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Optimizing antifungal dosing regimens

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Disclosures

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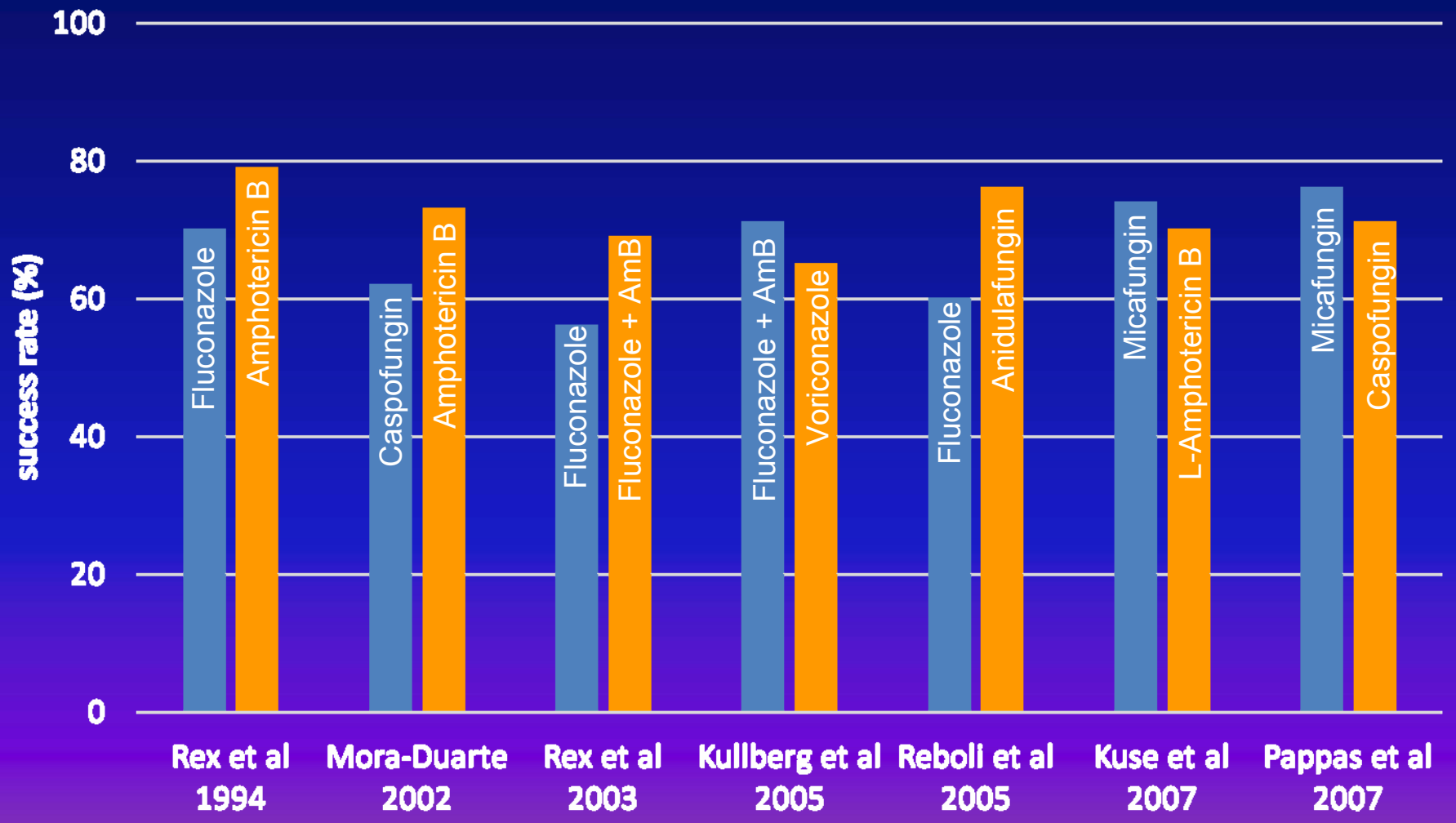
Invasive candidiasis

