TDM and PK/PD in antifungal therapy: when and why?

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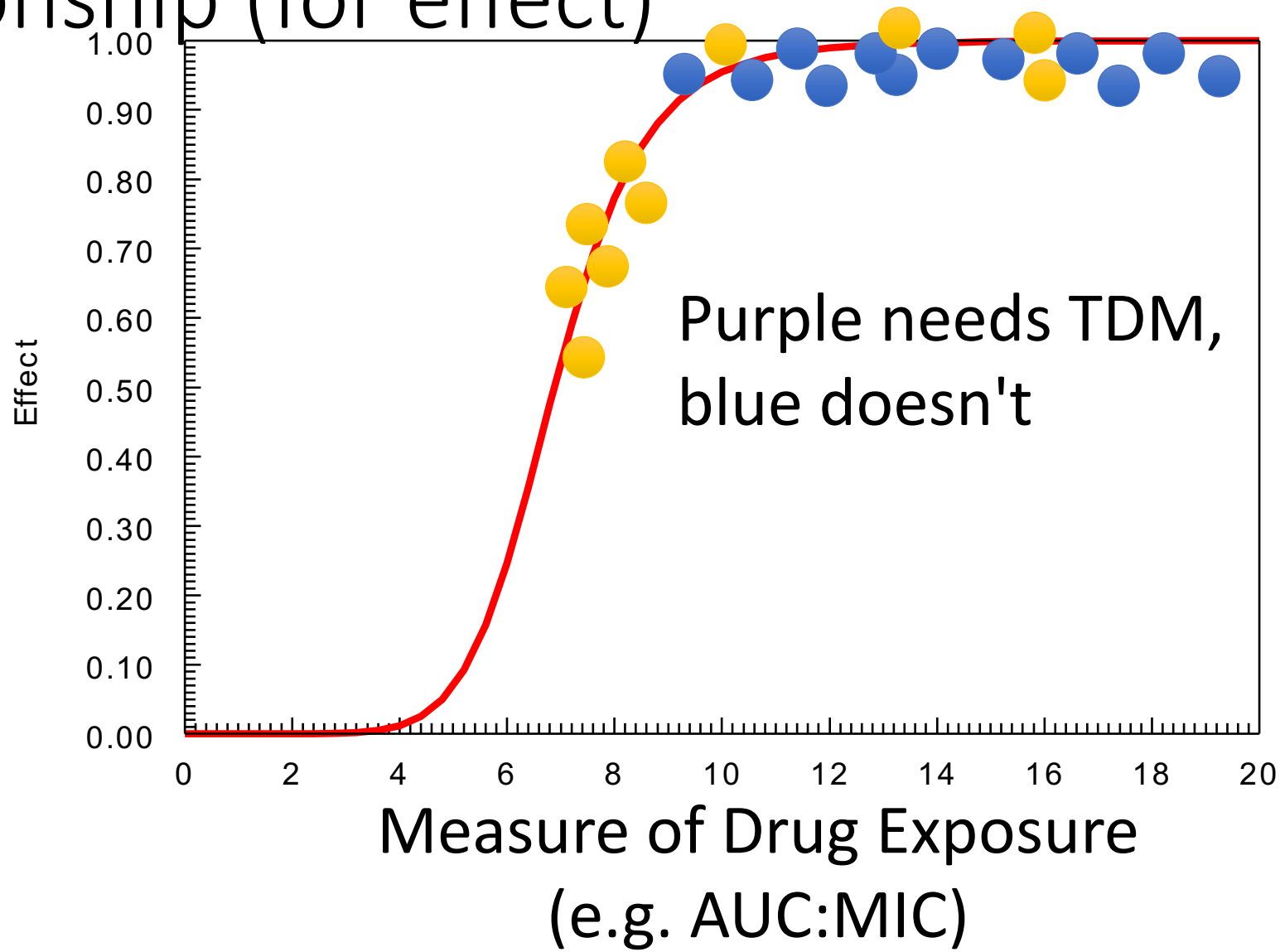
My disclosures

- William Hope holds or has recently held research grants with F2G, AiCuris, Astellas Pharma, Spero Therapeutics, Matinas Biosciences, Antabio, Amplyx, Allecra, Bugworks, NAEJA-RGM, AMR Centre, and Pfizer. He holds awards from the Medical Research Council, National Institute of Health Research, FDA and the European Commission. William Hope has received personal fees in his capacity as a consultant for F2G, Amplyx, Ausperix, Spero Therapeutics and BLC/TAZ.

The singular goal of antifungal therapeutics is the attainment of maximal antifungal effect (with toxicity<< disease)

TDM, combination chemotherapy, dose finding in early phase clinical studies, loading dosages, probability of target attainment etc. etc. are all expressions of this idea

Positioning on the exposure-response relationship (for effect)



Review of Current Best Practice

Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology

H. Ruth Ashbee[1]*, Rosemary A. Barnes[2], Elizabeth M. Johnson[3], Malcolm D. Richardson[4], Rebecca Gorton[5] and William W. Hope[6]

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What exactly did we codify?

