Pharmacokinetics & Pharmacodynamics of Echinocandins and Triazoles:

An Approach from the North Face

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Over-riding Theme For This Talk

<u>If antifungal therapy is not optimised</u>

1. Patients don't do well
2. Potentially drive antifungal resistance

Echinocandins

Fact Sheet

- Water soluble, linear PK
- Vc 10L, Clearance 1 L/h
- Extensively protein bound
- Few drug-drug interactions
- Safe in renal and hepatic impairment
- Well tolerated
- No TDM

Dosages established in clinical trials of candidemia, mostly in adults

- Micafungin 100 mg/day
- Caspofungin 70 mg load, followed by 50 mg/day
- Anidulafungin 200 mg load, followed by 100 mg/day

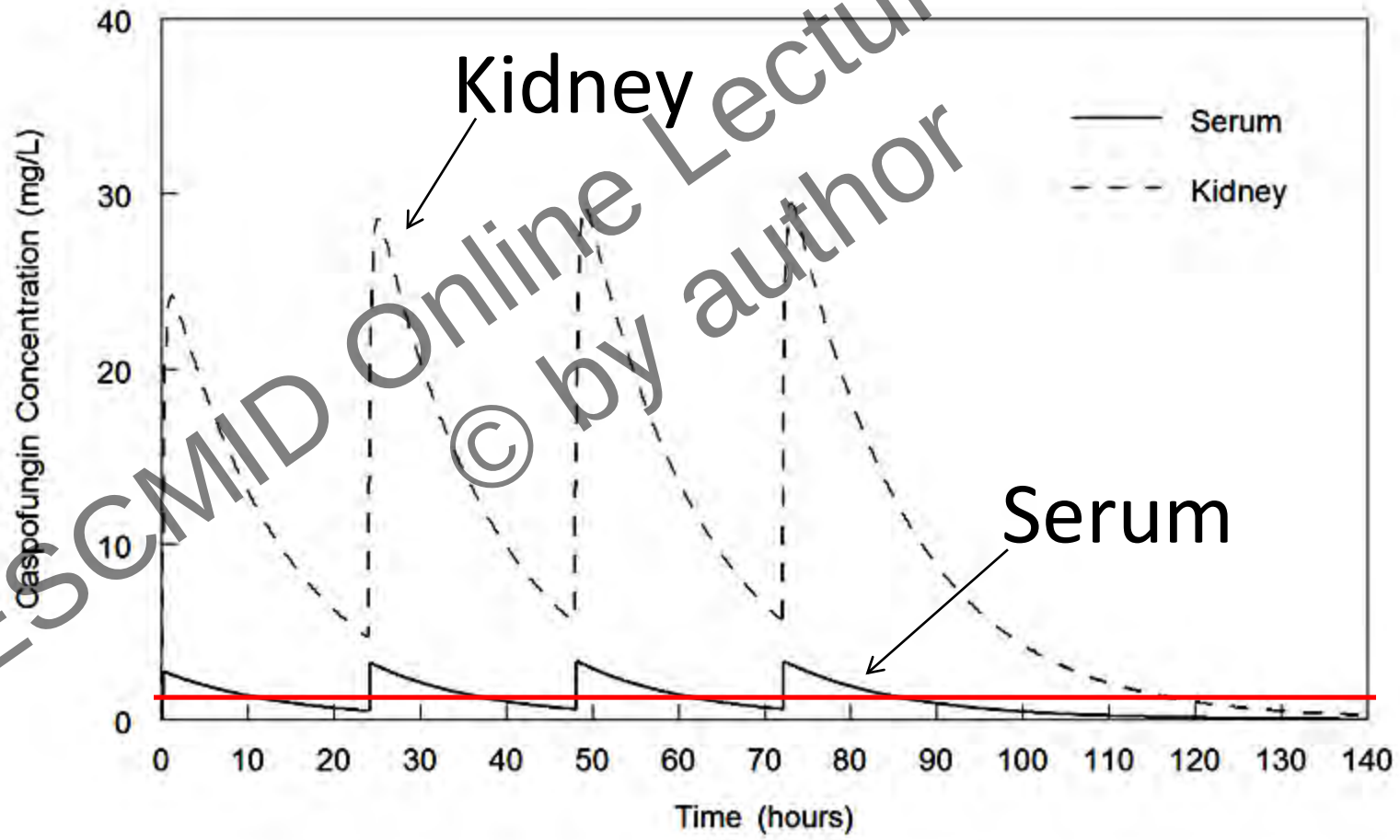
- + Equivalent regimens in children

See all recent ESCMID Guidelines for treatment of Candida infections

A Reflection on Dosing and Deviations from Standard Regimens

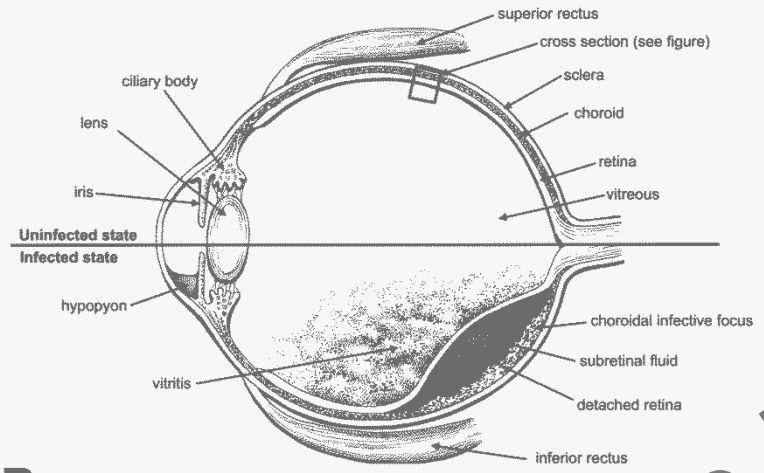
- As a function of the site of infection
- As a function of infecting organism
- As a function of resistance mechanism

