Translating PK-PD Concepts to the Clinic

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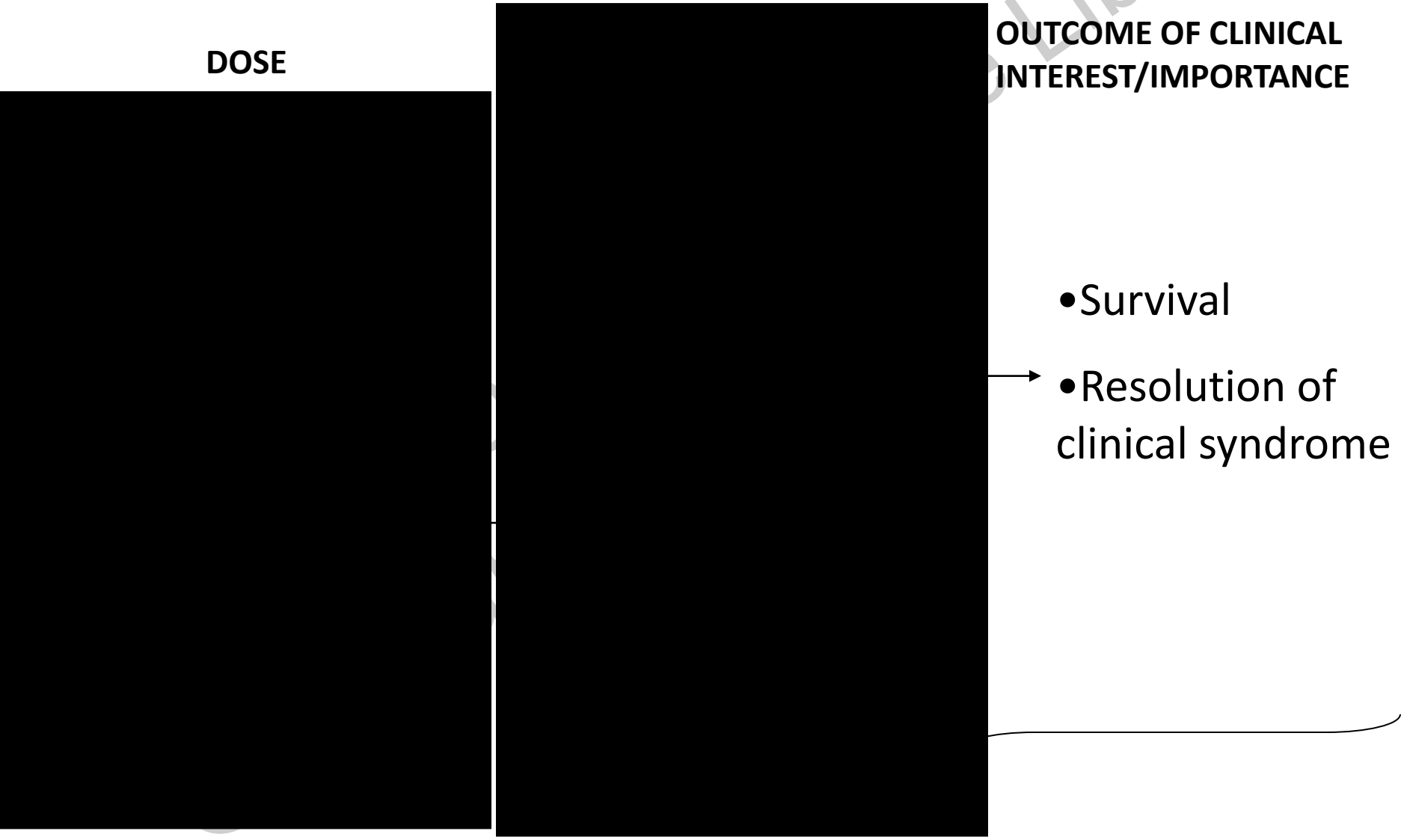
Translating PK-PD Concepts into the Clinic

Pharmacokinetics-Pharmacodynamics



Three Questions

- What is required for translation (bridging)?
- What problems can be solved by translation (bridging)?
- What are the threats to the validity of the process?

Let's assume the first part is done, and done well

- The PK-PD of Drug x against pathogen y has been established
  - Good idea of the PD index that best links drug exposure with the observed effect
    - e.g. AUC:MIC, Peak:MIC, T>MIC
- Good idea of the magnitude of the PD index that is required to generate an effect
  - e.g. relationship between AUC:MIC and orders of logarithmic killing

To enable statements like…

(1) Drug x is AUC:MIC driven

(2) An AUC:MIC of 250.46 is associated with a 1-log kill

(3) An AUC:MIC of 356.8 is associated with a 2-log kill etc. etc.

Or some variant of this…

What is the purpose of bridging? There are two:

- Identification of dosages and schedules of drug administration that are likely to be safe and effective for patients
    - Nontoxic and associated with near maximal antimicrobial activity
- Setting/ Establishing/ Verifying *in vitro* susceptibility breakpoints

What then is required for the translation (bridge) to the clinic?

