



# TDM-GUIDED DOSE OPTIMISATION OF ANTIFUNGAL (AZOLE) THERAPY FOR HAEMATOLOGY PATIENTS

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10 APR 2025, 1120-1200H

# DISCLOSURES

- No financial disclosures
- No conflict of interests

# AGENDA

- Attempt questions from 2 case scenarios
  - Using voriconazole to treat aspergillosis
  - Using posaconazole prophylaxis
- Discussion
- Q&A

# LET'S MAKE THIS INTERACTIVE!

<https://forms.office.com/r/2SiLxYnekn>

There are 2 Cases

15-20 minutes to attempt **ALL** questions

Feel free to discuss with your peers



# CASE 1

- Mdm TDM, 45 years old, Chinese, female, 62.2kg (BMI: 19.5)
- No known drug allergies
- Past medical history:
  - Hepatitis B core antibody positive – previous exposure vs occult infection?
  - JAK2+ chronic myeloid lymphoma (CML)

# CASE 1

- Admitted from haematology clinic in view of blast crisis; presenting with fever associated with nausea, vomiting and giddiness.
- Septic workup (blood cultures, inflammatory markers, imaging) was done, and she was started on IV antibiotics.
- Bloods taken at clinic was found to have high peripheral blast and decision was to initiate chemotherapy, KIV stem cell transplant.

# CASE 1

- About one month into admission, patient was still having persistent fevers with no localising infective symptoms, despite a prolonged course of broad-spectrum antibiotics.
- Aspergillus PCR was indeterminate
- Serum galactomannan (GM) was elevated.
- CT chest, abdomen and pelvis: Background of myelofibrosis with features of extensive disease involvement. **New cavitory lesion in the superior segment of the right lower lobe.** No new pulmonary nodule or consolidation. No infective focus in the rest of the chest, abdomen pelvis.

# CASE 1

- Decision to start IV voriconazole for probable invasive pulmonary aspergillosis and request for BAL
- **Before you start voriconazole and recommend azole TDM, what do you need to consider first?**



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# WHAT TO CONSIDER?

- Pathogen identity and susceptibility
- Site of infection
- Prior antifungal exposure
- Pharmacokinetics (obesity, liver function)
- Drug-drug interactions
- Pharmacogenomics (CYP2C19)

# ACTIVE MEDICATIONS

- IV Meropenem 1g q8h (d14 of broad spectrum antibiotics)
- IV Caspofungin 50mg OM
- PO Asciminib 160mg BD
- PO Olaparib 300mg BD
- PO Acyclovir 400mg BD
- PO Co-trimoxazole 960mg 3 times/week
- PO Entecavir 0.5mg OM
- PO Omeprazole 40mg BD
- PO Lactulose 10ml TDS PRN



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# WHAT DOSE WILL YOU START?

**Mdm TDM, 45 years old female, 62.2kg  
(BMI: 19.5)**

- IV 370mg q12h x 2 doses, then 250mg q12h
- IV 250mg q12h
- Depends...



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# WHEN TO STOP CASPOFUNGIN?

- Today
- 3 days later
- 5 days later
- 1 week later
- Depends...



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# WHEN TO CHECK VORICONAZOLE LEVEL?

- TDM not required
- Tomorrow
- Day 3
- Day 5
- 1 week later
- Depends...



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# WHAT VORICONAZOLE LEVEL TO CHECK?

- Peak
- Trough
- Peak and Trough
- Random Timing



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# VORICONAZOLE TDM RESULTS CAME BACK...

Day 5: 7.56 mg/L

Is this therapeutic?

# Voriconazole

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

- **Trough or Cmin**

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

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)

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 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.  
 Takesue Y, et al. Clin Ther. 2022;44(12):1604-1623.



# WHAT ELSE DO YOU NEED TO CHECK?



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# HOW DO WE ADJUST VORICONAZOLE DOSE?

- Hold 1 dose, restart at IV 200mg q12h
- Reduce dose to IV 200mg q12h
- Hold 1 day, restart at IV 100mg q12h
- Reduce dose to IV 100mg q12h
- Hold 1 day, recheck level tomorrow
- Others



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# DOSE ADJUSTMENT BASED ON LEVELS (PART 1)

Voriconazole Trough	Dose Adjustment
< 0.5 mg/L	↑ dose by 50%
< 1 mg/L	↑ dose by 25%
1 – 5.5 mg/L (Candida) 2 – 5.5 mg/L (Aspergillus)	Maintain dose
> 5.5 mg/L	Hold 1 dose, ↓ subsequent dose by 25-50%

Note: Recommendations vary among various institutions and are mostly based on expert opinion

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# DOSE ADJUSTMENT BASED ON LEVELS (PART 2)

