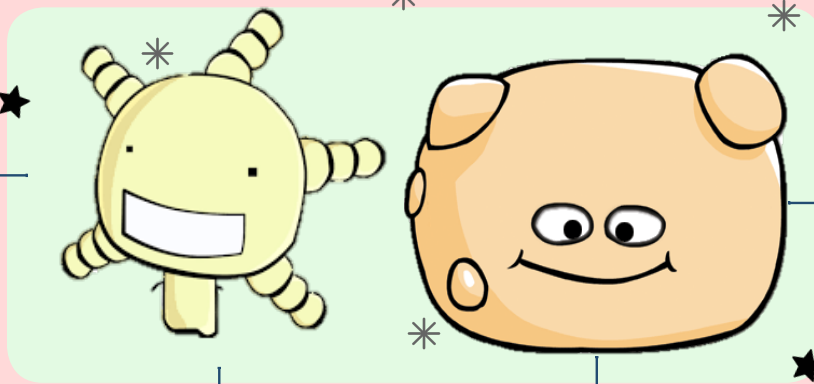


Antifungal Dosing Guidance and Therapeutic Drug Monitoring (TDM) Pediatric UCSF



Summary of Resource



Voriconazole

Itraconazole

Posaconazole

Isavuconazole

TDM Tips

Spectrum

HOW TO 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.

Antifungal Spectrum

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Antifungal	Yeast				Cryptococcus	Dimorphic	Mold	
	Candida					Coccidioides	Aspergillus	Zygomycetes
	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 $\geq 5X$ ULN

CYP3A4 Interactions

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

Legend

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

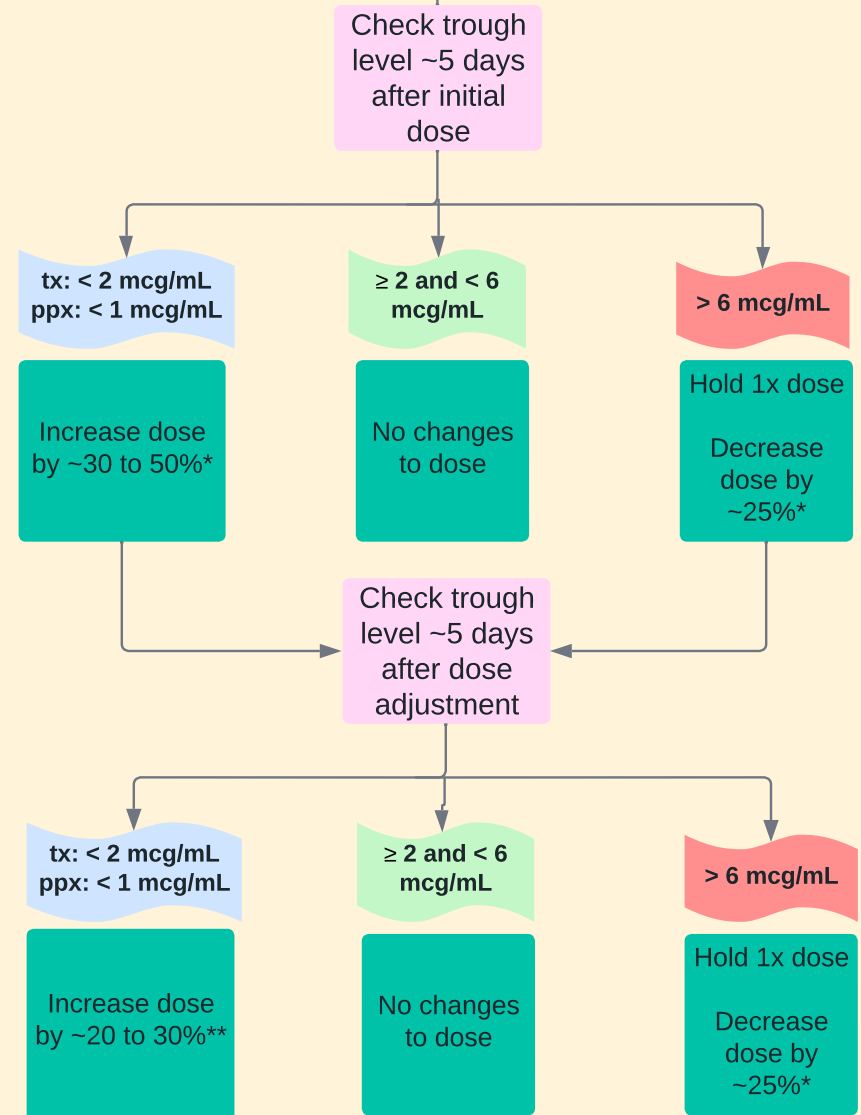
- Trough levels should be drawn before dose on day ~5
- Labs are processed Monday, Wednesday, and Friday
- Labs take about 2-3 days to result

