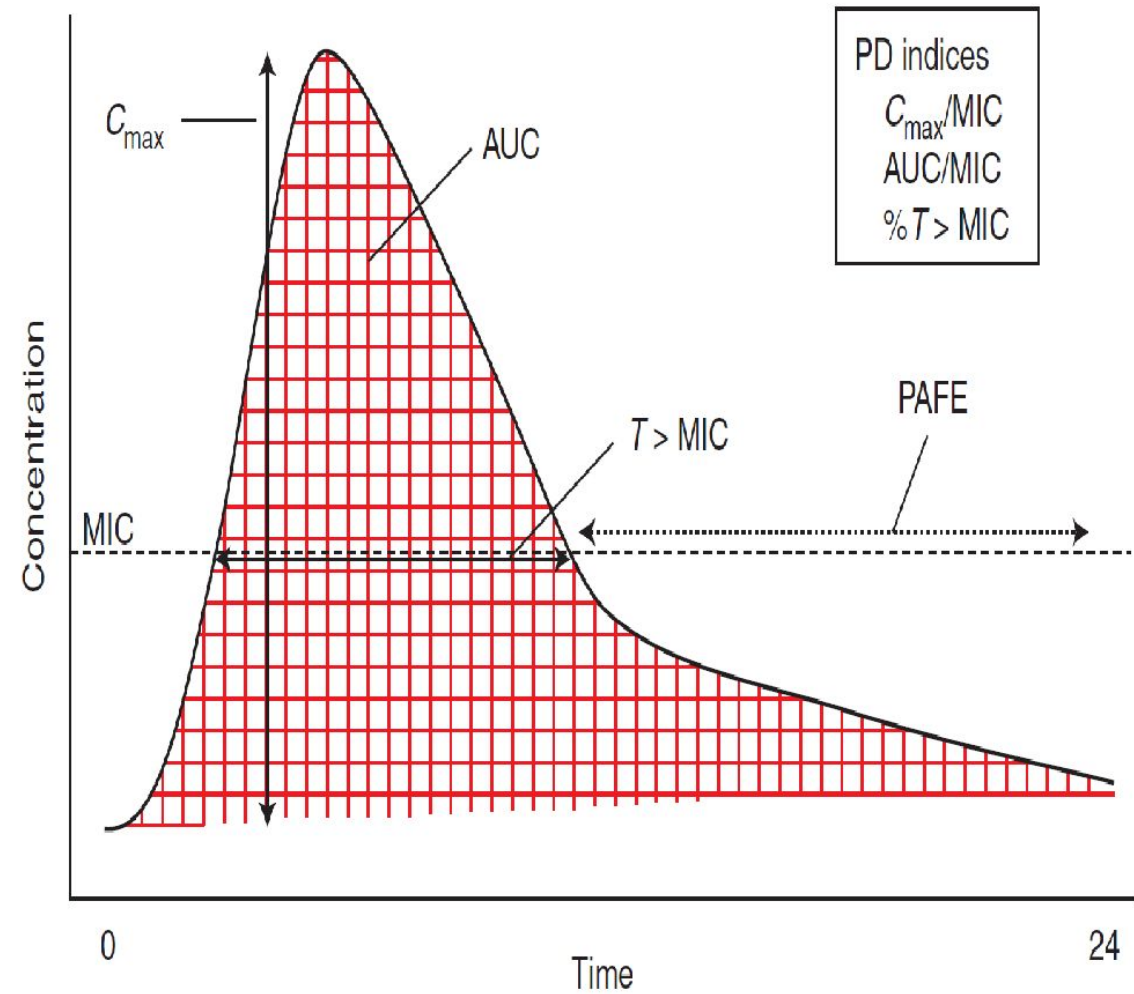


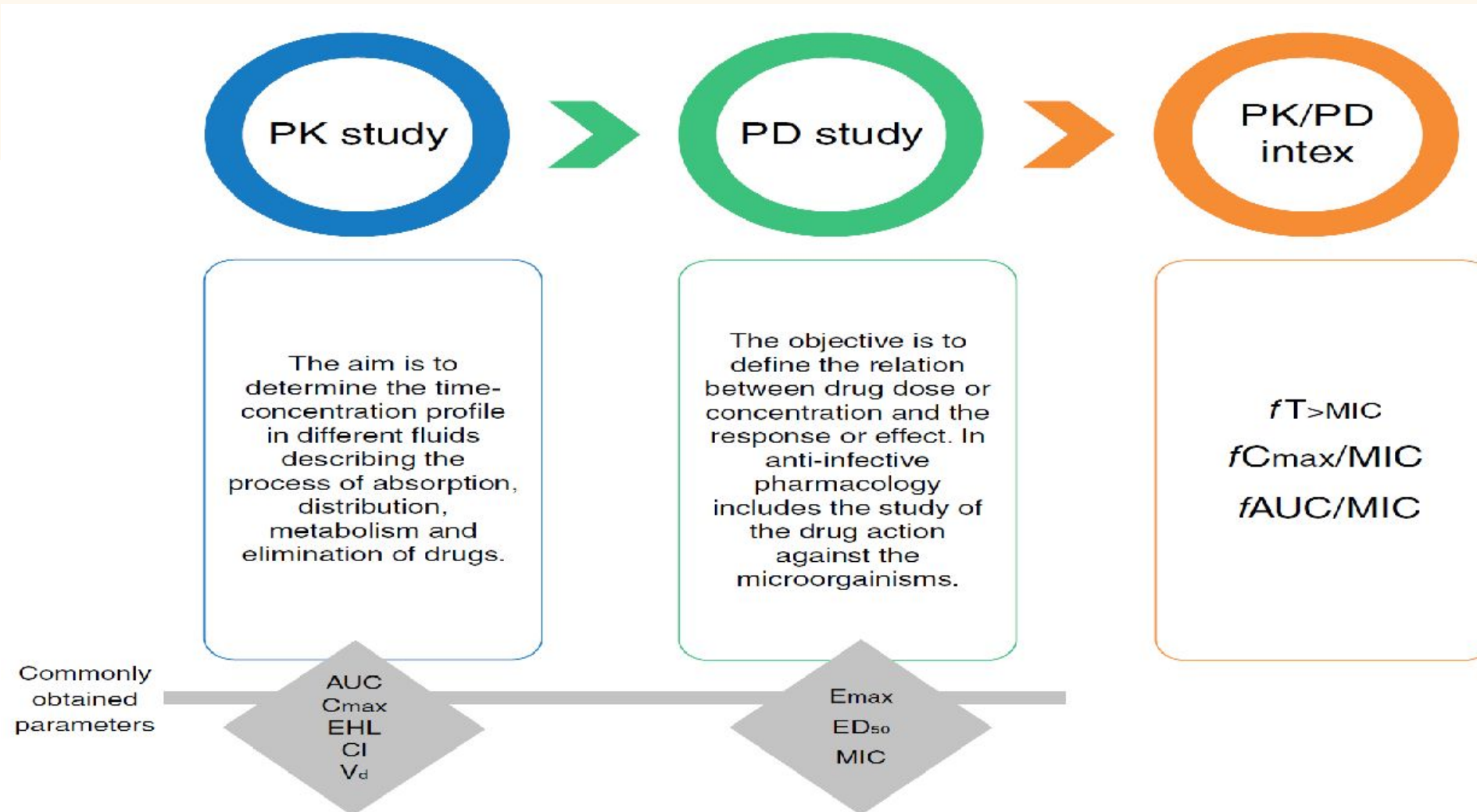
ANTIFUNGALS PK/PD IN CLINICAL PRACTICE

DR LOW LEE LEE
INFECTIOUS DISEASE
PHYSICIAN
HOSPITAL SULTANAH BAHIIYAH

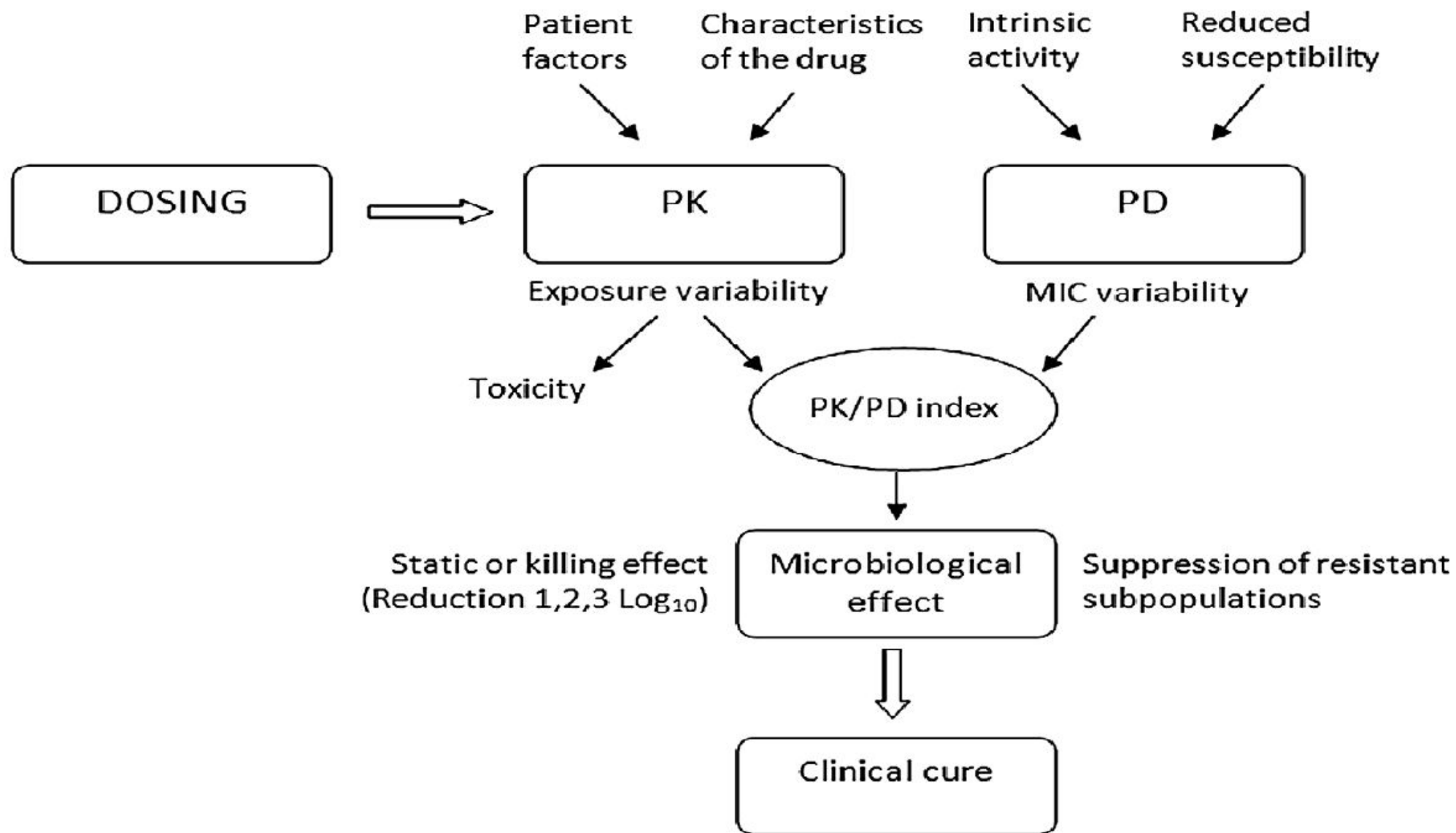
PHARMACOKINETIC PHARMACODYNAMIC



PK/PD ANTIFUNGALS



Pharmacokinetics (PK), pharmacodynamics (PD) and PK/PD integration. Pharmacokinetic parameters. AUC, area under the time curve; C_{max}, maximal concentration or peak; EHL, elimination half-life; Cl, clearance; V_d, volume of distribution.



