Difficult-to-treat fungal infections CNS

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ME161
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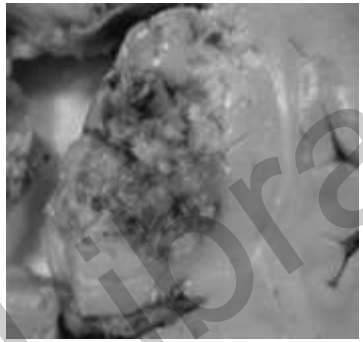
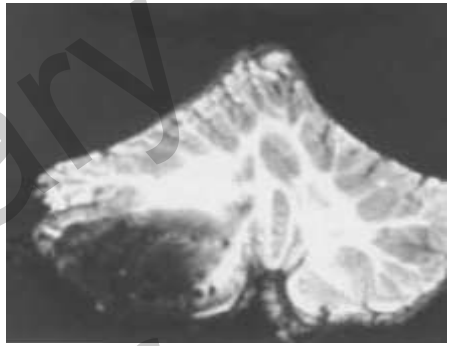
Types of CNS fungal infections

abcess +/- haemorrhage

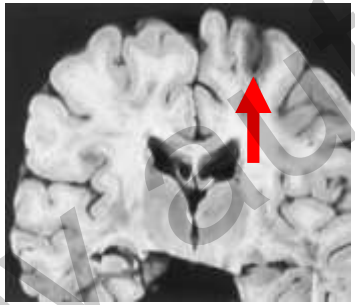




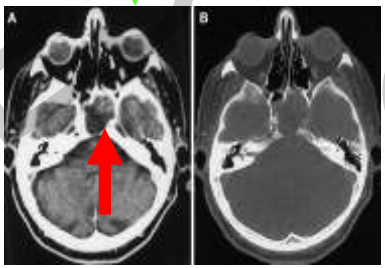
meningitis

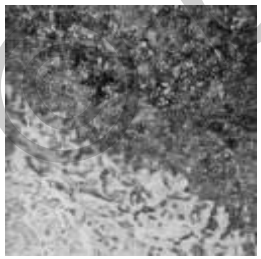
mycotic aneurysm

ischemic infarction

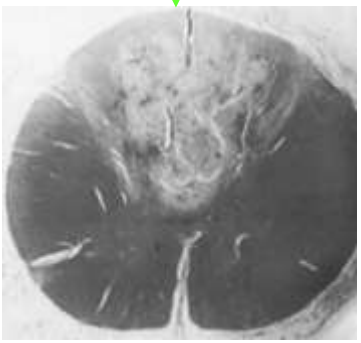


granuloma





myelitis



1. Kleinschmidt-DeMasters BK. *Hum Pathol.* 2002;33:116-124. **2.** Ho CL, Deruytter MJ. *Acta Neurochir* 2004;146:851. **3.** Petrick M, et al. *Neurosurgery.* 2003;52:955-958.

Predisposing conditions

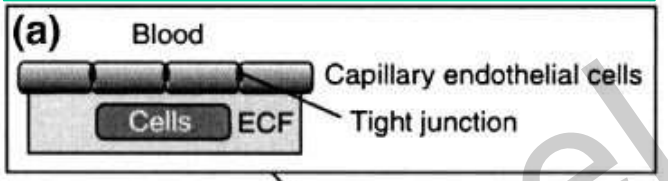
Disease-induced immunosuppression	Prototype pathogen
HIV-Infection	*Cryptococcus neoformans*
Haematological malignancies, neutropenia (e.g., acute leukaemia, aplastic anaemia)	*Aspergillus* species
Premature neonates	*Candida* species
Diabetes, iron overload	Mucorales
Treatment-induced immunosuppression	
Medical immunosuppression (e.g. corticosteroids)	*Aspergillus* species
Haematopoietic stem cell transplantation	*Aspergillus* species
Solid organ transplantation	*Candida* species
Inherited immunodeficiencies	
Chronic granulomatous disease	*Aspergillus* species
CARD9 deficiency	*Candida* species
Medical interventions	
Neurosurgery, spinal anaesthesia or injection, injections with contaminated compounds	*Aspergillus* species, other moulds
Intravascular/intracranial devices	*Candida* species
Environmental exposure	
Exposure in endemic areas	*Coccidioides* species
Inhalation of fungal spores	*Cryptococcus* species

Types of Fungi

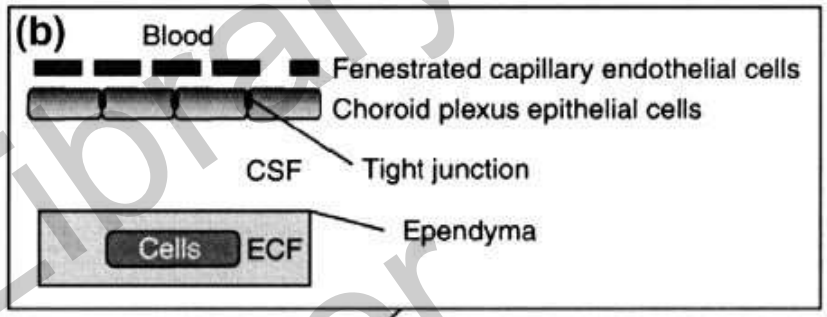
Pathogen	Predominant clinical characteristics	Diagnostic features
Moulds ***Aspergillus* spp.** **Mucorales, …**	**Abscess, mass lesions, infarction, haemorrhage** unspecific or focal CNS symptoms Primary (lung > sinus) infection	**Imaging:** lesions +/-haemorrhage, target lesions (MRI, ADC) **CSF:** cultures mostly -ve, GM and PCR potentially useful **Biopsy:** mostly required for diagnostic proof
***Cryptococcus* spp.**	**Meningoencephalitis** Primary lung infection (not always clinically apparent)	**Imaging:** meningeal enhancement (MRI), cryptococcomas, pseudocysts **CSF:** india ink stain, antigen test, culture
***Candida* spp.**	**Meningoencephalitis** Disseminated infection frequent	**Imaging:** meningeal enhancement (MRI), microabscesses **CSF:** culture, mannan antigen/antibody and PCR testing potentially useful
Uncommon yeasts ***Geotrichum candidum*** ***Malassezia* spp.** ***Rhodotorula* spp., …**	**Meningitis* or brain abscess** *Disseminated infection frequent	**Imaging:** meningeal enhancement (MRI), hydrocephalus, mass lesions **CSF:** sensitivity of cultures varies, PCR potentially useful
Dimorphic fungi ***Blastomyces* spp.** ***Coccidioides* spp.** ***Penicillium marneffei*** ***Sporothrix schenckii, …***	**Meningitis* or brain abscess** *with or without disseminated infection	**Imaging:** meningeal enhancement, abscess/granuloma formation with reduced diffusion (MRI) **CSF:** sensitivity of cultures varies, PCR potentially useful **Serology:** useful in selected fungi

