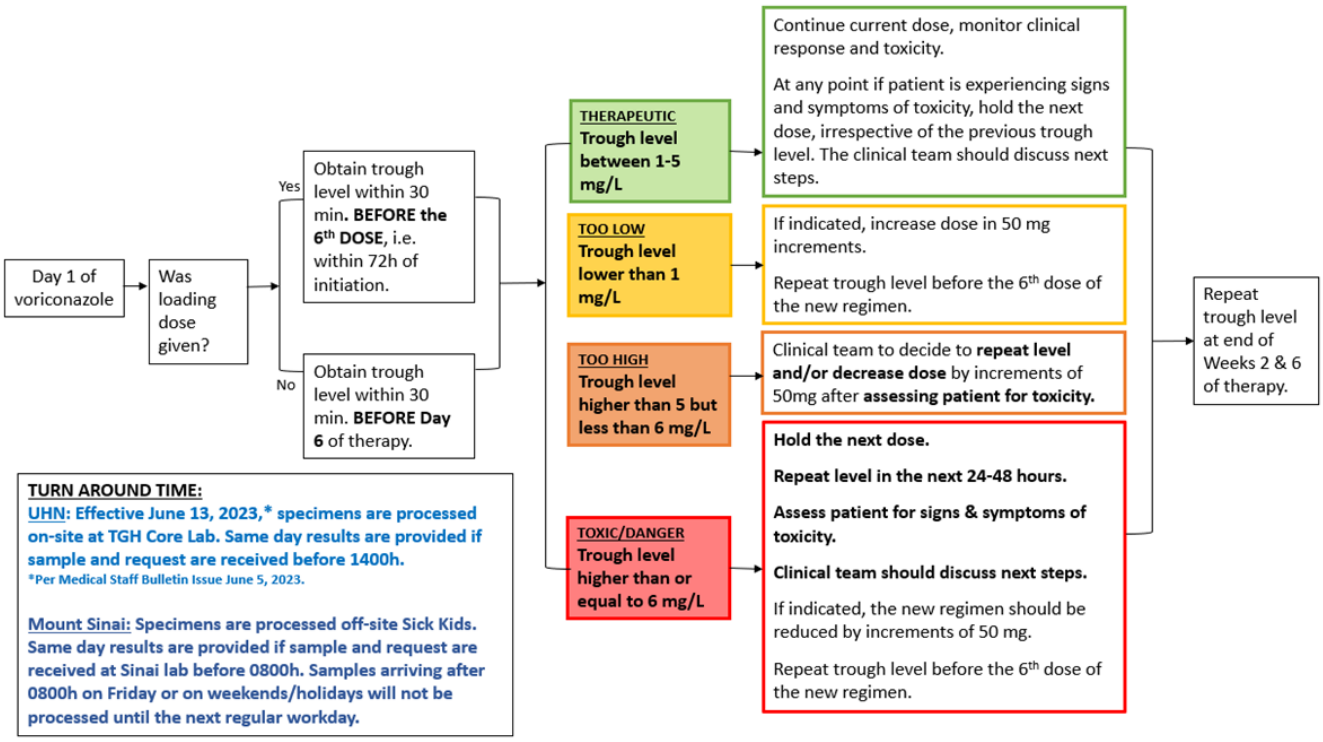
Voriconazole

Dosing:

- **Invasive aspergillosis:** 6 mg/kg IV or PO Q12H x 2 doses, followed by 4 mg/kg IV or PO Q12H
- **Invasive candidiasis (not 1st line):** 6 mg/kg IV or PO Q12H x 2 doses, followed by 3 mg/kg IV or PO Q12H

Accepted therapeutic range: 1-5 mg/L



Rationale for monitoring voriconazole levels: safety and efficacy

- Associated with high level, neurotoxicity can present as visual and/or auditory hallucinations, altered mental status, agitation and involuntary myotonic movements.
    - IMPORTANT: neurotoxicity is to be *distinguished from transient visual disturbances* (photopsia), which can occur a few minutes after receiving voriconazole (PO or IV), and is related to higher doses, e.g. at loading dose. They generally resolve as therapy continues, therefore, it is not an indication to stop therapy.

- Transaminitis can be associated with trough levels greater than 5.5-6 mg/L, with the potential development of hepatitis.
- Voriconazole is metabolized by CYP isoenzymes 2C9, 2C19, and 3A4. Drug-drug interactions involving voriconazole are common and wide-ranging.
    - Examples (not exhaustive): cyclosporine, tacrolimus, tyrosine kinase inhibitors, sulfonylureas (glyburide, gliclazide, glimepiride, glipizide), rifamycins, benzodiazepines, phenytoin, carbamazepine.
    - Conduct a thorough review of potential interactions when initiating therapy and monitor drug levels accordingly if voriconazole is indicated. The addition of a medication that interacts with voriconazole should trigger a recheck of voriconazole level.
- Voriconazole has a non-linear relationship between dose and serum level, coupled with genetic polymorphism of 2C19, there is wide variability in serum level.
- Subtherapeutic levels may be associated with poor clinical response to therapy.

References

1. Vfend product monograph in RxTx.
2. Purkins, L., Wood, N., Greenhalgh, K., et al. The pharmacokinetics and safety of intravenous voriconazole - a novel wide-spectrum antifungal agent. British Journal of Clinical Pharmacology 2003;56:2–9. doi: 10.1046/j.1365-2125.2003.01992.
3. Ashbee HR, Barnes RA, Johnson EM et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society of Medical Mycology. J Antimicrob Chemother 2014;69:1162-1176.
4. Luong M, Al-Dabbagh M, Groll AH et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother 2016;71:1786–1799.
5. Jin H, Wang T, Falcione B et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. J Antimicrob Chemother 2016;71:1772-1785.
6. Mourad A and Perfect JR. Tolerability profile of the current antifungal armoury. J Antimicrob Chemother 2018;73(S1):i26-i32.
7. Lagrou K, Duarte R, Maetens J. Standards of CARE: what is considered ‘best practice’ for the management of invasive fungal infections? A haematologist’s and a mycologist’s perspective. J Antimicrob Chemother 2019;74(2)ii3-ii8.
8. Garcia-Vidal, Carratalà J, Lortholary O. Defining standards of CARE for invasive fungal diseases in solid organ transplant patients. J Antimicrob Chemother 2019;74(2)ii6-ii20