Factors associated with a good response to antifungal treatment:

Susceptible to MIC or MEC

Early therapy

Sufficient drug exposure in relation to MIC

Adequate drug concentration at the effected site

Factors associated with poor response to antifungal treatment:

High fungal burden

High MIC or MEC

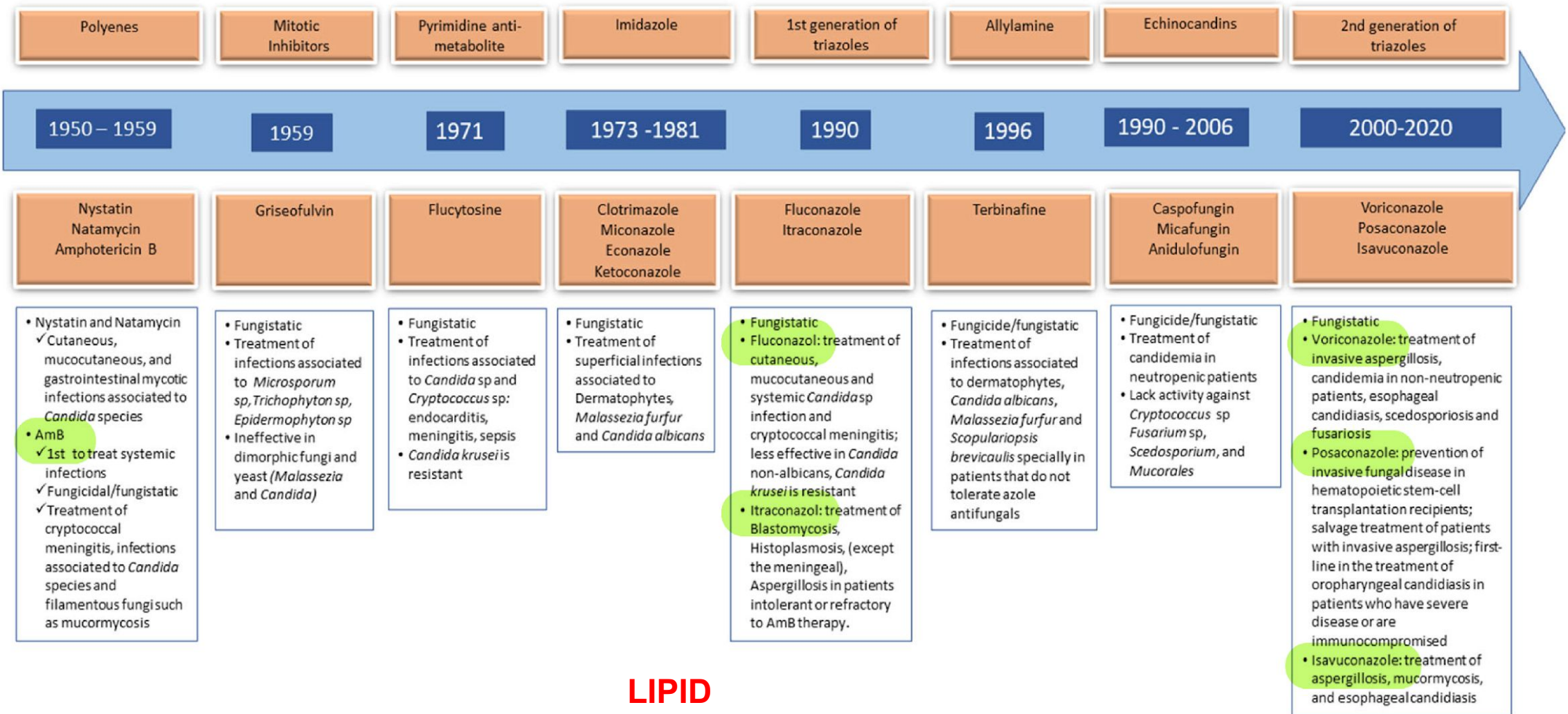
Intrinsically resistant fungi

Insufficient drug exposure in relation to MIC

Severely immunocompromised patients

Multifocal/disseminated disease

Delayed in therapy



**LIPID
formulation
Amphotericin B**

NEW KIDS ON THE BLOCK

Antifungal agents

Fosmanogepix

Ibrexafungerp

Olorofim

Opelconazole

Rezafungin

ORAL NANOCRYSTAL
AMPHOTERICIN B

PK/PD INDICES AS PREDICTORS OF CLINICAL EFFICACY

Drug class	Concentration dependent	Prolonged PAFE	PD index predictive of efficacy
Polyene	Yes	Yes	C_{\max}/MIC
Flucytosine	No	No	$T > MIC$
Azoles	No	Yes	AUC/MIC
Echinocandins	Yes	Yes	C_{\max}/MIC or AUC/MIC

