Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2021

Introduction

Therapeutic drug monitoring (TDM) is a key component of antifungal stewardship.[1] TDM is suggested for drugs that have either large dose-exposure variability due to drug or patient characteristics and/or narrow therapeutic windows with defined exposures for safety or efficacy.[2] Flucytosine (5-FC) and the older mould-active triazole antifungals, including itraconazole, posaconazole and voriconazole, fulfil the majority of these characteristics.[3] Previous studies have demonstrated that only 54–86% of patients on itraconazole,[4, 5] 49–60% of patients on voriconazole,[6, 7] and 29–93% of patients on posaconazole[8-14] have serum drug concentrations within therapeutic ranges. Therefore, TDM of these antifungals is important to improve adequacy of drug exposure, optimise clinical outcomes in those with highly morbid invasive fungal disease (IFD), and reduce adverse drug reactions.[15, 16]

These guidelines aim to build on detailed information presented in the 2014 Consensus Guidelines.[16] They provide clinicians with clear and practical recommendations on the TDM of antifungal agents, as well as updated advice on potential antifungal drug interactions, with the aim of minimising drug toxicity and optimising outcomes in patients with cancers or post-haemopoietic stem cell transplantation (HSCT). The current guidelines also include recommended practitioner competencies, as required for optimal interpretation of TDM for antifungal agents, new clinical evidence and recommendations for antifungal drug monitoring, and suggested resources for identifying and analysing antifungal drug-drug

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interaction. The current guidelines address nine key questions, covering areas the Steering Committee deemed to be of significant clinical interest and/or where new data have emerged since the previous guidelines.

Methodology

Questions asked

This update addresses the following questions:

1. What resources exist to assist assessment of potential antifungal drug-drug interactions and drug toxicities in haematology and oncology patients?

2. What are the present antifungal TDM targets, sampling and sample type, time-to-resampling and dose adjustment?

3. How do we prioritise patients for TDM who receive posaconazole suspension or itraconazole capsule and solution versus newer formulations of posaconazole modified-release tablet or SUBA®-itraconazole?

4. When should fluconazole TDM be used?

5. Is there any role for area under the curve (AUC) / minimum inhibitory concentration (MIC)-based, as opposed to trough concentration-based, dose adjustment for triazole antifungal agents?

6. When adjusting azole antifungal agents for subtherapeutic concentrations, is there a recommended 'maximum' dose and when should we consider switching agents?

7. Is flucytosine TDM required in cryptococcal infections?

8. What TDM and interpretation is required for 'sanctuary site' infections, including central nervous system (CNS), bone and eye?

9. What are the barriers and challenges in TDM implementation?

Search strategy

A literature review was performed using PubMed and Medline to identify articles that pertained to 'antifungal drug interactions', 'antifungal drug toxicities', 'antifungal pharmacokinetics', 'antifungal TDM' and 'pharmacogenomics evaluation'.

Question 1 What resources exist to assist assessment of potential antifungal drug-drug interactions and drug toxicities in haematology and oncology patients?

Antifungal agents are administered concomitantly with numerous other medications, and often for prolonged periods. Therefore, assessment of potential drug-drug interactions is essential to ensure effective therapy and reduce the risk of drug toxicity. Of all antifungal agents, azole antifungals are most frequently associated with drug-drug interactions. In general, azole antifungals are metabolised by the cytochrome P450 (CYP450) system, although posaconazole primarily undergoes uridine diphosphate (UDP) glucuronidation[17] and fluconazole is largely renally excreted.[18] Echinocandins and amphotericin B are less commonly implicated in clinically significant drug-drug interactions. Previous studies have found that drug-drug interactions occur in approximately 30% of patients receiving anticancer therapy.[19]

Drug interactions can occur during the absorption, distribution, metabolism, and clearance of drugs (see Table 1 for selected examples and Table 2 for the inhibitory potency of antifungal agents on selected CYP enzymes).[20] Concurrent treatment with medications that induce or inhibit CYP450 enzymes and antifungals that are CYP450 substrates can influence the serum concentrations of these antifungal agents, resulting in reduced efficacy or increased toxicity. If there is no alternative to the offending agent and the clinical use of this combination is deemed necessary, adjust antifungal doses and monitor antifungal concentrations closely (if applicable), particularly on initiation and cessation of the offending drugs. The extent of drug interaction may vary between patients, and thus TDM is essential to guide dose adjustment and optimise antifungal therapy.[21, 22]

Table 1 Selected examples of the pharmacokinetic interactions of antifungal agents

	Mechanism	Examples of implicated antifungals
Absorption	pH	• Itraconazole capsules[23-25]
		• Posaconazole suspension[26]
	Food	• Posaconazole suspension [26]
		• Itraconazole (Sporanox®)[23, 27]
		• Voriconazole[28]
Metabolism	CYP450 system	• Posaconazole[29]
		• Itraconazole[29]
		• Voriconazole[29]
		• Isavuconazole[29]
		• Ibrexafungerp[29]
		• Olorofim[29]
Excretion	P-glycoprotein	• Itraconazole[20]
		• Posaconazole[30]
	Renal elimination/toxicity	• Amphotericin[20]

Table 2 Inhibitory potency of antifungal agents with selected CYP enzymes[29-36]

	CYP2C9		CYP2C19		CYP3A4	
	Substrate	Inhibition	Substrate	Inhibition	Substrate	Inhibition
Itraconazole	0	0	0	0	√	+++
Posaconazole	0	0	0	0	0	+++
Voriconazole	√	+	√	++	√	+++
Fluconazole	0	++	0	+++	0	++(#)
Isavuconazole	0	0	0	0	√	++
Caspofungin	0	0	0	0	0	0
Anidulafungin	0	0	0	0	0	0
Micafungin	0	0	0	0	0	0
Olorofim	*	*	*	*	√	+
Rezafungin	0	0	0	0	0	0
Ibrexafungerp	*	*	*	*	√	+

+ , weak; ++, moderate; +++, strong; classification based upon US Food and Drug Administration guidance[37]; √ , CYP substrate; * , still being evaluated in clinical trials with limited published data available; # , dose ≥200 mg

Drug interaction databases

There are numerous databases that can be used to assess for drug interactions, many of which are routinely available in Australian hospitals (see Table 3 for some examples). In addition to these databases, there are also free, online drug-drug interaction databases that specifically focus on the interactions between antifungal agents and other prescription and non-prescription medications (see Table 4 for examples).[38, 39]

Table 3 Example databases providing detailed drug-drug interaction data

Drug resource	Link
MIMS drug interactions	https://www.mimsonline.com.au/
Lexi-Interact	http://online.lexi.com/
Stockley's interactions checker	https://about.medicinescomplete.com/publication/stockleys-interactions-checker/
Micromedex® drug interactions	https://www.micromedexsolutions.com/
DrugBank	https://go.drugbank.com/
Cancer Drug Interactions	https://www.cancer-druginteractions.org/checker This is also available as a smartphone app and can be downloaded from Google Play or iTunes: https://apps.apple.com/gb/app/cancer-ichart/id1414833100 (iOS) https://play.google.com/store/apps/details?id=com.liverpooluni.ichartoncology (Android)

Table 4 Databases providing detailed drug-drug interaction data specific to antifungal agents

Antifungal drug interaction database	Link
Fungal Pharmacology	http://www.fungalpharmacology.org/tool This tool was developed by the Radboud University Medical Centre in Nijmegen, the Netherlands. However, it does not include interactions for newly registered antifungal agents (e.g. isavuconazole). It is also available as a smartphone app and can be downloaded from Google Play or iTunes (search term, Fungal Pharmacology).
Antifungal Drug Interactions Database by Aspergillus Website and Fungal Infection Trust	http://www.antifungalinteractions.org.uk/ This is available as a smartphone app and can be downloaded from Google Play at: https://play.google.com/store/apps/details?id=com.aspergillus.antifungalinteractionsnew

In haematology populations, where an antifungal-associated drug interaction is likely, guidance can be obtained from the 2014 Consensus Guidelines[16] and the review article by Lindsay *et al*. 2019.[40] Co-administration of medications that are CYP450 substrates with antifungal agents that inhibit CYP450 enzymes may increase the serum concentrations of CYP450 substrates. If there is no appropriate alternative, adjust the medication doses accordingly and monitor patients for toxicities. If TDM assay is available for the CYP450 substrates (e.g. tacrolimus, ciclosporin, sirolimus), monitor serum concentrations closely, particularly upon commencement and cessation of the antifungal agent.[16]

Adverse effects of antifungal agents

The toxicity and adverse effects of currently available systemic antifungal agents are summarised in Table 5. There are also many drug reference databases available with comprehensive adverse effect profiles of antifungal agents (see Table 6 for examples).

