

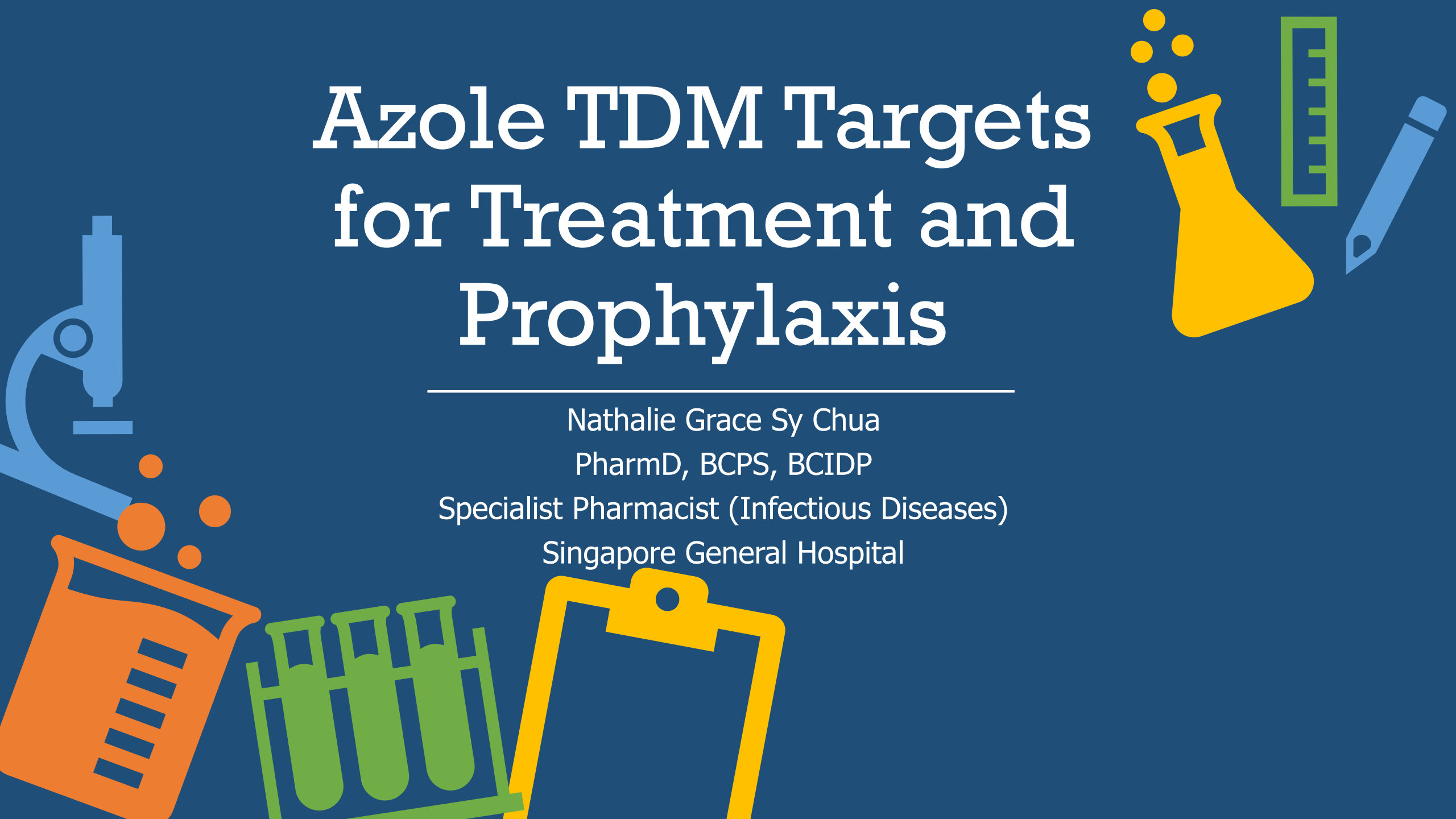
Azole TDM Targets for Treatment and Prophylaxis

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- No financial disclosures
- No conflict of interests



Objectives

- What influences therapeutic targets?
- Common reference ranges for azoles
- Caveats/Limitations



What Influences Therapeutic Targets

Remember the 3 "P"s

Pathogen

Pharmacokinetics

Pharmacodynamics



What Influences Therapeutic Targets (continued)

Other factors to consider

Indication

Site of Infection

Evidence



The Evidence

Table 2. Overall summary of the need for therapeutic drug monitoring when using antifungal agents (see individual tables for detailed recommendations in specific indications)

Antifungal	GRADE quality of evidence and strength of recommendation ⁵	Prophylaxis	Treatment	Toxicity	s
Itraconazole	evidence quality recommendation	moderate strong	moderate strong	moderate weak	
Voriconazole	evidence quality recommendation	low weak	high strong	high strong	
Posaconazole	evidence quality recommendation	moderate strong	moderate strong	high strong against	
Fluconazole	evidence quality recommendation	high strong against	high strong against	high strong against	
Flucytosine	evidence quality recommendation	NA	low weak	moderate strong	
Echinocandins	evidence quality recommendation	high strong against	high strong against	high strong against	
Polyenes	evidence quality recommendation	high strong against	high strong against	high strong against	