**Note: Recommendations vary among various institutions and are mostly based on expert opinion**

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

Voriconazole	
Drug Level (mg/L)	Consider Dose Adjustments
Supratherapeutic: >4.0 (Asians)-5.5 (Non-Asians) <sup>1</sup>	<ul style="list-style-type: none"><li>• If levels are very high, consider holding 1-2 doses and restart at lower dose</li><li>• Oral Tablets: Decrease the daily dose by 50-100 mg and recheck level in 4 days</li></ul>
Therapeutic: 0.5 to 4-5.5 (depending on indication)	No change
Subtherapeutic: 0.5-2.0 (depending on indication)	<ul style="list-style-type: none"><li>• Oral Tablets: Increase daily dose by 50-100 mg and recheck level in 4 days</li><li>• IV: Increase IV therapy by 50% to a maximum of 6 mg/kg</li></ul>
Subtherapeutic: <0.5	<ul style="list-style-type: none"><li>• Patient may be a rapid metabolizer; split the dose to q 8h and recheck level in 2 days</li><li>• Evaluate for DDIs and adherence</li></ul>

# DOSE ADJUSTMENTS ARE NOT BY PROPORTION

- Usually adjusted by 50 mg per dose ( $\sim 25\%$ )

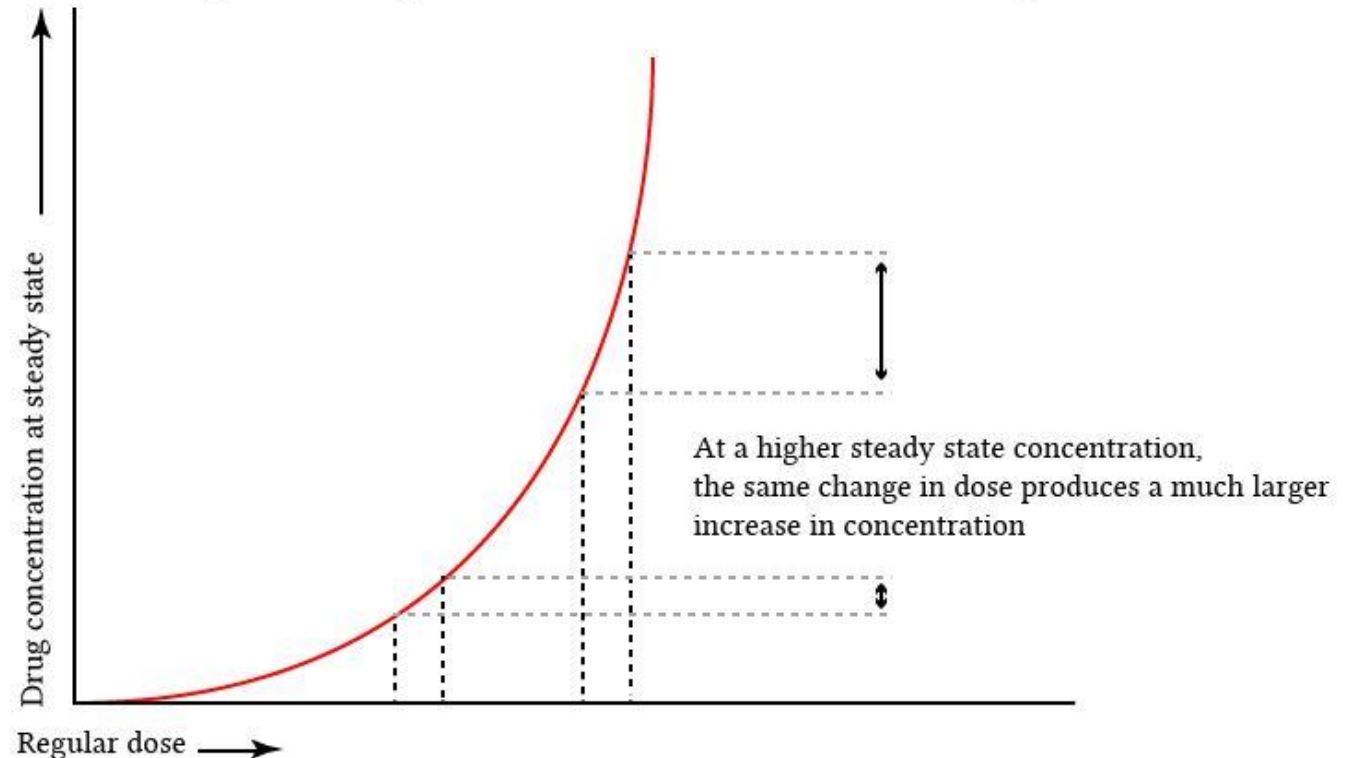
**WHY?**

# SATURABLE METABOLISM

- Michaelis-Menten Kinetics
- Non-linear pharmacokinetics

<https://derangedphysiology.com/main/cicm-primary-exam/pharmacokinetics/Chapter-337/first-order-zero-order-and-non-linear-elimination-kinetics>

Michaelis-Menten elimination kinetics:  
relationship of steady-state concentration and changes in dose



# WHEN TO RECHECK LEVELS AFTER DOSE ADJUSTMENT?

- Tomorrow
- Day 3
- Day 5
- 1 week later
- Depends...