PK exposure



PD response

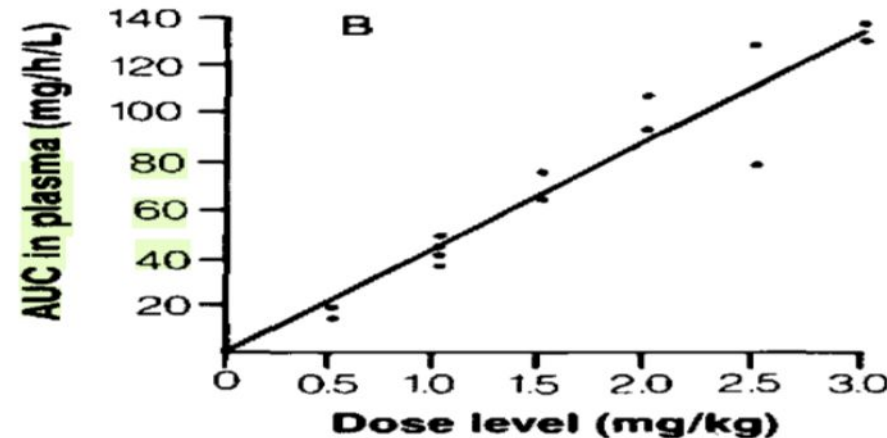
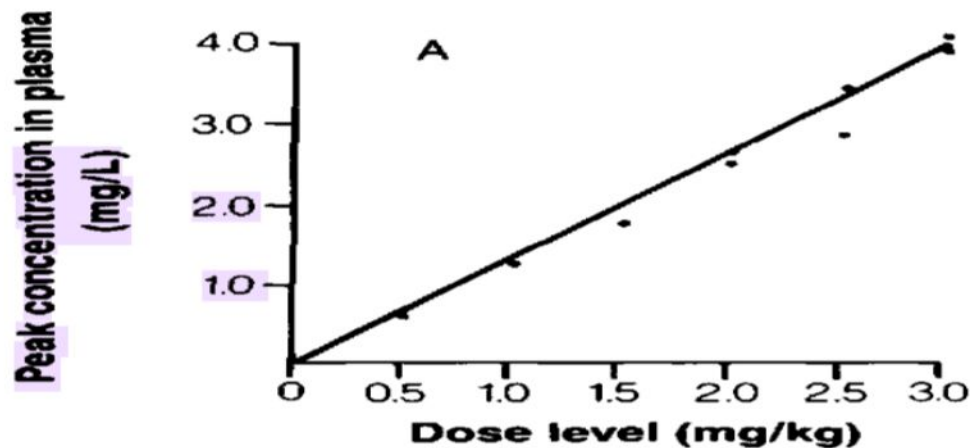


outcome

FLUCONAZOLE

- High (>90%) oral bioavailability
- The plasma half-life : 30 hours
- The steady state achieved within 5-7 days following once-daily dosing.
- Loading dose : steady state level achieved within 24h
- 80% excreted by kidney as unchanged drug.
- Predictable blood levels: every 100 mg results in level of 5µg/ml, 800mg = 40µg/ml in healthy volunteers

- The PK/PD index best related to outcome is the AUC/MIC or DOSE/MIC
- The dose is a good surrogate for the AUC.
- There is an almost 1:1 linear relationship between the AUC and the dose of fluconazole,
- In principle, a higher than two-fold increase in MIC during treatment could suggest development of resistance and the need for closer clinical monitoring



CANDIDIASIS

- $AUC/MIC > 100$ correlate with good clinical outcome
- 90% probability of cure when isolates with fluconazole MIC 2 mg/liter.
- 66% probability of cure when isolates with fluconazole MICs of 4 mg/liter but reached 100% when > 100 mg/day fluconazole was given.
- Only 11.8% patients responded when the fluconazole MIC was 8 mg/liter

Sensitive fungi : Trough > 2 mg/L

need several samples to estimate 24H AUC : eg 1, 4, 24 Hr

CRYPTOCOCCAL MENINGITIS

- Induction : $AUC/MIC > 384$
- Consolidation : $AUC/MIC > 100$

Rodríguez-Tudela, et al. Correlation of the MIC and dose/MIC ratio of fluconazole to the therapeutic response of patients with mucosal candidiasis and candidaemia. . Antimicrob. Agents Chemother. **2007**, 51, 3599–3604

Pai Manjunath, P.; Turpin Robin, S.; Garey Kevin, W. Association of Fluconazole Area under the Concentration-Time Curve/MIC and Dose/MIC Ratios with Mortality in Nonneutropenic Patients with Candidemia. Antimicrob. Agents Chemother. **2007**, 51, 35–39.

Sudan et al. Pharmacokinetics and pharmacodynamics of fluconazole for cryptococcal meningoencephalitis: implications for antifungal therapy and in vitro susceptibility breakpoints. Antimicrob Agents Chemother **2013**, 57 (2013), pp. 2793-2800

FLUCONAZOLE

FLU clearance :

- Normal renal function : 20ml/min
- CVVH (25ml/min)
- CVVHD (38ml/min) has higher fluconazole clearance

In critically ill patients :