Pearls

- A trough of 1 mcg/mL may be appropriate 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- β cyclodextrin (potential for accumulation in renal insufficiency)
- Avoid use in severe hepatic dysfunction
- Consider CYP2C19 genotyping

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Voriconazole dose per IDMP



*: If using oral tablets or solution, attempt to round to the nearest tablet or 1/2 tablet size or easy to measure volumes (e.g. whole mL) when possible

** : If trough continues to be subtherapeutic consider discussion with ID/ASP

Posaconazole

Formulations

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

Dosing

Oral suspension:	6 mg/kg/dose PO TID (Max 400 mg/dose)
DR tablets	<ul style="list-style-type: none"> > 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
IV Solution:	

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

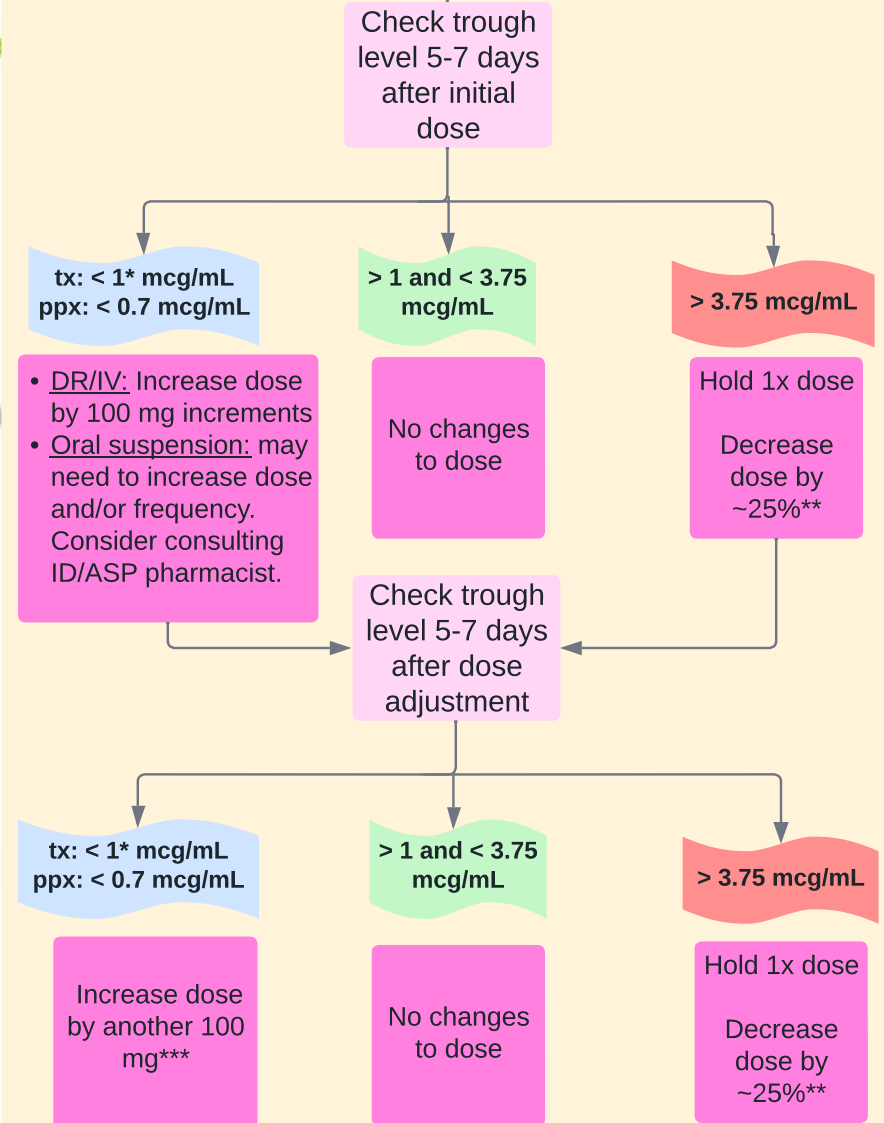
TDM

- 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)

