

Optimizing antifungal drug dosing and monitoring to avoid toxicity and improve outcomes in patients with haematological disorders

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Abstract

Antifungal prophylaxis, empirical therapy and treatment of established fungal infections in the haematology population may be associated with significant toxicity or drug interactions leading to sub-therapeutic antifungal drug concentrations and poorer clinical outcomes. These risks may be minimised by clinical assessment, laboratory monitoring of biochemical or haematological indices, avoidance of particular drug combinations and dose modification in certain circumstances. 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. For certain agents, therapeutic drug monitoring (TDM) is warranted where non-compliance, non-linear pharmacokinetics, a narrow therapeutic window, suspected drug interaction or unexpected toxicity are encountered. Pharmacokinetics and pharmacodynamics of clinical relevance to the haematology population are discussed for the azole, polyene and echinocandin classes of antifungal agents. The evidence supporting an association between TDM and enhanced treatment outcomes is presented for individual antifungal drugs, and recommendations for clinical practice are provided. Further randomised study of newer antifungal agents, such as posaconazole, is required to explore the potential for improved clinical outcomes in association with TDM.

Understanding a drug's pharmacokinetics and its pharmacodynamic effects affords the clinician the capacity to optimize drug exposure while minimizing or avoiding drug interactions and toxicities. Therapeutic drug monitoring (TDM) may also be employed during the treatment period to ensure that the selected drug dosage falls within the therapeutic window for an individual patient.

These clinical caveats are particularly relevant to the haematology population where the frequent requirement for polypharmacy and the complexity of comorbidities can significantly influence the success of antifungal therapy. This section of the guidelines describes the potential drug–drug interactions and toxicities related to antifungal use and how they may be avoided. It also considers the latest

evidence for TDM. Particular emphasis is placed upon factors specific to the haematology population.

Antifungal drug interactions

When considering the potential for a drug–drug interaction, it is important to be aware that individual drugs within each antifungal class may be metabolized by specific (and different) metabolic pathways. Thus, a ‘class effect’ cannot always be assumed.

Azoles

In general, the azole class of antifungal agents is metabolized by the cytochrome P450 (CYP450) system, although posaconazole primarily undergoes UDP glucuronidation.¹ The potential for drug–drug interactions is higher for itraconazole and voriconazole, as these are metabolized to a greater extent by CYP isoenzymes than fluconazole and posaconazole (Table 1).

Co-administration of an azole agent with drugs that induce CYP450 metabolism (e.g. isoniazid, carbamazepine, phenytoin, phenobarbitone, rifampicin and rifabutin) can result in undetectable levels of the azole antifungal agent and reduce antifungal efficacy.^{2–4} For this reason, co-administration of rifampicin is contraindicated with itraconazole, voriconazole and, where possible, should be avoided with fluconazole.⁵ Induction of glucuronidation by rifampicin may lead to a reduction of posaconazole plasma levels; therefore, co-administration with posaconazole is also contraindicated.⁶

Most drug interactions observed with azole antifungal agents arise from the inhibition of CYP3A4, which is involved in the metabolism of a wide array of therapeutic drugs, including drugs used to treat cardiovascular disease, diabetes, psychiatric disorders, cancer and infectious diseases (e.g. blood glucose levels should be monitored closely in patients receiving an azole drug with an oral hypoglycaemic agent due to the increased risk of hypoglycaemia).^{7–9} The azole antifungal agents may also

increase the plasma concentrations of the following CYP3A4 substrates: anastrozole, bexarotene, cytarabine, docetaxel, doxorubicin, etoposide, exemestane, opiate analgesics, letrozole, paclitaxel, teniposide, tretinoin and topotecan; however, published data describing the clinical significance of these interactions are lacking.

Cisapride, terfenadine, astemizole, pimozone and quinidine should not be co-administered with azole antifungal agents due to the risk of QT interval prolongation and *torsades de pointes*.^{10–14} Other medications that may prolong the QT interval (e.g. ciprofloxacin, co-trimoxazole and conventional antipsychotics) should be used with caution in the setting of azole therapy. Ergot alkaloids are contraindicated with azoles due to the risk of ergotism.^{10,15}

Variability in CYP enzyme activity may be observed between patients due to genetic polymorphisms. For example, polymorphisms in the CYP2C19 isoenzyme, observed in up to 5% of white Caucasian¹⁶ and up to 20% of Asian populations,^{10,16} are associated with slow voriconazole metabolism¹⁷ and may lead to two- to four-fold higher voriconazole exposure in these individuals. It has been suggested that CYP2C19 genetic variability influences the pharmacokinetics of voriconazole.¹⁸ While there is limited ability to apply pharmacogenomics to individual patients in a clinical context, clinicians should be aware that genetic variability might result in clinically significant alterations in drug metabolism within the azole class.

Fluconazole is a potent inhibitor of CYP2C9,¹⁹ resulting in reduced clearance of CYP2C9 substrates, including warfarin, phenytoin, sulfamethoxazole and losartan.^{19–24} If fluconazole is co-administered with warfarin or phenytoin, dose reduction of these drugs may be required, and close monitoring of international normalized ratio and phenytoin plasma concentrations, respectively, is necessary.¹⁹

Drug interactions between the azole class and drugs commonly used in the haematology population are summarized in Table 2. Relevant drug–food interactions are outlined in Table 3.