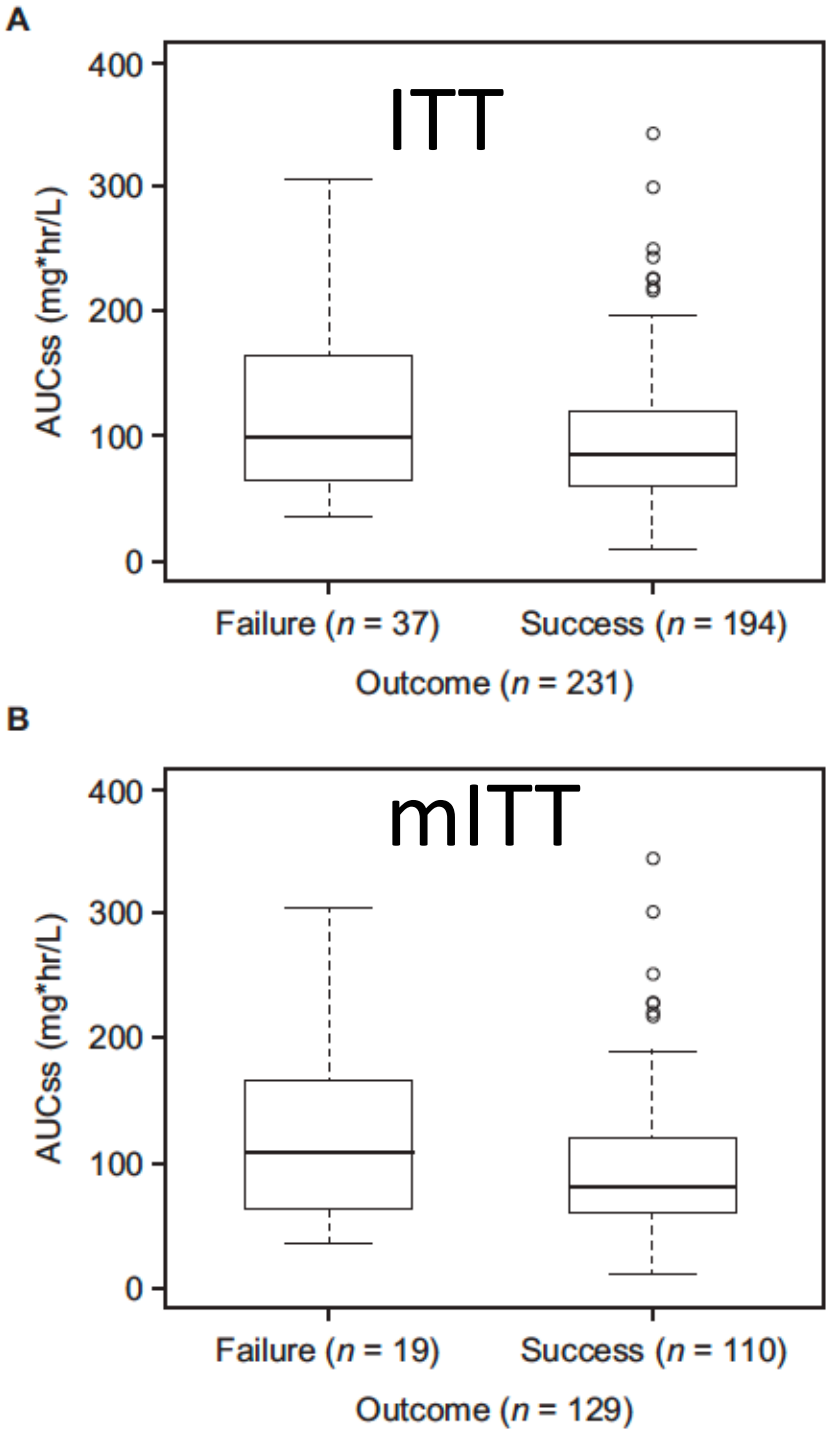
- Itraconazole should be measured for all patients
  - Trough >0.5 mg/L (HPLC), 5-17 mg/L (bioassay)
- Voriconazole should be measured for all patients
  - Trough 1 (or 2) to 5-6 mg/L
  - Trough:MIC 2-5
- Posaconazole should be measured for all patients
  - Trough > 1 mg/L

What didn’t we codify (because we didn’t know)

- Nothing about the quality systems and infrastructure that are required
  - Physicians trained in pharmacology
  - Drug measurement TAT <1 week
- Nothing about how to adjust dosages
  - Do your best and see how you go!
- Nothing too much about pharmacodynamics, except for one reference to MIC
- Nothing about isavuconazole

Isavuconazole

Is TDM required?