Posaconazole initial dose



- *: 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

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Isavuconazole

Formulations

Capsule:	186 mg
Intravenous:	372 mg/vial

Dosing

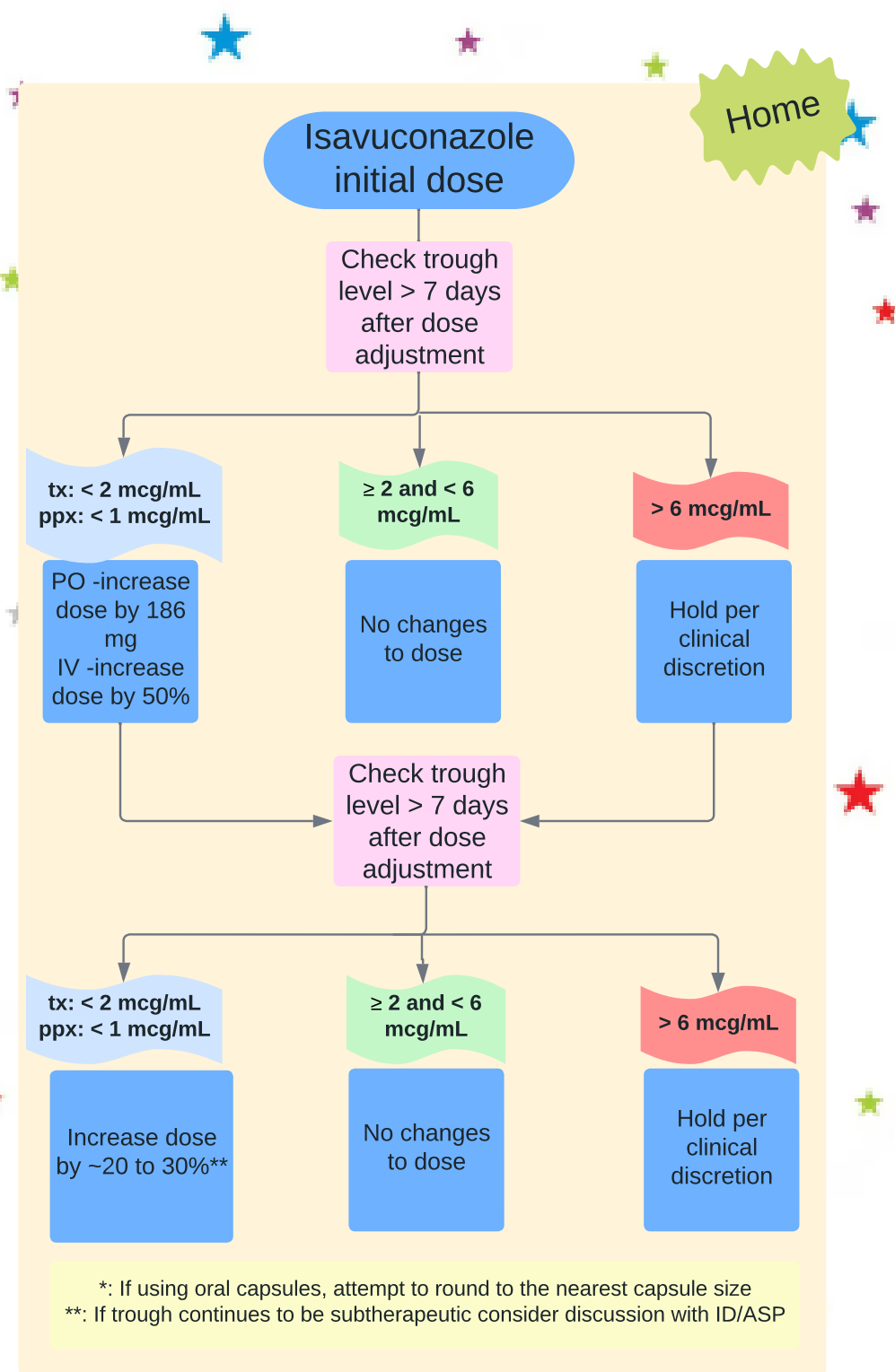
- Children and adolescents < 18 years:
 - IV/PO (Loading Dose):
 - 10 mg isavuconazonium sulfate/kg/dose q8h for 6 doses
 - Initial maximum dose: 372 mg/dose
 - IV/PO (Maintenance Dose):
 - 10 mg isavuconazonium sulfate/kg/dose q24h
 - Initial maximum dose: 372 mg/dose