Table 1 Potency of cytochrome interaction profiles of azole antifungal agents³⁵

	CYP3A4		CYP2C8/9		CYP2C19	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Fluconazole	++		++		+	+
Itraconazole	+++	+++	+			
Voriconazole	+	+	++	+	++	+++
Posaconazole	++					

+, weak; ++, moderate; +++, potent.

Table 2 Azole antifungal agents: selected drug–drug interactions relevant to the haematology population

Drug	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Aprepitant	Not documented, but co-administration of aprepitant with strong CYP3A4 inhibitors should be approached with caution ³⁶	Potential for increased plasma concentration of aprepitant (metabolism is inhibited completely by ketoconazole). ³⁷ Caution with this combination ³⁶	Not documented, but co-administration of aprepitant with strong CYP3A4 inhibitors should be approached with caution ³⁶	Not documented, but co-administration of aprepitant with strong CYP3A4 inhibitors should be approached with caution ³⁶
Atorvastatin	Atorvastatin levels may increase; risk of rhabdomyolysis. ³⁸ Monitor or change to pravastatin ³⁹	Increased atorvastatin C_{max} and possible increased risk for rhabdomyolysis. ⁴⁰ Change to alternative (cerivastatin, pravastatin) ⁴¹	Frequent monitoring for adverse events and toxicity related to statin class of drugs (e.g. rhabdomyolysis) ⁴²	Potential for increased plasma concentration and toxicity related to statin class of drugs ⁴³
Busulphan	Busulphan clearance unaffected ⁴⁴	Busulphan clearance decreased by 25% and increased AUC. Monitor busulphan levels ^{44,45}	Not documented. Busulphan levels are likely to be elevated ⁴⁴	Not documented. Busulphan levels are likely to be elevated ⁴⁴
Cimetidine	Small reduction in AUC and C_{max} of fluconazole, but not clinically significant ⁴⁶	Not documented	Not documented	In healthy volunteers, combination resulted in decreased C_{max} and AUC of posaconazole by 40%. ⁴⁷ No recommendations for dose modification available; avoid combination
Cyclophosphamide	Decreased cyclophosphamide clearance and increased $t_{1/2}$ ⁴⁸	Not documented. Interaction likely, significance unknown ⁴⁹	Not documented. Interaction likely, significance unknown ⁴⁹	Not documented. Interaction likely, significance unknown ⁴⁹
Cyclosporin (CSA)	Low-dose fluconazole (100 mg po) has minimal effect, ⁵⁰ higher dosing increases CSA AUC by 50%. Monitor and consider dose reduction of CSA ⁵¹	CSA trough levels increased 50–80%. ^{44,51} Monitor and reduce CSA dose by 50%. ⁴⁵ Effect persists for some time after cessation of itraconazole ^{44,51}	CSA AUC increased 70%. Monitor and reduce CSA dose by 50%. ⁴²	CSA levels increased in cardiac transplant recipients. Monitor levels and consider 30% dose reduction of CSA ⁴³
Dexamethasone (DXM)	Not documented	DXM AUC increased 3 to 4-fold. Increased risk of corticosteroid side-effects. Monitor, dose reduce or use prednisolone ^{51,52}	Not documented	Not documented
Diazepam	Not documented	Diazepam AUC and $t_{1/2}$ increased 35%, but sedation not altered; use with caution ⁵¹	Elevated diazepam levels likely. Use with caution ⁵¹	Not documented
Ifosfamide	Not documented. Reduced ifosfamide clearance possible ⁵¹	Interaction likely (ketoconazole inhibits activation of ifosfamide); monitor for efficacy ^{49,53}	Interaction possible (ketoconazole inhibits activation of ifosfamide); monitor for efficacy ^{49,53}	Not documented
Imatinib	Not documented	Potential for increased exposure to imatinib. Caution with this combination ⁵⁴	Substances that inhibit the CYP450 activity may decrease metabolism and increase imatinib concentrations ⁵⁴	Not documented

