Where does TDM make sense?

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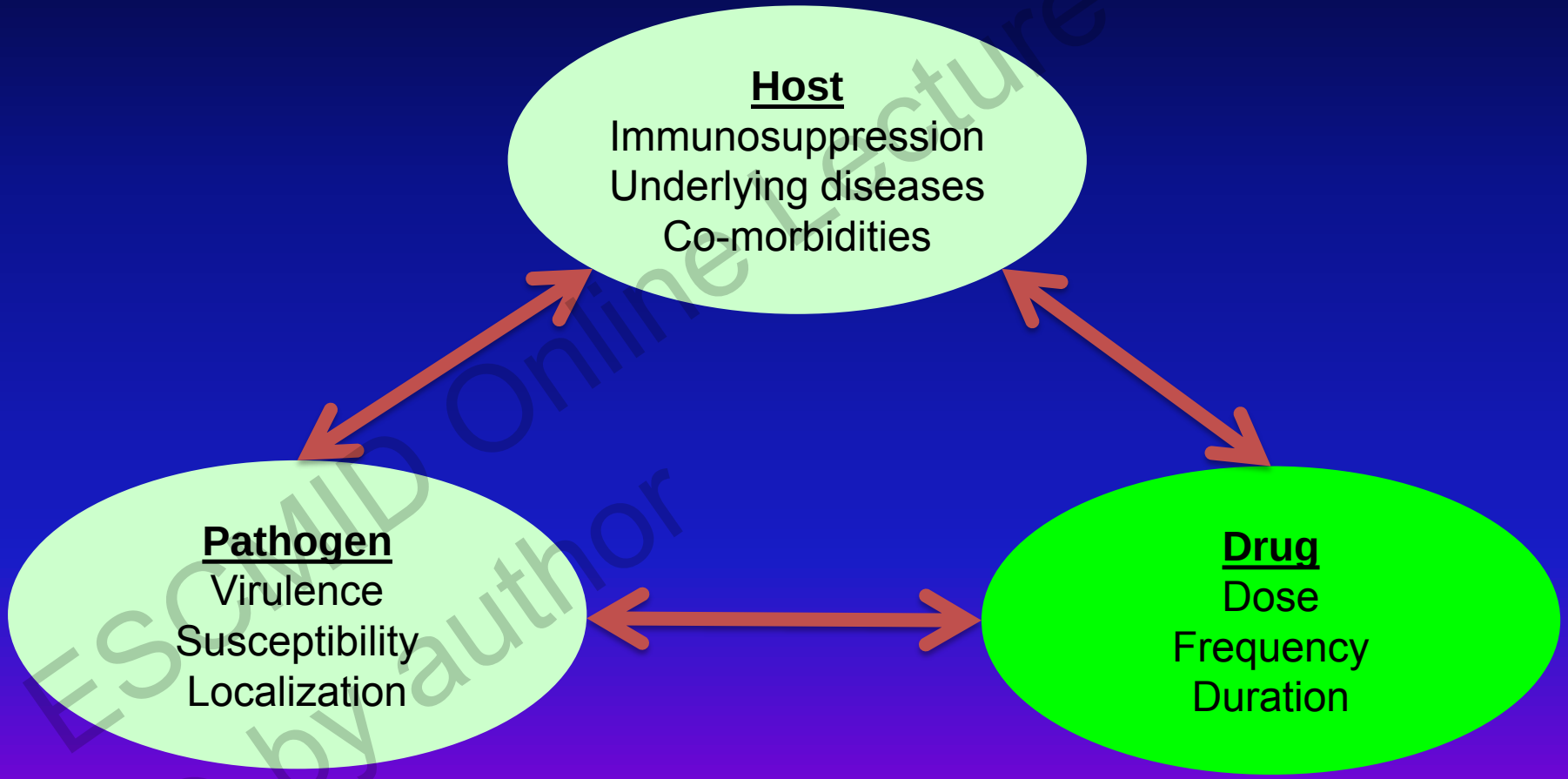
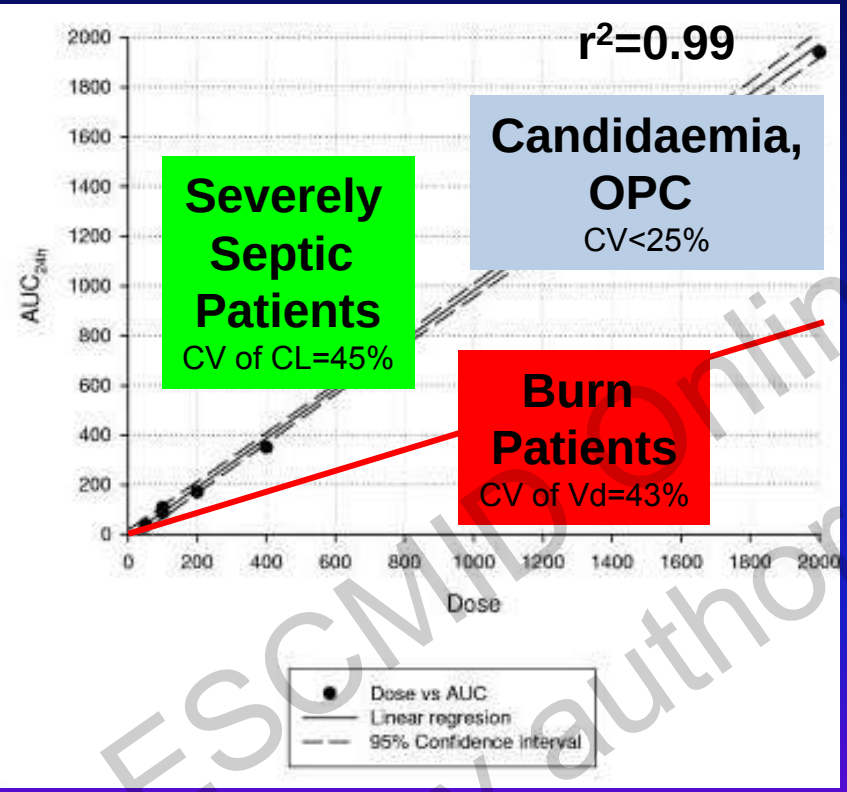
Determinants of clinical outcome



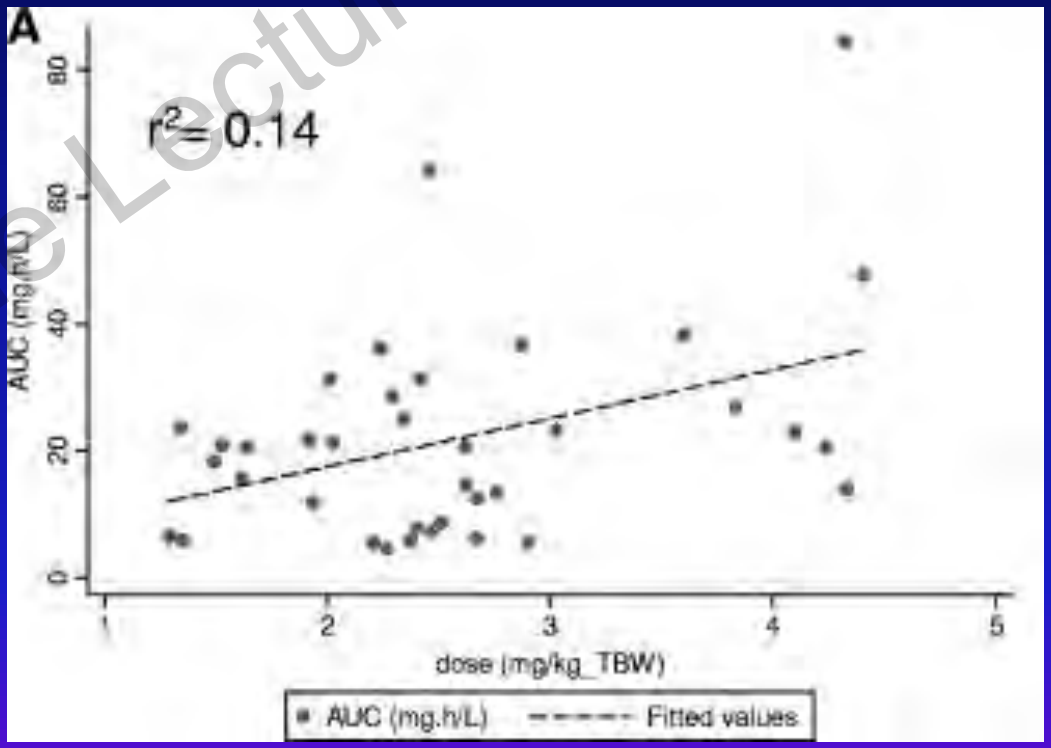
Dose and serum concentrations

Fluconazole



Rodriguez-Tudela et al, AAC 2007
Han et al, AAC 2013

Voriconazole



Pai et al, AAC 2011

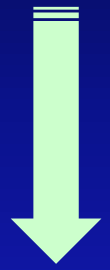
Sources of PK variation

- **Age**
  e.g. larger extracellular and total-body water spaces in neonates
- **Gender**
  e.g. women empty solids from stomach more slowly and have higher gastric pH
- **Physiological Factors**
  e.g. body size and composition, gastrointestinal physiology, hepatic status and renal excretion
- **Pathological conditions**
  e.g. renal or hepatic insufficiency
- **Drug Interactions**
- **Environmental Factors**
  e.g. pollutants or diet
- **Chemical Properties**
  e.g. $AUC_{0\text{-}48}$ of (−)-itraconazole > $AUC_{0\text{-}48}$ (+)-itraconazole
- **Genetic polymorphisms**
  e.g. SNPs in drug metabolizing enzymes and efflux proteins

Meletiadis CMR 2008

Therapeutic drug monitoring

Measure drug concentrations in blood and adjust the dose in order to



→ **Site of toxicity**

- Reduce toxicity
- Increase efficacy
- Prevent emergence of resistance
- Avoid breakthrough infections

Site of infection

Methods

A drug assay should be

- ✓ accurate,
- ✓ sensitive,
- ✓ precise,
- ✓ specific
- ✓ short turnaround time
- ✓ cost effective
- ✓ minimal sample volumes

