

TDM-GUIDED DOSE OPTIMIZATION OF ANTIFUNGAL (AZOLE) THERAPY IN THE ICU SETTING

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DISCLOSURES

- No financial disclosures
- No conflict of interests

AGENDA

- Attempt questions from 1 case scenario on voriconazole TDM
- Discussion
- Q&A

LET'S MAKE THIS INTERACTIVE!

<https://forms.office.com/r/tAwRzWwHU5>

10-15 minutes to attempt **ALL**
questions

Feel free to discuss with your peers



DISCLAIMER

- The purpose of the case discussion is to discuss the thought process when recommending dose adjustments based on azole TDM results
- Choice and duration of antifungal therapy may not always be ideal for the case scenario (but in view of time constraints, this is beyond the scope for today's session)

CASE 1

- **Mr MFBS, 58 years old, Malay, male 67.6kg (BMI 24)**
- No known drug allergy
- Past medical history
 - ESRF from IgA nephropathy, on peritoneal dialysis
 - Hypertension, Ischaemic heart disease with recurrent MI
 - Seizures
 - No hepatic impairment
- Admitted for recurrent PD peritonitis
 - Persistent fever and abdominal pain despite IV meropenem (day 10)
 - PD cell count continued to rise

CASE 1

- PD fluid grew: *Candida albicans*

Antifungal	MIC (mg/L)	Interpretation
Anidulafungin	0.06	S
Micafungin	0.06	S
Voriconazole	0.12	S
Fluconazole	16	R

CASE 1: MEDICATION LIST

- IV Meropenem 500mg q12h (Day 10)
- SQ Epoetin Beta (Recormon) Injection 4000 units once weekly
- PO Aspirin 100mg OM
- PO Famotidine 40mg OM
- PO Bisoprolol 2.5mg OM
- S/L GTN 0.5mg PRN
- PO Phenytoin 300mg OM
- PO Iron (polymaltose): elemental iron 200mg OM
- PO Sevelamer 1,600mg BD (Pre-meal)
- PO Alfacalcidol 1mcg 3 times per week
- PO Renal vitamin 1 tablet OM

CASE 1

<https://forms.office.com/r/tAwRzWwHU5>



- Patient is clinically stable in General Ward
- What PO voriconazole dose will you recommend?
- What do you need to check first before making any recommendations?



WHAT TO CONSIDER?

