Therapeutic Monitoring of Drug Levels for Invasive Aspergillosis

Dr Susan J Howard

Background

- Invasive aspergillosis increasing incidence, and is associated with high mortality (~50%)
- Global antifungal drug budget is significant (projected $US 5.7 billion in 2014)
- Minimise ‘costs’
- Therapeutic drug monitoring (TDM)
  – efficacy/resistance development/toxicity/$

Agenda

- Amphotericin B
- Itraconazole
- Voriconazole
- Posaconazole
- Echinocandins

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Amphotericin B

- IDSA guidelines ~ L-AMB/ABLC alternative treatment of IA if refractory/intolerant to 1st line therapy, and endophthalmitis/keratitis
- Serum levels poor despite increasing dosing (don't reflect variable tissue concs)
- Patient outcome/toxicities not related to serum level (?cumulative dose)
- Very little AMB resistance observed

No evidence to support routine TDM currently

Walsh et al CID 2008;46:327-60

Ashbee et al JAC 2014;69:1162-76

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- Amphotericin B
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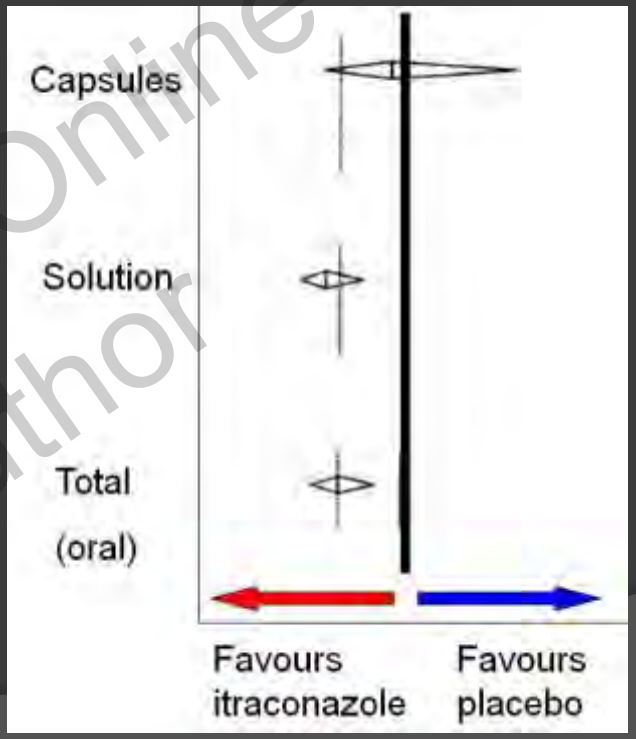
Itraconazole

- Alternative to treat IA
- Subtherapeutic levels common – especially in some patient groups
- IV and oral