20-40% mortality

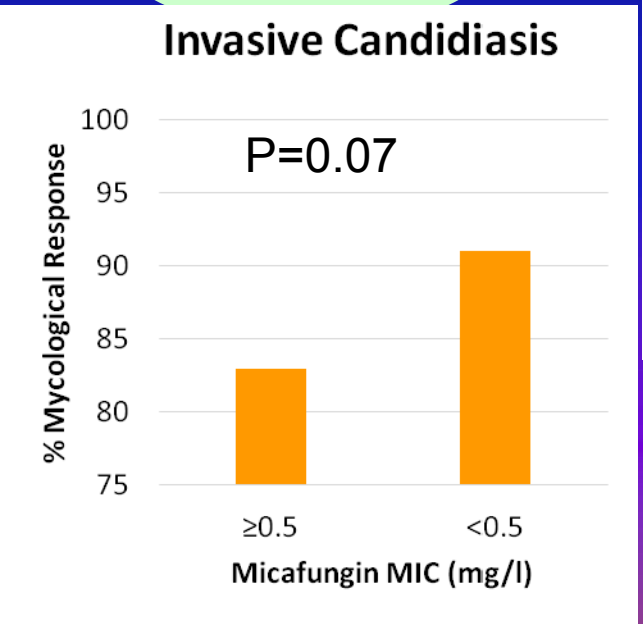


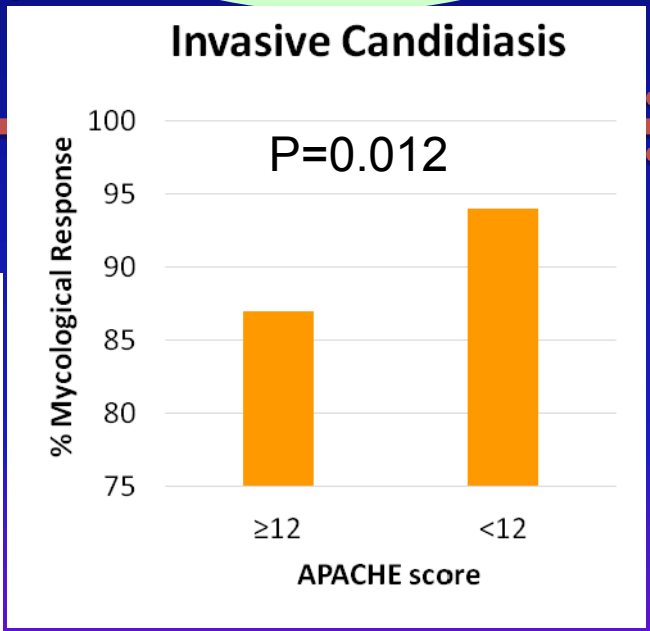
Determinants of clinical outcome

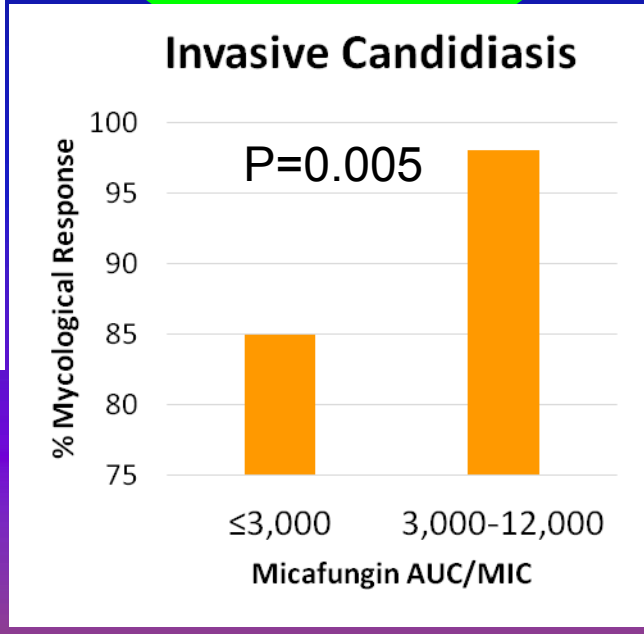
Host
Immunosuppression
Underlying diseases
Co-morbidities

