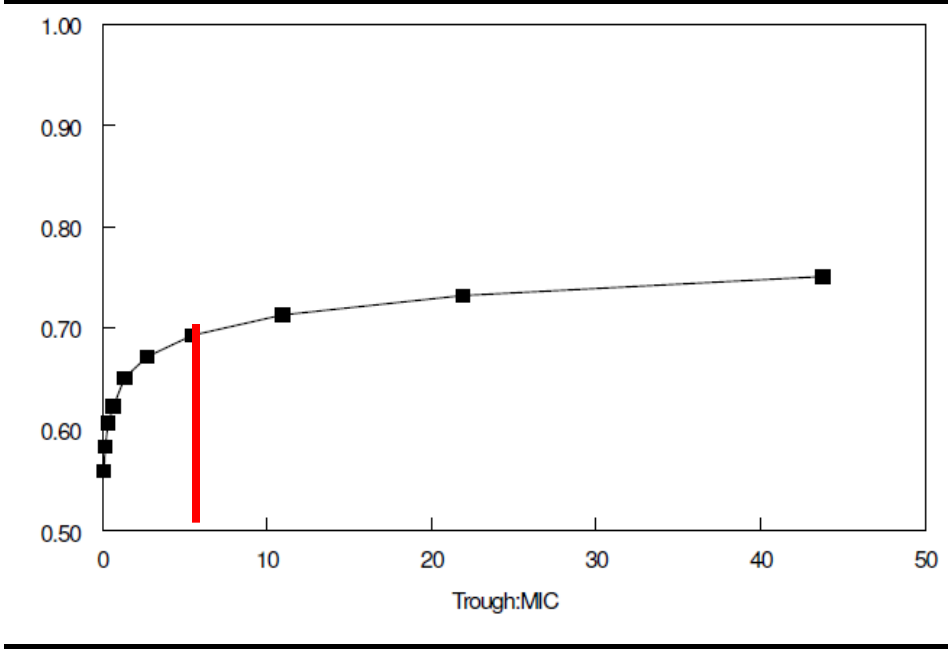
Antimicrobial Pharmacology



Voriconazole Serum PK and Outcome

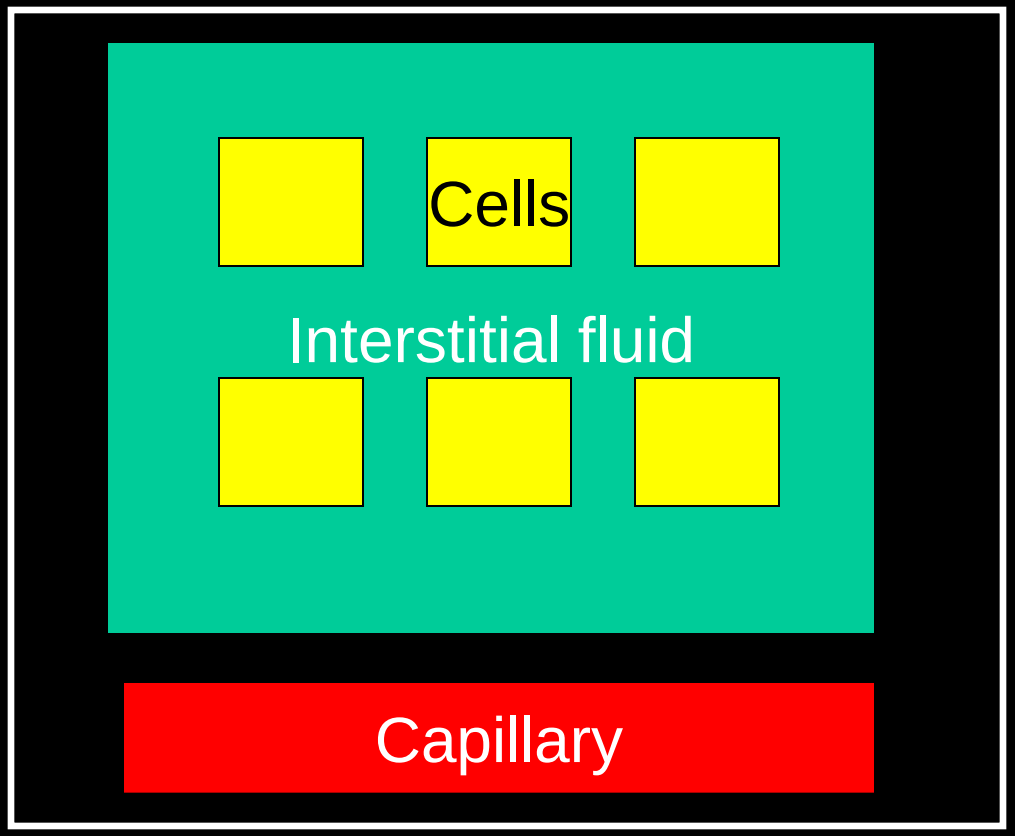




- **Retrospective, logistic regression analysis of 9 voriconazole clinical trial data**
- **N = 825 patients with *Aspergillus* and *Candida* infections**
- **Free AUC/MIC near 25, MIC ceiling 0.12 ug/ml**

Troke et al AAC 2011;55:4782

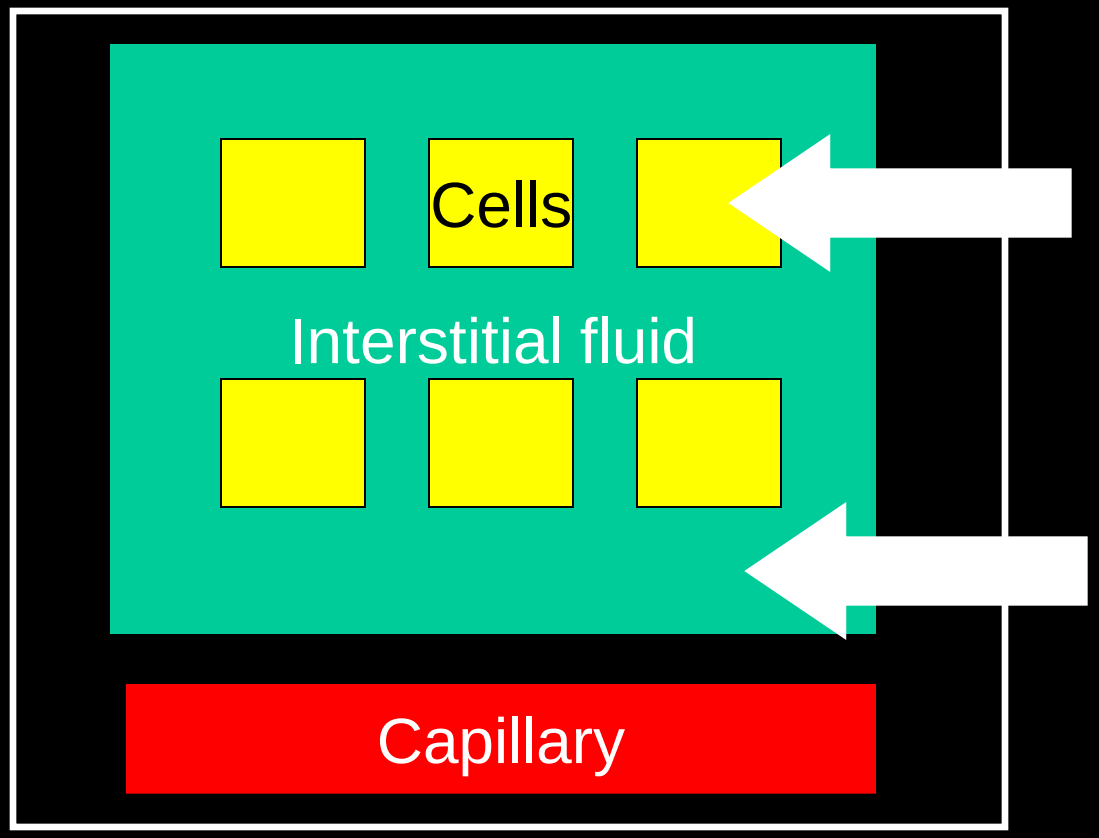
Where is the Fungus?