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

SPOT THE DRUG-DRUG INTERACTIONS

- IV Meropenem 500mg q12h (Day 10)
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- PO Aspirin 100mg OM
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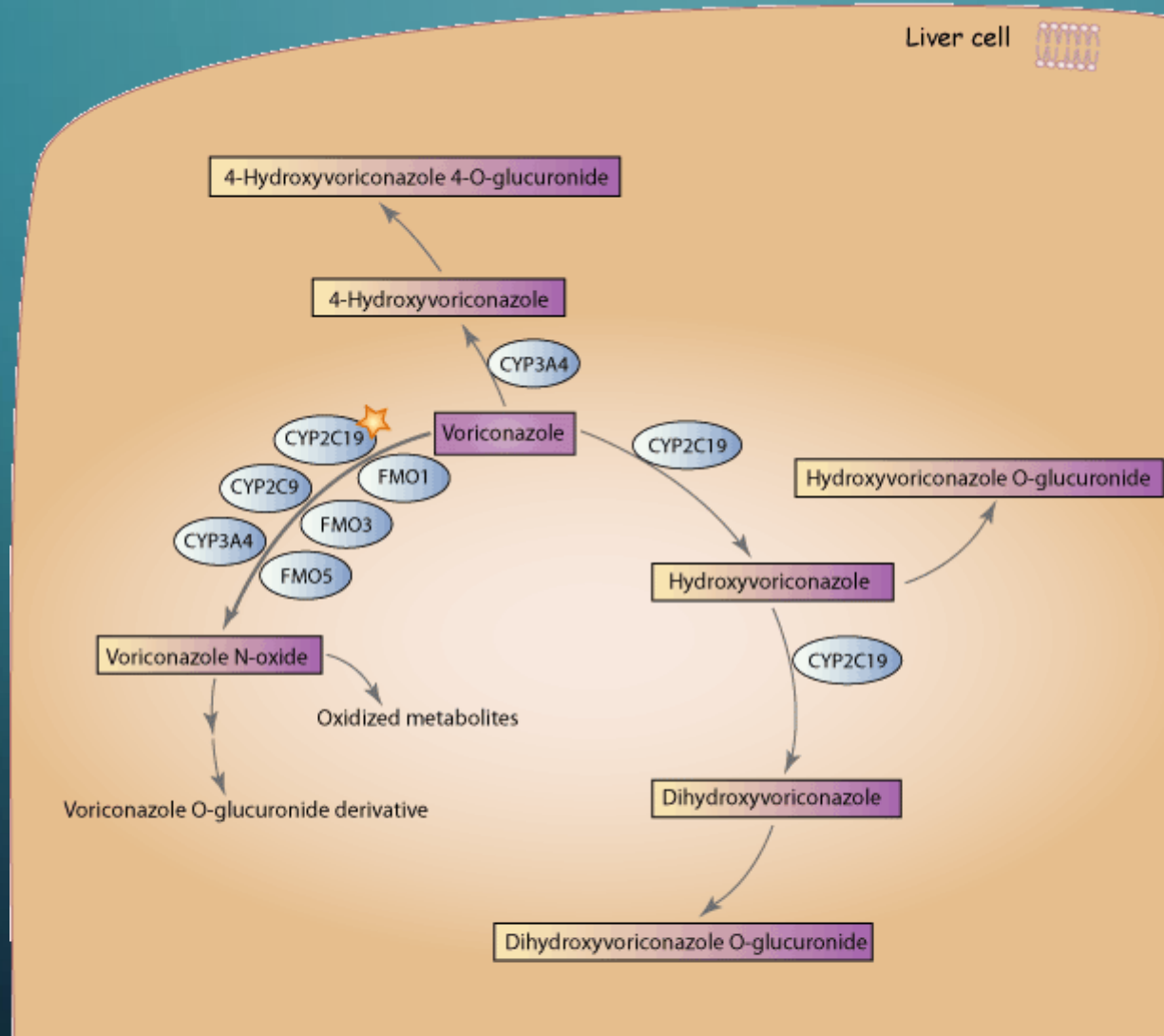
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SPOT THE DRUG-DRUG INTERACTIONS

- IV Meropenem 500mg q12h (Day 10)
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DRUG-DRUG INTERACTIONS