- eGFR < 60 : 400mg daily
- Normal eGFR : 600mg daily
- CVVHD : 800mg daily

Andes D. et al. and CAntimicrobAghemother. 1999.43(9):2116-2120

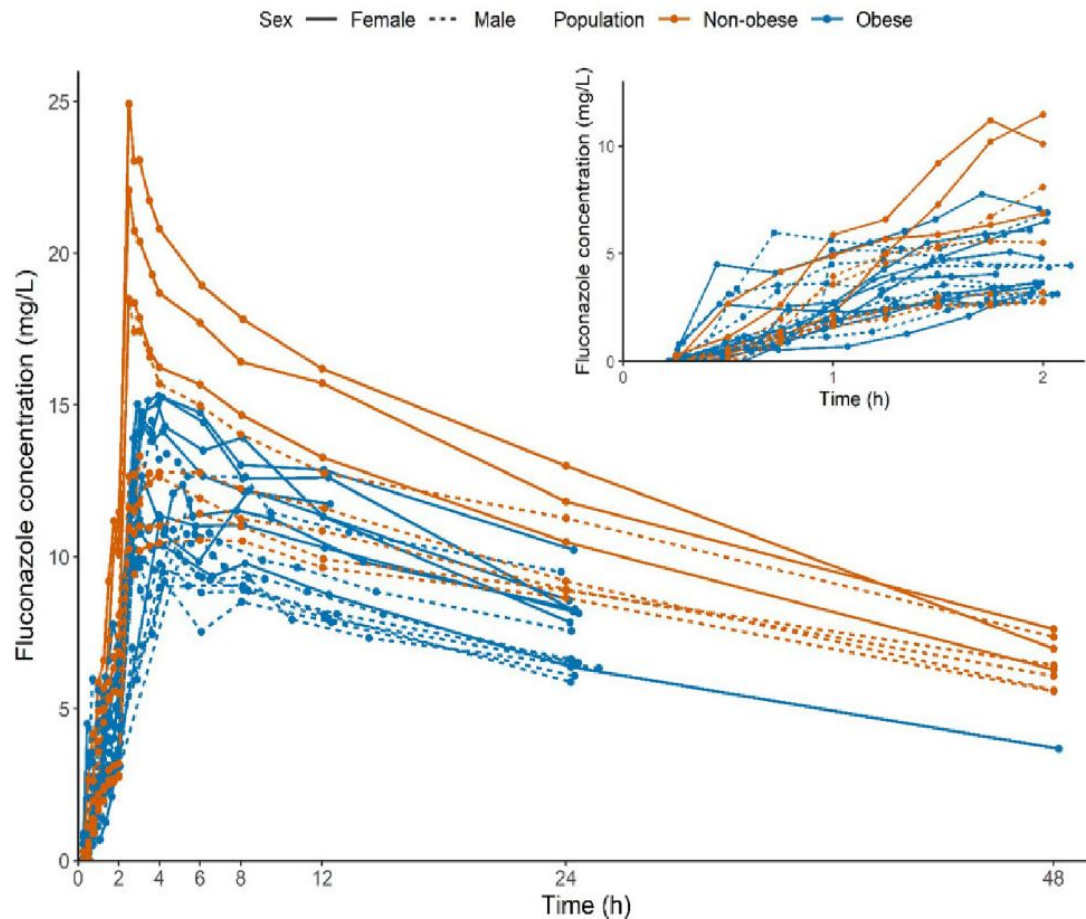
Clancy CJ, AntimicrobAgents Chemother. 2005 Aug;49(8):3171-7

Lu Chen et al. *Journal of Antimicrobial Chemotherapy*, 77(8) , 2022, 2217–2226

Muilwijk, Antimicrob Agents Chemother 64:e00984-20

Carmo et al. *Antibiotics* **2023**, 12, 884.

FLUCONAZOLE



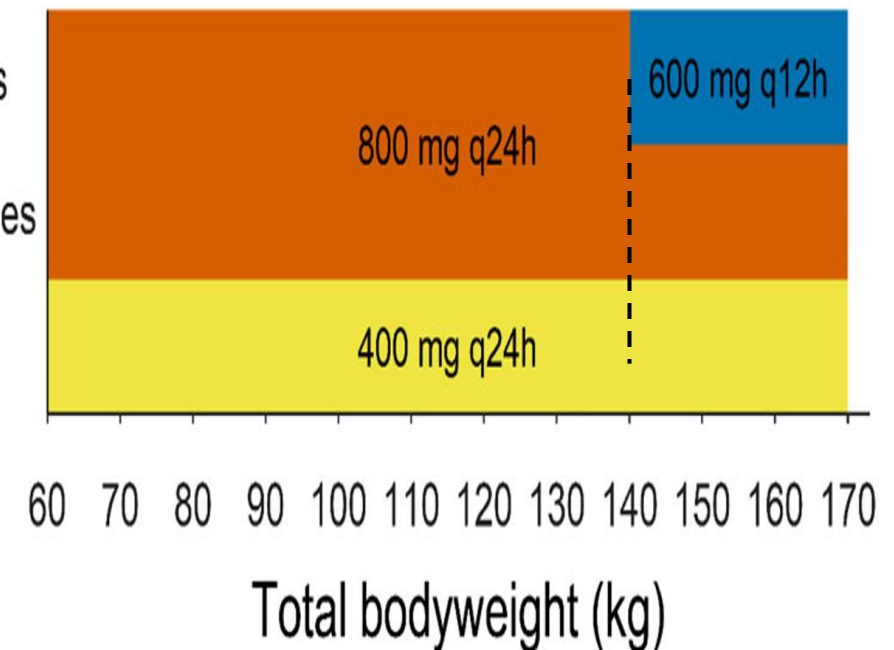
Obese patients

- Higher CL and V_d when Total bodyweight increased
- V_d in Male > female (lower H₂O composition in female)
- Male > 140kg (for AUC/MIC > 100, MIC < 2mg/L) :higher loading dose loading 1200mg

Loading dose for males

Loading dose for females

Maintenance dose



Andes D. et al. AntimicrobAg and Chemother. 1999.43(9):2116-2120

Clancy CJ, AntimicrobAgents Chemother. 2005 Aug;49(8):3171-7

Lu Chen et al. *Journal of Antimicrobial Chemotherapy*, 77(8) , 2022, 2217–2226

FLUCONAZOLE

CNS infections

- 20%–50% reduced fluconazole penetration into the CSF
- Flu 1200 mg daily dose for 2 weeks has shown good tolerance and no liver function disturbance in HIV patients with cryptococcal meningitis

TDM monitoring to guide dosage adjustment :

- when there is severe renal dysfunction or augmented renal clearance
- Deep seated infection : eg CNS
- Organism with high MIC

ITRACONAZOLE

- Oral bioavailability : 55%
- Absorption : depending on gastric pH
absorption increased with food
- $T_{1/2}$: 14-42H
- Daily dose : steady stage in 14 days
- Loading : shorter time to steady stage
- Hepatic Metabolism
- Interpatient PK variability : the same dose may lead to very different concentration–time profiles in different patients, and even to differences during the treatment of a single patient

Capsule	Bioavailability 55%
Solution	80% Empty stomach
<u>SUBA</u> <u>Super-BioAv</u> <u>ailable</u> <u>(SUBA)</u> <u>capsules</u>	Improved Not affected by gastric pH