AUC versus Mortality

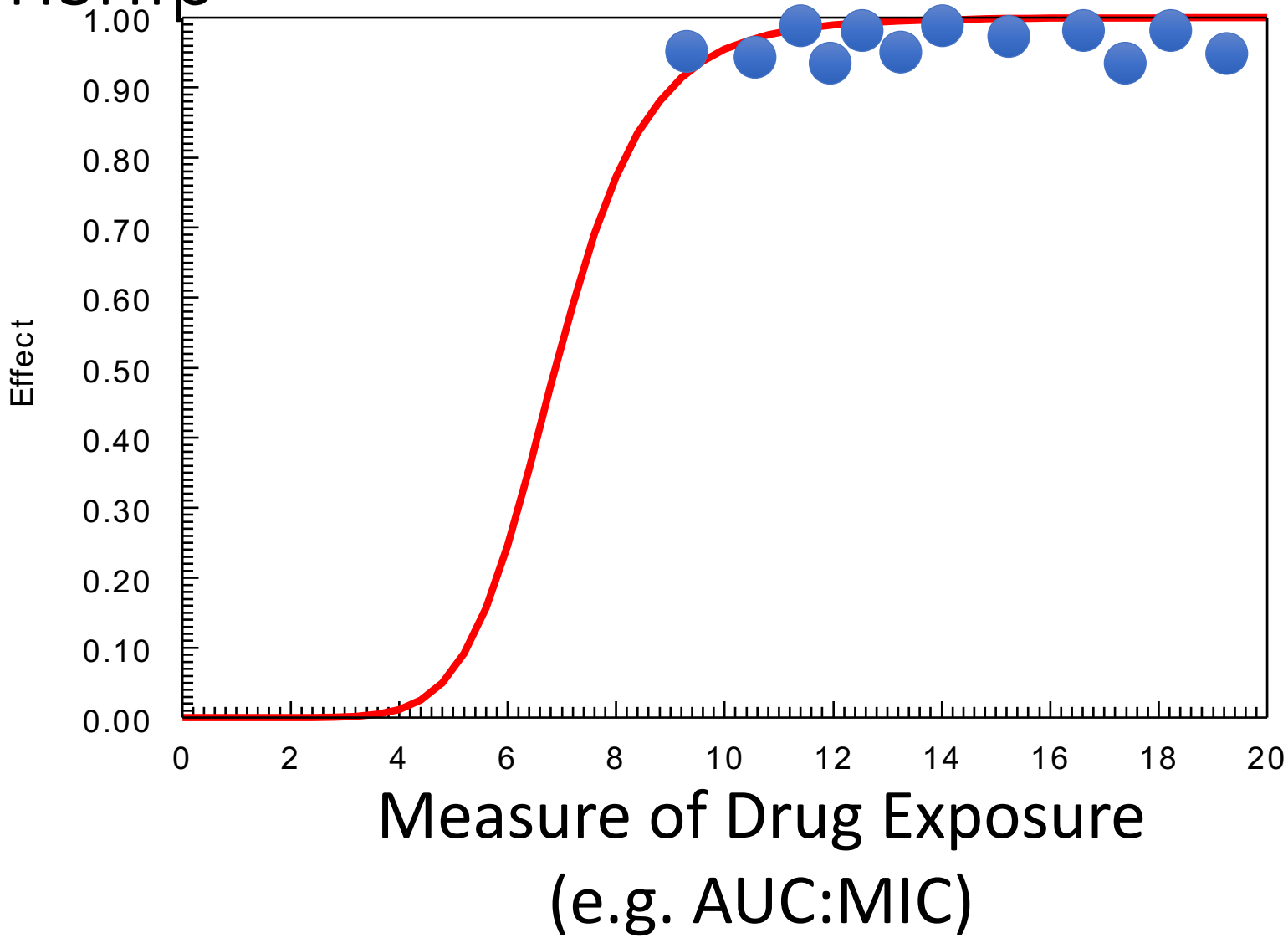
My interpretation

- There IS a drug threshold somewhere for effect (otherwise isavuconazole is not a drug)
- But, that threshold is not visible in the Phase III trial

Why isn't a signal observed?