Table 2 continued

Drug	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Irinotecan	Potent CYP3A4 inhibitors increase risk for irinotecan toxicity (ketoconazole increases irinotecan AUC by 109%). Dose reduction of irinotecan by 4-fold if co-administered with potent CYP3A4 inhibitors ⁵³	Potent CYP3A4 inhibitors increase risk for irinotecan toxicity (ketoconazole increases irinotecan AUC by 109%). Dose reduction of irinotecan by 4-fold if co-administered with potent CYP3A4 inhibitors ⁵³	Potent CYP3A4 inhibitors increase risk for irinotecan toxicity (ketoconazole increases irinotecan AUC by 109%). Dose reduction of irinotecan by 4-fold if co-administered with potent CYP3A4 inhibitors ⁵³	Not documented
Methylprednisolone	May increase steroid levels; monitor ⁵³	Methylprednisolone C _{max} , AUC and t _{1/2} increased, ⁵⁵ with increased risk of corticosteroid side effects. Dose reduce or use prednisolone ^{51,55}	May increase steroid levels; monitor ⁵³	Not documented
Midazolam	Midazolam peak, AUC and t _{1/2} increased 2-fold. Sedation and amnesia may be prolonged. Lorazepam, oxazepam or temazepam may also interact with fluconazole. Use with caution ⁵¹	Midazolam peak, AUC and t _{1/2} increased 2-fold for up to 4 days after ceasing itraconazole. Sedation and amnesia prolonged. Reduce dose or consider lorazepam, oxazepam or temazepam ⁵¹	Midazolam metabolism impaired <i>in vitro</i> . Prolonged sedation likely. Lorazepam, oxazepam and temazepam may also interact. Use with caution ⁵¹	Midazolam AUC increases 83%. Prolonged sedation likely. ⁴³ Reduce dose or consider lorazepam, oxazepam or temazepam
Nifedipine	Not documented. Increased nifedipine levels theoretically possible. Monitor for hypotension ⁵¹	Increased nifedipine levels likely. Monitor for hypotension ⁵¹	Not documented. Increased nifedipine levels likely. Monitor for hypotension ⁵¹	Not documented
Omeprazole	Not documented	Oral absorption of itraconazole capsules decreased 30–60% due to reduced gastric acidity. ^{51,56} Administer with cola beverage ⁴⁵	Omeprazole level doubled; recommend omeprazole dose reduction. Voriconazole AUC increased 41%, monitor for toxicity ⁴²	May decrease posaconazole bioavailability ⁴³
Pantoprazole	Not documented	Oral absorption of itraconazole capsules decreased 30–60% due to reduced gastric acidity. ⁵¹ Administer with cola beverage ⁴⁵	Not documented	May decrease posaconazole bioavailability ⁴³
Prednisolone	May increase steroid levels; monitor ⁵³	Increased prednisolone levels (13–30%), but clinical impact not likely to be significant ^{45,57}	Increased steroid levels (11–34%); monitor ⁴²	Not documented
Ranitidine	Not documented	Itraconazole absorption from capsules decreased (30–60%), solution unaffected ^{45,51}	Oral ranitidine has no impact on voriconazole plasma concentration ¹⁸	Not documented. May decrease posaconazole bioavailability ⁴³
Simvastatin	Not documented. Simvastatin levels may increase; monitor or change to pravastatin ⁵¹	Simvastatin t _{1/2} increased 10-fold, with increased risk of rhabdomyolysis; withhold statin or change to fluvastatin, pravastatin or rosuvastatin ⁵¹	Not documented. Increased simvastatin levels likely; withhold statin or change to fluvastatin, pravastatin ⁵¹ or change to pravastatin ⁵¹	Not documented. Increased simvastatin levels likely; withhold statin or change to fluvastatin, pravastatin or rosuvastatin ⁵¹ continued

Sirolimus	Large increase in sirolimus levels seen by day 3 after initiation of 200 mg po fluconazole; consider 50–75% sirolimus dose reduction and monitor levels ⁴⁸	Single dose sirolimus in patients on ketoconazole increased sirolimus AUC 11-fold. ⁵¹ Increased sirolimus levels likely. Use with extreme caution ⁴⁵	Single voriconazole dose leads to 7-fold increase in sirolimus C _{max} ; sirolimus dose reduction and monitoring of levels if co-administered ^{42,55,59}	Not documented. Increase in sirolimus levels likely, monitor levels ⁴³
Tacrolimus	Low fluconazole doses (100 mg po) increase tacrolimus AUC 1.4 times. Higher oral doses (200 mg) increase tacrolimus AUC 3.1 times. Consider 50% dose reduction of tacrolimus and monitor ⁴⁰	Tacrolimus trough level increased 5-fold (both drugs po); reduce tacrolimus dose and monitor. ⁵¹ Tacrolimus trough increased 88% when both drugs IV; reduce tacrolimus 50% and monitor ⁴⁴	Tacrolimus C _{max} doubles and AUC triples; reduce tacrolimus dose to 1/3 and monitor levels ⁵²	Single dose study: 121% increase C _{max} IV tacrolimus and 358% increase AUC; consider dose reduction and monitor levels ⁴³
Triazolam	Triazolam peak, AUC, and t _{1/2} increased 1.25- to 2.5-fold. Sedation and amnesia prolonged. Lorazepam, temazepam or zolpidem may also interact with fluconazole. Use with caution ⁵¹	Triazolam peak, AUC increased 2-fold and t _{1/2} increased 20-fold for up to 24 h after cessation of itraconazole. Sedation and amnesia prolonged. Substitute lorazepam, oxazepam, temazepam or zolpidem ⁵¹	Elevated triazolam levels likely. ^{42,51} Substitution of lorazepam, oxazepam or temazepam may also interact. Use with caution	Not documented. Increased triazolam levels likely, ⁴³ reduce dose or consider lorazepam, oxazepam or temazepam
Vinblastine	Not documented	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ⁴⁵	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ^{42,53}	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ⁴³
Vincristine	Not documented	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ^{45,61–63}	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ^{42,53}	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ^{43,64}
Vinorelbine	Not documented	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ⁴⁵	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ^{42,53}	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered ⁴³
Warfarin	Increase in INR (38%); ⁵¹ dose-reduce warfarin and monitor INR ⁶⁵	INR may be increased; dose-reduce warfarin and monitor INR ⁵¹	Increase in INR (41%); dose-reduce warfarin and monitor INR ⁵¹	Not documented

Note: Interactions studied via the oral route may not predict the degree of interaction via other routes. AUC, area under the curve; C_{max}, peak concentration; INR, international normalized ratio; IV, intravenous; po, oral; t_{1/2}, half-life.