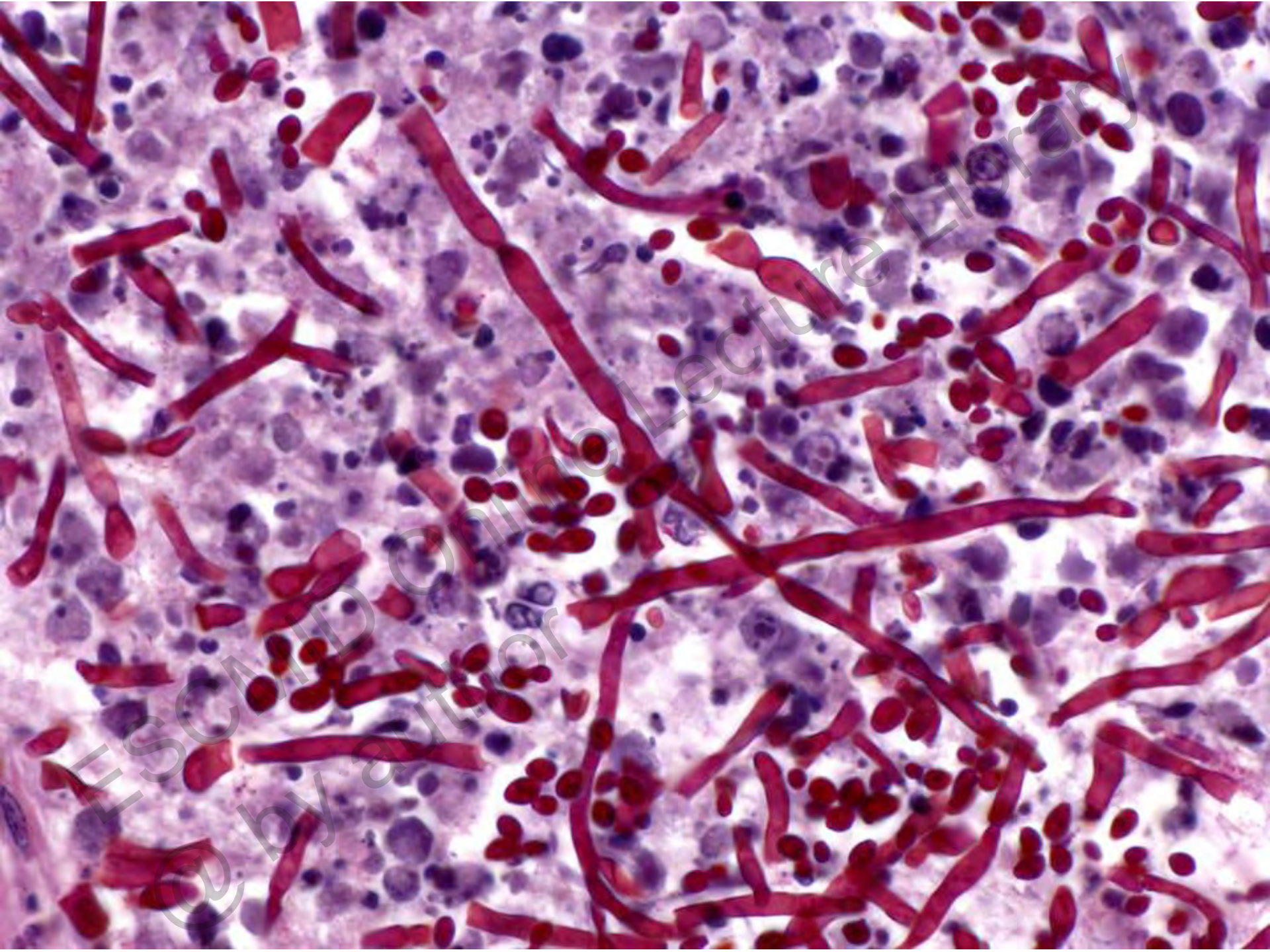
Bridging Experimental Data: Population PK

- Population PK provides an estimate of central tendency and **variability** of drug behaviour within a population
- Or, put differently, Pop PK enables a description of the **distribution** of drug exposures (AUC:MIC, trough concentration, T>MIC etc. etc.) that develop when a population of patients is administered a given dosage
- And, since drug exposure is linked to effect, the impact of inherent PK variability on the antimicrobial effect can be estimated

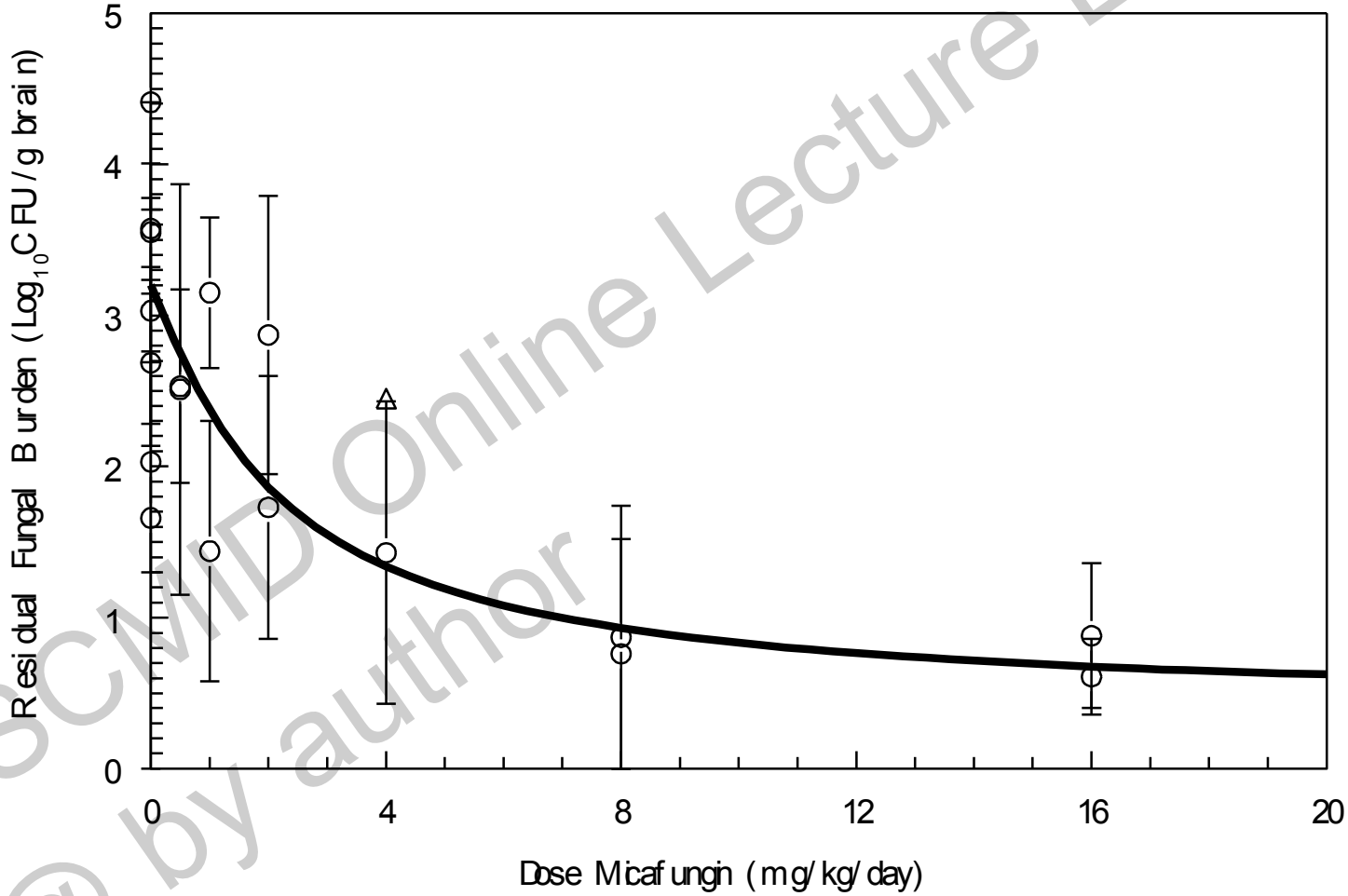
Bridging Experimental Data Monte Carlo simulation

