Triazole Antifungal Therapeutic Drug Monitoring Guidance

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The purpose of this document is to provide guidance on when to perform therapeutic drug monitoring (TDM) and obtain serum concentrations of triazole antifungals. For additional guidance on monitoring for adverse effects and lab frequency, see the "Antimicrobial Monitoring" document in the Housestaff Manual.

The general intent of triazole antifungal TDM is to improve efficacy by achieving a therapeutic serum concentration based on evidence and guidelines, monitor adherence, and improve safety by identifying supratherapeutic serum concentrations that may increase the risk of toxicity. Of note, other antifungals, including amphotericin products and echinocandins do not require TDM.

Performance of triazole antifungals TDM includes obtaining plasma or serum specimens which are sent to an outside laboratory for analysis (consider Send-Out Lab hours to improve turnaround time).

All serum concentration goals below are based on a steady state trough concentration, which is the lowest concentration in the body before the next dose. All blood collections should occur 30 minutes prior to administration of the next dose at steady state to obtain a clinically relevant and interpretable serum concentration (see individual triazole content below for timing TDM).

Triazole antifungal	Trough goals	When to perform TDM	How to perform TDM	Adverse effects and comments
Voriconazole	Treatment: 1 – 5.5 mcg/mL[1] (some experts recommend ≥ 2 mcg/mL for severe disease) Prophylaxis: 1 – 5.5 mcg/mL[1-3] (consider rechecking level if 0.7 to < 1.0 before dose adjusting)	Recommend TDM routinely for all treatment courses Consider TDM for prophylaxis courses	Measure serum concentration on day 5 of consecutive therapy (presumed steady state) and 4 days after change in dose Repeat one week after initial trough to confirm within therapeutic range Repeat for any of the following: • Patient's clinical condition (e.g., disease progression, diarrhea with enteral formulation, GVHD, concern for non-adherence) • Concomitant interacting medications (see comments) • Suspected toxicity (e.g., neurotoxicity, hepatotoxicity)	Hepatotoxicity, QTc prolongation, visual disturbances (e.g., hallucinations, skin photosensitivity), SJS, TEN, periostitis due to fluorosis, and with long-term use, dermatological complications (e.g., cutaneous malignancies) Serum levels >5.5 mcg/mL may be associated with increased risk of visual disturbances, neurotoxicity, and hepatotoxicity IV formulation contains sulfobutylether-beta-cyclodextrin which undergoes renal elimination and may accumulate when CrCl <50 ml/min Drug-drug interactions: Strong inhibitor and substrate of CYP3A4 (e.g., cyclosporine, tacrolimus, and vincristine metabolism inhibition), moderate inhibitor and substrate of CYP2C19 and weak inhibitor of CYP2C9.

Triazole antifungal	Trough goals	When to perform TDM	How to perform TDM	Adverse effects and comments
Posaconazole	Treatment: >1 mcg/mL (1000 ng/mL)[1] (some experts recommend >1.25 mcg/mL [>1250 ng/mL] for salvage therapy)[4] Prophylaxis: >0.7 mcg/mL (>700 ng/mL)[1,4]	Routine monitoring for all treatment and prophylaxis courses	Measure serum concentration on day 5 of therapy (presumed steady state) and 4 days after change in dose Repeat TDM as clinically relevant, such as: • Patient's clinical condition (e.g., disease progression, ***diarrhea with enteral formulation, GVHD***, concern for non-adherence) • Concomitant interacting medications • Suspected toxicity (e.g., QTc prolongation, hepatotoxicity)	Hepatotoxicity, QTc prolongation, thrombocytopenia, leukopenia, electrolyte abnormalities, derm. complications (e.g., rash) Serum levels > 3.75 mcg/mL (>3750 ng/mL) have not been well studied and may be associated with adverse effects[5,6] Delayed release tablets are not interchangeable with immediate release oral suspension due to dose differences (bioavailability improved with ***high fat meals and/or acidic beverage***) Drug-drug interactions: Strong CYP3A4 inhibitor, e.g., vincristine contraindicated[7]
Isavuconazole	Treatment: Not established, consider 1 – 7 mcg/mL (some experts recommend 3 – 6 mcg/mL)[8,9] Prophylaxis: NA	Given predictable PK and lack of concentration-dependent relationships for efficacy or safety, routine monitoring is not required		Hepatotoxicity, QTc shortening Intravenous and enteral formulations are interchangeable Drug-drug interactions: Major substrate of CYP3A4 and moderate inhibitor
Fluconazole	Treatment: Not established, AUC: MIC > 100 may be an appropriate target[10] Prophylaxis: NA	Given predictable PK, attainment of serum concentration is rarely indicated, but can be considered for CNS disease, renal replacement therapy, organisms with a high MIC, or adherence		Hepatotoxicity, QTc prolongation Primarily renally eliminated, dose adjustment advised for CrCl <50 mL/min Drug-drug interactions: Strong inhibitor of CYP2C19, moderate inhibitor of CYP3A4 and CYP2C9
Itraconazole*	Add the itraconazole and hydroxy-itraconazole levels to assess target serum concentration Treatment: 1 – 4 mcg/mL[11] Prophylaxis: 0.5 – 4 mcg/mL	Routine monitoring for all treatment and prophylaxis courses	Because of the long half-life, serum concentrations vary little during a 24-h dosing interval and blood specimen can be collected at any time. Measure serum concentration after 2 weeks of therapy (presumed steady state)	Hepatotoxicity, QTc prolongation, heart failure exacerbation, CNS depression, neuropathy Formulations are not interchangeable. Oral solution bioavailability taken on an empty stomach improves absorption while capsules should be taken after meals. HPLC procedure for TDM is preferred over bioassay which may be the analytic assay used at other labs.[12] Results are not interchangeable as bioassays (~ 2 to 10 times higher than HPLC). Drug-drug interactions: Strong inhibitor and substrate of CYP3A4

* Non-formulary at LPCHS

HPLC: high-performance liquid chromatography GVHD: Graft versus host disease; PK: Pharmacokinetics; NA: Not available; SJS: Stevens-Johnson syndrome; TDM: Therapeutic drug monitoring; TEN: Toxic epidermal necrolysis

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