<u>Predominately Extracellular</u>
Candida
Aspergillus (except conidia)

<u>Predominately Intracellular</u>
Histoplasmosis
Cryptococcus

Where is the Antifungal?



Antifungals vary in tissue site distribution

Tissue Homogenates = Multiple compartments

- Intravascular
- Intracellular
- Interstitial

Antifungal Physiochemical Properties

Drug	MW (diameter)	LogD	Protein Binding	VD (L/kg)
Fluconazole	305	0.5	10	0.7
Itraconazole	706	>5	99.8	11
Voriconazole	349	1.8	58	4.6
Posaconazole	700	2.15	>99	7-25
AmB	924 (<0.4)	-2.8	95-99	0.5-5
L-AmB	924 (0.08)	-2.8	95-99	0.1-0.7
ABLC	924 (1.6-11)	-2.8	95-99	1.1-8.8
5FC	120	-2.34	5	0.6-2.2
Anidulafungin	1140	-3.32	98	0.8
Caspofungin	1093	-3.88	97	0.15
Micafungin	1291	-1.62	99.8	0.24

Antifungal Tissue Site PK and Relevance

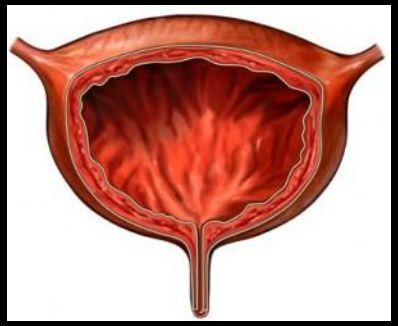
Sites	Organism	PK	Relevance
Urine			
CNS			
Eye			
Lung			

Urine Antibacterial PK - Outcome

	Clearance of Bacteruria	Failure to Clear Urine
Positive Urine Inhibitory Levels	18/20 (90%)	5/13 (38%)

Stamey et al. Serum versus urinary antimicrobial concentrations in cure of urinary tract infections. NEJM 1974;291:1159

	Clearance of Bacteruria
Positive Urinary Inhibitory Levels	49/70 (70%)
No Urine Inhibitory Levels	0/14 (0%)



McCabe et al. Treatment of pyelonephritis – bacterial, drug, and host factors in success or failure among 252 patients. NEJM 1965;272:1037

Urine Excretion (%) of Antifungals

AmB	3-20%
ABLC	30%
L-AmB	4.5%

Bekersky et al J Clin Pharmacol 2001,
Bekersky et al AAC 2002

Caspofungin	<2%
Anidulafungin	
Micafungin	

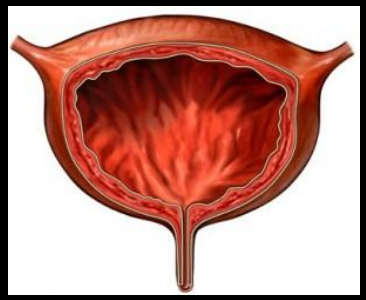
Balani et al Drug Metab Disp

Fluconazole	>90% (10X serum)
Itraconazole	1-10%
Voriconazole	<2%
Posaconazole	<1%

Saag et al AAC 1988

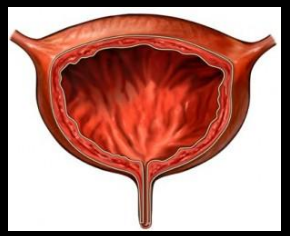
5FC >90%

Polak A et al Chemotherapy 1976



Candiduria 10% all urine cultures
Most common isolate in ICU

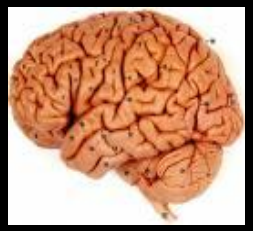
Clinical Experience



Drug	Eradication
Fluconazole	50-78%
Flucytosine	70%
AmB	72% (single dose)
Lipid AmB	Multiple case failures

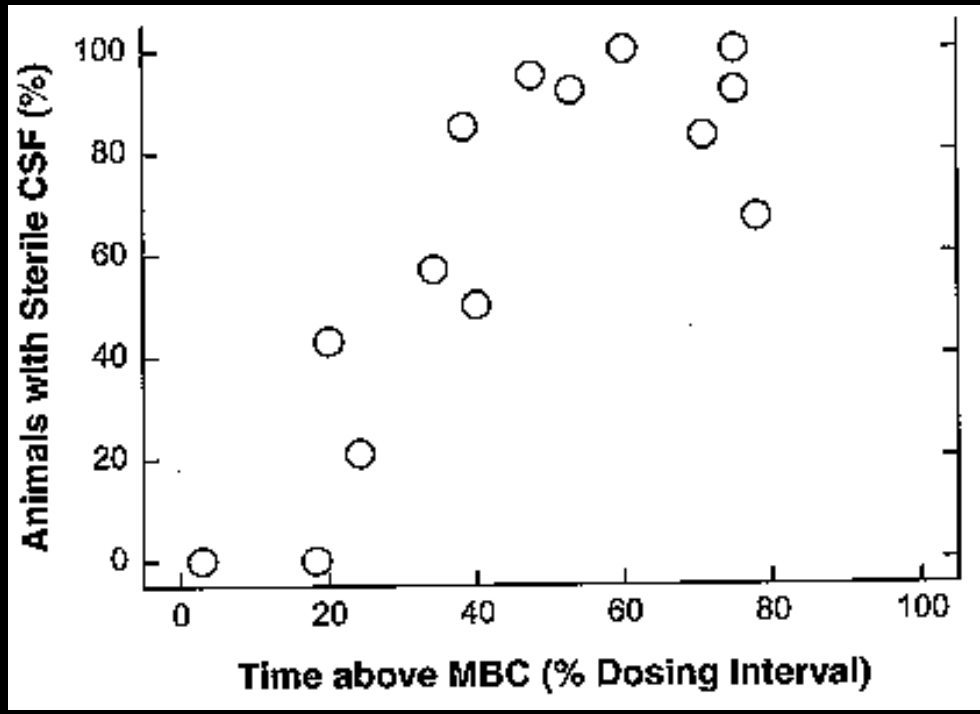
Fisher et al CID 2011;52:s457

Sobel et al Clin Infect Dis 2000;30:19-24, Schonebak ISHAM Paris 1971
Wise et al Urology 1974;3:708-11, Fisher et al Clin Microbiol Infect 2003;9:1024-7
Leu et al Clin Infect Dis 1995;20:1152-7

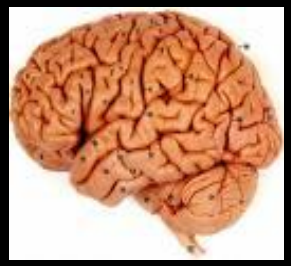


CSF Antibacterial Pharmacokinetics and Outcome

- Beta-lactams
- S. pneumoniae meningitis
- CSF T>MIC
- Bacteriologic outcome



Andes D and Craig WA. Infect Dis Clin N Amer. 1999;13:595-618



Fungal CNS Involvement

Invasive Candidiasis	15-64%
Invasive Aspergillosis	6% (90% + mortality)
Cryptococcosis	67-84% HIV
Histoplasmosis	5-20% Disseminated
Coccidioidomycosis	25% Disseminated
Blastomycosis	40% HIV

