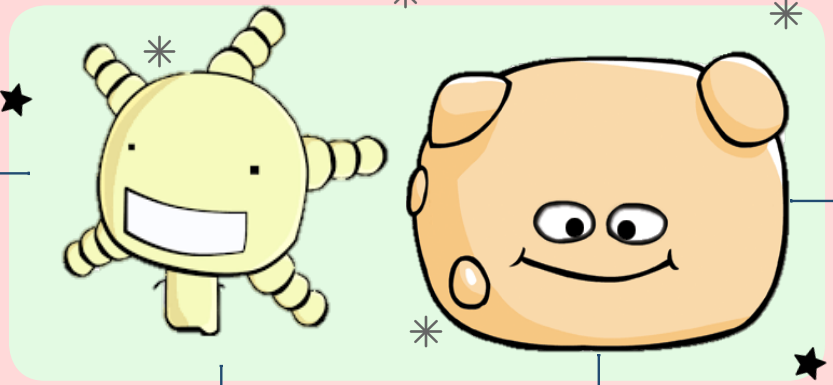
Antifungal Dosing Guidance and Therapeutic Drug Monitoring (TDM) Pediatric UCSF

UCSF Benioff Children's Hospitals

Summary of Resource



Voriconazole

Posaconazole

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Itraconazole

TDM TIps

Spectrum

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HOWTO USE THESE GUIDELINES

This resource was created as a reference document for clinical pharmacists at UCSF caring for pediatric patients who are receiving an azole and need therapeutic drug monitoring.

This guideline is HIGHLY interactive! There are **lots of hyperlinks** embedded within each page so please try clicking around on different sections for ease of navigation. Each slide also has a link back to the main page. Can also simply read through as a PDF too.

Disclaimer: When utilizing these resource, always use clinical judgment.

This document was developed by the Pediatric Antimicrobial Stewardship Program Lead Pharmacist
(Last Updated: 05/2023)

Antifungal Spectrum

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Antifungal	Yeast					Dimorphic	Mold	
	Candida				Cryptococcus	Coccidioides	Aspergillus	Zygomyces
	Albicans Tropicalis	Glabrata	Krusei	Lusitaniae				
Fluconazole (Diflucan)	++	+/-	--	++	++	++	--	--
Voriconazole (Vfend)	+	+/-	+	+	+	+	++	--
Posaconazole (Noxafil)	+	+/-	+	+	+	+	++	+
Isavuconazole (Cresemba)	+	+/-	+	+	+	+	++	+
Itraconazole (Sporanox)	+	+/-	--	+	+	++	+/-	--
Micafungin, Caspofungin	++	++	++	++	--	--	+	--
Amphotericin B (Ambisome)	++	++	++	--	++	++	++	++

Side Effects

N/V/D, Rash, ↑ LFTs, visual disturbances (voriconazole)

Transient increases in LFTs are common and asymptomatic; they often do not warrant changing antifungal agents unless they are >= 5X ULN

CYP3A4 Interactions

CYP3A4 Inhibition: Itra, Posa,Vori > Fluc, Isavu

Legend

- ++ First-line agent
- + Active (potential alternative)
- +/- Variable activity
- -- Not recommended (poor activity or insufficent data)

