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Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2014

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Key words
antifungal therapy, toxicity, drug interaction, therapeutic drug monitoring, pharmacogenomics.

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Abstract

Antifungal agents may be associated with significant toxicity or drug interactions leading to sub-therapeutic 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 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 proposed.

Introduction

The following guideline has been developed to assist clinicians in the identification of potential drug interactions and to minimise drug toxicity when antifungal therapies are administered to patients with haematological malignancy. Recommendations for therapeutic drug monitoring (TDM) of voriconazole and posaconazole are also provided. During the formulation of this guideline, a review of literature published between 2008 and 2014 was performed, and previously published Australian recommendations[1] were updated. Further to the guidelines published in 2008,[1] the relevance of pharmacogenomic evaluation to administration of azole therapy has been reviewed, and content has been assessed for consistency and relevance to paediatric populations. In accordance with National Health and Medical Research Council standards, grading (A–D) has been applied to recommendations.

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Table 1 Potency of cytochrome interactions for azole antifungal agents[4,5]

	CYP3A4		CYP2C8/9		CYP2C19	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Fluconazole	++	0	++	0	+	+
Itraconazole	+++	+++	+	0	0	0
Voriconazole	++ to +++	+	++	+	++	+++
Posaconazole	++	0	0	0	0	0

+ , Weak; ++, moderate; +++, potent; CYP, cytochrome.

Methodology

Questions asked

In preparing this update, we aimed to address the following questions:

1 Which antifungal drug interactions relevant to patients with haematological malignancy have been identified over the last 6 years?

2 Which antifungal toxicities and treatment strategies to ameliorate or reduce these toxicities have been reported over the last 6 years?

3 What is the role of voriconazole and posaconazole drug monitoring in patients with haematological malignancy requiring antifungal prophylaxis or treatment?

4 What is the role of pharmacogenomics evaluation in patients with haematological malignancy requiring administration of azole antifungal agents?

Search strategy

A literature review was performed using PubMed and Medline to identify papers published since 2007 that pertained to antifungal drug interactions, antifungal drug toxicities, antifungal TDM and pharmacogenomics evaluation in patients with haematological malignancy and patients of haemopoietic stem cell transplantation.

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 metabolised by specific (and different) metabolic pathways. Therefore, a 'class effect' cannot always be assumed.

Azole drug interactions

In general, the azole class of antifungal agents is metabolised by the cytochrome P450 (CYP450) system, although posaconazole primarily undergoes uridine diphosphate (UDP) glucuronidation[2] and fluconazole is largely renally excreted.[3] The potential for drug–drug interactions is higher for itraconazole and voriconazole, as these are metabolised to a greater extent by cytochrome isoenzymes than fluconazole and posaconazole (Table 1).

Co-administration of an azole agent with drugs that induce CYP450 metabolism (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin and rifabutin) can result in substantial reduction in the plasma concentrations of the azole antifungal agent and reduce antifungal efficacy.[6–8] For this reason, co-administration of rifampicin is contraindicated with itraconazole and voriconazole and, where possible, should be avoided with fluconazole.[9] Induction of glucuronidation by rifampicin may lead to a reduction of posaconazole plasma levels; therefore, co-administration with posaconazole should also be avoided.[10]

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 when patients on oral hypoglycaemic agents are also prescribed an azole drug because of the increased risk of hypoglycaemia).[11–13] The magnitude of these drug interactions may be more pronounced if the interacting drug has high presystemic elimination (low oral bioavailability), is primarily metabolised by CYP3A4 and is administered orally.[14] The azole antifungal agents may also increase the plasma concentrations of the following antineoplastic CYP3A4 substrates: anastrazole, bexarotene, cytarabine, docetaxel, doxorubicin, etoposide, exemestane, letrozole, paclitaxel, teniposide, tretinoin and topotecan. However, published data describing the clinical significance of these interactions are lacking. Fluconazole and voriconazole are significant inhibitors of CYP2C9, resulting in reduced clearance of CYP2C9 substrates, including warfarin and phenytoin.[6,15–19] Fluconazole also inhibits sulfamethoxazole metabolism.[20] If fluconazole or voriconazole is co-administered with warfarin or phenytoin, dose reduction of these drugs may be required, and close monitoringof international normalised ratio and phenytoin plasma concentrations, respectively, is necessary.[15,21]

Cisapride, terfenadine, astemizole, pimozide and quinidine should not be co-administered with azole antifungal agents due to the risk of QT interval prolongation and *torsades de pointes*.[22–25] Other medications that may prolong the QT interval (e.g. ciprofloxacin, co-trimoxazole, macrolide antibiotics and conventional antipsychotics) should be used with caution in the setting of azole therapy because of additive risks of QT interval prolongation.[22,26] Ergot alkaloids are contraindicated with azoles because of the risk of ergotism.[27,28]

Variability in CYP enzyme activity between patients may be observed due to genetic polymorphisms. For example, CYP2C19 genotype has been identified as an important determinant of the highly variable pharmacokinetics of voriconazole[29] and may influence the extent of drug interactions between voriconazole and other concomitant medications.[30] Details concerning clinical indications for pharmacogenomics testing are provided elsewhere in this guideline.

Drug interactions between the azole class and drugs commonly used in the haematology population are summarised in Table 2. Specific interactions with antiretroviral medications have recently been reviewed,[118] and the University of Liverpool human immunodeficiency virus (HIV) drug interaction chart is also available for assessment of potential azole drug interactions in patients with HIV infection.[119] Relevant drug–food interactions are outlined in Table 3.

Polyene drug interactions

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).[130,131] Associated hypokalaemia may be exacerbated by the administration of other potassium-depleting agents (e.g. hydrocortisone, non-potassium sparing diuretics). The cardiotoxicity of digitalis may also be enhanced by this mechanism.[132,133] Therefore, renal function and electrolyte levels should be monitored closely. AmB-D-associated nephrotoxicity is typically less severe in infants and children.[134] Liposomal AmB-D is also well tolerated in infants.[135]

Echinocandin drug interactions

The echinocandin class of drugs is not significantly metabolised by the CYP450 system. Anidulafungin is not metabolised by these enzymes,[136] caspofungin is a poor substrate for CYP450 enzymes[137] and hydrolysis by CYP3A plays only a minor role in the metabolism of micafungin.[136] These agents can therefore be co-administered with most drugs without the need for dose modification or monitoring.[138]

Concomitant administration of CYP450 inducers (e.g. rifampicin) with some echinocandins (e.g. caspofungin) may reduce serum antifungal drug concentration.[139] 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 and dexamethasone).[140] Combination therapy with caspofungin and cyclosporin may lead to transient elevations in transaminases. Caspofungin may also reduce plasma concentrations of tacrolimus.[141]

Anidulafungin is not expected to alter the plasma concentrations of either cyclosporin or tacrolimus.[142,143] Thirty-five healthy subjects were given a single 5-mg oral dose of tacrolimus 3 days before and on day 10 of a course of intravenous anidulafungin. Anidulafungin did not have any significant adverse effects on the pharmacokinetics of tacrolimus, and no serious adverse effects were reported.[143] For cyclosporin, it has been demonstrated both *in vitro* and *in vivo* that anidulafungin is unlikely to affect the metabolism of this drug.[142] One study did show that cyclosporine caused a 22% increase in the steady-state concentration of anidulafungin, but this increase was not considered to be clinically significant.[142] Rifampicin does not appear to alter the clearance of anidulafungin.[144] Micafungin, however, may have varied effects on the pharmacokinetics of cyclosporine; therefore, monitoring of plasma cyclosporine concentration is recommended[145] (Table 4).

Antifungal drug monitoring in haematology

TDM of azole drugs and flucytosine can be used to evaluate the adequacy of drug exposure and potential for drug toxicity (see Table 5). While correlation between drug concentrations and clinical outcomes (efficacy/toxicity) has not been well established by randomised trials, monitoring is beneficial in the presence of clinical dilemmas or uncertainty. For example, monitoring may be helpful if poor absorption of an oral antifungal agent is suspected, in the presence of non-compliance, if breakthrough invasive fungal infection (IFD) is thought to be present or if toxicity is suspected. If TDM reveals consistently low azole blood levels despite an optimal dosing regimen, adequate absorption and absence of significant drug–drug interactions, investigation for CYP450 polymorphism should be considered (please refer to later discussion on pharmacogenomics for further information).

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

Drug	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Aprepitant or fosaprepitant	Not documented.	Potential for increased plasma concentration of aprepitant (aprepitant AUC and mean terminal $T_{1/2}$ increased approximately fivefold and threefold respectively when co-administered with ketoconazole).‡ Caution with this combination.[31]	Not documented, but co-administration of aprepitant with strong CYP3A4 inhibitors should be approached with caution.[31]	Not documented.
Atorvastatin	May increase atorvastatin levels. A reported case of rhabdomyolysis with this combination.[32] Monitor for toxicity or change to pravastatin.[33]	$T_{1/2}$, C_{max} and AUC of atorvastatin increased, respectively, by 60%, 2.4-fold and 47% when co-administered with itraconazole.[34] Possible increased risk for rhabdomyolysis.[35] Change to pravastatin,[36] fluvastatin or rosuvastatin.[21]	Not documented. Likely to increase atorvastatin levels. Consider dose reduction. Monitor for toxicity (e.g. rhabdomyolysis).[37]	Not documented. Likely interaction with statin class of drugs. Use with caution.[38]
Bortezomib	Not documented.	Ketoconazole‡ increased bortezomib AUC by 35%.[39] Interaction likely. Case reports of new or worsening peripheral neuropathy when co-administered with itraconazole. Use with caution.[40]	Interaction likely. New onset of peripheral neuropathy reported when co-administered with voriconazole. Use with caution.[41]	Not documented.
Busulphan	Busulphan clearance unaffected.[42]	Busulphan clearance decreased by 25% and increased AUC in HSCT patients. Monitor busulphan levels.[42]	Not documented. Busulphan levels are likely to be elevated.[42]	Not documented. Busulphan levels are likely to be elevated.[42]
Cimetidine	Fluconazole AUC reduced by 13% in healthy volunteers. Not clinically significant.[43]	Cimetidine $AUC_{0\text{-}240\ min}$ increased by 25% following itraconazole administration; significant reduction in cimetidine clearance in healthy volunteers has been reported.[44]	C_{max} and AUC of voriconazole increased by 18.3 and 22.5%, respectively, in healthy volunteers. Not clinically significant.[45]	In healthy volunteers, combination resulted in decreased C_{max} and AUC of posaconazole by 40%.[46] No recommendations for dose modification available; avoid combination.
Cyclophosphamide	Decreased IV cyclophosphamide clearance by 43% and increased $T_{1/2}$ by threefold in children with cancers when co-administered with IV/PO fluconazole.[47] Unknown clinical significance.[48]	Higher exposure to toxic metabolites of cyclophosphamide, and higher bilirubin and creatinine levels within the first 20 days after HSCT, were reported in HSCT patients receiving itraconazole compared with fluconazole for prophylaxis. Caution with co-administration.[49]	Not documented. Interaction likely, significance unknown.[48]	Not documented. Interaction likely, significance unknown.[48]
Cyclosporin (CSA)	Fluconazole 100 mg PO has minimal effect in HSCT patients;[50] higher dosing increases CSA AUC by 50%. Monitor and consider CSA dose reduction.[21] Co-administration of IV 400 mg fluconazole and IV CSA in HSCT patients increased CSA levels and decreased clearance by 21%, considered not clinically significant.[51]	CSA trough levels increased 50–80%.[21] Monitor and reduce CSA dose by 50%.[52] Effect persists for some time after cessation of itraconazole.[21]	Increased the median CSA concentration-to-dose ratio by about 80% in HSCT patients. Wide individual variability (ranging from −9.4 to 266.9%) in the magnitude of this drug interaction. Route of voriconazole administration had no effect on results.[53,54] Monitor CSA levels and consider 50% dose reduction of CSA.[55]	Co-administration increased CSA levels requiring 14–29% dose reductions in three heart transplant patients.[56] Monitor, may need to adjust CSA dose.
Dasatinib	Not documented. May increase risk of QT interval prolongation.[57]	Not documented. Interaction likely. Ketoconazole‡ increased dasatinib C_{max} and AUC by about fourfold and fivefold in cancer patients.[58] Monitor for toxicity.[59]	Not documented. Interaction likely. Drugs inhibiting CYP3A4 activity may increase exposure to dasatinib.[59] May also increase risk of QT interval prolongation.[60]	Not documented. May increase risk of QT interval prolongation.[61]
Dexamethasone (DXM)	Not documented. May increase DXM levels; monitor.[62]	IV/PO DXM AUC increased threefold to fourfold in healthy volunteers. Increased risk of corticosteroid side effects. Monitor, reduce dose or use prednisolone.[21,63]	Not documented. May increase DXM levels; monitor.[62]	Not documented.
Diazepam	Increased AUC of PO diazepam by 2.5-fold and prolonged $T_{1/2}$ from 31 to 73 h in healthy volunteers. No effect on C_{max}. Consider dose reduction if diazepam is given repeatedly.[37]	Diazepam AUC and $T_{1/2}$ increased 35%, but sedation not altered; use with caution.[21]	Increased AUC of PO diazepam by 2.2-fold and prolonged $T_{1/2}$ from 31 to 61 h in healthy volunteers. No effect on C_{max}. Consider dose reduction if diazepam is given repeatedly.[37]	Not documented.
Ifosfamide	Not documented. Reduced ifosphamide clearance possible.[48]	Not documented. Interaction likely (ketoconazole decreased clearance of ifosfamide by 11%, increased AUC by 14%, increased urinary elimination by 26% and slightly decreased the fraction metabolised to the active metabolite, 4-hydroxyifosfamide[64]);‡ monitor for efficacy.[62]	Not documented. Interaction possible (ketoconazole decreased clearance of ifosfamide by 11%, increased AUC by 14%, increased urinary elimination by 26% and slightly decreased the fraction metabolised to the active metabolite, 4-hydroxyifosfamide[64]);‡ monitor for efficacy.[62]	Not documented.
Imatinib	Not documented.	Not documented. Potential for increased exposure to imatinib (ketoconazole increased C_{max} and AUC of imatinib by 26 and 40%, respectively in healthy volunteers).‡ Caution with this combination.[65]	Interaction possible.[66] Drugs inhibiting CYP3A4 activity may decrease metabolism and increase imatinib concentration.[65]	Not documented.
Lorazepam	Not documented.	Not documented.	Not documented.	Concomitant administration may reduce posaconazole serum concentrations.[67]