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

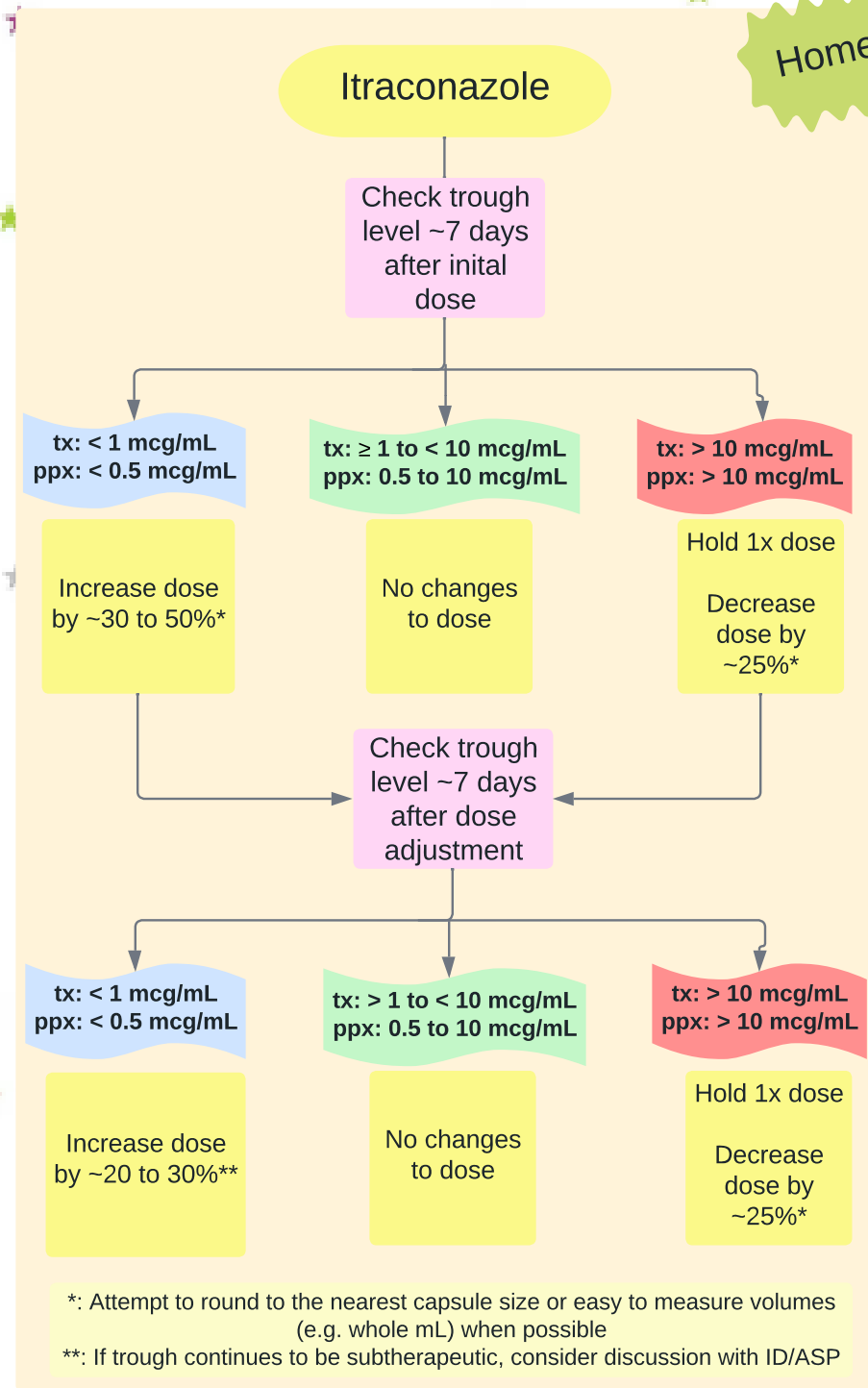
- Oral: 5 mg/kg/dose twice daily
- Initial max 200 mg/dose

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

When to consider rechecking a level

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Per clinical discretion:

- After a change in dose
- Introduction or discontinuation of drugs with significant interaction potential
- Hepatic impairment 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**



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