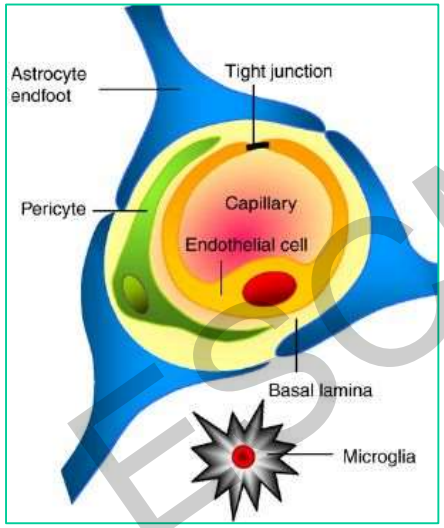
Protecting Barriers

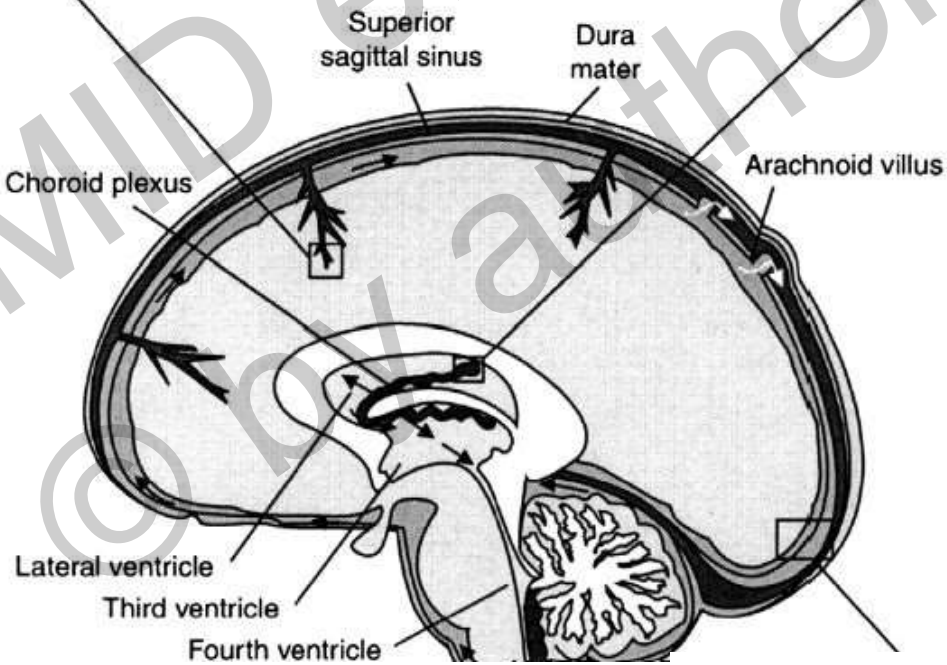
Blood Brain Barrier
~ 12-18m^2



Blood CSF Barrier

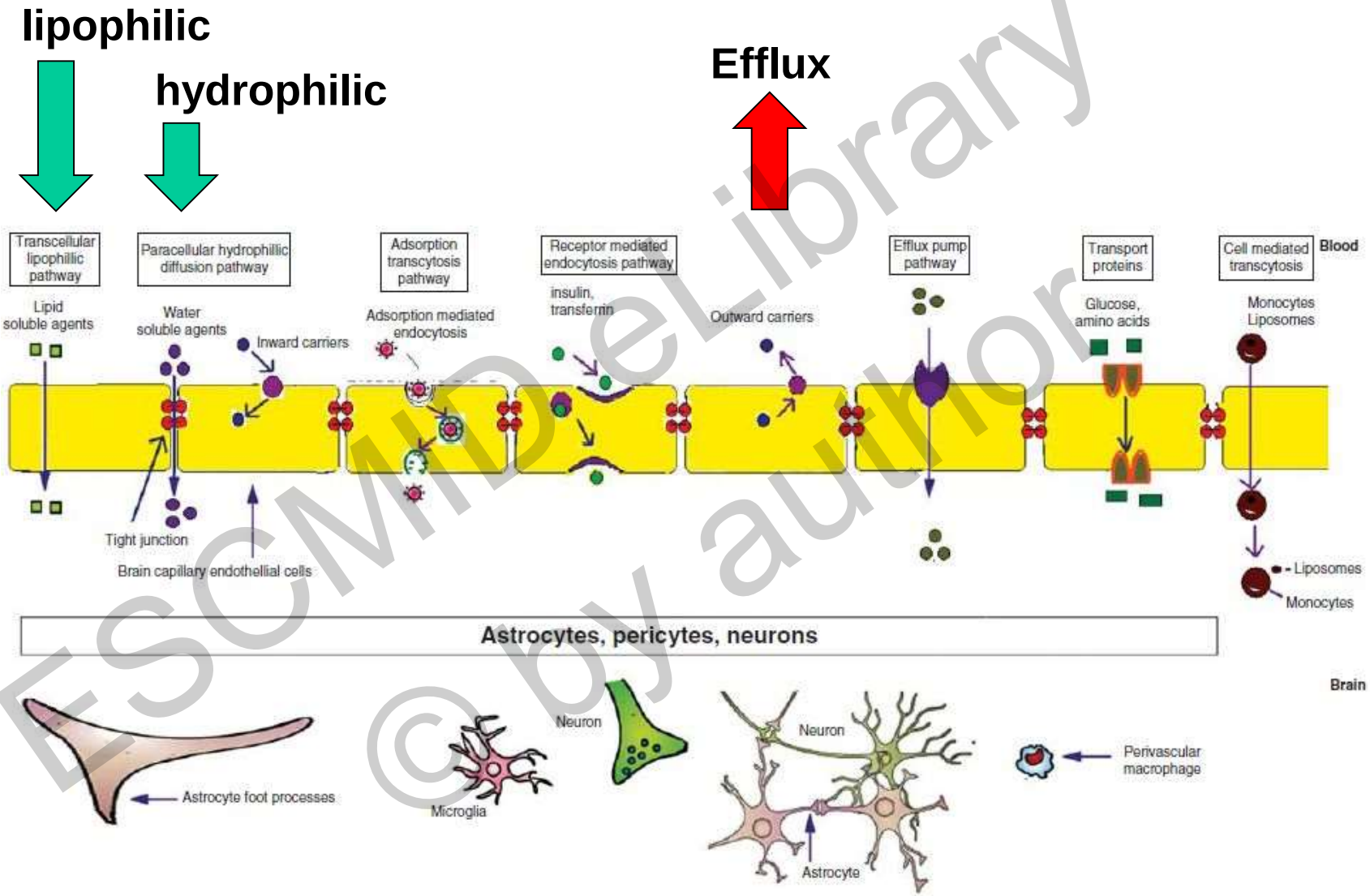






Abbott NJ, et al. *Neurobiol Dis* 2010; 37: 13-25

BBB Trafficking

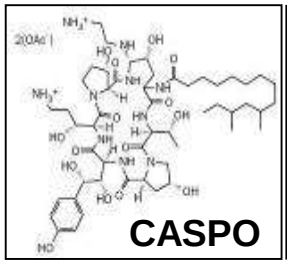


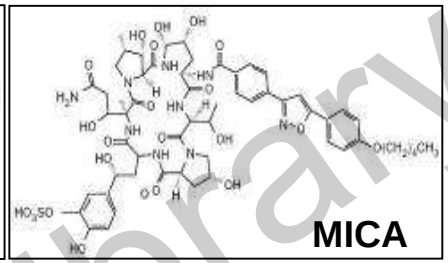
Nagpal K, et al. *Expert Opin Drug Deliv* 2013; 10: 927-55

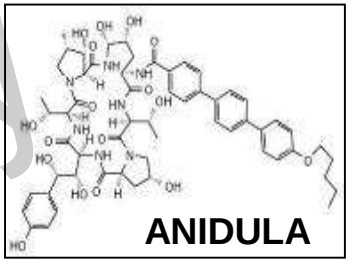
Molecular Size of Antifungal Drugs

Molecular weight (Da)

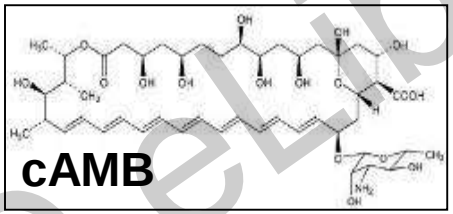
~1200

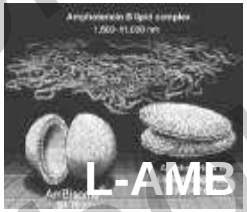




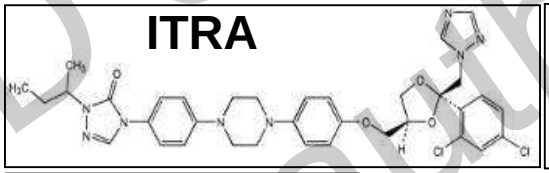


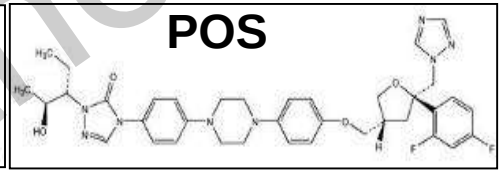
924





705/708

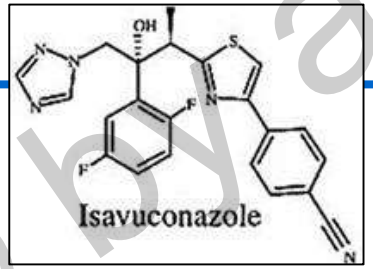




400-600

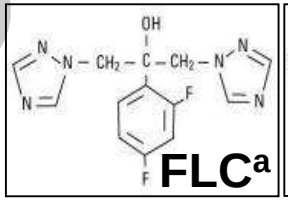
Transcellular lipophilic diffusion across the intact BBB