Table 3 Azole antifungal agents: drug–food interactions relevant to clinical practice

	Drug–food interaction		Recommendation for clinical practice
	Absorption and bioavailability	Pharmacokinetics	
Fluconazole	Absorption not significantly influenced by concomitant food intake ⁶⁶	Nil reported	Administer with or without food ⁶⁵
Itraconazole	Absorption of capsules is enhanced when taken with or after food, ⁶⁶ while absorption of the oral solution is enhanced when taken before food. ⁶⁷ If hypochlorhydric or concurrently taking H ₂ -receptor antagonists, co-administration of an acidic solution enhances the bioavailability of itraconazole ⁶⁸	Grapefruit juice may impair the metabolism of itraconazole capsules or solution via competitive inhibition of intestinal CYP3A4, ^{69,70} but the clinical significance of this is not known ⁷¹	Itraconazole capsules: administer with or after food Itraconazole solution: administer before food. Co-administer an acidic beverage (e.g. cola) to improve bioavailability in patients who are hypochlorhydric or who are taking gastric acid suppressants
Voriconazole	In healthy subjects, oral absorption is delayed in the non-fasted state (AUC reduced by 22%) ⁷²	Nil reported	Administer one hour before or one hour after food ⁴²
Posaconazole	In healthy subjects, oral absorption is increased when given with nutritional supplement ⁷³ or high-fat meal ⁷⁴	Nil reported	Administer with high-fat meal or nutritional supplement

AUC, area under the curve.

Amphotericin B

Amphotericin B (AmB-D) and its lipid-based formulations are renally excreted and may be associated with nephrotoxicity, hypokalaemia and hypomagnesaemia. The nephrotoxic potential of amphotericin preparations is enhanced when used alongside other nephrotoxic medications (e.g. cisplatin, cyclosporin, ganciclovir, aminoglycosides and tacrolimus).^{25,26} Associated hypokalaemia may be exacerbated by the administration of other potassium-depleting agents (e.g. hydrocortisone, non-potassium sparing diuretics).²⁷ The cardiotoxicity of digitalis may also be enhanced by this mechanism.²⁸ Therefore, renal function and electrolyte levels should be monitored closely. Consider reducing the dose of amphotericin B if using a drug combination with additive nephrotoxicity.

Echinocandins

The echinocandin class of drugs is not significantly metabolized by the CYP450 system. Anidulafungin is not metabolized by these enzymes,²⁹ caspofungin is a poor substrate for CYP450 enzymes,³⁰ and hydrolysis by CYP3A plays only a minor role in the metabolism of micafungin.²⁹ These agents can therefore be co-administered with most drugs without the need for dose modification or monitoring.³¹

Concomitant administration of CYP450 inducers (e.g. rifampicin) with some echinocandins (e.g. caspofungin) may reduce serum antifungal drug concentration.³² It

has been suggested that the daily dose of caspofungin should be increased to 70 mg during co-administration with enzyme inducers (e.g. phenytoin, rifampicin, dexamethasone).³³

Combination therapy with caspofungin and cyclosporin may lead to transient elevations in transaminases. Caspofungin may also reduce plasma concentrations of tacrolimus.³⁴

Minimizing antifungal toxicity

The development of new antifungal agents has been driven, in part, by the toxicities observed with conventional amphotericin B (AmB-D). Both the relative toxicity of a drug and its efficacy will influence a clinician's choice of antifungal therapy. Table 4 summarizes known antifungal drug toxicities and adverse effects relevant to the haematology population, along with recommendations for risk reduction.

Nephrotoxicity

Nephrotoxicity is observed in approximately one third of adults who are treated with AmB-D. The cause of AmB-D-induced nephrotoxicity is multifactorial but includes drug-induced intrarenal arteriolar constriction, resulting in decreased renal blood flow and a reduced glomerular filtration rate, and the drug's direct toxic effect on epithelial cell membranes (e.g. acute tubular necrosis and distal tubulopathy).^{26,75,76}

Table 4 Toxicity and adverse effects of currently available systemic antifungal agents