Voriconazole

Formulations

Tablets:	50 mg, 200 mg
Oral solution:	40 mg/mL
Intravenous:	200 mg/vial

Dosing

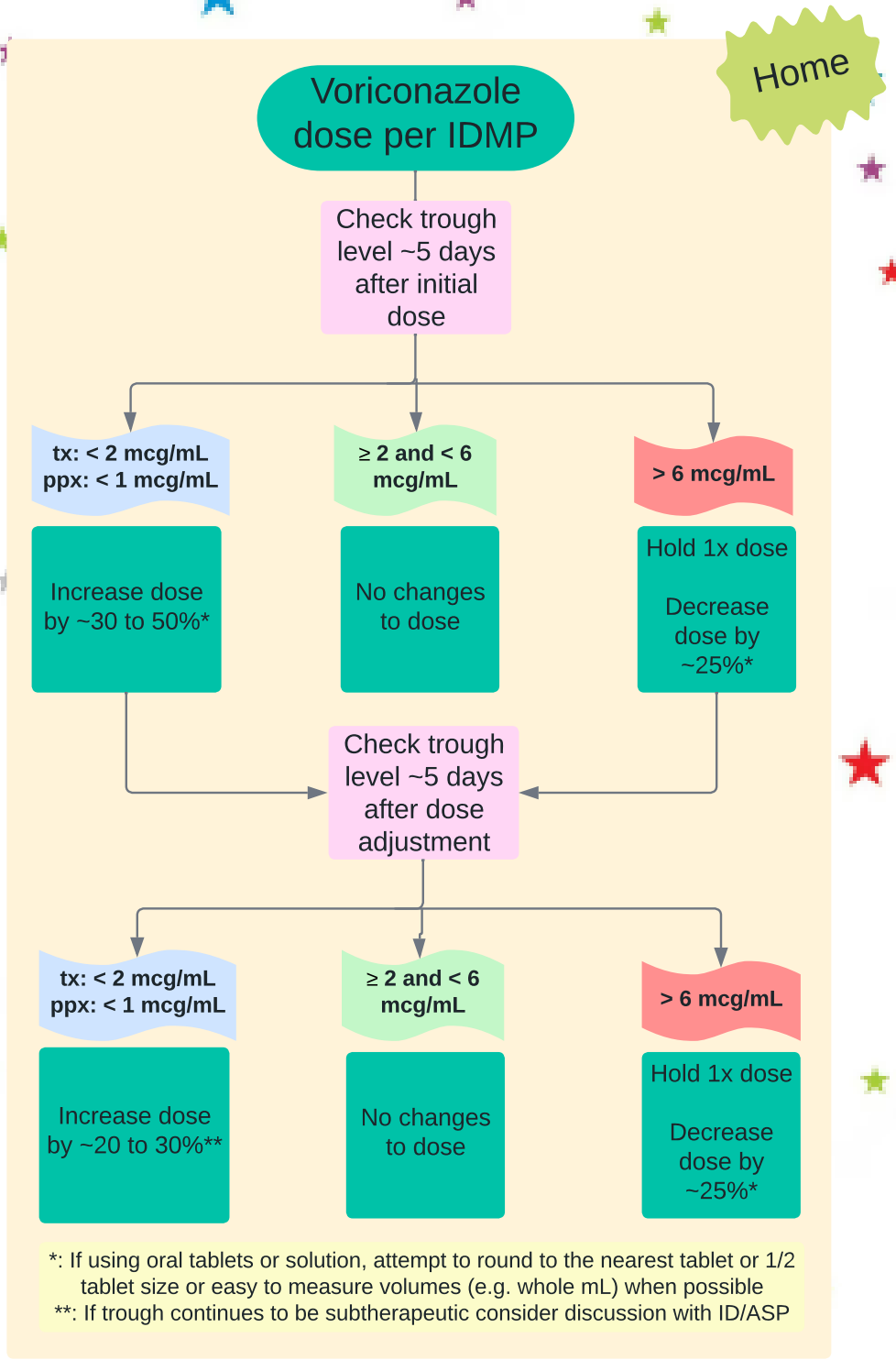
- Please visit [UCSF IDMP] for voriconazole dose recommendations

TDM

- Trough levels should be drawn before dose on day ~5
- Labs are processed Monday, Wednesday, and Friday
- Labs take about 2-3 days to result

Pearls

- A trough of 1 mcg/mL may be appropraite if low MIC with good source control or discussion with ID/ASP team
- If concerned for toxicity, hold dose and consider contacting ID/ASP team
- Use IV formulation with caution - contains sulfobutylether-βcyclodextrin (potential for accumulation in renal insufficiency)
- Avoid use in severe hepatic dysfunction
- Consider CYP2C19 genotyping