437



Isavuconazole

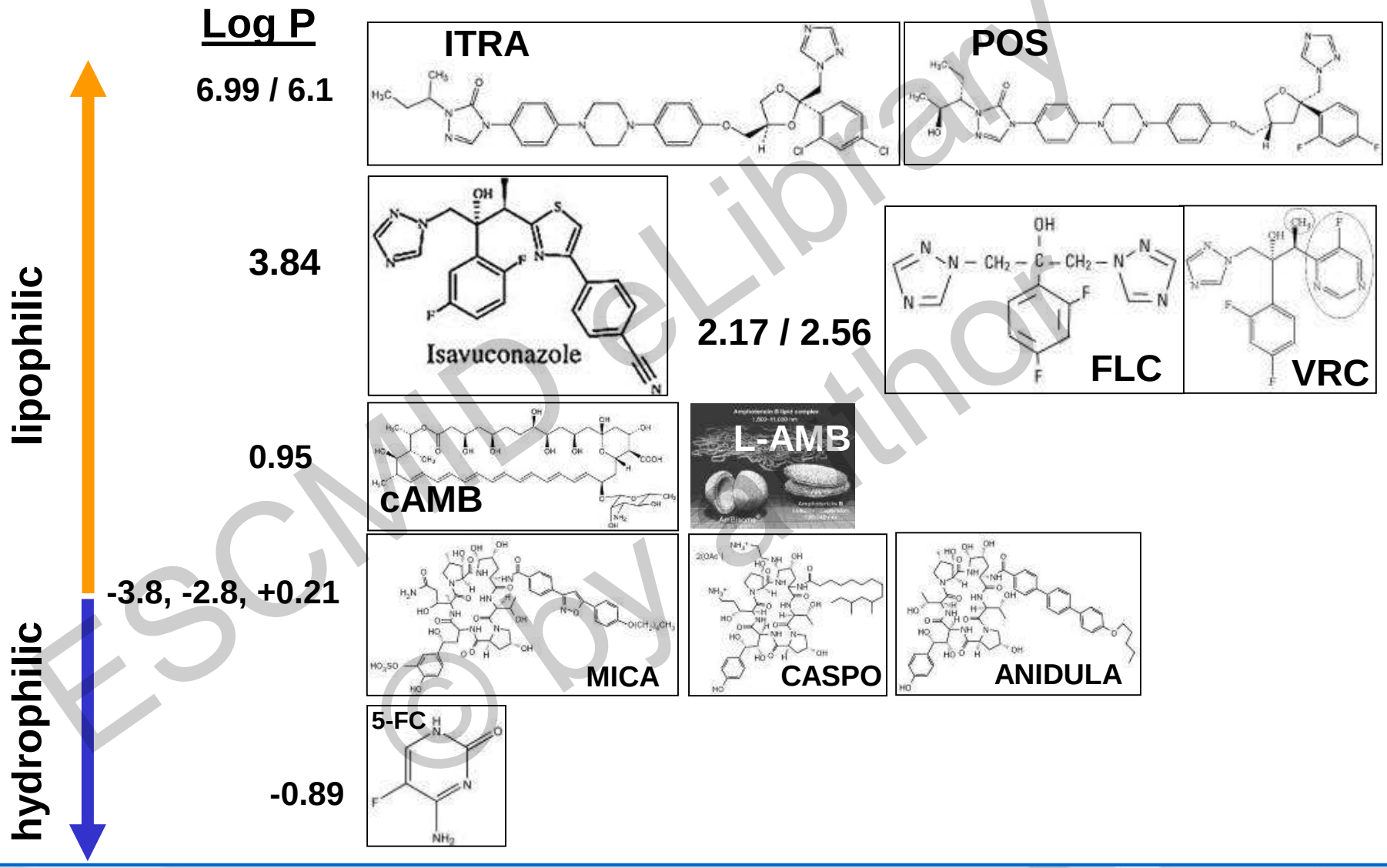
306/349



[a]Fluconazole
[b]Voriconazole

Kethireddy S & Andes D, *Expert Opin Drug Metab Toxicol* 2007; 3: 573

octanol/water-gradient

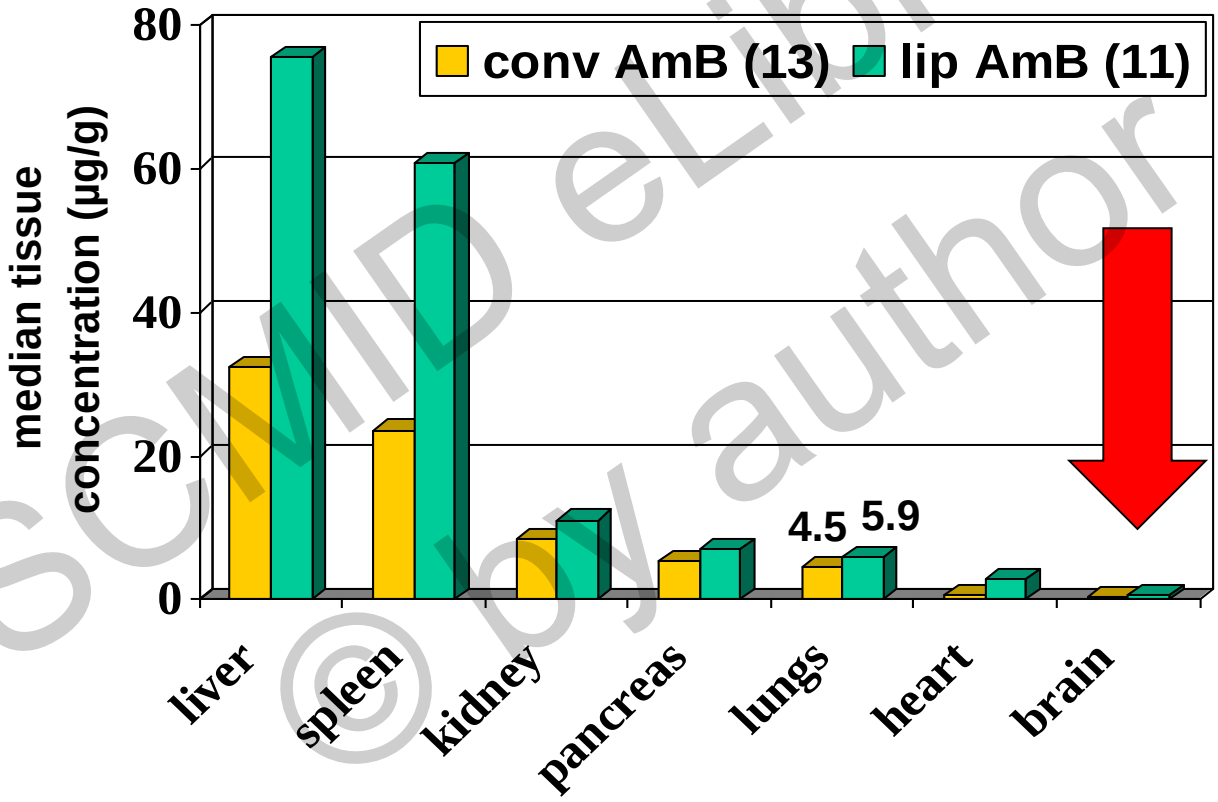


Kethireddy S & Andes D, *Expert Opin Drug Metab Toxicol* 2007; 3: 573

Tissue Levels of Amphotericin B

Tissue specimens from necropsy

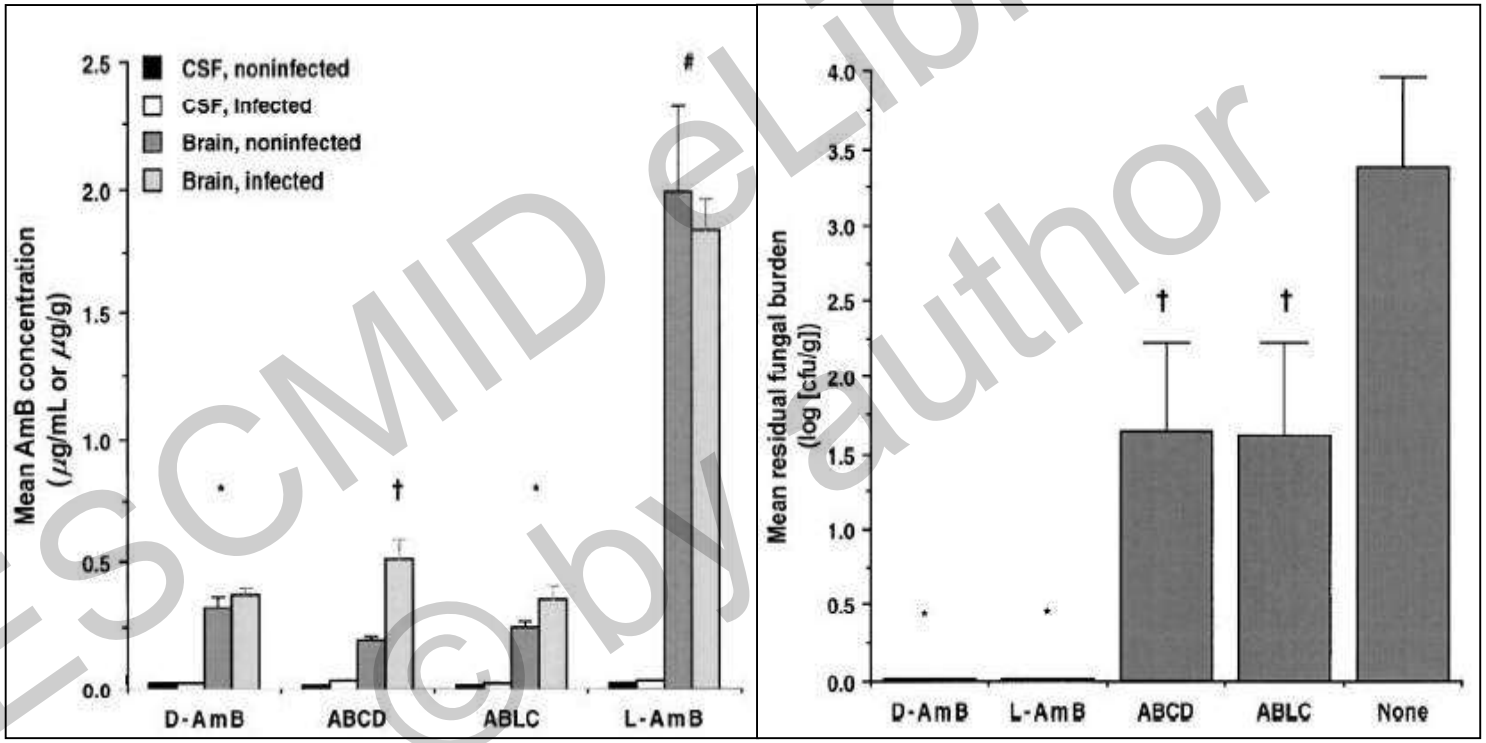
methanolic extraction -> HPLC



Collette N, et al. *Antimicrob Agents Chemother.* 1989;33:362-368.
Collette N, et al. *J Antimicrob Chemother.* 1991;27:535-548.

CNS concentrations AmB

Rabbits +/- *C. albicans* meningoencephalitis
7 days of antifungal treatment with
D-AmB[a] 1mg/kg; ABCD[b], ABLC[c], or L-AmB[d] 5mg/kg



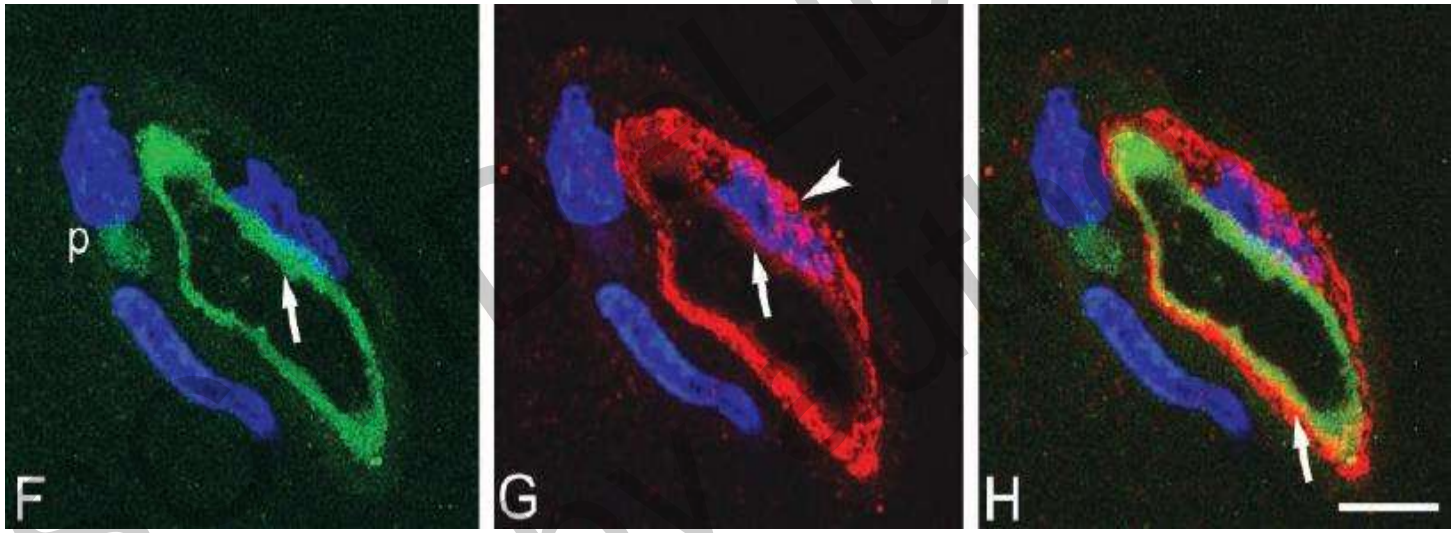
[a]Amphotericin B deoxycholate; [b]Amphotericin B colloidal dispersion;