Table 5 Toxicity and adverse effects of currently available systemic antifungal agents

Antifungal agent	Commonly reported side-effects	Evidence and suggestions for risk reduction
AmB-D L-AMB ABLC ABCD	Nephrotoxicity	• Reported rates of renal toxicity: AmB-D 32–33% ; L-AMB 15% ; ABLC 16% ; ABCD 21% [41, 42] • Nephrotoxicity may be minimised by pre-hydrating with sodium chloride 0.9% (500 ml over 1 h in adult patients) and avoiding hyponatraemia and hypovolaemia[43-45] • Similar rates of nephrotoxicity are observed for AmB-D through continuous infusion and L-AMB although no adequately powered direct comparison has been performed[46] • Renal toxicity is substantially more likely in patients receiving more than two nephrotoxins concomitantly or undergoing HSCT; consider a lipid-based product in these circumstances[47, 48]
	IRAE	• IRAE occur frequently with AmB-D: fever 34–51%; chills or rigors 28–74%; nausea 18–19%.[42, 47, 49, 50] More severe IRAE occur less frequently: bronchospasm 7%; hypotension 1–11%[42, 48, 51, 52]

	• Premedication is frequently used to help reduce the incidence of IRAE of AmB-D, although data supporting this practice are limited[49, 50]
	• AmB-D through continuous infusion causes significantly less IRAE compared with standard therapy[46]
	• L-AMB is responsible for less IRAE compared with other lipid preparations: fever 11%; chills or rigors 37%; nausea 12%[42, 48, 53, 54]
	• Rates of IRAE with ABLC are similar to AmB-D whereas ABCD is associated with higher rates of IRAE[42, 53, 55-57]
	• Tolerance to IRAE generally develops within the first seven days of initiating therapy[49, 50]
Electrolyte abnormalities	• Electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia) commonly occur with AmB-D because of renal losses (serum potassium ≤2.5 mmol/L: 12–31%); monitor electrolyte levels closely and replace if necessary[47, 54]
	• Electrolyte disturbances are observed less frequently with L-AMB and ABLC compared with AmB-D; monitor electrolyte levels closely and replace if necessary[47, 54, 55]

		• Consider using amiloride (10 mg daily) to decrease urinary potassium loss, increase serum potassium and reduce potassium replacement requirements[57]
	Hepatotoxicity	• Hepatotoxicity (bilirubin or transaminases > 3 times baseline) occurs in 16% of patients receiving AmB-D; this is not significantly different to rates observed with the lipid preparations[42]
	Other	• Rash is reported in 1–5% of patients receiving amphotericin products[51, 58-60] • A reversible normochromic, normocytic anaemia (mediated by a suppression of erythropoietin production) may occur with prolonged use[61, 62]
Fluconazole	Gastrointestinal toxicity	• Gastrointestinal symptoms (nausea, vomiting and diarrhoea) occur in a minority of patients; 0–9%[51, 63-67]
	Hepatotoxicity	• The rate of hepatotoxicity varies greatly depending on the patient population and definition used. Most trials report rates between 1–18% ; this is not significantly different to AmB-D and L-AMB[42, 51, 63, 66-70] • Discontinuation due to hepatotoxicity is rare (0–5%)[42, 51, 63, 66-69]
	Dermatological toxicity	• Rash is reported in 4–6% of patients[51, 64]

	Other	• Nephrotoxicity occurs in 1–3% of patients receiving fluconazole (significantly less than AmB-D)[51, 65, 68] • IRAE are rarely reported with fluconazole: fever and/or chills 0–1% (significantly less than AmB-D)[51, 70] • QT prolongation has been reported[71]
Itraconazole	Gastrointestinal toxicity	• Gastrointestinal symptoms are reported in 13–24% of subjects receiving itraconazole[42, 52, 64, 65, 72, 73] • Compared with fluconazole and posaconazole, itraconazole causes significantly more gastrointestinal toxicity[51, 65, 74] • The incidence of diarrhoea increases with higher doses of the oral solution due to the cyclodextrin vehicle[75]; oral-loading doses can be difficult to tolerate. In practice, it is probably more feasible to load with 400 mg capsules twice daily (swapping to the oral solution 200 mg twice daily for ongoing therapy), or starting the itraconazole solution (200 mg twice daily) 1–2 weeks before the prophylactic effect is required[76]
	Hepatotoxicity	• Rates of hepatotoxicity vary depending on the patient population and definition used (7–32%); this is not significantly different to fluconazole and posaconazole[52, 64, 65, 72, 74, 77]

	Dermatological toxicity	• Rash is reported in 4–7% of patients[64, 72]
	Other	• Nephrotoxicity occurs in 5–7% of patients receiving itraconazole[52, 65] • There has been a case report of itraconazole-induced hypertension and hypokalaemia due to inhibition of 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2); symptoms resolved on cessation of itraconazole treatment. This patient was on itraconazole 300 mg twice daily and itraconazole concentration was 2.11 mg/L[78]
Voriconazole	Ocular toxicity	• Dose-related visual disturbances, including blurred vision, photophobia, and altered visual and colour perception, occur in 22–45% of patients.[59, 79, 80] The visual disturbances are transient and resolve without intervention, usually within the hour. There is evidence that the effect is attenuated with repeated dosing. It is generally not necessary to stop therapy
	Hepatotoxicity	• Significant transaminitis (ALT/AST >5 times baseline) is observed in 4–9% of patients.[59, 79, 80] Hyperbilirubinaemia (>3 times baseline level) occurs in up to 18% of patients.[79] While controversial, some data suggest that increased serum voriconazole concentrations correlate with the development of hepatitis, and discontinuation may result in normalisation of hepatic enzymes.[81, 82] The rate of

	hepatotoxicity was not significantly different to AmB-D, L-AMB and fluconazole in comparative trials[59, 79, 83]
Dermatological toxicity	• Rash, pruritus or photosensitivity occurs in 7–9% of patients.[59, 80, 84] Monitor any rash closely and cease voriconazole therapy if the rash progresses. Patients should be advised to take adequate precautions to avoid exposure to sunlight during voriconazole therapy, as there have been reports of squamous cell carcinoma and melanoma after long-term exposure to voriconazole[85-88]
Neurological toxicity	• Neurological toxicity (agitation, dizziness, confusion, anxiety and tremor) has been reported in 14% of patients. Auditory and visual hallucinations have also been reported.[89] Neurological toxicity is associated with voriconazole concentrations >5.5 mg/L[90]
Skeletal toxicity	• Periostitis, exostosis and elevated serum fluoride concentrations have been reported in association with long-term voriconazole use in patients with haematologic malignancy or following solid organ transplantation.[91-96] Discontinuation of voriconazole therapy results in improvement of pain and normalisation of alkaline phosphatase and fluoride levels[97]
Other	• Nephrotoxicity occurs in 1–7% of patients receiving voriconazole (significantly less than AmB-D)[59, 79, 83]

		• IRAE occur less frequently compared with amphotericin B preparations: fever and/or chills 3–14% [59, 79] • Cardiovascular events have been reported rarely (including QT prolongation and *torsade de pointes*), usually in association with other risk factors (e.g. pro-arrhythmic medications, cardiomyopathy)[98, 99]
Posaconazole	Gastrointestinal toxicity	• Gastrointestinal symptoms are the most frequent cause of toxicity in patients receiving posaconazole: nausea 4–12%; vomiting 2–9%; abdominal pain 2–5% and diarrhoea 2–9%.[8, 63, 100-103] These rates are not significantly different to those observed with fluconazole during a comparative trial with posaconazole suspension[63]
	Hepatotoxicity	• Hepatotoxicity is infrequently reported with posaconazole (1–5%).[8, 63, 74, 100-102] This is not significantly different to rates reported with fluconazole or itraconazole when compared with posaconazole suspension[63, 74] • In two studies, elevation of hepatic enzymes tended to be transient and self-limiting, and rarely required treatment cessation[100, 104]
	Other	• Rash and headache are reported in 1–6% and 1–9% of patients, respectively[8, 63, 74, 100-102]