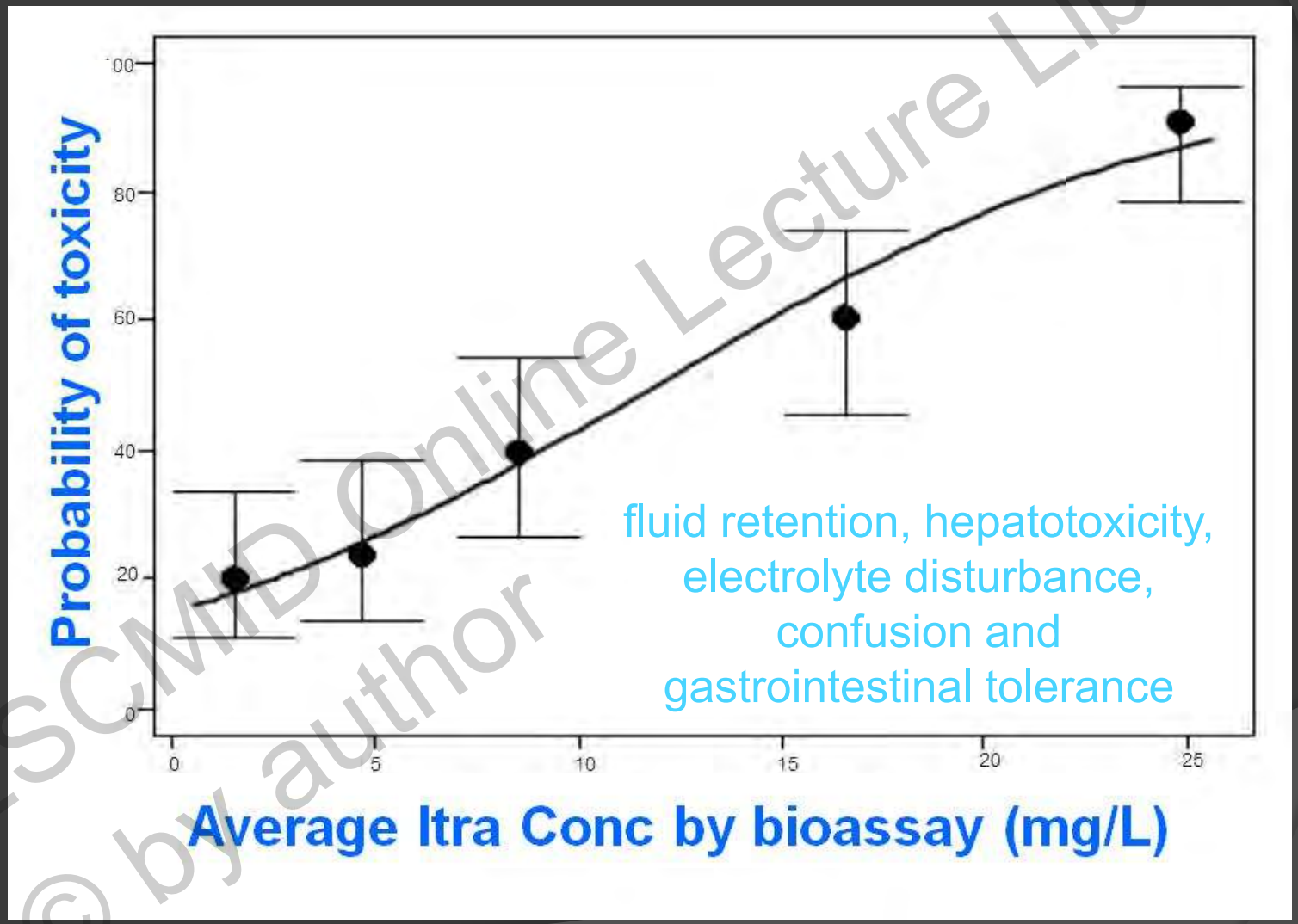
Glasmacher et al JCO 2003;24:4615-26

The Case for Itra TDM

- Large interpatient variability
- Unpredictable gastrointestinal absorption (increased bioavailability of capsules with cola/food)
- Non-linear pharmacokinetics
- Manufacturer variability
- Disproportionate higher clearance rates in children
- Itraconazole trough <0.5mg/L associated with higher mortality/breakthrough infections
- Drug interactions
- Toxicities

Glasmacher et al Mycoses 1999;42:443-51

Risk of Toxicity



Lestner et al CID 2009;49:928-30

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TDM recommended

Itra TDM Recommendations

- Trough level >0.5 mg/L (HPLC/MS)
- Average level <17 mg/L (bioassay – HPLC ~5-fold lower)