PHENYTOIN & VORICONAZOLE

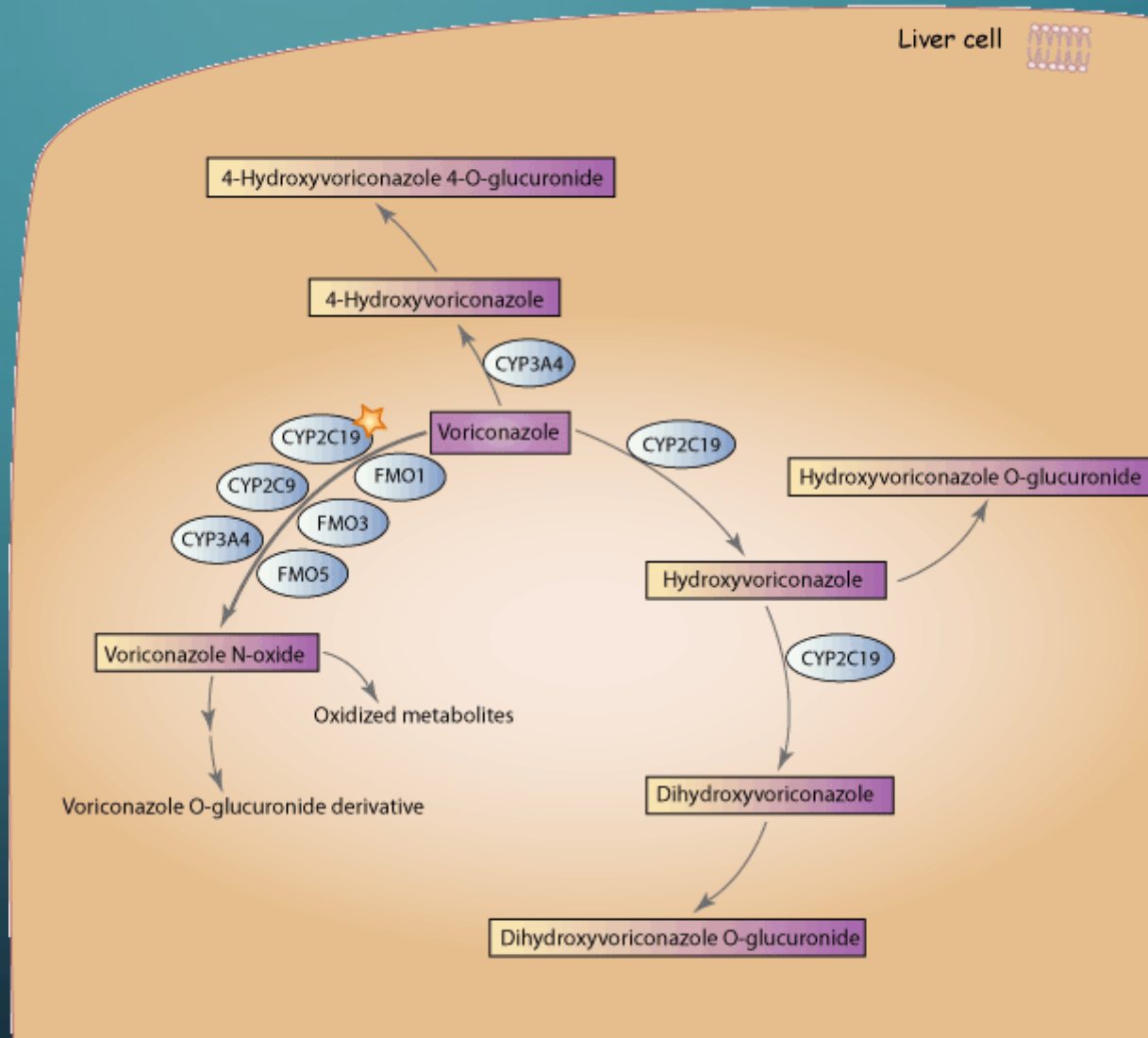
- Phenytoin

- CYP3A4 enzyme inducer
- ↓ voriconazole levels
- ↑ voriconazole maintenance dose to
 - IV 5mg/kg q12h or
 - PO 400mg q12h if >40kg; PO 200mg q12h if <40kg

- Voriconazole

- CYP2C19, 2C9 and 3A4 enzyme inhibitor
- ↑ phenytoin levels
- Monitor phenytoin levels closely

CYP2C19 GENETIC POLYMORPHISM



<https://www.pharmgkb.org/pathway/PA166160640>

CYP2C19 GENETIC POLYMORPHISM

- 30 variant alleles

Most common allele	Function	Frequency in Asians
*1	Normal	
*2	Loss of enzyme function	29-34%
*3	Loss of enzyme function	2-9%
*17	↑ enzyme function	2% East Asians 17% South or Central Asians

CYP2C19 GENETIC POLYMORPHISM

Phenotype	Genotype	Frequency
Ultrarapid metaboliser (UM)	*17/*17	2-5%
Rapid metaboliser (RM)	*1/*17	2-30%
Normal metaboliser (NM)	*1/*1	35-50%
Intermediate metaboliser (IM)	*1/*2 or *1/*3 *2/*17 or *3/*17	18-45%
Poor metaboliser (PM)	*2/*2 or *3/*3 or *2/*3	2-15%

Moriyama B, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther. 2017;102(1):45-51.