Tissue concentrations important for understanding echinocandin effect



Louie et al AAC 2005

A



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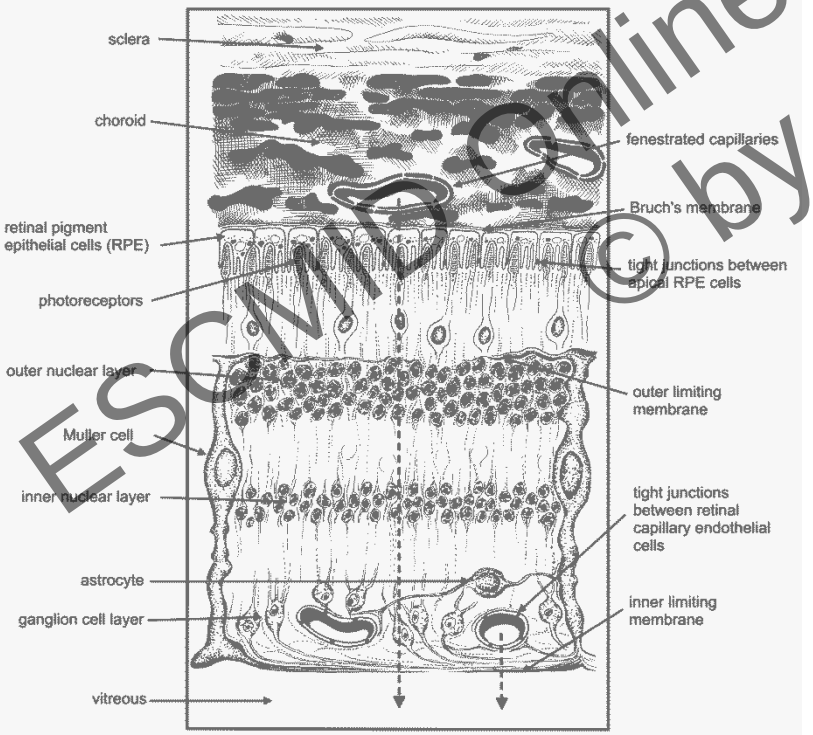
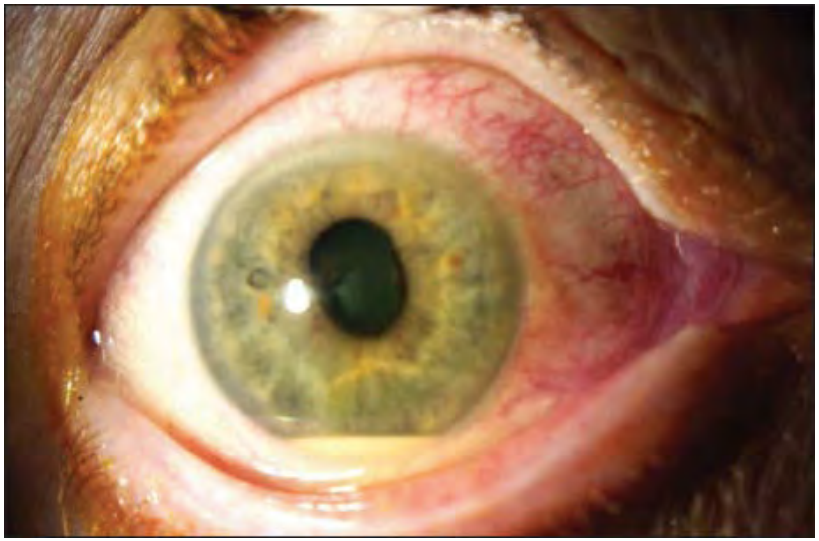
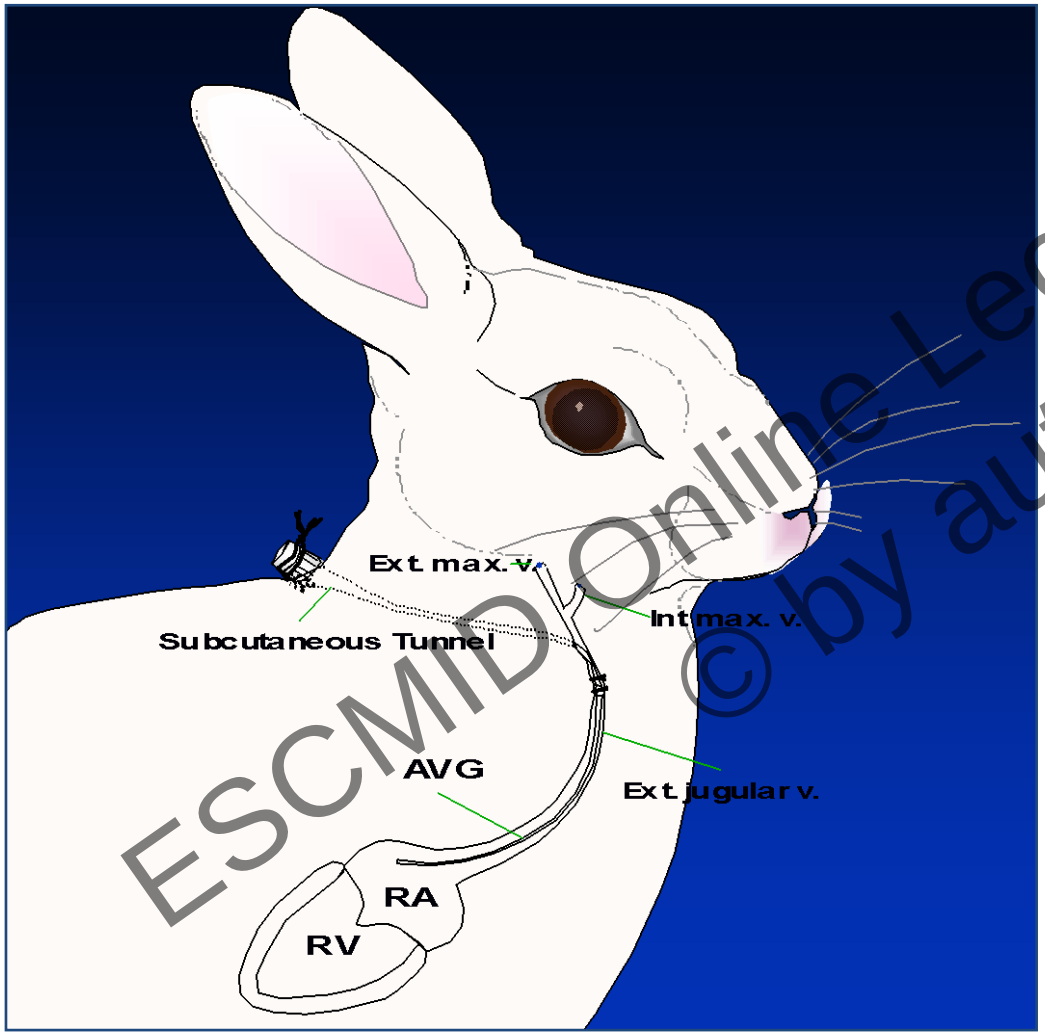
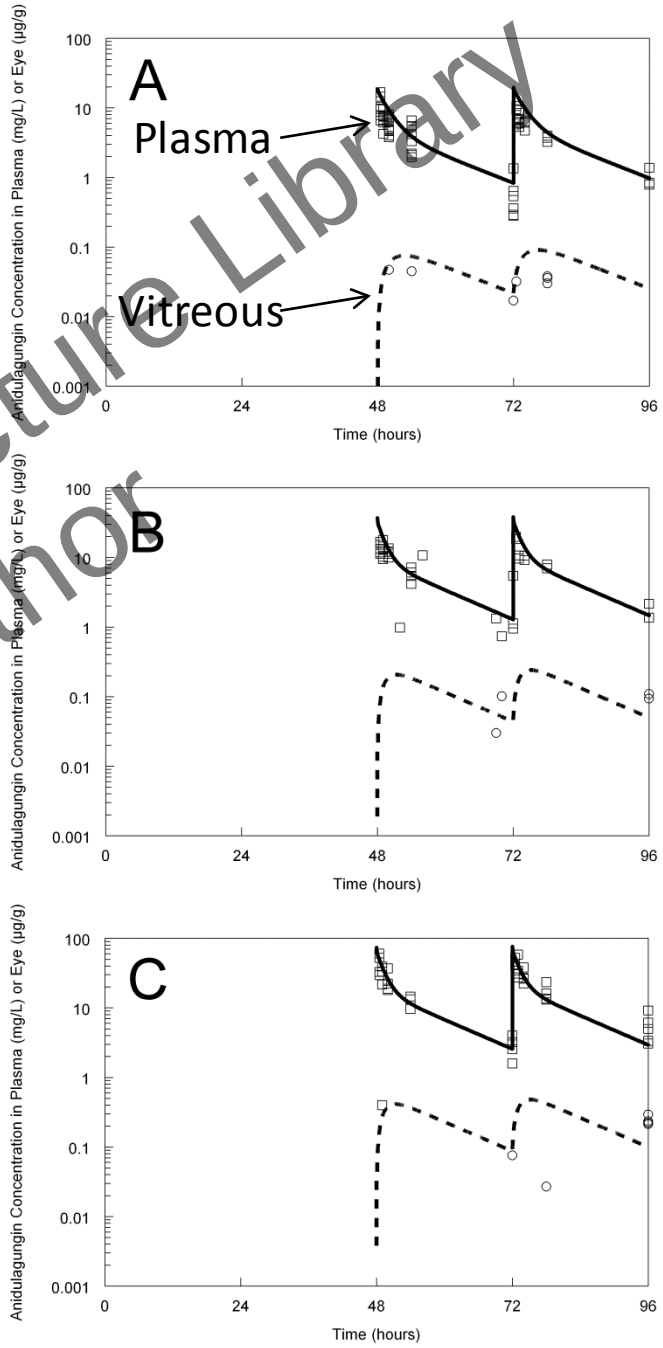