Pathogen
Virulence
Susceptibility
Localization

Drug
Dose
Frequency
Duration



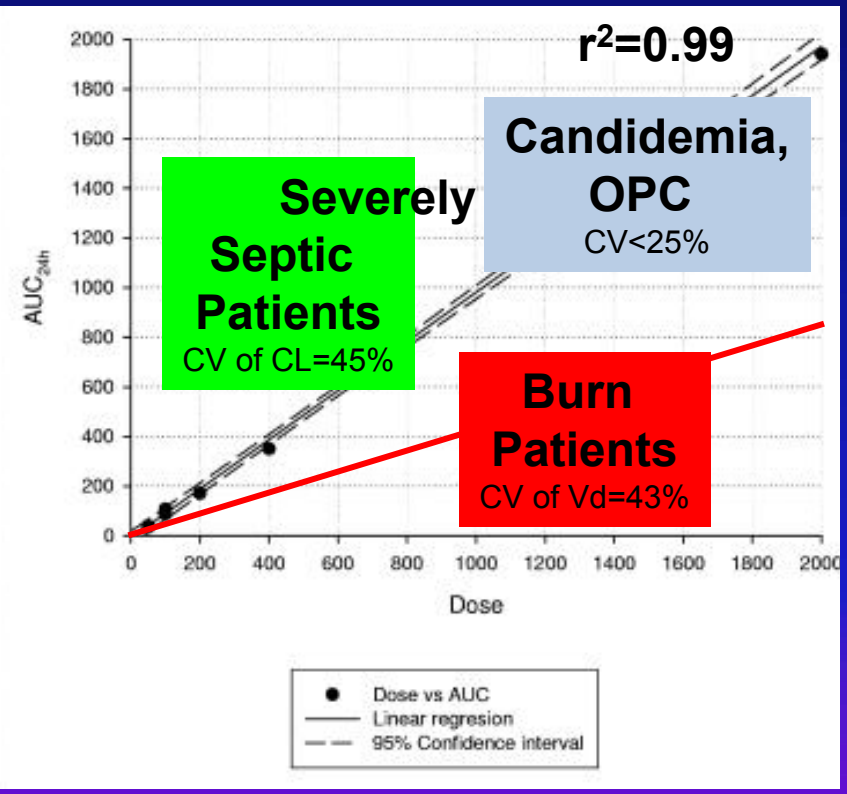




Andes AAC 2011