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# REPEAT VORICONAZOLE TDM RESULTS CAME BACK...

1 week later: 5.23 mg/L

Is this therapeutic?

# BAL CULTURES ALSO RETURNED...

- *Aspergillus fumigatus* complex

Antifungal	MIC (mg/L)	Interpretation
Anidulafungin	$\leq 0.015$	No interpretive criteria available
Posaconazole	0.25	Wild Type
Voriconazole	1	Wild Type
Amphotericin B	4	Wild Type

# HOW DO WE ADJUST VORICONAZOLE DOSE?



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- Change antifungal therapy
- Keep the same dose (IV 200mg q12h)
- Reduce to IV 150mg q12h
- Hold 1 dose
- Hold 1 dose

**Remember to  
review for IV to  
PO switch**



# WHEN TO RECHECK LEVELS?

- TDM no longer required
- Tomorrow
- Day 3
- Day 5
- 1 week later
- Depends...



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# CASE 2

- Mr CYC, 47 years old, Chinese, male, 55.5kg (BMI: 21)
- No known drug allergies
- Past medical history:
  - Congenital ventricular septal defect and hypoplastic right lung (no surgery done)
  - HIV diagnosed in 2014, virologically suppressed since 2016
  - Acute myeloid leukaemia (Favourable risk, FLT3 negative, normal cytogenetics) diagnosed Jan 2025
  - No hepatic or renal impairment

# MEDICATION LIST (16 JAN 25)

- IA (Cytarabine + Idarubicin) 3+7 (Start date 16 Jan 2025)
- PO Dovato (Dolutegravir 50mg + Lamivudine 300mg) 1 tablet OD since Mar 2024
- PO Aciclovir 400mg BD
- **PO Posaconazole MR 300mg BD x 1 day then 300mg OM**
- PO Ciprofloxacin 500mg BD
- PO Cotrimoxazole 960mg 3x/week (discontinued on 15 Jan 2025)
- PO Allopurinol 300mg OM
- PO Pravastatin 20mg ON
- PO Omeprazole 20mg BD for GERD
- PO Magnesium trisilicate mixture 10mL TDS PRN for gastric discomfort

# WHEN TO CHECK POSACONAZOLE LEVEL?

- TDM not required
- Tomorrow
- Day 3
- Day 5
- 1 week later
- Depends...



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# POSACONAZOLE TDM RESULTS CAME BACK...

Day 10: 0.35 mg/L

Is this therapeutic?



# Posaconazole

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

Prophylaxis	Treatment
$> 0.5 - 0.7 \text{ mg/L}$ (steady state) OR $> 0.35 \text{ mg/L}$ (48 h after initiation of therapy)	$> 1 - 1.5 \text{ mg/L}$

- ***Suggested Target for Safety (not well established):***
  - **Trough or Cmin  $< 3 - 3.75 \text{ mg/L}$**

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



# WHAT ELSE DO YOU NEED TO CHECK?



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# HOW DO WE ADJUST POSACONAZOLE DOSE?

- Continue PO 300mg OM (not at steady state yet)
- Increase to PO 400mg OM
- Increase to PO 600mg OM
- Increase to PO 300mg BD



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# WHEN TO RECHECK POSACONAZOLE LEVEL?

- TDM not required
- Tomorrow
- Day 3
- Day 5
- 1 week later
- Depends...



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# POSACONAZOLE TDM RESULTS CAME BACK...

1 week later: 0.61 mg/L

Is this therapeutic?

# HOW DO WE FURTHER ADJUST POSACONAZOLE DOSE?

- Continue PO 400mg OM
- Increase to PO 500mg OM
- Increase to PO 600mg OM
- Increase to PO 300mg BD



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# WHEN TO RECHECK POSACONAZOLE LEVEL?

- TDM not required
- Tomorrow
- Day 3
- Day 5
- 1 week later
- Depends...



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# SUMMARY

- Azole TDM dose adjustment algorithms are mostly based on expert opinions and institutional experiences
- Thinking out of the box may be needed to overcome limitations in azole assays (long turn-around times, less frequent assay runs)





# ACKNOWLEDGEMENTS

- Dr Narendran S/O Koomanan, Principal Clinical Pharmacist, Singapore General Hospital
- Ms Tan Sock Hoon, Principal Pharmacist (Clinical), Singapore General Hospital
- Ms Yvonne Zhou Peijun, Specialist Pharmacist, Singapore General Hospital

# THANK YOU!

For questions:

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