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MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Antifungal TDM

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Disclosures

- The speaker declares no conflict of interest.

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Introduction

- Intra-individual variability in PK & PD of antifungals are important causes of treatment failure and toxicity
- TDM guided precision dosing helps to improve the safety and efficacy
- Antifungal drug (Azoles) interactions are contributing to treatment failure, morbidity and mortality

Lewis RE, Curr Opin Infect Dis. 2021 Aug 1;34(4):288-296.

Which drugs needs TDM

- **Antifungal Agent Properties**
  - With well- defined exposure-response relationship
  - Narrow therapeutic index
  - Substantial pharmacokinetic variability
  - Potential for genetic polymorphisms to impact clearance

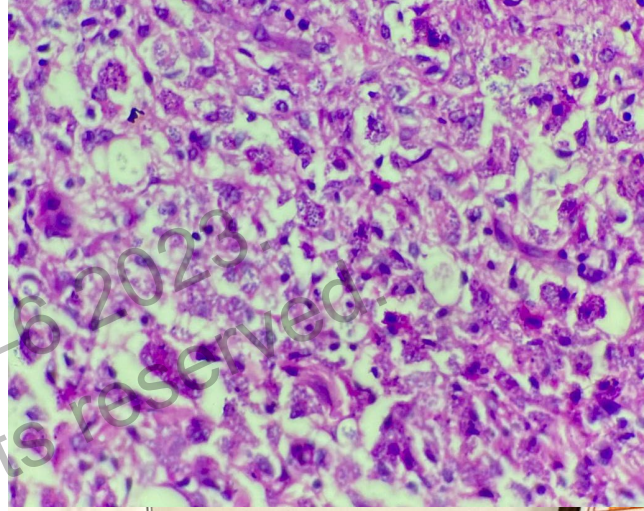
- **Patients' Clinical Scenarios:**
  - Hepatic or renal dysfunction
  - Extremes of age or weight
  - Patient adherence or absorption issue
  - Treatment of organisms with elevated MIC
  - Drug-drug interactions potentially impacting antifungal serum concentrations

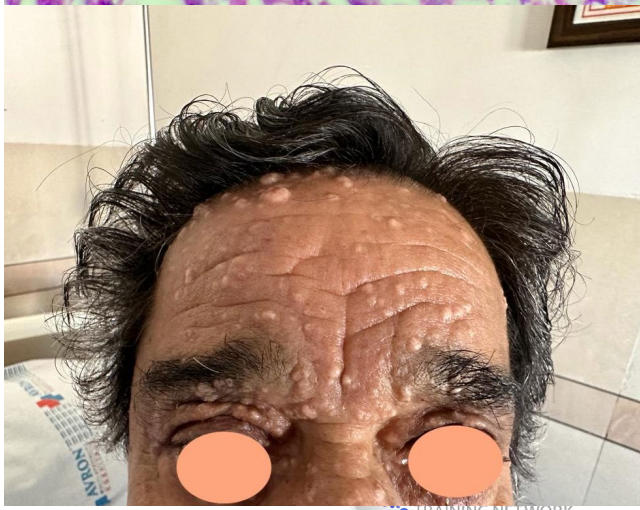
Jamie John, Expert Opinion on Drug Metabolism & Toxicology, 15:11, 881-895, S. Grau, S. Luque / Enferm Infecc Microbiol Clin. 2015;33(5):295–297

Case history

- 73/Male, residing at Banswara, Rajasthan, Farmer, No travel History, No comorbidities
- Well before 3 months
- Cough, Progressive weight loss (18 kg), weakness
- Difficulty in chewing for last two months
- Nodular skin lesions started from the forehead, rapidly progressive & involve entire forehead, face, limbs, back and right axillae for last 1 month
- Fever for last 10 days

- Physical exam:
  - Vitals: 104/58 (postural hypotension with 6 mm fall)
  - Multiple gums nodular lesions
  - Firm hepatosplenomegaly (Liver 5 fingers and spleen 4 fingers below the costal margin)
- Patient was worked up at other hospital with CT scan showing two small pleural based nodules rest unremarkable
- HIV/HBsAg Non-reactive
- Skin Biopsy:
- Referred to our clinic, Admitted and started with
- L-AmB 3 mg/kg/day along with Cap Itraconazole 200 mg TDS X 3 days followed by 200mg BID started





