Antifungal Dosing and Monitoring Clinical Practice Guideline

This resource was created as a reference document for clinical pharmacists at Children's Wisconsin caring for pediatric patients who are receiving an –azole antifungal and need therapeutic drug monitoring (TDM). The document is designed to guide the pharmacist through the process of initial dosing, TDM, dose adjustment based on TDM, and documentation in the electronic medical record. Dosing and recommendations for TDM are based on published literature where available. When no data exists and a recommendation is necessary, clinical expertise or local data is used to guide therapy. Use clinical judgment when using this document, including evaluation of unique patient characteristics which may require dose and TDM individualization.

Azole antifungals exhibit activity by binding to the ergosterol molecule in the fungal cell membrane, causing holes to form, which eventually kills the fungus. Azole antifungals are primarily metabolized in the liver. They are both substrates and inhibitors of cytochrome P450 and therefore involved in a numerous drug-drug interactions. The spectrum of activity varies by agent (Table 1). Key characteristics of azole antifungals are described in Table 2. Because of the high mortality of invasive fungal infections, appropriate exposure (confirmed by therapeutic drug monitoring) to antifungals is crucial for therapeutic efficacy and safety.

Table 1. Spectrum of activity of azole antifungals

Genus		Fluconazole	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
Candida	albicans tropicalis	++	+	+	+	+
	glabrata	+/-	+/-	+/-	+/-	+/-
	krusei	-	+	+	+	-
	lusitaniae	++	+	+	+	+
Cyrptococcus		++	+	+	+	+
Blastomyses		+	+	+	+	++
Aspergillus		-	++	++	++	+/-
Mucorales		-	-	+	+	-

Legend: ++ First line; + Active (potential alternative); +/- Variable activity; - Poor activity or insufficient data

Table 2. Key pharmacologic characteristics of azole antifungals

	Fluconazole	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
Bioavailability (%)	90	Adult: 96 Ped: 40-80	Variable	98	Variable
Protein binding (%)	10	58	98-99	99	99.8
Half-life (hours)	20-50	Variable	20-66	130	Adult: 16-28 Ped: 36

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Voriconazole

Initial Dosing Recommendations: Treatment or Prophylaxis[a]

Formulation	Loading dose (x 2 doses)		Maintenance		Maximum
	Dose	Frequency	Dose	Frequency	
IV					N/A
< 12 years old	9 mg/kg	Q12h	8 mg/kg	Q12h	
≥ 12 years old	6 mg/kg	Q12h	4 mg/kg	Q12h	
Oral tablets or suspension[b]					
< 12 years old	No loading dose		9 mg/kg	Q12h	350 mg/dose
≥ 12 years old			200-300 mg	Q12h	

[a]*No difference in dosing recommendations for prophylaxis vs. treatment (see specific serum drug concentration targets for each below)*

[b]*Oral formulations are not recommended as initial therapy for treatment; dosing can be converted to oral after significant clinical improvement has been observed*

Dosing considerations:

- Use adjusted body weight for dose calculations in obese patients
- For serious infection, consider addition of a second anti-fungal agent until voriconazole concentrations are therapeutic and (if organism is known) susceptibilities are confirmed

Conversion of dosage forms:

- Oral bioavailability is highly variable in children under 12 years of age (45-80%)
- When converting IV dose to enteral in children < 12 years old, a dose increase may be necessary; rounding for tablet size is acceptable
- If a return to IV is necessary after administration of enteral product in children < 12 years old, a dose decrease is warranted
- For children > 12 years old, a 1:1 conversion is recommended

Administration considerations:

- Tablet/suspension: administer one hour before or after meals

Dose Adjustments Based on Renal or Hepatic Dysfunction

Formulation	Renal	Hepatic
Oral	No adjustment needed	Mild-moderate (Child-Pugh Score 5-9): Usual loading dose; reduce maintenance dose by 50%; Severe (Child-Pugh Score 10-15): drug not recommended
IV	Accumulation of vehicle may occur in patients with renal dysfunction; enteral preferred	