<https://www.pharmgkb.org/pathway/PA166160640>

CYP2C19 GENETIC POLYMORPHISM

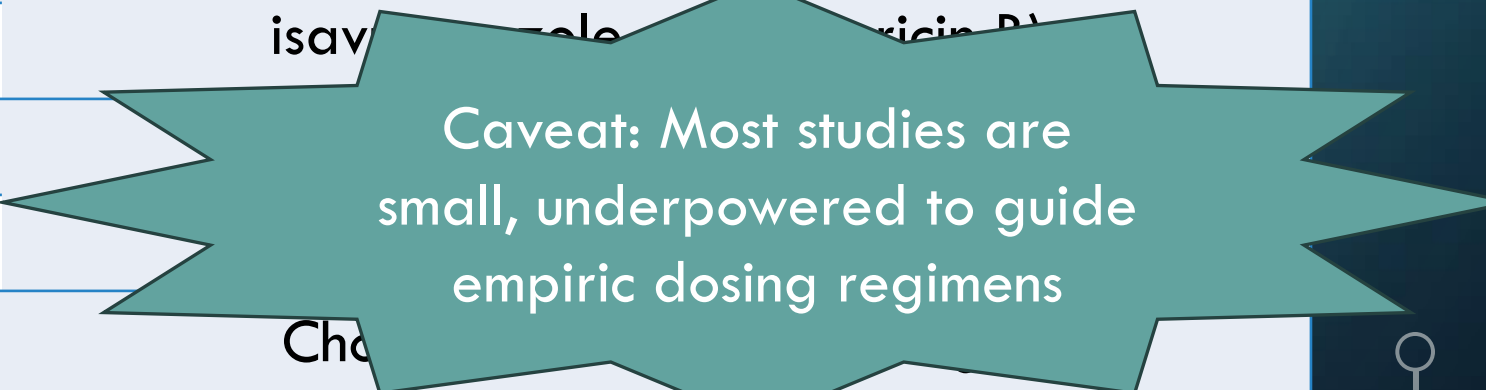
Poor
Metaboliser

PMs %

Total number n	EM genotypes				PM genotypes		PMs %
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	
Malay	27	20	4	2	1	0	5.6
Chinese	25	26	4	4	8	1	19.1
Indian	7	11	0	2	0	0	10.0
Total	59	57	8	8	9	1	

Yang YS, et al. Genetic polymorphism of cytochrome P450 2C19 in healthy Malaysian subjects. Br J Clin Pharmacol. 2004;58:332-5.

EMPIRIC DOSE ADJUSTMENTS BASED ON CYP2C19 PHENOTYPE (CPIC GUIDELINES)

Phenotype	Therapeutic Recommendation
Ultrarapid metaboliser (UM)	Choose alternative antifungal (e.g. posaconazole, isavuconazole, voriconazole)
Rapid metaboliser (RM)	
Normal metaboliser (NM)	 Caveat: Most studies are small, underpowered to guide empiric dosing regimens
Intermediate metaboliser (IM)	
Poor metaboliser (PM)	
	Choose lower dose Or Initiate at lower dose with TDM

Moriyama B, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther. 2017;102(1):45-51.

EMPIRIC DOSE ADJUSTMENTS BASED ON CYP2C19 PHENOTYPE

- Singapore Experience?
- CYP2C19 genetic polymorphism not routinely tested
- All voriconazole therapy is guided by **TDM**
- **But what if we happen to know CYP2C19 phenotype?**

EMPIRIC DOSE ADJUSTMENTS BASED ON CYP2C19 PHENOTYPE

- Singapore Experience?

Phenotype	Therapeutic Recommendation
Ultrarapid metaboliser (UM)	Initiate at standard dose (round up)
Rapid metaboliser (RM)	TDM on day 3 to detect subtherapeutic levels early
Normal metaboliser (NM)	Initiate at standard dose + TDM
Intermediate metaboliser (IM)	Initiate at standard dose (round down)
Poor metaboliser (PM)	TDM on day 3 to detect supratherapeutic levels early Regular TDM during first few weeks of treatment to detect drug accumulation

WHAT DOSE WILL YOU START?

- **Mr MFBS, 58 years old, Malay, male 67.6kg (BMI 24)**
- You find out that his phenytoin was discontinued 2 months ago and the patient was no longer receiving any phenytoin dose during admission
- What PO voriconazole dose will you recommend?
 - PO 400mg q12h x 2 doses then 250mg q12h
 - PO 400mg q12h x 2 doses then 300mg q12h
 - PO 400mg q12h
 - PO 250mg q12h
 - PO 300mg q12h
 - Depends...