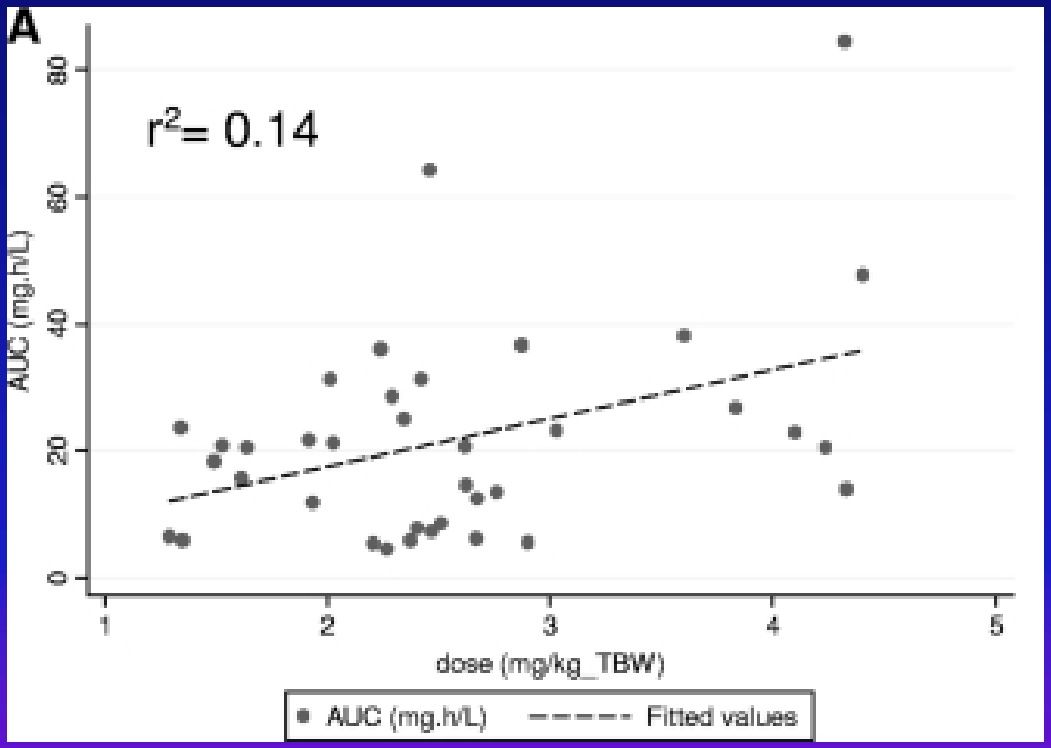
Dose and serum concentrations

Fluconazole



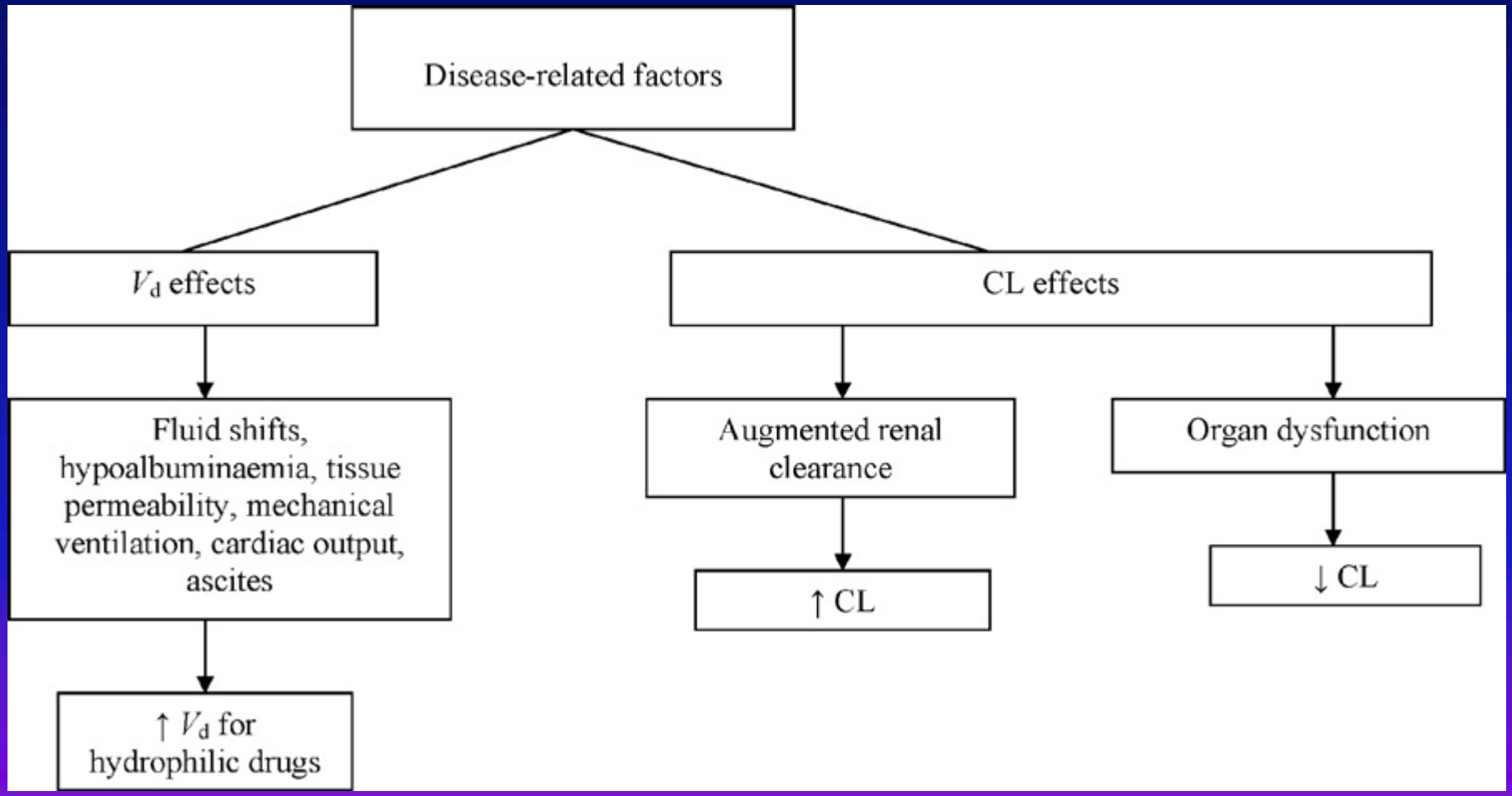
Rodriguez-Tudela et al, AAC 2007
Han et al, AAC 2013