Therapeutic Drug Monitoring (TDM):

- Routine turnaround time: 1-2 days (send out test)
    - Shipping available Monday-Friday; courier at 5:30pm
    - Mayo labs: TDM testing Monday-Saturday at 4pm
- Target serum trough concentration for **treatment**: 2-6 mcg/ml
    - Serum trough concentration as low as 1 mcg/ml may be appropriate for select patients without evidence of disseminated or CNS infection in consultation with ID
- Target serum trough concentration for **prophylaxis**: 0.5-6 mcg/ml
    - TDM for prophylaxis is intended for safety (avoid toxicities/adverse events)
    - Consider increasing total daily dose by 25% if trough concentration < 0.5 mg/ml
- Check TDM at steady state: 5 days (or as early as 2 days if a loading dose is administered) after initiation of therapy, dose adjustment, or with the initiation or cessation of an interacting medication
- Critically ill patients may require more frequent monitoring due to more pronounced pharmacokinetic variability in this population
- Re-check serum trough concentration:
    - Routine re-check every 1-2 weeks once therapeutic (auto-induction reported)
    - If change in hepatic function or toxicities suspected
    - If changing route of administration; *oral bioavailability is highly variable in children*

Dose Adjustment based on TDM

Concentration (mcg/ml)	Dose adjustment
< 2	Increase total daily dose by 50%; if 2 consecutive TDM sub-therapeutic or patient < 2 years old, consider dividing the total daily dose into three equal doses
2-6	No change
> 6 and asymptomatic	Decrease total daily dose by 25%
> 6 with drug-related toxicities	Hold 1 dose and decrease total daily dose by 50% (if toxicity is not reversed, consider an alternative antifungal agent)

Adverse effects have been associated with voriconazole, including hepatotoxicity, neurotoxicity, photosensitivity, and cutaneous reactions. Of these, hepatotoxicity and neurotoxicity (particularly visual hallucinations) have been directly correlated with elevated plasma concentrations of voriconazole. Pooled data suggests a threshold of 6 mcg/mL to be most predictive of toxicity. Liver enzymes should be monitored while on therapy. Patients should be counseled to avoid sun exposure and use sunscreen.

Posaconazole

Invasive Fungal Infection Treatment (alternative/salvage), initial dosing:

Formulation	Loading dose (x 2 doses)[a]		Maintenance	
	Dose	Frequency	Dose	Frequency
IV				
< 12 years old	6-10 mg/kg	Q12h	6-10 mg/kg	Q24h
≥ 12 years old	300 mg	Q12h	300 mg	Q24h
Delayed-release (DR) tablet[b] (preferred product for enteral administration)				
< 12 years old	6-10 mg/kg	Twice daily	6-10 mg/kg	Once daily
≥ 12 years old	300 mg	Twice daily	300 mg	Once daily
Immediate-release (IR) oral suspension				
< 34 kg	No loading dose		4-6 mg/kg	Four times daily
≥ 34 kg			200 mg	Four times daily

[a] Loading dose not needed when converting IV to enteral

[b] If unable to swallow tablet, ok to crush DR tablet(s) for oral or feeding tube administration; round to nearest ½ tablet

Invasive Fungal Infection Prophylaxis (neutropenic patients), initial dosing:

Formulation	Loading dose (x 2 doses)[a]		Maintenance	
	Dose	Frequency	Dose	Frequency
IV				
< 12 years old	6 mg/kg	Q12h	6 mg/kg	Q24h
≥ 12 years old	300 mg	Q12h	300 mg	Q24h
Delayed-release (DR) tablet[b] (preferred product for enteral administration)				
< 12 years old	6 mg/kg	Twice daily	6 mg/kg	Once daily
≥ 12 years old	300 mg	Twice daily	300 mg	Once daily
Immediate-release (IR) oral suspension				
< 34 kg	No loading dose		4-6 mg/kg	Three times daily
≥ 34 kg			200 mg	Three times daily