		• Neutropenia reported in 7% of patients; this is not significantly different to rates reported with fluconazole or itraconazole[74] • Hypokalaemia reported in 1–10% of patients[8, 102, 105] • There are multiple case reports of posaconazole-induced hypertension and hypokalaemia consistent with pseudohyperaldosteronism, due to inhibition of 11βHSD2 and/or 11β-hydroxylase. Posaconazole concentrations were reported in seven cases and ranged from 3.0 to 7.98 mg/L.[106-110] A single centre retrospective analysis revealed that posaconazole-induced pseudohyperaldosteronism (PIPH) is associated with higher serum posaconazole concentrations (median = 3.0 mg/L), older age and pre-existing hypertension. All patients with concentrations ≥4 mg/L in this study developed PIPH[111]
Isavuconazole	Gastrointestinal toxicity	• Gastrointestinal symptoms are amongst the most frequently reported side-effects: nausea 10–27.6%; vomiting 15.5–27%; diarrhoea 15.5–32%[112-114]
	Hepatotoxicity	• Hepatobiliary disorders have been reported to occur in 8.6%–9%, but generally did not require drug discontinuation; however, consider monitoring liver function tests.[112, 113] In a comparative study, the rate of hepatotoxicity was reported to be lower than voriconazole[113]

	Other	• Hypokalaemia reported in 17.5–18.2% of patients[112, 113] • Headache occurred in 16% of patients[112, 113] • Shortened QTc interval has been reported[115, 116] • Infusion-related reactions also reported; to reduce risk of IRAE, infuse over at least one hour in 250 mL of a compatible diluent[117]
Caspofungin	Gastrointestinal toxicity	• Gastrointestinal toxicity is infrequently seen with caspofungin: nausea 2–6%; vomiting 2–3.5%; diarrhoea 1–4%[58, 60, 77, 118]
	Hepatotoxicity	• Hepatotoxicity (elevated ALT, AST or bilirubin) occurs in 1–15% of patients[60, 77, 119, 120] • Early data demonstrated an increase in the serum concentrations of caspofungin and increased transaminases when caspofungin was concomitantly administered with ciclosporin; the Product Information states that the combination may be used when the potential benefits outweigh the potential risk.[121] However, several observational studies in children and adult subjects have demonstrated the safety of this combination[122-124]
	Other	• Nephrotoxicity occurs in 0–8% of patients (significantly less than AmB-D)[58, 60, 119]

		• Hypokalaemia occurs in 11% of patients after the 70-mg dose and < 4% of patients after the 50-mg dose[125] • IRAE occur less frequently than that of amphotericin B preparations: chills 0–14%.[58, 60, 119] IRAE can be prevented by slowing the infusion and giving antihistamines[126] • It appears that caspofungin may have a higher propensity for causing histamine-induced reactions compared with other echinocandins. These reactions may manifest as rash, facial swelling, pruritus, sensation of warmth and/or bronchospasm[127] • Unexplained cardiovascular decompensation (postulated to be due to histamine release) has been observed during central venous administration of caspofungin and anidulafungin.[128-130] *In vitro* studies have shown decreases in left ventricular contractility with concentrations of caspofungin and anidulafungin achievable with therapeutic dosing[131] • Rash is infrequently observed with caspofungin: 1–6%[58, 118]
Anidulafungin	IRAE	• IRAE occur in 1.3% of Candida-treated patients (0.8% of which were hypotension) and 18% of aspergillus-treated patients[132]

		• Slowing the infusion prevents histamine-release like reactions.[133] Histamine-release like reactions rarely seen if rate of 1.1 mg/min not exceeded[127]
		• Facial erythema, which resolved with slowing the infusion rate, was observed in a paediatric patient[134]
	Hepatotoxicity	• Hepatotoxicity (elevated enzymes) occurs in 1.5% of patients[135]
	Other	• Diarrhoea and hypokalaemia occur in 3% of patients[135]
		• Headache and thrombophlebitis occur in 1.3% of patients[136]
		• Neutropenia and nausea occur in 1% of patients[136]
		• Unexplained cardiovascular decompensation (postulated to be due to histamine release) has been observed during central venous administration of caspofungin and anidulafungin.[128-130] *In vitro* studies have shown decreases in left ventricular contractility with concentrations of caspofungin and anidulafungin achievable with therapeutic dosing[131]
Micafungin	Gastrointestinal toxicity	• Most commonly reported gastrointestinal symptoms: nausea 2.4–5.8%; vomiting 2.8–5.1%; diarrhoea 2.1–5.8%[137-143]

	Hepatotoxicity	• Hyperbilirubinaemia reported in 2.9–13.3% and liver transaminase elevation in 0.7–6.8%.[138-145] The rate of hepatotoxicity was not significantly different to fluconazole or L-AMB in comparative trials but less than those reported with voriconazole[137]
	Other	• IRAE occurred in 0–17% of patients.[139, 140, 143, 146] Infusing the drug more rapidly than one hour may cause more histamine-mediated reactions[147] • Hypokalaemia reported in 0.4–6.8% of patients[138-140, 145] • No significant differences in adverse events between micafungin and caspofungin observed in a randomised controlled trial for treatment of candidaemia[148]
Flucytosine	Gastrointestinal toxicity	• Gastrointestinal toxicity occurs in approximately 6% of patients treated with flucytosine[149]
	Hepatotoxicity	• The incidence of hepatotoxicity can vary markedly (from 0–40%) depending on the definition used.[149-151] Hepatotoxicity appears to be dose-dependent, occurring more frequently when peak flucytosine concentrations are above 100 mg/L

	Bone marrow suppression	• Leukopenia, thrombocytopenia or pancytopenia have all been reported with flucytosine therapy. The incidence is dose-dependent (observed when concentrations are >100 mg/L) and influenced by comorbidities, pre-existing bone marrow suppression and disease[149]

ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; ALT, alanine aminotransferase; AmB-D, amphotericin B deoxycholate (conventional amphotericin); AST, aspartate aminotransferase; HSCT, haemopoietic stem cell transplant; IRAE, infusion-related adverse event; L-AMB, liposomal amphotericin B

Table 6 Databases providing data on adverse effects of antifungal drugs

Drug resource	Link
MIMS	https://www.mimsonline.com.au/
Lexicomp®	http://online.lexi.com/
Micromedex®	http://www.micromedexsolutions.com
LiverTox®	https://www.ncbi.nlm.nih.gov/books/NBK547852/ A comprehensive database for medication-induced hepatic toxicities

Question 2 What are the present antifungal TDM targets, sampling and sample type, time-to-resampling and dose adjustment?

When determining what TDM targets found in clinical studies should be used, it is important to assess whether the clinical studies have similar ethnicity, treatment regimen and organism epidemiology to the local setting. Many TDM targets have not been evaluated extensively in large randomised controlled trials in the Australian setting and *Aspergillus* spp. have comprised the majority of IFD identified.[2, 6, 8, 22, 152] In the absence of organism-specific targets, the use of targets determined in a predominantly *Aspergillus* spp. setting seems reasonable for the prevention of the majority of moulds with similar susceptibility patterns, such as *Fusarium* spp. and *Scedosporium* spp.. Extrapolation of these targets to the treatment or prevention of more resistant fungi such as *Lomentospora prolificans* and the Mucorales may be less reliable. Table 7 outlines antifungal TDM targets, sampling and sample type, time-to-resampling, and suggested dose adjustment to subtherapeutic or supratherapeutic serum concentrations. Additional sampling is recommended if there are significant changes in the patient's clinical parameters, the presence of medication non-compliance or interacting drugs, if breakthrough IFD is thought to be present, or if toxicity is suspected.

When TDM is required, the complexity of dose adjustment strategies range from simple linear adjustments based on pre-determined static algorithms to individualised dose prediction requiring complex modelling supported by computing software.[153] Weight-based empiric dosing coupled with linear adjustment methods (pre-dose, steady-state concentration and subsequent dose adjustment), although routinely used, are suboptimal for a large proportion of patients on azole antifungal agents besides fluconazole.[6, 8, 154, 155]

Application of population pharmacokinetic models embedded in dosing software is less reliant on optimal timing of serum sampling. Only one small clinical trial has prospectively evaluated this and it has been shown to have 85.7% target attainment (12 of 14 patients) by the end of Day 5 of voriconazole therapy with target C_{min} (trough concentration) between 1 to 3 mg/L and no withdrawals from therapy. The C_{min} for the remaining two patients were 4.66 and 5.25 mg/L and still within the recommended therapeutic range.[153] The frequency of adverse drug reactions for voriconazole decreases on a continuum from 17% with no monitoring, 4–8.8% at best with crude dose adjustment methods, to 0% with the use of dosing software.[6, 90, 153] The downsides of population pharmacokinetic methods are the expertise and software required to perform these clinical interventions.