Method	Advantages	Disadvantages
Bioassay	-cheap -simple to perform	-interference from other drugs, including other antifungals and meta (e.g. itraconazole)
HPLC with ultraviolet fluorescence detection	-widely available; -commercially available assays; -multiple drugs in single sample	-interference from miscellaneous substances; -runtimes maybe slow
Liquid chromatography–mass spectrometry	-very sensitive and specific; -multiple drugs in single sample	-expensive; -not widely available

ePoster 0075

Characteristics of candidate drugs for TDM

A. Variable pharmacokinetics

1. Erratic/Saturable Absorption

- Itraconazole, posaconazole

2. Changes in Distribution

- fluconazole

3. Differential/Saturable Metabolism

- voriconazole

4. Altered Excretion

- fluconazole, flucytosine

B. Exposure-toxicity relationship

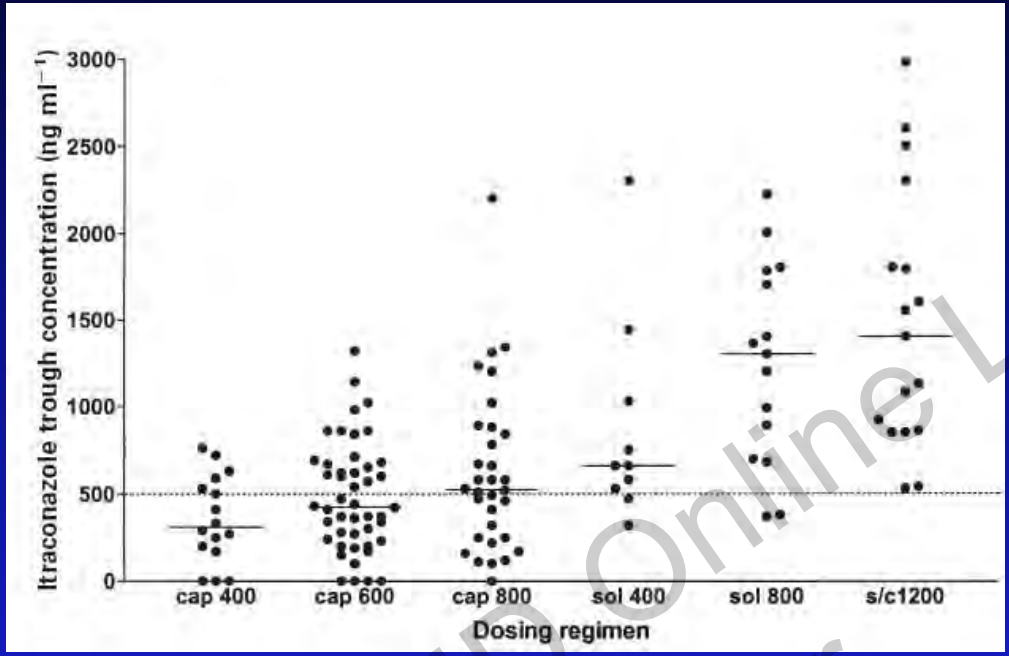
- flucytosine, itraconazole, voriconazole

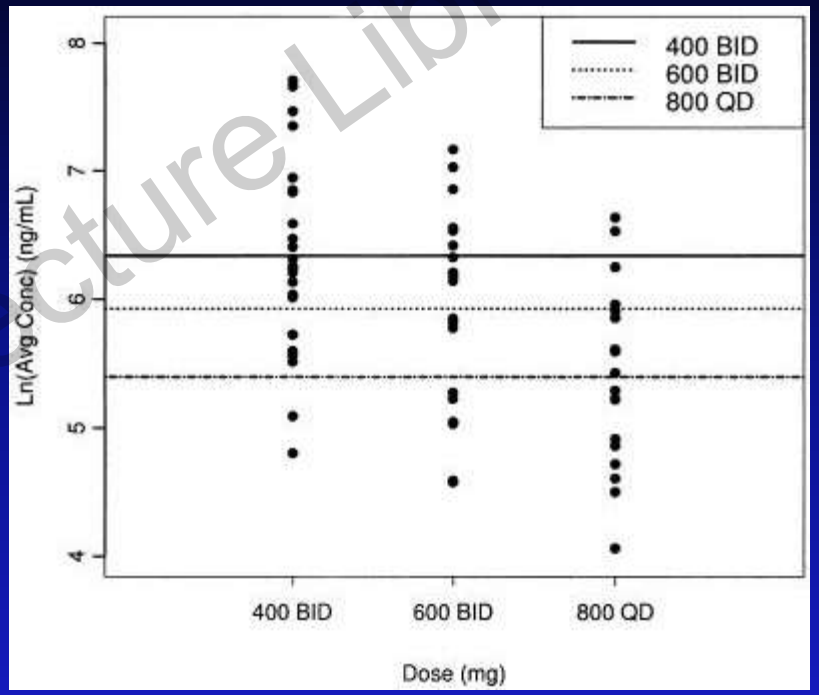
C. Exposure-response relationship

- voriconazole, itraconazole, posaconazole, flucytosine

1. PK variation-Absorption

itraconazole and posaconazole





- ↑ capsule solubility in acidic environment
- manufactures' variability
- ↓ absorption with PPI and H_2-antagonists
- Suspension: 20-50% higher bioavailability
- Extensive variability (CV=80-100%)

- saturated above 800 mg/day
- Better absorption with fatty food and low stomach pH
- ↓ absorption mucositis, diarrhea, PPI
- Large Variability (CV=80-100%)
- ↑ bioavailability with tablet/caps

De Beule et al, Drugs 2001, Ullmann et al , AAC 2006

2. PK variation-Distribution

fluconazole in burn and septic patients

Changes in clearance ➔

Changes in volume of distribution ➔

results

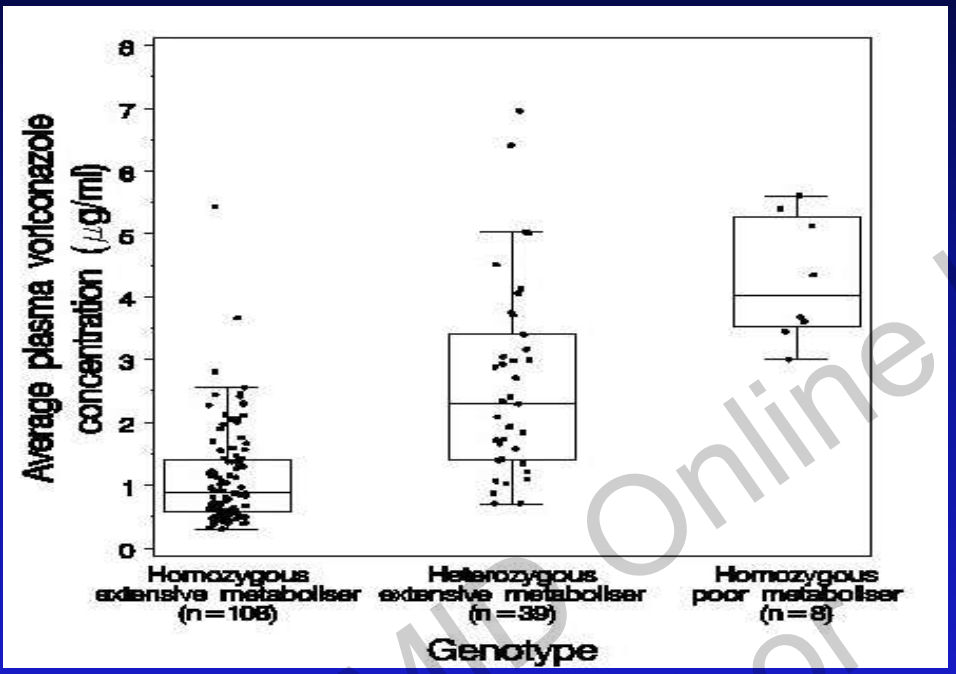
Description (units)	Estimation results (estimate [% RSE])[a]
CL intercept nonseptic, ≥30 days postburn patients without CRRT (liters/h)	0.693 (28.3)
CL in patients with CRRT (liters/h)	1.85 (4.3)
Proportionality constant between *CL* and CLCR/120	0.557 (28.9)
Increase of *CL* within 30 postburn days (liters/h)	0.504 (36.3)
Decrease of *CL* due to sepsis (liters/h)	−0.369 (45.0)
V intercept in nonedematous, ≥30 days postburn patients (liters)	NE[b]
Proportionality constant between *V* and WT (liters/kg)	50.3 (6.8)
Increase of *V* due to edema (liters)	13.6 (33.3)
Increase of *V* within 30 postburn days (liters)	9.61 (43.1)
BSV of *CL* in the patients without CRRT	35.7 (19.8)
BSV of *V*	17.4 (36.5)
BSV of *CL* in the patients with CRRT	16.1 (30.5)
Residual error (proportional)	0.111 (11.0)

Han et al AAC 2013

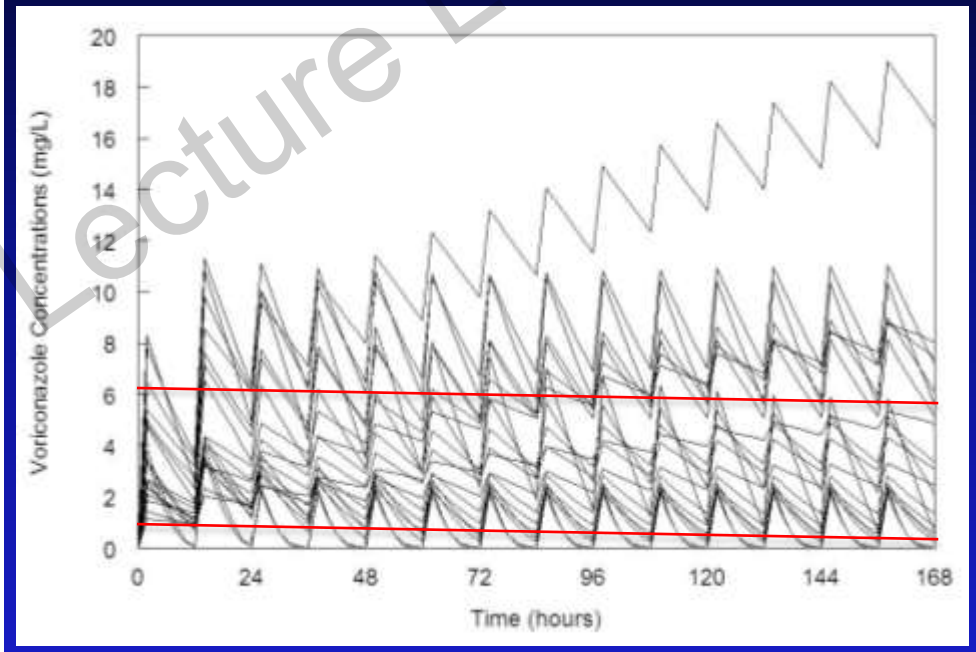
3. PK variation–Metabolism

voriconazole and hepatic metabolism

CYP genotype



Saturation



(CV=80-100%)