[c]Amphotericin B lipid complex; [d]liposomal Amphotericin B

Groll AH, et al. *J Infect Dis.* 2000; 182: 274-82

Cerebral P-gp Expression

Cortex specimens from patients with high-grade glioma
Confocal laser microscopy

Cortex microvessel



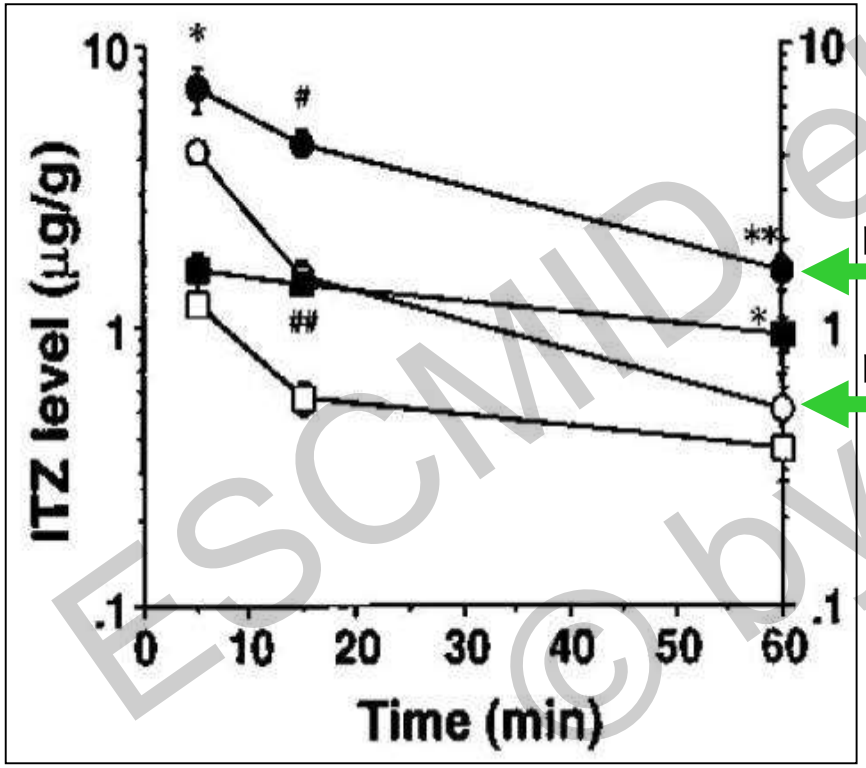
P-gp **Caveolin-1** **P-gp**
Caveolin-1

P-gp = P-glycoprotein

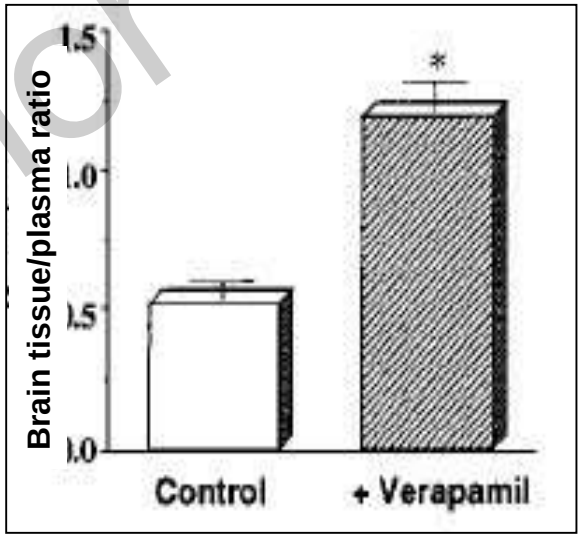
Virgintino D, et al. *J Histochem Cytochem* 2002; 50: 1671-76

Cerebral ITZ concentrations in mdr1 -/- mice

mdr1 knockout mice (mdr1 -/-) **vs** FVB (mdr1 +/+) mice
Itraconazole 5mg/kg iv



Rats treated iv with:
5mg/kg itraconazole
-/+ prior 5mg/kg verapamil



Miyama T, et al, *Antimicrob Agents Chemother.* 1998;42:1738-44

Penetration of Voriconazole into CSF

Guinea pigs without infection analysed hourly after 5 days of **2, 4, 10 mg/kg VRC q8h**