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WHEN WILL YOU CHECK VORICONAZOLE LEVEL?

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



<https://forms.office.com/r/tAwRzWwHU5>



WHAT SAMPLING TIMEPOINT WILL YOU RECOMMEND?



<https://forms.office.com/r/tAwRzWwHU5>

- Peak
- Trough
- Peak and Trough
- Random timepoint



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

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 TDM RESULTS CAME BACK...

Day 7: 3.57 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	> 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.

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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.
 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 DOSE ADJUSTMENT WILL YOU RECOMMEND?

- Keep the same dose
- Reduce dose by 25-50%
- Increase dose by 25-50%
- Depends...



<https://forms.office.com/r/tAwRzWwHU5>



WHEN WILL YOU RECHECK VORICONAZOLE LEVEL?



<https://forms.office.com/r/tAwRzWwHU5>

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



UNFORTUNATELY THE PATIENT BECAME CRITICALLY ILL

- The patient developed septic shock with GNB bacteraemia
 - Procalcitonin 200 ng/mL, CRP 390 mg/L, WBC 19k
- He is admitted to ICU
 - On triple inotropes
 - On CKRT (CVVHDF)
 - IV hydrocortisone 50mg q6h
 - Meropenem escalated to IV Ceftazidime-avibactam 1.25g q24h
 - Switched PO voriconazole to IV voriconazole 250mg q12h

REPEAT VORICONAZOLE LEVEL

Day 12 (Day 5 of IV): 8.49 mg/L

Is this therapeutic?
Is this expected?

WHAT WILL YOU CHECK BEFORE REACTING?



<https://forms.office.com/r/tAwRzWwHU5>



WHAT CONTRIBUTED TO THE VORICONAZOLE TREND?



<https://forms.office.com/r/tAwRzWwHU5>

- Use of IV hydrocortisone
- Use of IV ceftazidime-avibactam
- Switch from PO to IV voriconazole
- Severe inflammation
- Use of CKRT
- CYP2C19 polymorphism (poor metaboliser)
- Previous voriconazole level was not taken at steady state



COMMON PK CHANGES IN ICU

- Steroid – CYP enzyme induction (onset and offset may take 2-4 weeks)
 - ↓ voriconazole concentrations during steroid initiation or up titration
 - ↑ voriconazole concentrations during steroid taper
- Severe inflammation (reflected by high CRP) in critically ill patients may impair voriconazole metabolism - ↑ voriconazole concentrations
- Hypoalbuminaemia and hyperbilirubinaemia may ↑ voriconazole concentrations
- Impaired GI absorption
- Additional clearance mechanism e.g. sequestration by ECMO

Pascual A, et al. Clin Infect Dis. 2008;46:201-11.

Veringa A, et al. J Antimicrob Chemother. 2017;72:261-7.

Chantharit P, et al. Ther Drug Monitor. 2020;42:872-9.

Vanstraelen K, et al. Antimicrob Agents Chemother. 2014;58:6782-9.

Cojutti P, et al. Basic and Clinical Pharmacology and Toxicology. 2016;118:474-9.

OTHER CONCERNS IN ICU

- Sulfobutylether-beta-cyclodextrin (SBECD) found in voriconazole injection may accumulate in renal impairment >> nephrotoxicity risk
 - Watch renal function closely
 - Switch to oral as soon as possible

UPON FURTHER CHECKING

- LFTs (rising trend)
- QTc 465 ms
- Occasional jerking of upper limbs noted

LFTs	Values	Reference Range
ALP	238 U/L	39-99 U/L
ALT	89 U/L	6-66 U/L
AST	96 U/L	12-42 U/L
GGT	102 U/L	14-94 U/L
Total Bilirubin	35 mcmol/L	7-32 mcmol/L
Albumin	36 g/L	40-51 g/L

WHAT DOSE ADJUSTMENT WILL YOU RECOMMEND?