- The initial idea of simulation was used to solve nuclear shielding problems
  - Problems too expensive or dangerous for experimentation
  - Problems too complicated for an analytical solution
- For PK, a computer generates virtual patients
  - Each with an individual set of PK parameters (Vc, SCL etc.)
  - Based on the population PK parameter means and covariance matrix given by the population PK model
- Each virtual patient receives a drug and the resultant drug exposure is calculated (e.g. AUC:MIC)
- The drug exposure is then linked to the response via the drug exposure response relationship

An Example



Micafungin exhibits a dose-dependant fungicidal effect



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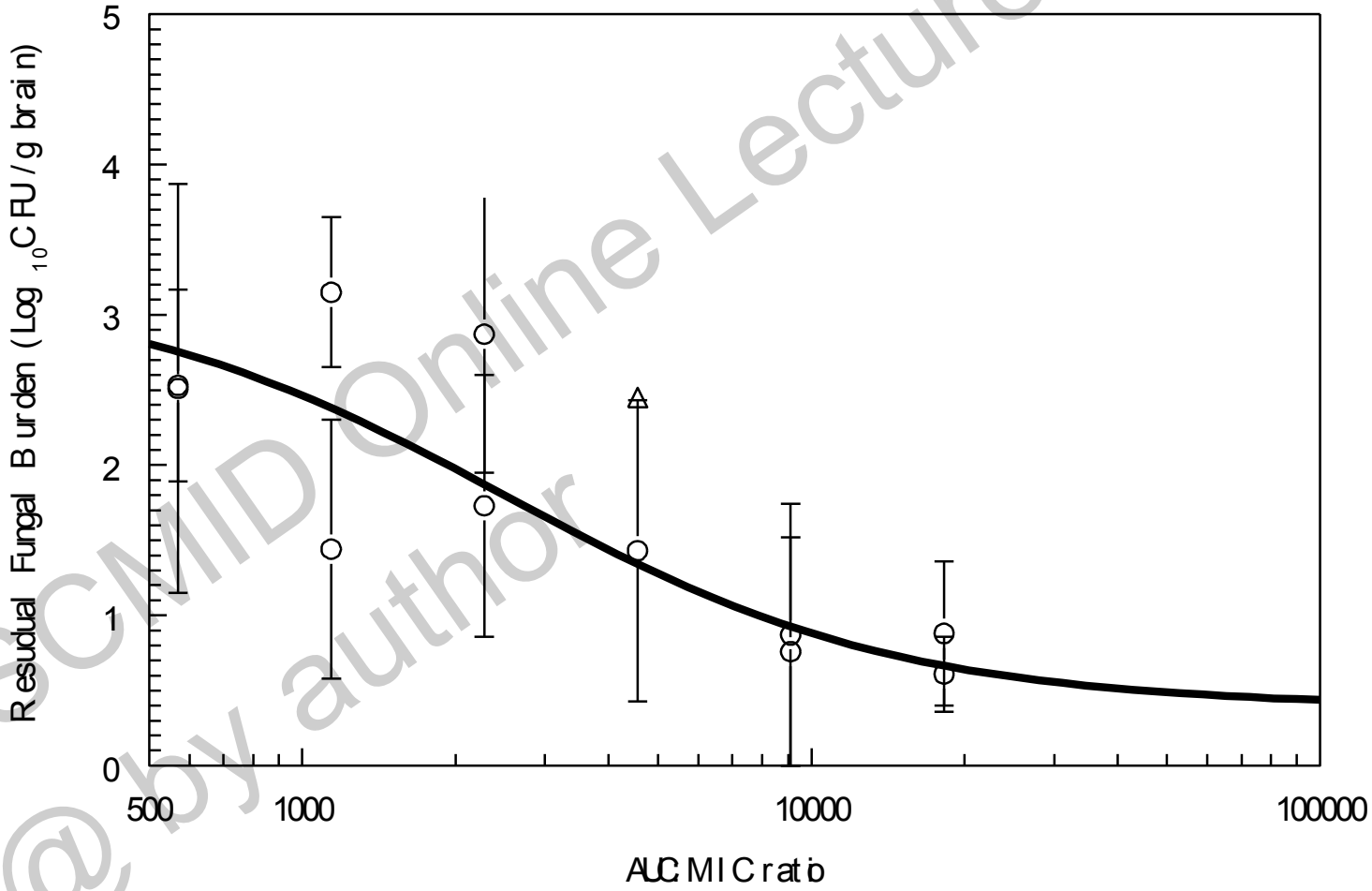
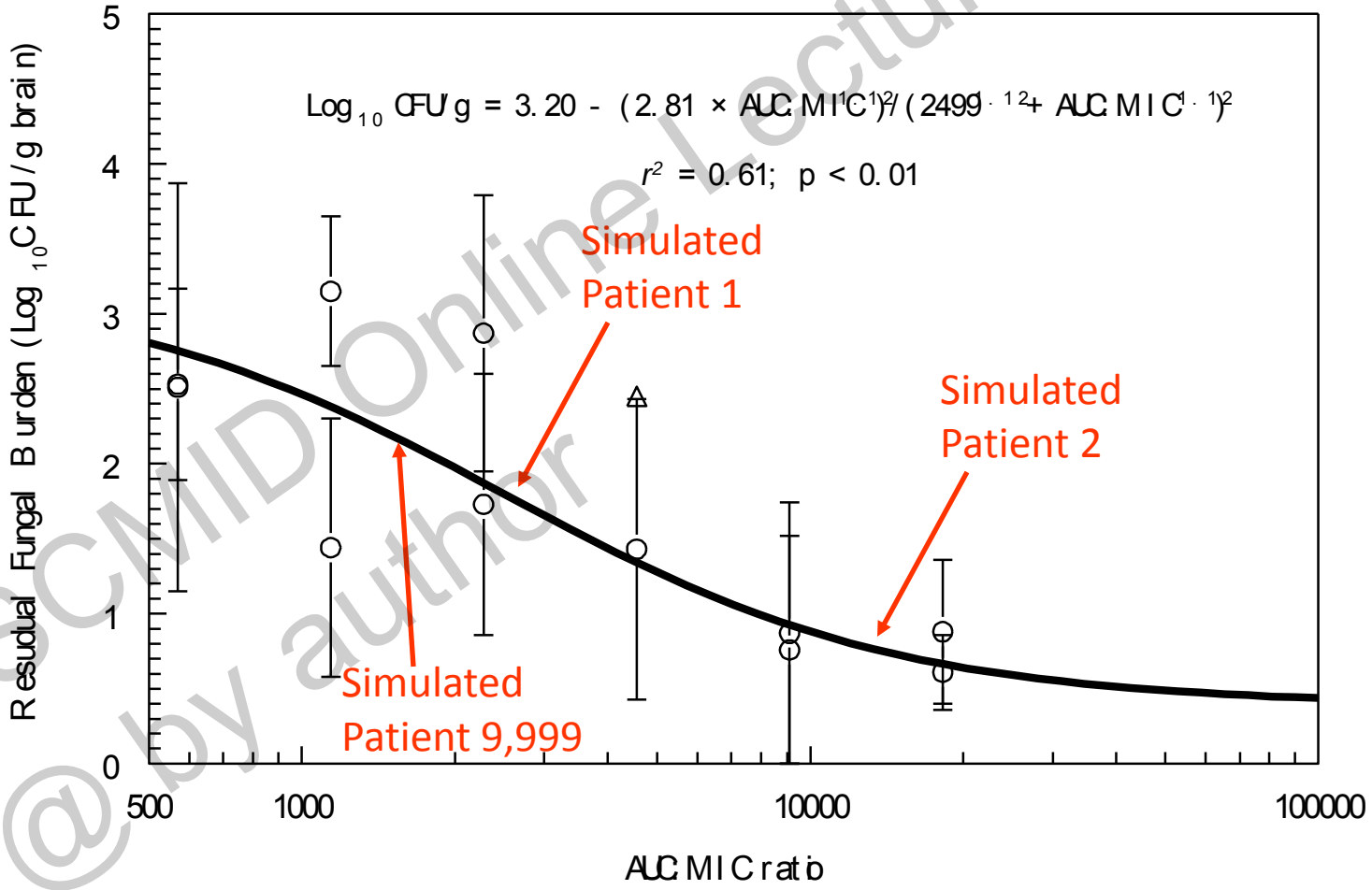
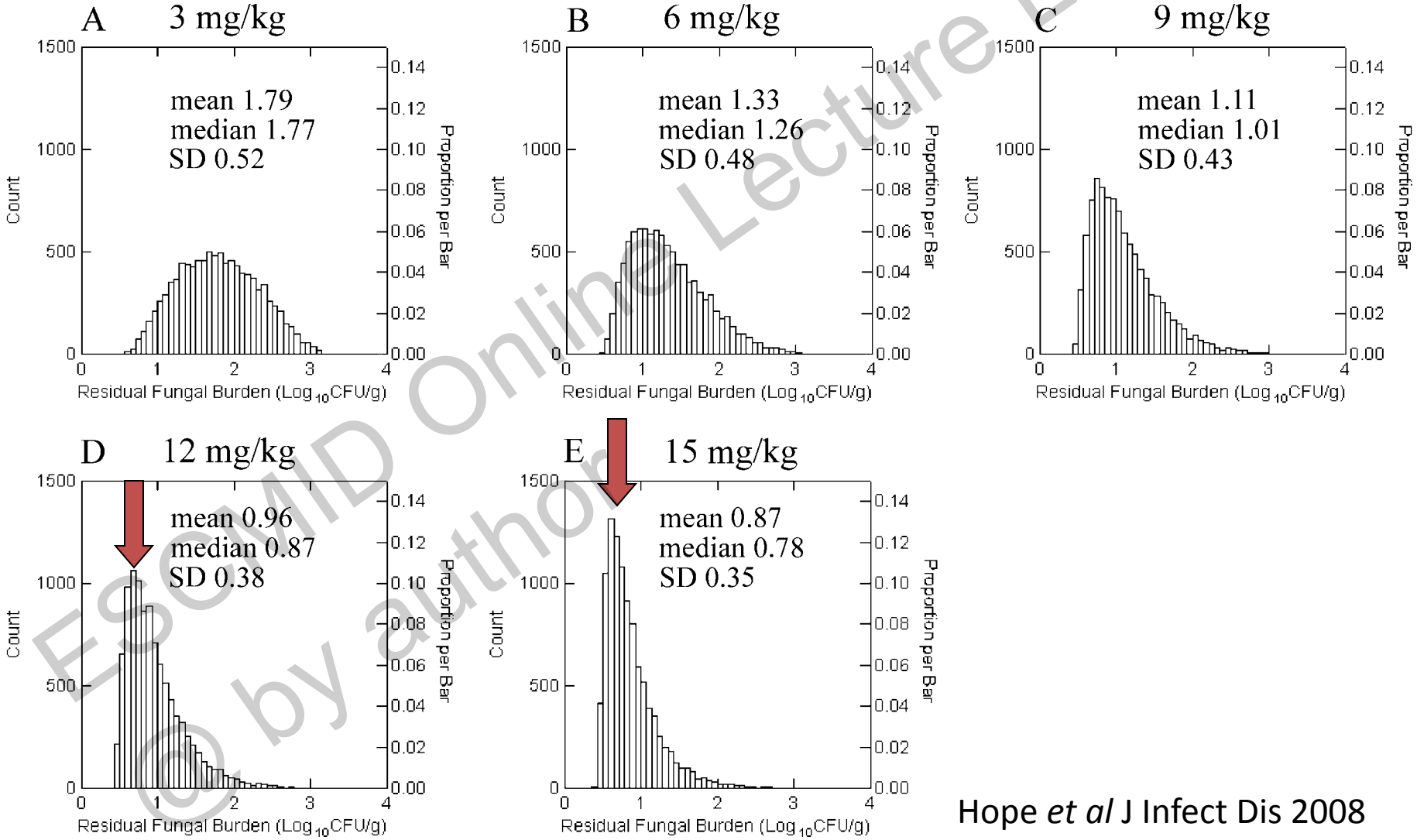
The transform: drug exposure is now quantified in terms of the common invading pathogen