Table 7 Recommendations for antifungal drug monitoring and suggested dose adjustment based on trough concentrations

Antifungal agent	Pharmacokinetic considerations	TDM	Indication/s for TDM	Timing of first sample	Timing of sample in relation to dose	Time-to-resampling	Target serum concentration range (mg/L) [SoR/QoE]	Published guidance for dose adjustment for TDM
Amphotericin B and lipid-based preparations		No	–	–	–	–	–	–
Echinocandin class		No	–	–	–	–	–	–
Flucytosine		Routine	To monitor for toxicity and minimise	3–5 days	Trough concentration	3–5 days	Peak concentration of <100 (minimise	–

			drug resistance		Peak concentration: 2 hours post-oral dose or 30 minutes post-IV dose		toxicity)[150, 156] [AII] Trough concentration of 25–40 (minimise drug resistance)[157] [BIII]	
Fluconazole	Linear pharmacokinetics and high oral bioavailability	May be utilised in certain clinical circumstances for IFD treatment (e.g. critically ill	–	–	–	–	–	–

	About 80% of drug is renally excreted	patients with sepsis, patients with altered renal function, sanctuary site infections such as CNS, treatment failure or concerns for medication non-compliance)

Itraconazole	Non-linear pharmacokinetics with slow accumulation of drug with no effective half-life Super bioavailable SUBA®-itraconazole (Lozanoc®) demonstrated improved bioavailability when compared with itraconazole	Routine for treatment irrespective of formulations Routine for prophylaxis with itraconazole capsule and oral solution Recommended in selected cases at risk of	To ensure adequate absorption, therapeutic concentration	5–7 days with loading doses or 10–14 days without loading doses[22]	Trough concentration	7 days[3, 161]	Prophylaxis: 0.5–4 (HPLC)[161-165] [AII for efficacy, BIII for toxicity] Treatment: 1–4 (HPLC)[72, 161, 163, 166, 167] [AII for efficacy, BIII for toxicity]	If subtherapeutic, increase itraconazole (Sporanox®) dose by 25–50%[3, 22] If taking itraconazole (Sporanox®) capsules, also consider switching to itraconazole solution or SUBA®-itraconazole capsules[22]

	capsule and oral solution[158, 159] Steady state may not be reached until two weeks of treatment without loading doses.[160] Measure itraconazole concentrations regularly until stable concentrations are achieved	low exposure receiving SUBA®-itraconazole prophylaxis (e.g. drug-drug interactions, patients with gastrointestinal complications, and young children)		Ensure itraconazole (Sporanox®) capsule is taken with food, and avoid H_2 antagonist and proton pump inhibitor[23] Ensure itraconazole solution is taken on empty stomach[27]

Voriconazole	Non-linear pharmacokinetics, progressive accumulation in some patients due to saturable clearance Dose modification or significant clinical changes may result in unpredictable concentrations	Routine for treatment and is recommended for prophylaxis	To detect therapeutic and toxic concentrations	2–5 days[3, 161]	Trough concentration (Population pharmacokinetic modelling: as specified by the dose prediction software)	5 days[2, 22, 154, 168] Repeat samples should also be collected to confirm stable concentrations[3, 161]	Prophylaxis: 1–5.5[169-171] [AII] Treatment: 1–5.5[6, 90, 170, 172-174] [AII] CNS infection, bulky disease, multifocal infection: >2[3] [BIII]	For crude adjustment method if trough concentration: • 0.0–0.5 mg/L: increase dose by 50%; • >0.5–<1.0 mg/L: increase dose by 25%; • 1.0–5.5 mg/L: no change; • >5.5 mg/L and asymptomatic:

	Consider taking additional samples until stable concentrations are achieved							decrease dose by 25%; • >5.5 mg/L with drug-related toxicities: hold one dose and decrease subsequent doses by 50% Modified from John *et al*. 2019[22]
Posaconazole	Slow accumulation of drug over the first 7 days and then plateau	Routine for treatment irrespective of formulations	To ensure adequate absorption,	After 5–7 days[3, 161]	Trough concentration	7 days[3]	Prophylaxis: >0.5[14, 177-179] [AII for	For suspension: • Prophylaxis: if subtherapeutic, increase to 200

Saturable oral absorption with dose escalation above 800 mg/day resulting in slight to no increases in drug concentrations Modified-release tablet demonstrated improved bioavailability when compared	Routine for prophylaxis with suspension Recommended for selected cases at risk of low exposure receiving prophylaxis with new modified-release tablet formulation	therapeutic concentration	Untimed concentrations may also be used, given consistent serum concentrations over time Early monitoring (e.g. Day 2) may be	suspension; BII for tablets†] Treatment: >1.0[14, 100] [AII]	mg four times daily or 300 mg three times daily[22, 155] • Treatment: if subtherapeutic, increase to 400 mg three times daily[22] • Ensure patient taking suspension with food and/or acidic beverage, and avoid H_2

	with suspension[9, 12]	(e.g. drug-drug interactions, patients with gastrointestinal complications, and young children)	predictive of steady-state concentration and allow for timely dosing modification[175, 176]	antagonists and proton pump inhibitors[13] • Switch to modified-release formulation if patient can swallow tablets For modified-release tablet: • If subtherapeutic,

			increase to 400 mg daily[180] • Consider administering modified-release tablet with high-fat meal if previously taken posaconazole tablets in fasted state[181] For intravenous formulation: • No data

Isavuconazole	No	–	–	–	–	–	–
Olorofim	No	–	–	–	–	–	–
Ibrexafungerp	No	–	–	–	–	–	–
Fosmanogepix	No	–	–	–	–	–	–

[†]There is limited evidence for routine TDM in all patients receiving prophylaxis with posaconazole tablets, although about 5–30% of patients do not achieve target concentrations with tablets.[8-10, 182] – , no guidance exists; CNS, central nervous system; HPLC, high-performance liquid chromatography; IV, intravenous; QoE, quality of evidence; SoR, strength of recommendation

Question 3 How do we prioritise patients for TDM who receive posaconazole suspension or itraconazole capsule and solution versus newer formulations of posaconazole modified-release tablet or SUBA®-itraconazole?

Recommendations

- TDM is indicated for all patients receiving itraconazole or posaconazole for IFD treatment irrespective of the formulation [Strong recommendation, Level II evidence].
- TDM is indicated for prophylaxis in all patients receiving posaconazole suspension or itraconazole capsule and solution [Strong recommendation, Level II evidence].
- TDM is indicated for selected cases at risk for low exposure receiving prophylaxis with the new oral formulations of posaconazole modified-release tablet or SUBA®-itraconazole (e.g. drug-drug interactions, patients with gastrointestinal complications, and young children) [Moderate recommendation, Level II evidence], and may be considered in other patient populations receiving posaconazole modified-release tablet or SUBA®-itraconazole for prophylaxis [Marginal recommendation, Level III evidence].

TDM is indicated for all patients receiving IFD treatment irrespective of the formulation of posaconazole and itraconazole.[3, 161] The underlying reason for variability in itraconazole and posaconazole drug exposure is inconsistent bioavailability related to the highly lipophilic base molecular structure. Despite the enhanced absorption of itraconazole solution with cyclodextrin formulation,[165] neither itraconazole oral solution nor posaconazole oral suspension achieve the recommended target concentrations in a substantial number of patients.[13, 14, 183]

Increasing the dose of the posaconazole oral suspension is not consistently effective because of saturable absorption.[184] Therefore, improved oral dosage formulations were developed for both itraconazole and posaconazole. 'Super-bioavailable' SUBA®-itraconazole (Lozanoc®) and posaconazole modified-release tablets demonstrate improved bioavailability when compared with older formulations.[105, 159, 185] As a result, TDM for patients receiving the oral posaconazole tablet formulation is considered less important for patients undergoing prophylaxis.[8, 186] Therefore, TDM is indicated for patient groups at risk of low exposure who are receiving prophylaxis with the new posaconazole tablet formulation (e.g. patients with cystic fibrosis[187], presence of graft-versus-host disease[10, 182], drug-drug interactions including those on concurrent corticosteroids and proton pump inhibitors[10, 188], obese patients, [189, 190] young children,[191-194] and patients with gastrointestinal complications including diarrhoea[10, 190, 195, 196]).