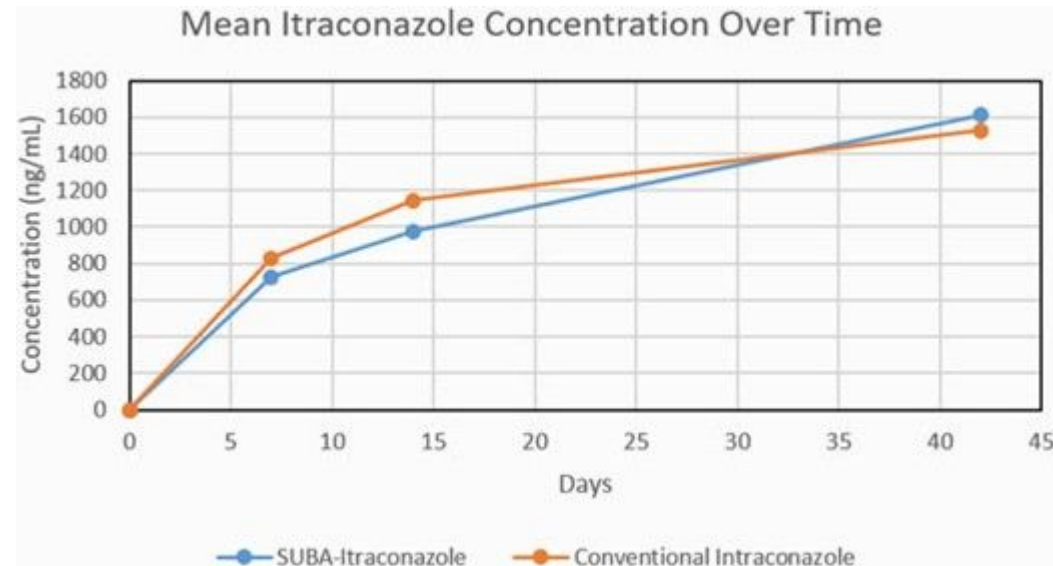
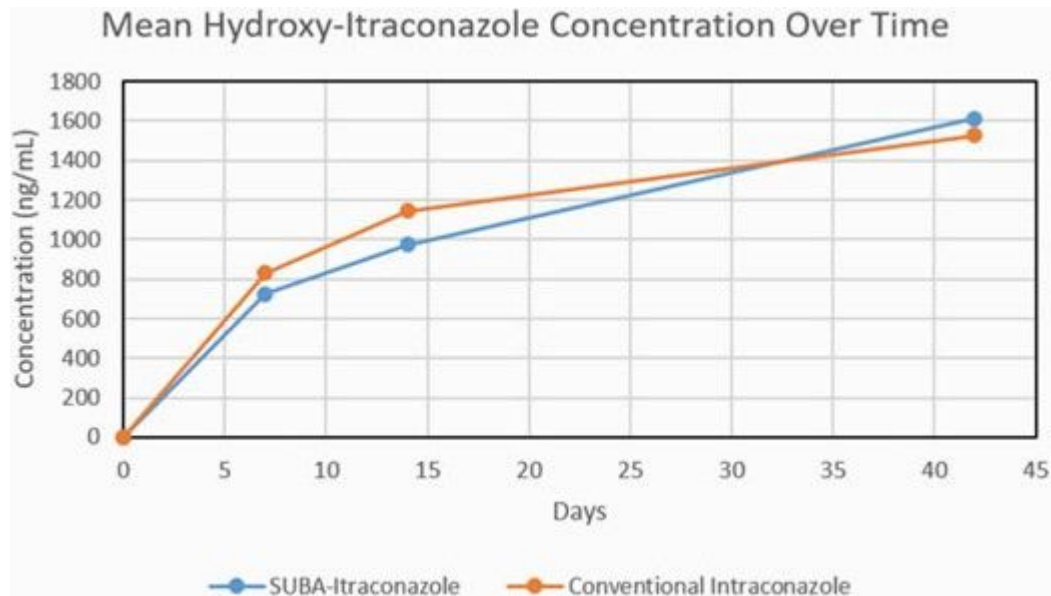
AN OPEN-LABEL COMPARATIVE TRIAL OF SUBA-ITRACONAZOLE (SUBA) VERSUS CONVENTIONAL ITRACONAZOLE (C-ITRA) FOR TREATMENT OF PROVEN AND PROBABLE ENDEMIC MYCOSES (MSG-15): A PHARMACOKINETIC (PK) AND ADVERSE EVENT (AE) ANALYSIS

SUBA itraconazole with relative bioavailability of 173% comparing to c-itraconazole

SUBA is formulated as nanoparticles allowing for absorption in the small bowel while not relying on gastric acidity for optimal absorption.

Minimal interpatient PK variability

SUBA 130 mg po bid or c-itra 200 mg po bid



Pappas et al. Open forum infectious Disease 2024
Abuhelwa et al. Antimicrobial agent and Chemotherapy, 59(9) 2015

ITRACONAZOLE

Concentration-efficacy relationship:

- Itraconazole treatment : 1-2 mg/L
- Prophylaxis : 0.5 mg/L

Concentration- toxicity :

- Upper limit has not been defined
- Bioassay method : < 17 mg/L
- (87% of patients with level ≥ 17 are predicted to have toxicity)

VORICONAZOLE

In children :

- Linear PK
- Increase clearance in children
- High dose :
IV 7 mg/kg 12Hrly or 200 mg p.o. BD (aged 2 to <12 years) are comparable to exposure levels observed in adult

ADULTS

- Non-linear PK
- inter- and intra-patient PK variability
- Due to genetic polymorphism CYP2C19
- Autoinduction of Voriconazole metabolism in
Long-term exposure - autoinduction of cytochrome P450 isoenzymes, resulting in decreasing voriconazole concentration
- Oral bioavailability > 90%
- T_{1/2} : 6 hours
- Steady stage 5-7 days
- With loading dose 3-5 days
- Hepatic metabolism (substrate of CYP450)

VORICONAZOLE

Concentration-efficacy :

Meta analysis (Hamada et al 2012):

- VRZ level > 1mg/L associated with significantly higher success rates ([odds ratio (OR) 7.23, 95% confidence interval (CI) 2.84–18.37, $P < 0.0001$]
- higher blood concentrations, increase incidence of liver dysfunction but no accurate cutoff values were obtained.
- Target: 1-4 mg/l

Randomised CT (Park et al. 2012)

- A complete or partial response was observed in 81% (30 of 37) of patients in the TDM group compared to 57% (20 of 34) in the non-TDM group ($P = 0.04$).
- Target : 1-1.5 mg/L

VORICONAZOLE

concentration-toxicity

TROUGH : 1-5.5 MG/L

Neurotoxicity

- The incidence of neurological adverse effects increased significantly at a cutoff value of 4.0 µg/ml (range of 3.0–6.0 µg/ml) (OR 2.23, 95% CI 1.12–4.46, $P = 0.02$).