Itraconazole trough level after 7 days

	Day 8 ITR 200mg TDS X 3 days Followed by 200 mg BID	Day 12 ITR SUBA 300mg BID	Day 16 ITR SUBA 300mg BID	Posacon--azole	ITR SUBA 300mg TID
Itraconazole µg/ml	0.064	0.23	0.41		0.43
Hydroxyitraconazole µg/ml	0.19	0.21	0.47		1.0
Total µg/ml	0.13	0.44	0.88	< 0.25	1.43

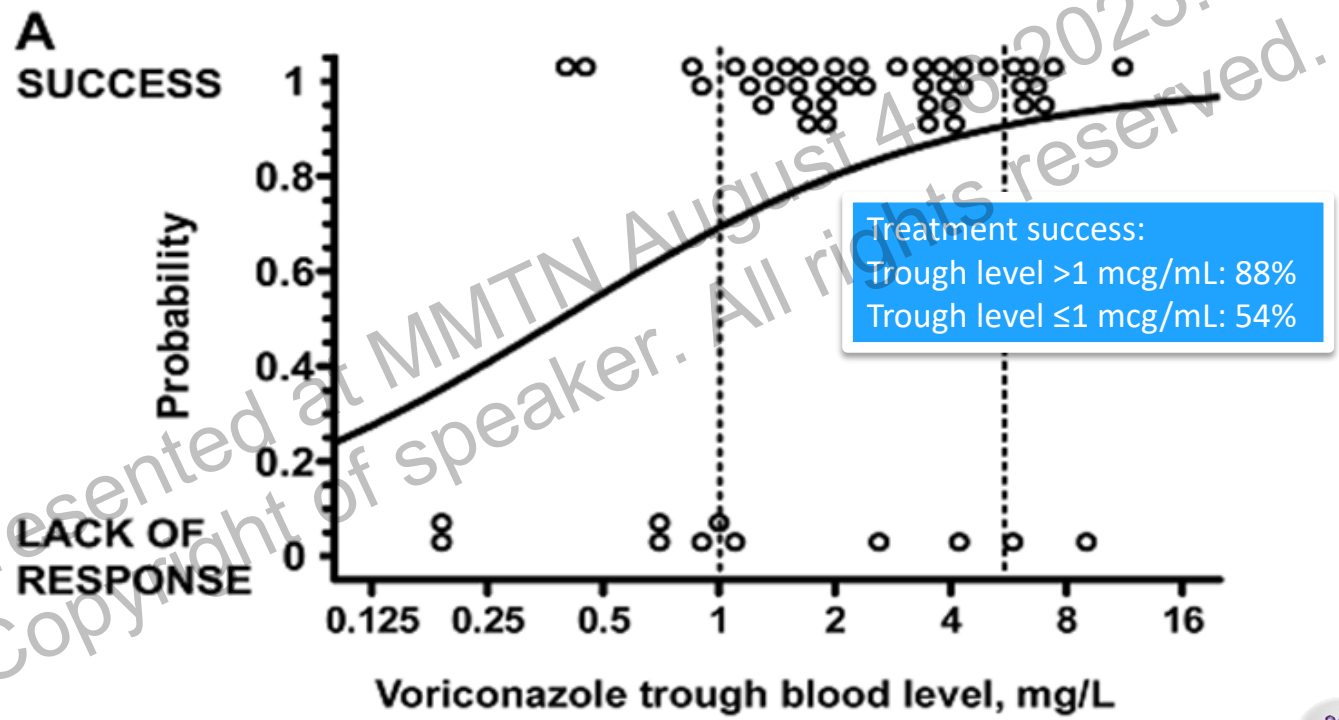
Patient completed 4 months on antifungal, gums lesions improved and started eating/chewing food, complete regressions in hepatosplenomegaly, marked reduction in skin nodules