Antifungal agent	Commonly reported side effects	Evidence and suggestions for risk reduction
<ul style="list-style-type: none"> • <i>AmB-D</i> • <i>L-AMB</i> • <i>ABLC</i> • <i>ABCD</i> 	Nephrotoxicity	<ul style="list-style-type: none"> • Reported rates of renal toxicity: AmB-D 32–33%; L-AMB 15%; ABLC 16%; ABCD 21%^{77,79} • Nephrotoxicity may be minimized by pre-hydrating with sodium chloride 0.9% (500 mL over 1 h in adult recipients) and avoiding hyponatraemia and hypovolaemia^{94–96} • Similar rates of nephrotoxicity are observed for AmB-D via continuous infusion and L-AMB although no adequately powered direct comparison has been performed^{101,102} • 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^{90,91}
	IRAEs	<ul style="list-style-type: none"> • IRAEs occur frequently with AmB-D: fever 34–51%; chills or rigors 28–74%; nausea 18–19%.^{79,91,97,98} More severe IRAEs occur less frequently: bronchospasm 7%; hypotension 1–11%^{79,82,85,91} • Premedication is frequently used to help reduce the incidence of IRAEs, although data supporting this practice are limited^{97,98} • AmB-D via continuous infusion causes significantly less IRAEs compared to standard therapy¹⁰¹ • L-AMB is responsible for less IRAEs compared with other lipid preparations: fever 11%; chills or rigors 37%; nausea 12%^{79,91,99,104} • Rates of IRAEs with ABLC are similar to AmB-D whereas ABCD is associated with higher rates of IRAEs^{79,99,105,114,115} • Tolerance to IRAEs generally develops within the first seven days of initiating therapy^{97,98}
	Electrolyte abnormalities	<ul style="list-style-type: none"> • Electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia) commonly occur with AmB-D due to renal losses (serum potassium \leq 2.5 mmol/L: 12–31%); monitor electrolyte levels closely and replace if necessary^{91,104} • Electrolyte disturbances are observed less frequently with L-AMB and ABLC compared to AmB-D; monitor electrolyte levels closely and replace if necessary^{91,104,105} • Consider using amiloride (10 mg daily) to decrease urinary potassium loss, increase serum potassium and reduce potassium replacement requirements¹¹⁶
	Hepatotoxicity	<ul style="list-style-type: none"> • Hepatotoxicity (defined as tripling of the baseline bilirubin or transaminases) occurs in 16% of patients receiving AmB-D; this is not significantly different to rates observed with the lipid preparations⁷⁹
	Other	<ul style="list-style-type: none"> • Rash is reported in 1–5% of patients receiving amphotericin products^{82,84,89,107} • A reversible normochromic, normocytic anaemia (mediated by a suppression of erythropoietin production) may occur with prolonged use^{117,118}
Fluconazole	Gastrointestinal toxicity	<ul style="list-style-type: none"> • Gastrointestinal symptoms (nausea, vomiting and diarrhoea) occur in a minority of patients; 0–9%^{82,110–112,119,120}
	Hepatotoxicity	<ul style="list-style-type: none"> • 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^{79,82,86,110,119–122} • Discontinuation due to hepatotoxicity is rare (0–5%)^{79,82,86,110,119–121}
	Dermatological toxicity	<ul style="list-style-type: none"> • Rash is reported in 4–6% of patients^{82,111}
	Other	<ul style="list-style-type: none"> • Nephrotoxicity occurs in 1–3% of patients receiving fluconazole (significantly less than AmB-D)^{82,86,112} • IRAEs are rarely reported with fluconazole: fever and/or chills 0–1% (significantly less than AmB-D)^{82,122}
Itraconazole	Gastrointestinal toxicity	<ul style="list-style-type: none"> • Gastrointestinal symptoms are reported in 13–24% of subjects receiving itraconazole^{79,85,111,112,123,124} • Compared with fluconazole and posaconazole, itraconazole causes significantly more gastrointestinal toxicity^{109,111,112} • The incidence of diarrhoea increases with higher doses of the oral solution due to the cyclodextrin vehicle; oral loading doses can be difficult to tolerate. In practice, it is probably more feasible to load with 400 mg capsules bd (swapping to the oral solution 200 mg bd for ongoing therapy), or starting the itraconazole solution (200 mg bd) 1–2 weeks before the prophylactic effect is required¹²⁵
	Hepatotoxicity	<ul style="list-style-type: none"> • Rates of hepatotoxicity vary depending on the patient population and definition used (7–32%); this is not significantly different to fluconazole and posaconazole^{85,108,109,111,112,123}
	Dermatological toxicity	<ul style="list-style-type: none"> • Rash is reported in 4–7% of patients^{111,123}