Voriconazole



Pai et al, AAC 2011

Disease-related factors that could affect the antifungal PKs



↓ plasma Concentration

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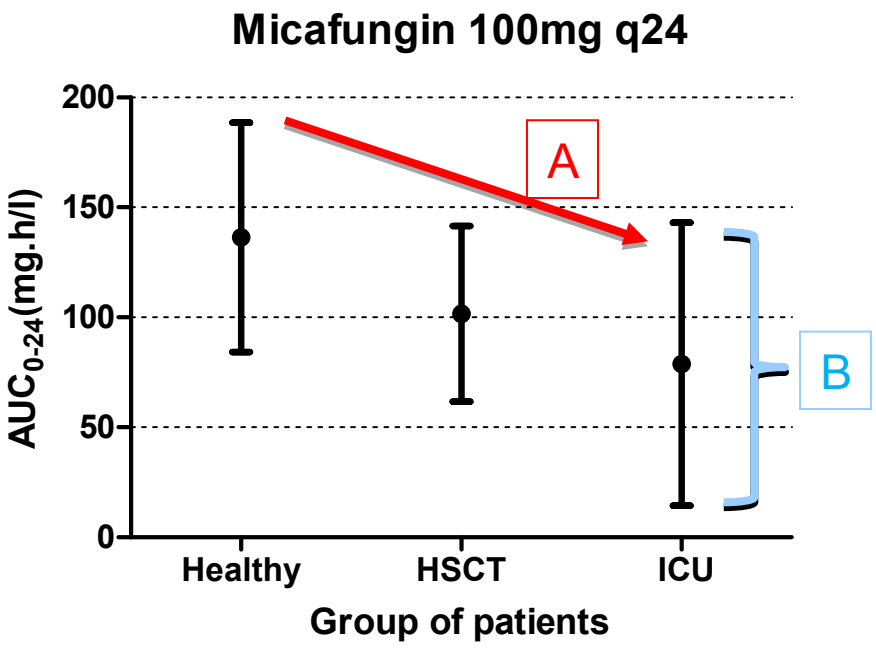
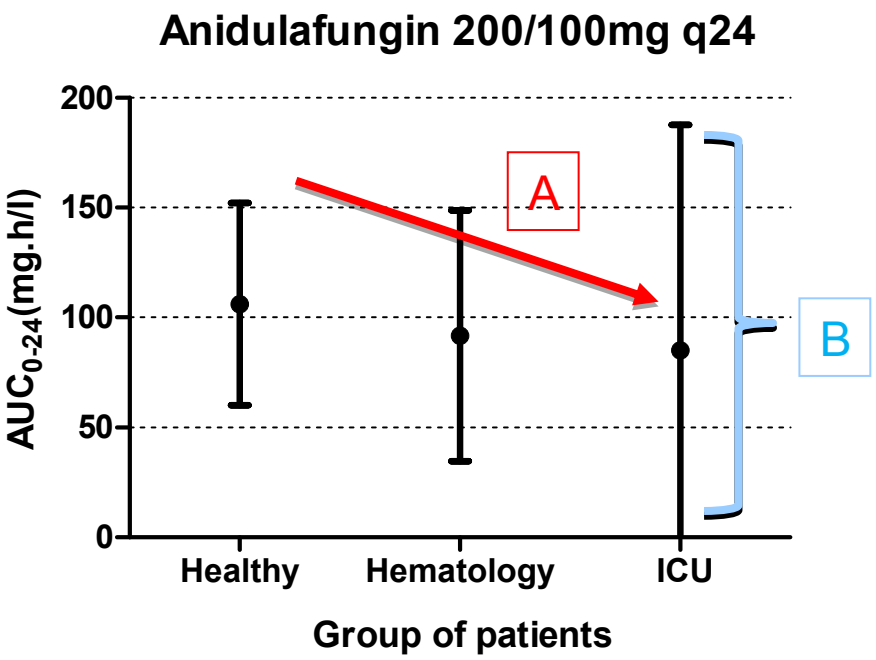
Sinnollareddy et al, Int J Antimicrob Agents 2012

Pharmacokinetics of echinocandins





A. Lower levels in ICU patients

B. Greater variation in ICU patients

Mainas ECCMID 2017,
Mainas ECCMID 2016,
Bruggemann AAC 2017
Lempers AAC2015

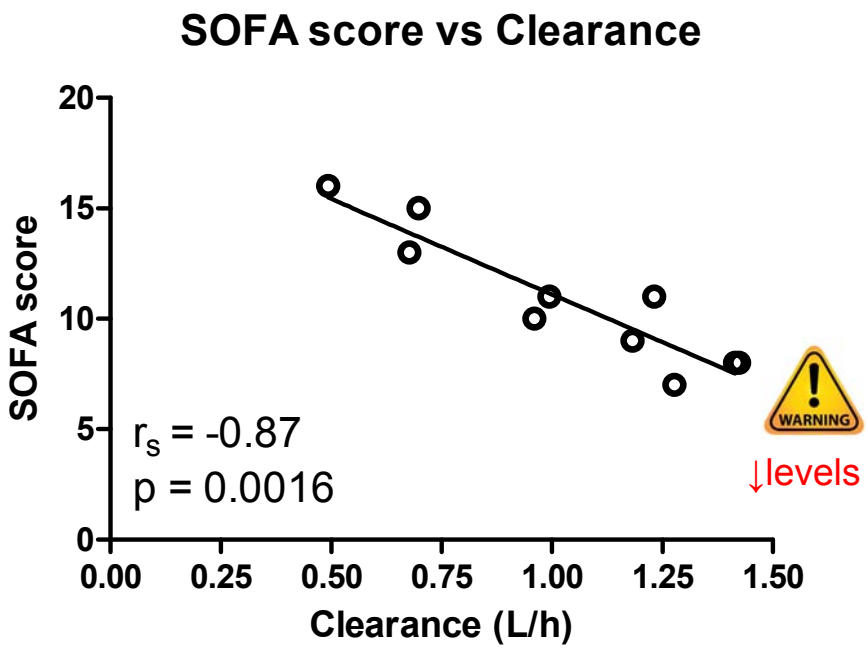
Strategies for optimizing antifungal dosing regimens