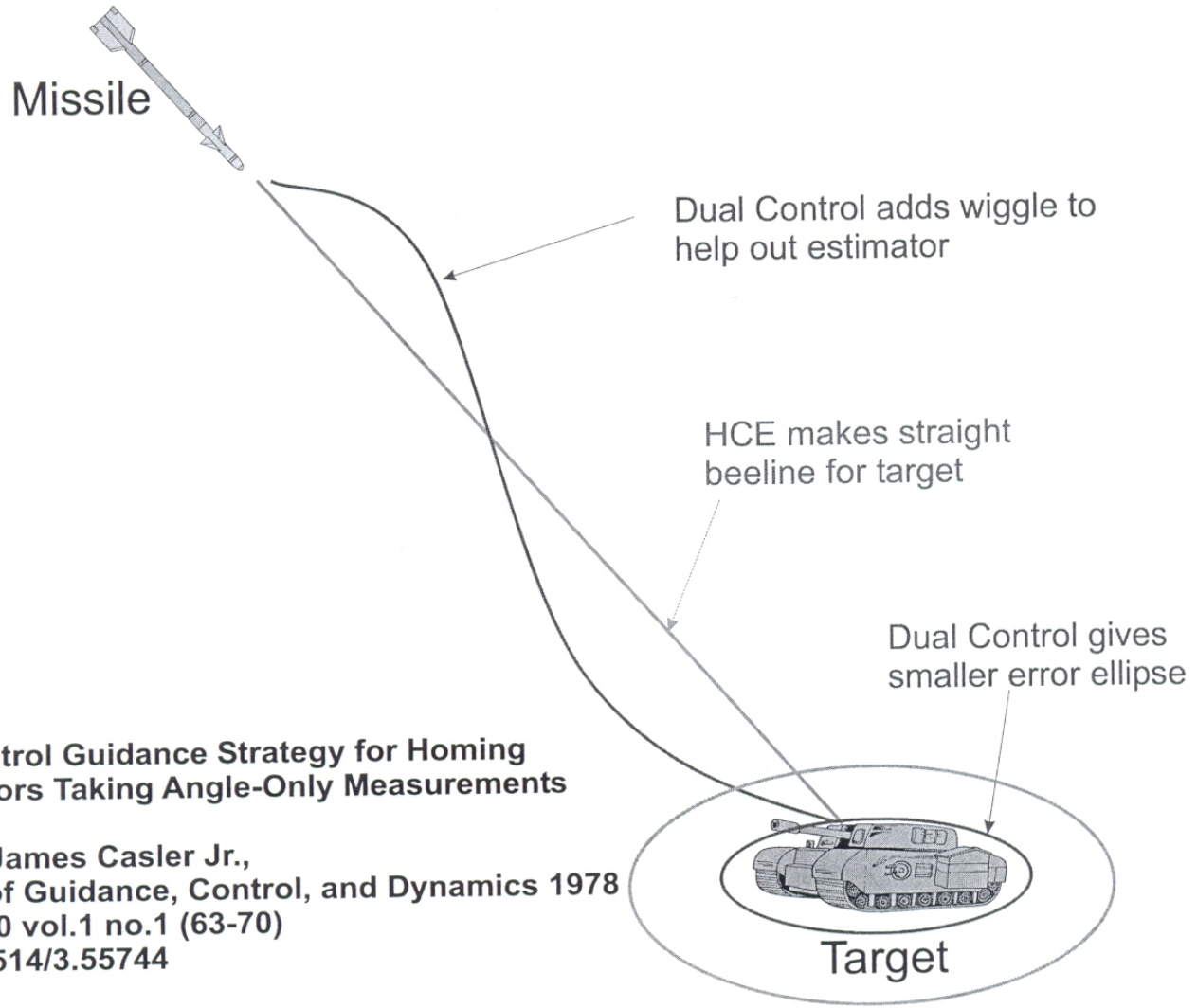
- On top of exposure response relationship
- Dissociation of measures of drug exposure and observed effect
  - Drug measured early, clinical outcomes late
- Compliance
- Inaccurate measures of PK and changing PK
- Patient heterogeneity
  - Too much noise

Sitting on top of the exposure-response relationship



What to do about dosage adjustment?

Dual Control for Missile Interception Problem



Dual-Control Guidance Strategy for Homing Interceptors Taking Angle-Only Measurements

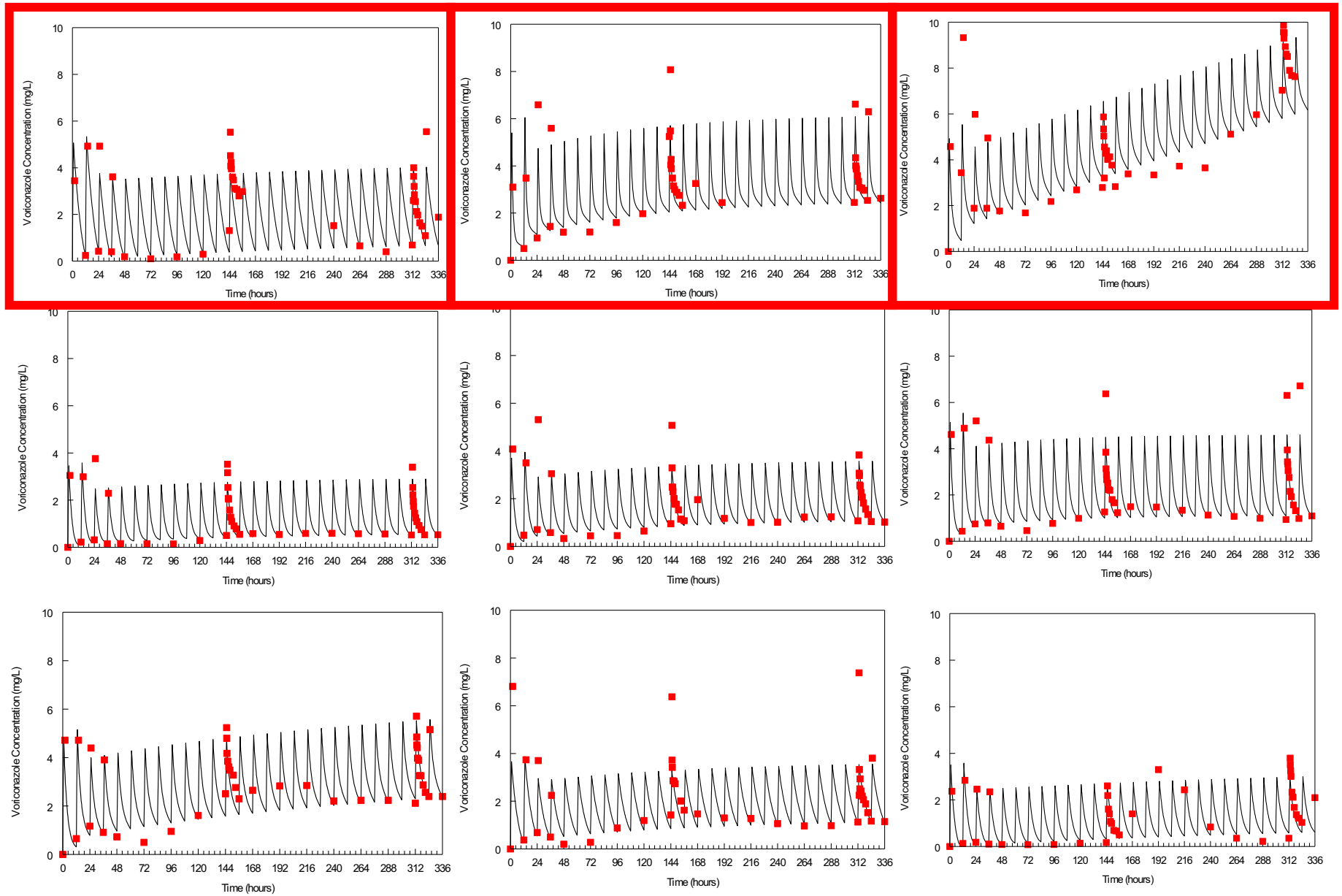
Richard James Casler Jr.,
Journal of Guidance, Control, and Dynamics 1978
0731-5090 vol.1 no.1 (63-70)
doi: 10.2514/3.55744