Histological features

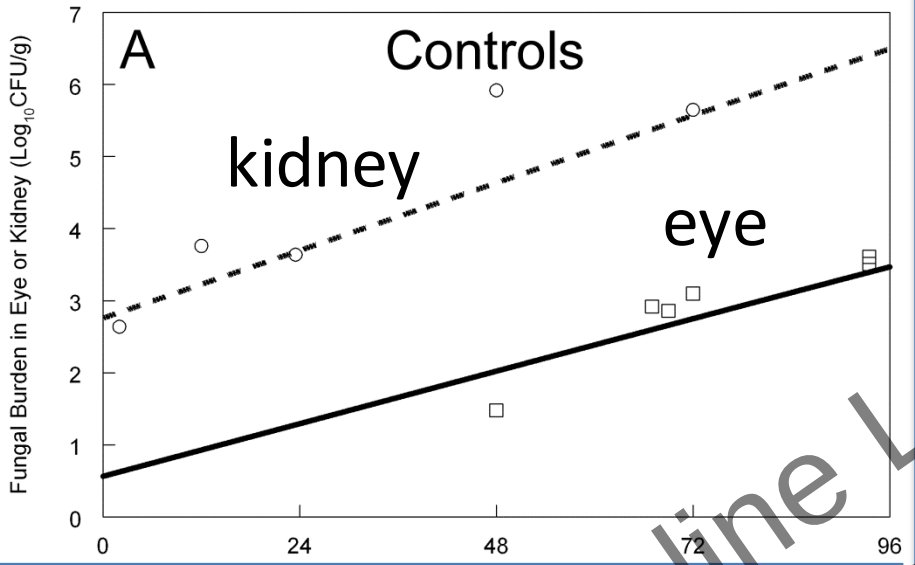
Barriers to infective haematogenous vitritis





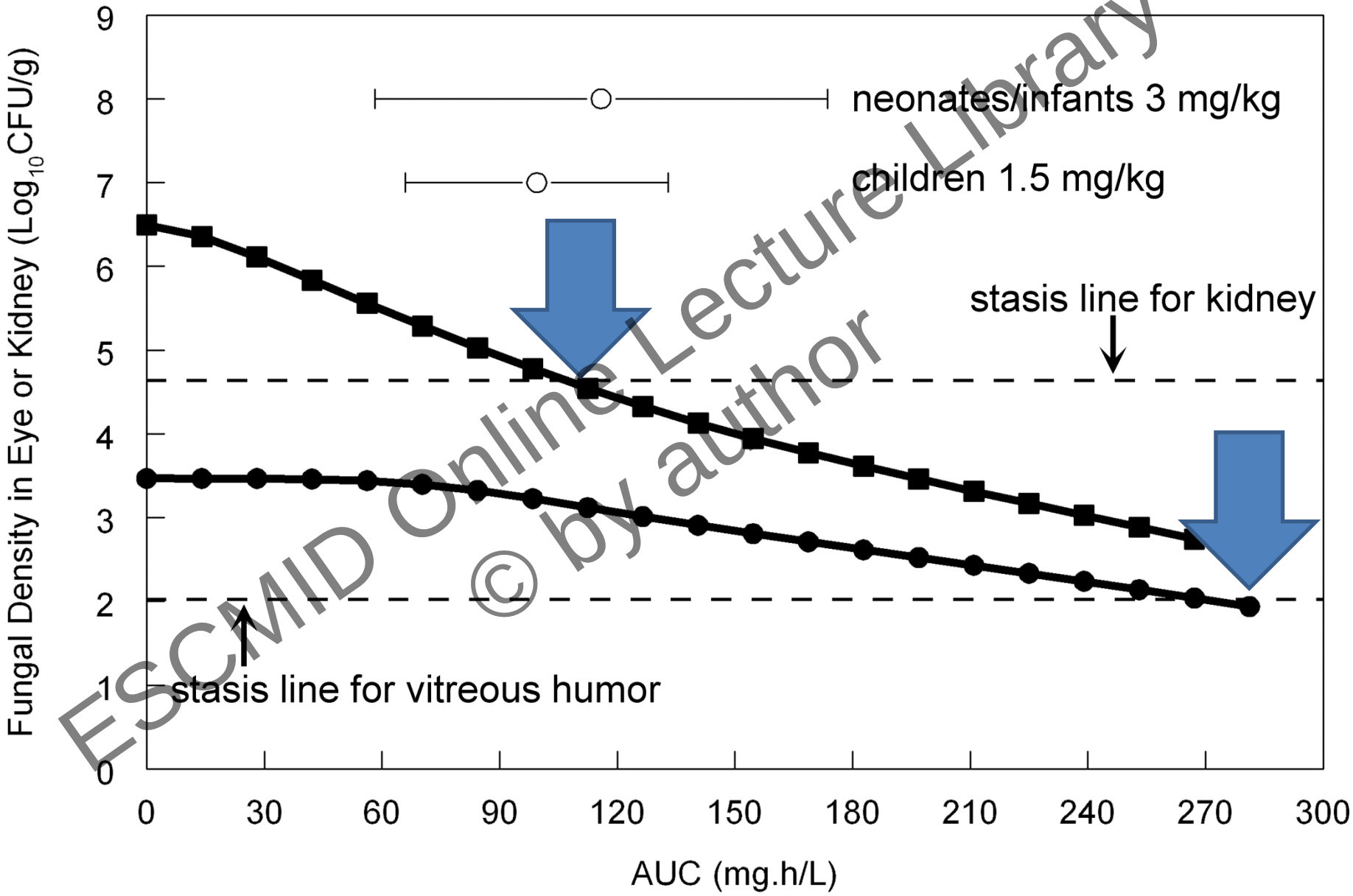


Livermore et al AAC 2013



Time (hours)

Livermore et al AAC 2013



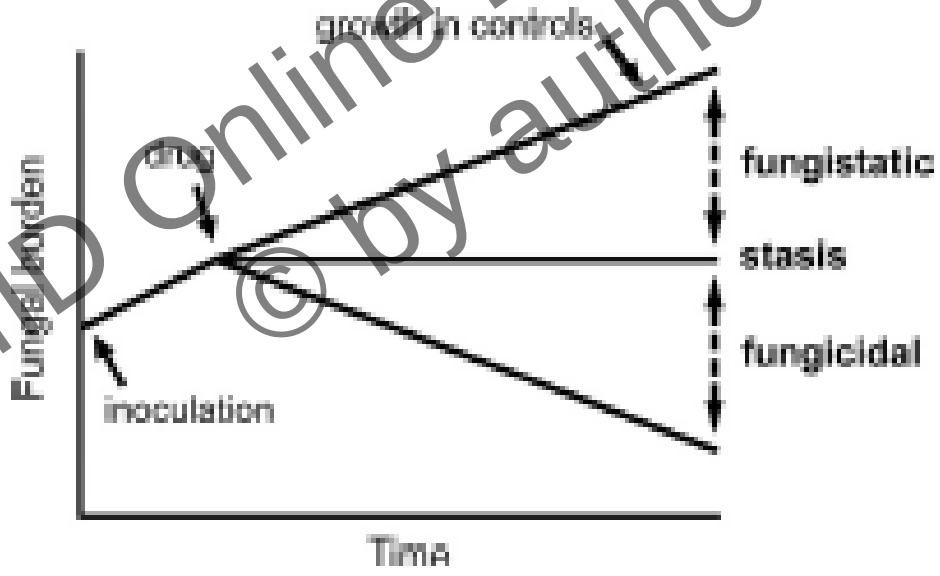
Livermore et al AAC 2013

Summary 1.