[a] Loading dose not needed when converting IV to enteral

[b] If unable to swallow tablet, ok to crush DR tablet(s) for oral or feeding tube administration; round to nearest ½ tablet

Dosing/administration considerations:

- Use total body weight in obese patients
- Due to wide variability in pharmacokinetics, DR tablet preferred over suspension to maximize probability of achieving target serum concentrations
- If using IR suspension, administration with a high fat meal, liquid nutritional supplement, or acidic carbonated beverage is advised

Dose Adjustments Based on Renal or Hepatic Dysfunction

Formulation	Renal	Hepatic
Oral	No adjustment	No adjustment
IV	Accumulation of vehicle may occur in patients with renal dysfunction; enteral preferred	No adjustment

Therapeutic Drug Monitoring:

- Routine turnaround time: 1-3 days (send out test; shipping available Monday-Friday)
- Trough concentrations are preferred; random concentrations are acceptable
- Target serum concentration for treatment: 1-3.75 mcg/mL
- Target serum concentration for prophylaxis: 0.7-3.75 mcg/mL
    - TDM for prophylaxis is intended for safety (avoid toxicities/adverse events)
- Check TDM at steady state: 7 days after initiation (or 5 days if a loading dose is administered) of therapy, a dose adjustment, or with the initiation or cessation of an interacting medication
- Critically ill patients may require more frequent monitoring due to more pronounced pharmacokinetic variability in this population
- Re-check serum trough concentration:
    - Routine re-check every 4 weeks once therapeutic
    - If toxicities suspected

Dose Adjustment based on TDM

Concentration (mcg/ml)	Dose adjustment
< 1	First optimize administration (use DR tablet if possible or switch to IV if applicable; take with high fat meal or nutritional supplement or acidic beverage for oral suspension)
	Increase total daily dose by 30%
1-3.75	No change
> 3.75	Limited data regarding upper limit; consider dose reduction if experiencing adverse effects
Toxicity suspected	Discontinue (or hold) and consider alternative therapy

** Round to nearest ½ tablet size if using tablets*

Adverse effects include neurologic (headache, fatigue, dizziness), gastrointestinal intolerance, cardiac (hyper/hypotension, peripheral edema), and respiratory (cough/dyspnea). Adverse

effects are more frequent when serum trough concentrations exceed 3.75 mcg/mL. Hepatotoxicity is commonly observed when serum trough concentration is > 5 mcg/mL. Liver enzymes should be monitored while on therapy.

Isavuconazole

Initial Dosing Recommendations: Treatment

Dosage expressed as isavuconazonium sulfate[a]

Formulation	Loading dose (x 6 doses)		Maintenance (begin 12-24 hours following last loading dose)	
	Dose	**Frequency**	**Dose**	**Frequency**
IV				
< 3 years old	15 mg/kg	Every 8 hours	15 mg/kg	Every 24 hours
≥ 3 years old	10 mg/kg (max 372 mg)		10 mg/kg (max 372 mg)	
PO – available as 74.5 mg or 186 mg capsules[b]				
< 6 years old	No data available			
≥ 6 years old:				
16 to < 18 kg	149 mg	Every 8 hours	149 mg	Every 24 hours
18 to < 25 kg	223.5 mg		223.5 mg	
25 to < 32 kg	298 mg		298 mg	
≥ 32 kg	372 mg		372 mg	

[a] 372 mg isavuconazonium sulfate = 200 mg isavuconazole

[b] Opening capsules for oral or feeding tube administration is allowed for patients unable to swallow capsules whole

Dosing considerations:

- Not routinely used for prophylaxis
- Use total body weight in obese patients

Dose Adjustments Based on Renal or Hepatic Dysfunction:

