Optimising TDM in Asia: The Way Forward

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Therapeutic drug monitoring (TDM)

- Target drug concentration at the site : not feasible to measure drug concentration at the site of action

- Measurement of antifungal concentrations in the plasma or blood concentrations serves as a valuable surrogate of drug exposure

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

Lepak AJ, Andes DR. Antifungal pharmacokinetics and pharmacodynamics. Cold Spring Harb Perspect Med. 2014 Nov 10;5(5):a019653

PK/PD target : AUC/MIC

- Varies in between different types of fungus
- Varies between the species of the fungus
- Depends on the indications (Treatment vs Prophylaxis)

Minimum inhibitory concentration (MIC):
the lowest anti-fungal concentration that completely inhibits the visible growth of fungus

Candidate drugs for TDM

- large interindividual variability in pharmacokinetics
- Good concentration-efficacy relationship or concentration-toxicity relationship
- Tested in clinical trial to validate the concentration-efficacy/toxicity relationship
- A Target range has been defined

(Ideally a prospective randomized controlled clinical trials should be performed to validate proposed target values and the clinical utility of TDM)

	Prophylaxis	Treatment	Toxicity
Voriconazole	> 1mg/L	>1mg/L > 2mg/L CNS infection, bulky disease, multifocal infection **Trough:MIC ratio = 2 – 5 *** (MIC estimated using CLSI guidelines)	4-6 Neuro toxicity > 5 Asian : Hepatotoxicity > 3.0 Neuro toxicity > 4
Itraconazole +Hydroxyitra	> 0.5 mg/L	> 1.5 mg/L	Not established < 3 – 4 mg/L
Posaconazole	0.7 mg/L	> 1 – 1.5 mg/L	Not established Trough or Cmin < 3 – 3.75 mg/L
Isavuconazole		Not established, recommendation: Trough ≥ 1 – 2 mg/L	Trough or Cmin < 4.6 – 5.1 mg/L

*Trough /MIC ratio and clinical response :
Probability of clinical response increase with a higher Trough/MIC of > 2

Troke et al. Antimicrob Agents Chemother 2011;55:4782-8
TDM of antifungal agents form British Society for medical Mycology (Ashbee et al. J Antimicrob Chemother 2014;29: 1162-76)
IDSA Guidelines for diagnosis and management of aspergillosis 2016 (Pappas PG, et al. Clin Infect Dis 2016;62:e1-50.)
McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.
Gómez-López A. Clin Microbiol Infect. 2020;26(11):1481-7.
McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.

METHOD	ADVANTAGES	DISADVANTAGES
Bioassay	Inexpensive; easy to operate; commercially available	Interference because of drug-drug interactions; difficulty distinguishing the activity of some drugs from metabolites (e.g., itraconazole)
HPLC	Commercially available; multiplexed measurement; high chromatographic resolution	Interference from many substances; more time for running sample; complex sample preparation; limited specificity
LC-MS/MS	High sensitivity and specificity; small sample requirements; minimal sample preparation; rapid assay; multiplexed measurement; cost-effective	Expensive initial cost; not widely available; requires experienced personnel

Low Rates of Antifungal Therapeutic Drug Monitoring Among Inpatients Who Received Itraconazole, Posaconazole, or Voriconazole, United States, 2019–2021

- TDM was performed during 15.8% of hospitalizations at 50 hospitals (TDM uncommonly performed)
- 10/50 of those hospitals contributed 68% of the hospitalizations in which TDM was performed
- TDM use was 28.6% for itraconazole, 5.7% for posaconazole, and 17.9% for voriconazole.
- itraconazole + hydroxyitraconazole TDM: 36.2% had the first result was <1.0 µg/mL
- voriconazole TDM: 20.9% had a first result <1.0 µg/mL and 16.2% had a first result of >5.5 µg/mL.
- posaconazole TDM: 28.0% had a first result of ≤1 µg/ mL.

Benedict et al.Open Forum Infect Dis. 2023 Jul 20;10(8):ofad389. doi: 10.1093/ofid/ofad389.