Voriconazole

- Routine TDM of voriconazole is recommended
  - Significant interpatient pharmacokinetic variability
  - Non-linear PK in adults: Unpredictable drug exposure
  - Gastrointestinal absorption, drug-drug interactions
  - Genetic polymorphism CYP2C19: Voriconazole undergoes extensive hepatic metabolism, primarily mediated by CYP2C19 (CYP2C9, CYP3A4)
- AUC/MIC of >25 associated with clinical efficacy and patient survival against *Candida* and *Aspergillus* spp infection
- Patients receiving TDM had a significantly increased number of complete or partial responses (81% vs. 57%)
- The BSMM recommends a trough level >1 to <4–6 mcg/mL to maximize efficacy for IFIs, while minimizing toxicity

Matsumoto K, Int J Antimicrob Agents. 2009 Jul;34(1):91-4., Park WB. Clin Infect Dis. 2012 Oct;55(8):1080-7, Pascual A, Clin Infect Dis. 2008 Jan 15;46(2):201-11.

VCZ trough level and outcome



Pascual A el al. CID. 2008; 46:201-11

Posaconazole

- Need of posaconazole TDM is highly dependent upon the formulation
- **Posa suspension**: Saturable absorption leading to highly variable bioavailability and drug exposure
  - Bioavailability is affected by coadministration with food, gastric acidity and GI motility
- **Posa DR tablets, & intravenous formulation** has significant improved bioavailability and above factor doesn't influence
- Subtherapeutic posaconazole concentrations are associated with poor clinical outcomes
- **Higher posaconazole levels** than required for the treatment of Mucorales, *Scedosporium* and *Fusarium* spp. than treatment of IA
- Experts recommend a trough concentration of >1 mcg/mL for primary therapy and >1.25 mcg/ml for salvage therapy

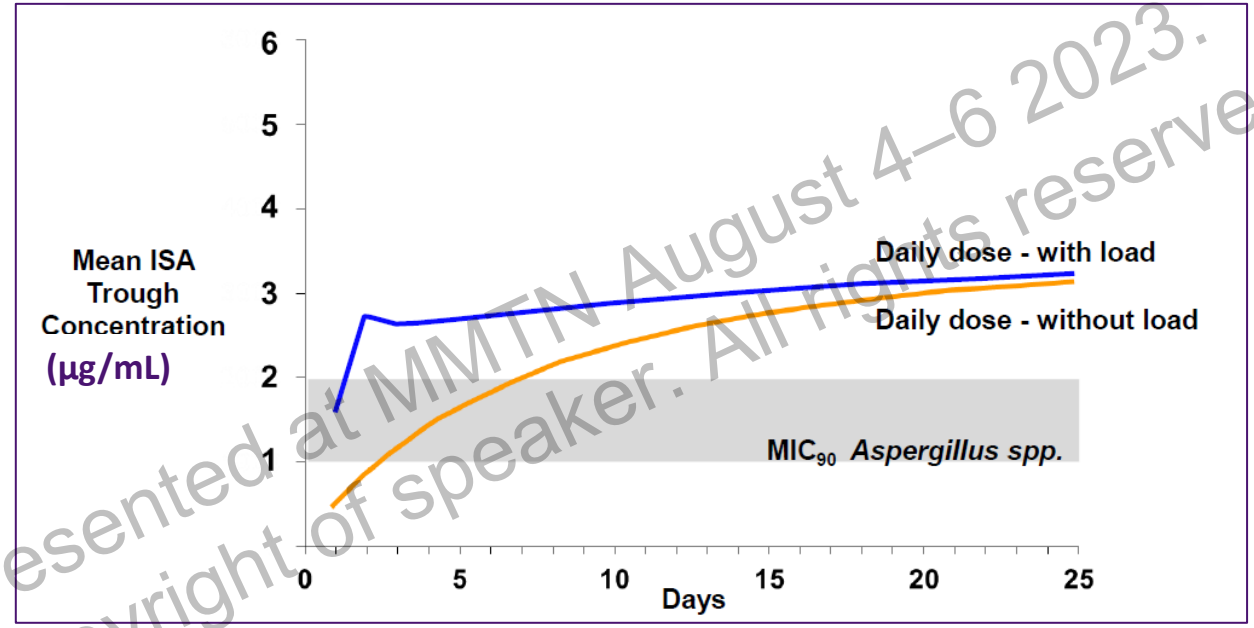
Kraft WK, Antimicrob Agents Chemother. 2014 Jul;58(7):4020-5., Krishna G, Antimicrob Agents Chemother. 2009 Mar;53(3):958-66, Dolton MJ, Antimicrob Agents Chemother. 2012 Jun;56(6):2806-13