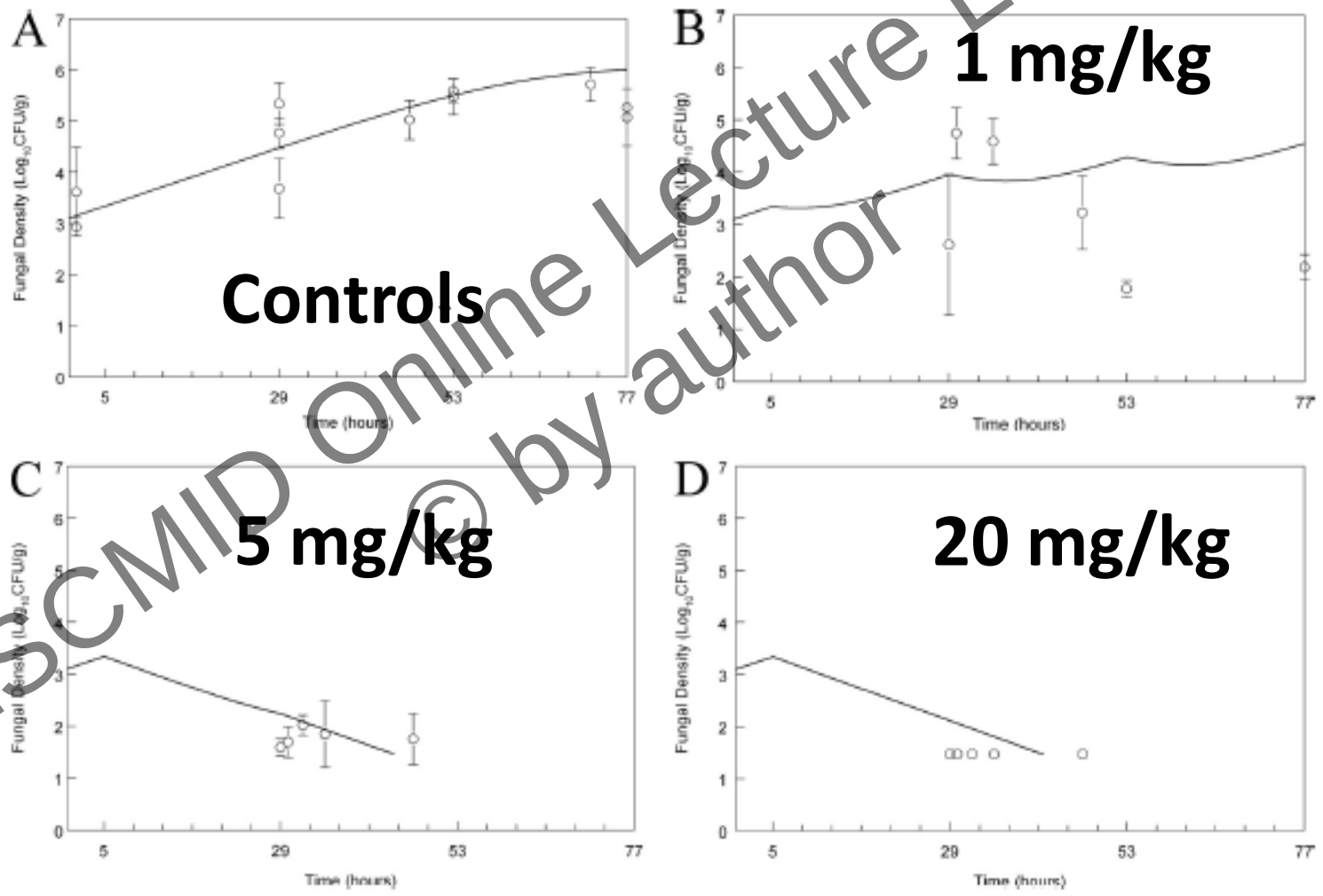
- Echinocandins do achieve effective concentrations in sanctuary sites
  - But, in a dose dependent manner
- Consider dose escalation for
  - Eye disease
  - CNS disease (neonates)
  - CNS aspergillosis

Dosage Adjustment as a function of Invading Pathogen

The Echinocandins are “Fungicidal”