No adjustment necessary

Therapeutic Drug Monitoring:

- Turnaround time: 1-3 days (send out test; shipping available Monday-Friday)
- Target serum trough concentration: 2-4 mcg/mL
- Check TDM at steady state: 10-14 days (or 5-7 days with a loading dose) after initiation of therapy or a dose adjustment
- Hospitalized patients: measure trough concentration
- Non-hospitalized patients: trough concentrations are preferred; random concentrations are acceptable after achieving steady state (note – data extrapolated from PK of the drug; limited published literature on random levels)
- Re-check serum trough concentration:
    - Routine re-check every 4-8 weeks once therapeutic

- If toxicities suspected
- If starting/stopping drugs with significant interaction potential

Dose Adjustment based on TDM

Note – isavuconazole displays linear kinetics; adjust dose accordingly

Concentration (mcg/ml)	Dose adjustment
< 2	Increase daily dose proportionally to target 2-4 mcg/ml *
2-4	No change
> 4	Reduce daily dose proportionally to target 2-4 mcg/ml*
Toxicity suspected	Discontinue (or hold) and consider alternative therapy

** Round to nearest capsule size when using capsules*

Adverse effects include gastrointestinal intolerance (most common), headache, hepatotoxicity, dyspnea, cough, and peripheral edema. Liver enzymes should be monitored while on therapy.

Itraconazole

Initial Dosing Recommendations

- Available PO only
    - Loading dose: 5 mg/kg/dose three times daily for three days (max 200 mg/dose)
    - Maintenance dose: 5 mg/kg/dose twice daily (max 200 mg/dose)
- No dosage adjustments needed for renal or hepatic dysfunction; adjust based on TDM
- Administration
    - Literature suggests improved absorption with oral solution, though experience is varied. Patient/family discussion is encouraged to determine cost implications (solution may be expensive) and preference to take with or without food when determining an appropriate formulation.
    - Capsule: with full meal; avoid acid suppression (e.g., PPI or H2RA)
        - If unable to avoid acid suppression therapy, then separate by 2 hours and administer with an acidic beverage
    - Oral solution: empty stomach (1 hour before or after meals)

Therapeutic Drug Monitoring

Note: HPLC assay measures itraconazole and hydroxyitraconazole concentration; both values should be added to obtain the total concentration

- Total serum concentration = itraconazole + hydroxyitraconazole
- Due to prolonged half-life, random serum concentration sampling is appropriate
- Turnaround time: 2-5 days (send out lab)
    - Courier available Monday-Saturday at 2:30pm
    - Quest labs: TDM testing Tuesday, Thursday, Saturday (time not specified)
- Target serum concentration (total) for prophylaxis: < 0.5-10 mcg/mL
- Target serum concentration (total) for treatment: 1-10 mcg/mL
- Check TDM at steady state: 10-14 days after initiation of therapy or a dose adjustment; may check earlier (at 5-7 days) if a loading dose administered
- Re-check serum trough concentration:
    - Routine re-check every 3 months for prolonged courses (assesses compliance)
    - If concerns for oral absorption or changing formulation
    - If lack of response suspected
    - If toxicities suspected
    - If starting/stopping drugs with significant interaction potential

Dose Adjustment based on TDM

Concentration (mcg/ml)	Dose adjustment
< 1	First address bioavailability issues (e.g., drug interactions, compliance, gastric pH) and use oral solution if possible

	Consider increasing dose or frequency of administration
1-10	No change
> 10	Limited data to guide adjustment; consider dose reduction if experiencing adverse effects
Toxicity suspected	Discontinue (or hold) and consider alternative therapy

Adverse effects may include gastrointestinal intolerance (most common), hepatotoxicity, neurologic effects (e.g., tremor, peripheral neuropathy), cardiovascular effects (e.g., worsening heart failure, QT prolongation), and pseudohyperaldosteronism. Liver enzymes should be monitored while on therapy.

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