Slow metabolisers

cirrhosis/CYP 2C19 polymorphism (3-5% Caucasians, 15-20% South East Asians)

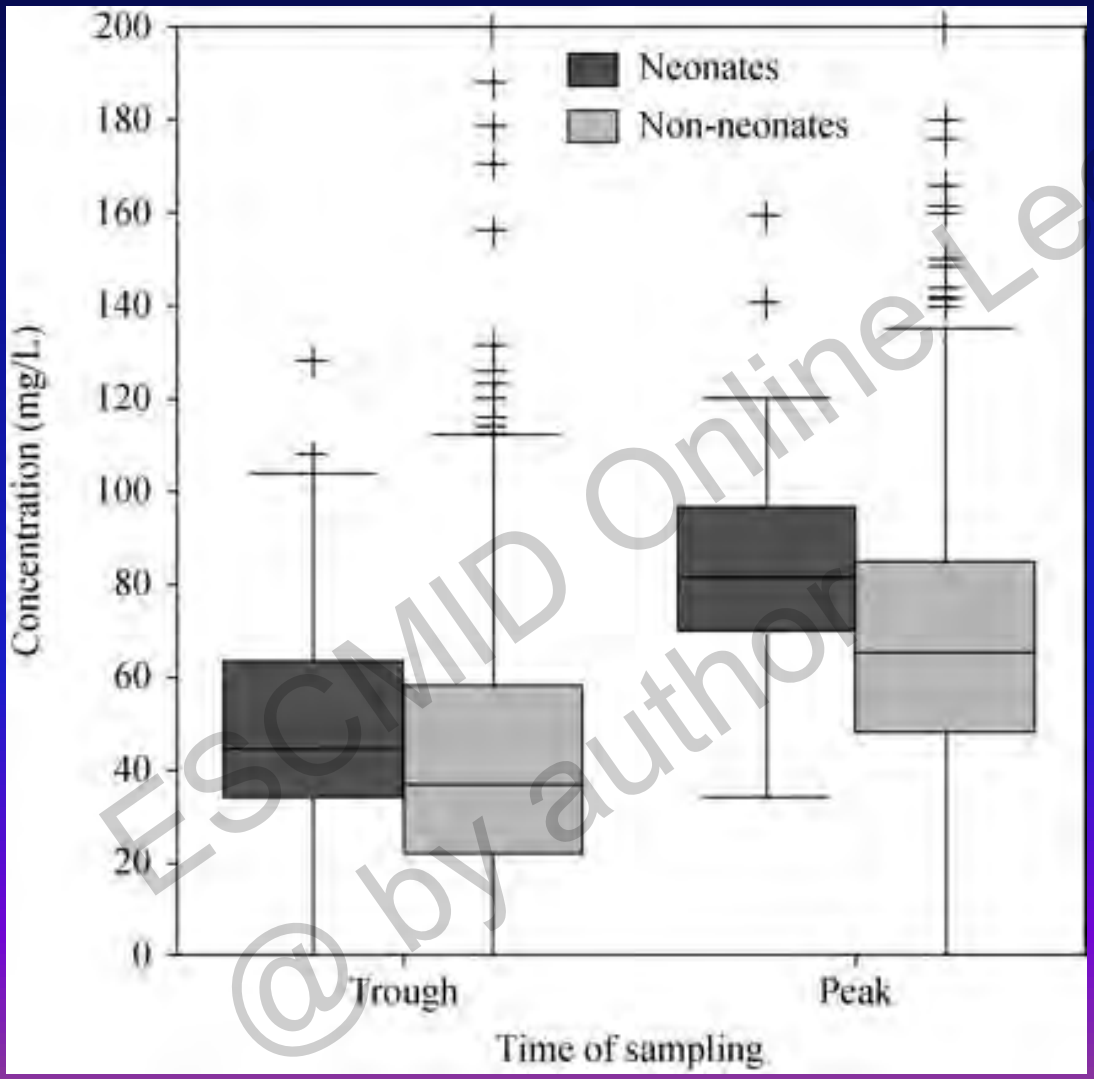
Fast metabolisers

small children/CYP 2C19 polymorphism (4% Chinese, 20% Swedes)

Theuretzbacher Clin Pharm 2006, Felton et al AAC

4. PK variation–Excretion

flucytosine in neonates

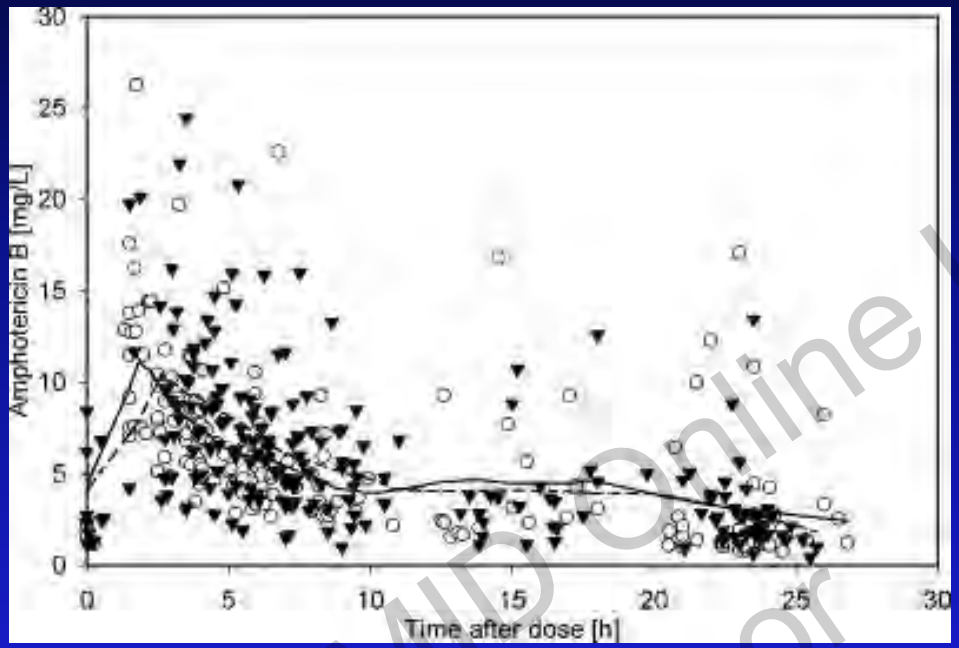


- 1071 levels, 233 patients,
  - 33 neonates
- Large variability **(CV 50-80%)**
- 40.5% low levels
  - 5.1% undetectable
- 38.9% high levels
  - 9.9% toxic
- High levels amongst neonates
  - immature renal system