Posaconazole

Formulations

DR Tablets:	100 mg
Oral solution:	40 mg/mL *(administer with fatty meal/nutritional supplement and/or acidic beverage; AVOID acid suppression i.e. PPI or H2RA if possible)*
Intravenous:	300 mg/vial

Dosing

Oral suspension: 6 mg/kg/dose PO TID (Max 400 mg/dose)

DR tablets / IV Solution:

- > 15 to ≤ 22 kg:
  Day 1: 100 mg IV/PO q12h/BID
  Day 2+: 100 mg IV/PO q24h/daily
- > 22 to < 40 kg:
  Day 1: 200 mg IV/PO q12h/BID
  Day 2+: 200 mg IV/PO q24h/daily
- ≥ 40 kg
  Day 1: 300 mg IV/PO q12h/BID
  Day 2+: 300 mg IV/PO q24h/daily

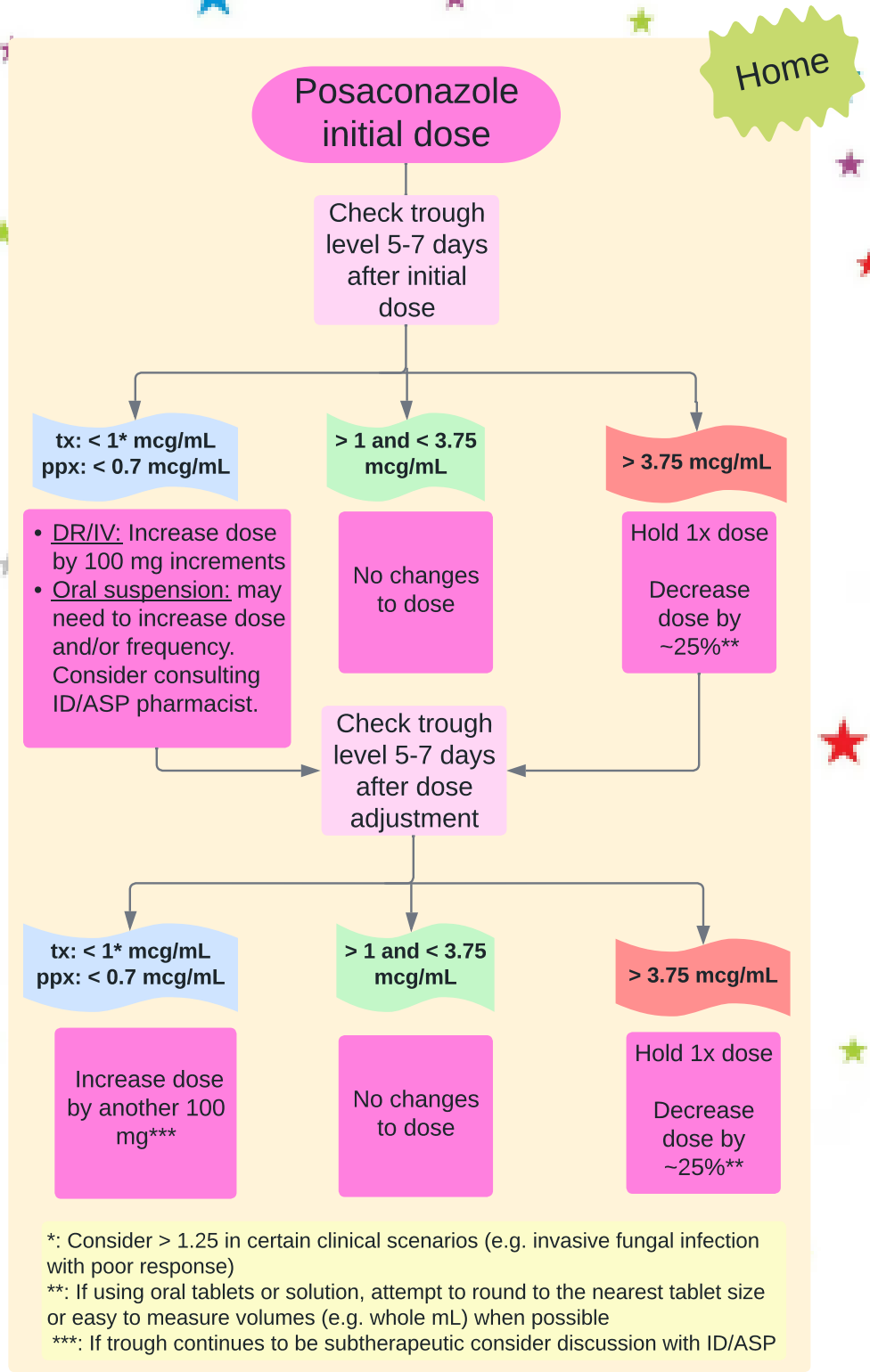
The dosing of oral suspension and DR tablets are NOT equivalent!