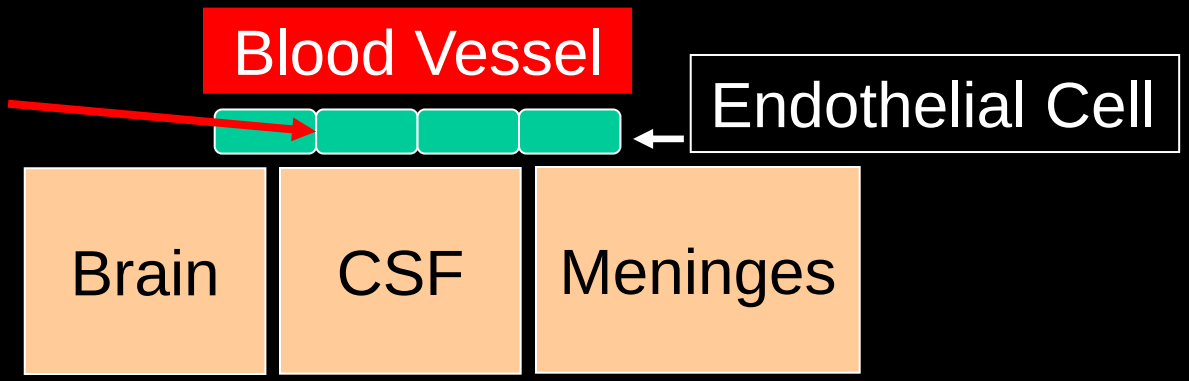
Lipton AJM 1984;76:101, Bayer Medicine 1976;55:477, Patterson Medicine 2000;79:250, Chapman CID 2000;30:679, Wheat CID 2000;30:688.

CNS is Pharmacologically Protected

Blood:Brain Barrier

Tight Junction

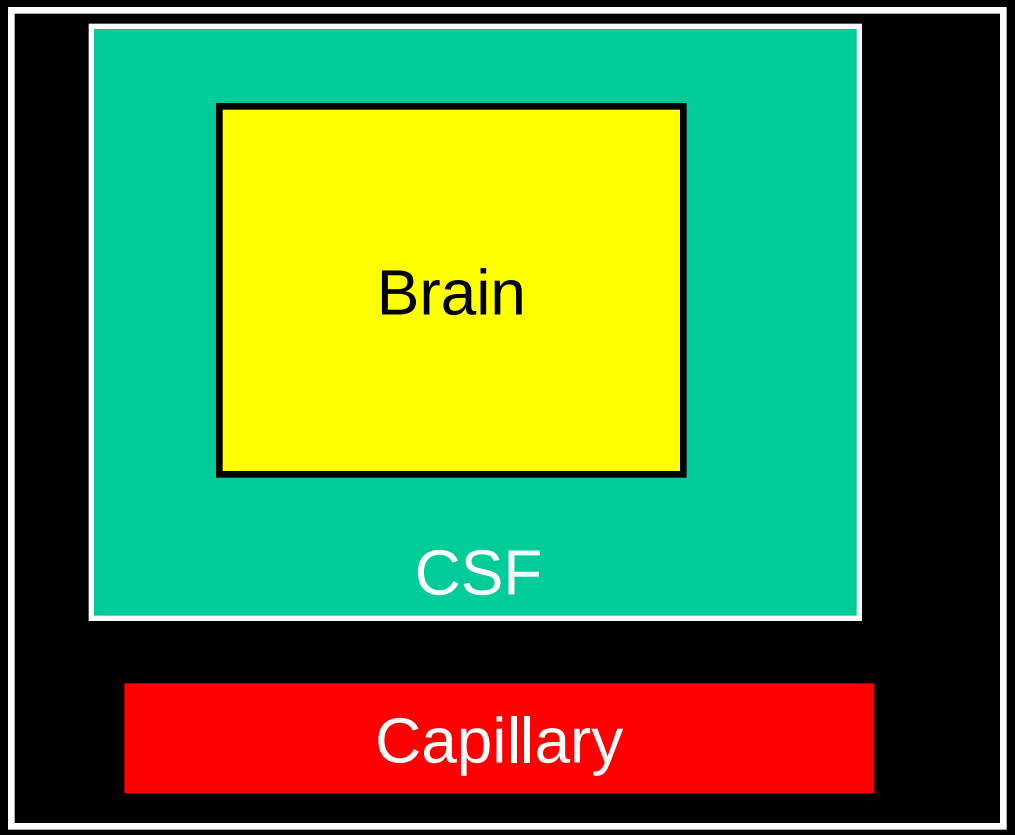
20 A



Fenestrated Junction

100 A

Where is the Fungus in CNS?



CSF
Candida
Cryptococcus
Histoplasmosis
Blastomycosis

Meninges and Brain
Candida
Cryptococcus
Histoplasmosis
Blastomycosis
Aspergillus

Antifungal CSF Penetration

Formulation	CSF Conc
AmB	0-4%
LAmB	
ABLC	LAmB>AmB and ABLC

Utz et al J Infect Dis 1975, Bindshadler and Bennett J Infect Dis 1969

Fluconazole	>60-90%
Itraconazole	<12%
Voriconazole	60%
Posaconazole	<1%

Brammer KW et al Rev Infect Dis 1990
Verweiji JCM 1999
Purkins 2002

5FC	75%

Utz et al J Infect Dis 1975

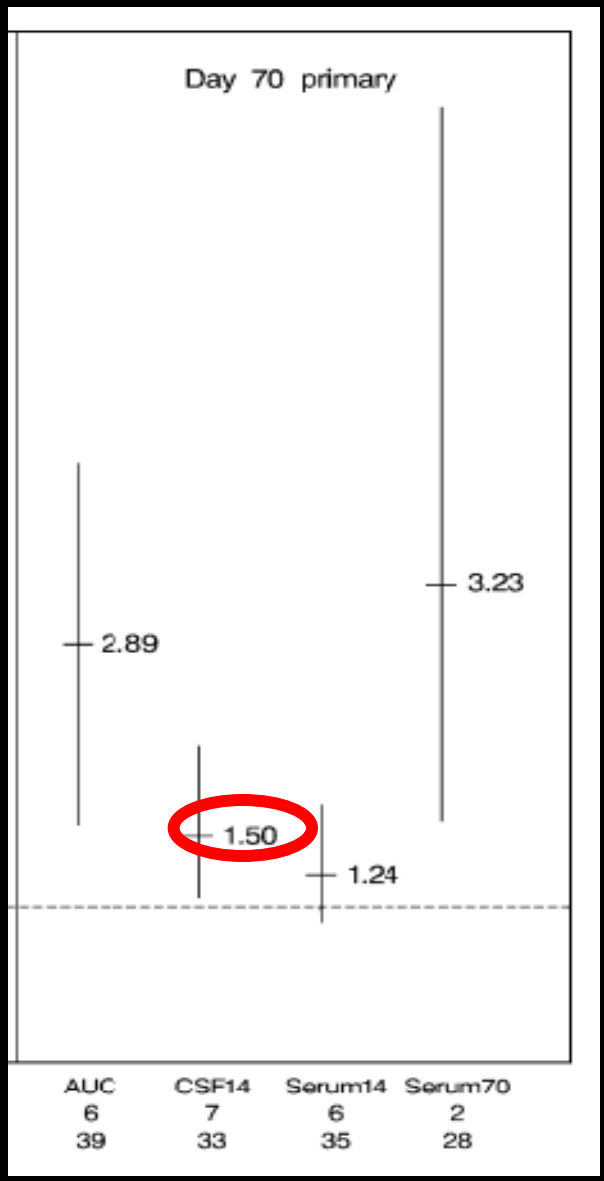
Fluconazole CSF Pharmacokinetics in Cryptococcal Meningitis