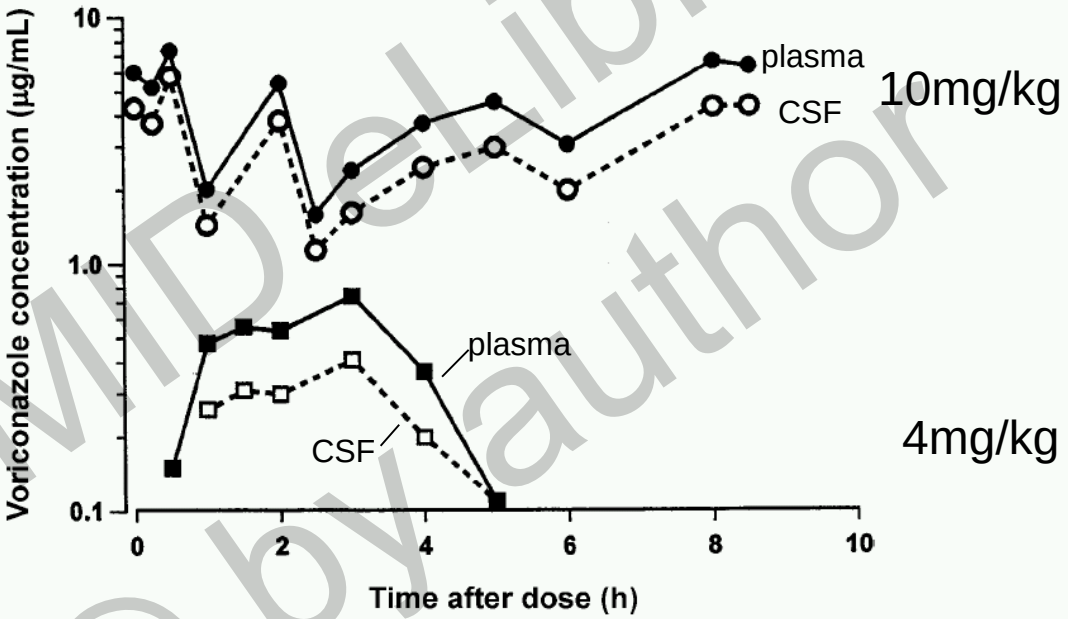
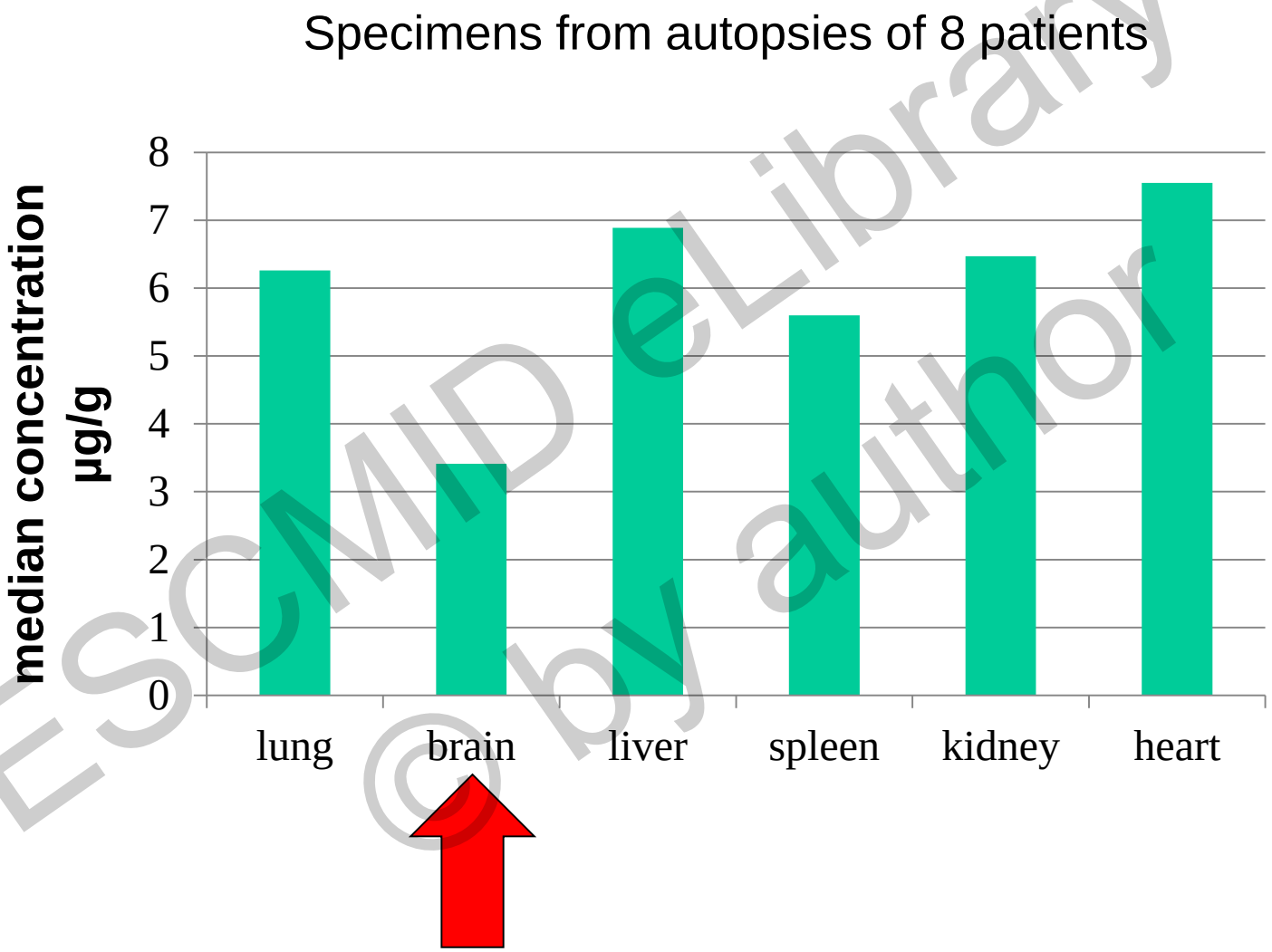


Figure 1. Concentrations of voriconazole in plasma *(solid markers)* and CSF *(empty markers)* samples obtained from guinea pigs. Animals received oral doses of 4 mg/kg *(squares)* or 10 mg/kg *(circles)* q8h for 5 days. On day 5, 1 animal per timepoint was killed for analysis of CSF and blood samples with validated high-performance liquid chromatography.

Lutsar, I, et al. *Clin Infect Dis* 2003; 37: 728-732

Tissue levels voriconazole



Weiler S, et al. *Antimicrob Agents Chemother* 2011; 55: 925

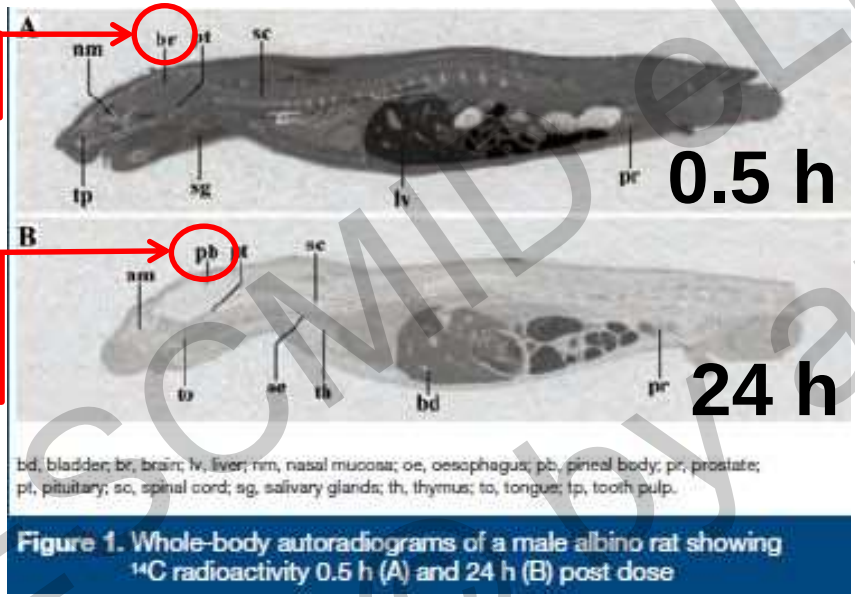
Tissue penetration of ISAV

$^{14}C/^{3}H$-Isavuconazonium -> ^{14}C label active drug moiety (ISAV)
-> ^{3}H label pro-moiety (BAL8728)