Table 4 continued

Antifungal agent	Commonly reported side effects	Evidence and suggestions for risk reduction
	Other	<ul style="list-style-type: none"> Nephrotoxicity occurs in 5–7% of patients receiving itraconazole^{62,85} IV itraconazole is available under the special access scheme in Australia and New Zealand. It is solubilized by hydroxypropyl-β-cyclodextrin (HPβCD), which is exclusively renally excreted; avoid using IV itraconazole in patients with a creatinine clearance less than 30 mL/min⁴⁵
Voriconazole	Ocular toxicity	<ul style="list-style-type: none"> Dose-related visual disturbances, including blurred vision, photophobia, and altered visual and colour perception, occur in 22–45% of patients.^{83,89,126} 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	<ul style="list-style-type: none"> Significant transaminitis (alanine and aspartate aminotransferases (ALT/AST) >5 times baseline) is observed in 4–9% of patients.^{83,89,126} Hyperbilirubinaemia (>3 times baseline level) occurs in up to 18% of recipients.⁸³ The rate of hepatotoxicity was not significantly different to AmB-D, L-AMB and fluconazole in comparative trials^{83,87,89}
	Dermatologic toxicity	<ul style="list-style-type: none"> Rash, pruritus or photosensitivity occurs in 7–9% of patients.^{89,126,127} 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
	Other	<ul style="list-style-type: none"> Nephrotoxicity occurs in 1–7% of patients receiving voriconazole (significantly less than AmB-D)^{83,87,89} IRAEs occur less frequently compared with amphotericin B preparations: fever and/or chills 3–14%^{83,89} IV voriconazole is solubilized by sulfobutylether-β-cyclodextrin (SBECD). SBECD is exclusively excreted by the kidney and accumulates in patients with renal impairment; use oral voriconazole instead of the IV formulation in patients with a creatinine clearance less than 50 mL/min^{42,128}
Posaconazole	Gastrointestinal toxicity	<ul style="list-style-type: none"> Gastrointestinal symptoms are the most frequent cause of toxicity in patients receiving posaconazole: nausea 4–12%; vomiting 4–7%; abdominal pain 2–5% and diarrhoea 3–11%.^{110,129–132} These rates are not significantly different to those observed with fluconazole¹¹⁰
	Hepatotoxicity	<ul style="list-style-type: none"> Hepatotoxicity is infrequently reported with posaconazole (1–3%); this is not significantly different to rates reported with fluconazole or itraconazole^{109,110,129,131,132}
	Other	<ul style="list-style-type: none"> Rash and headache are reported in 2–4% and 1–5% of subjects, respectively^{110,129–132} Neutropenia is reported in 7% of patients; this is not significantly different to rates reported with fluconazole or itraconazole¹⁰⁹
Caspofungin	Gastrointestinal toxicity	<ul style="list-style-type: none"> Gastrointestinal toxicity is infrequently seen with caspofungin: nausea 2–6%; vomiting 2–3.5%; diarrhoea 1–4%^{84,107,108,133}
	Hepatotoxicity	<ul style="list-style-type: none"> Hepatotoxicity (elevated transaminases) occur in 1–15% of patients^{84,88,107} Early data showed an increase in the plasma concentrations of caspofungin and increased transaminases when caspofungin was concomitantly administered with cyclosporin; the Product Information states that the combination may be used when the potential benefits outweigh the potential risk³⁴ However, a number of observational studies in children and adult subjects have demonstrated the safety of this combination^{62,134,135}
	Other	<ul style="list-style-type: none"> Nephrotoxicity occurs in 0–8% of patients (significantly less than AmB-D)^{84,88,107} IRAEs occur less frequently than they do with the amphotericin B preparations: chills 0–14%^{84,88,107} Rash is infrequently observed with caspofungin: 1–6%^{84,133}
5-FC	Gastrointestinal toxicity	<ul style="list-style-type: none"> Gastrointestinal toxicity occurs in approximately 6% of patients treated with 5-FC¹³⁶
	Hepatotoxicity	<ul style="list-style-type: none"> The incidence of hepatotoxicity can vary markedly (from 0–40%) depending on the definition used.^{136–138} Hepatotoxicity appears to be dose-dependent, occurring more frequently when peak 5-FC concentrations are above 100 mg/mL
	Bone marrow suppression	<ul style="list-style-type: none"> Leukopaenia, thrombocytopaenia or pancytopenia are all reported with 5-FC therapy. The incidence is dose-dependent (observed when levels are >100 mg/L) and influenced by comorbidities, pre-existing bone marrow suppression and disease¹³⁶

Toxicity data are taken from trials using doses expected to have a therapeutic effect on invasive fungal infections (i.e. fluconazole 400–800 mg or 6–12 mg/kg per day, itraconazole 200–400 mg or 5–10 mg/kg per day, voriconazole 200 mg or 4 mg/kg twice daily and posaconazole 600–800 mg per day). 5-FC, 5-flucytosine; ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; AmB-D, amphotericin B deoxycholate (conventional amphotericin); IRAEs, infusion-related adverse events; L-AMB, liposomal amphotericin B.

The lipid formulations of amphotericin are less nephrotoxic than AmB-D. Three meta-analyses reported that these agents reduced the incidence of nephrotoxicity by 49–75% compared with AmB-D, although they are not significantly different from each other in terms of their potential to cause nephrotoxicity.^{77–79} The time to onset of nephrotoxicity is also significantly longer for these agents.^{80,81} The azoles and echinocandins are both less nephrotoxic than AmB-D and L-AMB.^{82–89} No trials have compared ABLC or amphotericin B colloidal dispersion (ABCD) with the azoles and echinocandins.

The incidence of amphotericin-induced nephrotoxicity varies between populations. In one study, haematopoietic stem cell recipients (HSCT) were five times more likely to require haemodialysis when administered conventional amphotericin B for aspergillosis than solid organ and non-transplant related chemotherapy recipients.⁹⁰ In this cohort, dialysis was a significant risk factor for death.

Higher amphotericin B doses, pre-existing renal impairment, hyponatraemia, hypovolaemia and the concomitant use of other nephrotoxic medications, have all been shown to increase the risk of amphotericin-induced nephrotoxicity.^{26,76,90–95} The risk of amphotericin-induced nephrotoxicity has been shown to double when two or more nephrotoxic agents (e.g. cyclosporin, aminoglycosides or foscarnet) are used concurrently.⁹¹ Sodium loading prior to amphotericin use, avoiding hypovolaemia and restricting the concomitant use of other nephrotoxins, can decrease the risk of amphotericin-induced nephrotoxicity.^{94–96}

Infusion-related adverse events

Infusion-related adverse events (IRAEs) – most frequently chills, rigors, fever, nausea and vomiting – often complicate the administration of AmB-D; at least one IRAE was observed within the first 7 days of AmB-D therapy in 71% of adult recipients.^{97,98} Infusion-related toxicity is associated with the release of tumour necrosis factor (TNF) and interleukins 1 (IL-1) and 6 (IL-6) from monocytes and macrophages.⁹⁹ IRAEs are much more likely to occur in younger age groups.¹⁰⁰

Antihistamines, corticosteroids and paracetamol (in varying combinations) are frequently used as ‘pre-medication’ to help prevent IRAEs. There are limited data, however, demonstrating the benefit of pre-medication on reducing the incidence of IRAEs.^{97,98}