The emerging Infections Network survey by CDC and IDSA : Antifungal TDM practices

Online survey to infectious disease physicians and other health care professionals in North America

- 91 % are Infectious disease Physician
- 73% are from university or teaching hospital

AF as Prophylaxis	AF as treatment
65% reported TDM for Voriconazole	90% reported TDM for Voriconazole
55% for Posaconazole	72 % for Posaconazole
32% for Itraconazole	72% for Itraconazole
27% for Isavuconazole	40% for Isavuconazle
3% for Fluconazole	10% for fluconazole

Beneditc et al. Open Forum Infect Dis, 10(9) 2023:ofad468

Barrier to AF TDM practice

Long turn around time (74%) : outsourcing
Difficulties in coordinating testing logistics (48%)
Uncertainty about TDM recommendations (39%)
Difficulty in interpretation of results (28%)
Uncertainty about TDM benefits (18%)
Costs (14%)
Challenges with insurance coverage (11%)

Therapeutic drug monitoring practices of anti-infectives: An Asia-wide cross-sectional survey

Jingjing Hou[1,2], Debbie Marriott[3], Dario Cattaneo[4],

IATDMCT society

Respondents

- 10 countries
- 60% are pharmacists

TABLE 1 Number of respondents by country.

Country	n (N = 150[a])	%
China	54	36.0
India	31	20.7
Indonesia	7	4.7
Japan	4	2.7
Kuwait	1	0.7
Malaysia	41	27.3
Nepal	1	0.7
Singapore	5	3.3
Thailand	2	1.3
Vietnam	4	2.7

Frontier in Pharmacology . DOI 10.3389/fphar.2022.992354

The TDM available for anti-infective agents

Antibiotic TDM

- 15.3 % : No TDM service for any anti-infectives

- 71.3% : Glycopeptides, 46.7% : aminoglycosides

AntiFungal TDM

- 53.3% : No Antifungal TDM

- 40.0 % Voriconazole
- 13.3% Posaconazole

Quantitative testing for anti-infectives TDM performed by

	%
Pharmacy laboratory	38.8
Clinical pharmacology laboratory	28.1
Analytical chemical laboratory	24.0
Pharmacology or microbiology laboratory	5.8
University, private laboratory or other third party	3.3

Interpretation of TDM results

	%
Clinical pharmacist	86.8
Clinician	50.4
Laboratory staff	18.2
Microbiologist and other health professionals	5.0

Methods used for TDM

	%		%
HPLC	39.3	Chemiluminescence immunoassay	24.0
HPLC/MS-MS or LC/MS-MS	36	Fluorescence polarization immunoassay	14.0
HPLC-UV or LC -UV	9.3	Enzyme linked immunosorbent assay	9.3
Ultra performance liquid chromatography	8.0	Enzyme Immunoassay	1.4
gas chromatography.	2.0		

Stumbling block to TDM practice

- ‘Lack of funding or equipment’ for implementing TDM (71.1%)
- ‘lack of interest or “lack of cooperation from clinicians’ (47.0%)
- ‘lack of TDM expertise’ (42.3%)

WHY TDM ?

- Itraconazole and posaconazole, exhibit great interpatient pharmacokinetic variability related to absorption.

Capsule itraconazole (C-ITZ) exhibits inconsistent absorption profiles leading to variability in pharmacokinetics

Bioavailability 50-60% , requires acidic gastric environment for dissolution and adequate absorption

Suspension Itraconazole : the absorption is not pH dependent

SUBA Itraconazole : dissolution and absorption in duodenum

The lower SUBA itraconazole trough concentration observed in HSCT or hematology malignancy with lower gastrointestinal symptoms

Neid et al. J Antimicrob Chemother 2019; 74: 3049–3055

Posaconazole

Suspension Posaconazole

- The bioavailability is highly variable, high inter-individual variability
- The absorption is significantly increased when administered with a meal (high fat), and low gastric pH
- Increased gastric motility reduce POS level in blood
- Absorption is satiable (≥ 800mg per day)

Posaconazole Delayed-Release tablet

- The bioavailability 54% , still shows substantial interpatient variability
- POSA Tablet is released in small intestine, the absorption is only moderately affected by food.
- The posaconazole exposure increased by 1.5-fold (Tablet) compared to a 4-fold increase in exposure (suspension) when administered with a high-fat meal

Dekker et al. Curr Fungal Infect Rep (2016) 10:51–61
Lipp etl al. Br J Clin Pharmacol. 2010 Oct;70(4):471-80.
Chen et al. Drugs (2020) 80:671–695