Table 2 Continued

Drug	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Methyl-prednisolone	Not documented. May increase methylprednisolone levels; monitor.[62]	IV/PO methylprednisolone C_{max}, AUC and $T_{1/2}$ increased by approximately twofold to threefold in healthy volunteers,[68–70] with increased risk of corticosteroid side effects. Dose-reduce or use prednisolone.[21,68,71]	Not documented. May increase methylprednisolone levels; monitor.[62]	Not documented.
Metoclopramide	Not documented.	Not documented.	Not documented.	Suspension: In healthy volunteers, metoclopramide decreased the mean C_{max} and AUC of a single dose of 400-mg posaconazole by 21 and 19%, respectively.[72] In patients receiving posaconazole prophylaxis, metoclopramide significantly reduced posaconazole serum concentration.[73] Monitor closely for breakthrough fungal infections if administered concomitantly.[74] Tablet: In healthy volunteers administered metoclopramide, C_{max}, AUC, $T_{1/2}$ unaffected for a single dose of 400-mg posaconazole.[75]
Midazolam	Midazolam peak, AUC and $T_{1/2}$ increased by about twofold in healthy volunteers. Sedation and amnesia may be prolonged. Use with caution.[21]	Midazolam peak, AUC and $T_{1/2}$ increased twofold for up to 4 days after ceasing itraconazole. Sedation and amnesia prolonged. Reduce dose or consider lorazepam, oxazepam or temazepam.[21]	C_{max} and AUC of PO midazolam increased by 3.8- and 10.3-fold, respectively. Psychomotor effects of PO midazolam profoundly increased. Avoid combination. Clearance of IV midazolam reduced by 72% and $T_{1/2}$ increased from 2.8 to 8.3 h in healthy volunteers. Use with caution.[76]	Midazolam AUC increased by threefold to sixfold in healthy volunteers. Use with caution.[77]
Nifedipine	Increased nifedipine C_{max} and AUC by about threefold. Monitor for hypotension.[78]	Increased nifedipine trough levels by 4.5-fold.[79] Monitor for hypotension.[21]	Not documented. Likely increase nifedipine levels. Monitor for hypotension.[21]	Not documented.
Nilotinib	Not documented. May increase risk of QT interval prolongation.[57]	Likely increase nilotinib exposure (ketoconazole‡ increased C_{max} and AUC of nilotinib by 1.8- and 3-fold in healthy volunteers);[80] avoid concurrent use. Monitor for toxicity.[81]	Not documented. Potential risk of additive QT interval prolongation.[60] May increase nilotinib serum concentration; avoid concurrent use. Monitor for toxicity.[81]	Not documented. May increase risk of QT interval prolongation.[61]
Omeprazole or esomeprazole	C_{max} and AUC of PO omeprazole increased by 2.4-fold and 6.3-fold, respectively, in healthy subjects. Monitor for toxicity.[82] Fluconazole pharmacokinetics not affected by omeprazole in healthy volunteers.[83]	Omeprazole reduced AUC and C_{max} of itraconazole (Sporanox (Janssen-Cilag Pty Ltd, Sydney, NSW, Australia) capsules by 64 and 66%, respectively, in healthy volunteers, due to reduced gastric acidity.[21,84] Administer with cola beverage.[52] Omeprazole did not significantly affect AUC, C_{max} and T_{max} of single dose of 400 mg itraconazole solution in healthy volunteers.[85]	Voriconazole increased omeprazole C_{max} and AUC by 116 and 280%; 50% reduction of omeprazole dose recommended.[86] Omeprazole increased PO voriconazole C_{max} and AUC by 15 and 41% in healthy volunteers. No dose adjustment of voriconazole required.[87] Esomeprazole exposure may be increased by more than double by voriconazole. Dose adjustment of esomeprazole with normal dosage is not required according to Australian product information.[88]	*Suspension:* significant reduction in posaconazole serum trough concentration reported with concomitant omeprazole.[89] Co-administration with esomeprazole decreased mean posaconazole C_{max} and AUC by 46% and 32%, respectively, in healthy volunteers.[72] Analysis of patient-level data indicates decreased posaconazole exposure.[73] Avoid concurrent use.[90] *Tablet:* C_{max}, AUC, T_{max} and $T_{1/2}$ of single 400-mg dose of posaconazole unaffected by esomeprazole in healthy volunteers.[75]
Pantoprazole	Not documented.	Not documented. Oral absorption of itraconazole (Sporanox) capsules decreased by 30–60% when co-administered with omeprazole or H_2-receptor antagonists, due to reduced gastric acidity.[21] Administer with cola beverage.[52]	Not documented.	Suspension: population pharmacokinetic model suggest pantoprazole and other PPI reduces posaconazole exposure.[91] Analysis of patient-level data suggests decrease in posaconazole exposure.[73] Avoid concurrent use.[90] *Tablet:* not documented.
Phenytoin	Oral fluconazole increased phenytoin AUC and trough levels by 75 and 128%, respectively, in healthy volunteers. Fluconazole trough levels not affected by phenytoin. Monitor phenytoin levels and consider dose reduction.[19,92]	Phenytoin reduced itraconazole AUC by more than 90% and $T_{1/2}$ from 22.3 to 3.8 h. Itraconazole increased phenytoin AUC by 10.3%. Avoid concomitant use.[93]	Phenytoin reduced voriconazole C_{max} and AUC in healthy volunteers by 49% and 69%, respectively. Voriconazole increased phenytoin C_{max} and AUC by 67 and 81%, respectively. Monitor levels closely and adjust dose accordingly.[6] Avoid concomitant use if possible.[86]	Reduced posaconazole C_{max} and AUC by 44 and 52%, respectively, in healthy volunteers. Phenytoin C_{max} and AUC increased by 24 and 25%, respectively, but not statistically significant. Avoid concomitant use.[90,94]
Prednisolone	Not documented. May increase prednisolone levels; monitor.[62]	Increased prednisolone AUC and $T_{1/2}$ by 13–30% in healthy volunteers, but clinical impact not likely to be significant.[68,95]	Increased C_{max} and AUC of prednisolone by 11 and 34% in healthy volunteers. No dose adjustment; monitor.[86]	Not documented.
Ranitidine	Not documented.	Oral ranitidine decreased AUC of itraconazole (Sporanox) capsule by 44% and C_{max} 52% in healthy volunteers. Administer with cola beverage.[96] Itraconazole solution unaffected.[21]	Oral ranitidine has no impact on voriconazole plasma concentration.[45]	Suspension: Regression analysis of patient-level data suggests decrease in posaconazole exposure.[73] Avoid concomitant use.[90] Tablet: C_{max}, AUC, T_{max} and $T_{1/2}$ of single 400-mg dose of posaconazole unaffected by ranitidine in healthy volunteers.[75]

Simvastatin	May increase simvastatin levels. Cases of rhabdomyolysis have been reported.[97] Monitor or change to pravastatin.[33]	Simvastatin C_{max} and AUC increased by more than 10-fold, with increased risk of rhabdomyolysis; withhold statin or change to fluvastatin, pravastatin or rosuvastatin.[21]	A fatal case of rhabdomyolysis reported.[98] Likely to increase simvastatin levels. Consider dose reduction and monitor for toxicity (e.g. rhabdomyolysis)[86] or change to pravastatin.[21]	Posaconazole significantly increased simvastatin C_{max} (7- to 11-fold) and AUC in healthy volunteers (5- to 11-fold). Avoid concomitant use.[77]
Sirolimus	Large increase in sirolimus levels after initiation of 200-mg PO fluconazole in a renal transplant patient, where levels increased from 10 to 19 μg/L after 3 days and peak at 35 μg/L on day 7 despite dose reduction. Consider 50–75% sirolimus dose reduction and monitor levels.[99]	In a HSCT patient who was on long-term itraconazole solution, sirolimus trough level was 17.5 on day 5 after starting sirolimus and increased to 35.6 μg/L on day 7, despite reducing sirolimus dose.[100] Use with extreme caution.	Increased sirolimus C_{max} and AUC by 556 and 1014%.[86] Empirical dose reduction by 75–90%, with close monitoring of sirolimus trough levels recommended.[101,102]	Increase sirolimus C_{max} and AUC by 6.7- and 8.9-fold, respectively, in healthy volunteers.[103] Empiric 33% to 50% sirolimus dose reduction and close monitoring sirolimus trough levels recommended.[104]
Sorafenib	Not documented. May increase risk of QT interval prolongation.[57]	Not documented. Ketoconazole‡ had no effect on AUC, C_{max} and $T_{1/2}$ of a 50 mg dose of sorafenib administered to healthy volunteers despite significant reduction in sorafenib N-oxide formation.[105]	Potentially inhibits N-oxide formation *in vitro* and reduced sorafenib N-oxide formation in children.[106] May increase risk of QT interval prolongation.[60]	Potentially inhibit N-oxide formation *in vitro* and reduced sorafenib N-oxide formation in children.[106] May increase risk of QT interval prolongation.[61]
Tacrolimus	Fluconazole 100-mg PO and 200-mg PO increased PO tacrolimus trough levels in transplant patients by 1.4- and 3.1-fold, respectively. Consider 50% dose reduction of PO tacrolimus and monitor.[107] Fluconazole 400-mg IV co-administered with IV tacrolimus in HSCT patients increased tacrolimus levels and decreased clearance by 16%, no dose adjustment recommended.[51]	Tacrolimus trough level increased by fivefold (both drugs PO).[21] Tacrolimus trough increased by 83% when both drugs administered intravenously.[108] Consider decreasing tacrolimus dose by 50–60% and monitor levels.[55]	In HSCT patients administered PO tacrolimus, PO voriconazole increased the median tacrolimus concentration-to-dose ratio by 138.8% (range −32.0 to 685.7%), with wide individual variability.[109] Case reports of significant increase in PO tacrolimus trough levels by ~60% when IV voriconazole switched to PO,[110] and fourfold increase when both drugs were changed from IV to PO.[111] Monitor levels and consider 66% dose reduction of tacrolimus.[55]	Increased PO tacrolimus C_{max} by 121% and AUC by 358% in healthy volunteers.[56] Consider 75–80% dose reduction and monitor levels.[55]
Vinblastine	Not documented. May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity.[3]	A case reported of severe neurotoxicity and myelosuppression following co-administration of itraconazole, vinblastine, doxorubicin and methotrexate.[112] May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered.[52]	Not documented. May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered.[86]	Not documented. May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered.[90]
Vincristine	Cases of neurotoxicity have been reported.[113] May increase plasma levels of vinca alkaloids. Dose adjustment of the vinca alkaloid should be considered.[3] Use of non-azole antifungal agent recommended.[113]	Cases of neurotoxicity have been reported with median time to adverse events being 9.5 days (range 2–28 days).[113] May increase plasma concentrations of the vinca alkaloids. Dose adjustment of the vinca alkaloid should be considered.[52,114] Use of non-azole antifungal agent recommended.[113]	Cases of neurotoxicity have been reported with median time to adverse events being 30 days.[113] May increase plasma concentrations of the vinca alkaloids. Dose adjustment of the vinca alkaloid should be considered.[62,86] Use of non-azole antifungal agent recommended.[113]	Cases of neurotoxicity has been reported with median time to adverse events being 13.5 days (range 12–15 days).[113] May increase plasma concentrations of the vinca alkaloid. Dose adjustment of the vinca alkaloid should be considered.[90,115] Use of non-azole antifungal agent recommended.[113]
Vinorelbine	Not documented. May increase the plasma levels of the vinca alkaloids and lead to neurotoxicity.[3]	Not documented. May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered.[52]	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered.[62,86]	May increase plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Dose adjustment of the vinca alkaloid should be considered.[90]
Warfarin	Increase in INR by 38%;[21] dose-reduce warfarin and monitor INR.[3]	Increased concentration of (*S*)-warfarin (by 7.3-fold) but not (*R*)-warfarin has been reported in one patient.[116] INR may be increased; dose-reduce warfarin and monitor INR.[21]	Prothrombin time approximately doubled; dose-reduce warfarin and monitor INR.[117]	Not documented.

†Interactions studied for PO administration may not predict the degree of interaction for IV administration. ‡Ketoconazole is the strongest CYP3A4 inhibitor within the azole class. Although ketoconazole drug interactions may not predict drug interactions for other azole agents, data have been included as an alert to potential interaction/s where specific drug interaction data are lacking. AUC, area under the curve; C_{max}, peak concentration; CYP, cytochrome; DXM, dexamethasone; HSCT, haemopoietic stem cell transplant; INR, international normalised ratio; IV, intravenous; PO, oral; PPI, proton pump inhibitor; $T_{1/2}$, 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.[120]	Nil reported.	Administer with or without food.[3]
Itraconazole	Absorption of itraconazole (Sporanox) capsules is enhanced when taken with or after food,[120] whereas absorption of the oral solution is enhanced when taken taken on an empty stomach.[121] If hypochlorhydric or concurrently taking gastric suppressants, co-administration of an acidic solution enhances the bioavailability of Sporanox capsules.[96] The dissolution of itraconazole from Lozanoc (Mayne Pharma International, Adelaide, SA, Australia) capsules is unaffected by increased pH. Bioavailability is unlikely to be reduced by achlorhydria or concomitant use of gastric acid suppressants.[122]	Grapefruit juice increased AUC of itraconazole oral solution by 17%, through inhibition of intestinal CYP3A4[123] but reduced AUC of itraconazole capsules by 43%, probably by impairing absorption in healthy volunteers.[124] Clinical significance of this is not known.[125]	Itraconazole (Sporanox) capsules: administer with or after food. Co-administer an acidic beverage (e.g. cola) to improve bioavailability in patients who are hypochlorhydric or who are taking gastric acid suppressants. Itraconazole (Lozanoc) capsules: may be taken with or without food.[122] Itraconazole solution: administer on an empty stomach at least one hour before food.
Voriconazole	In healthy subjects, oral absorption is delayed in the non-fasted state (AUC reduced by 22%).[126]	Nil reported.	Administer 1 h before or 1 h after food.[86]
Posaconazole	In healthy subjects, oral absorption of posaconazole suspension is increased when given with acidic carbonic beverage,[72] nutritional supplement[72,127] or high-fat meal.[72,128] For tablet and capsule preparations, posaconazole exposure not markedly affected by concomitant food intake.[129]	Nil reported.	Administer oral suspension with high-fat meal or nutritional supplement.[90] US prescribing information recommends administering delayed-release tablet with food.[74]

AUC, area under the curve; CYP, cytochrome.