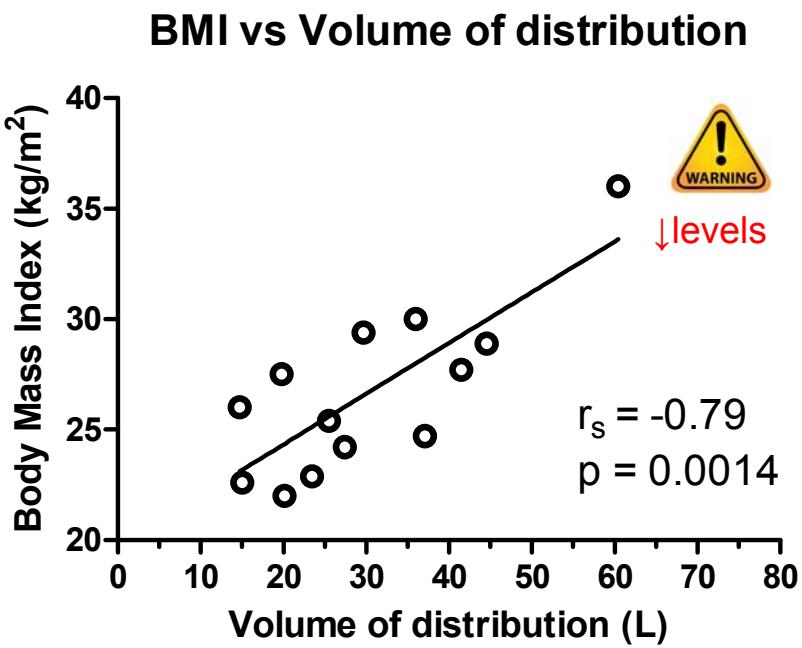
- **Population pharmacokinetic modelling**
  - Specific patient population
  - Identify important co-variates
  - Adjust dose to optimize drug exposure

- **Therapeutic drug monitoring**
  - Measure drug levels in serum
  - Adjust dose to optimize drug exposure

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

Population pharmacokinetics of anidulafungin





Population pharmacokinetics of micafungin

- Significant correlation between clearance and body weight
  - **Patients >100 kg** → 30% increased clearance
  - **Patients <45 kg** → 30% reduced clearance

CL = 1.04 x (weight/66)$^{0.75}$

Andes AAC 2011

Table 3. Mean micafungin AUC (mg·h/L) with respect to albumin and SOFA score for a typical patient of 84 kg and comparison with literature data (either $AUC_{0-\infty}$ after the first dose or AUC_{0-24} at steady-state)

	Present study				
SOFA score	albumin ≤25 g/L	albumin >25 g/L	ICU patients	Non-ICU patients	Healthy subjects
≥10	87.3	99.5	78[a]	100[b]	134.5[c]
<10	65.5	74.6			

Jullien, JAC2017

Doses of echinocandins

	Caspofungin	Anidulfungin	Micafungin
Loading dose (LD)	70 mg	200 mg	-
Maintenance dose (MD)	50 mg	100 mg	50 mg (prophylaxis) 100 mg (invasive) 150 mg (oesophageal)
Adults	**>80kg:** 70 mg	**BMI >40 kg/m²:** **LD/MD:**300/150 mg Lemper Clin Pharmacokinet. 2016	**>40kg:** up to 200 mg **≤40kg:** 4 mg/kg
Children	**LD:** 70 mg/m² **MD:** 50 mg/m²	0.75-1.5 mg/kg	**>40kg:** 100 mg **≤40kg:** 2 mg/kg
Infants/Neonates	**<3mo:** 25 mg/m² **3mo-2y:** 50 mg/m² Saez-Llorens X et al AAC 2010	**LD:** 3 mg/kg **MD:** 1.5 mg/kg Cohen et al Clin Pharm Ther 2011	4-15 mg/kg Bejmamin et al Clin Pharm Ther 2010
Burn patients			200-300 mg Sasaki et al AAC 2012

Muilwijk, Exp Rev Anti-inf Ther 2015
SPCs

Fluconazole doses in obese critically ill patients (BMI >30 kg/m^2)

- *Vd* was related to BMI
- CL is correlated with measured CL_{CR}
- a standard dose of 400 mg daily (6 mg/kg) resulted in suboptimal exposures
- loading dose of 12 mg/kg/day followed by a maintenance dose of 6 mg/kg/day
- Loading doses: weight based
  Maintenance doses: according to renal function

Alobaid AAC 2016

Antifungal Dosage Adjustment in Hepatic Failure

Drug	Effect of hepatic impairment	Adjustment
Amphotericin B	NA	No
ABLC	NA	No
ABCD	NA	No
L-AMB	↑deposition in the lung	No
Flucytosine	No	No
Fluconazole	↓clearance, ↑ AUC and $t_{1/2}$	Consider 50% reduction in dosage in mild to moderate hepatic impairment
Itraconazole		
Voriconazole		
Posaconazole		Use only if benefits outweighs risk in patients with severe hepatic impairment.
Caspofungin	↓clearance, ↑ AUC	Reduce maintenance dose to 35 mg/day in moderate hepatic dysfunction
Micafungin	No	No
Anidulafungin	No	No