Voriconazole

- **Target for Efficacy (Treatment):**
 - **Trough or Cmin**

Fungi	Infectious Diseases Society of America	British Society of Medical Mycology
Candida	> 1 mg/L (> 2 mg/L if ocular infection)	> 1 mg/L > 2 mg/L for disease with poor prognosis (CNS infection, bulky disease, multifocal infection) Trough:MIC ratio = 2 – 5 (MIC estimated using CLSI guidelines)
Aspergillus	> 1 – 1.5 mg/L	

Ashbee HR, et al. J Antimicrob Chemother. 2014;69(5):1162-76.

Gómez-López A. Clin Microbiol Infect. 2020;26(11):1481-7.

Pappas PG, et al. Clin Infect Dis 2016;62:e1-50.

Patterson TF, et al. Clin Infect Dis 2016;63:e1-60.

McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.



Voriconazole

- **Target for Safety:**
 - **Trough or Cmin**

Fungi	Infectious Diseases Society of America	British Society of Medical Mycology	Japanese Society of TDM
Candida	< 5.5 mg/L	< 4 – 6 mg/L	< 4 mg/L (Asians)
Aspergillus	< 5 – 6 mg/L		<5.5 mg/L (Non-Asians)

Ashbee HR, et al. J Antimicrob Chemother. 2014;69(5):1162-76.
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McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.
Takesue Y, et al. Clin Ther. 2022;44(12):1604-1623.



Voriconazole

- When to take levels?
 - Trough or Cmin

	Infectious Diseases Society of America	British Society of Medical Mycology	Society of Infectious Diseases Pharmacist
First TDM	Steady-state (4 – 7 days)	Within 2 – 5 days	2 – 5 days 2 days (with loading dose) 5 days (without loading dose)
Subsequent TDM	Depends on infection severity, cost, assay availability	Preferred to ensure no drug accumulation	Recommended since metabolism is nonlinear

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Posaconazole

- **Target for Efficacy:**

- **Trough or Cmin**

Prophylaxis	Treatment
<p>> 0.5 – 0.7 mg/L (steady state) OR > 0.35 mg/L (48 h after initiation of therapy)</p>	<p>> 1 – 1.5 mg/L</p>

- ***Suggested Target for Safety (not well established):***

- **Trough or Cmin < 3 – 3.75 mg/L**

Ashbee HR, et al. J Antimicrob Chemother. 2014;69(5):1162-76.
Gómez-López A. Clin Microbiol Infect. 2020;26(11):1481-7.
McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.



Posaconazole

- When to take levels?
 - Trough or Cmin

British Society of Medical Mycology	Society of Infectious Diseases Pharmacist
7 days (for prophylaxis: use lower target if level taken at 48h)	5 – 7 days 5 days (with loading dose) 7 days (without loading dose)

Posaconazole half-life = 26-31 h (MR tablet); 35 h (suspension)

Steady-state is reached around 7 days

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Gómez-López A. Clin Microbiol Infect. 2020;26(11):1481-7.
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Itraconazole

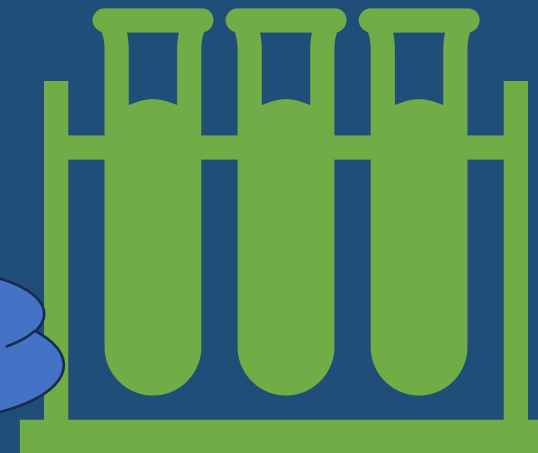
- **Target for Efficacy:**

- **Trough or Cmin**
- **Check if main active metabolite: hydroxy-itraconazole is included in measurement**
- Bioassay levels are three- to seven-fold higher than those measured by HPLC

	Prophylaxis	Treatment
Itraconazole only	> 0.5 mg/L	> 1 mg/L
Itraconazole + hydroxy-itraconazole		> 1.5 mg/L

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Reference ranges only
apply to HPLC or LC-MS
assays!