There are currently several methods that can be employed to determine drug concentrations. These include bioassays, high-performance liquid chromatography and liquid chromatography in conjunction with mass spectrometry. There are advantages and disadvantages to each of these assays. Due to inter-method variability, results are not comparable between assays. Absence of laboratory standards prevents comparison between laboratories.

Timing of sample collection is critical in terms of interpretation and subsequent dose modification. These considerations together with indications for TDM are provided in Table 5. Result turnaround time may limit the use of antifungal TDM. Due to costs and expertise required to perform assays, few laboratories can offer this service on-site. Turnaround times for results of assays performed off-site can be 3–7 days. Access to a local reference laboratory is limited in most Australian states (see Australian Society for Antimicrobials's website: http://www.asainc.net.au/assays), and this has also been demonstrated in a recent review of Australian practice (see accompanying paper by van Hal *et al*., 2014 appearing elsewhere in this supplement).

The clinical value of site-specific drug concentrations (e.g. pulmonary epithelial lining fluid), free or total drug levels, and intracellular compared with extracellular levels is not clear. Currently, there are no data to support additional benefit of these levels and, as such, total serum trough concentrations remain the test of choice.

TDM in paediatric populations

In the child population, as in the adult, the voriconazole dose exposure relationship is not well defined, and there is significant inter-patient variability. Children have higher elimination rates of voriconazole than adults, demonstrated by linear kinetics for lower doses in paediatrics.[234] Drug elimination also correlates with CYP2C19 phenotype in children.

Posaconazole pharmacokinetics have not been studied in children <8 years of age. Older children have comparable pharmacokinetics to adults.[235] The main factor that influences serum posaconazole concentrations is absorption from the gastrointestinal tract. This is inhibited by diarrhoea and suppression of gastric acid production. Administration performed more frequently (6–8 hourly), and with fatty food, will improve absorption, as will the use of the delayed-release tablet formulation. No adverse events related to elevated posaconazole plasma levels have been described.

Recommendations for TDM during voriconazole use

Monitoring of voriconazole drug levels has been reported in several studies, reporting use of this agent for prophylaxis or treatment, and these are summarised in Appendix I.

Only one randomised (assessor-blinded) single-centre trial has been performed.[236] In this trial, no difference in voriconazole adverse events (the primary endpoint) between patients randomised to TDM compared with

Table 4 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%[146,147] • 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[148–150] • Similar rates of nephrotoxicity are observed for AmB-D through continuous infusion and L-AMB although no adequately powered direct comparison has been performed[151] • 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[152,153]
	IRAE	• IRAE occur frequently with AmB-D: fever 34–51%; chills or rigors 28–74%; nausea 18–19%.[147,153–155] More severe IRAE occur less frequently: bronchospasm 7%; hypotension 1–11%[147,153,156,157] • Premedication is frequently used to help reduce the incidence of IRAE, although data supporting this practice are limited[154,155] • AmB-D through continuous infusion causes significantly less IRAE compared with standard therapy[151] • L-AMB is responsible for less IRAE compared with other lipid preparations: fever 11%; chills or rigors 37%; nausea 12%[147,153,158,159] • Rates of IRAE with ABLC are similar to AmB-D whereas ABCD is associated with higher rates of IRAE[147,158,160–162] • Tolerance to IRAE generally develops within the first seven days of initiating therapy[154,155]
	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[153,159] • Electrolyte disturbances are observed less frequently with L-AMB and ABLC compared with AmB-D; monitor electrolyte levels closely and replace if necessary[153,159,160] • Consider using amiloride (10 mg daily) to decrease urinary potassium loss, increase serum potassium and reduce potassium replacement requirements[163]
	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[147]
	Other	• Rash is reported in 1–5% of patients receiving amphotericin products[156,164–166] • A reversible normochromic, normocytic anaemia (mediated by a suppression of erythropoietin production) may occur with prolonged use[167,168]
Fluconazole	Gastrointestinal toxicity	• Gastrointestinal symptoms (nausea, vomiting and diarrhoea) occur in a minority of patients; 0–9%[156,169–173]
	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[147,156,169,172–176] • Discontinuation due to hepatotoxicity is rare (0–5%)[147,156,169,172–175]
	Dermatological toxicity	• Rash is reported in 4–6% of patients[156,170]
	Other	• Nephrotoxicity occurs in 1–3% of patients receiving fluconazole (significantly less than AmB-D)[156,171,174] • IRAE are rarely reported with fluconazole: fever and/or chills 0–1% (significantly less than AmB-D)[156,176] • QT prolongation has been reported[23]
Itraconazole	Gastrointestinal toxicity	• Gastrointestinal symptoms are reported in 13–24% of subjects receiving itraconazole[147,157,170,171,177,178] • Compared with fluconazole and posaconazole, itraconazole causes significantly more gastrointestinal toxicity[170,171,179] • 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 required[180]
	Hepatotoxicity	• Rates of hepatotoxicity vary depending on the patient population and definition used (7–32%); this is not significantly different to fluconazole and posaconazole[157,170,171,177,179,181]
	Dermatological toxicity	• Rash is reported in 4–7% of patients[170,177]
	Other	• Nephrotoxicity occurs in 5–7% of patients receiving itraconazole[157,182] • IV itraconazole is available under the special access scheme in Australia and New Zealand. It is solubilised by hydroxypropyl-b-cyclodextrin (HPbCD), which is exclusively renally excreted; avoid using IV itraconazole in patients with a creatinine clearance less than 30 mL/min[8]
Voriconazole	Ocular toxicity	• Dose-related visual disturbances, including blurred vision, photophobia, and altered visual and colour perception, occur in 22–45% of patients.[165,183,184] 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 (alanine and aspartate aminotransferases (ALT/AST) >5 times baseline) is observed in 4–9% of patients.[165,183,184] Hyperbilirubinaemia (>3 times baseline level) occurs in up to 18% of patients.[183] 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.[185,186] The rate of hepatotoxicity was not significantly different to AmB-D, L-AMB and fluconazole in comparative trials[165,183,187]
	Dermatologic toxicity	• Rash, pruritus or photosensitivity occurs in 7–9% of patients.[165,184,188] 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 and melanoma after long-term exposure to voriconazole[189–192]
	Skeletal toxicity	• Periostitis, exostosis and elevated serum fluoride levels have been reported in association with long-term voriconazole use in patients with haematologic malignancy or following solid organ transplantation.[193–198] Discontinuation of voriconazole therapy in results in improvement of pain and normalisation of alkaline phosphatase and fluoride levels[199]
	Other	• Nephrotoxicity occurs in 1–7% of patients receiving voriconazole (significantly less than AmB-D)[165,183,187] • IRAE occur less frequently compared with amphotericin B preparations: fever and/or chills 3–14%[165,183] • IV voriconazole is solubilised by sulfobutylether-b-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.[35,36] There is evidence that SBECD is dialysable. However, accumulation with repeat dosing has been demonstrated, although the clinical significance is not clear.[200,201] Oral voriconazole may be safely administered to patients undergoing dialysis • Neurological (agitation, dizziness, confusion, anxiety and tremor) have been reported in 14% of patients. Auditory and visual hallucinations have also been reported.[202] Neurological toxicity is associated with voriconazole levels >5.5 mg/L[203] • 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)[204,205]

Table 4 Continued

Antifungal agent	Commonly reported side-effects	Evidence and suggestions for risk reduction
Posaconazole	Gastrointestinal toxicity	• 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%.[169,206–209] These rates are not significantly different to those observed with fluconazole[169]
	Hepatotoxicity	• Hepatotoxicity is infrequently reported with posaconazole (1–3%); this is not significantly different to rates reported with fluconazole or itraconazole[169,179,206,208,209]
	Other	• Rash and headache are reported in 2–4% and 1–5% of subjects, respectively[169,206–209] • Neutropenia is reported in 7% of patients; this is not significantly different to rates reported with fluconazole or itraconazole[179]
Caspofungin	Gastrointestinal toxicity	• Gastrointestinal toxicity is infrequently seen with caspofungin: nausea 2–6%; vomiting 2–3.5%; diarrhoea 1–4%[164,166,181,210]
	Hepatotoxicity	• Hepatotoxicity (elevated ALT, AST or bilirubin) occur in 1–15% of patients[166,183,211,212] • Early data demonstrated 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 risk[52] • However, several observational studies in children and adult subjects have demonstrated the safety of this combination[171,213–215]
	Other	• Nephrotoxicity occurs in 0–8% of patients (significantly less than AmB-D)[164,166,211] • Hypokalaemia occurs in 11% of patients after the 70-mg dose and <4% of patients after the 50-mg dose[216] • IRAE occur less frequently than they do with the amphotericin B preparations: chills 0–14%.[164,166,211] IRAE can be prevented by slowing the infusion and giving antihistamines[217] • 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, facial swelling, sensation of warmth and/or bronchospasm[218] • Unexplained cardiovascular decompensation (postulated to be due to histamine release) has been observed during central venous administration of caspofungin and anidulafungin.[219–221] *In vitro* studies have shown decreases in left ventricular contractility with concentrations of caspofungin and anidulafungin achievable with therapeutic dosing.[222] Hypokalaemia occurs in 2% of patients[212] • Rash is infrequently observed with caspofungin: 1–6%[164,210]
Anidulafungin	IRAE	• IRAE occur in 1.3% of candida treated patients (0.8% of which were hypotension) and 18% of aspergillus-treated patients[223]
	Hepatotoxicity	• Hepatotoxicity (elevated enzymes) occurs in 1.5% of patients[224]
	Other	• Diarrhoea and hypokalaemia occurs in 3% of patients[224] • Headache and thrombophlebitis occurs in 1.3% of patients[225] • Neutropenia and nausea occurs in 1% of patients[225] • Slowing the infusion prevents histamine-release like reactions.[226] Histamine-release like reactions rarely seen if rate of 1.1 mg/min not exceeded[101] • Facial erythema, which resolved with slowing the infusion rate, was observed in a paediatric patient[227] • Unexplained cardiovascular decompensation (postulated to be due to histamine release) has been observed during central venous administration of caspofungin and anidulafungin.[219–221] *In vitro* studies have shown decreases in left ventricular contractility with concentrations of caspofungin and anidulafungin achievable with therapeutic dosing[222]
Flucytosine	Gastrointestinal toxicity	• Gastrointestinal toxicity occurs in approximately 6% of patients treated with flucytosine (5-FC)[228]
	Hepatotoxicity	• The incidence of hepatotoxicity can vary markedly (from 0–40%) depending on the definition used.[228–230] Hepatotoxicity appears to be dose-dependent, occurring more frequently when peak flucytosine concentrations are above 100 mg/mL
	Bone marrow suppression	• Leukopenia, thrombocytopenia or pancytopenia have all been reported with flucytosine therapy. The incidence is dose-dependent (observed when levels are >100 mg/L) and influenced by comorbidities, pre-existing bone marrow suppression and disease[228]

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

standard therapy was observed. However, patients undergoing TDM were significantly less likely to have voriconazole discontinued because of adverse events ($P = 0.02$). Furthermore, complete and partial responses were significantly more likely in monitored patients ($P = 0.04$) and may reflect drug continuation in this group.

Based on available evidence, the following recommendations can be made concerning voriconazole TDM:

1 In haematology patients requiring voriconazole prophylaxis (e.g. allogeneic transplantation, acute myeloid leukaemia), TDM is recommended (B) and should be considered in other patients with haematological malignancy who require prophylaxis (D).

2 In haematology patients requiring voriconazole treatment for invasive aspergillosis, TDM (trough levels) is recommended (B) and may be of benefit in treatment of other fungal infections (D).

3 A target trough level ≥1–2 mg/L is recommended for clinical efficacy (C).

4 A trough level >5–6 mg/L is associated with an increased probability of neurological toxicity, including visual disturbances, hallucinations and encephalopathy (C). An inconsistent association between higher trough levels and raised liver function tests has been reported (D).

5 Dose modification should be re-evaluated with TDM as voriconazole displays non-linear pharmacokinetics (B).

Voriconazole TDM is recommended in paediatric patients because of less predictable pharmacokinetics in children. The targets provided above, while largely based upon adult studies, should be applied to paediatric populations.

Table 5 Recommendations for antifungal drug monitoring

Antifungal agent	Pharmacokinetic considerations	TDM	Indication/s for TDM	Timing of first sample	Timing of sample in relation to dose	Target range (mg/L)
Amphotericin B and lipid-based preparations		No	–	–	–	–
Echinocandin class		No	–	–	–	–
Flucytosine		Routine	To monitor for toxicity	3–5 days	2-H post-oral dose or 30-min post-IV dose	<100 Toxicity 30–80 (Cryptococcosis)
Fluconazole		No†	–	–	–	–
Itraconazole	Non-linear pharmacokinetics with slow accumulation of drug with no effective half-life	Targeted	To ensure adequate absorption, therapeutic concentration	7–15 days	Trough level	Prophylaxis: >0.5 Treatment: >0.5–1 (depending on MIC of fungal isolate)
Voriconazole	Non-linear pharmacokinetics, progressive accumulation in some patients due to saturable clearance Dose modification, IV to PO switches or significant clinical changes may result in unpredictable concentrations Consider taking additional samples until stable concentrations are achieved	Targeted	To detect therapeutic and toxic concentrations	2–5 Days (repeat sample should also be collected to ensure stability)	Trough level	Prophylaxis: 1–6 Treatment: 1–6 (*Aspergillus* spp.)
Posaconazole	Slow accumulation of drug over the first 7 days and then plateau Saturable oral absorption with dose escalation above 800 mg/day resulting in slight to no increases in drug concentrations	Targeted	To ensure adequate absorption, therapeutic concentration	After 5–7 days	Trough level‡	Prophylaxis: > 0.7 Treatment: >1

†May be utilised in certain rare clinical circumstances (e.g. treatment of an organism with high MIC, CNS infections), with collection of several samples throughout dosing interval to estimate AUC. A target AUC : MIC ratio of >100 has been proposed.[231] ‡Untimed levels may also be used, given consistent plasma concentrations over time. Early monitoring (e.g. day 2) may be predictive of steady-state levels and allow for timely dosing modification.[232,233] AUC, area under the curve; CNS, central nervous system; IV, intravenous; MIC, minimum inhibitory concentration; PO, oral.

Recommendations for TDM during posaconazole use

Monitoring of posaconazole drug levels has been reported in several studies with use of this agent for treatment or prophylaxis, and these are summarised in Appendix II.