Hepatotoxicity

- Hagiwara et al : Troughs level requiring discontinuation were >4.0 µg/ml
- Ueda et al. : Trough >6 µg/ml frequently asso with hepatic toxicity
- 7–17 % increase in the odds of an ALT , AST, ALP, or bilirubin level for every 1 lg/mL increase in the plasma concentration of VRZ

Hamada et al. J Infect Chemother. 2012;18:501–7

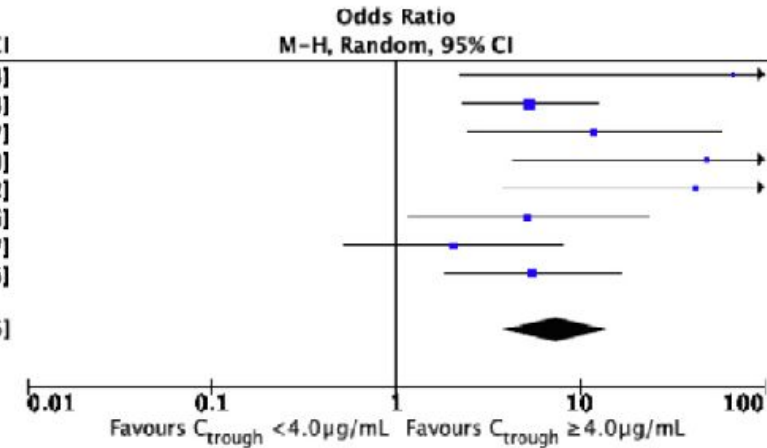
Nanya et al. Int J Hematol. 2009;89:592–9.

Hagiwara et al. Nihon Kokyuki Gakkai Zasshi. 2009;47:93–7

Lutsar et al. Clin Infect Dis. 2003;36:1087–8

A. Hepatotoxicity

Study or Subgroup	C _{trough} ≥4.0µg/mL		C _{trough} <4.0µg/mL		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Hagihara E 2009	3	4	0	14	3.5%	67.67 [2.24, 2041.43]
Hamada Y 2020	14	92	10	309	24.4%	5.37 [2.30, 12.54]
Hirata A 2019	9	15	3	27	12.3%	12.00 [2.46, 58.47]
Matsumoto K 2009	9	12	1	17	6.4%	48.00 [4.33, 532.30]
Okuda T 2008	8	11	1	17	6.4%	42.67 [3.81, 478.42]
Suzuki Y 2013	7	14	4	25	13.2%	5.25 [1.18, 23.46]
Ueda K 2009	9	15	8	19	14.8%	2.06 [0.52, 8.17]
Wang T 2014	7	20	11	124	19.1%	5.53 [1.83, 16.75]
Total (95% CI)		183		552	100.0%	7.39 [3.81, 14.36]
Total events	66		38			
Heterogeneity: Tau ² = 0.28; Chi ² = 10.45, df = 7 (P = 0.16); I ² = 33%						
Test for overall effect: Z = 5.91 (P < 0.00001)						



B. Neurotoxicity

Study or Subgroup	C _{trough} ≥4.0µg/mL		C _{trough} <4.0µg/mL		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Hagihara E 2009	3	4	3	14	6.0%	11.00 [0.82, 147.86]
Hamada Y 2020	23	100	15	301	82.9%	5.70 [2.84, 11.44]
Okuda T 2008	1	11	0	17	3.7%	5.00 [0.19, 134.32]
Wang T 2018	4	24	1	10	7.4%	1.80 [0.18, 18.47]
Total (95% CI)		139		342	100.0%	5.41 [2.87, 10.21]
Total events	31		19			
Heterogeneity: Tau ² = 0.00; Chi ² = 1.17, df = 3 (P = 0.76); I ² = 0%						
Test for overall effect: Z = 5.21 (P < 0.00001)						

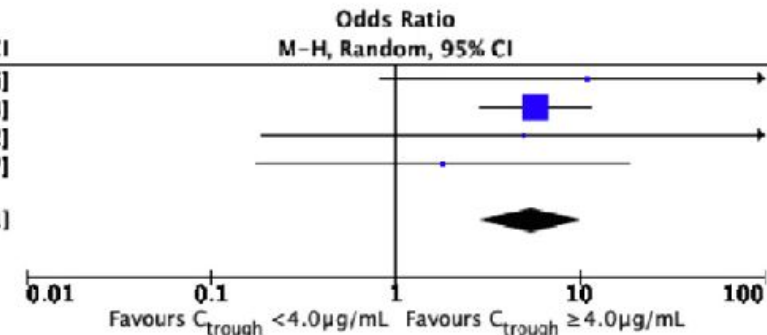


Figure 1. Risk of hepatotoxicity and neurotoxicity at a cutoff trough level of 4.0 µg/mL in studies conducted in Asian locations.

Hepatotoxicity : OR = 7.39; 95% CI, 3.81–14.36

Neurotoxicity : OR = 5.41; 95% CI, 2.87–10.21

Table II. Recommendations for voriconazole TDM in non-Asian and Asian patients.