Sprague-Dawley albino rats
-> single infusion of 3 mg/kg of labelled drug

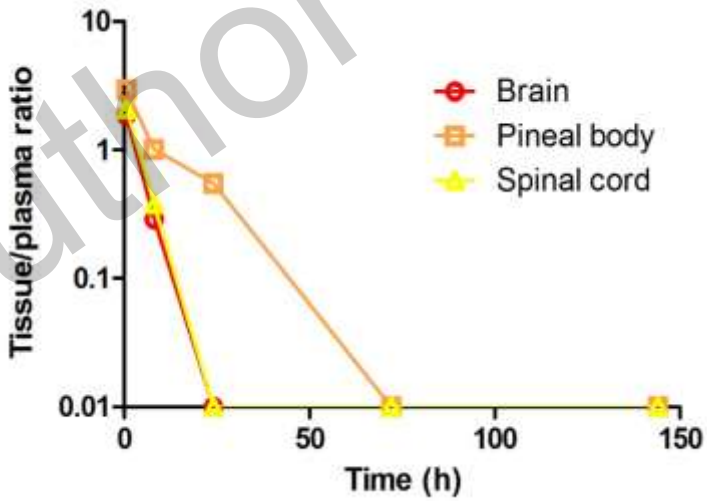
brain

Pineal body



bd, bladder; br, brain; lv, liver; nm, nasal mucosa; oe, oesophagus; pb, pineal body; pr, prostate; pt, pituitary; sc, spinal cord; sg, salivary glands; th, thymus; to, tongue; tp, tooth pulp.

Figure 1. Whole-body autoradiograms of a male albino rat showing ^{14}C radioactivity 0.5 h (A) and 24 h (B) post dose



Lung tissue: 2.28µg/g (0.5 h), 0.64µg/g (24 h)

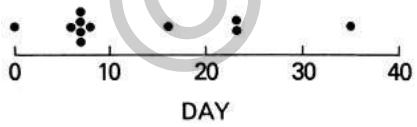
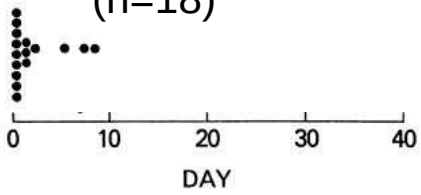
Cryptococcal meningitis: Combination therapy

66 patients with cryptococcal meningitis

R

cAmB 0,4mg/kg tgl. -> Tag 42
0,8mg/kg jeden 2.Tag ->Tag 70

cAmB 0,3mg/kg tgl. -> Tag 42
+ **5-FC** 150mg/kg tgl. -> Tag 42

cured/improved	15/32 (47%)	**p>0.05**	23/34 (68%)
relapse	11/32 (34%)	**p=0.02**	3/34 (9%)
sCreatinine (mean) (normal baseline)	200µM (n=16)	**p=0.05**	140µM (n=18)
CSF sterilisation (day last CSF +ve)		**p<0.001**	

Bennett JE, et al. *N Engl J Med* 1979; 301: 126

Cryptococcal meningitis: other combinations

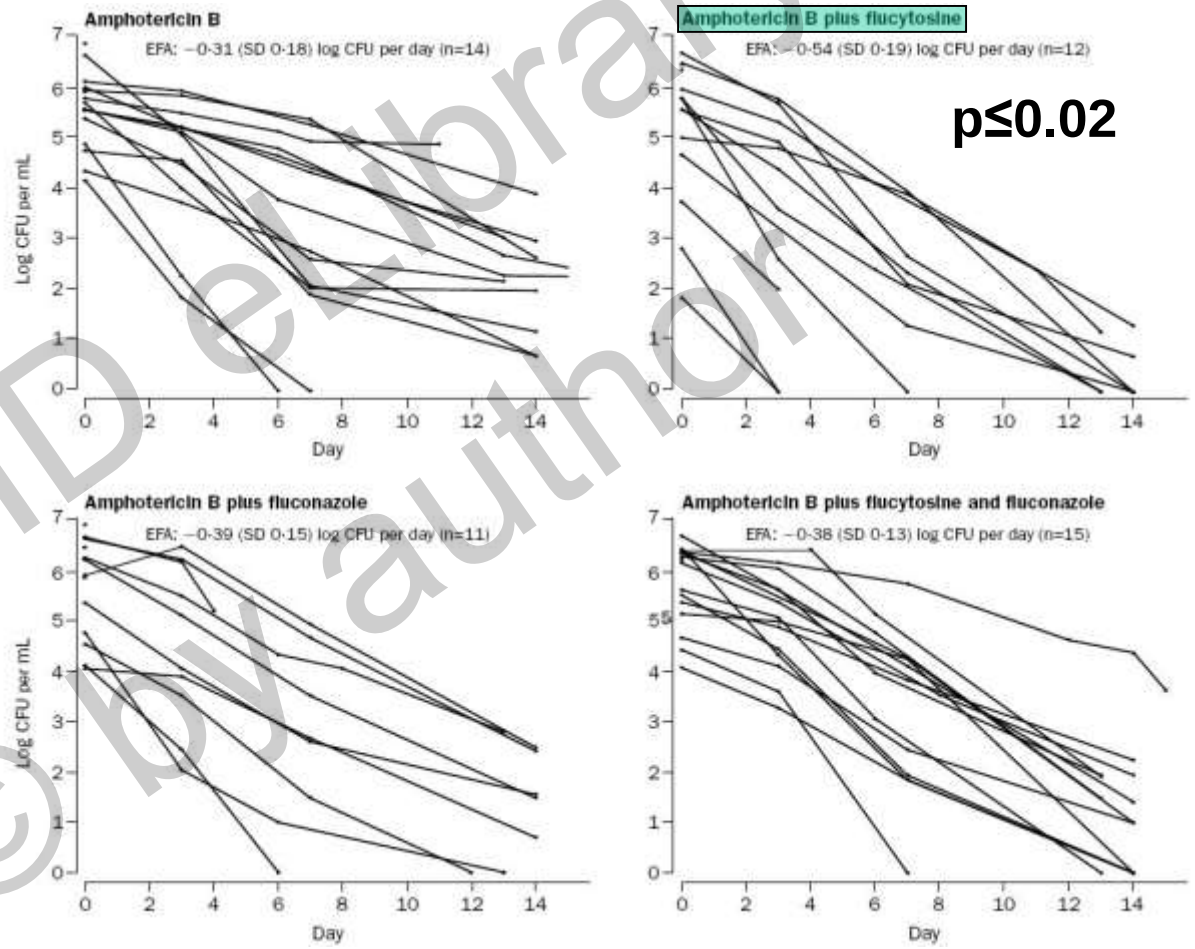
64 HIV+ pts with cryptococcal meningitis

cAMB 0,7mg/kg

R

None
or
+ 5-FC 100mg/kg
or
+ fluconazole 400mg
or
+ 5-FC 100mg/kg
+ fluconazole 400mg

fluconazole 400/200mg



Brouwer AE, et al. *Lancet* 2004; 363: 1764

Cryptococcal meningitis: raised CSF pressure

~50% of HIV+ pts with CM with CSF opening pressure >25cmH_2O
~25% of HIV+ pts with CM with CSF opening pressure >25cmH_2O

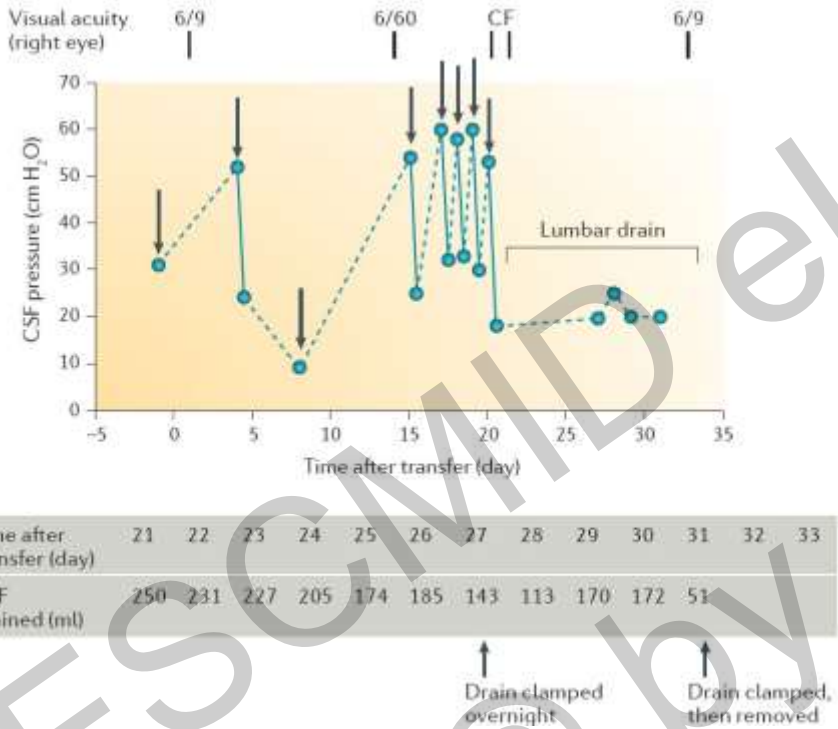


Figure 3 | **Raised cerebrospinal fluid pressure in a patient with HIV-associated cryptococcal meningitis.** Depicted here is time course of changes in cerebrospinal fluid (CSF) pressure, visual acuity, and volume of CSF drained through a temporary lumbar drain in situ over 11 days. Arrows indicate times of lumbar puncture. During the third week of antifungal therapy, and despite the fact that CSF cultures had become negative, the patient developed severely raised CSF pressure that was unresponsive to repeated daily lumbar punctures, but did respond to CSF drainage via a temporary lumbar drain. Symptoms of high CSF pressure recurred when the drain was clamped after 6 days, but did not recur when it was clamped and then removed after 10 days. CF, counting fingers (indicating severely reduced visual acuity). Adapted with permission from Elsevier Ltd © Macsween, K. F. *et al. J. Infect.* **51**, e221–e224 (2005).