Proton pump inhibitor and Itraconazole

PPI	Itraconazole formulation	Serum Itraconazole concentration	
		AUC	Cmax
PPI	Capsule Itraconazole	↓ 62 %	↓64%
PPI	Suspension Itraconazole	↔ Itraconazole or OH-Itra	
PPI	SUBA Itraconazole	↑ 22%	↑31 %

Jaruratanasirikul S et al. Eur J Clin Pharmacol. 1998 Apr;54(2):159-61
Johnson et al. J Antimicrob Chemother 51:453–457
Lindsay et a;. Antimicrob Agents Chemother. 2018 .26;62(12):e01723-18.
Van Peer et al, Eur J Clin Pharmacol 1989:36:423-6.
Willems et al.Journal of Clinical Pharmacy and Therapeutics (2001) 26, 159±169" 2001
Spec et al. *Open Forum Infectious Diseases*, 11(3) 2024
. Rauseo et al. . Antimicrob Agents Chemother . 202165:e00134-21
Thompson III GR et al Antimicrob Agents Chemother. 2020;64(8):e00400-20.
Linsay et al. Antimicrob Agents Chemother. 2018 Nov 26;62(12):e01723-18

PPI and Posaconazole

- Suspension Posaconazole : PPI causing higher gastric pH, decreased the posaconazole C(max) and AUC by 46% and 32%, respectively.
- DR posaconazole Tablet : PPI does not significantly affect DRT POSA concentrations
- **Co-administration of proton pump inhibitors and posaconazole delayed-released tablets in adult patients with haematological malignancies:** were significantly associated with decreased C_{min} POSA ($P = 0.008$)
- Reduced absorption and serum POS concentration in patient with severe mucositis

Krishna et al . Antimicrob Agents Chemother. 2009 Mar;53(3):958-66
Qu et al . Front. Pharmacol. 15:1450120. 2024. doi: 10.3389/fphar.2024.1450120
Jansen et al. / Clinical Microbiology and Infection 28 (2022) 1003e1009

Voriconazole (VOR)

- Voriconazole has linear pharmacokinetics in children but exhibits nonlinear pharmacokinetics in adults.
- Voriconazole clearance is more rapid and unpredictable in children due to a three to five higher rate of CYP2C19 metabolism and enhanced activity of flavin-containing monooxygenase 3

- The non-linear kinetics in adults due to :