Antifungal Dosage Adjustment in Renal Dysfunction

Drug	Dose normal renal function	GFR > 50	GFR 10-50	GFR < 10	Hemo-dialysis	CAPD	CRRT
Ampho B	0.25-1.5 mg/kg q24h	-	-	q24-q36h	-	q24-q36h	-
ABLC	5 mg/kg q24h	-	-	q24-q36h	-	q24-q36h	-
ABCD	3-5 mg/kg/day	-	-	q24-q36h	-	q24-q36h	-
L-AMB	3-5 mg/kg q24h	-	-	q24-q36h	-	q24-q36h	-
Flucytosine	37.5 mg/kg q6h	q6h	q12h-24h	q24-q48h	Dose after dialysis	0.5-1 g/d	-
Fluconazole	100-800 mg q24h	-	50% dose or interval	50% dose or interval	Dose after dialysis	50% dose or interval	(50% dose or interval)
Itraconazole	200-400 mg q12h	-	-	- IV not recommended	- IV not recommended	-	-
Voriconazole	6/4 mg/kg IV q12h or 200 mg PO q12h	-	- IV not recommended	- IV not recommended	-	-	-
Posaconazole	600-800 mg day in divided doses	-	-	-	-	-	-
Caspofungin	70/50 mg q24	-	-	-	-	-	-
Micafungin	50-150mg q24	-	-	-	-	-	-
Anidulafungin	200/100mg q24	-	-	-	-	-	-

Therapeutic drug monitoring

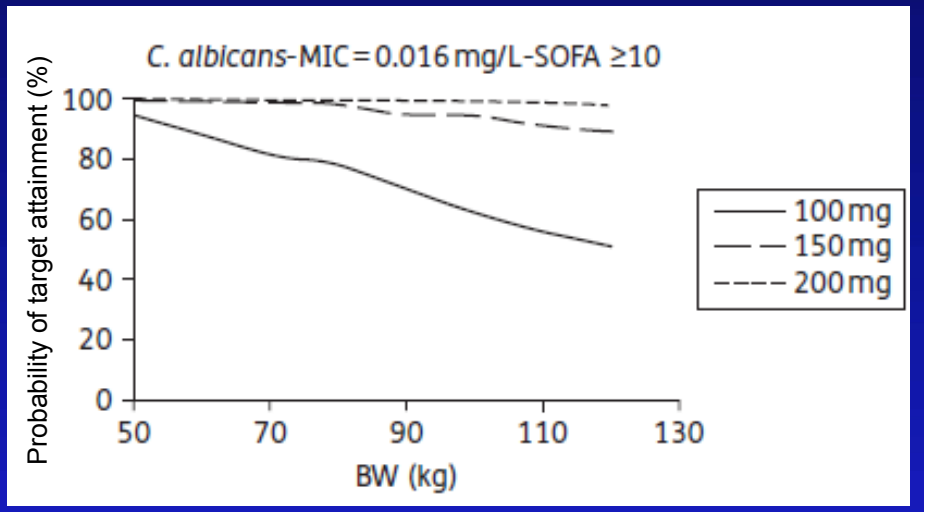
Drug	Significant PK variability (CV)	Main Source of PK variation	Day for TDM	Target blood concn[a] (µg/ml) for:			
				Efficacy	Evidence	Safety	Evidence
Amphotericin B	No (<50%)		-	NA	-	NA	-
Echinocandins	No (<50%)		-	NA	-	NA	-
Flucytosine	Yes, **(50-80%)**	Excretion	3-5	**Prophylaxis**: NA **Therapy**: 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/iv <50-75%)	Absorption	5-7 3	**Prophylaxis**: C_{min}>0.5-0.7; **Therapy**: C_{min}>1-1.25 C_{min}>0.35	Moderate Moderate	NA	