-> check CSF opening pressure repeatedly
if elevated -> daily CSF drainage or lumbar drain/VP-shunt

Williamson PR, et al. *Nat Rev Neurol* 2017; 13: 13

Outcomes in cerebral aspergillosis

amphotericinB/itraconazole

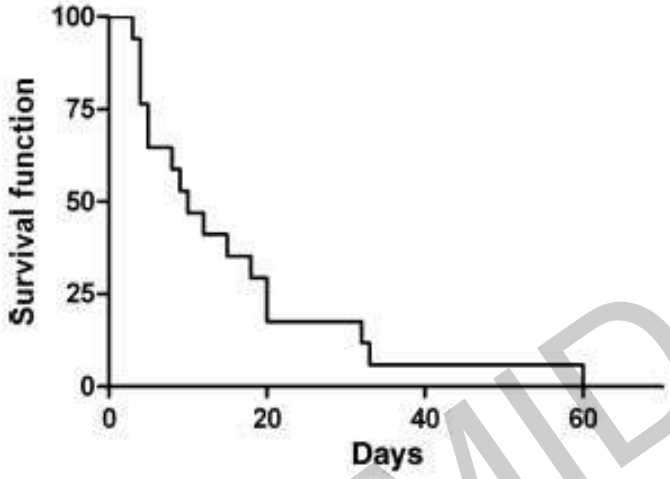


Figure 1 Kaplan–Meier survival curve of 17 patients with definite or probable central nervous system (CNS) aspergillosis. Survival was calculated from first occurrence of CNS symptoms or first positive brain imaging until last follow up.

17 patients with proven/probable CNS infection

cAmB (13), L-AmB (5), 5-FC (3), Itra (2), none (2)

Schwartz S, Ruhnke M, et al. *Mycoses.* 2007;50:196

voriconazole

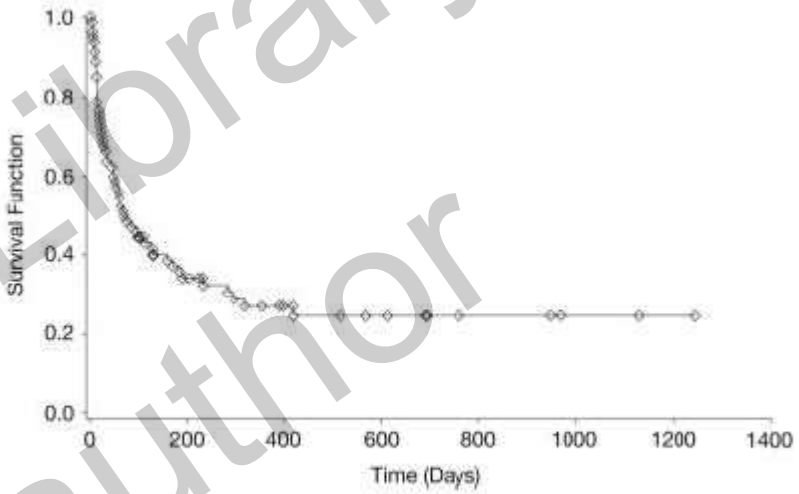


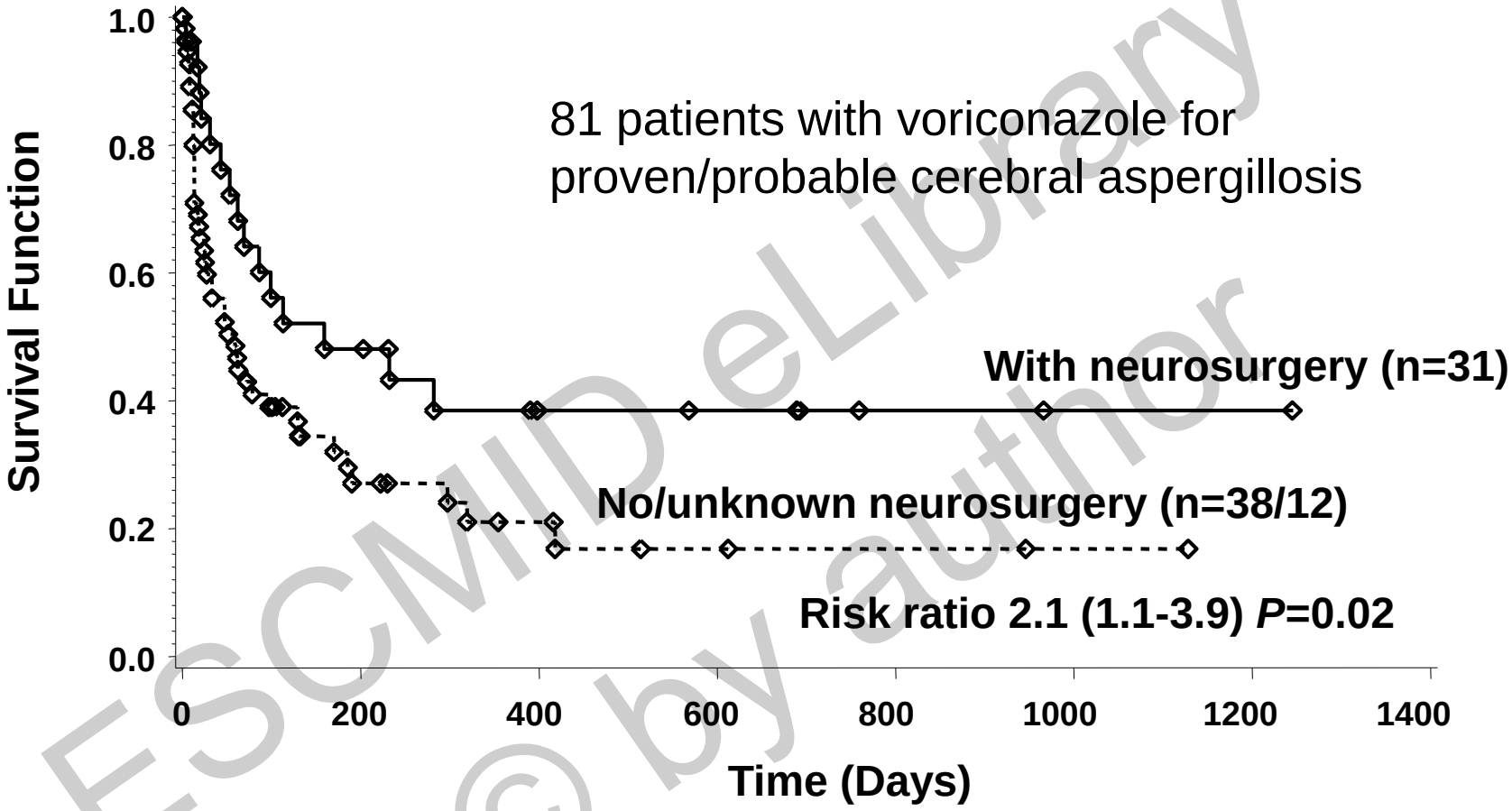
Figure 2. Kaplan-Meier survival curve of patients with CNS aspergillosis. Survival curve of 81 patients with primary/salvage voriconazole therapy.