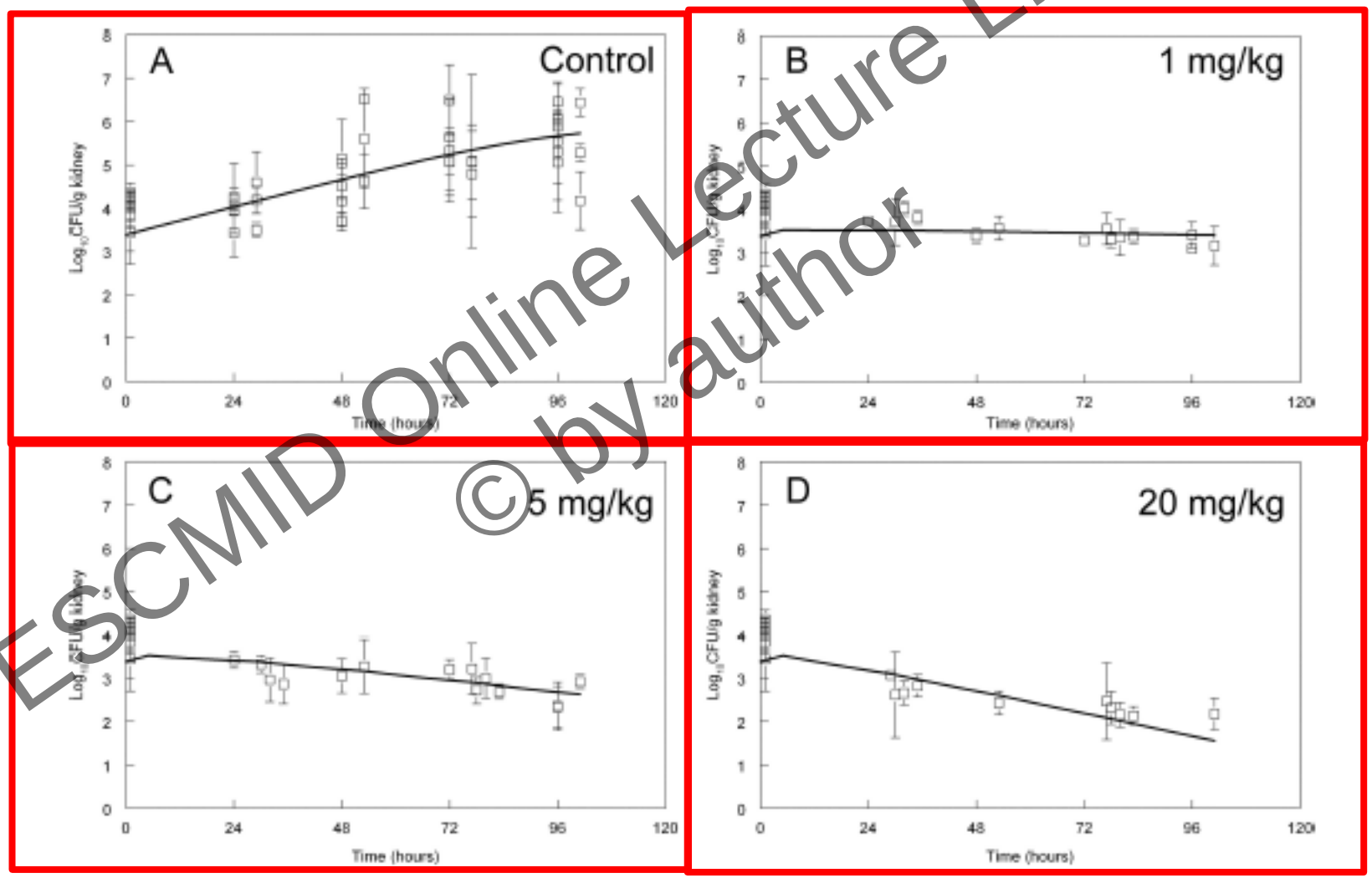


Echinocandins are certainly fungicidal against *Candida albicans*



Slater et al 2011 AAC

Echinocandins appear fungistatic at clinical dosages against *Candida glabrata*



Howard et al AAC 2011

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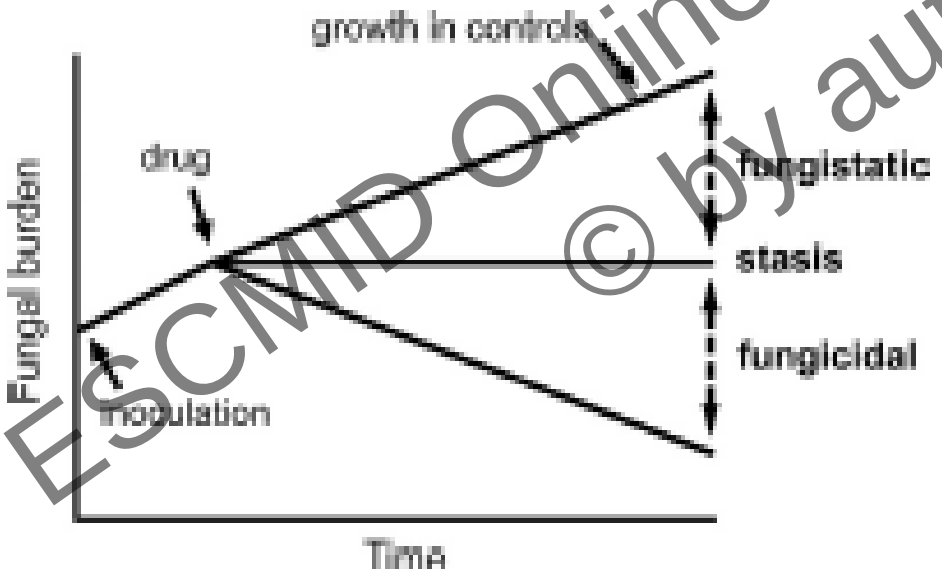
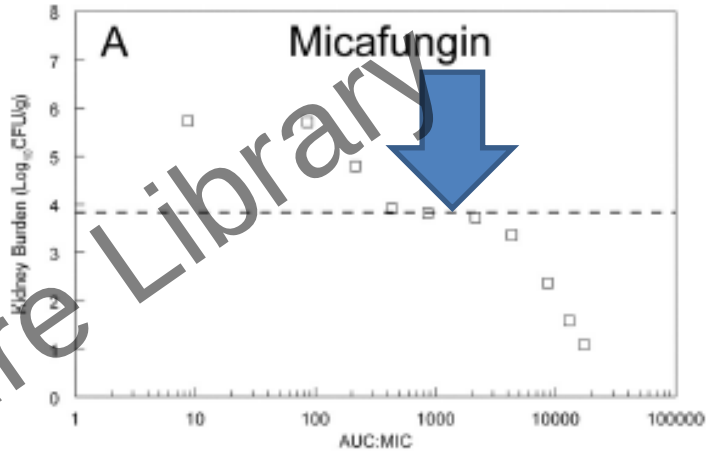
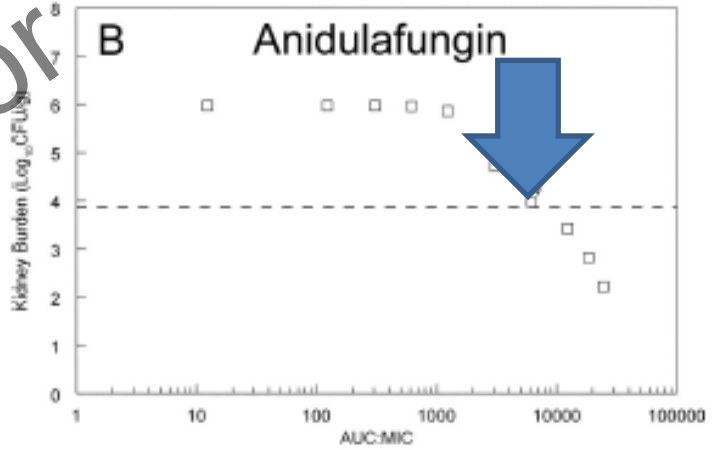
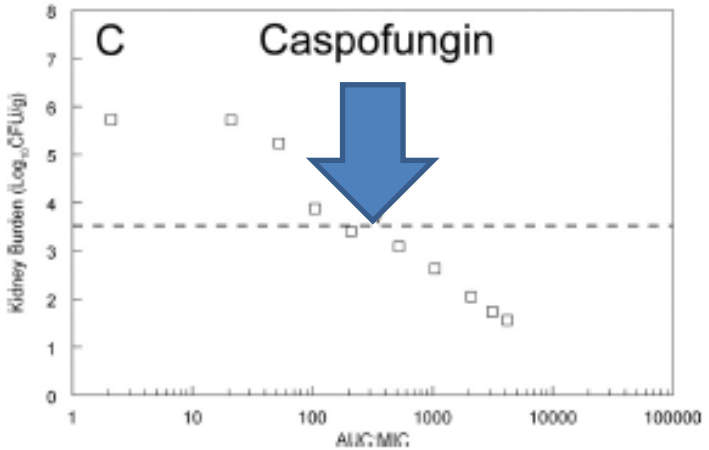








Howard et al AAC 2011

Dosage Adjustment as a function of Genotype of Invading Pathogen

Prominent mutations confer **cross-resistance** to echinocandins

Organism	Hot Spot1	Hot Spot 2
C. albicans	FLTLSLRDP	DWIRRYTL
C. kruseii	FLILSIRDP	DWIRRYTL
C. glabrata	FLILSIRDP	DWIRRYTL
C. guilliermondii	FMALSIRDP	DWIRRYTL
C. lypolytica	FLILSIRDP	DWIRRCVL
C. parapsilosis	FLTLSIRDA	DWIRRYTL
C. orthopsilosis	FLTLSIRDA	DWVRRYTL
C. metapsilosis	FLTLSIRDA	DWIRRYTL
C. rugosa	FLTLSIRDP	DWIRRYTL
C. tropicalis	FLTLSIRDP	DWIRRYTL
C. dubliniensis	FLTLSIRDP	DWIRRYTL