<https://forms.office.com/r/tAwRzWwHU5>

Assuming we are persisting with IV voriconazole treatment

- Hold 1-2 doses, recheck voriconazole level tomorrow
- Hold 1-2 doses, resume at IV 100mg q12h
- Hold 1-2 doses, resume at IV 150mg q12h
- Hold 1-2 doses, resume at IV 200mg q12h



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
Suprathereapeutic: >4.0 (Asians)-5.5 (Non-Asians) ¹	<ul style="list-style-type: none">• If levels are very high, consider holding 1-2 doses and restart at lower dose• Oral Tablets: Decrease the daily dose by 50-100 mg and recheck level in 4 days
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">• Oral Tablets: Increase daily dose by 50-100 mg and recheck level in 4 days• IV: Increase IV therapy by 50% to a maximum of 6 mg/kg
Subtherapeutic: <0.5	<ul style="list-style-type: none">• Patient may be a rapid metabolizer; split the dose to q 8h and recheck level in 2 days• Evaluate for DDIs and adherence

DOSE ADJUSTMENTS ARE NOT BY PROPORTION

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

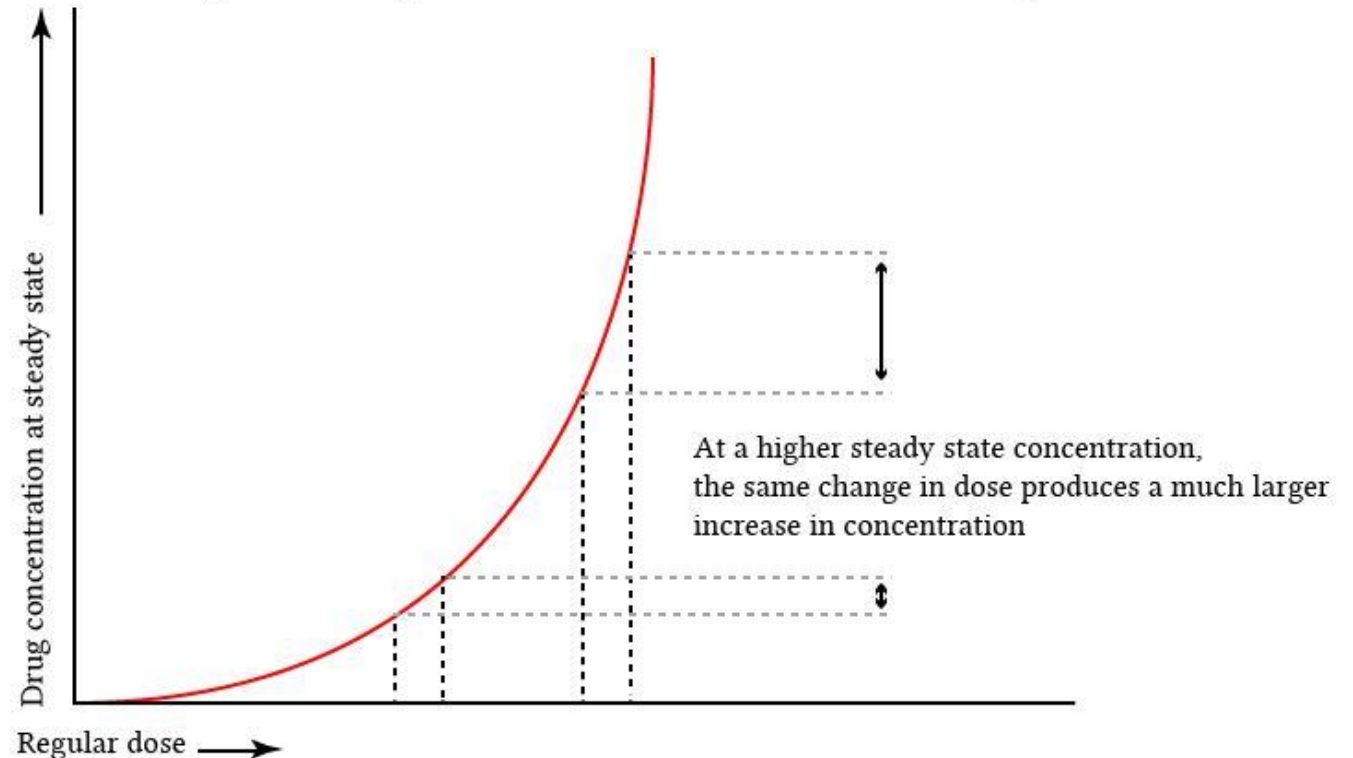
WHY?