TDM

- Trough levels should be drawn before dose after 5-7 days of therapy

Pearls

- Posaconazole DR/IV formulation: PK are linear and dose proportional until higher doses are reached (~800 mg at which saturable kinetic occurs)
- Posaconazole oral suspension has saturable absorption and erratic pharmacokinetics
- Can crush DR tablets but may need a higher dose due to lower oral bioavailability
- Use IV formulation with caution - contains sulfobutylether-βcyclodextrin (potential for accumulation in renal insufficiency)



*: Consider > 1.25 in certain clinical scenarios (e.g. invasive fungal infection with poor response)
**: If using oral tablets or solution, attempt to round to the nearest tablet size or easy to measure volumes (e.g. whole mL) when possible
***: If trough continues to be subtherapeutic consider discussion with ID/ASP

Isavuconazole

Formulations

Capsule:	186 mg
Intravenous:	372 mg/vial

Dosing

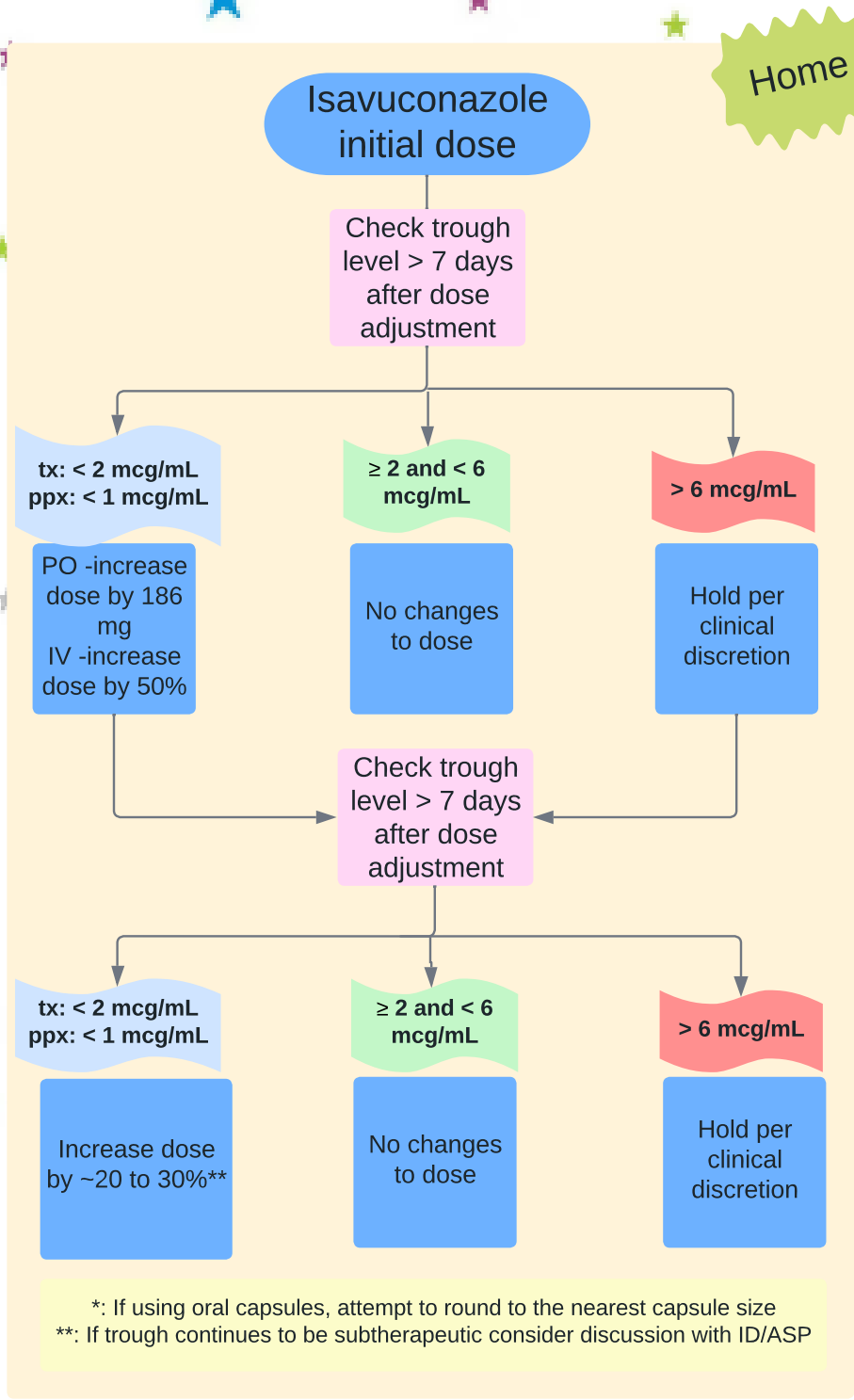
- Children and adolescents < 18 years:
  - IV/PO (Loading Dose):
    - 10 mg isavuconazonium sulfate/kg/dose q8h for 6 doses
    - Initial maximum dose: 372 mg/dose
  - IV/PO (Maintenance Dose):
    - 10 mg isavuconazonium sulfate/kg/dose q24h
    - Initial maximum dose: 372 mg/dose

TDM

- TDM monitoring is not routinely recommended
  - Pediatric patients started on IV isavuconazole for prophylaxis do not routinely require trough level monitoring
  - Pediatric patients started on enteral isavuconazole for prophylaxis without gut GVHD may not require trough level monitoring
- If drawing trough levels, draw after 1 to 2 weeks
- Labs are processed Monday, Wednesday, and Friday
- Labs take about 2-3 days to result

Pearls

- If concerned for toxicity, hold dose and contact ID/ASP team
- Isavuconazole PK are linear and dose proportional
- Use has been associated with a shortened QT interval