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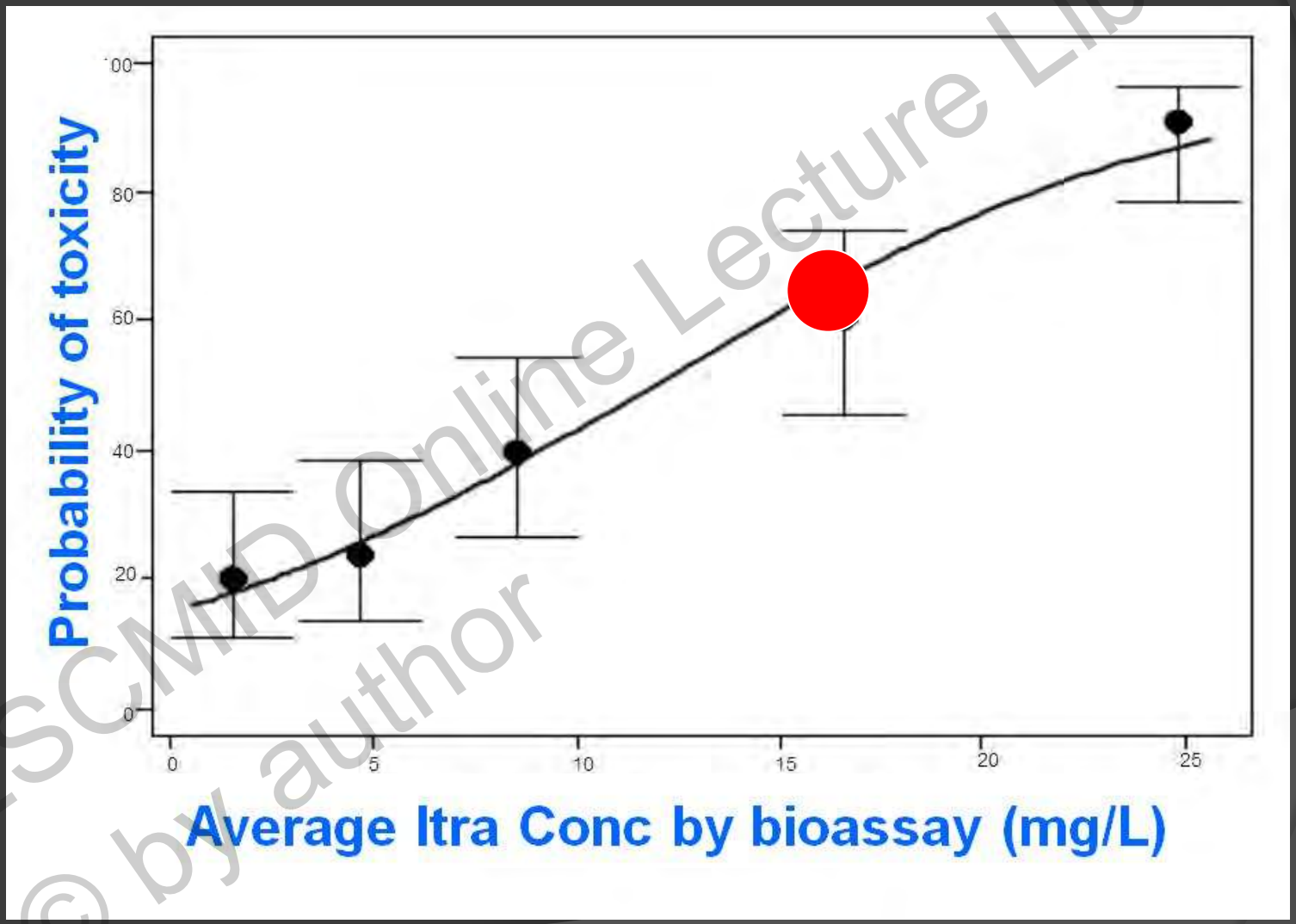
Upper Limit



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Itra TDM Recommendations

- Trough level >0.5 mg/L (HPLC/MS)
- Average level <17 mg/L (bioassay – HPLC ~5-fold lower)
- First trough measurement 5-7 days after initiation of therapy or change in dosage
- Frequency depends on clinical scenario – formulation change, clinical parameters, deterioration, toxicity, change in concomitant therapy (potential interaction)