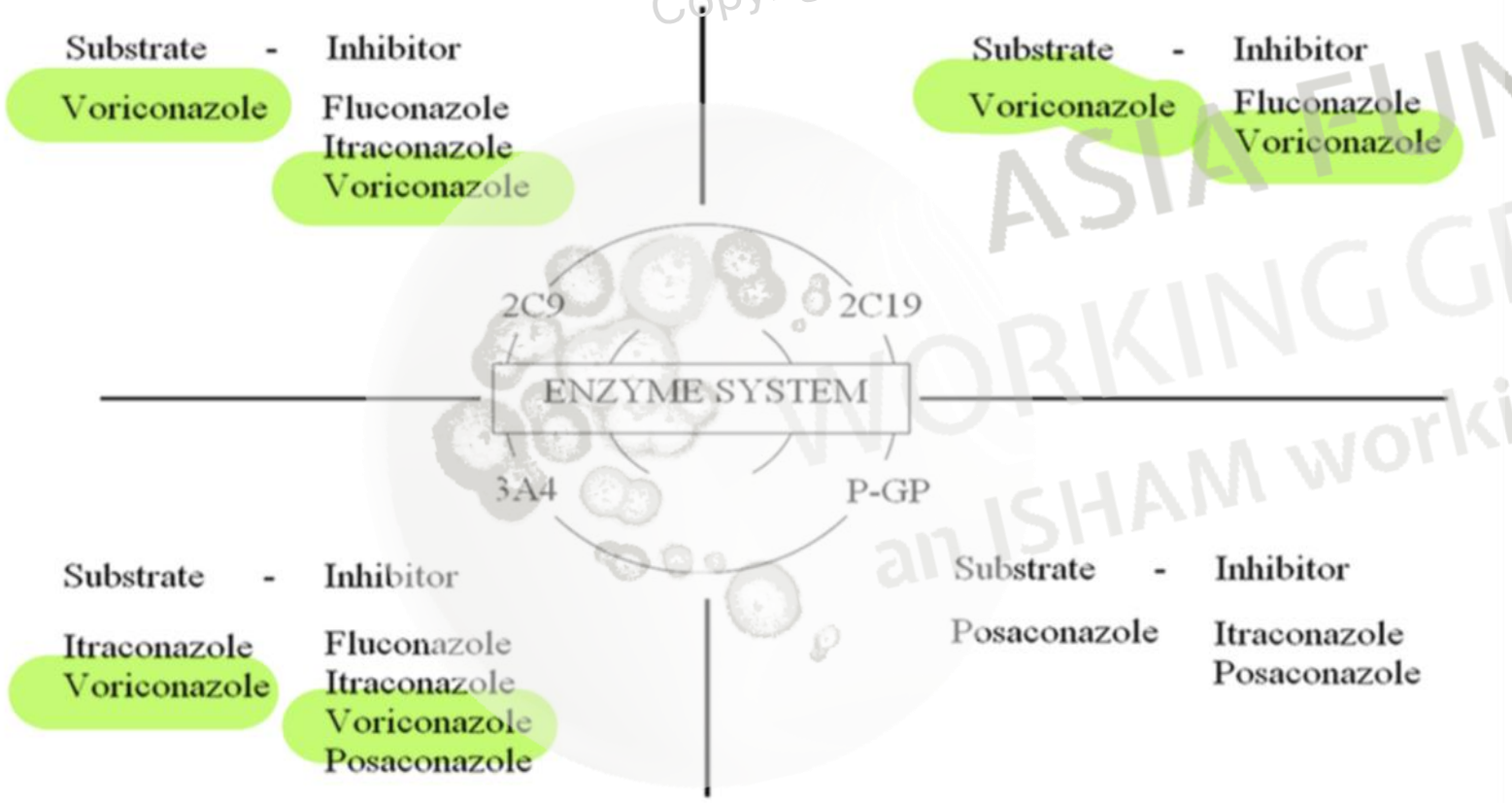
a) Voriconazole is a substrate and inhibitor of CYP3A4 and CYP2C19 and thus an autoinhibitor of its own metabolism.

b) saturable metabolism

- At standard doses, VCZ exhibits both **inter- and intra-patient PK** variabilities

Resztak et al. European Journal of Clinical Pharmacology (2024) 80:1829–1840

Drug-drug interaction



- Interacting drugs should be avoided, it can lead to either overdosing or underdosing of both drugs
- **Co-administered with CYP inducers** (rifampin, rifabutin and phenytoin) may lower plasma concentrations of azoles

Bru¨ggemann et al. CID 2009; 48:1441–58

1) Breakthrough IFI while on POSA prophylaxis (haematology patients)

Multicenter-retrospective (Dolton et al 2012) :

- 17% with breakthrough IFI with serum Posa concentration lower than patient without breakthrough IFI (median 289 vs 485ng/ml, P<0.01)

Observational study in AML patients (Cattaneo et al, 2015)

- More patients with median Posa level < 500ng/ml developed breakthrough IFI comparing with patients with level ≥500ng/ml (10%vs 2.7% , p=0.19)

Analysis of the drug exposure-response based on two randomized controlled clinical studies (Jang et al 2010):

- Mean POSA level 289, 736, 1239, 2607 ng/ml coincides with the failure of prophylaxis : 44%, 21%, 18%, 18 % respectively

Dolton et al. Antimicrob. Agents Chemother. 2012, 56, 5503–5510.
Jang, S.H et al Cin. Pharmacol. Ther. 2010, 88, 115–119
Cattaneo, et al. Mycoses 2015, 58, 362–367

Break through IFI while on VOR prophylaxis (transplant recipients)

Prospective observational study of VOR as prophylaxis in lung transplant recipients (Mitsani et al 2012)

- IFI or fungal colonization were more likely when serum VOR is < 1.5ug/ml than patients with trough ≥ 1.5ug/ml (P=0.01)

Observational study : Voriconazole prophylaxis in allogenic HSCT (Trifilio et al 2007)

- Breakthrough invasive candidiasis seen in 14% of pstients with vori ≤ 2ug/ml , None when level > 2 ug/ml (P=0.061)
- 4 cases of breakthrough mucormycosis

Mitsani et al. Antimicrob. Agents Chemother. 2012, 56, 2371–2377
Trifilio, S. et al. Bone Marrow Transplant. 2007, 40, 451–456.