Picture taken from Bayard, D “Stochastic Control”

The Control Process…

Information from past experiences from many patients is “stored” in population PK models

A “multiple model” file is a mathematical summary of this stored experience



Raw data from Bruggeman et al J Antimicrob Chemother. 2010 Jan;65(1):107-13.

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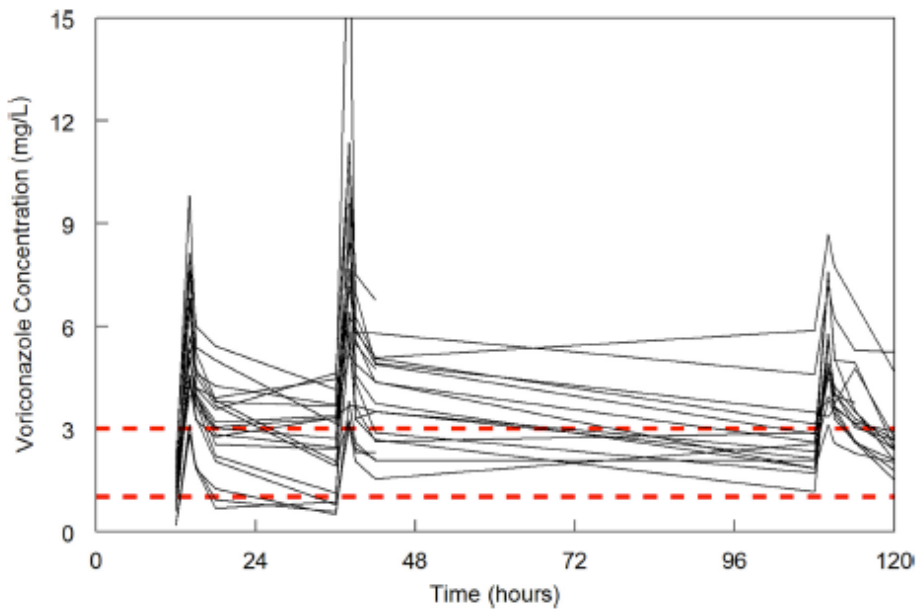
CLINICAL THERAPEUTICS

Software for Dosage Individualization of Voriconazole: a Prospective Clinical Study

William Hope,[a,b] Gary Johnstone,[c] Silvia Cicconi,[c] Timothy Felton,[d,e] Joanne Goodwin,[a] Sarah Whalley,[a] Anahi Santoyo-Castelazo,[a] Virginia Ramos-Martin,[a] Jodi Lestner,[a] Leah Credidio,[b] Aaron Dane,[a,f] Daniel F. Carr,[g] Munir Pirmohamed,[b,g] Rahim Salim,[b] Michael Neely[h]



Expected only 1/3 patients in range 1-3 mg/L

All fine, well done you say, but surely this is only half the problem?