Ashbee et al JAC 2014;69:1162-76

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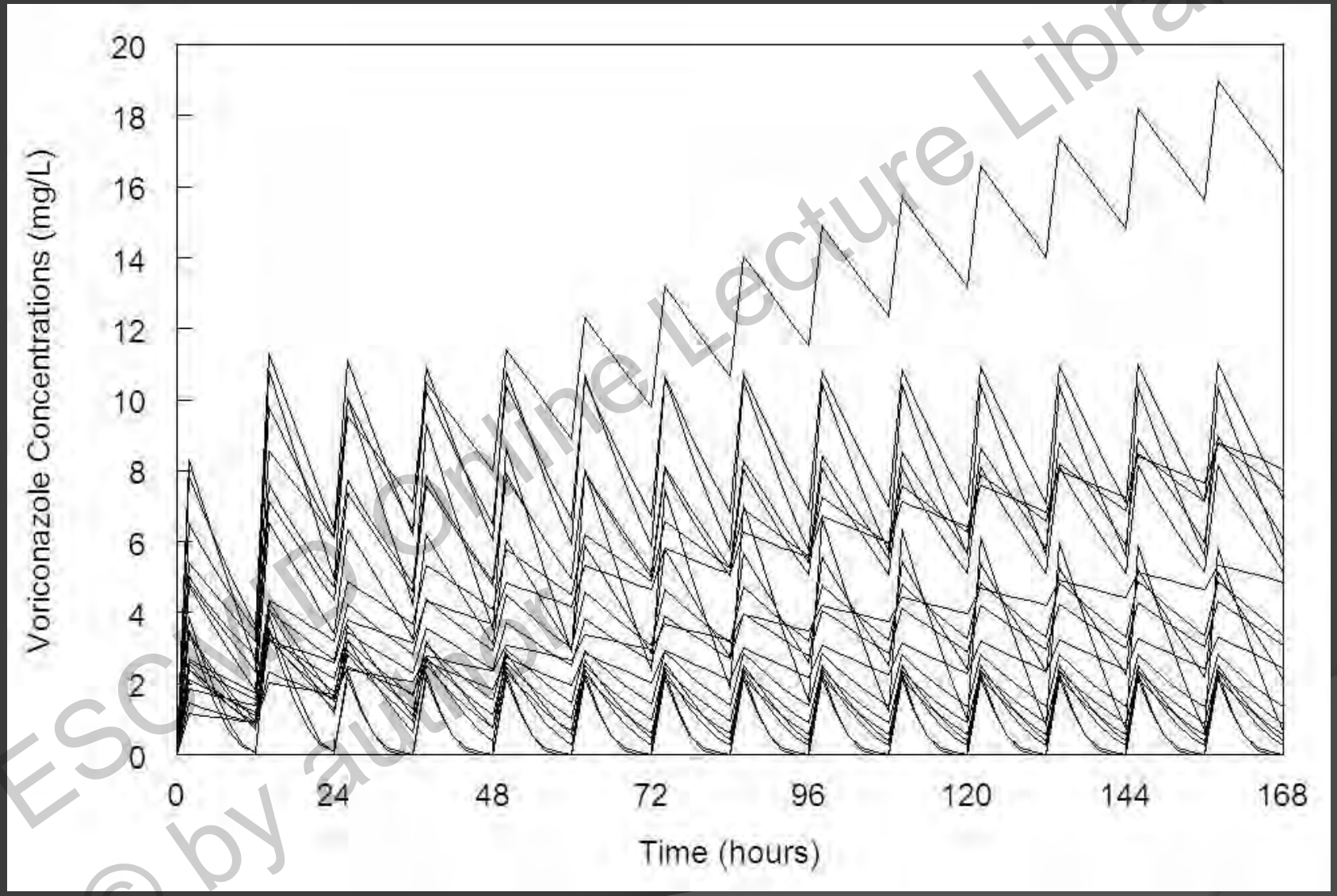
Voriconazole

- First line therapy for IA (and other forms, particularly CNS)
- IV and oral formulations (capsule and oral solution for children)
- Considerable intra- and inter-patient variability