Treatment response

Retrospective observational study : Logistic regression analysis

Treatment response : POSA Cmin >1.0 μg/mL was associated with a >80% probability of successful treatment response

- The incidence of treatment failure in patients with C_{min} <1.0 μg/mL was 36.4%, only 12.5% (2 IFIs in 16 patients) in patients who attained C_{min} ≥ 1.0 μg/mL.

Open-label, multicenter study in patients with invasive aspergillosis and other mycoses who were refractory to or intolerant of conventional antifungal

- higher plasma POS concentrations (> 1250 ng/ml) were associated with higher response rates.

The plasma concentration is closely associated with therapeutic efficacy

Jia et al. Front Pharmacol. 2020 Oct 8;11:575463
Walsh et al. Clinical Infectious Diseases 2007; 44:2–12

The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections: A Randomized Controlled Trial

Blood drawn on the fourth day after the initiation of voriconazole for TDM

Baseline characteristics including the CYP2C19 genotype were comparable between the two groups

- N= 55 in each arms
- 77% were haematological disorder, 40% were neutropenic
- Voriconazole was discontinued due to adverse events :
  Less patients in TDM group (4%) vs non-TDM (17%) (P=0.02)
- A complete or partial response was observed (probable or proven IFI)
  in 86% of patients in the TDM group vs 57% in the non-TDM group (P = 0.04).

ParK et al.Clinical Infectious Diseases 2012;55(8):1080–7

Voriconazole therapeutic drug monitoring: results of a prematurely discontinued randomized multicenter trial

Neofytos et al. Transpl Infect Dis. 2015 ; 17(6): 831–837

- Prospective, randomized, non-blinded multicenter study to compare clinical outcomes in adult patients randomized to standard dosing (n=15, clinician-driven) vs. TDM (n=14, doses adjusted based on levels).
- Clinical responses were assessed at day 42 after study enrollment.

- **Failed clinical responses**
  33.3% standard-arm vs 7.1% TDM-arm; (P = 0.17)
- **Successful treatment outcome** (stable, partial, or complete responses):
  46.7% standard-arm and 85.7% TDM-arm recipients;(**P = 0.05**).

Voriconazole therapeutic drug monitoring: results of a prematurely discontinued randomized multicenter trial

Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole for invasive aspergillosis in haematological patients: a multicentre, prospective, cluster randomised, crossover clinical trial☆

Haematological malignancy or an allogeneic stem cell transplant, diagnosed with **possible**, probable or proven IA (80% were neutropenic)

Voriconazole trough sample was collected around Day 3 after treatment initiation and twice weekly N= 83 (TDM), N= 87 (non-TDM)

- Median initial trough level : TDM group 3.8 mg/L and non-TDM group 3.9 mg/L; ($P = 0.614$)
- 80.6% of all patients with the initial voriconazole concentration was within the therapeutic range (1–6 mg/L)
- 3.9% of the patients had a trough concentration < 1 mg/L.
- Treatment response 28 ±10 days, Mortality within 28 days, treatment discontinuation due to an ADR : NOT significantly different between the TDM and non-TDM group:

Anette Veringa et al. International Journal of Antimicrobial Agents 61 (2023) 106711

Clinical Infectious Diseases
MAJOR ARTICLE

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

CID 2020:71 (15 September)