Individualised Therapy

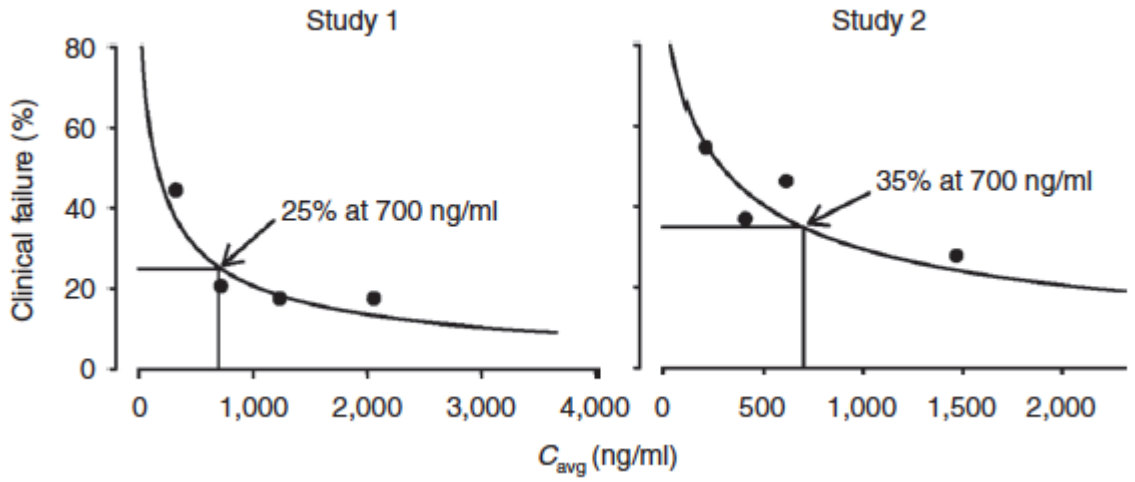
Pharmacokinetics

- Fixed Effects
  - Weight
  - CYP genotype
  - Acid
  - Food
  - DDI
  - Renal function
  - Hepatic function
- Residual Variability
  - What's left over

Pharmacodynamics

- Fixed Effects
  - MIC
  - Fungal species and strain
  - Infectious burden
  - Immune status and genotype
  - Delay in initiation of therapy
  - Site of infection
- Residual Variability
  - What's left over
- [that patient isn't responding as I would expect]

Clinical Pharmacodynamics



Jang et al

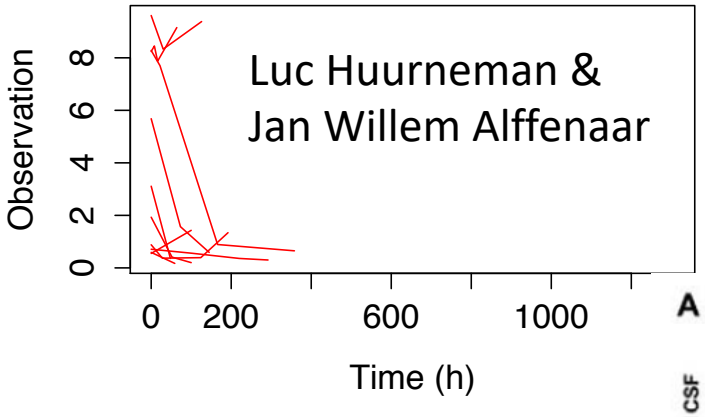
In other words, an individualised assessment (TDM measurement) gets linked to an average population target

And that is not (and never will be)
“true individualised therapy” or
“patient specific”

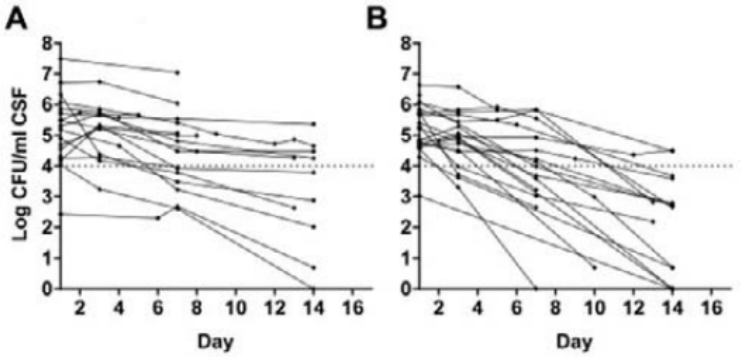
Which brings me to the idea of individualised pharmacodynamics