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 WILL YOU CHECK VORICONAZOLE LEVEL AFTER DOSE ADJUSTMENT?



<https://forms.office.com/r/tAwRzWwHU5>

- Next day
- Day 3
- Day 5
- 1 week later
- Depends...



WHAT HAPPENS NEXT...

- You decide to hold dose for 24h
- Resume IV voriconazole 24h later at 150mg q12h
- The laboratory only runs voriconazole assays twice weekly (next assay run is 3 days later)
- Hence, you recommend checking voriconazole trough 3 days later (i.e. 2 days after dose reduction)

REPEAT VORICONAZOLE LEVEL

Day 15

(Day 2 of Dose Reduction):

6.13 mg/L

Jerking has resolved

LFTs down-trending

WHAT WILL YOU DO NEXT?



<https://forms.office.com/r/tAwRzWwHU5>

- Continue IV voriconazole 150mg q12h
- Hold 1 dose and resume IV voriconazole at 150mg q12h
- Hold 1 dose and resume IV voriconazole at 100mg q12h
- Hold 2 doses and resume IV voriconazole at 100mg q12h



WHEN WILL YOU RECHECK VORICONAZOLE LEVEL?



<https://forms.office.com/r/tAwRzWwHU5>

- TDM no longer required
- Next day
- Day 3 of dose change
- Day 5 of dose change
- 1 week after dose change
- Depends...



RECOVERY

- 3 days later, patient has improved clinically and is transferred out of ICU
- He is now alert
- LFTs continue to down-trend
- IV voriconazole has been switched to PO voriconazole 150mg q12h

REPEAT VORICONAZOLE LEVEL

Day 23 (Day 5 of PO): 0.88 mg/L

What happened?

WHAT WILL YOU CHECK BEFORE REACTING?



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WHAT CONTRIBUTED TO THE VORICONAZOLE TREND?

- Discontinuation of IV hydrocortisone
- Switch from IV to PO voriconazole
- Diarrhoea/Vomiting
- Recovery from sepsis
- Discontinuation of CKRT
- CYP2C19 polymorphism (rapid metaboliser)



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ASSUMPTIONS

- Patient has been compliant (no missed doses)
- Timings for drug administration and voriconazole trough sampling are correct
- No vomiting/diarrhoea/malabsorption concerns
- No changes to medications aside from discontinuation of inotropes and hydrocortisone

WHAT DOSE ADJUSTMENT WILL YOU RECOMMEND?



<https://forms.office.com/r/tAwRzWwHU5>

- Continue PO voriconazole 150mg q12h
- Increase PO voriconazole to 200mg q12h
- Increase PO voriconazole to 250mg q12h
- Switch back to IV voriconazole 150mg q12h



REPEAT VORICONAZOLE LEVEL

Day 28

(Day 5 of dose increase):

<0.5 mg/L

What is going on?!



WHAT WILL YOU DO?

- Investigate
- Repeat level
- Increase dose
- Switch agent



<https://forms.office.com/r/tAwRzWwHU5>



UNEXPECTED LOW VORICONAZOLE TROUGH



- The ward nurse found several voriconazole tablets hidden in the patient's bedside drawer
- The patient admits that he has been hiding/throwing away his voriconazole tablets since his transfer out of ICU

SUMMARY

- Be cognizant of expected pharmacokinetic changes in your patient
 - Think before reacting to results
 - Are the TDM results expected and fit your patients' profile?
- Dose adjustment algorithms vary among institutions and are mostly based on expert opinions
- Treat the patient and not just the numbers
- Consider the most convenient formulation when adjusting doses
- Be aware of limitations with azole TDM – careful deviation from recommendations sometimes happens (e.g. sampling before steady-state)

ACKNOWLEDGEMENTS

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- Ms Yvonne Zhou Peijun, Specialist Pharmacist (Infectious Diseases), Singapore General Hospital

THANK YOU!

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