In a study evaluating SUBA®-itraconazole for IFD prophylaxis in patients with haematological malignancies or HSCT, SUBA®-itraconazole achieved therapeutic concentrations faster, with significantly higher itraconazole concentrations and less interpatient variability, than itraconazole oral solution.[159] Similar to posaconazole, use of gastric acid suppression and diarrhoea were found to be associated with lower trough itraconazole concentrations in this patient population.[185] It has also been reported that only 59% of children who received SUBA®-itraconazole achieved therapeutic concentrations.[197]

TDM may be considered in other patient populations receiving posaconazole modified-release tablet or SUBA®-itraconazole for prophylaxis, such as where there are significant changes in a patient's clinical parameters, in the setting of prolonged antifungal prophylaxis or medication non-compliance, or if toxicity is suspected. The registered posaconazole tablet

dose of 300 mg once daily was selected to achieve a serum concentration between 0.5–2.5 mg/L in 90% of patients.[105] However, higher posaconazole concentrations are not uncommon.[187, 188, 190, 195, 198, 199] Although the drug is well tolerated, dose reduction should be considered if adverse drug effects occur and the posaconazole concentration is >2.5 mg/L, with follow-up TDM recommended. As there is no established clear threshold concentration for toxicity, a case-by-case approach is suggested.

Question 4 When should fluconazole TDM be used?

Recommendations

- We recommend against routine TDM of fluconazole [Not recommended, Level II evidence].
- Fluconazole TDM may be considered in a limited number of scenarios for IFD treatment, including:
  - altered renal function including acute kidney injury, patient receiving continuous or prolonged forms of renal replacement therapy, or patients with augmented renal clearance, defined as a creatinine clearance >130 mL/min [Marginal recommendation, Level III evidence]
  - critical illness with sepsis [Marginal recommendation, Level III evidence]
  - infections involving sanctuary sites such as the central nervous system [Marginal recommendation, Level III evidence]
  - inadequate clinical response or therapeutic failure [Marginal recommendation, Level III evidence]
  - medication non-compliance concerns [Marginal recommendation, Level III evidence].

To date, fluconazole TDM has not been routinely recommended due to a relatively predictable pharmacokinetic and an excellent safety profile.[3, 200-202] Fluconazole has high oral bioavailability (90%) and low protein binding (10–12 %).[203, 204] However, there is evidence that certain populations with altered pharmacokinetics may be at risk of unpredictable dose-

exposure relationships[201, 205] and TDM may be utilised in these selected cases, as discussed below.

Fluconazole undergoes renal elimination through glomerular filtration and tubular reabsorption. Recent studies have suggested glomerular filtration rate may not accurately reflect clearance of the drug, making accurate dose adjustments in renal impairment to ensure adequate drug exposures more difficult.[206, 207] Elimination rates of fluconazole can vary considerably during continuous renal replacement therapy depending on the modality and settings prescribed, which can both influence the extent of extracorporeal clearance.[208] Similar findings have also been shown in critically ill patients with sepsis,[209, 210] and paediatric populations with augmented renal clearance,[211, 212] which increases the risk of fluconazole underexposure. In obesity, limited population pharmacokinetic data have suggested total body weight-based dosing should be used to achieve target exposure concentrations.[213-215] Clinical studies on fluconazole use as induction treatment in cryptococcal meningitis indicate substantial variability in the extent of fluconazole penetration into the central nervous system, with only two-thirds of patients achieving the desired exposures.[216, 217]

Question 5 Is there any role for AUC / MIC-based, as opposed to trough concentration-based, dose adjustment for triazole antifungal agents?

Recommendations

- Monitoring of trough concentrations is recommended over AUC / MIC for triazole antifungal agents based on current clinical data [Moderate recommendation, Level II evidence].

Posaconazole

Animal and *in vitro* models have demonstrated that the total posaconazole AUC / MIC ratio is most predictive of therapeutic efficacy in invasive aspergillosis.[218-221] However, the application of target ratios derived from animal models to the clinical setting is ill-defined.[14, 222, 223] An AUC / MIC ratio of 200 has been suggested for infections involving *Aspergillus* spp. in clinical practice. However, the practicality of achieving this target has previously been limited by formulation and applied dosing regimen for posaconazole suspension.[220, 221] The more favourable pharmacokinetic properties of the modified-release tablet and intravenous formulations can facilitate the higher exposures required for isolates with raised MIC.[224]

Linear regression analysis have established a correlation between posaconazole AUC and C_{min} in healthy subjects,[221] where a C_{min} / MIC ratio of 5 to 8 corresponds to an AUC / MIC ratio of 200.[220] As AUC determination requires multiple sampling collections, C_{min} / MIC is a practical surrogate marker for AUC / MIC-based dosing with posaconazole.

Voriconazole

In vitro studies have found AUC / MIC in experimental models of candidiasis, aspergillosis and scedosporiosis reflective of voriconazole efficacy.[172, 225, 226] However, studies validating these pharmacodynamic indexes in the clinical setting are scarce.[227, 228] Several pharmacokinetic studies have demonstrated good correlation between C_{min} with AUC[174, 221, 229, 230] where C_{min} of 1 mg/L and 4.5 mg/L correlated with AUC_{0-24} of 43 and 151 mg.h/L respectively.[221] Therefore, adopting a C_{min} / MIC approach to optimise dosage regimens of voriconazole has been proposed.[174, 229, 231] Modelling studies have demonstrated a target of C_{min} / MIC >2 correlates with clinical efficacy in *Candida* and *Aspergillus* infections when MICs were determined using ETEST® or the Clinical and Laboratory Standards Institute (CLSI) methodology.[174, 232] Until further data becomes available, use of trough concentration (C_{min})-based dosing remains appropriate to guide voriconazole TDM.

Fluconazole

In the selected cases where TDM has a role to ensure adequate exposure is achieved, AUC / MIC ratio has been demonstrated to be the best predictor of clinical efficacy.[205, 233] However, there is no current consensus on pharmacodynamic targets for fluconazole, with evidence indicating an AUC / MIC ratio of >100 (using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards) should be the target.[3] Pharmacokinetic studies have confirmed there is an excellent linear correlation between fluconazole dosage up to 2 g and AUC,[234, 235] and thus a dose / MIC ratio can be considered for convenient dosing decisions where severely altered pharmacokinetics are not expected. A dose / MIC ratio of >100 has been suggested for treatment of invasive candidiasis when MIC is determined using EUCAST methodology.[207, 236] Pharmacokinetic studies in critically ill children have shown a C_{min} of >11 mg/L to be representative of an AUC ≥400 mg.h/L.[212] These data

suggest that AUC / MIC-based dosing is not necessary for fluconazole, with C_{min} / MIC most suitable, and dose / MIC relevant for high MIC pathogens.

Question 6 When adjusting azole antifungal agents for subtherapeutic concentrations, is there a recommended 'maximum' dose and when should we consider switching agents?

Recommendations

- Consider switching to alternative antifungal agent and CYP2C19 genotype testing if voriconazole serum concentrations remain subtherapeutic despite two appropriate dose adjustments [Moderate recommendation, Level III evidence].
- Consider antifungal agents other than voriconazole if patient is a known CYP2C19 ultrarapid metaboliser [Strong recommendation, Level III evidence].
- Consider seeking specialist advice for dose adjustment and/or alternative antifungal therapy if posaconazole dose of 300 mg twice daily for tablet or 400 mg three times daily for suspension is needed due to subtherapeutic posaconazole concentrations [Moderate recommendation, Level III evidence].