N = 64 with PK

Fluconazole 400 mg and 800 mg

Concentration (mg/L)		
Serum	24.7	37.0
CSF	25.1	32.7

Survival associated with both serum and CSF kinetics (p=0.081)



Manosuthi et al HIV Medicine 2009;11:276

Antifungal CNS PK Controversy

Crypto Meningitis - Rabbits

	Serum	CSF	CSF CFU
Itra	12.3	<0.08	1.5 cfu/ml
Fluc	73.3	45.1	0.9 cfu/ml

Perfect et al. Antimicrob Agents Chemother. 1986;29:579

Cocci Meningitis - Rabbits

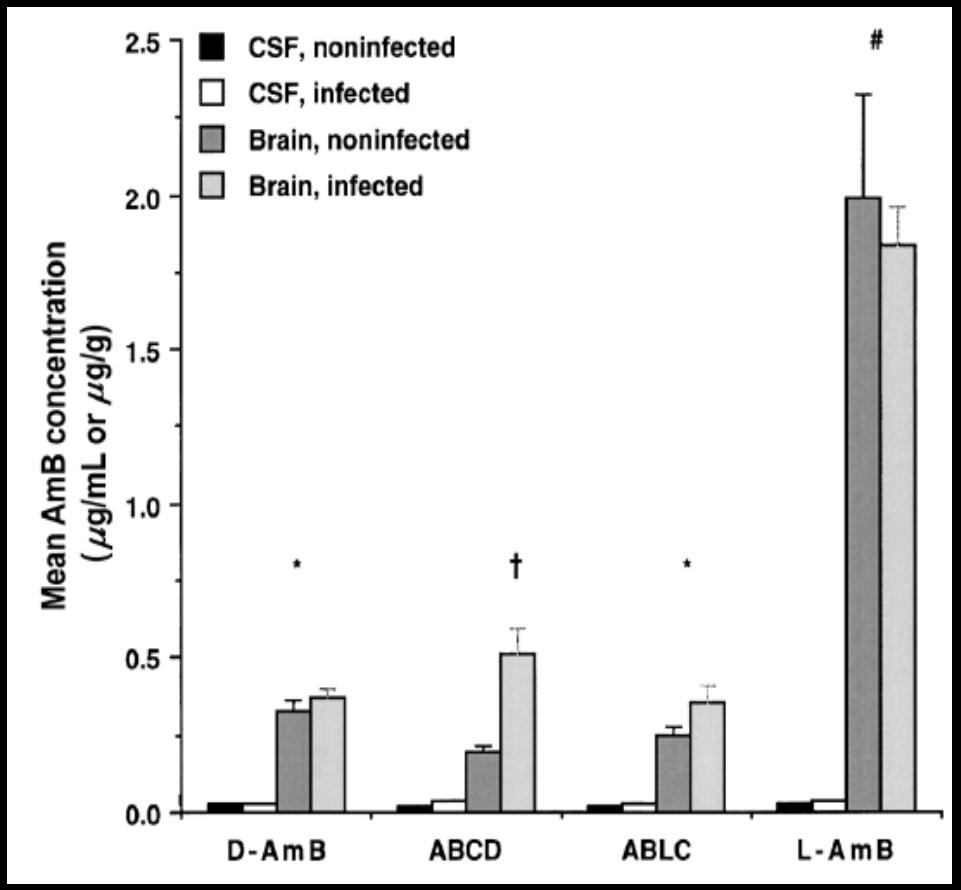
	Serum	CSF	CSF CFU	Brain CFU
Fluc	40	30	0	1.2
Itra	2.51	0	0	1.5

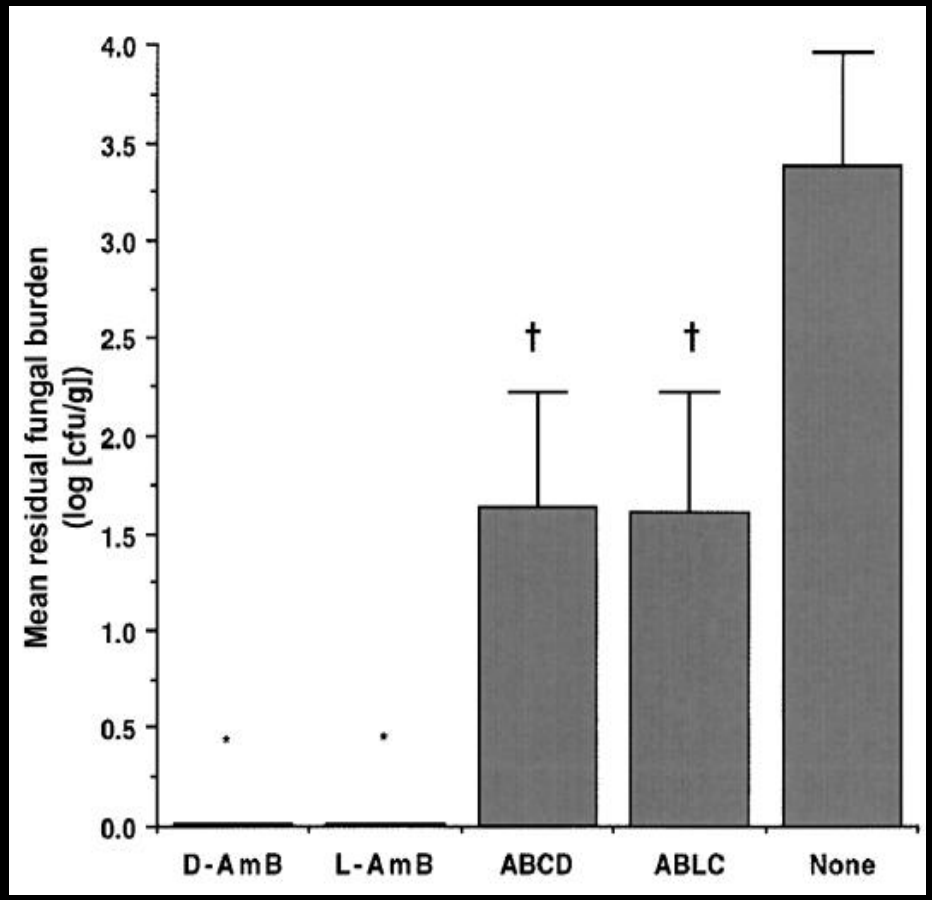
Sorensen et al. Antimicrob. Agetns Chemother. 2000;44:1512

Rabbits

Comparison of ABLC and LAmB

CNS Kinetics and Effect





Rabbits, Candida meningitis

Groll et al J Infect Dis 2000;182:274

Clinical Experience Lipid vs AmB

1] Retrospective, transplant cryptococcal meningitis (N=75)

- Mortality AmB 73%vs LAmB 27%, p=0.007
- LAmB survival advantage OR 0.11 95% CI 0.02-0.57, p=0.008

2] Leenders more rapid sterilization with LAmB vs AmB (n=28, $p<0.05$)

3] Sharkey = ABLC vs AMB, equivalent

4] Hamill LAmB = AMB, no significant difference

Sun et al CID 2009;49:1721, Leenders et al AIDS 1997;11;1463, Hamill RJ et al 39th ICAAC, Sharkey et al CID 1996;22:315

Clinical Experience Voriconazole

1] Retrospective, CNS IFI (mostly aspergillosis N = 192)

- 48% response (much better than historical control)
- Primary therapy success in 63% versus 45% for salvage (p = 0.06 NS).