Evidence for posaconazole TDM in treatment of IFD is limited to one study by Walsh *et al*., 2007,[206] which reported improved clinical outcomes with progressively higher average posaconazole plasma concentrations in the setting of salvage therapy for invasive aspergillosis. A clinical response rate of 74% was achieved in patients with an average concentration of 1.25 mg/L, whereas response dropped to 24% in patients with an average concentration of 0.13 mg/L. It is reasonable to aim for a steady-state plasma concentration of at least 1 mg/L, acknowledging that it may not be possible to achieve this target with dose optimisation or escalation due to saturable absorption. It is unclear if these targets are necessary or optimal when posaconazole is used in primary treatment for non-*Aspergillus* infections. Ideally, the minimum inhibitory concentration of the organism should be considered when interpreting plasma concentrations.

The evidence for a target plasma concentration in the setting of prophylaxis is relatively weak. A target concentration greater than 0.7 mg/L has been proposed,[237–240] and this has been derived from post-hoc analysis of phase 3 clinical trials evaluating the safety and efficacy of posaconazole prophylaxis in haematology patients[179] by Jang *et al*., 2010.[237] The analysis identified higher clinical failure rates in patients achieving concentrations less than 0.7 mg/L in both study data sets. Criticisms of this study include the use of a composite endpoint and overall low numbers of breakthrough IFDs.[241,242]

Several real-world observational studies have attempted to further evaluate this relationship, with mixed results (Appendix II). These studies identified difficulties in achieving target plasma concentrations such as 0.7 mg/L in haematology patient groups, with 10–76% of patients not achieving the desired targets. The largest of these was a retrospective, multi-centred cohort of mainly haematology patients, where the relationship between plasma concentration and clinical outcome and toxicity was assessed.[238] Twelve of 72 patients receiving prophylaxis were identified as having breakthrough IFD during posaconazole prophylaxis. In this group, significant lower median plasma concentrations of posaconazole were observed (0.29 mg/L), compared with patients without IFD (0.49 mg/L). The inclusion of three cases not fitting the criteria for proven, probable or possible IFD according to internationally recognised diagnostic classifications casts doubt over the strength of these findings. These observational studies demonstrate a trend of increasing efficacy with greater drug exposure.

Based on available evidence, the following recommendations can be made concerning posaconazole TDM:

1 In haematology patients requiring posaconazole prophylaxis, TDM should be considered, especially in the setting of possible malabsorption (D).

2 In haematology patients requiring posaconazole treatment, TDM (trough levels) is recommended (D).

3 A target trough level of ≥1 mg/L is reasonable for treatment settings. A target trough level of ≥0.7 mg/L is reasonable for prophylaxis, but is less studied (C).

4 Dose modification should be re-evaluated with TDM, as saturable absorption affects pharmacokinetics (D).

Posaconazole TDM is recommended in paediatric patients because of variable gastrointestinal absorption in children. The targets provided above, while largely based upon adult studies, should be applied to paediatric populations.

Impact of pharmacogenomics on antifungal metabolism

Polymorphisms are common in genes-encoding pathway components of antifungal drug metabolism, especially the CYP450. Individual variations in antifungal metabolism have the potential to alter therapeutic-drug levels and patient outcomes.[203,236,243,244]

Pharmacogenomics and voriconazole metabolism

Voriconazole is primarily metabolised through the CYP450 system, in particular by CYP2C19.[245–248] Despite several factors affecting voriconazole exposure (presence of food, protein binding, liver function, age, concurrent drug use, non-linear pharmacokinetics and inter-patient variability), 40–49% of variations of plasma levels are accounted for by variations CYP450 metabolism in mixed patient populations.[29,249]

Polymorphisms in the CYP2C19-encoding gene result in different rates of non-linear voriconazole clearance (Table 6). In healthy-volunteer studies, the impact of CYP2C19 on voriconazole exposure is evident.[284] Poor metabolisers (PM) have three to fivefold times higher voriconazole area under the curve or C_{max} levels than extensive metabolisers (EM), irrespective of administration.[248,285,286] Ultra-rapid metabolisers (URM) have lower voriconazole exposure than EM and PM.[254,261,287] In some populations, 17/17 genotypes are associated with lower peak and total voriconazole exposure than 1/1 genotypes.[29,262] A simplified classification including EM or PM

Table 6 Reported incidence of CYP2C19 genotypes by ethnic subpopulation

Genotype†	Phenotype§	Incidence
17/17‡	URM	4% Caucasians[250,251] 0.5–1% Japanese[252,253] 2% Hispanic[251] 1–4% Chinese and Korean[254,255]
1/1§	EM	18–42% Caucasians[251] 58% Hispanic[251] 59% will carry a single (*1) allele[256]
17 or 1/ 2 or 3	MM	18–20% Caucasians[250,251] 20% Hispanic[251]
2/2 or 3/3	PM	13–23% Asians, Polynesians and Micronesians[254] 3–6% Caucasians and Africans[254,257–259] 0.8% Hispanic[251]

Adapted from Strom *et al*., 2012 and Desta *et al*., 2002.[251,260] †CYP2C19 genotype. Note that early studies of allelic frequency were performed prior to identification of the CYP2C19*17 allele. ‡No standardised nomenclature for *17 heterozygotes. Reports that heterozygote CYP2C19 17/1 may exhibit URM phenotype. If CYP2C19*17/1 considered URM, phenotypic frequency for URM would be 27% of Caucasians, 18% Africans, 16% Hispanic and 4% Asians.[251,254,261,262] §External factors, such as sepsis/inflammatory response may cause CYP450 down-regulation and alter phenotypic expression.[263,264] CYP, cytochrome; EM, extensive metaboliser; MM, moderate/intermediate metaboliser; PM, poor metaboliser; URM, ultra-rapid metaboliser.

has been proposed, as URM fail to differ clinically from these subgroups.[250] However, consensus regarding the use of this classification has not been reached.[288]

No large clinical studies have evaluated the impact of CYP2C19 testing on voriconazole dosing for IFD. In a prospective study of 21 patients receiving oral voriconazole therapy for IFD, voriconazole exposure differed irrespective of CYP2C19 genotype. However, PM patients were not included, and the effects of concurrent medications were not evaluated.[289] In a small study of voriconazole therapy in haemopoietic stem cell transplant patients, increased voriconazole clearance was noted in EM compared with moderate metabolisers (MM) (14.15 vs 9.71 L/h, $P = 0.762$) but findings were limited by small subject numbers and an absence of URM and slow metaboliser (SM) phenotypes.[290] One study demonstrated that MM require a shorter time to reach therapeutic voriconazole levels and statistically significantly lower maintenance doses compared with URM or EM, suggesting a clinically relevant role for CYP2C19 genotyping in voriconazole-treated patients.[249] The effect of CYP2C19 polymorphisms on paediatric voriconazole dosing has not been demonstrated in a population with limited PM,[291] although in one paediatric study, voriconazole exposure was significantly higher in the PM and MM compared with the EM and URM ($P = 0.004$).[292] Voriconazole toxicity in SM or those receiving concurrent CYP2C19 inhibitors is widely reported.[87,203,293,294]

Successful augmentation of voriconazole exposure in patients with EM or URM metaboliser phenotypes has been achieved through deliberate CYP2C19 inhibition with concurrent omeprazole or cimetidine therapy.[293,295,296]

Commercial CYP2C19 genotypic assays using patient whole blood (5 mL in ethylenediaminetetraacetic acid) or buccal cells (mouth swab) are available from multiple pathology providers across Australia. A variety of methods are currently used to identify genetic variants, and results are generally provided within 2 weeks of testing.

Impact of pharmacogenomics on the metabolism of other agents

While polymorphism is common in other drug metabolism enzymes, these have limited clinical impact because of the limited availability of commercial assays. Commonly used triazoles (fluconazole, itraconazole and posaconazole) are not metabolised by CYP2C19. Fluconazole is an inhibitor but not a significant substrate for CYP450,[17,297] whereas posaconazole pharmacokinetics is primarily related to gastrointestinal absorption and UDP-glucuronosyltransferase metabolism.[298] Itraconazole is a substrate and inhibitor of several drug transporters, including CYP3A4.[298–300] Although a commercial assay for CYP3A4 is available, CYP3A4 testing in patients receiving itraconazole is unlikely to adequately reflect more complex enzyme metabolism. Echinocandins and amphotericin formulations are not metabolised through CYP450 pathways.[298]

Potential clinical applications of genotyping

CYP2C19 genotype impacts voriconazole exposure and dosing. Despite the availability of a commercial assay in Australia, there remains a lack of *in vivo* controlled studies, and evidence-based guidelines cannot currently be proposed. Targeted applications for genotyping do exist, based upon clinical assessment. For example, utility of genotyping may be greater in ethnic groups with higher URM or PM phenotypes (Table 6). Standardised timely point-of-care pharmacogenomics testing may allow:

- Risk prediction of voriconazole toxicity.
- Estimation of azole-chemotherapeutic drug interactions (PM).
- Investigation of sub-therapeutic voriconazole levels (URM and EM) and identification of patients who may require deliberate CYP2C19 inhibition.
- Development of voriconazole dose-titrating algorithms.

These potential applications should inform future research exploring the clinical utility and relevance of CYP2C19 genotyping.

Conclusion

Antifungal agents may be associated with significant toxicity or drug interactions. These 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. TDM of antifungal agents is warranted, especially where non-compliance, non-linear pharmacokinetics, inadequate absorption, a narrow therapeutic window, suspected drug interaction or unexpected toxicity are encountered. We look forward to further research on the potential clinical applications of pharmacogenomic evaluation to help guide future recommendations.

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References

1 Worth LJ, Blyth CC, Booth DL, Kong DC, Marriott D, Cassumbhoy M *et al*. Optimizing antifungal drug dosing and monitoring to avoid toxicity and improve outcomes in patients with haematological disorders. *Intern Med J* 2008; **38**: 521–37.
2 Ghosal A, Hapangama N, Yuan Y, Achanfuo-Yeboah J, Iannucci R, Chowdhury S *et al*. Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). *Drug Metab Dispos* 2004; **32**: 267–71.
3 Pfizer Australia Pty Ltd. Diflucan (fluconazole) Australian approved product information, 11 June 2014.
4 Lewis RE. Managing drug interactions in the patient with aspergillosis. *Med Mycol* 2006; **44**: 349–56.
5 Jeong S, Nguyen PD, Desta Z. Comprehensive in vitro analysis of voriconazole inhibition of eight cytochrome P450 (CYP) enzymes: major effect on CYPs 2B6, 2C9, 2C19, and 3A. *Antimicrob Agents Chemother* 2009; **53**: 541–51.
6 Purkins L, Wood N, Ghahramani P, Love ER, Eve MD, Fielding A. Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety, and toleration. *Br J Clin Pharmacol* 2003; **56**: 37–44.
7 Krishna G, Parsons A, Kantesaria B, Mant T. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. *Curr Med Res Opin* 2007; **23**: 545–52.
8 Panomvana Na Ayudhya D, Thanompuangseree N, Tansuphaswadikul S. Effect of rifampicin on the pharmacokinetics of fluconazole in patients with AIDS. *Clin Pharmacokinet* 2004; **43**: 725–32.
9 Chen SC, Sorrell TC. Antifungal agents. *Med J Aust* 2007; **187**: 404–9.
10 Hohmann C, Kang EM, Jancel T. Rifampin and posaconazole coadministration leads to decreased serum posaconazole concentrations. *Clin Infect Dis* 2010; **50**: 939–40.
11 Park JY, Kim KA, Shin JG, Lee KY. Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br J Clin Pharmacol* 2004; **58**: 397–402.
12 Abad S, Moachon L, Blanche P, Bavoux F, Sicard D, Salmon-Céron D. Possible interaction between gliclazide, fluconazole and sulfamethoxazole resulting in severe hypoglycaemia. *Br J Clin Pharmacol* 2001; **52**: 456–67.
13 Hatorp V, Hansen KT, Thomsen MS. Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 2003; **43**: 649–60.
14 Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000; **38**: 41–57.
15 Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; **38**: 111–80.
16 Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. *Br J Clin Pharmacol* 1998; **45**: 525–38.
17 Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. *Biol Pharm Bull* 2005; **28**: 1805–8.
18 Crussell-Porter LL, Rindone JP, Ford MA, Jaskar DW. Low-dose fluconazole therapy potentiates the hypoprothrombinemic response of warfarin sodium. *Arch Intern Med* 1993; **153**: 102–4.
19 Cadle RM, Zenon GJ 3rd, Rodriguez-Barradas MC, Hamill RJ. Fluconazole-induced symptomatic phenytoin toxicity. *Ann Pharmacother* 1994; **28**: 191–5.
20 Mitra AK, Thummel KE, Kalhorn TF, Kharasch ED, Unadkat JD, Slattery JT. Inhibition of sulfamethoxazole hydroxylamine formation by fluconazole in human liver microsomes and healthy volunteers. *Clin Pharmacol Ther* 1996; **59**: 332–40.
21 Gubbins PO, Amsden JR. Drug–drug interactions of antifungal agents and implications for patient care. *Expert Opin Pharmacother* 2005; **6**: 2231–43.
22 Owens RC Jr. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; **64**: 1091–124.
23 Pham CP, de Feiter PW, van der Kuy PH, van Mook WN. Long QTc interval and torsade de pointes caused by