Pasqualotto et al, JAC 2007

PK variation of other drugs

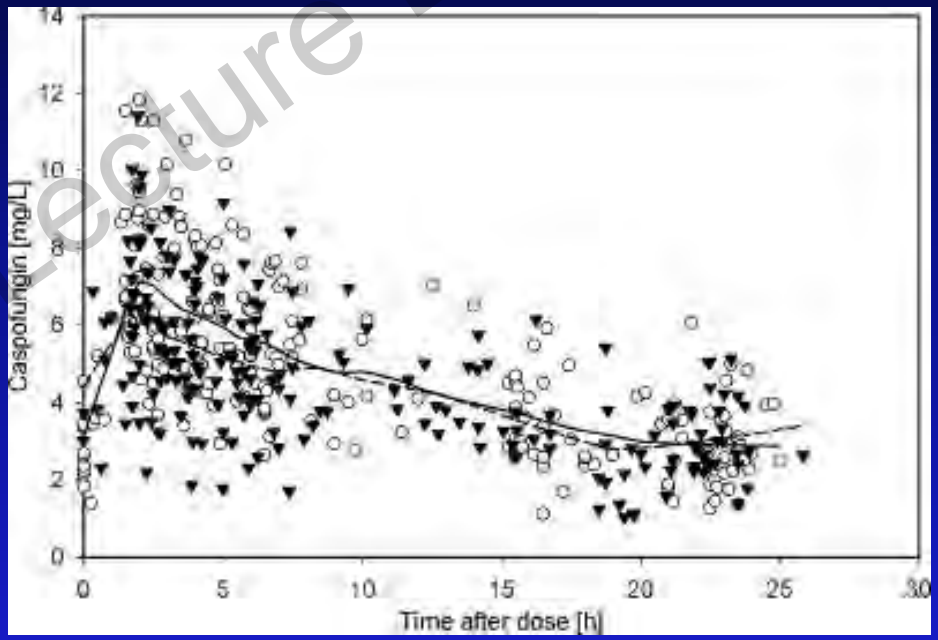
Liposomal amphotericin B



C_{max}=18.0 ± 8.6

CV=47%

Caspofungin



C_{max} = 8.47 ± 2.73

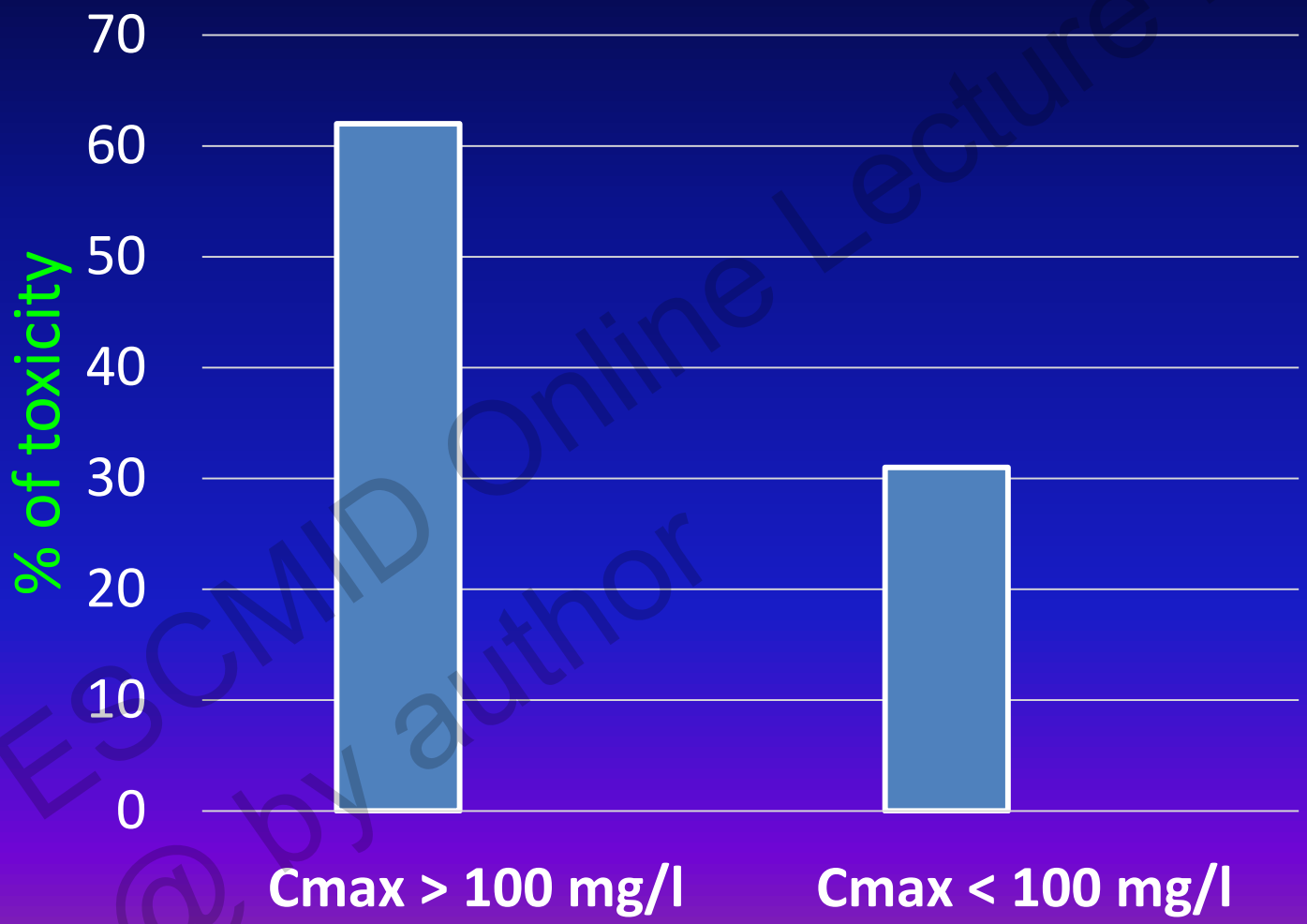
CV=32%

Würthwein et al AAC2012

B. Exposure-toxicity relationships

Flucytosine and toxicity

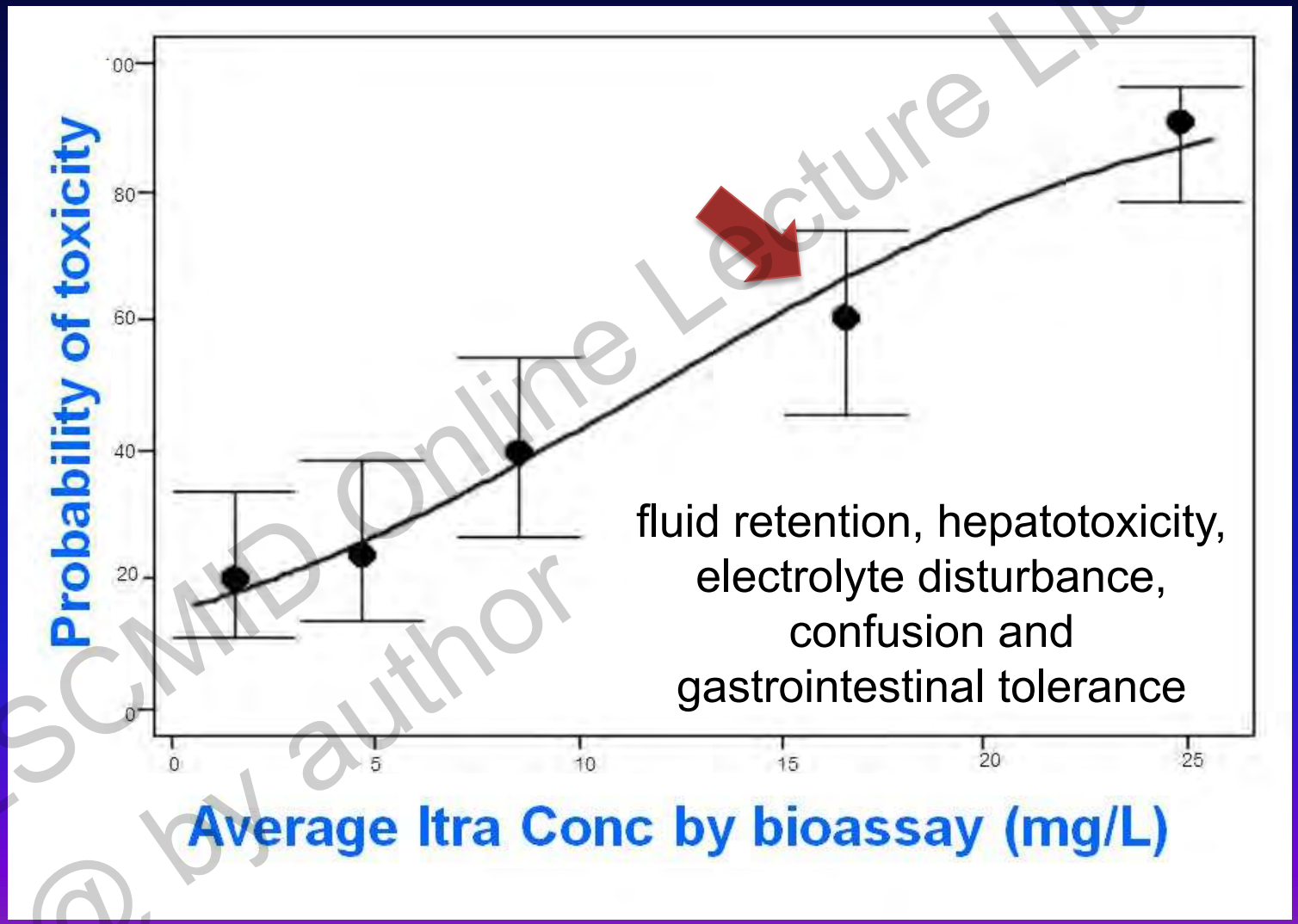
AMB+FC in cryptococcal meningitis



Bone marrow toxicity, hepatotoxicity,

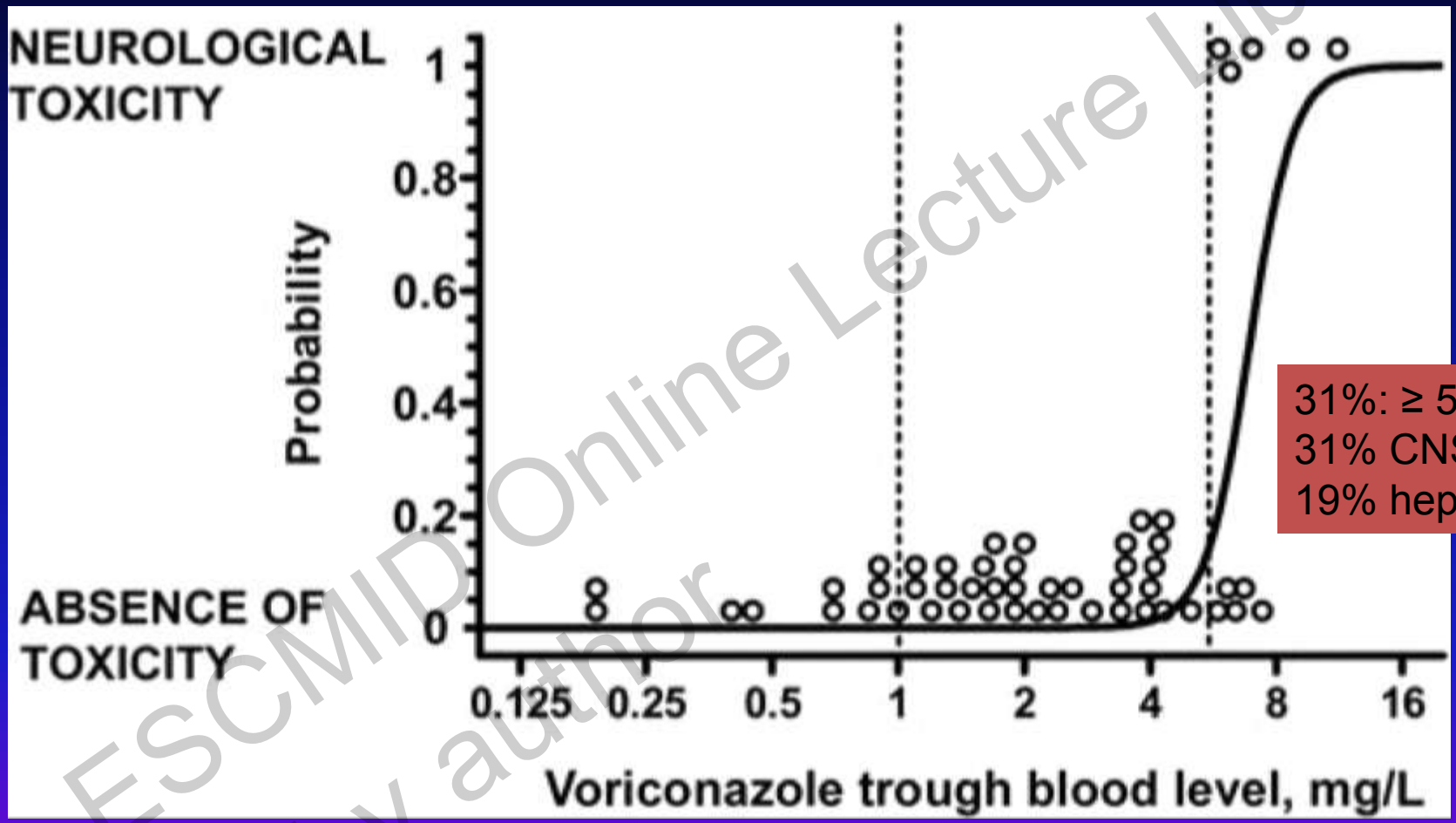
Stamm AM,et al. Am J Med 1987

Itraconazole and toxicity



Lestner et al CID 2009

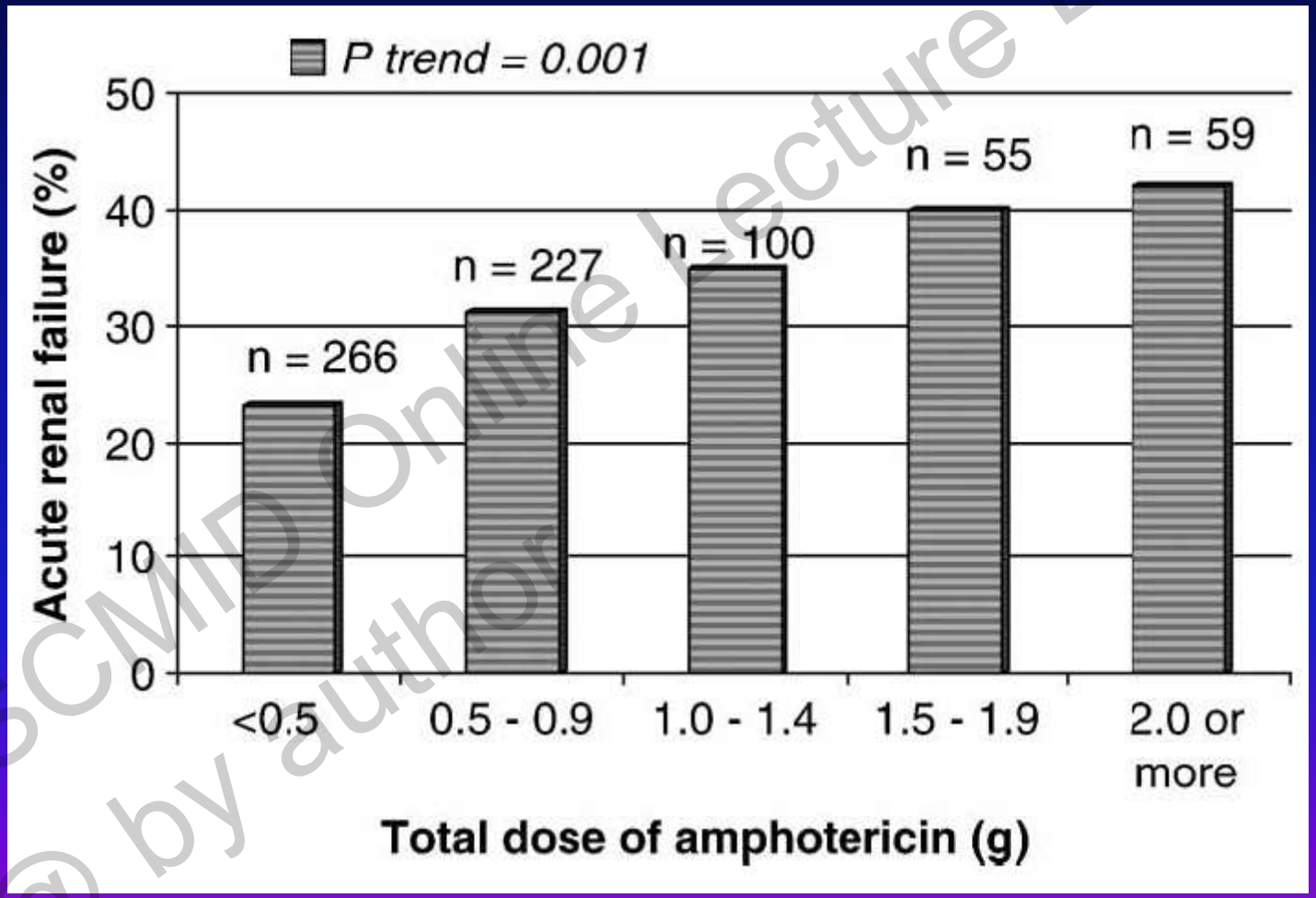
Voriconazole and toxicity