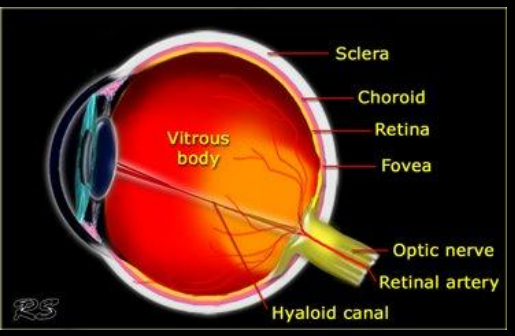
2] *Exerohilum* meningitis outbreak (N=391)

Voriconazole and/or LAmB recommended based upon CNS kinetics

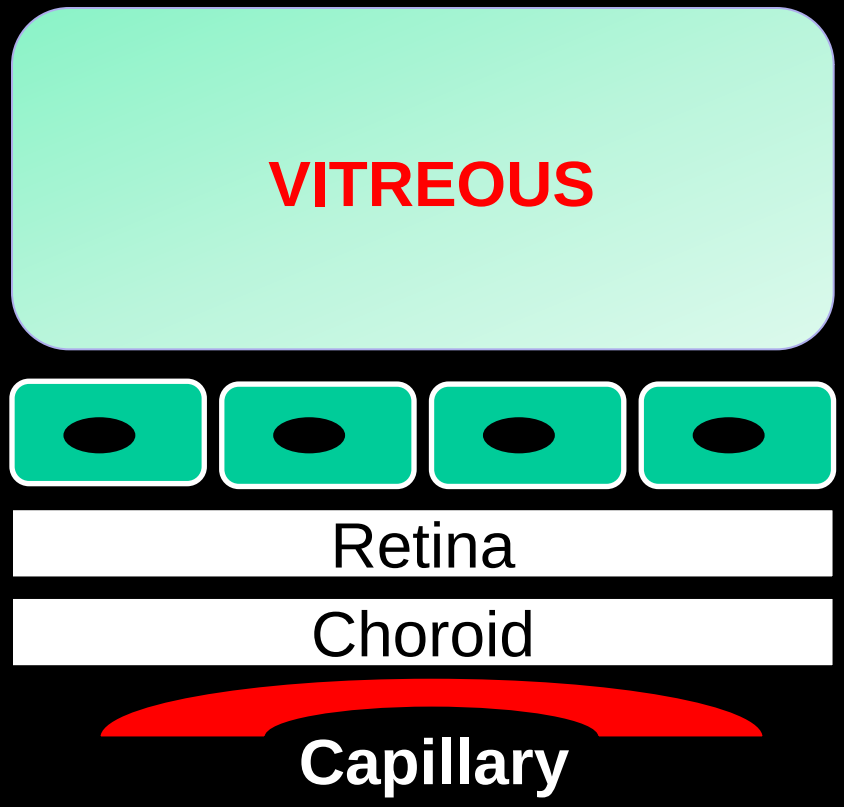
Outcomes from CDC after the shutdown is over!

Schwartz et al Infection 2011;39:201, CDC.gov

CSF 60% of serum



Fungal Ocular Infection



Endophthalmitis

Blood-Ocular Barrier

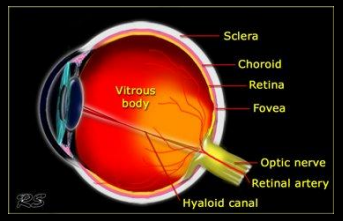
Chorioretinitis

Candida 3-25%, Aspergillus 1%

Vitreal Penetration of Antifungals

	Species	Vitreous (mg/L)	%Serum
AmB/L-AmB/ABLC	Rabbit/Human	0-0.47	0-38%
5-FC	Rabbit/Human	10-22	49%
Fluconazole	Rabbit/Human	10-66	50-75%
Itraconazole	Rabbit	0.22	10%
Voriconazole	Human	0.81	38%
Micafungin	Rabbit	0.06-0.16	<1%
Caspofungin	Human	0	0

Goldblum et al AAC 2002, Louie et al AAC 1999, O'Day et al Arch Ophthal, Fisher et al JID 1983, Walsh et al Inest Ophthal Vis Sci, Hariprasad et al Arch Ophthalmol 2004, Groll AH et al AAC 2001, Savani et al AAC 1987, Mian et al J Ocul Pharmacol Ther, Abe J Eye 1991



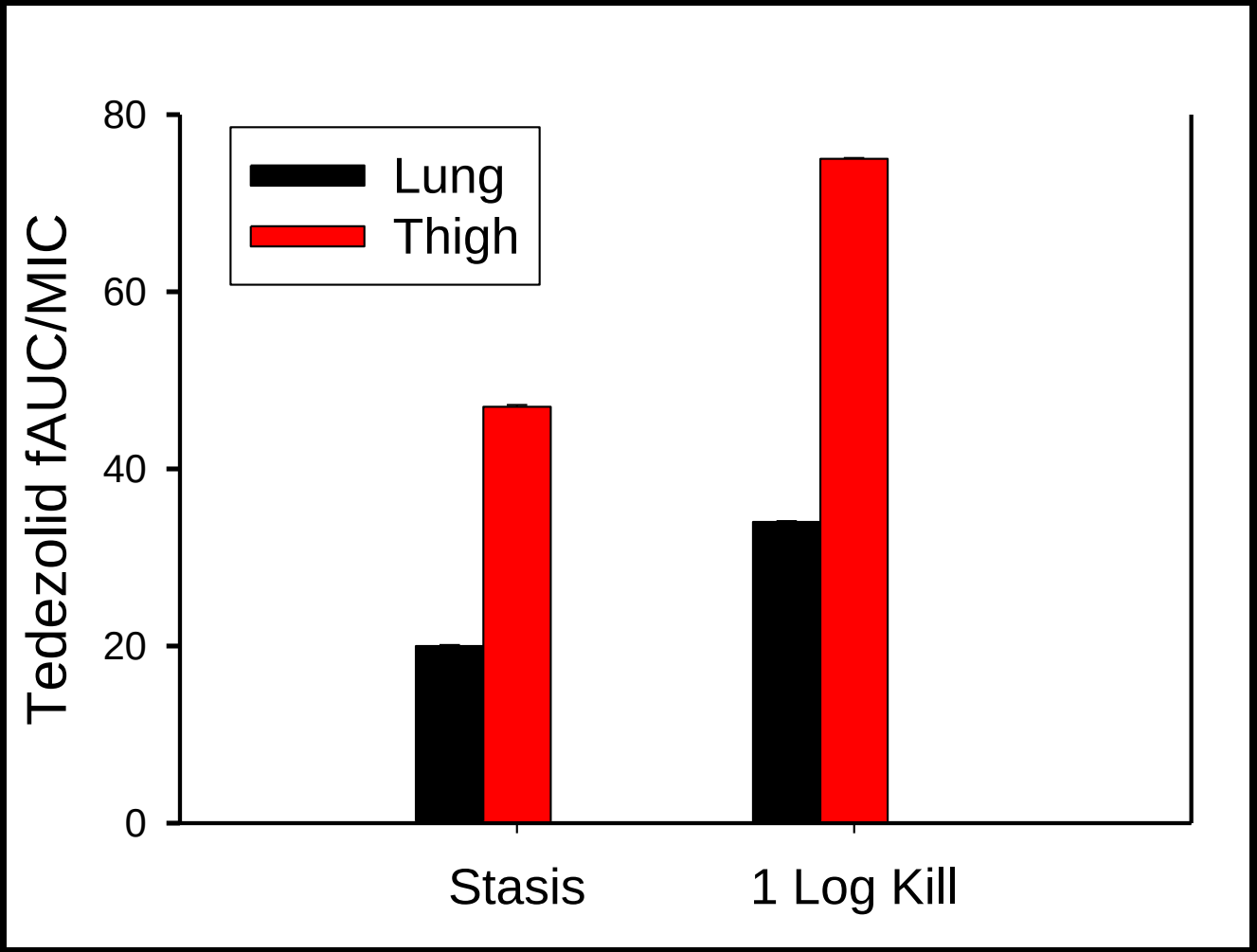
Clinical Experience

Drug	Efficacy
AmB	Failures common
Fluconazole	>90% (N >100)
Voriconazole	80-90% (N<10)
Echinocandins	0-55% (N=20s)

