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Triazole antifungal drug interactions—practical considerations for excellent prescribing

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Systemic antifungal therapy is critical for reducing the mortality from many invasive and chronic fungal infections. Triazole antifungals are the most frequently prescribed antifungals but require attention to dosing and drug interactions. Nearly 600 severe drug–drug interactions and over 1100 moderate interactions requiring dose modifications are described or anticipated with systemic antifungal agents (see https://www.aspergillus.org.uk/antifungal-drug-interactions/). In this article, we address the common and less common, but serious, drug interactions observed in clinical practice with triazole antifungals, including a group of drugs that cannot be prescribed with all or most triazole antifungals (ivabradine, ranolazine, eplerenone, fentanyl, apomorphine, quetiapine, bedaquiline, rifampicin, rifabutin, sirolimus, phenytoin and carbamazepine). We highlight interactions with drugs used in children and new agents introduced for the treatment of haematological malignancies or graft versus host disease (midostaurin, ibrutinib, ruxolitinib and venetoclax). We also summarize the multiple interactions between oral and inhaled corticosteroids and triazole antifungals, and the strategies needed to optimize the therapeutic benefits of triazole antifungal therapy while minimizing potential harm to patients.

Introduction

Drug interactions are a common problem that jeopardize the efficacy and safety of both antifungal therapy and concomitant medications. In an analysis of 6952 patient electronic medical records collected from over 150 hospitals, Andes *et al.*[1] detected drug–drug interactions (DDIs) in 86%–93% of patients receiving mould-active triazoles, with more than one-quarter of the interactions classified as 'contraindicated' combinations. Although many interactions are unlikely to harm the patient, DDIs affecting the metabolism and clearance of narrow therapeutic index drugs or the absorption, metabolism and clearance of antifungals can result in life-threatening complications if not recognized early and managed appropriately. Therefore, an in-depth understanding of how these interactions occur and their potential clinical implications is essential for effective use of systemic antifungal therapy.

The prevalence of antifungal DDIs varies widely according to the antifungal class. Triazole antifungals are associated with the highest number of DDIs owing to their properties as both inhibitors and substrates of Phase 1 [cytochrome P450 (CYPP450) biotransformation] or Phase 2 (conjugation) pathways involved in the metabolism and clearance of common anaesthetics, cardiovascular medication, anticoagulants, anti-infectives, and immunosuppressive and chemotherapy agents (Table 1).[2] Triazoles also act as inhibitors and substrates of many transporter proteins [e.g. P-glycoprotein (P-gP) and organic-anion transporter polypeptides (OATPs)] involved in drug absorption and distribution.[3] The magnitude of the DDIs can be influenced by the interplay of host pharmacogenetics, patient age, comorbidities and concomitant therapies (Figure 1). Therefore, recommendations for managing these interactions, such as those found in the Summary of Product Characteristics (SPC; manufacturer drug package labelling) or printed drug

Table 1. Totality of antifungal interactions present, corresponding to the severity (severe, moderate, mild or unlikely) for the given combination in the Antifungal Interaction Database for 1628 licensed individual drugs with a possible interaction

Severity	Polyenes		Echinocandins			Azoles						
	AmBisome	Ampho B	Anidula	Mica	Caspo	Isavu	Fluco	Posa	Itra	Vori	Otese	Ibrexa	Terbinafine
Severe	22	23	0	0	6	49	57	118	160	173	0	1	1
Moderate	133	133	7	11	46	141	215	212	181	194	1	2	15
Mild	120	122	82	92	92	79	223	189	163	189	0	15	96
Unlikely	1353	1350	1539	1525	1484	1359	1133	1109	1124	1072	1627	1610	1516

Ampho B, amphotericin B; Anidula, anidulafungin; Mica, micafungin; Caspo, caspofungin; Posa, posaconazole; Vori, voriconazole; Fluco, fluconazole; Isavu, isavuconazole; Itra, itraconazole; Otese, oteseconazole; Ibrexa, ibrexafungerp.