fluconazole. *Ann Pharmacother* 2006; **40**: 1456–61.
24 Alkan Y, Haefeli WE, Burhenne J, Stein J, Yaniv I, Shalit I. Voriconazole-induced QT interval prolongation and ventricular tachycardia: a non-concentration-dependent adverse effect. *Clin Infect Dis* 2004; **39**: e49–52.
25 Owens RC Jr, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. *Clin Infect Dis* 2006; **43**: 1603–11.
26 Zeuli JD, Wilson JW, Estes LL. Effect of combined fluoroquinolone and azole use on QT prolongation in hematology patients. *Antimicrob Agents Chemother* 2013; **57**: 1121–7.
27 Link Medical Products Pty Ltd. Deseril (methysergide 1 mg [as maleate]) tablets Australian Approved Product Information, 8 October 2012.
28 Shakeri-Nejad K, Stahlmann R. Drug interactions during therapy with three major groups of antimicrobial agents. *Expert Opin Pharmacother* 2006; **7**: 639–51.
29 Weiss J, Ten Hoevel MM, Burhenne J, Walter-Sack I, Hoffmann MM, Rengelshausen J *et al*. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. *J Clin Pharmacol* 2009; **49**: 196–204.
30 Mikus G, Scholz IM, Weiss J. Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics* 2011; **12**: 861–72.
31 Merck Sharp & Dohme (Australia) Pty Ltd. Emend (arepitant) Australian approved product information, 1 April 2014.
32 Kahri J, Valkonen M, Backlund T, Vuoristo M, Kivisto KT. Rhabdomyolysis in a patient receiving atorvastatin and fluconazole. *Eur J Clin Pharmacol* 2005; **60**: 905–7.
33 Kantola T, Backman JT, Niemi M, Kivisto KT, Neuvonen PJ. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000; **56**: 225–9.
34 Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004; **94**.
35 Kantola T, Kivisto KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998; **64**: 58–65.
36 Mazzu AL, Lasseter KC, Shamblen EC, Agarwal V, Lettieri J, Sundaresen P. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Clin Pharmacol Ther* 2000; **68**: 391–400.
37 Saari TILK, Bertilsson L, Neuvonen PJ, Olkkola KT. Voriconazole and fluconazole increase the exposure to oral diazepam. *Eur J Clin Pharmacol* 2007; **63**: 941–9.
38 Pfizer Australia Pty Ltd. Lipitor (atorvastatin) Australian approved product information, 19 June 2013.
39 Venkatakrishnan K, Rader M, Ramanathan RK, Ramalingam S, Chen E, Riordan W *et al*. Effect of the CYP3A inhibitor ketoconazole on the pharmacokinetics and pharmacodynamics of bortezomib in patients with advanced solid tumors: a prospective, multicenter, open-label, randomized, two-way crossover drug-drug interaction study. *Clin Ther* 2009; **31**(Pt 2): 2444–58.
40 Iwamoto T, Ishibashi M, Fujieda A, Masuya M, Katayama N, Okuda M. Drug interaction between itraconazole and bortezomib: exacerbation of peripheral neuropathy and thrombocytopenia induced by bortezomib. *Pharmacotherapy* 2010; **30**: 661–5.
41 Bortezomib/itraconazole/voriconazole interaction. *Reactions Weekly* 2013; **1444**: 12.
42 Buggia I, Zeca M, Alessandrino EP, Locatelli F, Rosti G, Bosi A *et al*. Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. GITMO (Gruppo Italiano Trapianto di Midollo Osseo). *Anticancer Res* 1996; **16**: 2083–8.
43 Lazar JD, Wilner KD. Drug interactions with fluconazole. *Rev Infect Dis* 1990; **12**(Suppl 3): S327–33.
44 Karyekar CS, Eddington ND, Briglia A, Gubbins PO, Dowling TC. Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol* 2004; **44**: 919–27.
45 Purkins L, Wood N, Kleinermans D, Nichols D. Histamine H2-receptor antagonists have no clinically significant effect on the steady-state pharmacokinetics of voriconazole. *Br J Clin Pharmacol* 2003; **56**(Suppl 1): 51–5.
46 Courtney R, Wexler D, Statkevich P, Lim J, Batra V, Laughlin M Effect of cimetidine on the pharmacokinetics of posaconazole in healthy volunteers. Interscience Conference Antimicrobial Agents Chemotherapy, 2002.
47 Yule SM, Walker D, Cole M, Mcsorley L, Cholerton S, Daly AK *et al*. The effect of fluconazole on cyclophosphamide metabolism in children. *Drug Metab Dispos* 1999; **27**: 417–21.
48 Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38**: 291–304.
49 Marr KA, Leisenring W, Crippa F, Slattery JT, Corey L, Boeckh M *et al*. Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; **103**: 1557–9.
50 Kruger HU, Schuler U, Zimmermann R, Ehninger G. Absence of significant interaction of fluconazole with cyclosporin. *J Antimicrob Chemother* 1989; **24**: 781–6.
51 Osowski CL, Dix SP, Lin LS, Mullins RE, Geller RB, Wingard JR. Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. *Transplantation* 1996; **61**: 1268–72.
52 Janssen Cilag Pty Ltd. Sporanox (itraconazole) oral solution. Australian approved product information, 31 January 2013.
53 Mori T, Aisa Y, Kato J, Nakamura Y, Ikeda Y, Okamoto S. Drug interaction between voriconazole and calcineurin inhibitors in allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2009; **44**: 371–4.
54 Kikuchi T, Mori T, Yamane A, Kato J, Kohashi S, Okamoto S. Variable magnitude of drug interaction between oral voriconazole and cyclosporine A in recipients of allogeneic hematopoietic stem cell transplantation. *Clin Transplant* 2012; **26**: E544–8.
55 Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy* 2006; **26**: 1730–44.
56 Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S,

Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. *Pharmacotherapy* 2007; **27**: 825–34.
57 Fluconazole. DRUGDEX system Micromedex 2.0. 2014 Truven Health Analytics Inc. [cited 2014 Apr 13]. Available from URL: http://www.micromedexsolutions.com [Internet].
58 Johnson FM, Agrawal S, Burris H, Rosen L, Dhillon N, Hong D *et al*. Phase 1 pharmacokinetic and drug-interaction study of dasatinib in patients with advanced solid tumors. *Cancer* 2010; **116**: 1582–91.
59 Bristol-Myers Squibb Australia Pty Ltd. Sprycel (dasatinib) Australian approved product information, 1 July 2014.
60 Voriconazole. DRUGDEX system Micromedex 2.0. 2014 Truven Health Analytics Inc [cited 2014 Apr 13]. Available from URL: http://www.micromedexsolutions.com [Internet].
61 Posaconazole. DRUGDEX system Micromedex 2.0. 2014 Truven Health Analytics Inc [cited 2014 Apr 13]. Available from URL: http://www.micromedexsolutions.com [Internet].
62 Lam MSH, Ignoffo RJ. A guide to clinically relevant drug interactions in oncology. *J Oncol Pharm Pract* 2003; **9**: 45–85.
63 Varis T, Kivisto KT, Backman JT, Neuvonen PJ. The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther* 2000; **68**: 487–94.
64 Kerbusch T, Jansen RLH, Mathôt RAA, Huitema ADR, Jansen M, van Rijswijk REN *et al*. Modulation of the cytochrome P450-mediated metabolism of ifosfamide by ketoconazole and rifampin. *Clin Pharmacol Ther* 2001; **70**: 132–41.
65 Novartis Pharmaceuticals Australia Pty Ltd. Glivec (imatinib) Australian approved product information, 18 February 2014.
66 Gambillara E, Laffitte E, Widmer N, Decosterd LA, Duchosal MA, Kovacsovics T *et al*. Severe pustular eruption associated with imatinib and voriconazole in a patient with chronic myeloid leukemia. *Dermatology* 2005; **211**: 363–5.
67 Heinz WJ, Grau A, Ulrich A, Helle-Beyersdorf A, Zirkel J, Schirmer D *et al*. Impact of benzodiazepines on posaconazole serum concentrations. A population-based pharmacokinetic study on drug interaction. *Curr Med Res Opin* 2012; **28**: 551–7.
68 Lebrun-Vignes B, Archer VC, Diquet B, Levron JC, Chosidow O, Puech AJ *et al*. Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol* 2001; **51**: 443–50.
69 Varis T, Kaukonen KM, Kivistö KT, Neuvonen PJ. Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. *Clin Pharmacol Ther* 1998; **64**: 363–8.
70 Varis T, Kivistö KT, Backman JT, Neuvonen PJ. Itraconazole decreases the clearance and enhances the effects of intravenously administered methylprednisolone in healthy volunteers. *Pharmacol Toxicol* 1999; **85**: 29–32.
71 Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. *Pharmacotherapy* 2010; **30**: 842–54.
72 Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. *Antimicrob Agents Chemother* 2009; **53**: 958–66.
73 Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. *Antimicrob Agents Chemother* 2012; **56**: 5503–10.
74 Merck Sharp & Dohme Corp. Noxafil (posaconazole) US prescribing information, June 2014.
75 Kraft WK, Chang P, van Iersel MPS, Waskin H, Krishna G, Kersemaekers W Effect of concomitant medications affecting gastric pH and motility on posaconazole (POS) tablet pharmacokinetics (PK). Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 2012.
76 Saari TI, Laine K, Leino K, Valtonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Clin Pharmacol Ther* 2006; **79**: 362–70.
77 Krishna G, Ma L, Prasad P, Moton A, Martinho M, O'Mara E. Effect of posaconazole on the pharmacokinetics of simvastatin and midazolam in healthy volunteers. *Expert Opin Drug Metab Toxicol* 2012; **8**: 1–10.
78 Kremens B, Brendel E, Bald M, Czyborra P, Michel MC. Loss of blood pressure control on withdrawal of fluconazole during nifedipine therapy. *Br J Clin Pharmacol* 1999; **47**: 707–8.
79 Tailor SA, Gupta AK, Walker SE, Shear NH. Peripheral edema due to nifedipine-itraconazole interaction: a case report. *Arch Dermatol* 1996; **132**: 350–2.
80 Tanaka C, Yin OQ, Smith T, Sethuraman V, Grouss K, Galitz L *et al*. Effects of rifampin and ketoconazole on the pharmacokinetics of nilotinib in healthy participants. *J Clin Pharmacol* 2011; **51**: 75–83.
81 Novartis Pharmaceuticals Australia Pty Ltd. Tasigna (nilotinib) Australian approved product information, 20 August 2014.
82 Kang BC, Yang CQ, Cho HK, Suh OK, Shin WG. Influence of fluconazole on the pharmacokinetics of omeprazole in healthy volunteers. *Biopharm Drug Dispos* 2002; **23**: 77–81.
83 Zimmermann T, Yeates RA, Riedel KD, Lach P, Laufen H. The influence of gastric pH on the pharmacokinetics of fluconazole: the effect of omeprazole. *Int J Clin Pharmacol Ther* 1994; **32**: 491–6.
84 Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. *Eur J Clin Pharmacol* 1998; **54**: 159–61.
85 Johnson MD, Hamilton CD, Drew RH, Sanders LL, Pennick GJ, Perfect JR. A randomized comparative study to determine the effect of omeprazole on the peak serum concentration of itraconazole oral solution. *J Antimicrob Chemother* 2003; **51**: 453–7.
86 Pfizer Australia Pty Ltd. Vfend (voriconazole) Australian approved product information, 4 September 2013.
87 Wood N, Tan K, Purkins L, Layton G, Hamlin J, Kleinermans D *et al*. Effect of omeprazole on the steady-state pharmacokinetics of voriconazole. *Br J*

Clin Pharmacol 2003; **56**(Suppl 1): 56–61.
88 AstraZeneca Australia Pty Ltd. Nexium (esomeprazole magnesium trihydrate) for oral suspension Australian approved product information, 5 June 2014.
89 Alffenaar JW, van Assen S, van der Werf TS, Kosterink JG, Uges DR. Omeprazole significantly reduces posaconazole serum trough level. *Clin Infect Dis* 2009; **48**: 839.
90 Merck Sharp & Dohme (Australia) Pty Ltd. Noxafil (posaconazole) oral suspension Australian approved product information, 29 July 2014.
91 Vehreschild JJ, Muller C, Farowski F, Vehreschild MJ, Cornely OA, Fuhr U *et al*. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. *Eur J Clin Pharmacol* 2012; **68**: 987–95.
92 Blum RA, Wilton JH, Hilligoss DM, Gardner MJ, Henry EB, Harrison NJ *et al*. Effect of fluconazole on the disposition of phenytoin. *Clin Pharmacol Ther* 1991; **49**: 420–5.
93 Ducharme MP, Slaughter RL, Warbasse LH, Chandrasekar PH, Van de Velde V, Mannens G *et al*. Itraconazole and hydroxyitraconazole serum concentrations are reduced more than tenfold by phenytoin. *Clin Pharmacol Ther* 1995; **58**: 617–24.
94 Krishna G, Sansone-Parsons A, Kantesaria B. Drug interaction assessment following concomitant administration of posaconazole and phenytoin in healthy men. *Curr Med Res Opin* 2007; **23**: 1415–22.
95 Varis T, Kivisto KT, Neuvonen PJ. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. *Eur J Clin Pharmacol* 2000; **56**: 57–60.
96 Lange D, Pavao JH, Wu J, Klausner M. Effect of a cola beverage on the bioavailability of itraconazole in the presence of H2 blockers. *J Clin Pharmacol* 1997; **37**: 535–40.
97 Hazin R, Abuzetun JY, Suker M, Porter J. Rhabdomyolysis induced by simvastatin-fluconazole combination. *J Natl Med Assoc* 2008; **100**: 444–6.
98 Doran E, Iedema J, Ryan L, Coombes I. Fatal rhabdomyolysis following voriconazole and simvastatin. *Aust Prescr* 2012; **35**: 88–9.
99 Cervelli MJ. Fluconazole-sirolimus drug interaction. *Transplantation* 2002; **74**: 1477–8.
100 Said A, Garnick JJ, Dieterle N, Peres E, Abidi MH, Ibrahim RB. Sirolimus-itraconazole interaction in a hematopoietic stem cell transplant recipient. *Pharmacotherapy* 2006; **26**: 289–95.
101 Marty FM, Lowry CM, Cutler CS, Campbell BJ, Fiumara K, Baden LR *et al*. Voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2006; **12**: 552–9.
102 Surowiec DDD, Carver PL. Concurrent administration of sirolimus and voriconazole: a pilot study assessing safety and approaches to appropriate management. *Pharmacotherapy* 2008; **28**: 719–29.
103 Moton A, Ma L, Krishna G, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetics of sirolimus. *Curr Med Res Opin* 2009; **25**: 701–7.
104 Kubiak DW, Koo S, Hammond SP, Armand P, Baden LR, Antin JH *et al*. Safety of posaconazole and sirolimus coadministration in allogeneic hematopoietic stem cell transplants. *Biol Blood Marrow Transplant* 2012; **18**: 1462–5.
105 Lathia C, Lettieri J, Cihon F, Gallentine M, Radtke M, Sundaresan P. Lack of effect of ketoconazole-mediated CYP3A inhibition on sorafenib clinical pharmacokinetics. *Cancer Chemother Pharmacol* 2006; **57**: 685–92.
106 Zimmerman EI, Roberts JL, Li L, Finkelstein D, Gibson A, Chaudhry AS *et al*. Ontogeny and sorafenib metabolism. *Clin Cancer Res* 2012; **18**: 5788–95.
107 Manez R, Martin M, Raman D, Silverman D, Jain A, Warty V *et al*. Fluconazole therapy in transplant recipients receiving FK506. *Transplantation* 1994; **57**: 1521–3.
108 Leather H, Boyette RM, Tian L, Wingard JR. Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2006; **12**: 325–34.
109 Mori T, Kato J, Yamane A, Sakurai M, Kohashi S, Kikuchi T *et al*. Drug interaction between voriconazole and tacrolimus and its association with the bioavailability of oral voriconazole in recipients of allogeneic hematopoietic stem cell transplantation. *Int J Hematol* 2012; **95**: 564–9.
110 Spriet I, Grootaert V, Meyfroidt G, Debaveye Y, Willems L. Switching from intravenous to oral tacrolimus and voriconazole leads to a more pronounced drug-drug interaction. *Eur J Clin Pharmacol* 2013; **69**: 737–8.
111 Inoue Y, Saito T, Takimoto M, Ogawa K, Shibuya Y, Suzuki Y *et al*. Highly activated oral bioavailability of tacrolimus on coadministration of oral voriconazole. *Int J Clin Pharmacol Ther* 2011; **49**: 291–2.
112 Bashir H, Motl S, Metzger ML, Howard SC, Kaste S, Krasin MP *et al*. Itraconazole-enhanced chemotherapy toxicity in a patient with Hodgkin lymphoma. *J Pediatr Hematol Oncol* 2006; **28**: 33–5.
113 Moriyama B, Henning SA, Leung J, Falade-Nwulia O, Jarosinski P, Penzak SR *et al*. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. *Mycoses* 2012; **55**: 290–7.
114 Gillies J, Hung KA, Fitzsimons E, Soutar R. Severe vincristine toxicity in combination with itraconazole. *Clin Lab Haematol* 1998; **20**: 123–4.
115 Mantadakis E, Amoiridis G, Kondi A, Kalmanti M. Possible increase of the neurotoxicity of vincristine by the concurrent use of posaconazole in a young adult with leukemia. *J Pediatr Hematol Oncol* 2007; **29**: 130.
116 Miura M, Takahashi N, Kanno S, Kato S, Nara M, Itoh M *et al*. Drug interaction of (S)-warfarin, and not (R)-warfarin, with itraconazole in a hematopoietic stem cell transplant recipient. *Clin Chim Acta* 2011; **412**: 2002–6.
117 Purkins L, Wood N, Kleinermans D. Voriconazole potentiates warfarin-induced prothrombin time prolongation. *Br J Clin Pharmacol* 2003; **56**(Suppl 1): 24–9.
118 Vadlapatla RK, Patel M, Paturi DK, Pal D, Mitra AK. Clinically relevant drug-drug interactions between antiretrovirals and antifungals. *Expert*