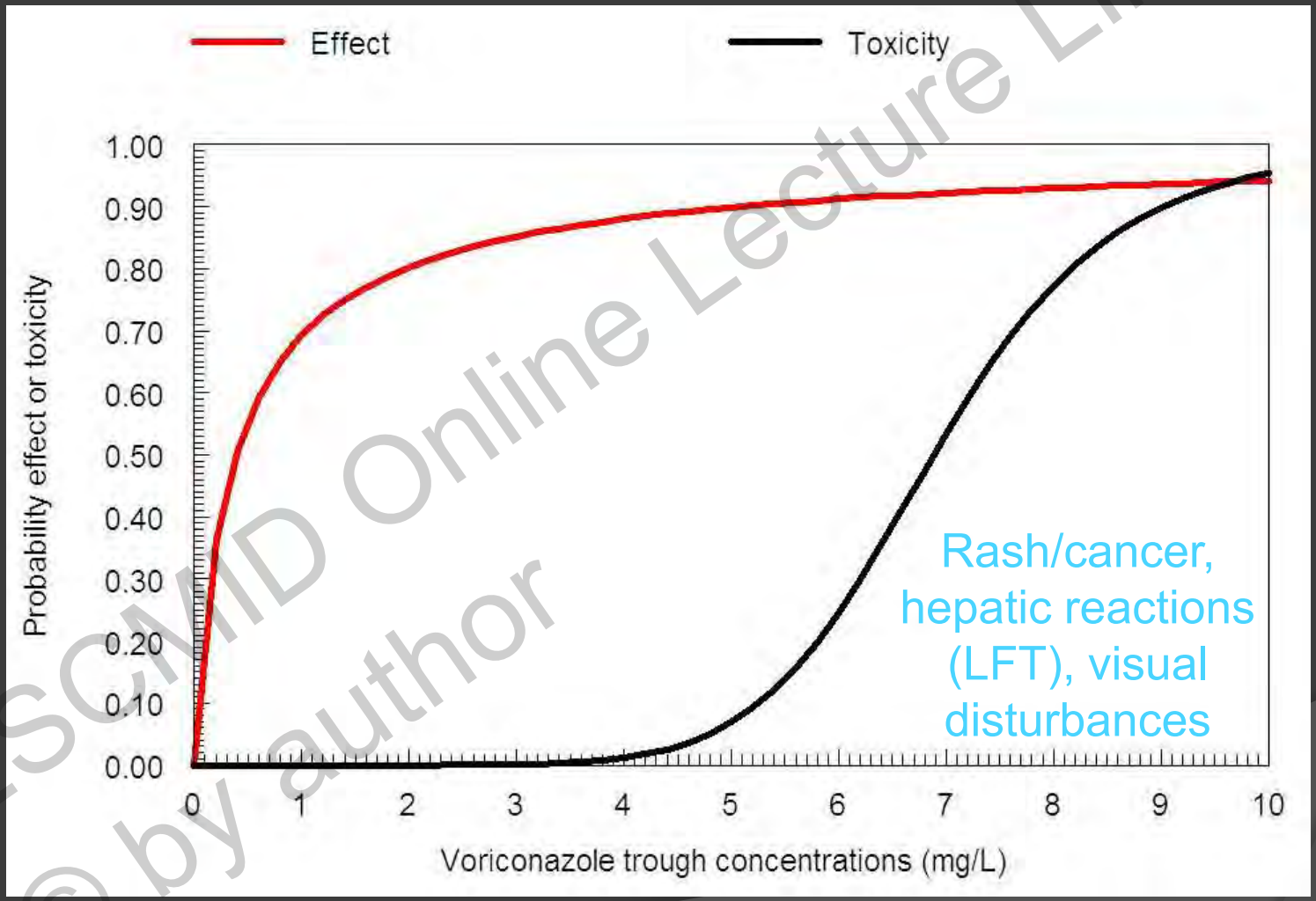


The Case for Vori TDM

- Non-linear (Michaelis-Menten) PK
- Slow metabolisers – cirrhosis/CYP 2C19 polymorphism (3-5% in Caucasians, but 15-20% in individuals from South East Asia)
- Fast metabolisers – small children and ultra-rapid metaboliser genotype (4% in Chinese people, but as high as 20% in Swedes)