Assume that the pharmacodynamics in the experimental system and babies are the same



The simulated effect in 9,999 neonates with HCME receiving micafungin



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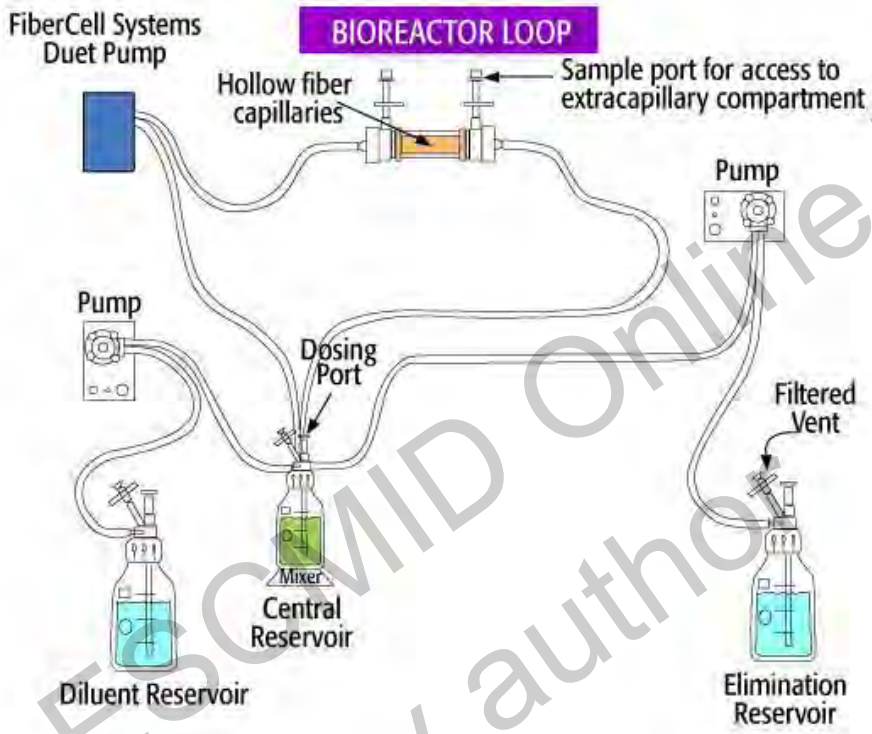
Once you have figured out how to use a simulator, bridging is pretty easy…the real question is whether you are right!

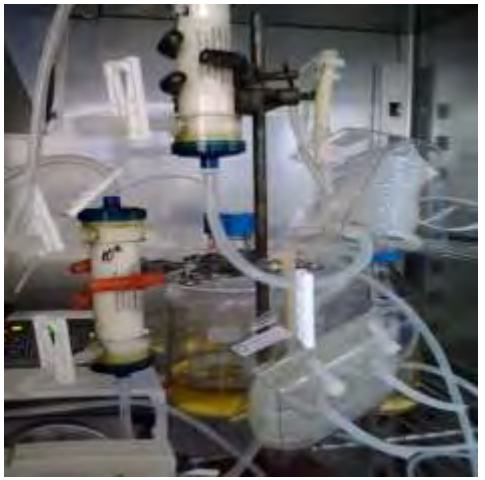
What are the threats to validity of bridging…a personal opinion

1. Is the preclinical PK-PD giving the right answers?

- The most important thing here is the experimental model
  - Is it a faithful mimic of human disease and pathogenesis?
  - Has it been characterized at a pathological level?
  - What about background immunosuppression?
  - What about the delay in administration of antimicrobial therapy
  - Are the strains “real” rather than pet laboratory strains
  - What about the severity of the model

“I don’t treat Hollow Fibre Infection Models…I treat patients”
How could HFIM ever be predictive?