Opin Drug Metab Toxicol 2014; **10**: 561–80.
119 Liverpool HIV Pharmacology Group, University of Liverpool. HIV drug interactions chart [cited 2014 April 1]. Available from URL: http://www.hivdruginteractions.org/Interactions.aspx
120 Zimmermann T, Yeates RA, Laufen H, Pfaff G, Wildfeuer A. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. *Eur J Clin Pharmacol* 1994; **46**: 147–50.
121 Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH *et al*. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. *Pharmacotherapy* 1998; **18**: 295–301.
122 Mayne Pharma International Pty Ltd. Itraconazole (Lozanoc) capsules Australian Approved Product Information, 16 April 2014.
123 Gubbins PO, McConnell SA, Gurley BJ, Fincher TK, Franks AM, Williams DK *et al*. Influence of grapefruit juice on the systemic availability of itraconazole oral solution in healthy adult volunteers. *Pharmacotherapy* 2004; **24**: 460–7.
124 Penzak SR, Gubbins PO, Gurley BJ, Wang PL, Saccente M. Grapefruit juice decreases the systemic availability of itraconazole capsules in healthy volunteers. *Ther Drug Monit* 1999; **21**: 304–9.
125 Royal Pharmaceutical Society. *Stockley's Drug Interactions [Internet]*. London, UK: Pharmaceutical Press. [cited 2014 Mar 8]. Available from URL: http://www.medicinescomplete.com
126 Purkins L, Wood N, Kleinermans D, Greenhalgh K, Nichols D. Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. *Br J Clin Pharmacol* 2003; **56**(Suppl 1): 17–23.
127 Sansone-Parsons A, Krishna G, Calzetta A, Wexler D, Kantesaria B, Rosenberg MA *et al*. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. *Antimicrob Agents Chemother* 2006; **50**: 1881–3.
128 Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. *Br J Clin Pharmacol* 2004; **57**: 218–22.
129 Krishna G, Ma L, Martinho M, O'Mara E. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. *Antimicrob Agents Chemother* 2012; **56**: 4196–201.
130 Ringden O, Andstrom E, Remberger M, Svahn BM, Tollemar J. Safety of liposomal amphotericin B (AmBisome) in 187 transplant recipients treated with cyclosporin. *Bone Marrow Transplant* 1994; **14**(Suppl 5): S10–14.
131 Luber AD, Maa L, Lam M, Guglielmo BJ. Risk factors for amphotericin B-induced nephrotoxicity. *J Antimicrob Chemother* 1999; **43**: 267–71.
132 Depont F, Vargas F, Dutronc H, Giauque E, Ragnaud JM, Galpérine T *et al*. Drug–drug interactions with systemic antifungals in clinical practice. *Pharmacoepidemiol Drug Saf* 2007; **16**: 1227–33.
133 Albengres E, Le Louet H, Tillement JP. Systemic antifungal agents. Drug interactions of clinical significance. *Drug Saf* 1998; **18**: 83–97.
134 Cohen-Wolkowiez M, Moran C, Benjamin DK Jr, Smith PB. Pediatric antifungal agents. *Curr Opin Infect Dis* 2009; **22**: 553–8.
135 Al Arishi H, Frayha HH, Kalloghlian A, Al Alaiyan S. Liposomal amphotericin B in neonates with invasive candidiasis. *Am J Perinatol* 1998; **15**: 643–8.
136 Cappelletty D, Eiselstein-McKitrick K. The echinocandins. *Pharmacotherapy* 2007; **27**: 369–88.
137 Stone EA, Fung HB, Kirschenbaum HL. Caspofungin: an echinocandin antifungal agent. *Clin Ther* 2002; **24**: 351–77.
138 Wagner C, Graninger W, Presterl E, Joukhadar C. The echinocandins: comparison of their pharmacokinetics, pharmacodynamics and clinical applications. *Pharmacology* 2006; **78**: 161–77.
139 Stone JA, Migoya EM, Hickey L, Winchell GA, Deutsch PJ, Ghosh K *et al*. Potential for interactions between caspofungin and nelfinavir or rifampin. *Antimicrob Agents Chemother* 2004; **48**: 4306–14.
140 Morris MI, Villmann M. Echinocandins in the management of invasive fungal infections, Part 2. *Am J Health Syst Pharm* 2006; **63**: 1813–20.
141 Merck Sharp & Dohme (Australia) Pty Ltd. Cancidas (caspofungin acetate) Australian approved product information, 29 January 2013.
142 Dowell JA, Stogniew M, Krause D, Henkel T, Weston IE. Assessment of the safety and pharmacokinetics of anidulafungin when administered with cyclosporine. *J Clin Pharmacol* 2005; **45**: 227–33.
143 Dowell JA, Stogniew M, Krause D, Henkel T, Damle B. Lack of pharmacokinetic interaction between anidulafungin and tacrolimus. *J Clin Pharmacol* 2007; **47**: 305–14.
144 Dowell JA, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. Population pharmacokinetic analysis of anidulafungin, an echinocandin antifungal. *J Clin Pharmacol* 2004; **44**: 590–8.
145 Hebert MF, Townsend RW, Austin S, Balan G, Blough DK, Buell D *et al*. Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 2005; **45**: 954–60.
146 Johansen HK, Gotzsche PC. Amphotericin B lipid soluble formulations vs amphotericin B in cancer patients with neutropenia. *Cochrane Database Syst Rev* 2000; (3): CD000969.
147 Girois SB, Chapuis F, Decullier E, Revol BG. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 138–49.
148 Llanos A, Cieza J, Bernardo J, Echevarria J, Biaggioni I, Sabra R *et al*. Effect of salt supplementation on amphotericin B nephrotoxicity. *Kidney Int* 1991; **40**: 302–8.
149 Stein RS, Alexander JA. Sodium protects against nephrotoxicity in patients receiving amphotericin B. *Am J Med Sci* 1989; **298**: 299–304.
150 Mayer J, Doubek M, Doubek J, Horky D, Scheer P, Stepanek M. Reduced nephrotoxicity of conventional amphotericin B therapy after minimal nephroprotective measures: animal experiments and clinical study. *J Infect Dis* 2002; **186**: 379–88.
151 Eriksson U, Seifert B, Schaffner A. Comparison of effects of amphotericin B deoxycholate infused over 4 or 24

hours: randomised controlled trial. *BMJ* 2001; **322**: 579–82.
152 Wingard JR, Kubilis P, Lee L, Yee G, White M, Walshe L *et al*. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis* 1999; **29**: 1402–7.
153 Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, Bodensteiner D *et al*. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999; **340**: 764–71.
154 Grasela TH Jr, Goodwin SD, Walawander MK, Cramer RL, Fuhs DW, Moriarty VP. Prospective surveillance of intravenous amphotericin B use patterns. *Pharmacotherapy* 1990; **10**: 341–8.
155 Goodwin SD, Cleary JD, Walawander CA, Taylor JW, Grasela TH Jr. Pretreatment regimens for adverse events related to infusion of amphotericin B. *Clin Infect Dis* 1995; **20**: 755–61.
156 Winston DJ, Hathorn JW, Schuster MG, Schiller GJ, Territo MC. A multicenter, randomized trial of fluconazole versus amphotericin B for empiric antifungal therapy of febrile neutropenic patients with cancer. *Am J Med* 2000; **108**: 282–9.
157 Boogaerts M, Winston DJ, Bow EJ, Garber G, Reboli AC, Schwarer AP *et al*. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy. A randomized, controlled trial. *Ann Intern Med* 2001; **135**: 412–22.
158 Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A *et al*. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. *Clin Infect Dis* 2000; **31**: 1155–63.
159 Prentice HG, Hann IM, Herbrecht R, Aoun M, Kvaloy S, Catovsky D *et al*. A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997; **98**: 711–18.
160 Subira M, Martino R, Gomez L, Marti JM, Estany C, Sierra J. Low-dose amphotericin B lipid complex vs. conventional amphotericin B for empirical antifungal therapy of neutropenic fever in patients with hematologic malignancies–a randomized, controlled trial. *Eur J Haematol* 2004; **72**: 342–7.
161 Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M *et al*. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis* 2002; **35**: 359–66.
162 White MH, Bowden RA, Sandler ES, Graham ML, Noskin GA, Wingard JR *et al*. Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. *Clin Infect Dis* 1998; **27**: 296–302.
163 Smith SR, Galloway MJ, Reilly JT, Davies JM. Amiloride prevents amphotericin B related hypokalaemia in neutropenic patients. *J Clin Pathol* 1988; **41**: 494–7.
164 Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A *et al*. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; **351**: 1391–402.
165 Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW *et al*. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347**: 408–15.
166 Villanueva A, Arathoon EG, Gotuzzo E, Berman RS, DiNubile MJ, Sable CA. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. *Clin Infect Dis* 2001; **33**: 1529–35.
167 MacGregor RR, Bennett JE, Erslev AJ. Erythropoietin concentration in amphotericin B-induced anemia. *Antimicrob Agents Chemother* 1978; **14**: 270–3.
168 Yeo EJ, Ryu JH, Cho YS, Chun YS, Huang LE, Kim MS *et al*. Amphotericin B blunts erythropoietin response to hypoxia by reinforcing FIH-mediated repression of HIF-1. *Blood* 2006; **107**: 916–23.
169 Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR *et al*. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007; **356**: 335–47.
170 Winston DJ, Maziarz RT, Chandrasekar PH, Lazarus HM, Goldman M, Blumer JL *et al*. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. *Ann Intern Med* 2003; **138**: 705–13.
171 Marr KA, Crippa F, Leisenring W, Hoyle M, Boeckh M, Balajee SA *et al*. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood* 2004; **103**: 1527–33.
172 Anaissie EJ, Vartivarian SE, Abi-Said D, Uzun O, Pinczowski H, Kontoyiannis DP *et al*. Fluconazole versus amphotericin B in the treatment of hematogenous candidiasis: a matched cohort study. *Am J Med* 1996; **101**: 170–6.
173 Novelli V, Holzel H. Safety and tolerability of fluconazole in children. *Antimicrob Agents Chemother* 1999; **43**: 1955–60.
174 Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE *et al*. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. *N Engl J Med* 1994; **331**: 1325–30.
175 Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S *et al*. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clin Infect Dis* 2003; **36**: 1221–8.
176 Viscoli C, Castagnola E, Van Lint MT, Moroni C, Garaventa A, Rossi MR *et al*. Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic

cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial. *Eur J Cancer* 1996; **32A**: 814–20.
177 Denning DW, Lee JY, Hostetler JS, Pappas P, Kauffman CA, Dewsnup DH *et al*. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. *Am J Med* 1994; **97**: 135–44.
178 Menichetti F, Del Favero A, Martino P, Bucaneve G, Micozzi A, Girmenia C *et al*. Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: a randomized, placebo-controlled, double-blind, multicenter trial. GIMEMA Infection Program. Gruppo Italiano Malattie Ematologiche dell' Adulto. *Clin Infect Dis* 1999; **28**: 250–5.
179 Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ *et al*. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.
180 Glasmacher A, von Lilienfeld-Toal M, Schulte S, Hahn C, Schmidt-Wolf IG, Prentice A. An evidence-based evaluation of important aspects of empirical antibiotic therapy in febrile neutropenic patients. *Clin Microbiol Infect* 2005; **11**(Suppl 5): 17–23.
181 Villanueva A, Gotuzzo E, Arathoon EG, Noriega LM, Kartsonis NA, Lupinacci RJ *et al*. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med* 2002; **113**: 294–9.
182 Marr KA, Hachem R, Papanicolaou G, Somani J, Arduino JM, Lipka CJ *et al*. Retrospective study of the hepatic safety profile of patients concomitantly treated with caspofungin and cyclosporin A. *Transpl Infect Dis* 2004; **6**: 110–16.
183 Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J *et al*. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346**: 225–34.
184 Perfect JR, Marr KA, Walsh TJ, Greenberg RN, DuPont B, de la Torre-Cisneros J *et al*. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis* 2003; **36**: 1122–31.
185 Cronin S, Chandrasekar PH. Safety of triazole antifungal drugs in patients with cancer. *J Antimicrob Chemother* 2010; **65**: 410–16.
186 Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J Clin Pharmacol* 2006; **46**: 235–43.
187 Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH *et al*. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* 2005; **366**: 1435–42.
188 Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E *et al*. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; **34**: 563–71.
189 McCarthy KL, Playford EG, Looke DF, Whitby M. Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. *Clin Infect Dis* 2007; **44**: e55–6.
190 Cowen EW, Nguyen JC, Miller DD, McShane D, Arron ST, Prose NS *et al*. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *J Am Acad Dermatol* 2010; **62**: 31–7.
191 Miller DD, Cowen EW, Nguyen JC, McCalmont TH, Fox LP. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. *Arch Dermatol* 2010; **146**: 300–4.
192 Morice C, Acher A, Soufir N, Michel M, Comoz F, Leroy D *et al*. Multifocal aggressive squamous cell carcinomas induced by prolonged voriconazole therapy: a case report. *Case Rep Med* 2010; **2010**: 351084.
193 Gerber B, Guggenberger R, Fasler D, Nair G, Manz MG, Stussi G *et al*. Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole. *Blood* 2012; **120**: 2390–4.
194 Bucknor MD, Gross AJ, Link TM. Voriconazole-induced periostitis in two post-transplant patients. *J Radiol Case Rep* 2013; **7**: 10–17.
195 Lustenberger DP, Granata JD, Scharschmidt TJ. Periostitis secondary to prolonged voriconazole therapy in a lung transplant recipient. *Orthopedics* 2011; **34**: e793–6.
196 Wang TF, Wang T, Altman R, Eshaghian P, Lynch JP 3rd, Ross DJ *et al*. Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. *Am J Transplant* 2009; **9**: 2845–50.
197 Wise SM, Wilson MA. A case of periostitis secondary to voriconazole therapy in a heart transplant recipient. *Clin Nucl Med* 2011; **36**: 242–4.
198 Ayub A, Kenney CV, McKiernan FE. Multifocal nodular periostitis associated with prolonged voriconazole therapy in a lung transplant recipient. *J Clin Rheumatol* 2011; **17**: 73–5.
199 Wermers RA, Cooper K, Razonable RR, Deziel PJ, Whitford GM, Kremers WK *et al*. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. *Clin Infect Dis* 2011; **52**: 604–11.
200 Luke DR, Wood ND, Tomaszewski KE, Damle B. Pharmacokinetics of sulfobutylether-beta-cyclodextrin (SBECD) in subjects on hemodialysis. *Nephrol Dial Transplant* 2012; **27**: 1207–12.
201 Hafner V, Czock D, Burhenne J, Riedel KD, Bommer J, Mikus G *et al*. Pharmacokinetics of sulfobutylether-beta-cyclodextrin and voriconazole in patients with end-stage renal failure during treatment with two hemodialysis systems and hemodiafiltration. *Antimicrob Agents Chemother* 2010; **54**: 2596–602.
202 Zonios DI, Gea-Banacloche J, Childs R, Bennett JE. Hallucinations during voriconazole therapy. *Clin Infect Dis* 2008; **47**: e7–10.
203 Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008; **46**: 201–11.
204 Eiden C, Peyriere H, Cociglio M, Djezzar S, Hansel S, Blayac JP *et al*. Adverse effects of voriconazole: analysis of the French Pharmaco vigilance Database. *Ann Pharmacother* 2007; **41**: 755–63.

205 Eiden C, Peyriere H, Tichit R, Cociglio M, Amedro P, Blayac JP *et al*. Inherited long QT syndrome revealed by antifungals drug–drug interaction. *J Clin Pharm Ther* 2007; **32**: 321–4.
206 Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R *et al*. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; **44**: 2–12.
207 Ullmann AJ, Cornely OA, Burchardt A, Hachem R, Kontoyiannis DP, Topelt K *et al*. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agents Chemother* 2006; **50**: 658–66.
208 Skiest DJ, Vazquez JA, Anstead GM, Graybill JR, Reynes J, Ward D *et al*. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. *Clin Infect Dis* 2007; **44**: 607–14.
209 Raad II, Graybill JR, Bustamante AB, Cornely OA, Gaona-Flores V, Afif C *et al*. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clin Infect Dis* 2006; **42**: 1726–34.
210 Maertens J, Raad I, Petrikkos G, Boogaerts M, Selleslag D, Petersen FB *et al*. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis* 2004; **39**: 1563–71.
211 Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J *et al*. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002; **347**: 2020–9.
212 Herbrecht R, Maertens J, Baila L, Aoun M, Heinz W, Martino R *et al*. Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study. *Bone Marrow Transplant* 2010; **45**: 1227–33.
213 Groll AH, Attarbaschi A, Schuster FR, Herzog N, Grigull L, Dworzak MN *et al*. Treatment with caspofungin in immunocompromised paediatric patients: a multicentre survey. *J Antimicrob Chemother* 2006; **57**: 527–35.
214 Sanz-Rodriguez C, Lopez-Duarte M, Jurado M, Lopez J, Arranz R, Cisneros JM *et al*. Safety of the concomitant use of caspofungin and cyclosporin A in patients with invasive fungal infections. *Bone Marrow Transplant* 2004; **34**: 13–20.
215 Morrissey CO, Bardy PG, Slavin MA, Ananda-Rajah MR, Chen SC, Kirsa SW *et al*. Diagnostic and therapeutic approach to persistent or recurrent fevers of unknown origin in adult stem cell transplantation and haematological malignancy. *Intern Med J* 2008; **38**: 477–95.
216 Sable CA, Nguyen BY, Chodakewitz JA, DiNubile MJ. Safety and tolerability of caspofungin acetate in the treatment of fungal infections. *Transpl Infect Dis* 2002; **4**: 25–30.
217 Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs* 2011; **71**: 11–41.
218 Eschenauer G, Depestel DD, Carver PL. Comparison of echinocandin antifungals. *Ther Clin Risk Manag* 2007; **3**: 71–97.
219 Hindahl CB, Wilson JW. Flash pulmonary oedema during anidulafungin administration. *J Clin Pharm Ther* 2012; **37**: 491–3.
220 Fink M, Zerlauth U, Kaulfersch C, Rab A, Alberer D, Preiss P *et al*. A severe case of haemodynamic instability during anidulafungin administration. *J Clin Pharm Ther* 2013; **38**: 241–2.
221 Lichtenstern C, Wolff M, Arens C, Klie F, Majeed RW, Henrich M *et al*. Cardiac effects of echinocandin preparations – three case reports. *J Clin Pharm Ther* 2013; **38**: 429–31.
222 Stover KR, Farley JM, Kyle PB, Cleary JD. Cardiac toxicity of some echinocandin antifungals. *Expert Opin Drug Saf* 2014; **13**: 5–14.
223 Schranz JKD, Henkel T. *Program and Abstracts of the 15th Congress of the International Society for Human and Animal Mycology (San Antonio, TX)*. Atlanta (GA): International Society for Human and Animal Mycology; 2003. Lack of infusion-related adverse events with anidulafungin [abstract 44].
224 Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D *et al*. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; **356**: 2472–82.
225 Krause DS, Simjee AE, van Rensburg C, Viljoen J, Walsh TJ, Goldstein BP *et al*. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis* 2004; **39**: 770–5.
226 Menichetti F. Anidulafungin, a new echinocandin: effectiveness and tolerability. *Drugs* 2009; **69**(Suppl 1): 95–7.
227 Benjamin DK Jr, Driscoll T, Seibel NL, Gonzalez CE, Roden MM, Kilaru R *et al*. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006; **50**: 632–8.
228 Vermes A, Guchelaar HJ, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46**: 171–9.
229 Vermes A, van Der Sijs H, Guchelaar HJ. Flucytosine: correlation between toxicity and pharmacokinetic parameters. *Chemotherapy* 2000; **46**: 86–94.
230 Stamm AM, Diasio RB, Dismukes WE, Shadomy S, Cloud GA, Bowles CA *et al*. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. *Am J Med* 1987; **83**: 236–42.
231 Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* 2014; **69**: 1162–76.
232 Cornely OA, Helfgott D, Langston A, Heinz W, Vehreschild J-J, Vehreschild MJGT *et al*. Pharmacokinetics of different dosing strategies of oral posaconazole in patients with compromised gastrointestinal function and who are at high risk for invasive fungal infection. *Antimicrob Agents Chemother* 2012; **56**: 2652–8.
233 Green MR, Woolery JE. Posaconazole serum level on day 2 predicts steady state posaconazole serum level. *Ther Drug Monit* 2012; **34**: 118–19.
234 Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data

from pediatric studies. *Antimicrob Agents Chemother* 2009; **53**: 935–44.
235 Krishna G, Sansone-Parsons A, Martinho M, Kantesaria B, Pedicone L. Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. *Antimicrob Agents Chemother* 2007; **51**: 812–18.
236 Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH *et al*. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis* 2012; **55**: 1080–7.
237 Jang SH, Colangelo PM, Gobburu JVS. Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. *Clin Pharmacol Ther* 2010; **88**: 115–19.
238 Dolton MJ, Ray JE, Chen SCA, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. *Antimicrob Agents Chemother* 2012; **56**: 5503–10.
239 Tonini J, Thiebaut A, Jourdil JF, Berruyer AS, Bulabois CE, Cahn JY *et al*. Therapeutic drug monitoring of posaconazole in allogeneic hematopoietic stem cell transplantation patients who develop gastrointestinal graft-versus-host disease. *Antimicrob Agents Chemother* 2012; **56**: 5247–52.
240 Bryant AM, Slain D, Cumpston A, Craig M. A post-marketing evaluation of posaconazole plasma concentrations in neutropenic patients with haematological malignancy receiving posaconazole prophylaxis. *Int J Antimicrob Agents* 2011; **37**: 266–9.
241 Cornely OA, Ullmann AJ. Lack of evidence for exposure-response relationship in the use of posaconazole as prophylaxis against invasive fungal infections. *Clin Pharmacol Ther* 2011; **89**: 351–2.
242 Hussaini T, Rüping MJGT, Farowski F, Vehreschild JJ, Cornely OA. Therapeutic drug monitoring of voriconazole and posaconazole. *Pharmacotherapy* 2011; **31**: 214–25.
243 Hamada Y, Seto Y, Yago K, Kuroyama M. Investigation and threshold of optimum blood concentration of voriconazole: a descriptive statistical meta-analysis. *J Infect Chemother* 2012; **18**: 501–7.
244 Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG *et al*. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother* 2006; **50**: 1570–2.
245 Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. *Br J Clin Pharmacol* 2003; **56**(Suppl 1): 10–16.
246 Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clin Pharmacokinet* 2006; **45**: 649–63.
247 Geist MJ, Egerer G, Burhenne J, Mikus G. Safety of voriconazole in a patient with CYP2C9*2/CYP2C9*2 genotype. *Antimicrob Agents Chemother* 2006; **50**: 3227–8.
248 Scholz I, Oberwittler H, Riedel KD, Burhenne J, Weiss J, Haefeli WE *et al*. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. *Br J Clin Pharmacol* 2009; **68**: 906–15.
249 Berge M, Guillemain R, Tregouet DA, Amrein C, Boussaud V, Chevalier P *et al*. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. *Eur J Clin Pharmacol* 2011; **67**: 253–60.
250 Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. *Br J Clin Pharmacol* 2010; **69**: 222–30.
251 Strom CM, Goos D, Crossley B, Zhang K, Buller-Burkle A, Jarvis M *et al*. Testing for variants in CYP2C19: population frequencies and testing experience in a clinical laboratory. *Genet Med* 2012; **14**: 95–100.
252 Myrand SP, Sekiguchi K, Man MZ, Lin X, Tzeng RY, Teng CH *et al*. Pharmacokinetics/genotype associations for major cytochrome P450 enzymes in native and first- and third-generation Japanese populations: comparison with Korean, Chinese, and Caucasian populations. *Clin Pharmacol Ther* 2008; **84**: 347–61.
253 Sugimoto K, Uno T, Yamazaki H, Tateishi T. Limited frequency of the CYP2C19*17 allele and its minor role in a Japanese population. *Br J Clin Pharmacol* 2008; **65**: 437–9.
254 Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L *et al*. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther* 2006; **79**: 103–13.
255 Kim KA, Song WK, Kim KR, Park JY. Assessment of CYP2C19 genetic polymorphisms in a Korean population using a simultaneous multiplex pyrosequencing method to simultaneously detect the CYP2C19*2, CYP2C19*3, and CYP2C19*17 alleles. *J Clin Pharm Ther* 2010; **35**: 697–703.
256 Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. *Clin Pharmacol Ther* 2008; **83**: 322–7.
257 Shimizu T, Ochiai H, Asell F, Shimizu H, Saitoh R, Hama Y *et al*. Bioinformatics research on inter-racial difference in drug metabolism I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19. *Drug Metab Pharmacokinet* 2003; **18**: 48–70.
258 Kaneko A, Lum JK, Yaviong L, Takahashi N, Ishizaki T, Bertilsson L *et al*. High and variable frequencies of CYP2C19 mutations: medical consequences of poor drug metabolism in Vanuatu and other Pacific islands. *Pharmacogenetics* 1999; **9**: 581–90.
259 Xie HG, Kim RB, Wood AJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol* 2001; **41**: 815–50.
260 Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet* 2002; **41**: 913–58.
261 Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L *et al*. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. *Eur J Clin Pharmacol* 2009; **65**: 281–5.
262 Autmizguine J, Krajinovic M, Rousseau J, Theoret Y, Litalien C, Marquis C *et al*. Pharmacogenetics and beyond: variability of voriconazole plasma levels in a patient with primary immunodeficiency. *Pharmacogenomics* 2012; **13**: 1961–5.