Posaconazole extended-release tablet

Once daily administration
Can be consume regardless of food
Less interpatient PK variability than suspension
Achieves higher and more consistent plasma level
Absorption is not affected by gastric pH and motility
Better systemic availability and early steady state level

Kate McKeage Drugs (2015) 75:397–406

Isavuconazole – pharmacokinetics



- 200 mg IV or orally administered every 8 hours for a total of six doses
- Followed by a 200 mg once-daily IV or oral dose

ISA, isavuconazole; IV, intravenous; MIC90, minimum inhibitory concentration for 90% of isolates; spp., species

Figure adapted from: Advisory Committee Briefing Document, January 22, 2015. Astellas; Cresemba® Summary of Product Characteristics, 2018.

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CLINICAL THERAPEUTICS

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]

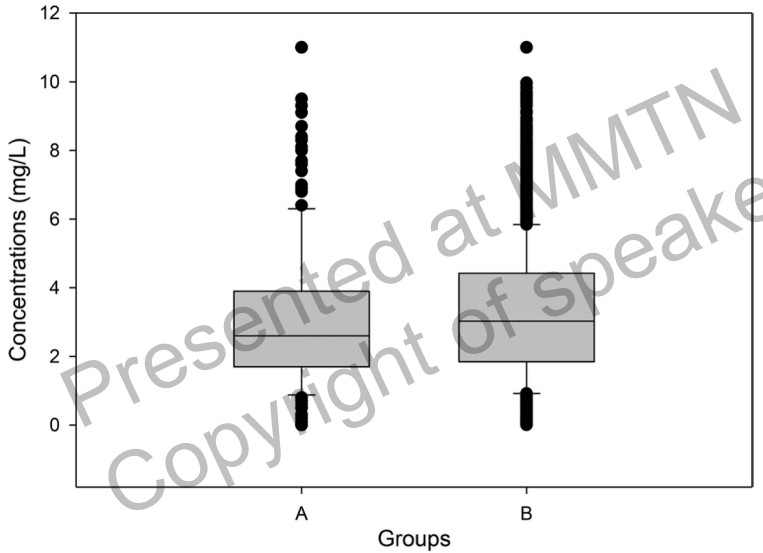

FIG 2 Box and whisker plot of clinical-use (A) and trial (B) isavuconazole concentrations.

Sample	Mean	Median	SD	Coefficient of variation
Real world: n= 283	2.98 µg/ml	2.6 µg/ml	1.91 µg/ml	64
Clinical trial: n= 2458	3.3 µg/ml	3.02 µg/ml	2.18 µg/ml	66

Mean concentrations in clinical use were statistically lower than those in trial patients (*P* =0.014)

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5 flucytosine (5-FC)

- 5-FC is primarily used in combination with amphotericin B for synergy and for prevention of development of 5-FC resistance
- Narrow Therapeutic Index (30–80 mg/L)
- Excretion: Kidney (90%)
  - Reduced 5-FC clearance with renal dysfunction
- Interpatient variability is attributed to **renal function**
- Drug concentration vs. toxicity
  - Concentration dependent toxicity (Peak >100 mg/L)
  - Blood dyscrasias, hepatic injury, or GI disturbances
  - Occurs with elevated levels for prolonged period (>2 weeks)
- 5-FC TDM is routinely performed in an effort to prevent these toxicities