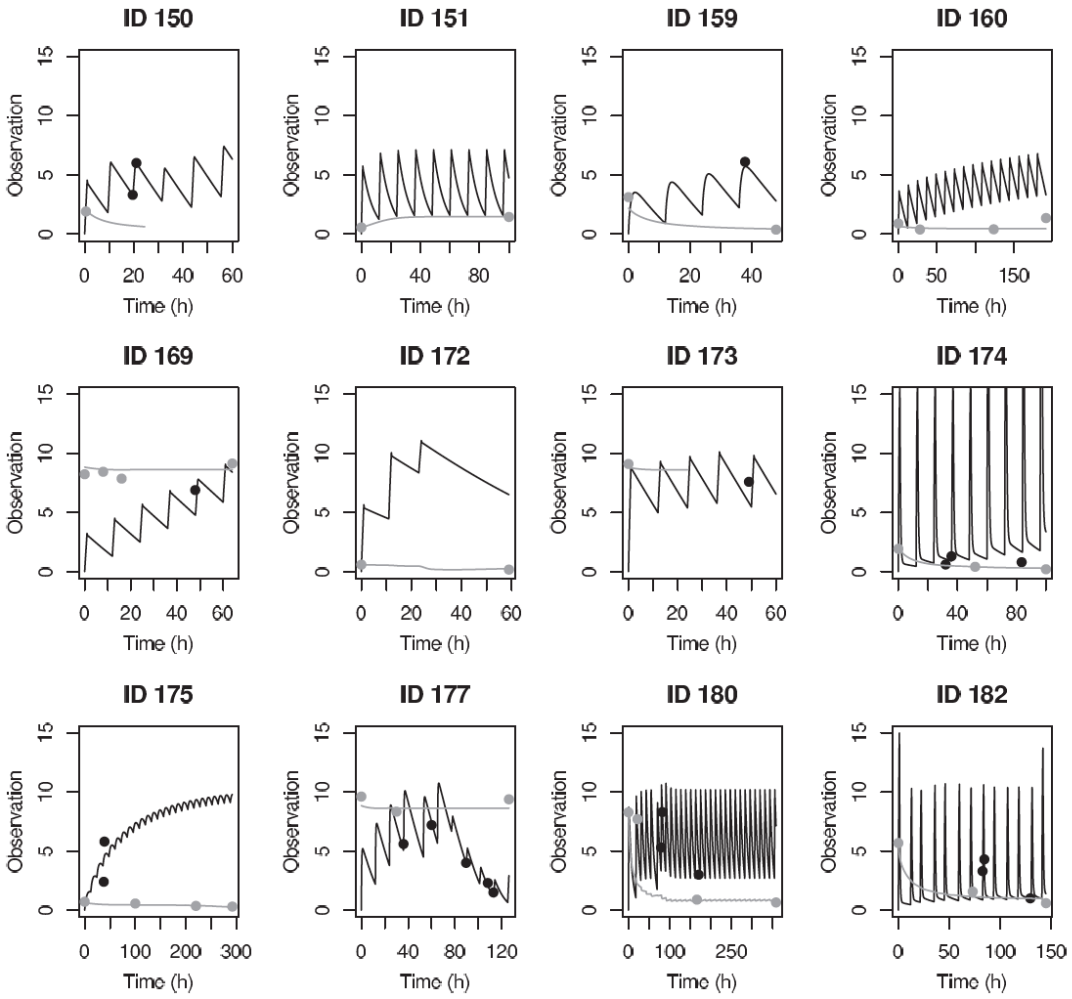
After all, isn't that what you really care about as clinicians?

Using biomarkers to follow disease: concept=dose the drug to move the biomarker



Following decline in cryptococcal counts in phase II &III clinical trials
Tom Harrison & Tihana Bicanic & Jeremy Day