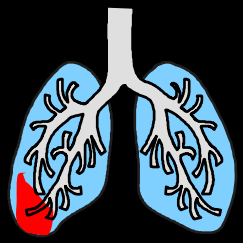
Riddell et al CID 2011;52:648

Fishman et al NEJM 1972;286:675, Bisbe et al CID 1992;15:910, Akler et al CID 1995;20:657
Breit et al Am J Ophthalmol 2005;19:485, Gauthier et al CID 2005;41:27, Reboli et al NEJM 2007;356:2472
Mora-Duarte et al NEJM 2002;347:2020, Pappas et al CID 2007;45:883, Betts et al CID 2009;48:1676

Differential Antibacterial Pneumonia Activity



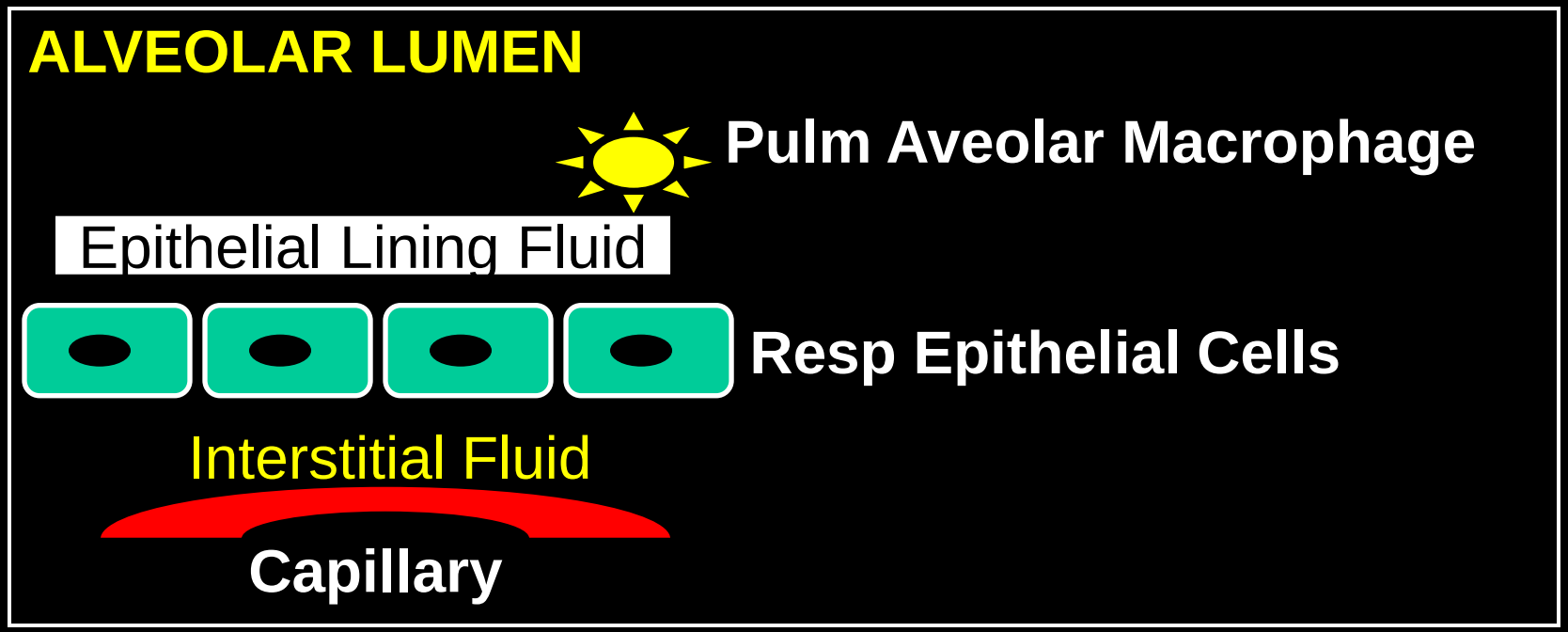
Oxazolidinone and MRSA



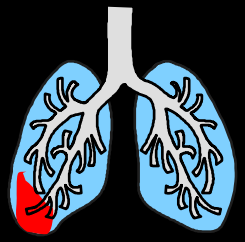
Mouse ELF:Blood Penetration > 10

Lepak AAC 2012;56:5916
Louie AAC 2011;55:3453

Antimicrobial Lung Kinetcs



Lamer C et al AAC 1993, Wunderink R et al Chest 2003, Conte JE et al AAC 2002,



Fungal Lung Involvement

Most common infection site for *Aspergillus, Histoplasma, Blastomyces, Coccidioides,* Zygomycetes

Lipton AJM 1984;76:101, Bayer Medicine 1976;55:477, Patterson Medicine 2000;79:250, Chapman CID 2000;30:679, Wheat CID 2000;30:688.

Lung Penetration of Antifungals

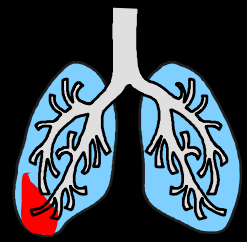
Formulation	Lung Conc	
Voriconazole	14.7 ug/g (n = 7)	
Itraconazole	4 X serum	
AmB	13 ug/g	10% serum
ABLC	222 ug/g	Pennington AAC 1974 (Dogs)
L-AmB	176 ug/g	