Itraconazole

Formulations

Capsules:	100 mg
Oral solution:	10 mg/mL

Dosing

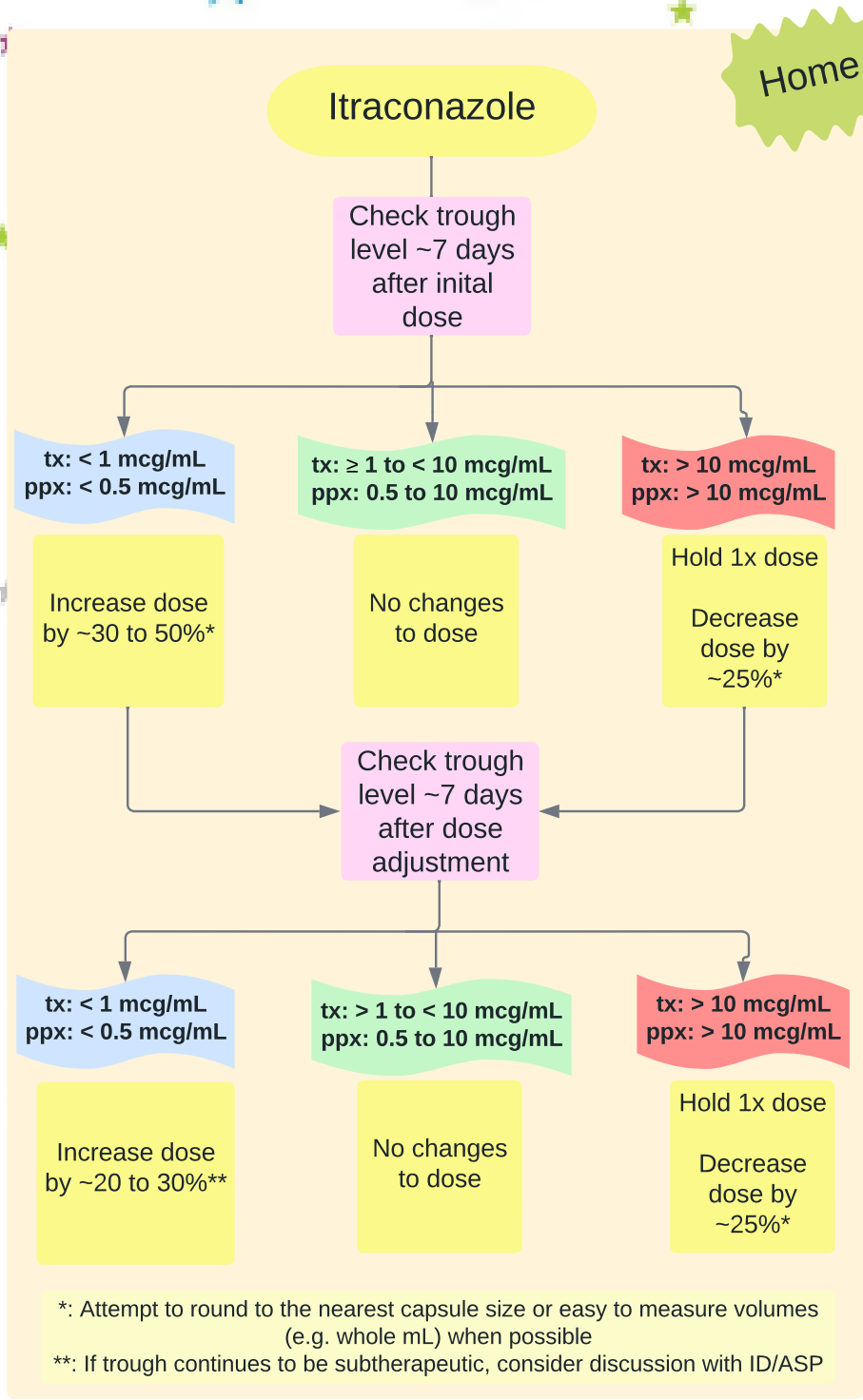
- Oral: 5 mg/kg/dose twice daily
- Initial max 200 mg/dose

TDM

- A trough level should be drawn before dose on day ~7 of therapy
- Turnaround time 3-5 days (sendout)
- HPLC assay measures itraconazole and hydroxyitraconazole levels. **Both values** should be **added** to evaluate **true level** (e.g. itraconazole 0.7 mcg/mL and hydroxyitraconazole 1.5 mcg/mL - **true level** would be 2.2 mcg/mL)

Pearls

- Administer the capsule formulation with a full meal
- Administer the oral solution on an empty stomach
- Consider administration with asorbic acid to enhance absorption