263 Aitken AE, Morgan ET. Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. *Drug Metab Dispos* 2007; **35**: 1687–93.
264 Carcillo JA, Doughty L, Kofos D, Frye RF, Kaplan SS, Sasser H *et al*. Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. *Intensive Care Med* 2003; **29**: 980–4.
265 Trifilio S, Singhal S, Williams S, Frankfurt O, Gordon L, Evens A *et al*. Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant* 2007; **40**: 451–6.
266 Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. *Antimicrob Agents Chemother* 2012; **56**: 4793–9.
267 US Food and Drug Administration. Background document for antiviral drug products. Advisory committee meeting. 2001. [cited 2013 Dec 15]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_fda_voriconazole.htm
268 Imhof A, Schaer DJ, Schanz U, Schwarz U. Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring. *Swiss Med Wkly* 2006; **136**: 739–42.
269 Miyakis S, van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. *Clin Microbiol Infect* 2010; **16**: 927–33.
270 Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis* 2010; **50**: 27–36.
271 Ueda K, Nannya Y, Kumano K, Hangaishi A, Takahashi T, Imai Y *et al*. Monitoring trough concentration of voriconazole is important to ensure successful antifungal therapy and to avoid hepatic damage in patients with hematological disorders. *Int J Hematol* 2009; **89**: 592–9.
272 Lee YJ, Lee SO, Choi SH, Kim YS, Woo JH, Chun S *et al*. Initial voriconazole trough blood levels and clinical outcomes of invasive aspergillosis in patients with hematologic malignancies. *Med Mycol* 2013; **51**: 324–30.
273 Racil Z, Winterova J, Kouba M, Zak P, Malaskova L, Buresova L *et al*. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. *Mycoses* 2012; **55**: 483–92.
274 Bruggemann RJ, van der Linden JW, Verweij PE, Burger DM, Warris A. Impact of therapeutic drug monitoring of voriconazole in a pediatric population. *Pediatr Infect Dis J* 2011; **30**: 533–4.
275 Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. *Pharmacotherapy* 2007; **27**: 1627–36.
276 Krishna G, AbuTarif M, Xuan F, Martinho M, Angulo D, Cornely OA. Pharmacokinetics of oral posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. *Pharmacotherapy* 2008; **28**: 1223–32.
277 Vaes M, Hites M, Cotton F, Bourguignon AM, Csergo M, Rasson C *et al*. Therapeutic drug monitoring of posaconazole in patients with acute myeloid leukemia or myelodysplastic syndrome. *Antimicrob Agents Chemother* 2012; **56**: 6298–303.
278 Hoenigl M, Raggam RB, Salzer HJF, Valentin T, Valentin A, Zollner-Schwetz I *et al*. Posaconazole plasma concentrations and invasive mould infections in patients with haematological malignancies. *Int J Antimicrob Agents* 2012; **39**: 510–13.
279 Gross BN, Ihorst G, Jung M, Wäsch R, Engelhardt M. Posaconazole therapeutic drug monitoring in the real-life setting: a single-center experience and review of the literature. *Pharmacotherapy* 2013; **33**: 1117–25.
280 Crombag M-RBS, Huisman C, Kemper EM, Brüggemann RJM, Bijleveld YA. Posaconazole treatment in hematology patients: a pilot study of therapeutic drug monitoring. *Ther Drug Monit* 2012; **34**: 320–5.
281 Neubauer WC, Engelhardt M, Konig A, Hieke S, Jung M, Bertz H *et al*. Therapeutic drug monitoring of posaconazole in hematology patients: experience with a new high-performance liquid chromatography-based method. *Antimicrob Agents Chemother* 2010; **54**: 4029–32.
282 Eiden C, Meniane JC, Peyrière H, Eymard-Duvernay S, Le Falher G, Ceballos P *et al*. Therapeutic drug monitoring of posaconazole in hematology adults under posaconazole prophylaxis: influence of food intake. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 161–7.
283 Lebeaux D, Lanternier F, Elie C, Suarez F, Buzyn A, Viard J-P *et al*. Therapeutic drug monitoring of posaconazole: a monocentric study with 54 adults. *Antimicrob Agents Chemother* 2009; **53**: 5224–9.
284 Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. *J Clin Pharmacol* 2002; **42**: 395–402.
285 Mikus G, Schowel V, Drzewinska M, Rengelshausen J, Ding R, Riedel KD *et al*. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clin Pharmacol Ther* 2006; **80**: 126–35.
286 Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. *Clin Pharmacol Ther* 2004; **75**: 587–8.
287 Hassan A, Burhenne J, Riedel KD, Weiss J, Mikus G, Haefeli WE *et al*. Modulators of very low voriconazole concentrations in routine therapeutic drug monitoring. *Ther Drug Monit* 2011; **33**: 86–93.
288 Dolton MJ, McLachlan AJ. Clinical importance of the CYP2C19*17 variant allele for voriconazole. *Br J Clin Pharmacol* 2011; **71**: 137–8.
289 Geist MJ, Egerer G, Burhenne J, Riedel KD, Weiss J, Mikus G. Steady-state pharmacokinetics and metabolism of voriconazole in patients. *J Antimicrob Chemother* 2013; **68**: 2592–9.
290 Bruggemann RJ, Blijlevens NM, Burger DM, Franke B, Troke PF, Donnelly JP. Pharmacokinetics and safety of 14 days intravenous voriconazole in allogeneic haematopoietic stem cell transplant recipients. *J Antimicrob Chemother* 2010; **65**: 107–13.
291 Driscoll TA, Frangoul H, Nemecek ER, Murphey DK, Yu LC, Blumer J *et al*. Comparison of pharmacokinetics and

safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. *Antimicrob Agents Chemother* 2011; **55**: 5780–9.

292 Narita A, Muramatsu H, Sakaguchi H, Doisaki S, Tanaka M, Hama A *et al*. Correlation of CYP2C19 phenotype with voriconazole plasma concentration in children. *J Pediatr Hematol Oncol* 2013; **35**: e219–23.

293 Moriyama B, Elinoff J, Danner RL, Gea-Banacloche J, Pennick G, Rinaldi MG *et al*. Accelerated metabolism of voriconazole and its partial reversal by cimetidine. *Antimicrob Agents Chemother* 2009; **53**: 1712–14.

294 Lemaitre F, Barbaz M, Scailteux LM, Uhel F, Tadie JM, Verdier MC *et al*. A case-report of unpredictable and massive voriconazole intoxication in a patient with extensive CYP2C19 and CYP2C9 polymorphisms. *Drug Metab Pharmacokinet* 2013; **28**: 439–41.

295 Boyd NK, Zoellner CL, Swancutt MA, Bhavan KP. Utilization of omeprazole to augment subtherapeutic voriconazole concentrations for treatment of Aspergillus infections. *Antimicrob Agents Chemother* 2012; **56**: 6001–2.

296 Trubiano JA, Paratz E, Wolf M, Teh BW, Todaro M, Thursky KA *et al*. Disseminated Scedosporium prolificans infection in an 'extensive metaboliser': navigating the minefield of drug interactions and pharmacogenomics. *Mycoses* 2014.

297 Bourcier K, Hyland R, Kempshall S, Jones R, Maximilien J, Irvine N *et al*. Investigation into UDP-glucuronosyltransferase (UGT) enzyme kinetics of imidazole- and triazole-containing antifungal drugs in human liver microsomes and recombinant UGT enzymes. *Drug Metab Dispos* 2010; **38**: 923–9.

298 Ashbee HR, Gilleece MH. Has the era of individualised medicine arrived for antifungals? A review of antifungal pharmacogenomics. *Bone Marrow Transplant* 2012; **47**: 881–94.

299 Colburn DE, Giles FJ, Oladovich D, Smith JA. In vitro evaluation of cytochrome P450-mediated drug interactions between cytarabine, idarubicin, itraconazole and caspofungin. *Hematology* 2004; **9**: 217–21.

300 Templeton IE, Thummel KE, Kharasch ED, Kunze KL, Hoffer C, Nelson WL *et al*. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. *Clin Pharmacol Ther* 2008; **83**: 77–85.

Appendix I

Drug monitoring in studies of voriconazole prophylaxis and treatment in patients with haematological malignancy

Study	Study design	No. of patients (% haematology patients)	Established target for efficacy†	Established target for toxicity†	Comments
TDM use in voriconazole prophylaxis studies					
Trifilio *et al*.[265]	Retrospective cohort.	71 (100)	>2‡	NR	Allogeneic HSCT patients.
TDM use in voriconazole treatment studies					
Dolton *et al*.[266]	Retrospective cohort	201 (45)	≥1.7	>5	–
FDA briefing document[267]	Retrospective cohort	280 (NR)	NF§	6	Subset of patients from registration trial[165] who had random voriconazole TDM performed
Imhof *et al*.[268]	Retrospective cohort	26 (100)	NR	≥4	Hazard ratio of 2.3 for a neurological adverse event per 1 μg/mL increase in voriconazole concentration
Miyakis *et al*.[269]	Retrospective cohort	25 (20)	>2.2	NR	–
Neely *et al*.[270]	Retrospective cohort	46 (46)	>1	NR	Paediatric study
Ueda *et al*.[271]	Retrospective cohort	34 (100)	>2	≥6	–
Pascual *et al*.[203]	Prospective observational	52 (65)	>1	>5.5	–
Smith *et al*.[244]	Retrospective cohort	28 (29)	>2.05¶	NR	–
Lee *et al*.[272]	Retrospective cohort	52 (100)	NF	NR	Early outcomes of IA not statistically different when initial trough levels (≤2 vs. >2) compared
Racil *et al*.[273]	Retrospective cohort	264 (100)	NF	NF	IA treatment outcomes and adverse effects not related to voriconazole levels
Park *et al*.[236]	Randomised controlled trial (TDM vs. non-TDM)	108 (77)	NF	NF	Voriconazole dose adjustment performed to achieve target trough levels (1–5.5) in TDM group
Bruggemann *et al*.[274]	Retrospective cohort	18 (89)	NF	NF	Paediatric study

†Patients achieving voriconazole concentrations above efficacy targets were statistically more likely to have better outcomes than patients with concentrations below established thresholds. Similarly, patients with voriconazole concentrations above toxicity targets were statistically more likely to have neurological adverse events compared with patient with concentrations below established thresholds. ‡Efficacy target observed only when four cases of zygomycetes were included in analysis ($P = 0.049$). §Efficacy target not determined – when a concentration of 0.5 mg/L was used no difference in outcome was seen in patients below compared with above this level. ¶Efficacy target only established when patients with refractory disease were excluded from the analysis. NR, not recorded; NF, not found.

Appendix II

Drug monitoring in studies of posaconazole prophylaxis and treatment in patients with haematological malignancy

Study	Study design	No. of patients (% haematology patients)	Established target for efficacy†	Established target for toxicity	Comments
TDM use in posaconazole prophylaxis studies					
Krishna *et al*.[275]	Retrospective cohort of PK data from[179]	246 (100)	NR‡	NR	Median plasma concentration in breakthrough IFD cases: 0.61 mg/L (n = 5).
Krishna *et al*.[276]	Retrospective cohort of PK data from Cornely *et al*.[179]	194 (100)	NR‡	NR	Median plasma concentration in breakthrough IFD cases: 0.45 mg/L (n = 6).
Jang *et al*.[237]	Retrospective cohort combination of PK data from Cornely *et al*.[179] and Tonini *et al*.[239]	467 (100)	>0.7¶	NF	–
Dolton *et al*.[238]	Retrospective cohort§	86 (91)	>0.29#	NF	Median plasma concentration in breakthrough IFD cases: 0.29 mg/L (n = 12). Recommended target >0.7 mg/L.
Vaes *et al*.[277]	Prospective cohort	40 (100)	>0.4††	NR	Composite endpoint including those who received empiric antifungal treatment. Median plasma concentration in breakthrough IFD cases: 0.4 mg/L (n = 18).
Hoenigl *et al*.[278]	Prospective cohort§	34 (100)	>0.3‡‡	NR	Median plasma concentration in breakthrough IFD cases: 0.3 mg/L (n = 3).
Tonini *et al*.[239]	Retrospective cohort	29 (100)	>0.99§§	NR	High median plasma concentration; significance of lower concentrations in breakthrough IFD unclear. Median plasma concentration in breakthrough IFD cases: 0.99 mg/L (n = 4).
Gross *et al*.[279]	Prospective cohort§	31 (100)	NF	NR	Median plasma concentration in breakthrough IFD cases: 0.96 mg/L (n = 4).
Crombag *et al*.[280]	Retrospective cohort§	17 (100)	NF	NF	One breakthrough IFD: 0.37 mg/L.
Neubauer *et al*.[281]	Prospective cohort	27 (100)	NF	NF	Median plasma concentration in breakthrough IFD cases: 0.9 mg/L (n = 2).
Bryant *et al*.[240]	Retrospective cohort	21 (100)	NF	NR	Plasma concentrations in breakthrough IFD cases: <0.5 mg/L (n = 3).
Eiden *et al*.[282]	Prospective cohort	63 (100)	NF	NR	Plasma concentrations in breakthrough IFD case: 0.22, 0.11 mg/L (n = 1).
Lebeaux *et al*.[283]	Retrospective cohort§	54 (69)	NF	NR	Plasma concentrations in breakthrough IFD cases: <0.5 mg/L (n = 2).
TDM use in posaconazole treatment studies					
Walsh *et al*.[206]	Prospective cohort with retrospective comparator group	107 (74)	≥0.7–1.25¶¶	NF	Salvage therapy in invasive aspergillosis. PK dataset from 67 patients. Timing of posaconazole plasma concentration not recorded.

†Patients achieving posaconazole plasma concentration above efficacy targets were statistically more likely to have better outcomes than patients with concentrations below established thresholds. ‡While lower average plasma concentrations were reported in those with breakthrough IFD compared with those without in these studies; analyses were not deemed appropriate in a statistical respect, owing to too few breakthrough IFD cases from both cohorts. §Mixed cohort of treatment and prophylaxis patients; majority received posaconazole prophylaxis. ¶Clinical failure rates at average plasma concentration of <0.7 mg/L were >25% ($P < 0.0001$) and >35% ($P = 0.0022$) in two and four study cohorts, respectively. #In patients receiving posaconazole prophylaxis, reported breakthrough IFD cases had significantly lower median plasma concentrations (0.29 mg/L) compared with those without breakthrough IFD (0.49 mg/L). All cases identified as breakthrough IFD had median concentration <0.5 mg/L. ††Eighteen courses switched to an alternative treatment antifungal, either empiric treatment (7/18) or for possible (9/18) or probable IFD (2/18). Median plasma concentration of 0.4 mg/L reported in this group compared with 0.45 mg/L in those without breakthrough IFD ($P = 0.02$). ‡‡In the three breakthrough IFD cases during prophylaxis, a median plasma concentration of 0.3 mg/L was significantly lower than the median plasma concentration of 0.61 mg/L in those who did not. §§Four patients with reported breakthrough IFD had statistically significant lower corresponding plasma concentrations (0.99 mg/L) compared with those without IFD (1.32 mg/L) ($P < 0.05$). ¶¶Average plasma concentration of 1.25 mg/L was associated with a higher response rate (74%) compared with 0.13 mg/L (24%), 0.41 mg/L (53%) and 0.72 mg/L (53%), respectively (statistical significance not reported). AML, acute myeloid leukaemia; IFD, invasive fungal infection; MDS, myelodysplastic syndrome; NF, not found; NR, not recorded; PK, pharmacokinetics.