- Drug interactions
- Efficacy/toxicity linked with serum levels

Pascual et al CID 2008;46:201-11
Pascual et al CID 2012;55:381-90

Effect/Risk of Toxicity



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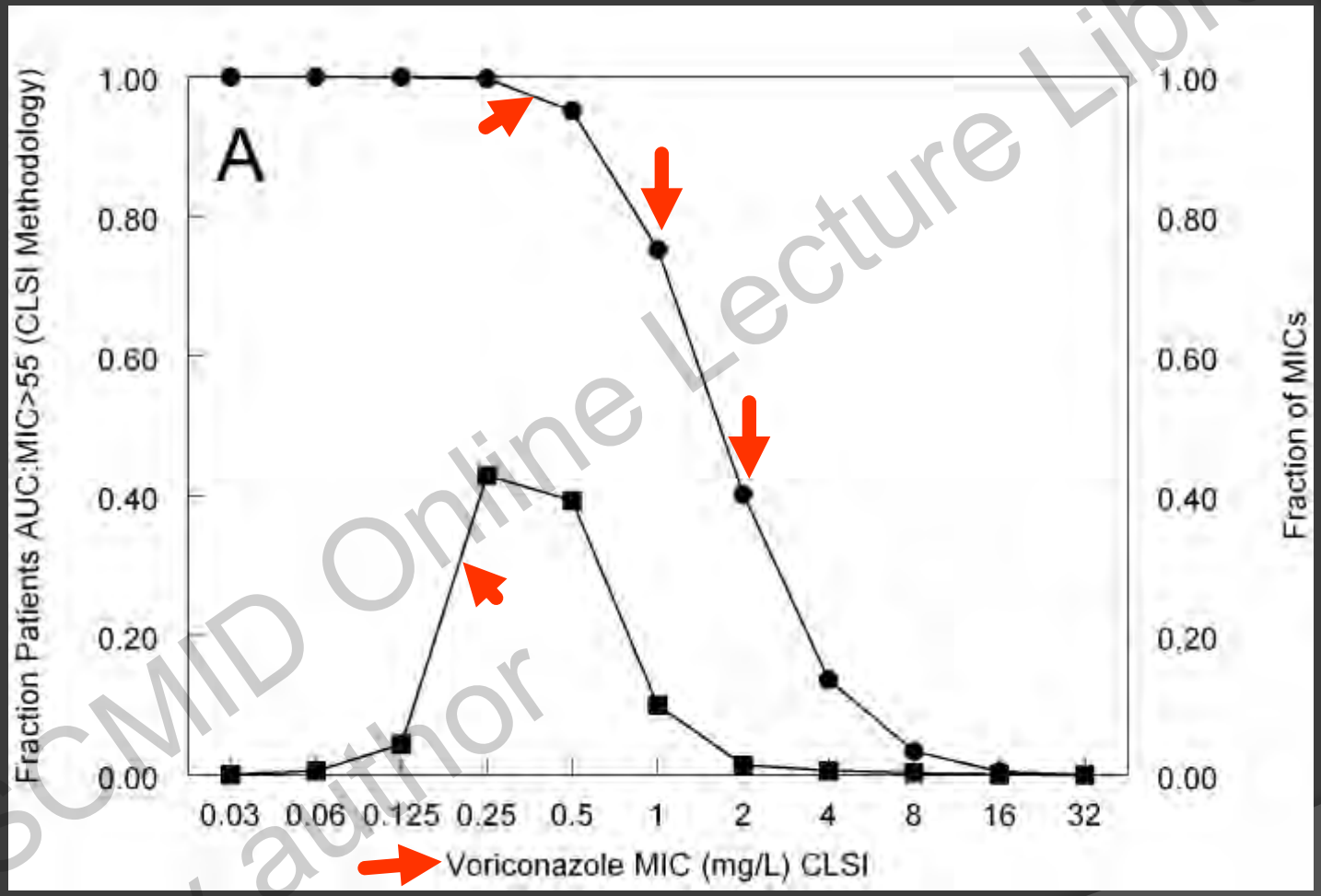
TDM advised