Possible

One host criterion
and
one clinical criterion
BUT
No microbiological evidence

Probable

One host criterion
and
one clinical criterion
AND
microbiological evidence

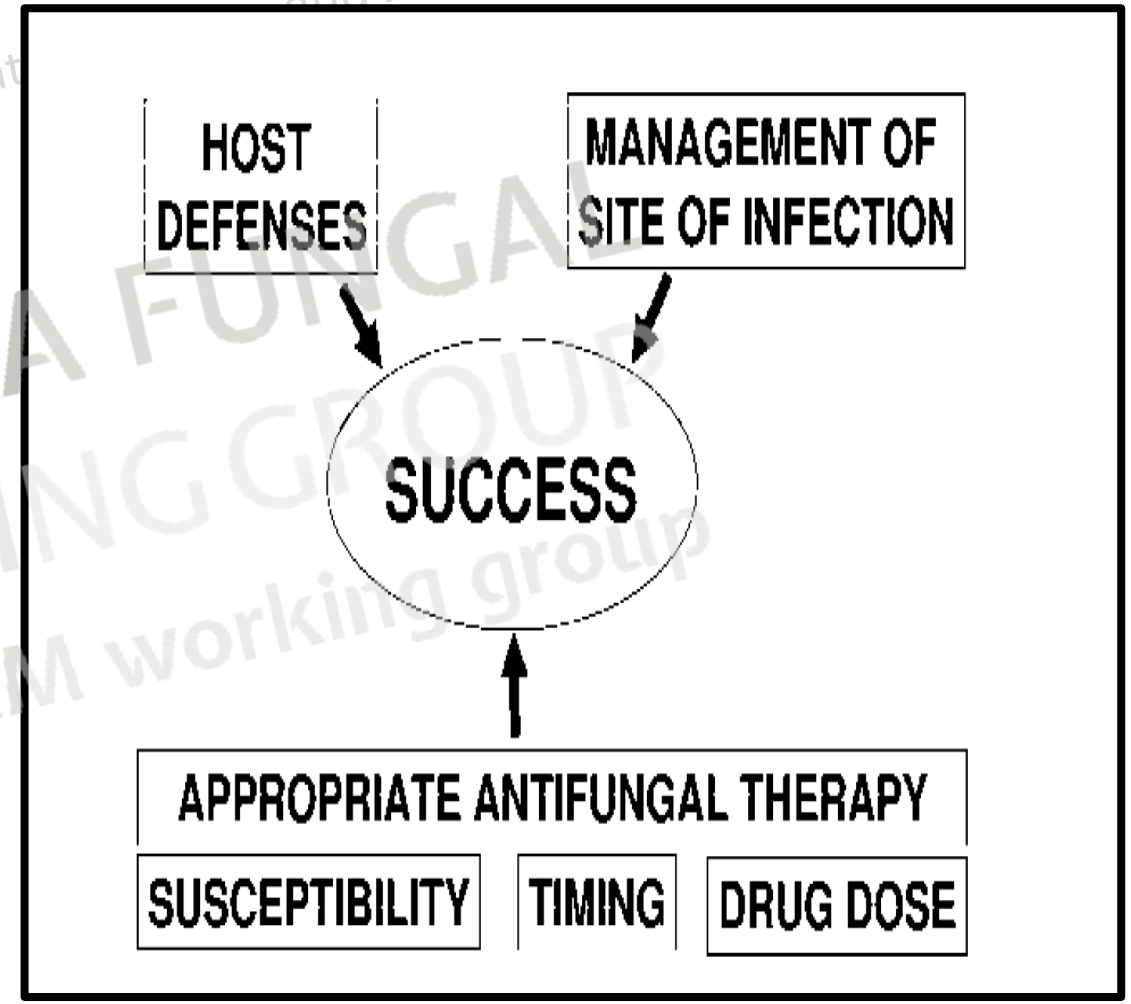
Proven

Histo/cytopathologic/ microscopic evidence or positive culture from sterile sites

- Veringa et al (2023) : 40–50% of patients had a possible IA.
- In contrast , Park et al (2012) ; 12 % of patients with possible IA, MAINLY probable and Proven IA
- 30% failed other antifungal therapy

- Veringa et al (2023) : individualised voriconazole treatment by routinely using TDM did not result in improved outcome in adult patients with IA

- TDM of voriconazole remains valuable in patients who failed on previous antifungal treatment or in patients with a more severe IFI



Andes et al. Antimicrobial agents and chemotherapy, . 2009, 24–34

Trough concentration and outcome relationship

Breakthrough fungal infections

Poor clinical response

? Emergence of antifungal resistance

Emergence of Flu-resistant *Candida spp following prolonged exposure*

In vivo study :Prolonged subtherapeutic Flu dosing regimens were associated with the emergence of azole-resistance C albicans. The MIC increased up to 16-fold from the 0.5-µg/ml

Flu-resistant *Candida* species were identified in the oral flora of fluconazole-exposed HIV-positive patients, no resistance was detected among the patients who were fluconazole-naïve (($p < 0.01$)

Recurrent Vulvovaginal Candidiasis among Iranian women : Fluconazole – resistant C*andida* spp arises following the exposure to azole therapy .