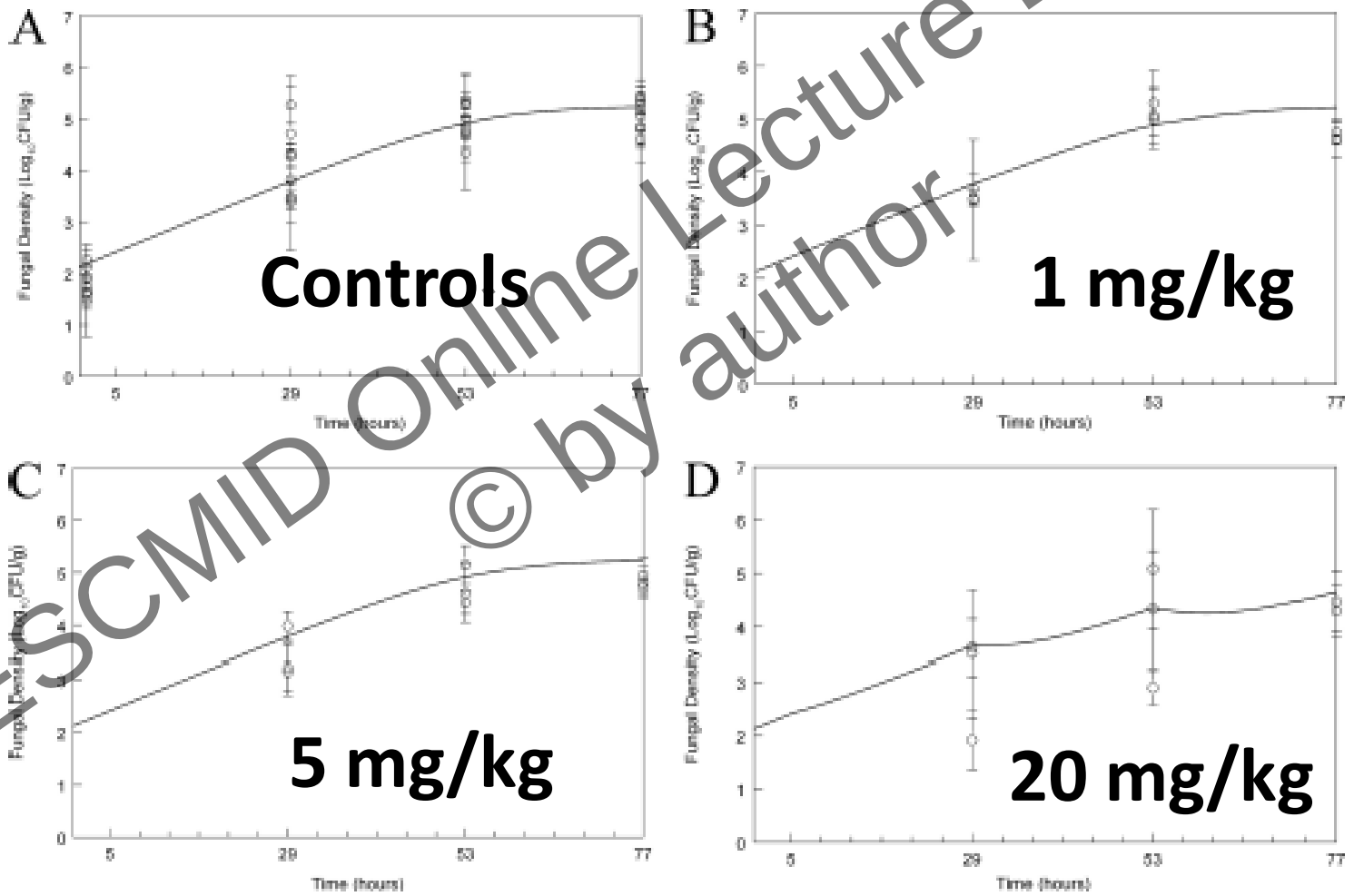
Resistance mutation

Silent mutation

Naturally-occurring Res. mutation

(Courtesy Prof David Perlin)

Echinocandins do not work with Ser645 Fks1 mutants



Slater et al AAC 2011 & Arendrup AAC 2012 for *Candida glabrata*

Triazoles

Fact Sheet

- Water insoluble,
- Linear & non linear PK
- Vc 100-1000 ++ L
- Variable protein binding (10%-99.9%)
- Significant drug-drug interactions
- Difficult to use in renal and hepatic impairment
- Narrow therapeutic index
- But, orally bioavailable and effective

The last 5 years has seen accumulating evidence that drug exposure:MIC can be used to inform triazole dosing

Essentially a Pan European Project

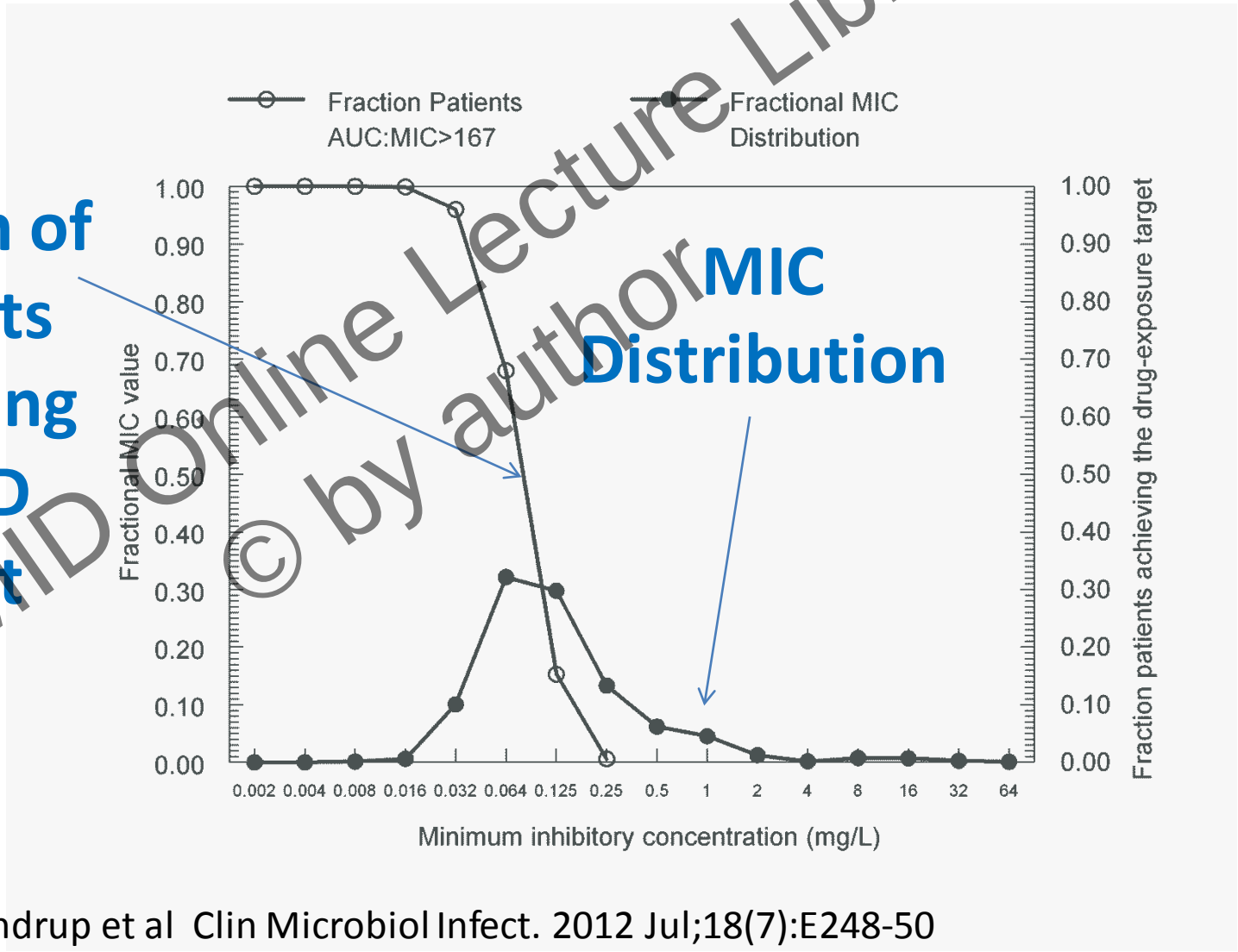
- Denning [Manchester, UK]
- Mouton, Meis and Verweij [Nijmegen, NL]
- Marchetti and Pascual [Lausanne, CH]
- [some North American help: Perlin, Andes]
- Then, formalised into a set of rules by EUCAST AFST
  - Arendrup, Cuenca-Estrella, Lass-Flörl, Hope
  - And our venerable predecesors

Dosage Adjustment is part of Standard Practice for use of triazoles

- [i.e. to achieve pharmacodynamic targets]
- Itraconazole
  - Trough >0.5 mg/L (HPLC), 5-17 mg/L (bioassay)
- Voriconazole
  - Trough 1-5 mg/L
  - Trough:MIC 2-5
- Posaconazole
  - Various estimates
  - e.g. AUC:MIC 170
- Plus, see www.EUCAST.org for breakpoints