The delay in achieving therapeutic concentrations for an antifungal agent, particularly in the setting of critical IFD, can be detrimental. However, there is a paucity of guidance for dose titration of azole antifungal agents for subtherapeutic concentrations (see Appendix 1 for selected publications on high-dose voriconazole or posaconazole guided by TDM). Addition of a second antifungal agent may be required in the treatment of IFD in critically unwell patients until the azole antifungal agent achieves therapeutic serum concentrations.[237]

Voriconazole

Higher than standard doses of voriconazole may be required to achieve target exposures in some patients, including those with CYP2C19 genetic variation and, in particular, an ultrarapid metaboliser phenotype.[238-242] Dosing recommendations for voriconazole treatment from the Clinical Pharmacogenetics Implementation Consortium (CPIC)[243] and the Dutch Pharmacogenetics Working Group (DPWG)[244] for each CYP2C19 phenotype are summarised in Table 8. The population/pharmacodynamic model by Mangal *et al.* 2018 proposed voriconazole doses of 500–600 mg 12-hourly without pantoprazole, or 300–400 mg 12-hourly with pantoprazole, for aspergillosis treatment in adult CYP2C19 ultrarapid or rapid metabolisers.[245]

If voriconazole concentrations remain subtherapeutic after two appropriate dose adjustments then this suggests the patient may be a rapid/ultrarapid metaboliser. In this case, we recommend considering a switch to an alternative antifungal agent and CYP2C19 genotype testing. However, if this is not clinically appropriate, consider increasing voriconazole frequency,[246-248] and adding pantoprazole[245] or omeprazole,[249, 250] and/or cimetidine,[246, 249] as a CYP450 inhibitor. In the paediatric population, consider switching to another antifungal agent if unable to achieve target concentrations with voriconazole 12 mg/kg bd for children <12 years of age and young adolescents 12–14 years of age weighing <50 kg.[22]

Table 8 Voriconazole dose recommendations from CPIC and DPWG based on CYP2C19 phenotype

CYP2C19 phenotype (examples of genotype)	CPIC recommendations in adults	CPIC recommendations in paediatrics	DPWG recommendations
CYP2C19 ultrarapid metaboliser (**17/*17*)	Alternative antifungal agent with metabolism not dependent on CYP2C19 is recommended		Administer 1.5-times the standard dose and monitor serum concentrations
CYP2C19 rapid metaboliser (**1/*17*)	Alternative antifungal agent with metabolism not dependent on CYP2C19 is recommended	Start voriconazole at recommended standard dose and titrate dose to target voriconazole C_{min}	
CYP2C19 normal metaboliser (**1/*1*)	Start voriconazole at standard dose		
CYP2C19 intermediate	Start voriconazole at standard dose		Monitor serum concentrations

metaboliser (**1/*2, *1/*3, *2/*17*)		
CYP2C19 poor metaboliser (**2/*2, *2/*3, *3/*3*)	Alternative antifungal agent with metabolism not dependent on CYP2C19 is recommended If voriconazole therapy is deemed clinically necessary, a lower than standard dose of voriconazole is recommended and monitor serum concentrations	Administer 50% of standard dose and monitor serum concentrations

Adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy[243] and Dutch Pharmacogenetics Working Group (DPWG) Guideline for voriconazole and CYP2C19[244]

Posaconazole

Increasing posaconazole tablets from 300 mg daily to 400 mg daily led to a disproportional 81.8% increase in median C_{min} in patients with haematological malignancies or HSCT.[180] If posaconazole tablet dosing of 400 mg daily is subtherapeutic, consider twice-daily dosing rather than once-daily dosing due to probable saturation of absorption.[222] However, extreme caution should be taken when using twice-daily dosing for posaconazole tablets, and three times-daily dosing of posaconazole tablets should be avoided. There are case reports of wrong oral formulations of posaconazole being prescribed and/or dispensed, with one case resulting in death.[251] Inadvertent prescribing of posaconazole 400 mg tablets 12-hourly to a 13-year-old cancer patient led to posaconazole toxicity with serum concentration of 9.5 mg/L three days after cessation of posaconazole. Toxicity symptoms included hypokalaemia, fatigue, anorexia, musculoskeletal pain and progressive anaemia, which all resolved within one week of posaconazole cessation.[252]

Doses of 300 mg 12-hourly for the tablet formulation and 400 mg 8-hourly for suspension have been reported in the literature, but if such doses are indicated, consider seeking specialist advice for dose adjustment and/or alternative antifungal therapy. There is no clear relationship between posaconazole serum concentrations and toxicities.[8, 253] No higher incidence of toxicities was observed in a study analysing the use of high-dose posaconazole in IFD treatment compared to those on standard dose, with C_{min} >3.0 mg/L in both groups.[224] However, elevated serum posaconazole concentrations have been recently reported to be associated with pseudohyperaldosteronism.[111] Monitor for adverse events closely with ECG monitoring if treatment with high-dose posaconazole tablets is required.

Itraconazole

There is limited evidence to support itraconazole (Sporanox®) doses above 300 mg 12-hourly for IFD treatment. In a case series of eight patients receiving itraconazole 300 mg capsule 12-hourly, six had an itraconazole concentration by bioassay >5 mg/L. One patient experienced hypertension with severe hypokalaemia while another experienced symptomatic hypoadrenalism, which resolved with dose reduction.[166] In a study evaluating six different dosing regimens for IFD prophylaxis, 46% of patients taking the 200 mg solution 6-hourly discontinued treatment due to severe nausea or vomiting, with nausea not related to serum itraconazole concentration. The recommended dosing from this study was a loading dose of 200 mg capsule 6-hourly for seven days, then 200 mg solution twice daily. No other severe adverse events related to itraconazole were observed, with hypokalaemia occurring in 35.1% of all cases.[76]

Isavuconazole

No significant relationship was identified between drug exposure and mortality, clinical responses, overall response or safety outcomes in the SECURE study.[254] However, inter-individual variation exists and one trial has demonstrated exposure-related gastrointestinal side-effects, with increased incidence for steady-state concentrations between 4.87 mg/L to 5.13 mg/L.[255] Based on Monte Carlo simulations, a maintenance dose of isavuconazole 400 mg daily may be a treatment option for *Aspergillus fumigatus* with isavuconazole MIC of 2 mg/L.[256]

Question 7 Is flucytosine TDM required in cryptococcal infections?

Recommendations

- TDM is recommended for flucytosine, with target peak serum concentrations <100 mg/L [Strong recommendation, Level II evidence] and trough concentration between 25–40 mg/L [Moderate recommendation, Level III evidence].

Flucytosine (5-FC) is a fluorinated pyrimidine analogue, which inhibits DNA synthesis and is primarily used as adjunctive therapy in cryptococcal meningitis (with amphotericin B or fluconazole), *Candida* endocarditis (with amphotericin B) and azole-resistant yeast infections of the urinary tract.[257] The relationship between 5-FC concentrations and drug-related toxicity has been well described.[150, 156, 258, 259] Therefore, TDM is recommended as standard of care to prevent toxicity.[257]

Concentration-related toxicities of flucytosine

The adverse effects of 5-FC, including leukopenia, thrombocytopenia and hepatotoxicity, are associated with peak serum concentrations >100 mg/L,[150, 156, 258, 259] especially if these concentrations are persistently >100 mg/L for two weeks.[151] Because of the interindividual variability in serum concentrations across populations, TDM is routinely recommended.[150]

Target concentrations and timing of TDM for treatment of cryptococcal infections

TDM should be performed between Days 3–5 after initiation of therapy or following dose adjustment,[22] particularly in patients with renal impairment or receiving concomitant

nephrotoxic agents.[260] Although recommendations for target concentrations are based on weak evidence, trough concentrations of 25–40 mg/L are often used (see Table 7).[3] Peak concentrations (measured 2 hours after an oral dose or 30 minutes after IV infusion) <100 mg/L are recommended to prevent toxicity.

Question 8 What TDM and interpretation is required for 'sanctuary site' infections, including CNS, bone and eye?

Recommendations

- Higher end of serum therapeutic range is recommended for azole antifungal agents in the treatment of 'sanctuary site' infection [Moderate recommendation, Level III evidence].
- Standard TDM targets for 5-FC is recommended for 'sanctuary site' infections [Moderate recommendation, Level III evidence].
- Consider monitoring concentrations of azole antifungal agents at infection site (e.g. cerebrospinal fluid [CSF]) where feasible [Marginal recommendation, Level III evidence].

A key prerequisite for antimicrobial efficacy is penetration into the infection site to achieve organism-eliminating concentrations. Data concerning the tissue concentrations of antifungal drugs is scarce. An added complexity is that drug penetration into areas of tissue infection may differ markedly from healthy tissue due to various factors, including altered tissue structure and permeability associated with tissue necrosis and/or fungal biofilm formation. Besides, fungi may be intracellular or extracellular; therefore, drug distribution within the host cell must be considered. There is an excellent summary of tissue penetration data for antifungal agents by Felton *et al.* 2014.[261] Table 9 provides an overview of antifungal penetration into sanctuary sites for drugs where TDM is relevant.