Itraconazole

- ***Suggested Target for Safety (not well established):***
 - **Trough or Cmin**

Assay Method	Threshold:	
Bioassay	< 17.1 mg/L	Itraconazole + hydroxy-itraconazole
HPLC or LC-MS	< 3 – 4 mg/L	Itraconazole + hydroxy-itraconazole

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Gómez-López A. Clin Microbiol Infect. 2020;26(11):1481-7.
Patterson TF, et al. Clin Infect Dis 2016;63:e1-60.
McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.
Lestner JM, et al. Clin Infect Dis. 2009;49(6):928-30.



Itraconazole

- **When to take levels?**
 - **Trough or Cmin**
 - Any point in the dosing interval is possible due to long elimination half-life

British Society of Medical Mycology	Society of Infectious Diseases Pharmacist
5 – 7 days	5 – 7 days (with loading dose) 10 – 14 days (without loading dose)

Itraconazole half-life = 34-42 h

Steady-state is reached after at least 7 days

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Fluconazole

- **Target for Efficacy (Treatment):**

- **AUC:MIC or Dose:MIC ratio \geq 50-100**

- Sampling at 1, 4 and 24 h to estimate AUC

- **Trough or Cmin = 10 – 15 mg/L**

(lower trough = \uparrow mortality)

- **Timing of trough: 5 – 7 days** (sooner with loading dose)

TDM not strictly recommended but may be considered in paediatric patients, those undergoing renal replacement therapies or those with absorption concerns

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Isavuconazole

- ***Target for Efficacy (Treatment):***
 - No target is established
 - Some experts consider Trough or Cmin $\geq 1 - 2$ mg/L
- ***Suggested Target for Safety:***
 - Trough or Cmin $< 4.6 - 5.1$ mg/L
- **When to take levels?**
 - **Trough** or any point in the dosing interval due to long half-life
 - 5 – 7 days (with loading dose)
 - 10 – 14 days (without loading dose)

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Gómez-López A. Clin Microbiol Infect. 2020;26(11):1481-7.
McCreary EK, et al. Pharmacotherapy. 2023;43(10):1043-50.



Caveats/Limitations

- **Targets are pathogen-specific:** Recommendations discussed earlier apply mostly to *Candida*, *Aspergillus*
 - MIC breakpoints not well established for other fungal species
 - If no data/recommendations exist, consider reported MIC, azole penetration to site of infection, severity of illness when deciding on therapeutic target
- **Assay interferences may complicate matters:** Important to know assay method. LC MS/MS is least affected.
- **Availability/frequency of assays may require deviation from ideal:** You may be forced to check levels before steady state if assay is not done daily. Interpret results with caution.
- **Data are often limited:** Recognise evidence gaps and adapt to constantly evolving recommendations
 - Therapeutic targets (e.g. toxicity limit not well established)
 - Penetration to sites of infections (especially newer antifungal agents)



The Evidence – Gaps Exist













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Summary

<https://funguseducationhub.org/wp-content/uploads/2024/07/TDM-Infographic-7.1-1.pdf>

How to perform TDM in adult patients					
Drug		TDM Recommendation		Timing of Samples	Target Trough Range
		Prophylaxis	Treatment	(after drug initiation, dose change, or change in interacting medication[s])	
Itraconazole	Sporanox capsule 	✓✓	✓✓	<div>Days</div> <div><div>1234567891011121314</div><div>With loading doseWithout loading dose</div></div>	<div>mg/L</div> <div>3-4</div> <div>1</div> <div>0.5</div> <div>Tx Range</div>
	Itraconazole suspension 	✓✓	✓		
	SUBA-itraconazole (Tolsura) 	Non-applicable	✓		
Posaconazole	Immediate-release suspension 	✓✓	✓✓	<div>Days</div> <div><div>1234567891011121314</div><div>With loading doseWithout loading dose</div></div>	<div>mg/L</div> <div>3-3.75</div> <div>1-1.5</div> <div>0.5-0.7</div> <div>Tx Range</div>
	Delayed-release tablet 	✓✓	✓		
	Delayed-release suspension 	✓✓	✓		
	Intravenous 				
Voriconazole	Tablet 	✓✓	✓✓	<div>Days</div> <div><div>1234567891011121314</div><div>With loading doseWithout loading dose</div></div>	<div>mg/L</div> <div>4-5.5</div> <div>1-2</div> <div>0.5</div> <div>Tx Range</div>
	Intravenous 				
	Suspension 				
Isavuconazole	Tablet 	Not Available	Consider in situations marked by pharmacokinetic variability (e.g., critical illness, alternative delivery, extremes in weight, etc.) or refractory illness.	<div>Days</div> <div><div>1234567891011121314</div><div>With loading doseWithout loading dose</div></div>	<div>mg/L</div> <div>4.6-5.1</div> <div>1</div> <div>Tx Range</div>
	Intravenous 				
<div>Key</div> <div><div>Therapeutic Upper Range (Toxicity Ceiling)</div><div>Therapeutic Lower Range</div><div>Prophylaxis Lower Range</div><div>✓✓ Recommended</div><div>✓ Consider</div></div>					



Thank you!

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