Pascual et al CID 2008;46:201-11

Pascual et al CID 2012;55:381-90

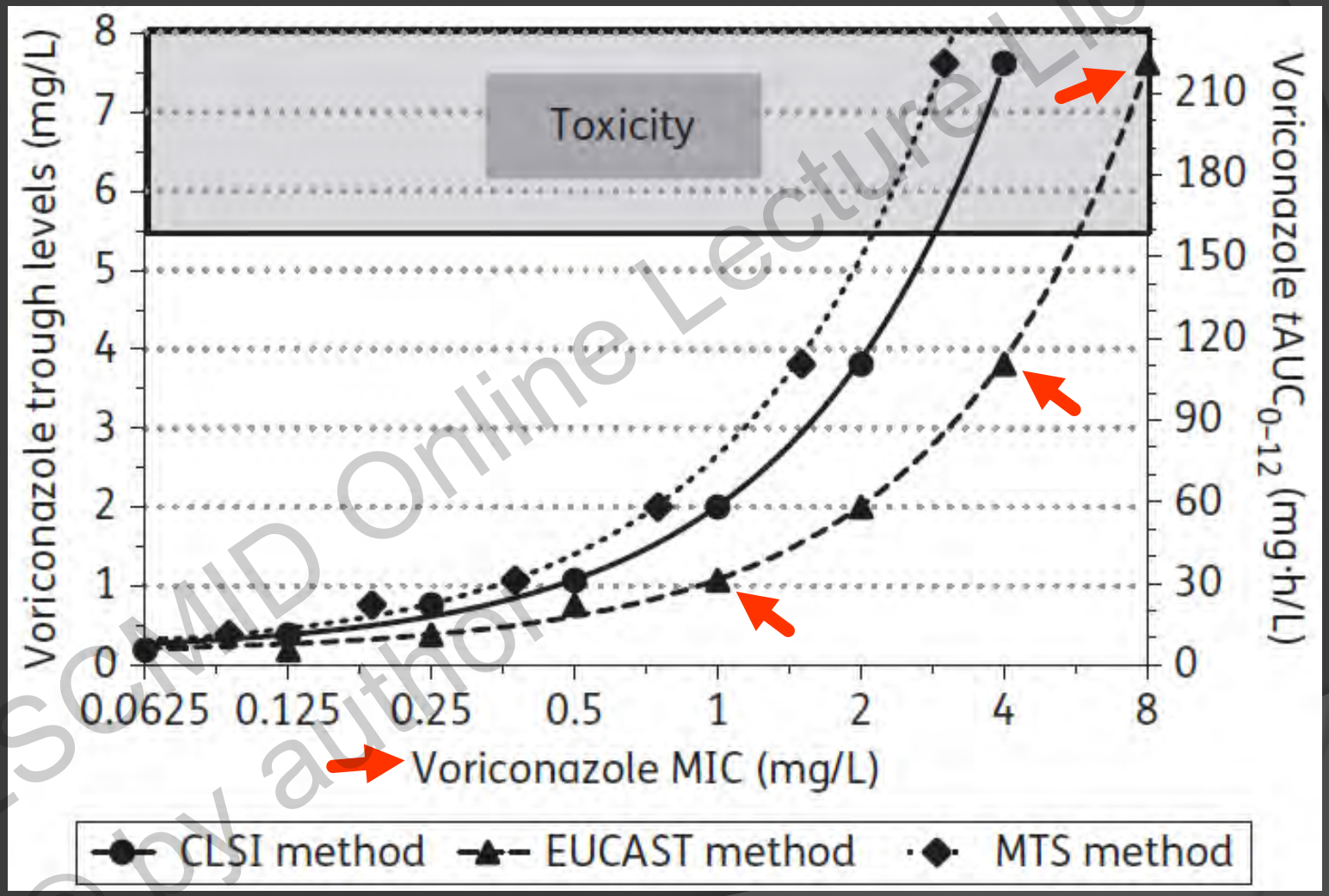
Impact of *In Vitro* Susceptibility



But may be treatable if higher than average drug exposures achieved

Jeans et al JID 2012;206:442-52

Impact of *In Vitro* Susceptibility

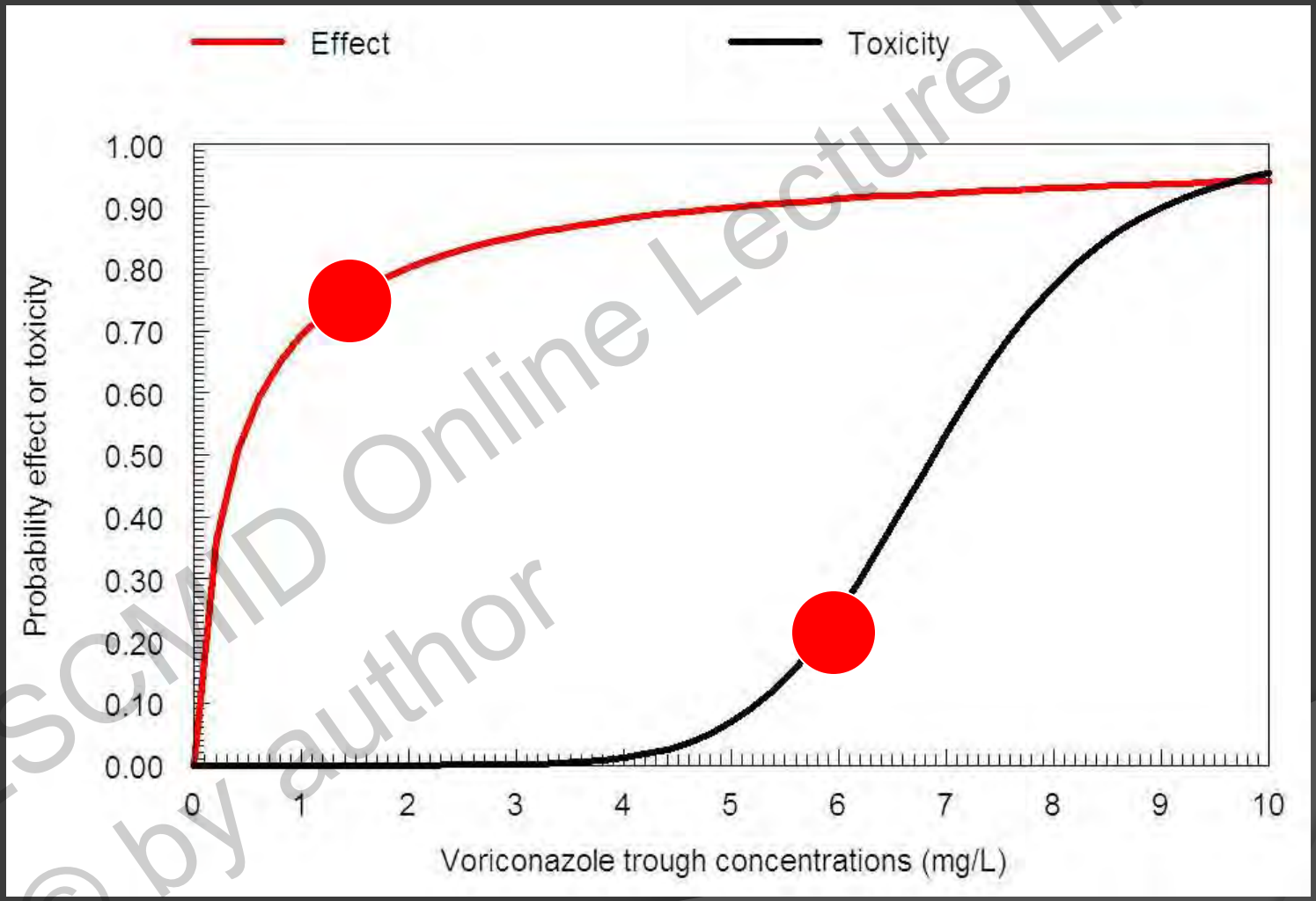


Siopi et al JAC 2014 Feb 17 Epud ahead of print

Vori TDM Recommendations

- Treatment >1-2 mg/L and <4-6 mg/L

Effect/Risk of Toxicity



Pascual et al CID 2008;46:201-11

Vori TDM Recommendations

- Treatment >1-2 mg/L and <4-6 mg/L
- Or concentration:MIC ratio of 2-5 (CLSI)
- First trough measurement 2-5 days after initiation of therapy or change in dosage, with a second sample routinely taken to ensure no progressive accumulation
- Frequency depends on the patients clinical condition and further dose adjustment

Ashbee et al JAC 2014;69:1162-76

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Posaconazole

- Prophylaxis and salvage therapy for IA
- Oral suspension, and recently FDA approved delayed-release tablets and IV
- Linear PK
- Less interactions than other triazoles
- Can cause nausea, vomiting and hepatotoxicity – but ? link with serum concentrations

The Case for Posa TDM

- PK variability in response to gut conditions (e.g. pH and fat)
- Saturable oral absorption >800 mg/day
  - Dosage escalation may not help
  - Fractionating dose
  - Removing H2 antagonists
  - Giving with acidic/fatty food (recommend)
  - Newer formulations may be helpful
- Potentially subtherapeutic levels are being reported clinically
  - (4% in 0.5 mg/L for patients receiving 200 mg q8)
- Serum concentration appears to be linked with efficacy

Walsh et al CID 2007;44:2-12

Cornely et al NEJM 2007;356:348-59

Exposure-Response Relationships

mean posaconazole concentration (mg/L)	% response
0.134	24
0.411	53
0.719	53
1.25	75

Walsh et al CID 2007;44:2-12