Comparative trials indicate that L-AMB is the amphotericin-based product least likely to cause IRAEs while similar rates of IRAEs are described for AmB-D, ABLC and ABCD.⁷⁹ Fluconazole, itraconazole, voriconazole and caspofungin are less likely to cause IRAEs than

AmB-D.^{82,85,88,89} Voriconazole and caspofungin are also less likely to cause IRAEs than L-AMB.^{83,84}

Continuous amphotericin B infusions result in less nephrotoxicity and IRAEs compared with intermittent amphotericin B infusions.^{101,102} Rates of nephrotoxicity and IRAEs observed with continuous amphotericin B infusions approximate those observed for L-AMB, yet no comparative trial has been performed. Experimental *in vitro* and *in vivo* studies have demonstrated that amphotericin’s fungicidal effects and antifungal efficacy are concentration-dependent; this suggests that a large daily dose of amphotericin may be more effective clinically and that achieving optimal peak drug concentrations may be important.¹⁰³ Although results of two trials are encouraging, with improved survival demonstrated in the continuous infusion arm, no adequately powered trial has compared the relative efficacy of continuous amphotericin B infusion with intermittent amphotericin B infusions or the lipid preparations.^{101,102}

Hepatotoxicity

Several trials have assessed the relative hepatotoxicity of different antifungal agents. From these trials we know that there is no significant difference in the hepatotoxicity of AmB-D compared with the various lipid formulations,^{91,104,105} fluconazole and voriconazole compared with AmB-D or L-AMB,^{82,83,86,89,106} caspofungin compared with AmB-D and fluconazole,^{88,107,108} or between different azoles.^{87,109–113}

Other adverse events

Rash is seen more frequently in adults administered fluconazole or voriconazole than amphotericin.^{82,89} Gastrointestinal symptoms are observed more frequently with itraconazole than the other azoles,^{109,111,112} while visual disturbance or eye symptoms are reported more frequently in adults who receive voriconazole.^{83,89}

Antifungal drug monitoring in haematology

TDM can indicate the adequacy of drug exposure. For example, the measurement of a single trough concentration of an azole antifungal can verify subtherapeutic serum levels resulting from drug interactions involving CYP450 3A4.

Typically, four criteria must be fulfilled to justify the measurement of serum or plasma drug concentrations to guide drug dosing or confirm clinical suspicions of a drug–drug interaction: (i) the assay must have appropriate sensitivity, specificity and ‘turn-around’ time; (ii) the clinical efficacy or toxicity of the drug must be delayed or

Table 5 Recommendations for antifungal drug monitoring

Antifungal agent	Drug monitoring recommended ³⁵	Indication for drug monitoring	Timing of sample	Target range ($\mu\text{g/mL}$)
Amphotericin B and lipid-based preparations	No	–	–	–
Caspofungin	No	–	–	–
5-FC	Routine	To monitor for toxicity	2 h post dose	<100 ¹⁴²
Fluconazole	No	Consider if renal insufficiency, suspected non-compliance or malabsorption	After 5–10 days of therapy ¹⁴³	Unknown
Itraconazole	Targeted	To ensure adequate absorption, therapeutic concentration	Trough after steady state reached (4–5 days)	>0.5 ^{140,141}
Voriconazole	Targeted	To detect therapeutic and toxic concentrations	Trough after steady state reached (1–2 days) [†]	1–6 ^{127,139}
Posaconazole	No [‡]	Consider if suspected malabsorption	Trough after steady state reached (5–6 days) ¹⁴⁴	Unknown

[†]Time to steady state (estimated by $5 \times t_{1/2}$) may vary according to dose for voriconazole, which has non-linear pharmacokinetics. Alternatively, serum concentration may be measured after administration of loading dose (at 48 h), providing an estimate of therapeutic serum concentration. [‡]Monitoring of posaconazole levels not widely available in Australia. 5-FC, 5-flucytosine.

difficult to measure directly; (iii) the drug must exhibit significant inter-patient variability in pharmacokinetics such that drug concentrations cannot be assumed from empirical dosing strategies and (iv) there must be established correlations between drug concentrations and clinical efficacy/toxicity.³⁵

Although antifungal therapy does not typically fulfil all four criteria, serum drug level monitoring may be helpful for certain antifungal agents where non-compliance, non-linear pharmacokinetics, a narrow therapeutic window, drug interactions or unexpected toxicity are encountered.

Randomized data supporting routine or targeted antifungal drug monitoring are not available to compare clinical outcomes in the presence and absence of monitoring strategies. TDM is most frequently indicated for 5-FC, itraconazole and occasionally voriconazole. For 5-FC¹³⁸ and voriconazole,^{127,139} available evidence is without a reference standard as comparator (level IV evidence), and for itraconazole, results of comparative studies^{140,141} are used to support monitoring (level III-3 evidence). Monitoring of amphotericin B and its lipid-based formulations, fluconazole and caspofungin is not routinely recommended. Currently, there is insufficient evidence to support routine or targeted monitoring of posaconazole concentrations. These recommendations are summarized in Table 5.