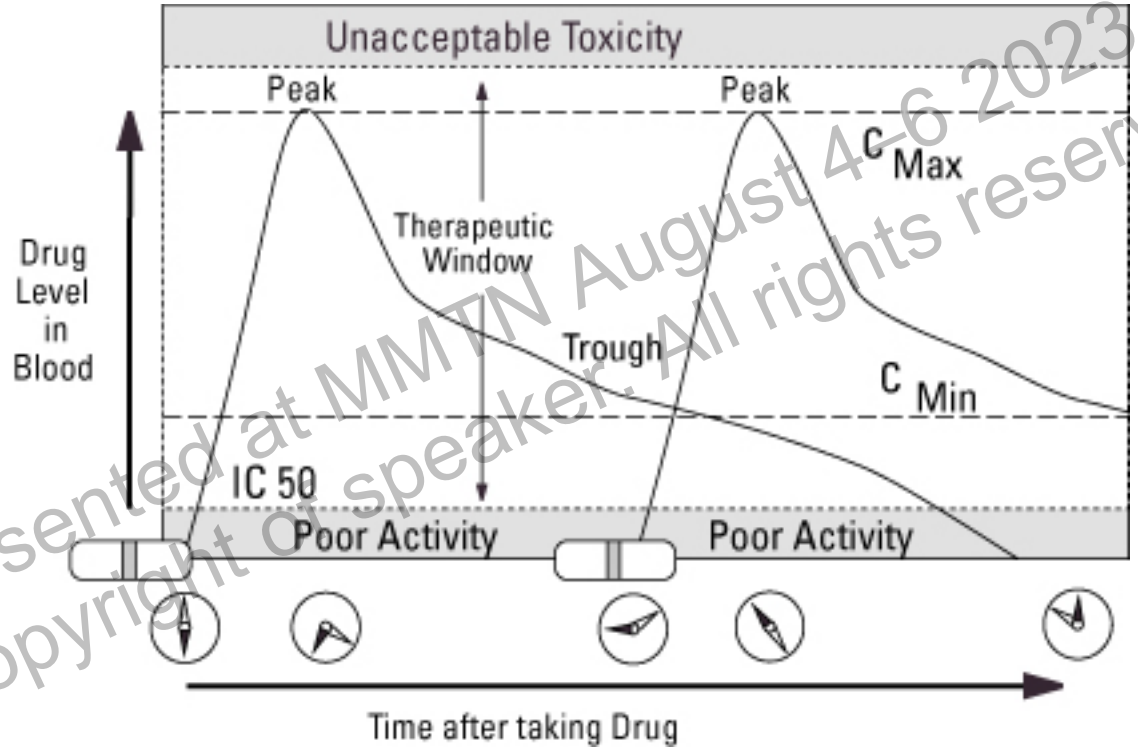
Andes D, Antimicrob Agents Chemother. 2009 Jan;53(1):24-34. Ashbee HR, J Antimicrob Chemother. 2014 May;69(5):1162-76.

TDM not necessary

- Amphotericin B
- Fluconazole
- Isavuconazole
- Echinocandins

John J, Expert Opin Drug Metab Toxicol. 2019 Nov;15(11):881-895.