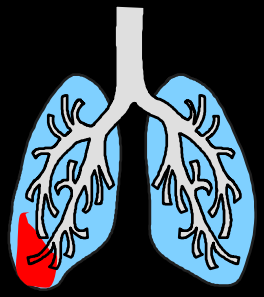
Wong-Beringer Clin Infect Dis 1998

AmB	2 ug/g
ABLC	23 ug/g
L-AmB	1 ug/g

Mitot et al Crit Care Med 2000

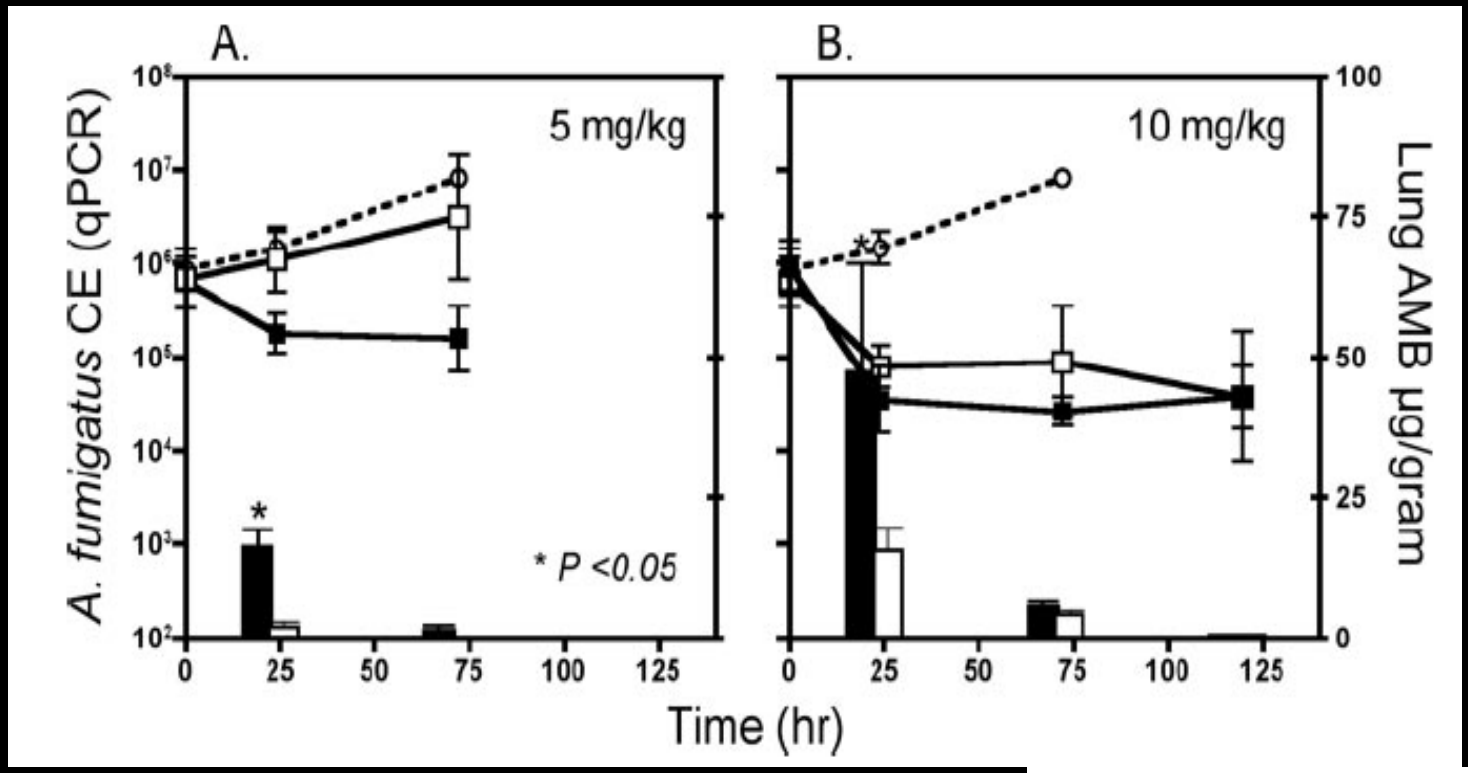
5FC	75% serum





Comparison of ABLC and LAmB

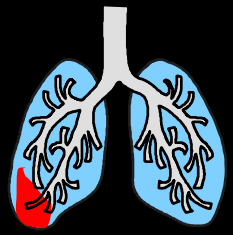
Lung Kinetics and Effect



LAmB

ABLC

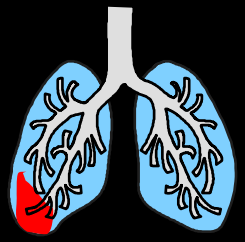
Lewis RE et al AAC 2007;51:1253



Clinical Experience

- Patients with leukemia and presumed and proven IFIs
- ABLC vs LAMB
- Subgroup (n = 15) with pulmonary IFIs demonstrated a nonsignficicant trend toward greater clinical response with ABLC 80% vs LAmB 56% p = 0.36

Fleming et al Leuk Lymph 2001;40:511



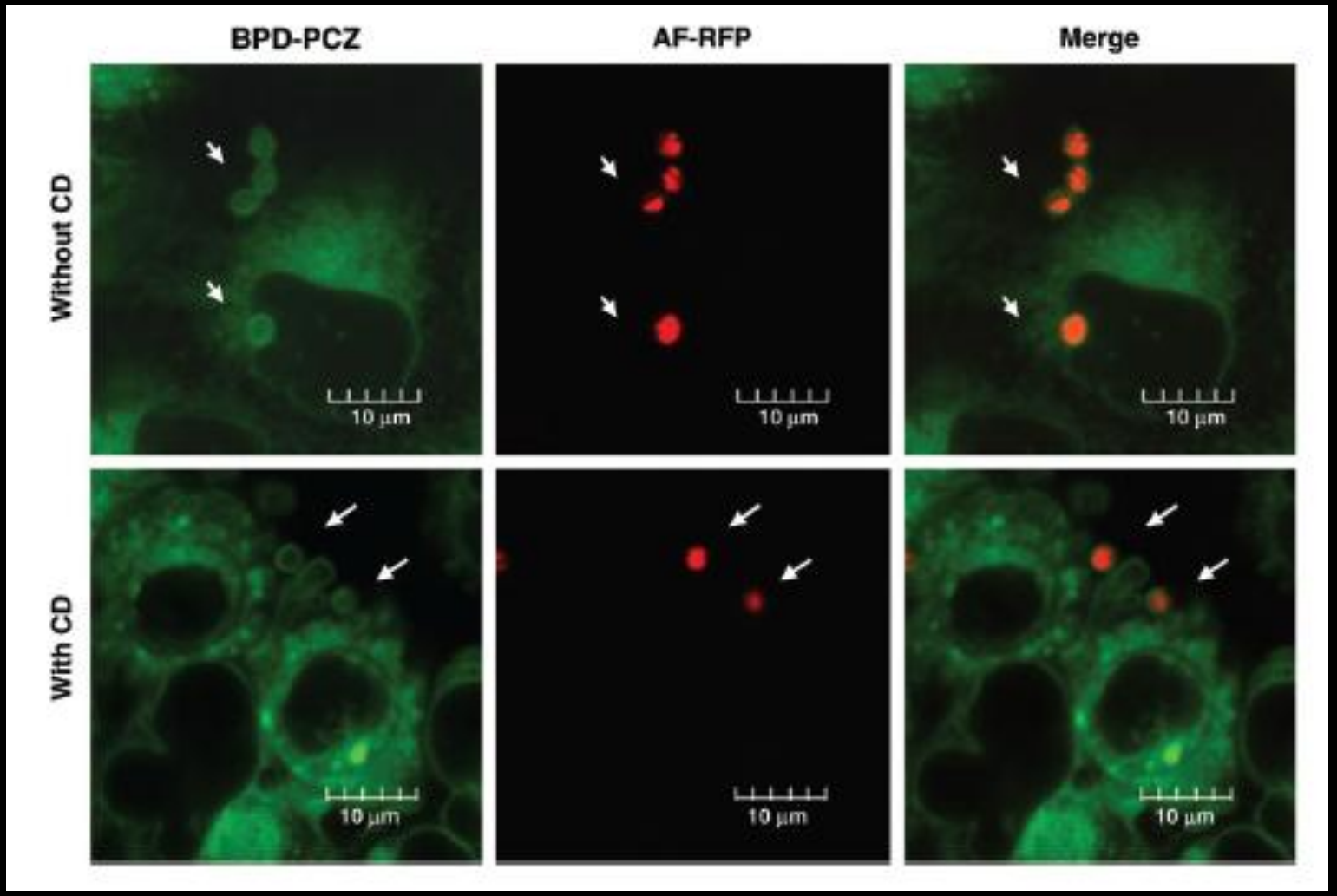
Human Intrapulmonary Antifungal Kinetics

	ELF/Plasma	AM/Plasma
ITC	0.21	2.97
OH-ITC	0.31	2.22
PCZ	0.83	32.6
VCZ	7.13	4.50
ANID	0.20	14.15
MICA	0.04	4.10