5-FC

Peak serum concentrations of 50–80 $\mu\text{g/mL}$ are observed within 1–2 h when a daily dose of 150 mg/kg is

administered in divided doses.¹⁴⁵ Elevated concentrations have been associated with drug toxicity (e.g. blood dyscrasias, hepatic injury, gastrointestinal disturbances).¹³⁸ A target peak concentration of 50–100 $\mu\text{g/mL}$ is associated with a low incidence of toxicity. In one report, 61% (23/38) of patients with 5-FC-induced haematological toxicity or hepatotoxicity had serum concentrations $\geq 100 \mu\text{g/mL}$ for more than 2 weeks of therapy, compared with 31% (15/48) of patients with lower serum concentrations.¹³⁸ Serum 5-FC levels should be routinely monitored along with serum creatinine, hepatic enzymes and neutrophil and platelet counts.

Itraconazole

Itraconazole achieves its maximum plasma concentration at 5.5 h following administration of the oral capsule (5.7 h for the oral solution). Absorption of the oral solution is enhanced by the fasting state.^{67,146} Itraconazole often has reduced or variable bioavailability in the presence of mucositis or GVHD, although there is significant interpatient variability in absorption. Quantitative assay can help confirm satisfactory absorption in this clinical setting.

Monitoring of plasma itraconazole levels is associated with an improved clinical outcome. In a study of 72 haematology patients receiving prophylactic itraconazole, the occurrence of invasive fungal infection (IFI) was significantly greater in the group for whom therapeutic plasma levels were not monitored.¹⁴⁰

A target trough level for clinical efficacy has been proposed from observational data. In a study of itraconazole prophylaxis (capsules or solution) in patients with haematological malignancy, 12/20 patients died due to IFI and 8/20 patients were diagnosed with a non-fatal IFI. The fatal IFI group had significantly lower median itraconazole concentrations compared with the non-fatal IFI group (0.120 µg/mL vs. 0.690 µg/mL, respectively).¹⁴¹ Only three patients with fatal IFI had itraconazole trough concentrations above 0.500 µg/mL. This trough level has subsequently been adopted by others as a target for optimal efficacy.¹⁴⁷

Voriconazole

Voriconazole reaches its maximum plasma concentration in plasma 1.41–1.8 h following oral administration.¹⁴⁸ Its bioavailability, estimated to be approximately 85% in healthy volunteers following oral administration,¹⁴⁸ is reduced with a high-fat meal.⁷² Oral voriconazole should be administered, therefore, 1 h before or 1 h after a meal.⁴²

The metabolism of voriconazole varies widely between individuals,¹²⁷ with less inpatient variability.¹⁴⁹ Voriconazole exhibits non-linear pharmacokinetics in adults; saturation of metabolizing hepatic enzymes leads to disproportionate increases in voriconazole exposure with increasing doses. Furthermore, polymorphisms in the cytochrome P450 isoenzyme, CYP2C19 (observed in up to 5% of white Caucasian¹⁶ and up to 20% of Asian populations^{10,16}, are associated with slow voriconazole metabolism and may lead to two- to fourfold higher voriconazole exposure in these individuals.

Clinicians should consider measuring voriconazole levels if oral absorption is uncertain or potential drug interactions are likely to have an impact upon drug metabolism. In patients with haematologic malignancy, the correlation between voriconazole concentration and daily dose is poor, in keeping with inpatient variability.¹⁵⁰ In pooled data from ten published clinical trials, the median average plasma concentration was reported as 2.51 µg/mL.¹³⁹ In a study assessing voriconazole as directed therapy for IFI ($n = 28$), voriconazole levels were measured in 17 patients with disease progression.¹³⁹ All 17 patients had serum voriconazole concentrations below the pooled median value but it is not clear if this reflects cause or effect of failing therapy.

In an open, non-comparative study of voriconazole's safety and efficacy for the management of IA in an immunocompromised patient population, an arbitrary sub-therapeutic plasma concentration of 1.000 µg/mL was applied.¹²⁷ Plasma concentrations were consistently <0.250 µg/mL in 5/122 patients; 3 of these patients

failed to respond to therapy, suggesting a possible threshold for clinical efficacy. Plasma concentrations were >6.000 µg/mL in 6/22 patients; abnormal liver function or liver failure was also observed in this group, suggesting a possible threshold for monitoring of toxicity. A significant correlation between serum voriconazole levels and aspartate aminotransferase (AST) and alkaline phosphatase was later demonstrated by another group.¹⁴⁹

Single-centre experience applying a target trough level of >1 µg/mL in 37 proven or probable IFIs has been reported retrospectively.¹⁵¹ Of nine patients with trough concentrations <1 µg/mL, six had treatment failure (the dose was increased with subsequent partial or complete response). Of the remaining 28 patients with trough concentrations >1 µg/mL, two had treatment failure and responded to salvage therapy. Given these observations, the proposed target range for voriconazole is 1–6 µg/mL.^{127,139}

Posaconazole

There are no data correlating serum levels of posaconazole and treatment outcomes. Thus, there is currently no accepted target drug concentration for posaconazole prophylaxis or treatment. Studies linking drug levels with efficacy are limited, although in one salvage study higher posaconazole levels were associated with more responders.¹²⁹

Conclusion

Antifungal therapy is becoming increasingly complex. Clinicians should consider patient comorbidities and concurrent medications when choosing an antifungal regimen for prophylaxis, empirical therapy or treatment. Despite careful consideration, toxicity may still occur. Toxicity may, in part, be avoidable with pre-treatment, careful observation and TDM. Furthermore, there is increasing evidence that adequate serum levels of some antifungal agents are associated with improved clinical outcomes for patients with IFI.

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