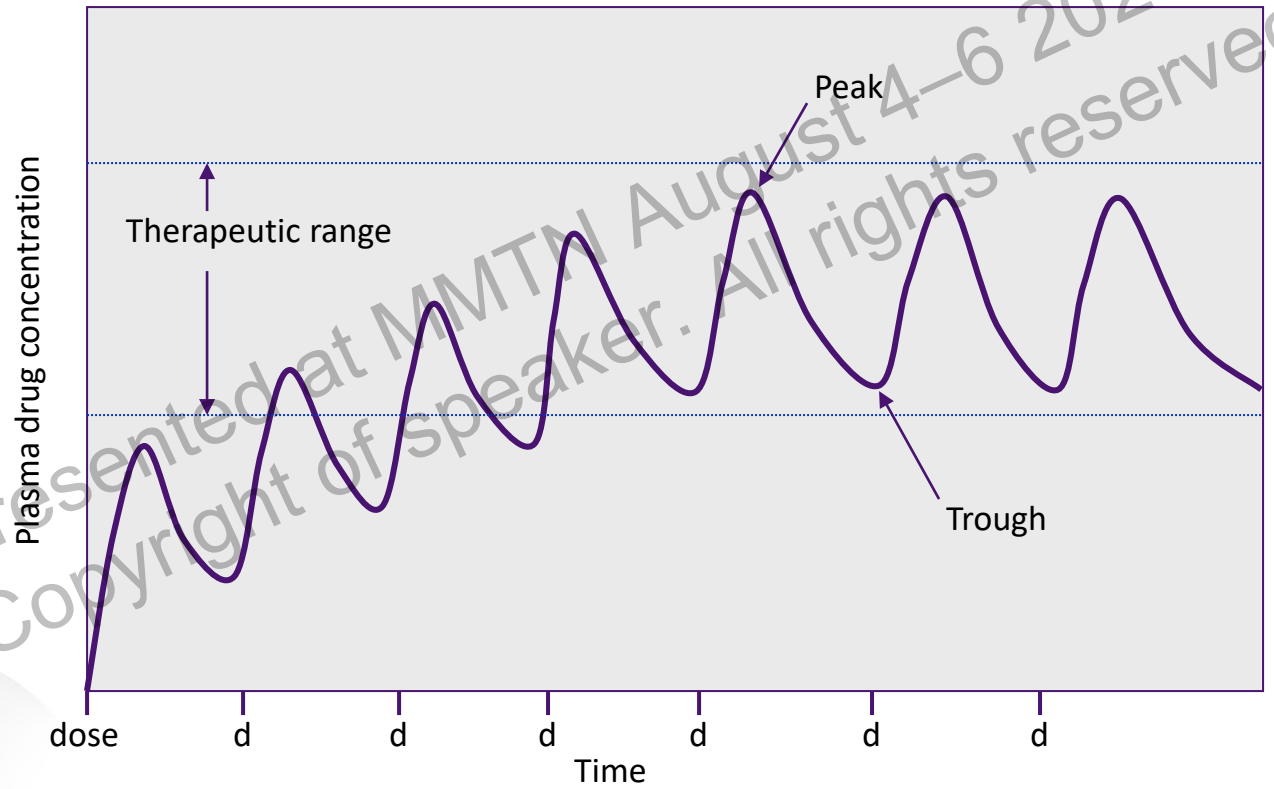
Timings of therapeutic drug monitoring



Courtesy The body.com

The Steady State

Shin-Woo Kim. Infect Chemother. 2008 May-Jun;40(3):133-139



TDM considerations of select antifungal Agents

Agent	Sampling timing (peaks, troughs)	Therapeutic goals (mcg/mL)	Dose-dependent adverse effects
Flucytosine	Peak: 3–5 days	Treatment: 40–60	>100 mcg/mL: Myelosuppression and hepatotoxicity
Itraconazole	Trough: 5–7 days (if received loading doses) or 10–14 days without loading doses	Treatment: 1–2	Gastrointestinal
*Voriconazole	Trough: 5–7 days	Treatment: 1–6	Trough >6 mcg/mL: Visual hallucinations, hepatotoxicity, and neurotoxicity
*Posaconazole	Trough: ≥7 days	Prophylaxis: >0.7 Treatment: >1	NA

*In critically ill patients, voriconazole and posaconazole levels may be obtained in the first 3 days

John J, Expert Opin Drug Metab Toxicol. 2019 Nov;15(11):881-895.

Take home message

- Pragmatic approach for antifungal TDM
- TDM helps in individualizing antifungal therapy, associated with improved clinical outcome and reduced toxicities
- TDM will be useful in certain difficult to treat situation
  - Site of fungal Infection (CNS)
  - Fungal pathogen (Mucorales, *Scedosporium*, *Fusarium* species)
  - Antifungal susceptibility (Resistant fungi, higher MIC)
  - Other factors potentially affect PK parameters (Drug interactions, absorption, liver/kidney disease, obesity)

Thank you