31%: ≥ 5.5 mg/L
31% CNS toxicity
19% hepatitis

Pascual et al CID 2008

Amphotericin B and toxicity



Bates et al CID 2001

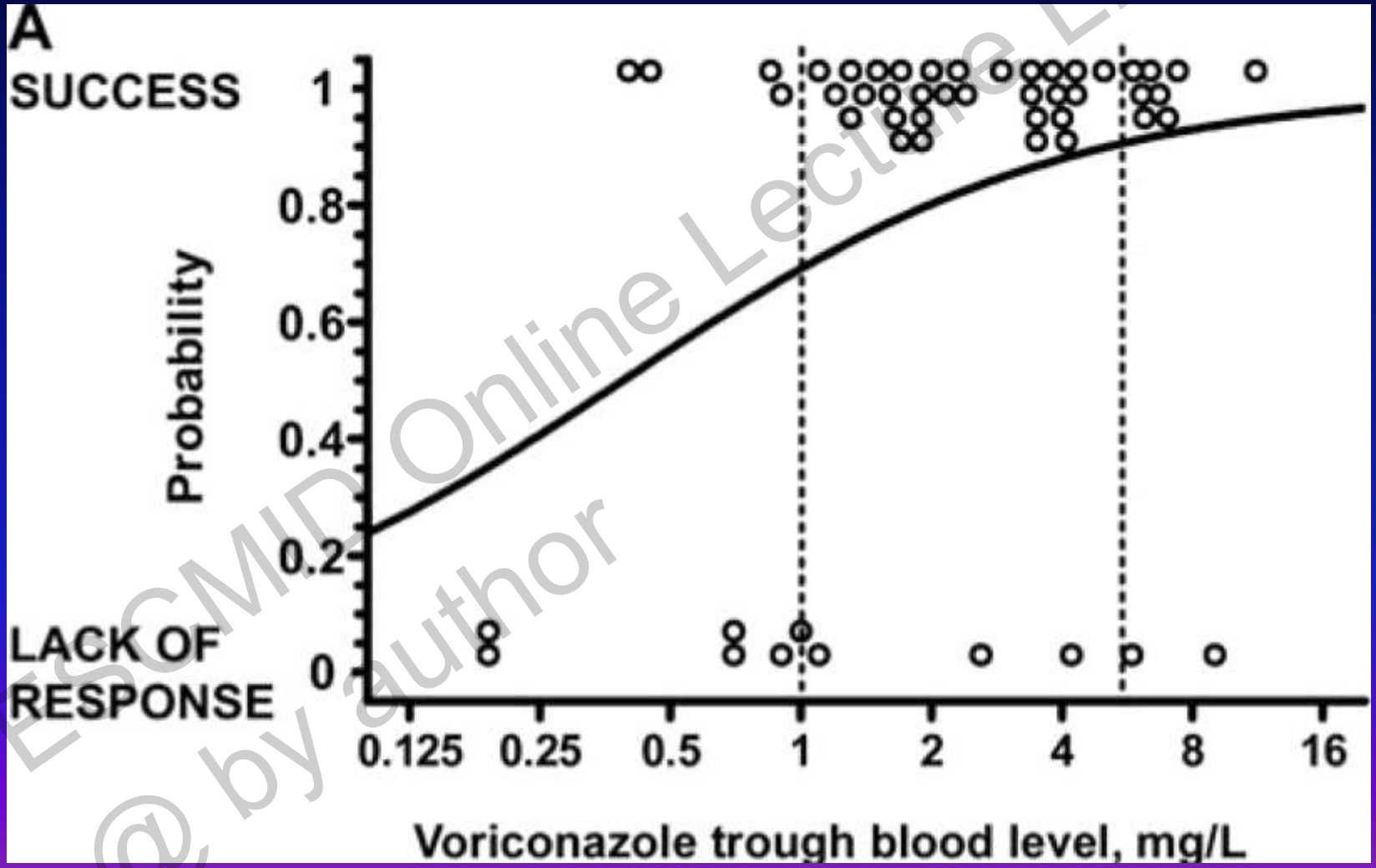
C. Exposure-response relationships

Itraconazole and response

- **Breakthrough** infections are more common in neutropenic patients with trough itraconazole concentrations <0.25–0.5 mg/L.
- **Mortality** is significantly higher in patients with concentrations <0.5 mg/L.
- **Response** is higher in patients with oropharyngeal and esophageal candidiasis if serum concentrations are >0.6–1 mg/L
- Several trials did not find correlation or they were inconclusive