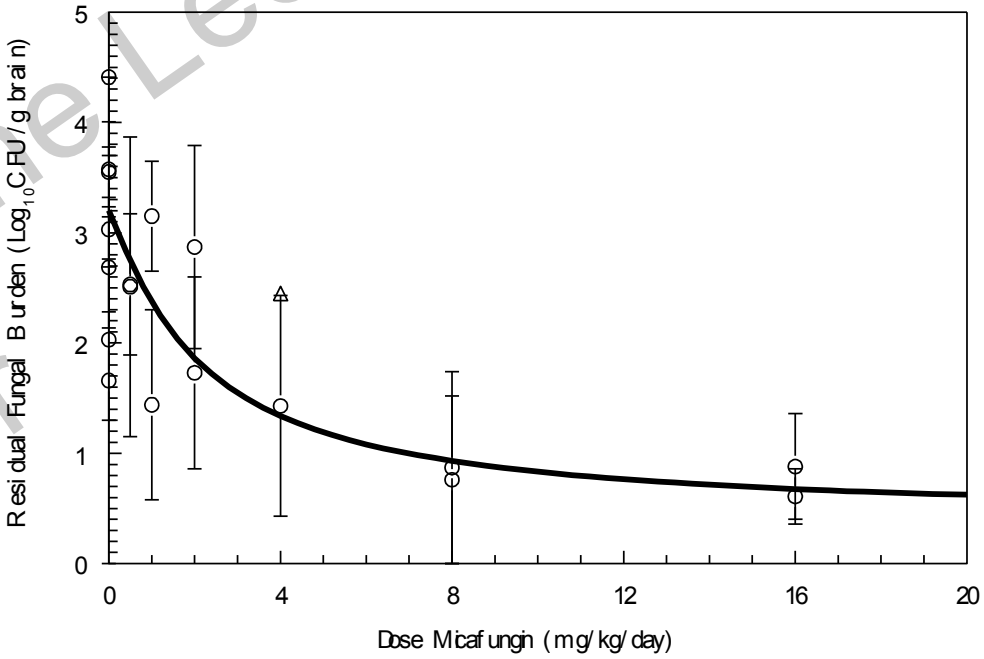
How to convince yourself conclusions from a HFIM (or any model) are real

- There isn't any rule about this
- No need to take anyone's word
  - Make your own mind up
- Consider carefully what you effect site is being modeled
  - Different tissue beds have different exposure response relationships
  - e.g. a HFIM may not be appropriate to model meningitis unless CSF concentrations are mimicked
  - or ELF concentrations are modeled for pneumonia
- Use some form of triangulation
  - Different experimental model (lab animal model)
  - Other published studies
  - Altered experimental conditions
- Be critical, stay cautious and play conservatively

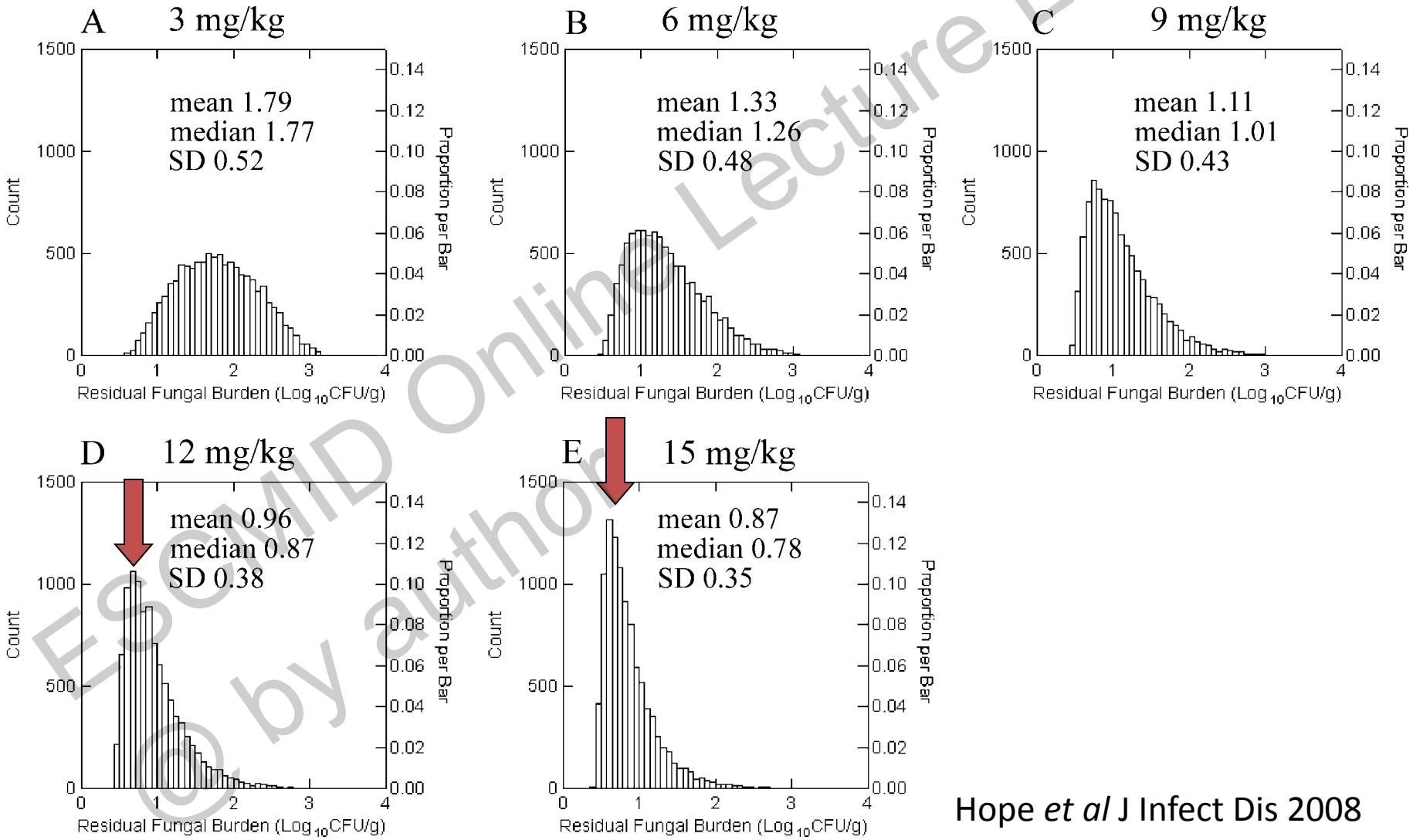
2. What is the magnitude of the “best” endpoint that is associated with an outcome of interest?