**** based on AUC_{tau}***

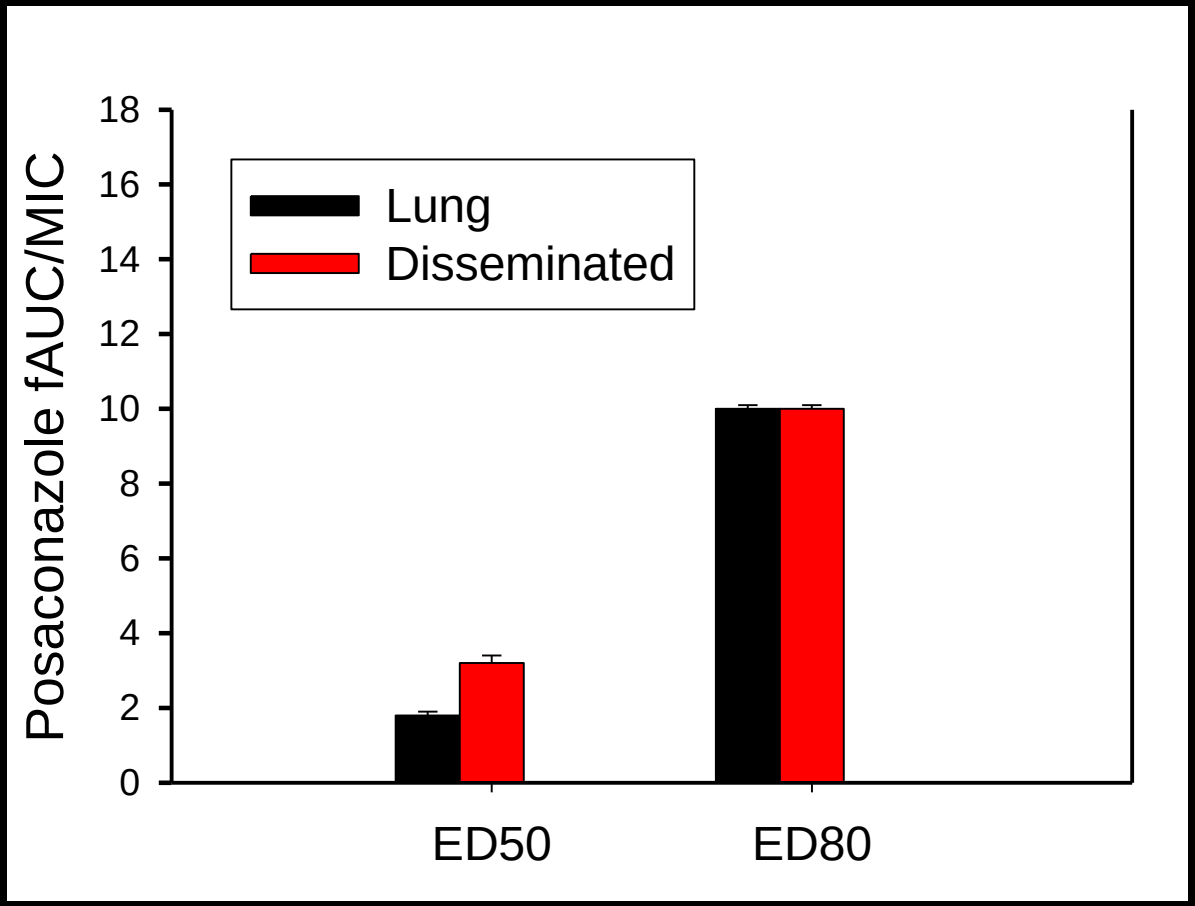
Conte et al. AAC 2004; Conte et al. AAC 2008;
Crandon et al. AAC 2009; Nicasio et al. AAC 2009

Concentration and Effect of Posaconazole within Host Cell Membranes



Campoli et al J Infect Dis. 2013 Sep 6

Posaconazole Lung and Dissemination - Treatment



ELF:Blood Ratio 0.8
AM:Blood Ratio 33

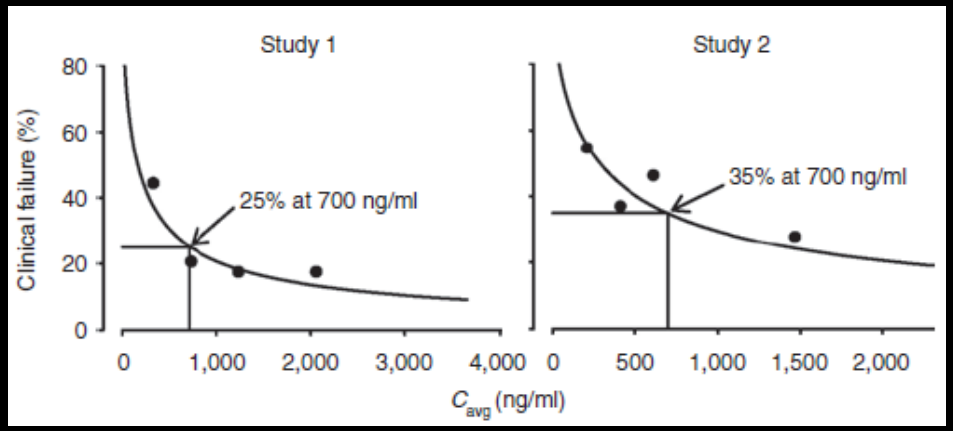
Antifungal:
Posaconazole
Aspergillosis

Similar in lung and disseminated

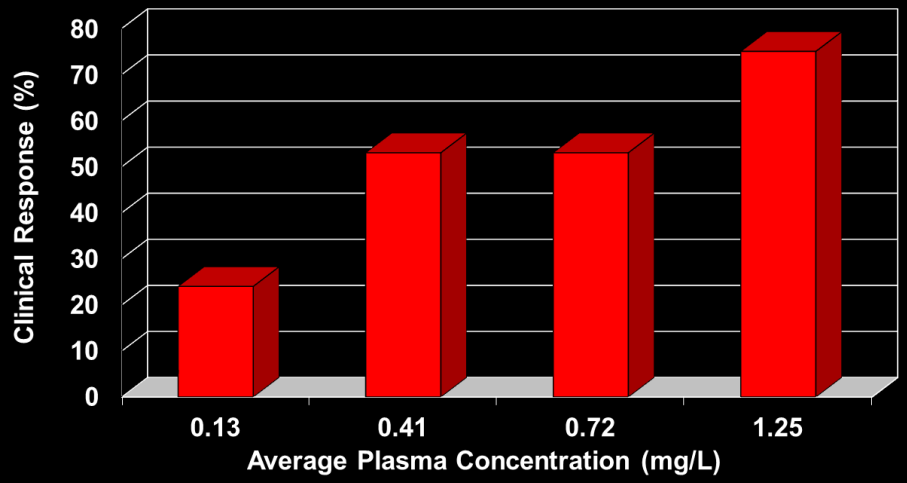
Lepak AAC 2013;57:579
Mavridou AAC 2010;54:860
Conte AAC 2009;53:703

Posaconazole Concentration Effect Prophylaxis vs Therapy

Prophylaxis Goal 0.70 mg/L



Treatment Goal >1.0 mg/L



Jang et al Clinical Pharmacology & Therapeutics July 2010
Walsh TJ et al. *Clinical Infectious Diseases* 2007; **44**: 2-12

Concluding Thoughts

- Antifungal drugs vary in their ability to accumulate in various organs due to distinct physiochemical properties.
- For many body sites, serum concentrations are a good surrogate of tissue concentrations.
- Exceptions for antifungals include the urine, vitreous, CNS, and lung
- There is a reasonable correlation between tissue site kinetics and efficacy.
- However, for organs with multiple kinetic compartments additional studies are needed to define the optimal tissue or cellular compartment.