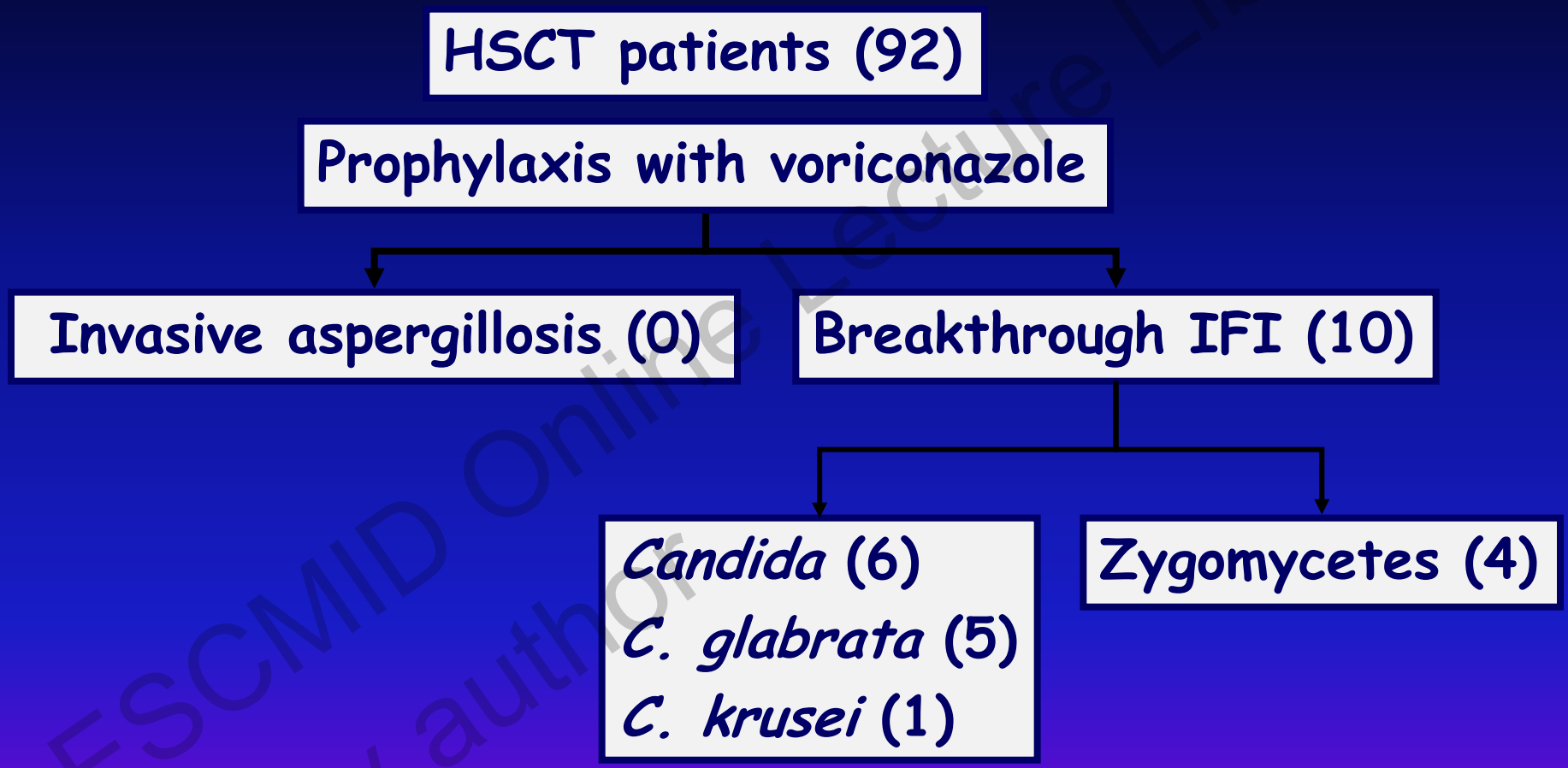
Buchkowsky, TDM 2005, Ashbee JAC 2014

Voriconazole and efficacy



Pascual et al CID 2008

Voriconazole and prophylaxis



Trifilio et al, BMT 2007

Clinical studies for voriconazole

Drug monitoring in studies of voriconazole prophylaxis and treatment in patients with haematological malignancy

Study	Study design	No. of patients (% haematology patients)	Established target for efficacy†	Established target for toxicity†	Comments
TDM use in voriconazole prophylaxis studies					
Trifilio *et al.*[265]	Retrospective cohort.	71 (100)	>2‡	NR	Allogeneic HSCT patients.
TDM use in voriconazole treatment studies					
Dolton *et al.*[266]	Retrospective cohort	201 (45)	≥1.7	>5	–
FDA briefing document[267]	Retrospective cohort	280 (NR)	NF§	6	Subset of patients from registration trial[165] who had random voriconazole TDM performed
Imhof *et al.*[268]	Retrospective cohort	26 (100)	NR	≥4	Hazard ratio of 2.3 for a neurological adverse event per 1 μg/mL increase in voriconazole concentration
Miyakis *et al.*[269]	Retrospective cohort	25 (20)	>2.2	NR	–
Neely *et al.*[270]	Retrospective cohort	46 (46)	>1	NR	Paediatric study
Ueda *et al.*[271]	Retrospective cohort	34 (100)	>2	≥6	–
Pascual *et al.*[703]	Prospective observational	52 (65)	>1	>5.5	–
Smith *et al.*[244]	Retrospective cohort	28 (29)	>2.05¶	NR	–
Lee *et al.*[272]	Retrospective cohort	52 (100)	NF	NR	Early outcomes of IA not statistically different when initial trough levels (≤2 vs. >2) compared
Racil *et al.*[273]	Retrospective cohort	264 (100)	NF	NF	IA treatment outcomes and adverse effects not related to voriconazole levels
Park *et al.*[736]	Randomised controlled trial (TDM vs. non-TDM)	108 (77)	NF	NF	Voriconazole dose adjustment performed to achieve target trough levels (1–5.5) in TDM group
Bruggemann *et al.*[274]	Retrospective cohort	18 (89)	NF	NF	Paediatric study

NF: not found, NR; not recorded

Chau et al, Int Med J 2014

Posaconazole and efficacy

Salvage therapy of invasive aspergillosis

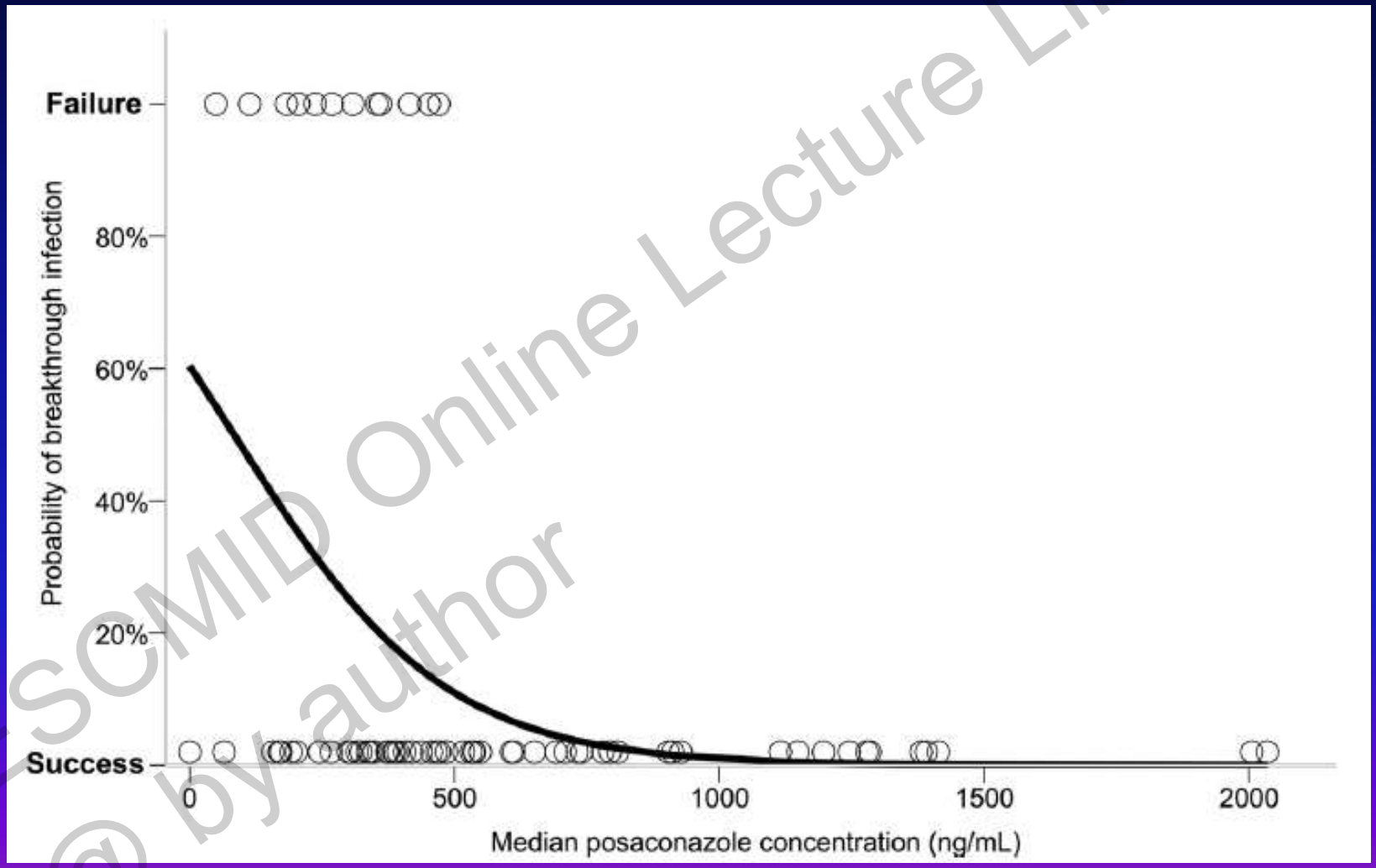
Quartile	No. of subjects[a]	Plasma C_{max} Mean ng/mL	Plasma C_{max} CV, %	Plasma C_{avg} Mean ng/mL	Plasma C_{avg} CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

NOTE. C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation.

[a] Data were available for 67 patients with available plasma concentrations of posaconazole.