CQ	Non-Asians	Asians
CQ1. PK/PD parameter	Trough level (II)	Trough level (II)
CQ2. Indication for TDM	TDM is generally recommended mainly to prevent subtherapeutic concentrations (II)	TDM is strongly recommended, mainly because of the risk for supratherapeutic concentrations (I)
CQ3. TDM timing	Day 3 after start of therapy (III-A)	Days 3–5 after start of therapy (III-A); if patient condition allows, delaying TDM until day 5 is suggested
CQ4. Target trough level	$\geq 1 \mu\text{g/mL}$ (I)	$\geq 1 \mu\text{g/mL}$ (I)
To improve efficacy outcome	$< 5.5 \mu\text{g/mL}$ is generally recommended (II)	$< 4.0 \mu\text{g/mL}$ is strongly recommended (I)
To prevent adverse effects		
CQ5. Dosing regimen		
Loading dose for initial day	6.0 mg/kg q12h (I)	6.0 mg/kg q12h (I)
Maintenance dose	4 mg/kg q12h (II)	3 mg/kg q12h is suggested to prevent overdose (III-A)

CQ = clinical question; PK/PD = pharmacokinetic/pharmacodynamic; q12h = every 12 hours TDM = therapeutic drug monitoring.

POSACONAZOLE

Oral suspension

- Poor oral absorption
- Fatty diet, low PH : enhance absorption
- Absorption improved QID > BD

Delayed release posaconazole tablet

- The absorption is less affected by food or gastric pH
- Elimination : 77% in feces, 13 % in urine
- Steady stage : Liquid 7 days, tablet : 5 days
- T $\frac{1}{2}$ - liquid: 20-66 hrs, tablet: 26-31 hrs

POSACONAZOLE

SUSPENSION :
TDM is recommended

DELAYED RELEASE
TABLET : NOT CLEAR

TDM IF :

- malabsorption (mucositis)
- drug-drug interaction
- obesity
 - weight > 120 kg
 - in haematological patient : weight > 90kg or BMI > 30

Prophylaxis

- RCT : higher rates of break through infections if serum trough < 0.7mg/L
- logistic regression results, the clinical failure rate of >25% and >35% when serum trough < 700mcg/mL or 0.7mg/L

Treatment

- External controlled study : trough > 1250mcg/mL
- associated with better outcome (75% success rate)

Concentration-toxicity relationship

- No clear relationship between posaconazole exposure and treatment-related toxicity
- No upper limit

Jang et al. Clin.Pharmacol Ther 88(1):115-9, 2010
Walsh et al. CID, 44 (1): 2-12, 2007
Miseli et al. 2015;58(7):432-6.

ISAVUCONAZOL E

IV and oral

- Linear PK
- Good oral bioavailability: 97 % (oral)
- T_{1/2} : 130 hours
- Concentration –response or
Concentration-toxicity relationship : not
established
- GI side effect asso with prolonged
administration. Level > 5 mcg/mL
- Treatment trough goal: 2-5 mcg/mL



Isavuconazole Concentration in Real-World Practice: Consistency with Results from Clinical Trials

David Andes,^a Laura Kovanda,^b A. Desai,^b Therese Kitt,^b M. Zhao,^a Thomas J. Walsh^c

Antimicrob Agents Chemother. 2018 Jun 26;62(7):e00585-18.

The concentration distributions from real-world use and clinical trials were nearly identical (>1 g/ml in 90% of patients)

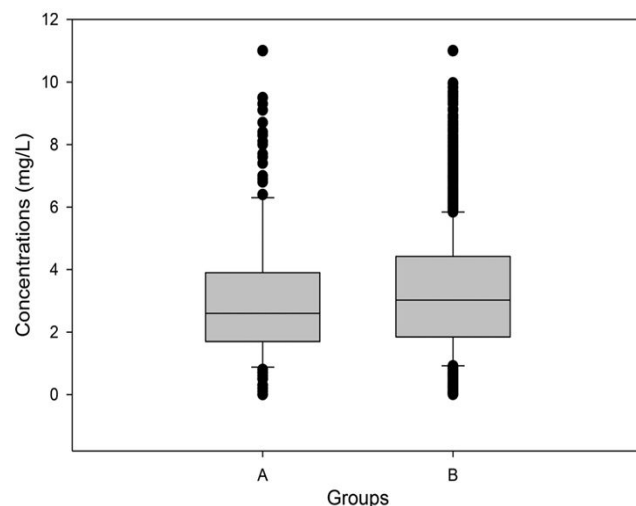


FIG 2 Box and whisker plot of clinical-use (A) and trial (B) isavuconazole concentrations.

Article

Population Pharmacokinetics and Pharmacodynamic Target Attainment of Isavuconazole against *Aspergillus fumigatus* and *Aspergillus flavus* in Adult Patients with Invasive Fungal Diseases: Should Therapeutic Drug Monitoring for Isavuconazole Be Considered as Mandatory as for the Other Mold-Active Azoles?

Pier Giorgio Cojutti^{1,2}, Alessia Canelutti³, Davide Lazzarotto⁴, Emanuela Sozio³, Anna Candoni⁴, Renato Fanin^{4,5}, Carlo Tascini^{3,5} and Federico Pea^{2,6,*}

Pharmaceutics 2021, 13, 2099

Retrospective cohort population PK/PD study :

The risk of $C_{trough} < 1.0$ mg/L was around 1%,

FLUCYTOSINE

ORAL

Obtain 2 hours post-dose within 72h after initiation or after 3 to 5 doses have been administered

25 - 100 mg/L

Peak and trough concentration : not significantly different

- Oral bioavailability : 76-89%
- Mainly eliminated by Kidney (> 90%)
- T $\frac{1}{2}$: 3-4 Hours
- Small molecule, not bound to protein
- Good penetration to CSF, Vitreous, inflamed joint
- No clear concentration-response relationship
- Concentration dependent toxicity (Peak >100 mg/L)
- Blood dyscrasias, hepatic injury, or GI disturbances
- Occurs with elevated levels for prolonged period (>2 weeks)

Vermes et al. J Antimicrob Chemother. 2000 Aug;46(2):171-9
Francis et al. CID,2007 15(6):1003-18



THANK YOU