Increasingly Apparent the Triazoles Operate in the Twilight Zone

Posaconazole: Target Attainment

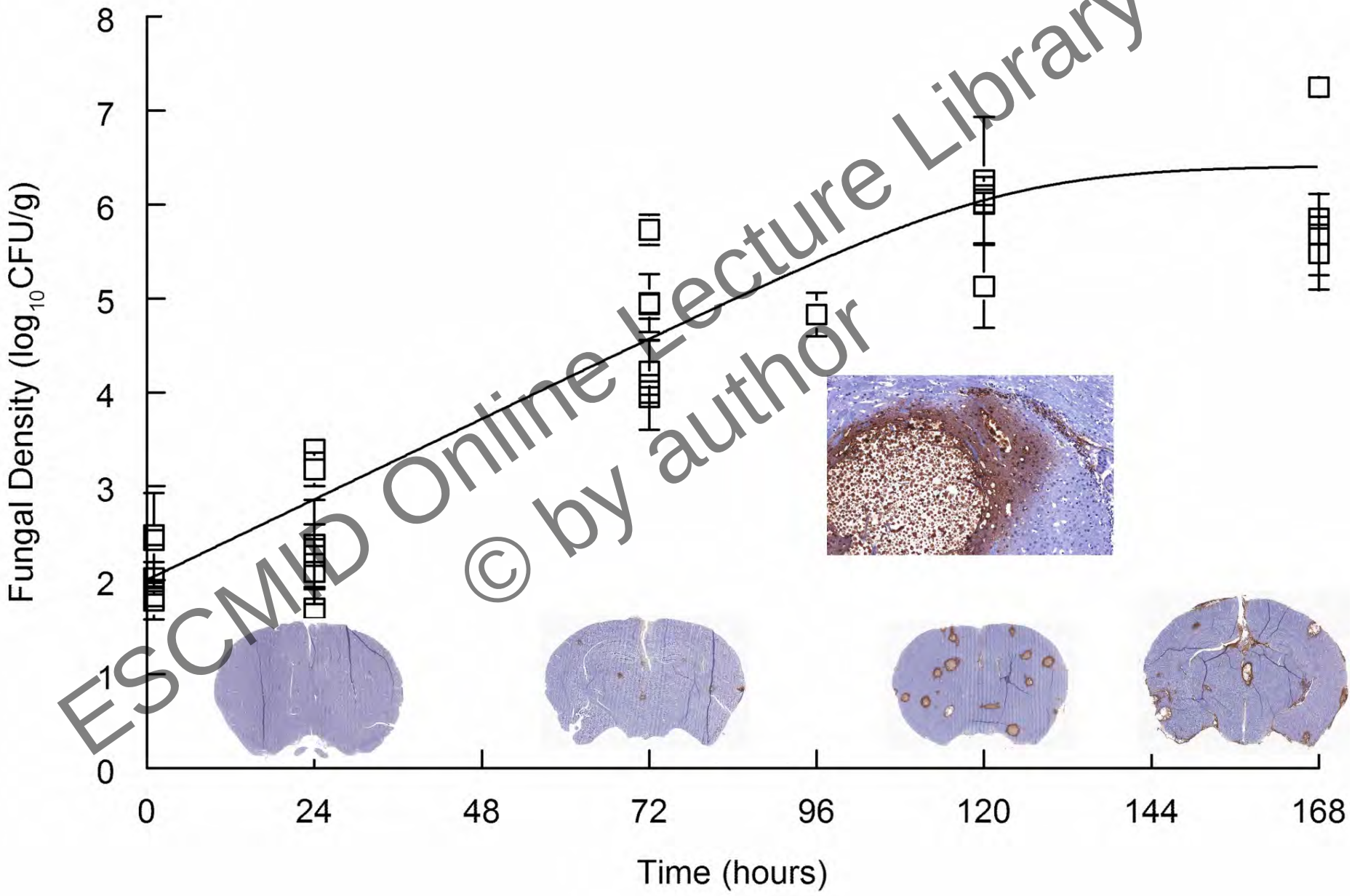


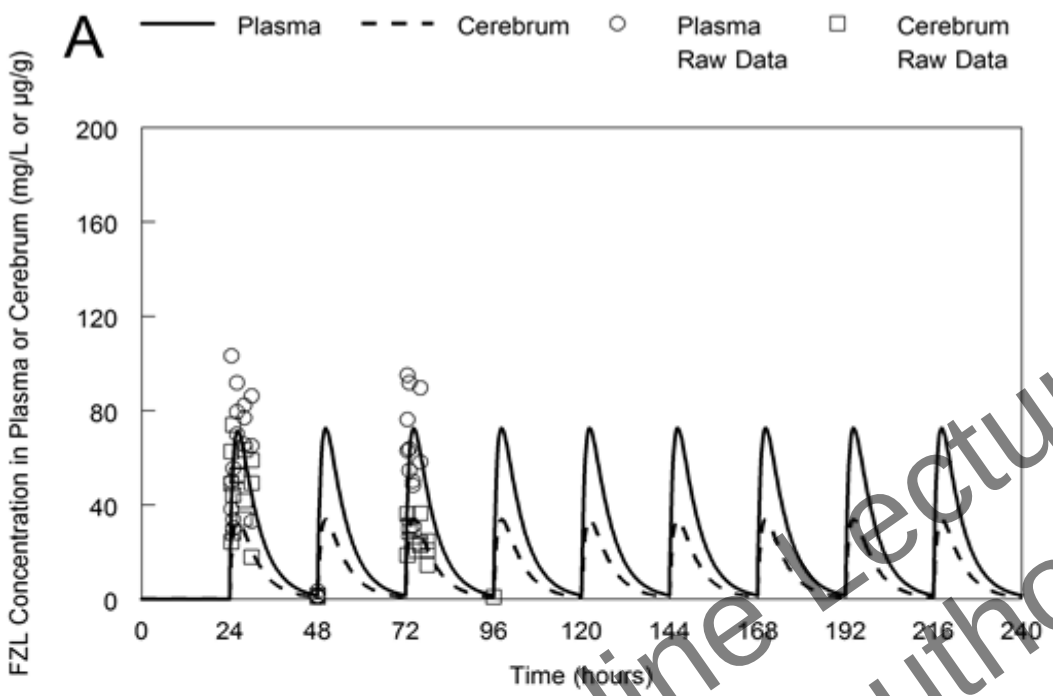
Fraction of Patients Achieving the PD Target

MIC Distribution

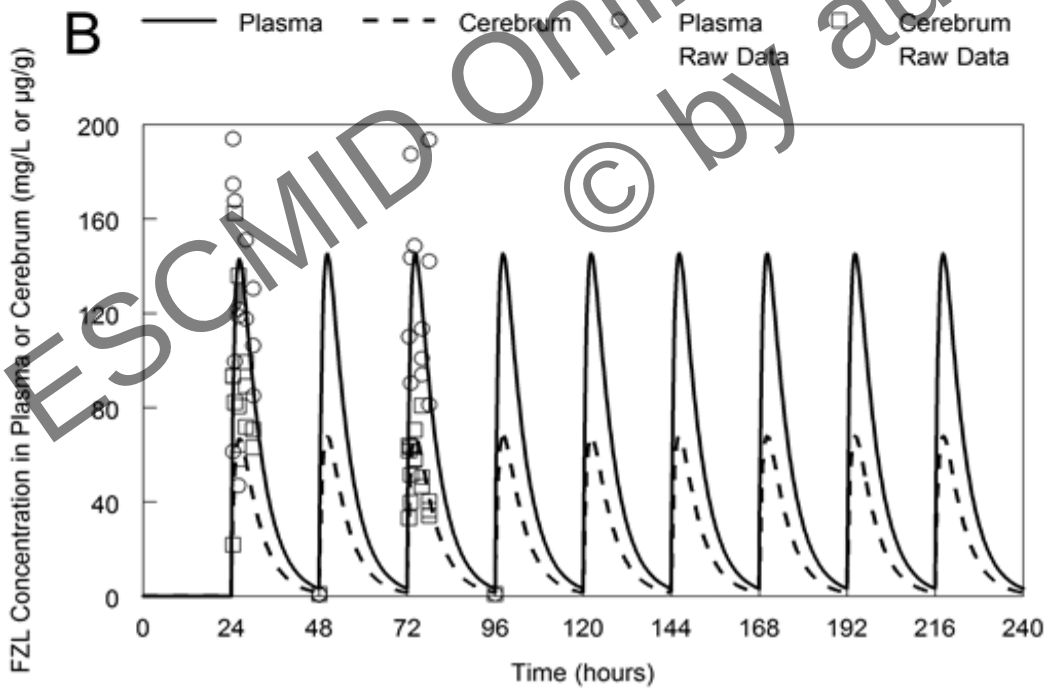
From Arendrup et al Clin Microbiol Infect. 2012 Jul;18(7):E248-50
and Posaconazole rationale at www.EUCAST.org