Walsh et al CID 2007

Posaconazole and prophylaxis



Dolton AAC 2012

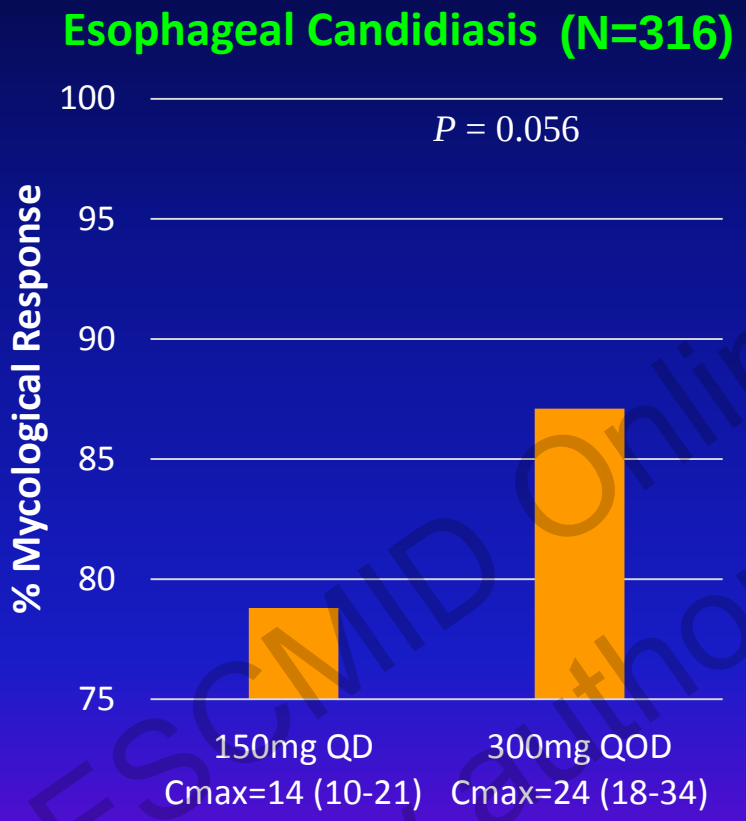
Clinical studies for posaconazole

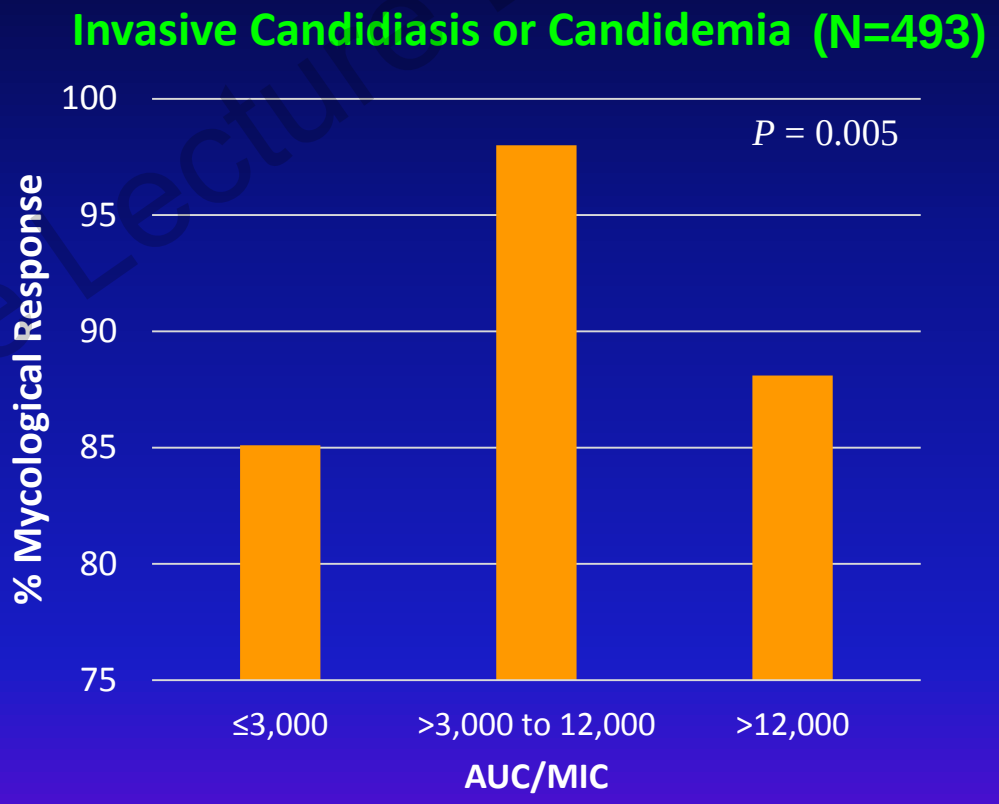
Study	Study design	No. of patients (% haematology patients)	Established target for efficacy†	Established target for toxicity	Comments
TDM use in posaconazole prophylaxis studies					
Krishna *et al.*[275]	Retrospective cohort of PK data from[179]	246 (100)	NR‡	NR	Median plasma concentration in breakthrough IFD cases: 0.61 mg/L (n = 5).
Krishna *et al.*[276]	Retrospective cohort of PK data from Cornely *et al.*[179]	194 (100)	NR‡	NR	Median plasma concentration in breakthrough IFD cases: 0.45 mg/L (n = 6).
Jang *et al.*[237]	Retrospective cohort combination of PK data from Cornely *et al.*[179] and Tonini *et al.*[239]	467 (100)	>0.7¶	NF	–
Dolton *et al.*[238]	Retrospective cohort§	86 (91)	>0.29#	NF	Median plasma concentration in breakthrough IFD cases: 0.29 mg/L (n = 12). Recommended target >0.7 mg/L.
Vaes *et al.*[277]	Prospective cohort	40 (100)	>0.4††	NR	Composite endpoint including those who received empiric antifungal treatment. Median plasma concentration in breakthrough IFD cases: 0.4 mg/L (n = 18).
Hoenigl *et al.*[278]	Prospective cohort§	34 (100)	>0.3‡‡	NR	Median plasma concentration in breakthrough IFD cases: 0.3 mg/L (n = 3).
Tonini *et al.*[239]	Retrospective cohort	29 (100)	>0.99§§	NR	High median plasma concentration; significance of lower concentrations in breakthrough IFD unclear. Median plasma concentration in breakthrough IFD cases: 0.99 mg/L (n = 4).
Gross *et al.*[279]	Prospective cohort§	31 (100)	NF	NR	Median plasma concentration in breakthrough IFD cases: 0.96 mg/L (n = 4).
Crombag *et al.*[280]	Retrospective cohort§	17 (100)	NF	NF	One breakthrough IFD: 0.37 mg/L.
Neubauer *et al.*[281]	Prospective cohort	27 (100)	NF	NF	Median plasma concentration in breakthrough IFD cases: 0.9 mg/L (n = 2).
Bryant *et al.*[240]	Retrospective cohort	21 (100)	NF	NR	Plasma concentrations in breakthrough IFD cases: <0.5 mg/L (n = 3).
Elden *et al.*[282]	Prospective cohort	63 (100)	NF	NR	Plasma concentrations in breakthrough IFD case: 0.22, 0.11 mg/L (n = 1).
Lebeaux *et al.*[283]	Retrospective cohort§	54 (69)	NF	NR	Plasma concentrations in breakthrough IFD cases: <0.5 mg/L (n = 2).
TDM use in posaconazole treatment studies					
Walsh *et al.*[206]	Prospective cohort with retrospective comparator group	107 (74)	≥0.7–1.25¶¶	NF	Salvage therapy in invasive aspergillosis. PK dataset from 67 patients. Timing of posaconazole plasma concentration not recorded.

NF: not found
NR; not recorded

Chau et al, Int Med J 2014

Micafungin exposure and clinical outcome





Co-variates: APACHE II score (p=0.012)
Corticosteroid use (p=0.025)

Andes et al AAC 2011, 2008

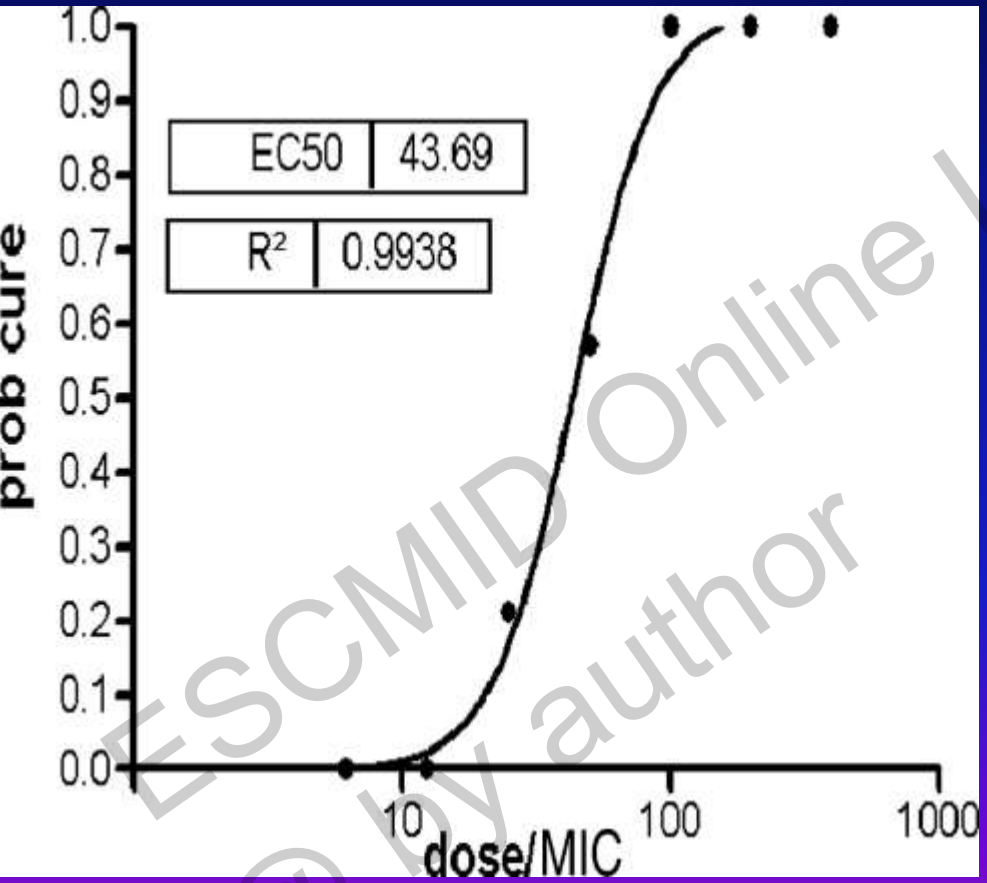
Clinical settings for TDM

- **Special patient populations**
  - neonates, children, elderly, obese
  - organ dysfunction, critical illness
  - haemodialysis, haemofiltration, extracorporeal membrane oxygenation, cardiopulmonary bypass
- **Changing pharmacokinetics**
  - physiological instability, critical illness, diarrhea, iv-to-oral switch, change dose
- **Interacting drugs**
  - antacids, histamine antagonists, proton pump inhibitors, aniepileptics, antiretrovials, antibiotics, barbiturates
- **Compliance**
  - longer-term consolidation therapy or secondary prophylaxis
- **Persistent and/or significant underlying immunological defects**
  - prophylaxis versus established disease
- **Poor prognostic disease**
  - extensive or bulky infection, CNS or multifocal infection, infections by resistant isolates