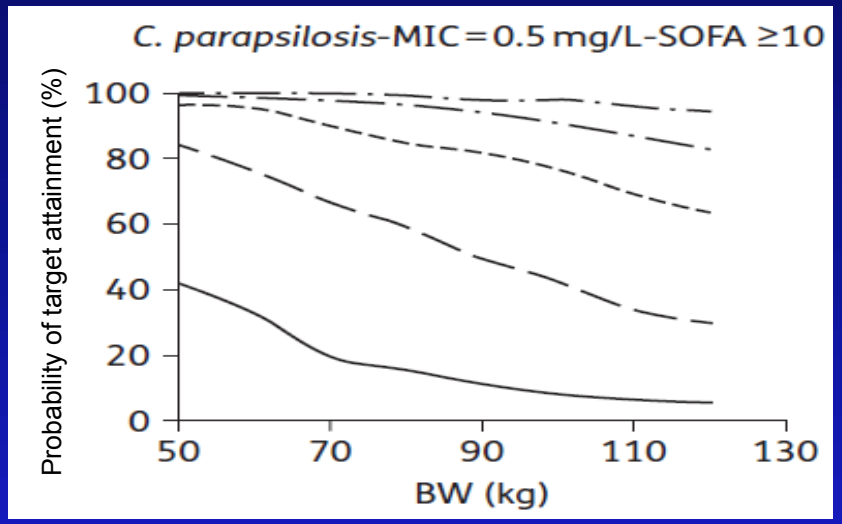
Ashbee et al. JAC 2014

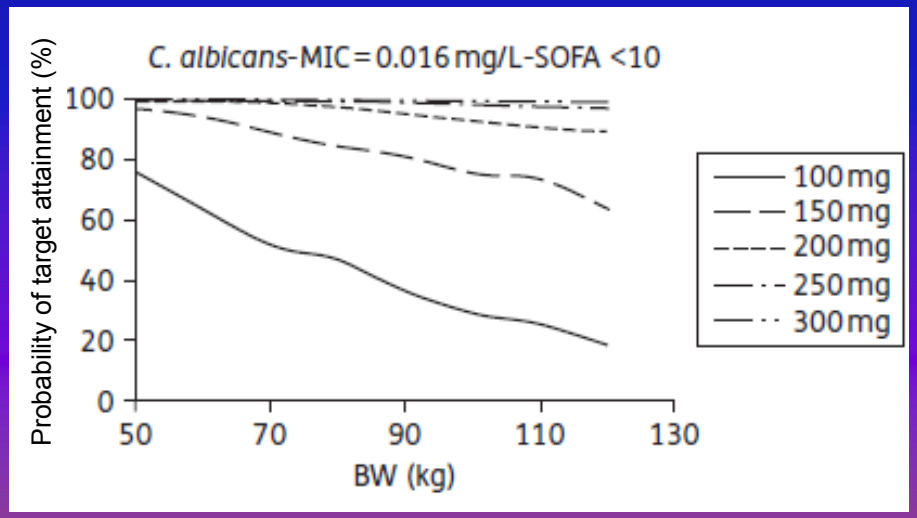
An integrated approach to optimize antifungal doses

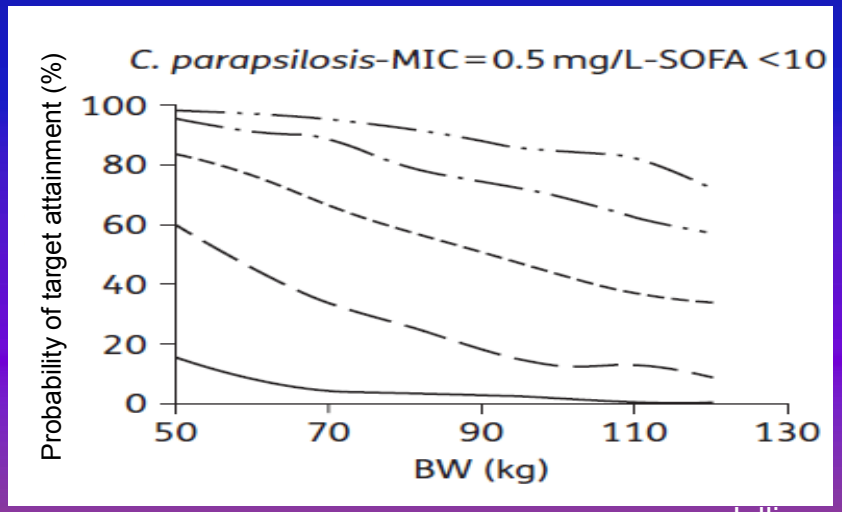
based on the SOFA score, body weight, albumin levels, *Candida* species and MIC

micafungin doses for ICU patients with albumin >25 g/L









Jullien, JAC2017

Take-home messages

- ✓ Antifungal drugs exhibit significant inter-patient variability
  - particularly in critically ill patients
- ✓ Dose adjustments are required for different patient populations
  - adults, pediatric, burn patients
- ✓ Significant co-variates have been identified
  - albumin, SOFA score and body weight
- ✓ Despite dose adjustment interpatient variability may be observed
- ✓ Therapeutic monitoring can optimize drug exposure
  - target concentrations for efficacy and toxicity are required
- ✓ Integrated approaches for optimizing antifungal dosing regimens
  - *Candida* species, MIC and covariates

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