But, the potential importance of the MIC is lurking in more places…

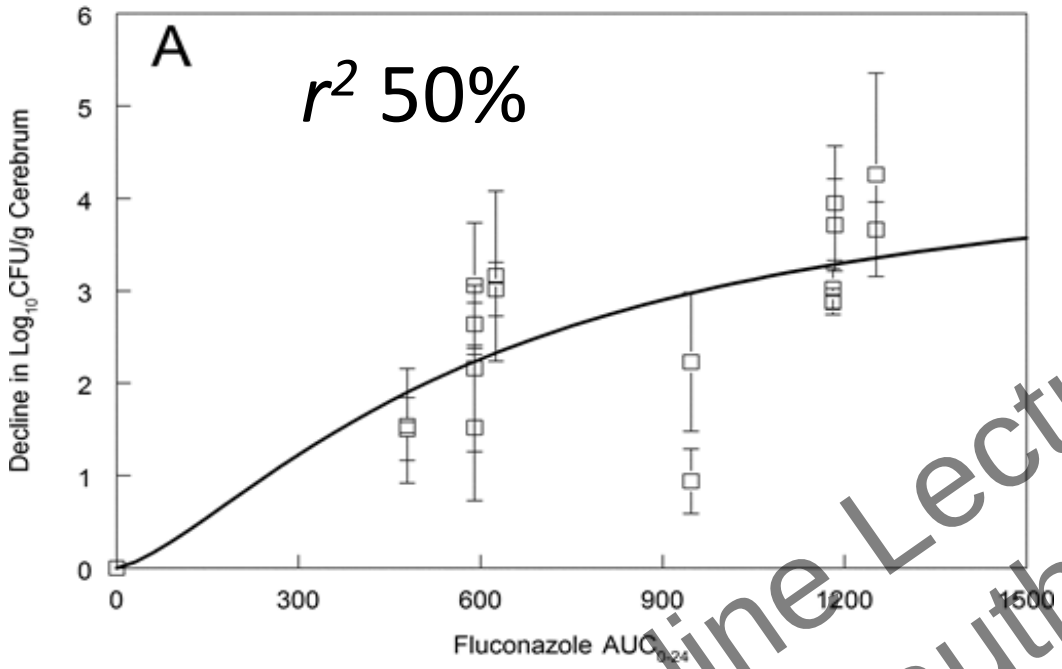




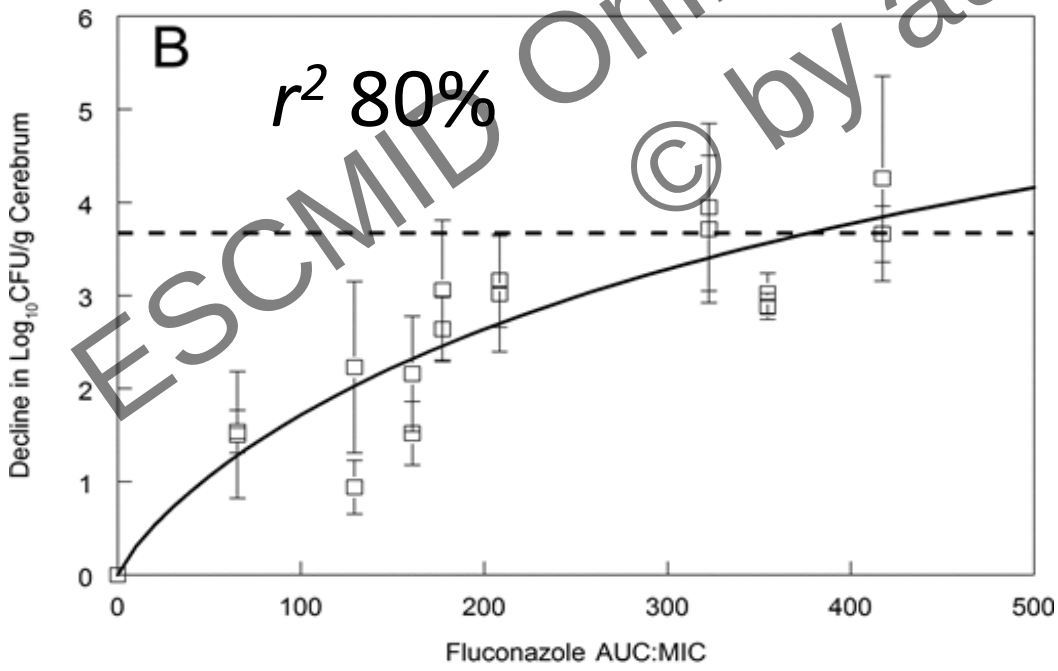
125 mg/kg/day



250 mg/kg/day

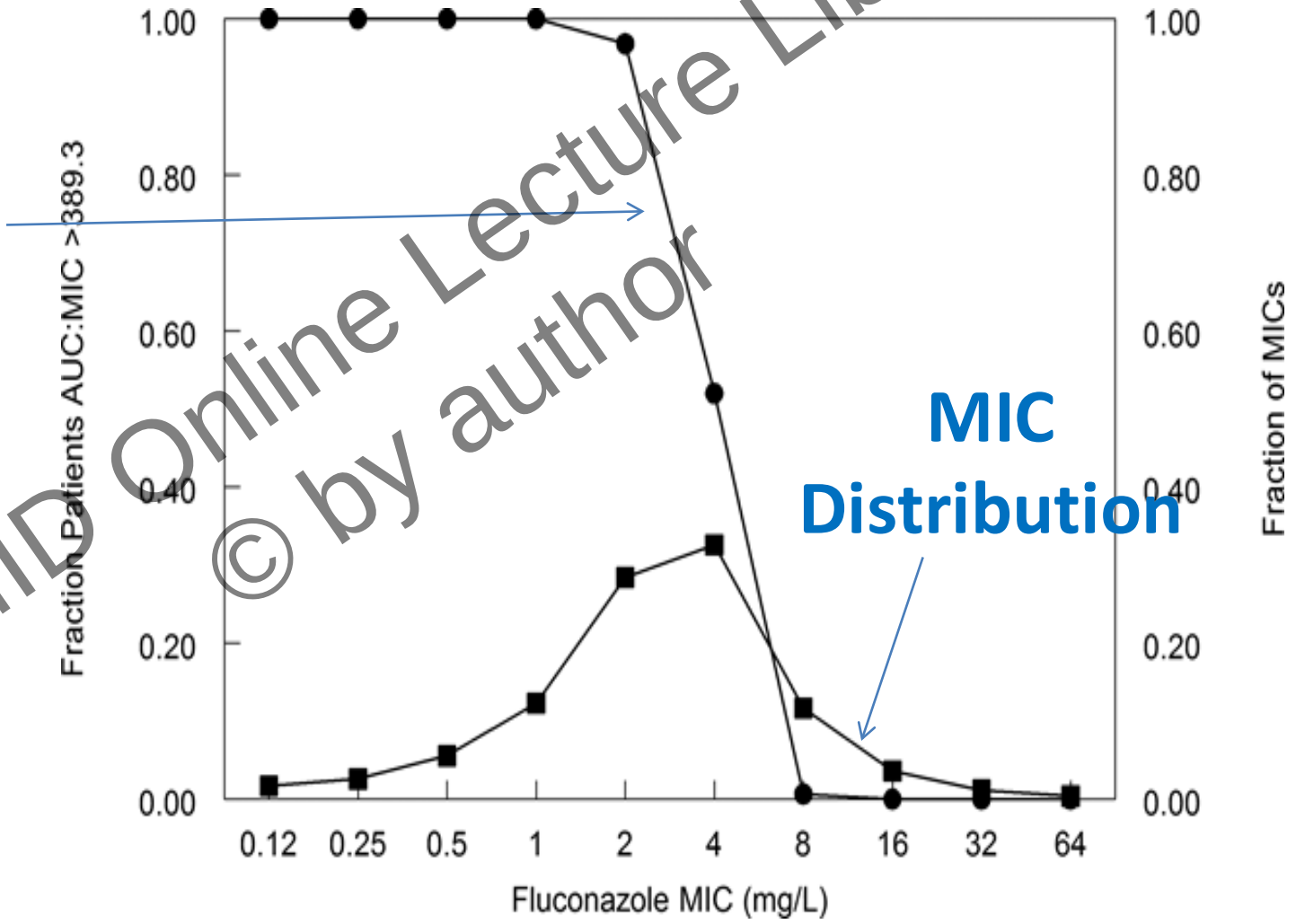


AUC versus effect



AUC:MIC versus effect

Fluconazole 1200 mg/day



Conclusions

- Fluconazole 1200 mg/day submaximal- cannot cover a satisfactory proportion of isolates
- Consistent with clinical data/ experience
- Foundation to explore alternative therapeutic options
  - Combinations, new orally bioavailable agents, access to 5FC etc. etc.

Fin

Thank you to people here in Rome who have helped develop many of these ideas