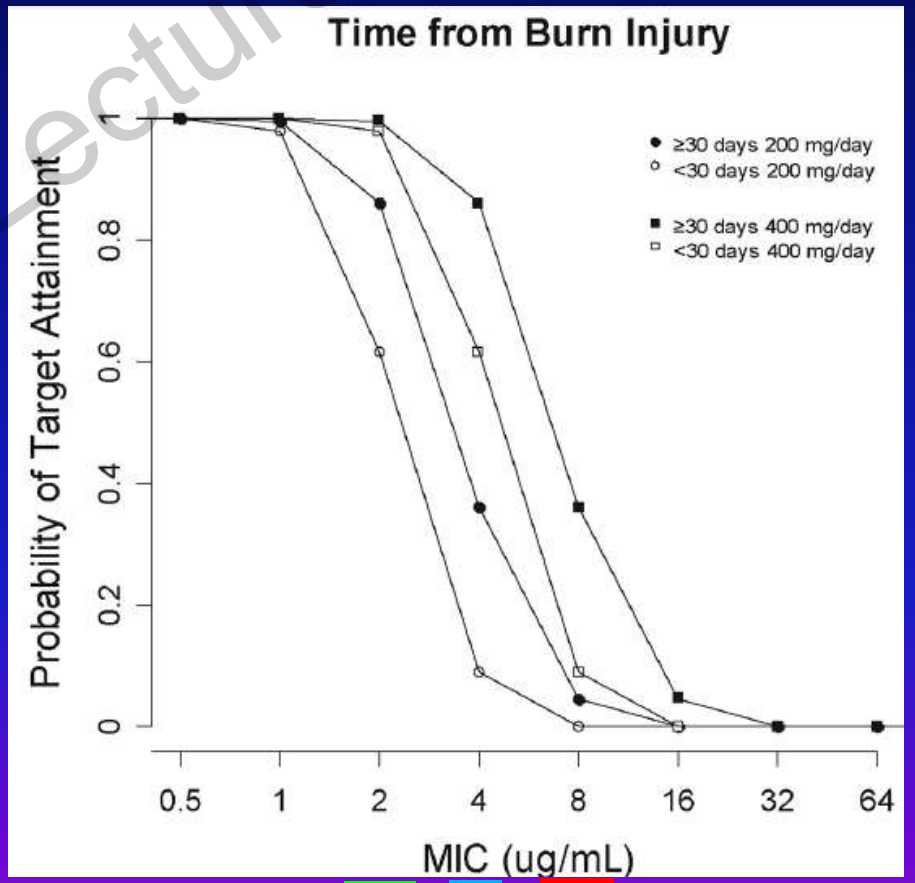
Ashbee et al. JAC 2014

TDM based on in vitro susceptibility and in special patient population

fluconazole and Candida



Rodriguez-Tudela et al, AAC 2007



Han et al, AAC 2013

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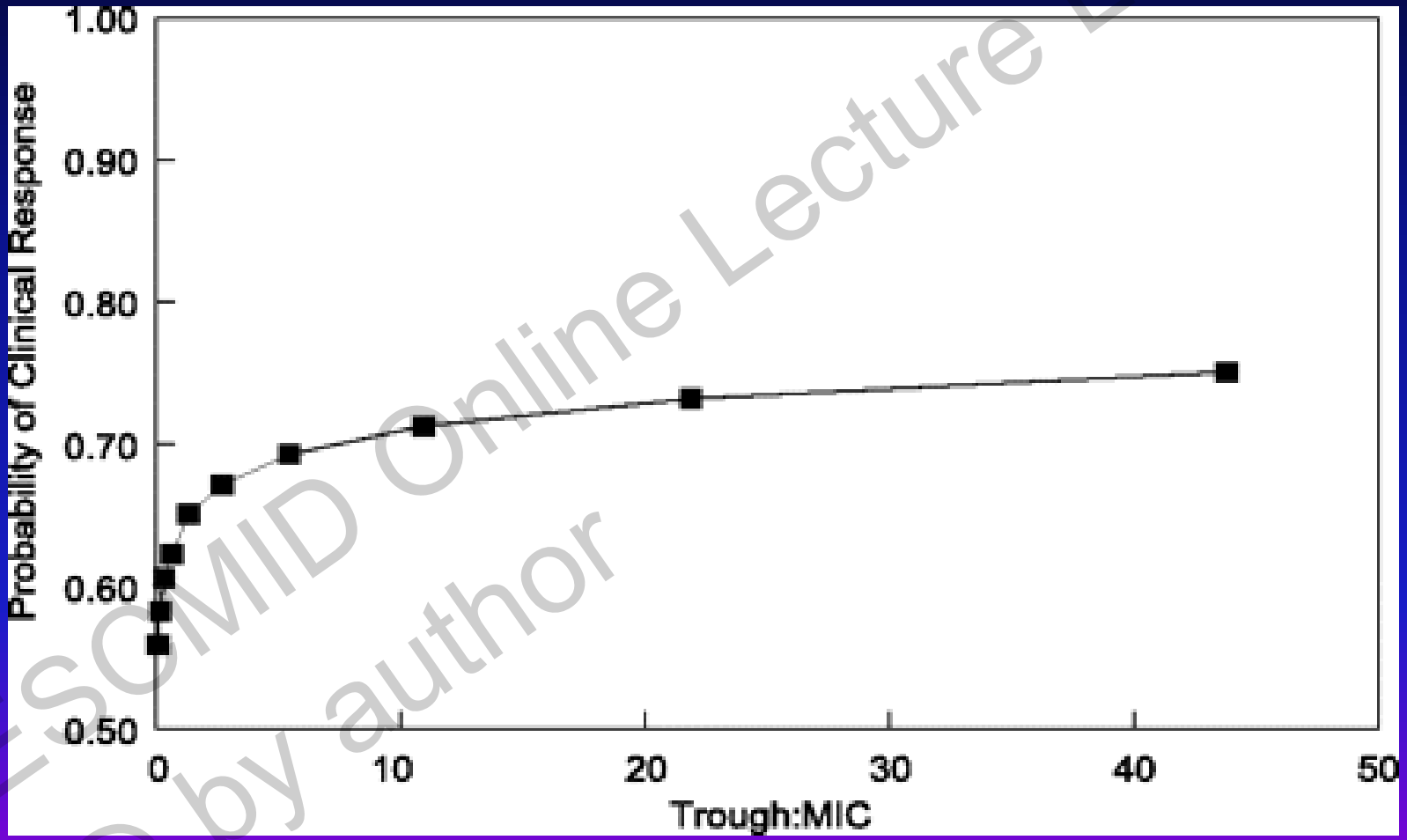
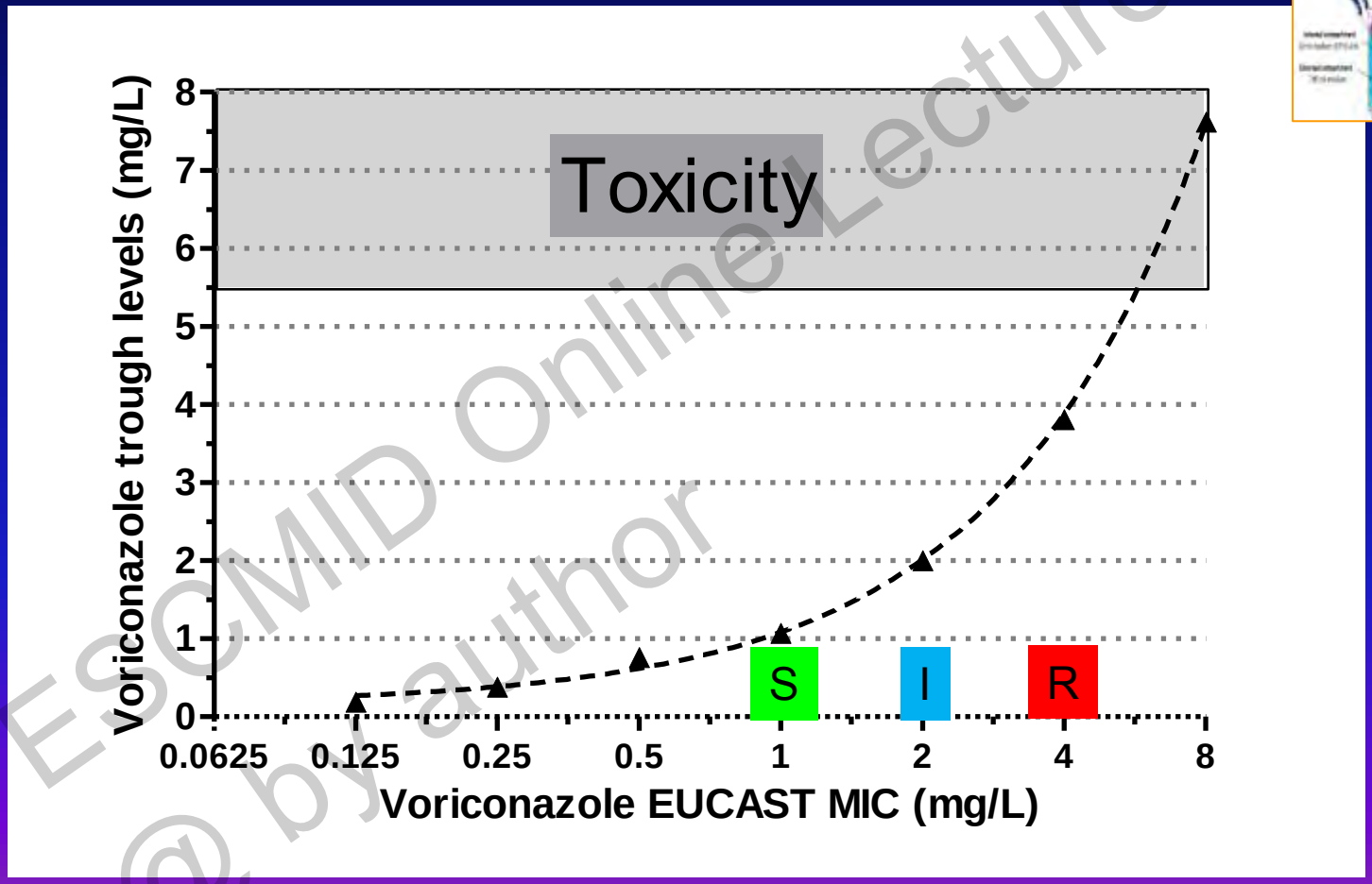
Outcome and voriconazole serum concentration/MIC ratio



Troke et al AAC 2011

TDM based on in vitro susceptibility

voriconazole and *Aspergillus fumigatus* in an in vitro PK-PD model



Siopi et al JAC 2014

Summary

Drug	Significant PK variability (CV)	Main Source of PK variation	Day for TDM	Target blood concn[a] (µg/ml) for:			
				Efficacy	Evidence	Safety	Evidence
Amphotericin B	No (<50%)		-	NA	-	NA	-
Echinocandins	No (<50%)		-	NA	-	NA	-
Flucytosine	Yes, **(50-80%)**	Excretion	3-5	**Prophylaxis**: NA **Therapy**: C_{min}>20	Low	C_{max}<100	Moderate
Fluconazole	No (<50%)		-	NA		NA	
Itraconazole	Yes, **(80-100%)**	Absorption, Metabolism	5-7	**Prophylaxis**: C_{min}>0.5; **Therapy**: C_{min}>0.5-1	High Moderate	Cavg<17 (bioassay)	Moderate
Voriconazole	Yes, **(80%-100%)**	Metabolism	3-5	**Prophylaxis**: C_{min}>0.5; **Therapy**: C_{min}>1-2	Low High	Cmin <4-6	High
Posaconazole	Yes, **(oral 80-100%)** (tablet/caps/iv <50%)	Absorption	5-7 3	**Prophylaxis**: C_{min}>0.5-0.7; **Therapy**: C_{min}>1-1.25 C_{min}>0.35	Moderate Moderate	NA	

Ashbee et al. JAC 2014