81 patients with proven/probable CNS infection

96% failure/intolerance to previous therapies

Schwartz S, Ruhnke M, Ribaud P, et al. *Blood.* 2005;106:2641

Impact of Neurosurgery on Survival



Craniotomy/abscess resection (14), abscess drainage (12), ventricular shunt (4), Ommaya-reservoir (1)

Schwartz S, et al. *Blood* 2005; 106: 2641

Expanded retrospective analysis

CNS infections treated with voriconazole

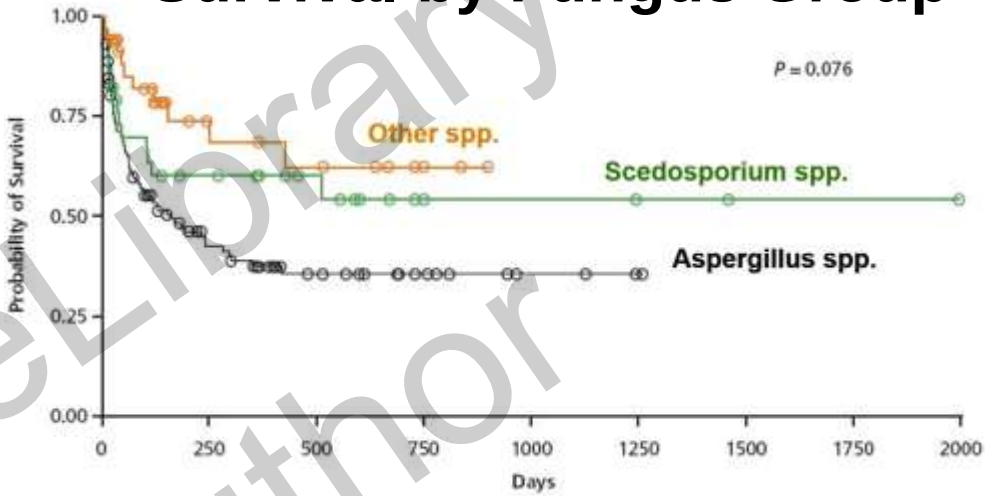
Voriconazole database
Literature 1/02 - 12/08

- **Aspergillosis - 110 pts**
- **Scedosporiosis - 34 pts**
- **Cryptococcosis + others* - 38 pts**

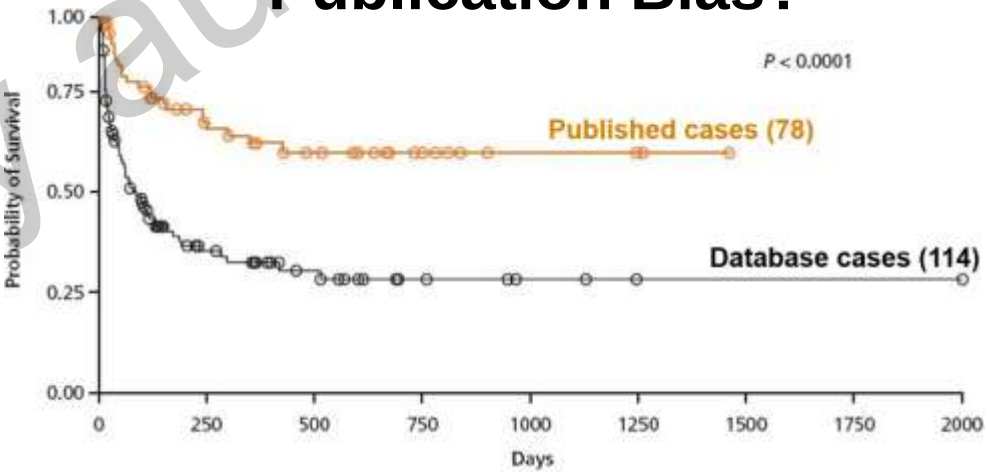
-> total of 192 patients

** Blastomyces dermatitidis = 5; Cryptococcus neoformans = 11; C. gattii = 1; Coccidioides immitis = 3; Cladophialophora bantiana = 5; Candida spp = 3 (C. albicans = 1, C. krusei = 1, Candida spp = 1); Chrysosporium spp = 1; Curvularia geniculata = 1; Fonsecaea monophora = 1; Fusarium spp = 3 (F. dimerum = 1, F. solani = 1, Fusarium spp = 1); Histoplasma capsulatum = 2; Ochroconis gallopavum = 1; Ramichloridium mackenzie = 1.*

Survival by Fungus Group



Publication Bias?



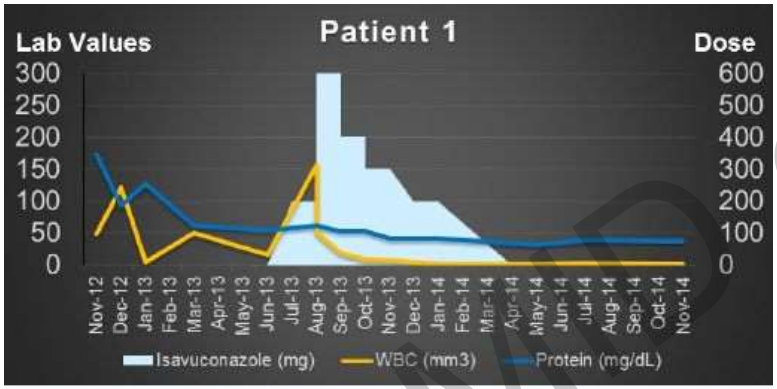
Schwartz S, et al., *Infection* 2011, 39: 201

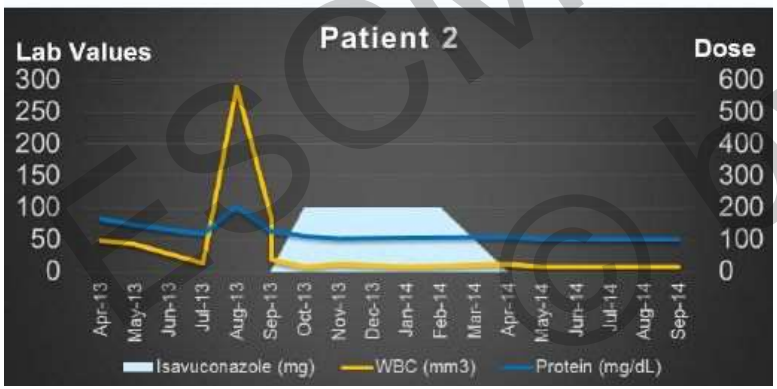
CSF penetration of ISAV

2 Pts with fungal meningitis after receiving a epidural corticosteroid injection from a contaminated lot (*E. rostratum*)

Previous therapies (9/11 months): L-AmB, VRC, ITRA -> failure, intolerance

Disease progression -> ISAV for 4/9 months





Isavuconazole Drug Levels			
Dose	Serum (ng/mL)	CSF (ng/mL)	% CSF
Patient 1			
200mg Q24H	3608.06	29.60*	0.8%
600mg Q24H	11936.14	91.73*	0.8%
600mg Q24H	16388.56	131.23	0.8%
400mg Q24H	13924.04	97.55*	0.7%
300mg Q24H	11749.23	109.07	0.9%
300mg Q24H	9371.29	N/A	N/A
200mg Q24H	6227.12	N/A	N/A
Patient 2			
200mg Q24H	4488.92	22.86*	0.5%
200mg Q24H	3798.07	40.45*	1.1%

*Values <100 ng/mL are extrapolated and are not actual measured drug concentrations.

Both patients remain infection free 12 months after therapy was completed

ISAV in disseminated (CNS) Mucormycosis

59 y male, AML relapse after alloHSCT

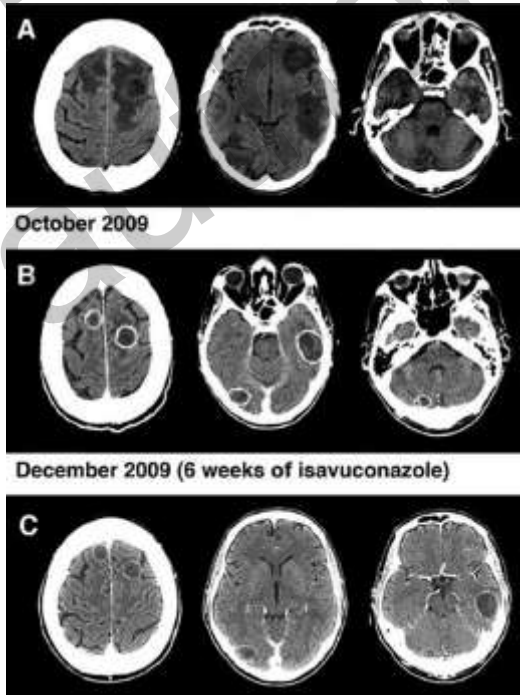
-> pneumonia, altered mental status and facial droop

-> Skin lesions -> biopsy: mucormycosis, PCR: *Rhizomucor pusillus*

-> L-AmB (4 weeks), POSA -> progression -> ISAV

<u>1 month ISAV:</u>
skin lesions + neurological symptoms resolved

<u>29 weeks ISAV:</u>
† due to refractory leukemia (no autopsy)



Peixoto D, et al. *J Clin Microbiol* 2014; 52: 1016

Thank you for your attention!