Andes et al. Antimicrob Agents Chemother. 2006;50(7):2384-94
Keith et al. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics, Volume 85, Issue 5, 558 – 564
Arastehfar et al.Front. Microbiol., 2021, 12 . https://doi.org/10.3389/fmicb.2021.655069

Azole resistant *Aspergillus* spp

- Azole resistance is an emerging problem for *Aspergillus* species
- Acquired resistance may be developed in patients on long-term azole exposure.
- In patients with ABPA (Allergic Bronchopulmonary Aspergillosis : prolonged exposure to subtherapeutic AF concentration, a potential trigger to the development of azole resistance

A retrospective 'real-world' cohort study of azole therapeutic drug monitoring and evolution of antifungal resistance in cystic fibrosis

A high prevalence of chronic subtherapeutic azole dosing was seen with voriconazole (60.8%) and itraconazole capsule (59.6%) use

- 21.4% probability of CF patients developing azole resistant Aspergillus isolate after 2 years
- No correlation between Subtherapeutic Drug level and resistance development

Wiederhold N et al. Semin Respir Crit Care Med. 2015;36:673–80
Howard et al. Clin Microbiol Infect 16:683-688, 2010
Paolo et al, JAC Antimicorb Resist 2021 16:3(1):dlab026.

Factors contributing to anti-fungal resistance

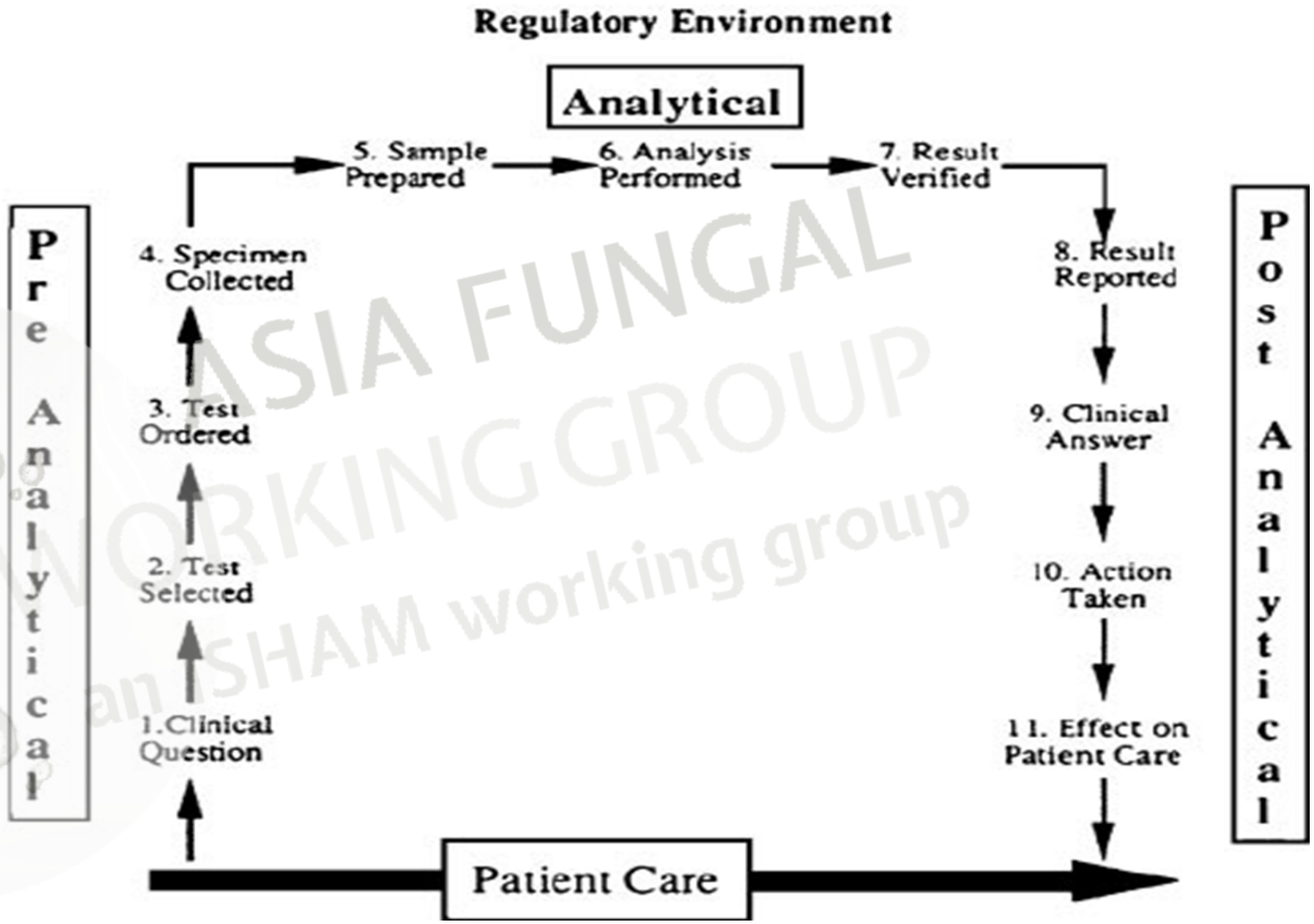
Environmental

Host (immunocompromised vs immunocompetent)

Fungus (Species and MIC)

Antifungal agent and TDM

Who to perform
and
Who to interpret



Schumacher GE, Barr JT. Clin Chem. 1998;44(2):370–4.

Microbiology lab

- Identification of fungus
- MIC

Targets are pathogen-specific: Recommendations discussed earlier apply mostly *to Candida, Aspergillus* MIC breakpoints not well established for other fungal species

Pre-analytical

Clinical Pharmacist:

Indication for TDM

DDI

Timing for sample collection

Analytical

Analytic biochemical lab :

Quantifying serum/ plasma drug concentrations

Post-analytical

Physician, pediatrician and clinical pharmacist