TDM Tips

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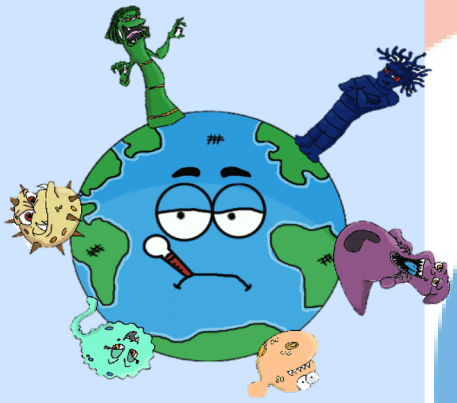
When to consider rechecking a level

Per clinical discretion:

- After a change in dose
- Introduction or discontinuation of drugs with significant interaction potential
- Hepatic impariment or worsening hepatic function
- Patients who are morbidly obese
- Disease progression
- Concern for toxicity
- Diarrhea and receiving oral formulation
- Changing route of administration and/or PO status
- **After 2 consecutive therapeutic levels consider reducing monitoring frequency**



References

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- Arrieta AC, Neely M, Day JC, et al. Safety, tolerability, and population pharmacokinetics of intravenous and oral isavuconazonium sulfate in pediatric patients. Antimicrob Agents Chemother. 2021;65(8):e00290-21.
- Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (Tdm) of antifungal agents: guidelines from the British Society for Medical Mycology. Journal of Antimicrobial Chemotherapy. 2014;69(5):1162-1176.
- Bartelink IH, Wolfs T, Jonker M, et al. Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. Antimicrob Agents Chemother. 2013;57(1):235-240.
- Celik IH, Demirel G, Oguz SS, Uras N, Erdeve O, Dilmen U. Compassionate use of voriconazole in newborn infants diagnosed with severe invasive fungal sepsis. Eur Rev Med Pharmacol Sci. 2013;17(6):729-734.
- Chen J, Chan C, Colantonio D, Seto W. Therapeutic drug monitoring of voriconazole in children. Therapeutic Drug Monitoring. 2012;34(1):77-84.
- Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother. 2003;47(9):2788-2795.
- Dekkers BGJ, Bakker M, van der Elst KCM, et al. Therapeutic drug monitoring of posaconazole: an update. Curr Fungal Infect Rep. 2016;10(2):51-61.
- Doby EH, Benjamin DK, Blaschke AJ, et al. Therapeutic monitoring of voriconazole in children less than three years of age: a case report and summary of voriconazole concentrations for ten children. Pediatric Infectious Disease Journal. 2012;31(6):632-635.
- Dolton MJ, Ray JE, Marriott D, McLachlan AJ. Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56(6):2806-2813.
- Döring M et al. Efficacy, safety and feasibility of antifungal prophylaxis with posaconazole tablet in paediatric patients after haematopoietic stem cell transplantation. J Cancer Res Clin Oncol. 2017;143(7):1281-1292.
- Elhence H, Mongkolrattanothai K, Mohandas S, Neely MN. Isavuconazole pharmacokinetics and pharmacodynamics in children. Pharmaceutics. 2022;15(1):75.
- Gerin M, Mahlaoui N, Elie C, et al. Therapeutic drug monitoring of voriconazole after intravenous administration in infants and children with primary immunodeficiency. Therapeutic Drug Monitoring. 2011;33(4):464-466.
- Isavuconazonium Sulfate. Lexi-Drugs. Hudson, OH: Lexicomp, 2023. http://online.lexi.com/. Accessed May 5, 2023.
- Itraconazole. Lexi-Drugs. Hudson, OH: Lexicomp, 2023. http://online.lexi.com/. Accessed May 5, 2023.
- Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (Secure): a phase 3, randomised-controlled, non-inferiority trial. The Lancet. 2016;387(10020):760-769.
- Posaconazole. Lexi-Drugs. Hudson, OH: Lexicomp, 2023. http://online.lexi.com/. Accessed May 5, 2023.
- Voriconazole. Lexi-Drugs. Hudson, OH: Lexicomp, 2023. http://online.lexi.com/. Accessed May 5, 2023.

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