Table 9 Tissue to plasma ratios of antifungal drugs for sanctuary sites

Drug	Bone	Brain	CSF	Eye
Fluconazole	0.3[262]	0.5–1.0[263]	0.5–1.0[264-267]	0.7–0.8[268]
Itraconazole	4.7[269]	<0.2[270]	<0.12[269]	<0.05[271, 272]
Posaconazole	ND	0.5–0.8[273, 274]	<0.009[275, 276]	0.2–0.6[277]
Voriconazole	5[278]	3.0[279]	0.22–1.0[280]	0.4–0.5[281]
Flucytosine	0.3[282]	ND	~1.0[282, 283]	>0.5–0.8[284]

ND = no data. CSF, cerebrospinal fluid

Azole antifungal agents have different tissue penetration properties based on their differences in molecular structures and physicochemical properties. Posaconazole CSF concentrations are low despite a disturbed blood-brain barrier.[275, 276] Animal models and autopsy studies involving the brain indicate high voriconazole tissue penetration,[285] and CSF studies demonstrate a penetration ratio of 0.46 (range 0.22–1.00).[280] There are little data concerning isavuconazole tissue penetration. In a murine model of aspergillosis, isavuconazole concentrations in the brain appear to exceed those in plasma.[286] With low and/or highly variable penetration across all agents, there is uncertainty around how to adequately dose triazoles in CNS infections.

Echinocandins have poor penetration into the CNS and eyes,[287-289] and are not the drugs of choice for these infections. 5-FC showed good tissue penetration, with most sanctuary sites reaching 20–50% and CSF concentrations reaching 71–85% of serum concentrations.[283] The current data support standard TDM of 5-FC for 'sanctuary site' infections like cryptococcal meningitis.

Question 9 What are the barriers and challenges in TDM implementation?

Access to TDM is a reported barrier for TDM implementation.[1, 290] Previous studies from Australia suggested that many facilities do not have access to on-site laboratory processing of antifungal serum concentrations, with a turnaround time of 3–5 days for the majority of TDM results.[291-293] The time to obtaining optimal drug exposures can commonly take one to two weeks in complex cases, and may be longer if the blood test samples are processed off-site. Thus, optimising the timing of samples, reducing processing turnaround times, and streamlining subsequent dose adjustments, could all improve time to adequate drug exposure.[292] Facilities should strive to ensure the provision of timely availability of serum drug concentrations and access to required software/dose adjustment algorithms for antifungal dose individualisation. Australian laboratories that perform serum/plasma antifungal assays can be found on the Australian Society for Antimicrobials website (www.asainc.net.au/assays). Please refer to the accompanying guidelines for antifungal stewardship by Khanina *et al*. 2021, which can be found elsewhere in this supplement, for the recommended quality metrics for antifungal TDM.

The ability to perform TDM, like any competency, requires application of three elements in a relevant clinical scenario: knowledge, skills and behaviours. In order to ensure consistent and effective application of TDM for antifungals, it is strongly advised that practitioners are able to meet various competencies consistent with the level of complexity of dose adjustment required. Proposed competencies for basic, intermediate and advanced practitioners for this highly challenging area are described in Table 10. Challenges exist in achieving advanced level competency in antifungal TDM, as opposed to other antimicrobials (e.g. vancomycin), due to the infrequent occurrence of IFD and case exposure to complex

TDM cases, and a lack of mentors and competency-based educational programs for antifungals. [294, 295] It is recommended that all facilities regularly prescribing antifungal agents that require TDM have access to practitioners with advanced competency in antifungal TDM, along with the required computing software to ensure safe and efficacious prescribing of antifungal agents.[153]

Table 10 Examples of competency elements in antifungal therapeutic drug monitoring and dose recommendations

	Elements	Basic	Intermediate	Advanced
Knowledge	Antifungal toxicities and drug interactions	Y	Y	Y
	Antifungal pharmacokinetics	Y	Y	Y
	Methods for adjusting drug doses	Y	Y	Y
	Approach to timing of TDM sampling	Y	Y	Y
	Species specific antifungal pharmacodynamics	N	Developing[†]	Y
	Expected fungal epidemiology	N	N	Y
Skills	Perform guidelines-based dose adjustment	Y	Y	Y
	Recognise patients requiring complex individualised dose adjustments	Y	Y	Y
	Make accurate recommendations for timing of TDM	Y	Y	Y
	Perform complex individualised dose adjustment in well-defined conditions with targets	N	Y	Y

	Perform complex dose individualisation in conditions without well-defined targets	N	Developing[†]	Y
Behaviours	Provide TDM review and feedback to relevant clinicians	Y	Y	Y
	Design interactive strategy in educating other clinicians on TDM skills and knowledge	N	Y	Y

[†]Have acquired the basic knowledge or skills but not able to apply the knowledge or skills effectively in practice

Conclusion

TDM is being increasingly utilised to optimise antifungal therapy due to various factors, including emerging resistant pathogens, antifungal agents with non-linear pharmacokinetics or narrow therapeutic window, antifungal drug interaction and drug toxicities, inadequate absorption or non-compliance of oral antifungals, and CYP450 gene polymorphism. Current evidence supports TDM for posaconazole, voriconazole, itraconazole and 5-FC for dosage optimisation, but its role still remains unclear for echinocandins and isavuconazole. Clearly there is a need for well-designed studies[296] to elucidate the role of TDM for these antifungal agents.

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Figure legends

Nil

Tables

See Tables within text for layout guidance and correct order of in-text citations

Figures

Nil

Appendices

See Appendix 1 next page

Appendix 1 Selected publications on high-dose voriconazole and posaconazole guided by TDM

Voriconazole studies	**Age (years)**	**Indication**	**Voriconazole MIC**	**Target concentrations**	**Maximum dose Serum C_{min} at this dose**	**PPI**	**Cimetidine**	**CYP2C19 genotype**
Moriyama *et al*. 2009[246]	56	Invasive pulmonary aspergillosis (*Aspergillus ustus* and *Aspergillus terreus)* in a HSCT patient	*Aspergillus ustus:* 4 mg/L	≥8 mg/L	600 mg IV four times daily (40 mg/kg/day) NR	Y	Y	NR
Ferguson *et al*. 2017[249]	36	Cerebral aspergillosis in a	NR	3–5 mg/L	700 mg PO twice daily (22 mg/kg/day)	Y	Y	NT

		patient with aHUS/TTP			~2.5–5 mg/L			
Trubiano *et al.* 2014[297]	67	Disseminated *Lomentospora prolificans* infection in an AML patient	NR	>1–2 mg/L	350 mg PO three times daily (~17.5 mg/kg/day) 1.2 and 2.3 mg/L	NR	Y	*1/*1
Cojutti *et al.* 2019[247]	56	Cerebral aspergillosis (*Aspergillus fumigatus)*	0.5 mg/L	C_{min} / MIC > 1	200 mg PO four times daily (11 mg/kg/day) Median C_{min}: 1.59 mg/L (1.22–1.83 mg/L). Median C_{min} / MIC 3.18 (2.45–3.65)	N	NR	*1/*17

Danion *et al.* 2018[248]	39	Cerebral aspergillosis in a CLL patient (*Aspergillus fumigatus)*	NR	2–5 mg/L	400 mg PO three times daily (21 mg/kg/day) ~ 3–4 mg/L	N	NR	*1/*17
	75	Cerebral aspergillosis (*Aspergillus fumigatus)* in a kidney transplant patient	NR	2–5mg/L	300 mg IV three times daily (20 mg/kg/day) 1–2 mg/L[†]	Y	NR	*17/*17
Boyd *et al.* 2012 [250]	22	Chronic intracranial aspergillosis	NR	>1 and ≤5.5 mg/L	300 mg PO three times daily (13.5 mg/kg/day) 1.5–1.8 mg/L	Y	NR	NT

		(*Aspergillus fumigatus)*						
Holmes *et al.* 2013[298]	44	Pulmonary *Lomentospora prolificans* infection in a lung cancer patient	>8 mg/L	1–5.5 mg/L	500 mg PO twice daily (16 mg/kg/day) 0.5–3.5 mg/L‡	Y	NR	NR
Hsu *et al.* 2015[299]	10	Invasive pulmonary aspergillosis in patient with SAA	NR	1–5.5 mg/L	250 mg PO three times daily (28 mg/kg/day) ~1.5–2 mg/L	NR	NR	NR