Dose optimization based on TDM

ORIGINAL

Are contemporary antifungal doses sufficient for critically ill patients? Outcomes from an international, multicenter pharmacokinetics study for Screening Antifungal Exposure in Intensive Care Units—the SAFE-ICU study

Jason A. Roberts[1,2,3,4*], Fekade B. Sime[1], Jeffrey Lipman[1,4,5], María Patricia Hernández-Mitre[1],

- prospective, open-label, multicenter pharmacokinetic study, intensive care unit (ICU)
- median APACHE II score 22 (IQR, 17–28)
- The most common indication for treatment was intra-abdominal infection (30.7%)
- low target attainment was noted for voriconazole (57.1%), posaconazole (63.2%), micafungin (64.1%) and amphotericin B (41.7%).

Intensive Care Med (2025) 51:302–317

Antifungal TDM in sub-group of population

FLUCONAZOLE	ISAVUCONAZOLE	ECHINOCANDIN
Critically ill (augmented renal clearance) On Renal replacement therapy Yeast with a high MIC Target not determined AUC/MIC > 100	- critically ill - ECMO - RRT patients - high BMI - Drug-drug interaction Target not determined 2.0 mg/L and < 5.0 mg/L.	- Critically ill patients in ICU - Obesity - ECMO - Suspecting drug-drug interaction - *Candida* spp with high MIC - Drug-drug interaction (caspofungin) Target not determiend

Märtson et alJ. Fungi 2022, 8, 18. https://doi.org/10.3390/jof8010018
Ashbee et al. J Antimicrob Chemother 2014;29: 1162-76
Gomez-Lopez et al. Clinical Microbiology and Infection 26 (2020) 1481e1487
Kim et al. Ther Drug Monit 2022;44:198–214
MärtsonJ. Fungi 2022, 8, 18. https://doi.org/10.3390/jof8010018
Tan et al, International Journal of Antimicrobial Agents, 2025, https://doi.org/10.1016/j.ijantimicag.2025.107619

Pick the low-hanging fruits

Convince your team then the stakeholder

TDM is needed in clinical practice

TDM aims to achieve better clinical outcomes

ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Co-organized with:

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

THANK YOU

- Use what you have.
- Do what you can.