- E_{50}
- 1 log drop in CFU/g
- 2 log drop in CFU/g
- Stasis

[these endpoints not absolute or devine!!]



One way to do this is not make a decision about log drop, but just show a histogram of effect



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Study Endpoints (cont.)

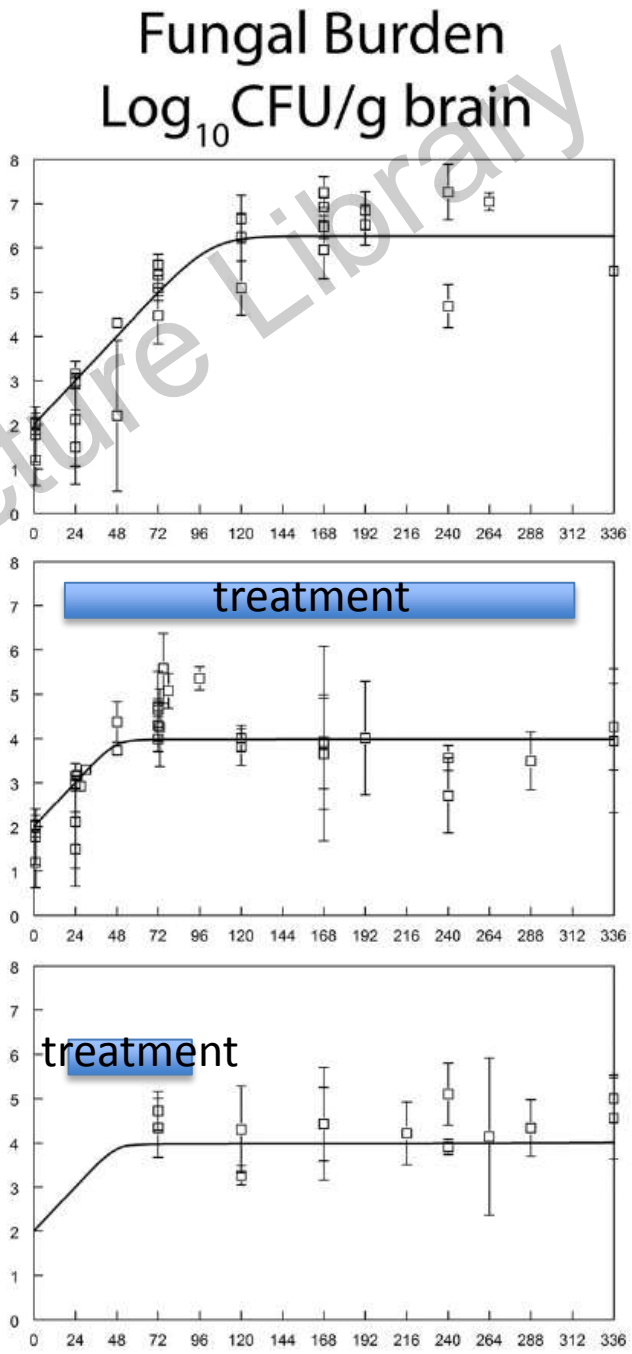
- I recently heard George Drusano talk about reducing burden to < 6 logs to enable neutrophils to kill in an optimal manner
  - That's OK if it also makes clinical sense like it does in VAP
  - But may not be applicable to every situation
  - Sometimes you have to admit you don't know (that's OK!)
  - Sometimes you can define a lower margin that is unlikely to be effective- that defines a minimum effect that is acceptable
  - Sometimes it may be appropriate to take as much effect as you can get given what you know about toxicity
- Can consider trying to triangulate other study endpoints
  - Survival
  - Histopathological findings
  - Clinical data if available

3. Beware of the following++

- Protein binding
  - Free drug generally modeled in HFIMs
  - Total drug generally measured in animals
  - I still don't quite know what to do about all of this, and beware of anyone that says they do know!
- "Invisible" immune effect (next slide)
- Emergence of drug resistance (next slide)
- Loading dosages (next slide)
  - Which AUC do you bridge?
  - The early one with the loading dose or at steady state?
- Duration (next slide)