The Case for Posa TDM

- PK variability in response to gut conditions (e.g. pH and fat)
- Saturable oral absorption >800 mg/day
- Potentially sub-therapeutic levels are being reported clinically

  (44% <0.5 mg/L for patients receiving 200 mg q8)
- Serum concentration appears to be linked with efficacy

Mounting evidence that TDM may be important

Walsh et al CID 2007;44:2-12

Cornely et al NEJM 2007;356:348-59

Posa TDM Recommendations

- Treatment >1 mg/L
- Prophylaxis >0.7 mg/L
- 7 days after initiation of therapy (when steady state achieved)
- Frequency – dose adjustment/ interactions/compliance/absorption concerns/clinical indications
- Lower therapeutic target of 0.35 mg/L >48h of therapy initiation

Ashbee et al JAC 2014;69:1162-76

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Echinocandins

- Alternative to first line therapy for IA
- TDM not generally advocated
  - limited understanding of their exposure-response relationships
  - limited PK/PD data
- But *in vitro* resistance increasingly reported
- Exposure-response relationship link with *Candida*, but the relationship is more challenging with *Aspergillus*

No evidence to support routine TDM currently

Walsh et al CID 2008;46:327-60

Summary

Antifungal Class	Current TDM Recommendations
Polyene	No indication
Triazole	Complex pharmacokinetics requiring TDM
Echinocandin	Insufficient evidence

Summary

Triazole Agent	Current TDM Targets for IA (mg/L)	
Itraconazole	>0.5 (HPLC)	<17 (Bioassay)
Voriconazole	>1-2	<4-6
Posaconazole	>1	-

Ashbee et al JAC 2014;69:1162-76

Conclusions

- Antifungal TDM is an increasingly important component of managing invasive disease
- Most evidence circumstantial
- Possible to manage without triazole TDM, but advisable for optimal efficacy & safety
- Must be accurate, available & cost effective
- Increasingly susceptibility and clinical factors should be taken into account

Thank you