Posaconazole studies	**Age (years)**	**Indication**	**Posaconazole MIC**	**Target concentrations**	**Maximum dose Serum C_{min} at this dose**	**Comments**
Schauwvlieghe *et al.* 2020[224]	2–69 (n = 16)	Voriconazole resistant invasive aspergillosis (n = 7) Salvage invasive aspergillosis therapy (n = 4)	Ranges from 0.031 mg/L to 2 mg/L	>3 mg/L	600 mg (IQR 400–750 mg) daily 6 patients: 3.0–4.0 mg/L 10 patients: >4.0 mg/L	Posaconazole tablet: 13 patients Posaconazole suspension: 1 patient Posaconazole tablet and suspension: 1 patient 3 / 16 patients ceased treatment due to Grade 2 arterial hypertension, QTc prolongation,

		Mucormycosis (n = 4) *Aspergillus* spondylodiscitis (n = 1)				increased cardiac troponin T and Grade 3 left ventricular failure, and Grade 4 leukopenia
Wasko *et al.* 2019[300]	51	Salvage therapy for invasive aspergillosis in a HSCT patient	NR	NR	400 mg tablets daily 1.9–3.2 mg/L	CYP2C19 *1/*17, changed to posaconazole due to subtherapeutic concentrations (target >2 mg/L) at 400 mg PO three times daily of voriconazole
Zhou *et al.* 2019[196]	43	Fungal pneumonia in a	NR	≥1 mg/L	400 mg suspension four times daily	Terminal ileum resection

		patient with AML			1.75 mg/L, 2.4 mg/L and 4.1 mg/L	Subtherapeutic posaconazole concentrations despite 200 mg tablets three times daily Posaconazole concentrations at 300 mg suspension four times daily: 1.9 mg/L and 1.5 mg/L
Pham *et al.* 2016[180]	≥18 (n = 20)	Prophylaxis and treatment of IFD in patients with haematological malignancies or HSCT	NR	Prophylaxis: ≥0.7 mg/L Treatment: ≥1 mg/L	400 mg tablets daily Median 1.0 mg/L (IQR 0.78–1.2 mg/L)	Median serum concentrations of 0.55 mg/L (IQR 0.4–0.6 mg/L) at 300 mg tablets daily 88.89% patients on posaconazole prophylaxis achieved ≥0.7 mg/L at 400 mg tablets daily

Leelawattanachai *et al*. 2019[222]	44	Invasive pulmonary aspergillosis and mucormycosis (*Aspergillus flavus*, *Aspergillus fumigatus*, *Rhizopus microsporus*, and *Lichtheimia corymbifera*)	*Aspergillus flavus*: 0.01 mg/L *Aspergillus fumigatus*: 0.12 mg/L *Rhizopus microsporus*: 0.25 mg/L *Lichtheimia corymbifera*: 0.25 mg/L	AUC / MIC ratio 300–500 for aspergillosis, and >100 for mucormycosis	400 mg tablets daily 2.48 mg/L and 2.59 mg/L	Dose reduced back to 300 mg tablets daily due to asymptomatic hypokalaemia

Kim *et al*. 2016[301]	65	IFD salvage therapy (*Alternaria spp.*) in a lung transplant patient	NR	NR	300 mg tablets twice daily 2.4–3.0 mg/L	Posaconazole concentration increased from 0.9 mg/L to 2.6 mg/L after increasing the dose of posaconazole tablets from 300 mg daily to 300 mg twice daily
Maleki *et al*. 2018[302]	57	Pulmonary aspergillosis in a patient with relapsed AML	NR	>0.7 mg/L	400 mg tablets daily 0.45 mg/L	Patient weight was 101 kg. Posaconazole concentration increased from 0.4 mg/L to 0.45 mg/L when the dose of posaconazole tablets increased from 300 mg to 400 mg daily; subsequently switched to voriconazole

Shields *et al.* 2011[303]	≥18 (n = 17)	IFD prophylaxis and treatment in cardiothoracic transplant recipients	NR	>0.5 mg/L	400 mg suspension four times daily (n = 3) ≥1 mg/L	No significant differences observed in median C_{min} among patients treated with 600 mg, 800 mg and 1200 mg posaconazole suspension daily Hepatic and gastrointestinal toxicities reported at 1600 mg dose
van der Elst *et al.* 2015[13]	≥17 (n = 70)	IFD prophylaxis and treatment	NR	Prophylaxis: ≥0.7 mg/L Treatment: ≥1.25 mg/L	Prophylaxis: increased posaconazole suspension to 200 mg four times daily in 5 / 25 patients; 4 achieved target concentrations	

					Treatment: increased posaconazole suspension to 300 mg four times daily or 400 mg four times daily in 8 / 45 patients; 4 achieved target concentrations NR	
Märtson *et al.* 2019[198]	≥18 (n = 47)	IFD prophylaxis and treatment in patients with haematological malignancies	NR	Prophylaxis: 0.7 to 3.75 mg/L Treatment: 1.5 to 3.75 mg/L	Treatment: 1 / 14 patients received posaconazole tablets 600 mg/day for IFD treatment NR	Two patients on 200 mg tablets daily for IFD prophylaxis

Anderson *et al*. 2017[304]	43	Gastrointestinal mucormycosis in a HSCT patient (*Rhizopus microsporus*)	0.5 mg/L	>0.7 mg/L	600 mg tablets daily 0.78 mg/L	Patient had Grade 4 gastrointestinal GVHD and received treatment with methylprednisolone, infliximab with basiliximab, and budesonide Also on IV liposomal amphotericin
Andrey *et al*. 2017[305]	30	Cerebral mucormycosis in a HSCT patient (*Rhizomucor pusillus*)	NR	NR	400 mg tablets daily >2 mg/L	Changed from posaconazole suspension 800 mg/day to 300 mg tablets daily due to subtherapeutic concentration (0.22 mg/L)

											Also on IV liposomal amphotericin

[†]60% of voriconazole concentrations <2 mg/L and eventually switched to isavuconazole. ‡Temporary cessation of voriconazole due to liver function derangement and eventually ceased due to nausea and vomiting, peripheral neuropathy and worsening of liver function abnormalities. aHUS, atypical haemolytic uremic syndrome; AML, acute myeloid leukaemia; AUC, area under the curve; CLL, chronic lymphocytic leukaemia; GVHD, graft-versus-host disease; HSCT, haemopoietic stem cell transplant; IFD, invasive fungal disease; IQR, interquartile range; IV, intravenous; MIC, minimum inhibitory concentration; NR, not reported; NT, not tested; PPI, proton pump inhibitor, either using pantoprazole or omeprazole in these case reports or series; PO, orally; SAA, severe aplastic anaemia; TTP, thrombotic thrombocytopenic purpura

Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2021

Short title

Optimising antifungal therapy guidelines 2021

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Conflicts of interest

The following working group members are consultants or advisory committee members or receive honoraria, fees for service, or travel assistance from; or have research or other associations with the organisations listed: J.A.R – Pfizer, Sandoz, Wolters Kluwer, Merck, Sharpe & Dohme, QPEX, Discuva Ltd, Accelerate Diagnostics, Bayer, Biomerieux, Cipla, The Medicines Company, Cardeas Pharma; A.G. – Merck, Sharpe & Dohme; J.T. – Merck, Sharpe & Dohme.

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Abstract

Antifungal agents may be associated with significant toxicity and/or drug interactions leading to subtherapeutic antifungal drug concentrations and poorer clinical outcomes for patients with haematological malignancy. These risks may be minimised by clinical assessment, laboratory monitoring, avoidance of particular drug combinations and dose modification. Specific measures, such as the optimal timing of oral drug administration in relation to meals, use of pre-hydration and electrolyte supplementation may also be required. Therapeutic drug monitoring (TDM) of antifungal agents is warranted, especially where issues like non-compliance, non-linear pharmacokinetics, inadequate absorption, a narrow therapeutic window, suspected drug interaction or unexpected

toxicity, are encountered. Recommended indications for voriconazole and posaconazole TDM in the clinical management of haematology patients are provided. With emerging knowledge regarding the impact of pharmacogenomics upon metabolism of azole agents (particularly voriconazole), potential applications of pharmacogenomic evaluation to clinical practice are also proposed.

Keywords

antifungal therapy, toxicity, drug interaction, therapeutic drug monitoring, pharmacogenomics