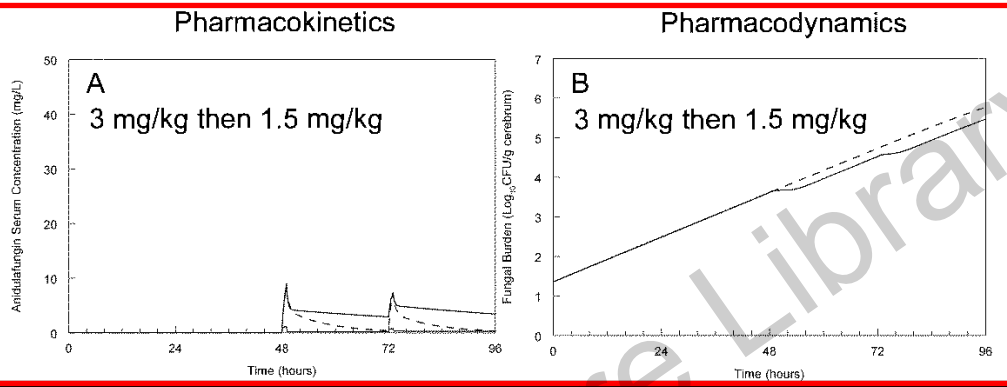
“Invisible” Immune Effects…even with proper controls

Drug holds the organism early on until there immune effectors become active- it is then possible to attribute ALL the antimicrobial effect to the drug (trust me, have made this mistake before!)

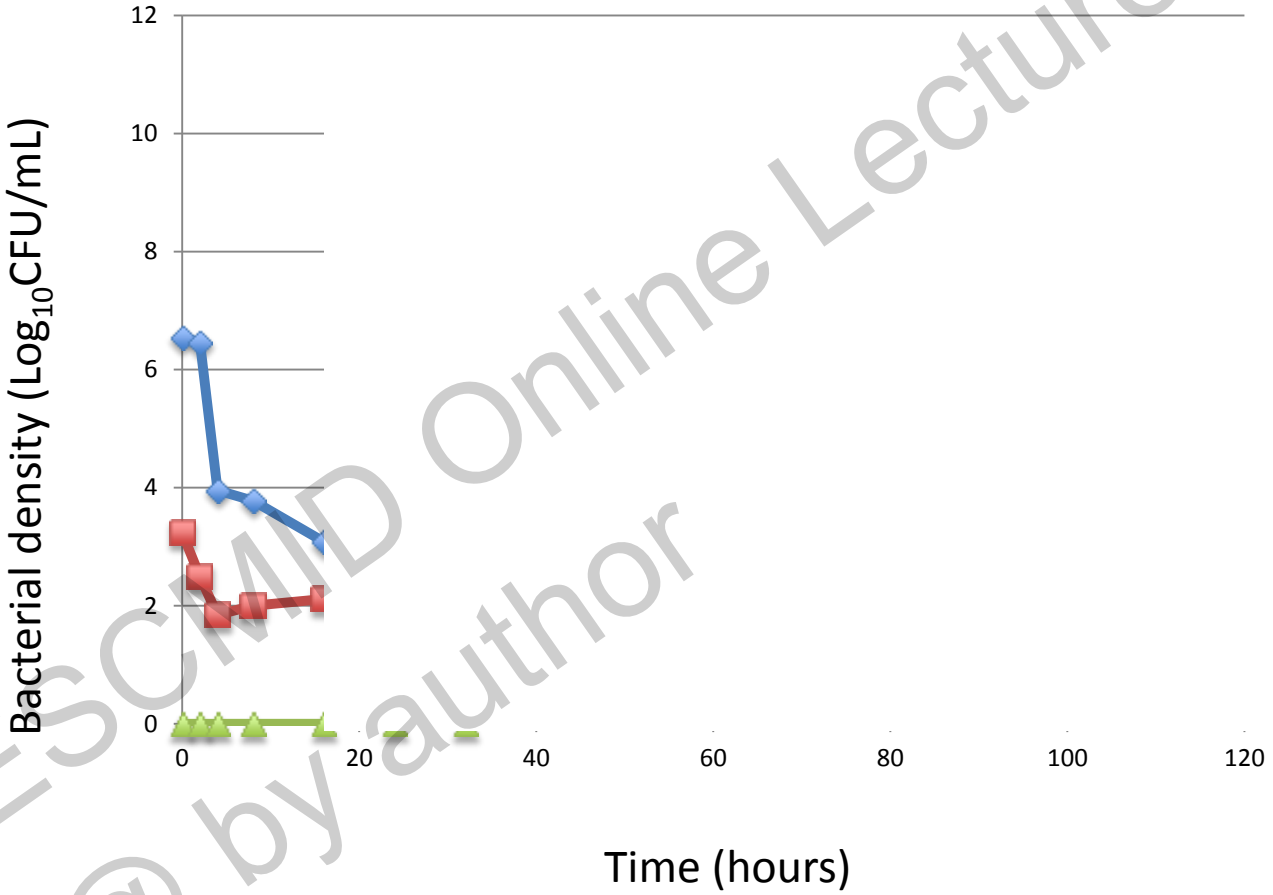


A way to handle the bridging when a loading dose is used

Adult AUC Equivalent



Fosfomycin 4 grams Q8: Emergence of Drug Resistance and Duration (courtesy Fernando Docobo-Perez)



4. Is the population PK right?

- Have an “adequate” number of patients been studied?
  - May under or over estimate variance with small numbers (both bad!)
  - 40 is a good number, but not always possible
- Has the right population group been studied (e.g. healthy volunteers, versus ICU patients)?
  - PK will change…especially estimates of variance
- Is the population PK concordant with other published studies
  - If not, why not?
- If using studies from the literature, how sure are you that you are simulating the right parameters?
  - Has caused confusion for me in the past (especially NONMEM papers)
  - Can ask authors just to give you their data, offer co-authorship and re-solve the problem…that’s safe and everyone wins

When all said and done…

- PK-PD bridging informs and derisks clinical development
  - It isn't the definitive answer that can be used to write treatment guidelines…it is a step on the path
- Now a critical part of the regulatory framework
- Is a fantastic way to learn about drugs and diseases!