Huurneman et al Antimicrobial Agents and Chemotherapy Feb 2016

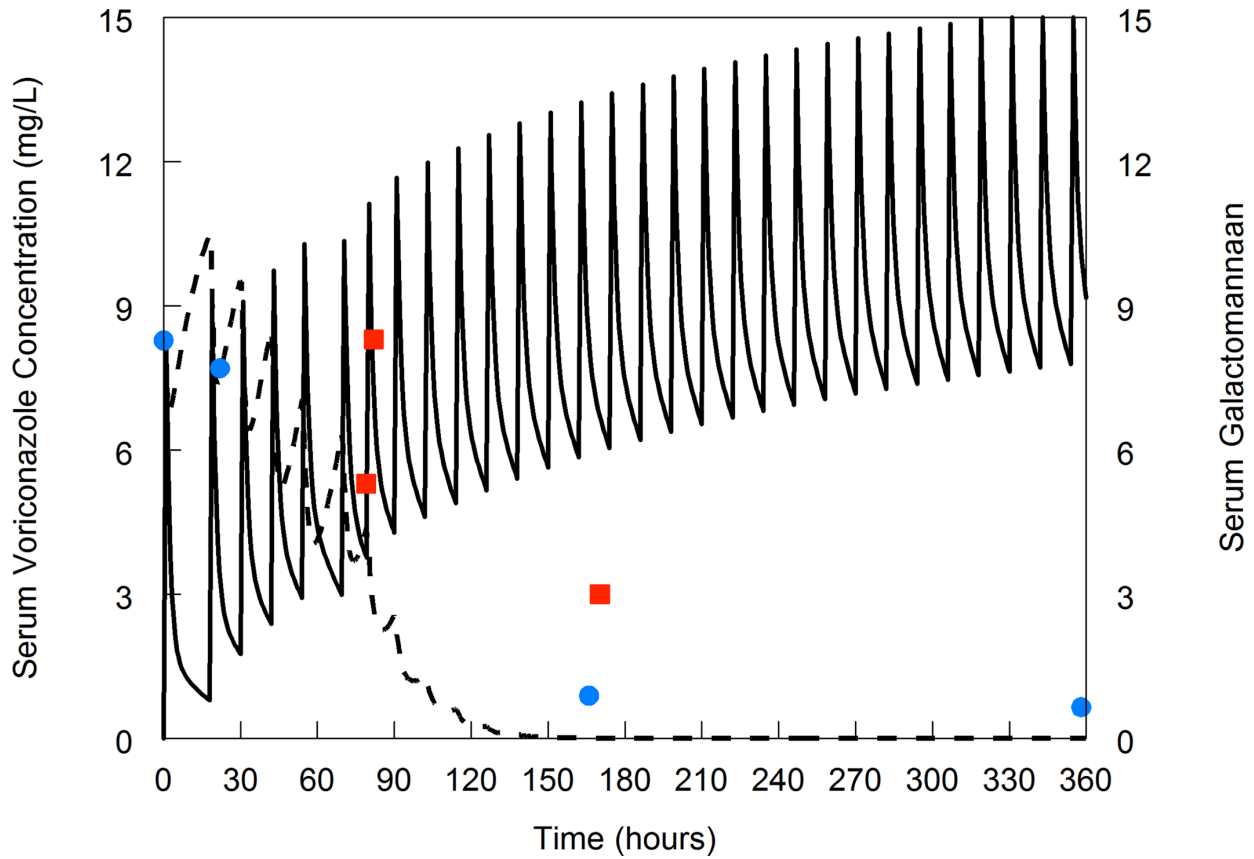
The purpose of showing that slide…

- The pharmacodynamics are fully stochastic
- In other words…***on average*** the GM response will be favourable
- But, *a priori* it is not possible to be sure which path a patient will follow

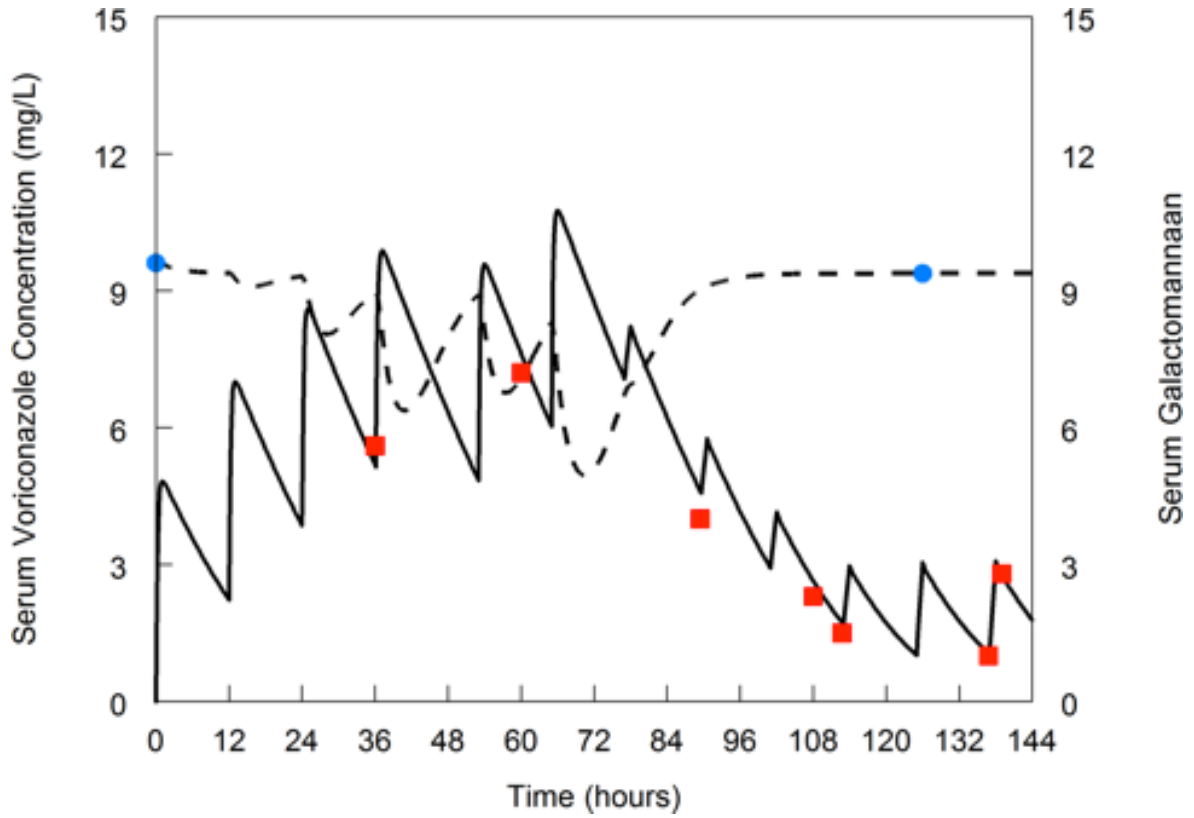
AUC:EC_{50} (the EC_{50} is an *in vivo* MIC)

- High with
  - High fungal burden
  - In vitro drug resistance (i.e. the MIC)
  - Profound immunosuppression
  - Infection within a sanctuary site
  - Delayed antifungal therapy
- But, requires some pharmacological expertise to estimate

Voriconazole: Low AUC:EC_{50}



Voriconazole: High AUC:EC_{50}



True individualized therapy: the future

- It’s hard enough just to get the job done. I recognize that
- There is no point in developing something if it is not used optimally
- We will need to do better
- In many cases have the necessary tools to do this, but our training and thinking accepts that near enough is good enough

Thank you

- Thank you
- We are at www.liverpool.ac.uk/apt

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