

RECOMMENDED THERAPEUTIC DRUG MONITORING (TDM) FOR SELECT ANTIFUNGAL AGENTS IN ADULT PATIENTS*

DUKE UNIVERSITY HEALTH SYSTEM (DUHS)

General Antifungal Considerations & Recommendations

- The table below is intended to provide general guidance and **should NOT** replace clinical judgement.
- Prior to dosing adjustment, consider the following:
 - Medication adherence
 - Drug formulation
 - Drug interactions
 - Gut absorption
 - IV incompatibilities (e.g. IV posaconazole; see [here](#) for specific examples)
 - Presence of hypermetabolic state (e.g. extensive burn injuries)
- For individualized dose adjustment recommendations, please feel free to page the covering [pharmacist](#) or ASET pharmacist at 970-6666.

Drug name	DUHS Formulations	Timing ^y	Target Concentration	Recommended Dose Adjustments	Notes
Azoles					
Posaconazole	Delayed Release (DR) tablet (100 mg) (preferred oral formulation) Oral suspension (40 mg/mL) Intravenous	5-7 days Type: trough (immediately prior to dose) Turnaround time 3-5 business days (send-out lab)	Prophylaxis: ≥ 0.7 mcg/mL Treatment: ≥ 1 mcg/mL (may consider ≥ 1.25 mcg/mL in select clinical cases) Toxicity Threshold: upper limit not established* *posaconazole-induced pseudohyperaldosteronism (PIPH) has been reported at higher troughs (i.e. >3-4 mcg/mL)	< 0.7 mcg/mL (prophylaxis) or < 1.0 mcg/mL (or < 1.25 mcg/mL) (treatment) DR tablet/IV: increase daily dose by 100 mg and re-check in 5-7 days. Larger dose increases may be necessary in patients with concentration < 0.5 mcg/mL. Oral Suspension: increase daily dose by 200-400 mg and re-check in 5-7 days (dose increases above 400 mg BID not recommended – consult ID pharmacist) > 3 mcg/mL with PIPH (unless specified by ID consult team) DR tablet: reduce daily dose by 100 mg and re-check in 5-7 days Oral Suspension: reduce daily dose by 200 mg and re-check in 5-7 days	DR tablets: preferred over suspension due to superior oral absorption. Should not be crushed IV: requires a central line for administration. Contains cyclodextrin (which may accumulate in renal insufficiency) Suspension: max individual dose is 400 mg due to saturable kinetics - Cyclodextrin is removed via HD and CRRT - If PIPH persists despite lower dose, consider switching azoles or symptom management (potassium repletion, blood pressure management, and addition of an aldosterone antagonist)

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Drug name	DUHS Formulations	Timing [¥]	Target Concentration	Recommended Dose Adjustments	Notes
Voriconazole	Tablets (50 mg, 200mg) Oral suspension (40mg/mL) Intravenous	5-7 days Type: trough (immediately prior to dose) Turnaround time 48 hours (run in-house)	Prophylaxis: ≥ 1 to ≤ 5.5 mcg/mL Treatment: ≥1 to ≤ 5.5 mcg/mL (Note: troughs >2 mcg/mL may be considered for select patients guided by ID consult team)	< 1 mcg/mL : increase daily dose by 50-100 mg and re-check in 5-7 days. Larger dose increases may be necessary in select patients (<i>e.g.</i> hypermetabolic states) > 5.5 mcg/mL : consider holding 1-2 doses and restarting at lower dose (decrease daily dose by 50-100 mg); recheck in 5-7 days	• High intra-patient PK variability due to polymorphisms in CYP2C19; nonlinear PK in adults • Take tablets/suspension on an empty stomach • Use adjusted body weight if obese • IV contains cyclodextrin (which may accumulate in renal insufficiency) • Cyclodextrin is removed via HD and CRRT • Visual disturbances or hallucinations may occur with higher exposure
Isavuconazole	Capsule (186 mg) Intravenous	Optimal population and timing for TDM not established; 5-7 days in select cases Type: trough (immediately prior to dose) Turnaround time 3-5 business days (send-out lab)	Prophylaxis/Treatment: not established; consider ≥1 mcg/mL in select cases Toxicity Threshold: not established	Not established if <1 mcg/mL consider increasing dose by 186 mg (1 capsule)	• IV can be given via a peripheral or central line (infuse with an in-line filter) • Consider further discussion with ID if concern for hypo or hyper metabolic state • Limited data exists for efficacy and toxicity thresholds. TDM may be warranted in select cases guided by ID consult team

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Itraconazole	Oral Capsule (100 mg) Oral Solution (10 mg/mL)	5-7 days after starting therapy if loading dose is used or 10-14 days if not loaded Type: trough levels are preferred (immediately prior to dose), but random levels are acceptable given long half-life with repeated dosing (34-42 hrs) Turnaround time 3-5 business days (send-out lab)	Prophylaxis*: ≥ 0.5 mcg/mL Treatment*: ≥ 1 mcg/mL *These concentration thresholds are based on the itraconazole component only as measured by chromatographic assays (e.g HPLC, LC/MS) (Not the sum of itraconazole+hydroxy-itraconazole) Threshold for Toxicity: Not established; monitor for signs and symptoms of pseudohyperaldosteronism (eg. new/worsening hypertension, hypokalemia)	< 0.5 mcg/mL (prophylaxis) or < 1 mcg/mL (treatment): Increase total daily dose by 100-200 mg	- Extensively metabolized into numerous metabolites, including hydroxy-itraconazole (active) Oral capsule (Sporanox®): Absorption is increased by low stomach pH and high-fat content meals. Discontinue unnecessary PPI or H2RA therapy. Absorption can be increased by taking capsules with an acidic drink (ie. Coca-cola) Oral solution: Higher bioavailability when taken on an empty stomach. Take solution 1 hour before or 2 hours after meals. - Avoid using > 400 mg/dose. Divided dosing is recommended to improve absorption
Pyrimidines					
Flucytosine	Capsule (250 mg, 500 mg) Oral suspension (10 mg/mL)	Day 3-5 Type: peak (2 hours after dose) Turnaround time 3-5 business days (send-out lab)	Cryptococcal Infections: 30-80 mcg/mL Candida Meningitis: 40-60 mcg/mL Toxicity Threshold: >100 mcg/mL Concentrations > 100 mcg/mL associated with myelosuppression and hepatotoxicity	Subtherapeutic by indication: Increase total daily dose. Changes in serum concentration are proportional to dose adjustments > 100 mcg/mL: Decrease total daily dose. Changes in serum concentration are proportional to dose adjustments. Consider holding 1-2 doses and restarting at lower dose/interval if serum concentration > 150 mcg/mL	- Renal insufficiency: requires dose adjustment - Once target concentration established, repeat serum concentration monitoring unnecessary unless concern for toxicity or changing renal function leading to dose changes - Obese patients: use IBW

¥ after drug initiation and/or subsequent dose changes

*amphotericin B (polyene) and fluconazole (azole) are not recommended for routine TDM

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