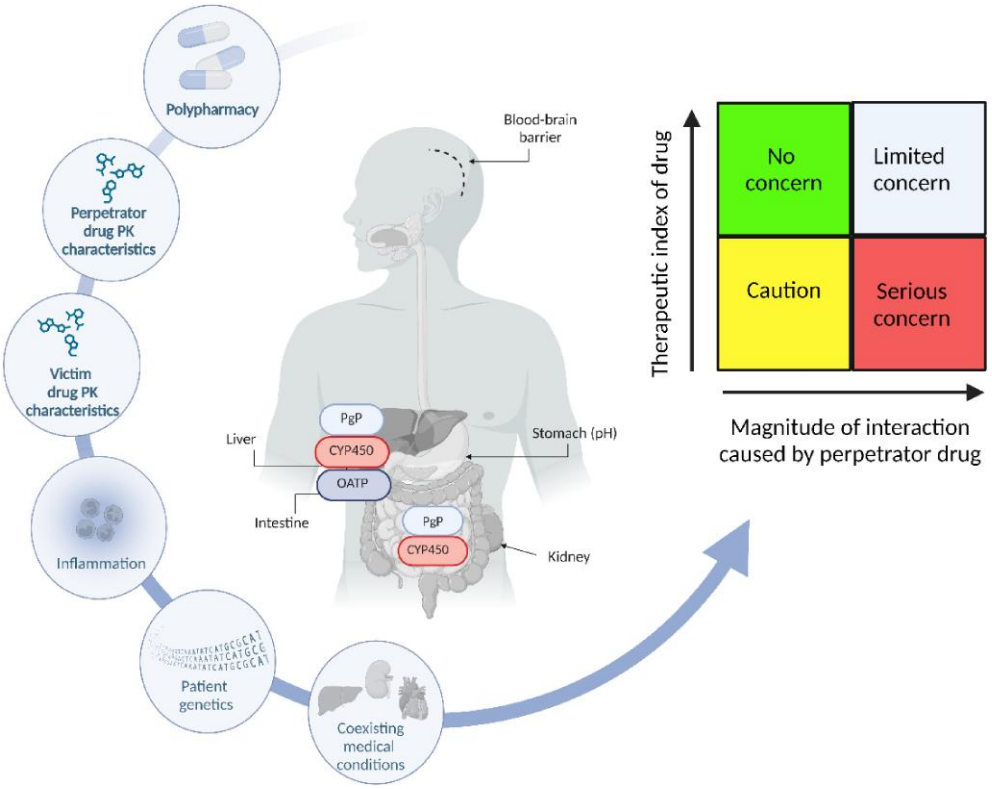

Figure 1. Factors influencing the type and degree of antifungal DDIs. Figure was created using www.biorender.com. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

references, can only be considered as general guidance, as they may not contain the most up-to-date information or predict the severity of pharmacokinetic (PK) interactions encountered in severely ill or frail patients. Indeed, antifungal DDIs often require therapeutic drug monitoring (TDM) for dosing guidance.[4–6]

The duration of drug interactions involving CYP P450 enzymes also varies depending on the type of interaction.[7] If a drug is a competitive inhibitor, the interaction duration is determined chiefly by the half-life of the perpetrating drug, e.g. fluconazole (20–50 h) versus isavuconazole (130 h). On the other hand, drugs that induce CYP P450 enzymes or act as irreversible inhibitors (e.g. voriconazole, posaconazole) alter the enzyme's structure or function. The recovery of metabolic capacity in these cases depends on the turnover of the enzyme, which cannot be directly measured in patients. However, PK studies have used drugs such as midazolam as CYPP450 'enzymatic probes' to estimate the duration of inhibitor interactions. Based on these studies, the recovery time after removing mechanism-based inhibitors typically is reported as 20–50 h, while recovery after removing enzyme inducers takes around 40–60 h. This suggests that more than 90% of CYP P450 recovery can occur within 10 days after stopping mechanism-based inhibitors and within 14 days after stopping inducers. As a general rule, close observation and dose adjustment should be considered during this period after perpetrator drugs are stopped if the victim drug has a narrow therapeutic index.[7]

Triazole antifungal drugs can exhibit competitive, irreversible inhibition or display mixed patterns of competitive and non-competitive inhibition depending on the combination of CYP

Table 2. DDIs to be absolutely avoided as a threat to life, cancer drugs excluded (see other tables for more information)

Drug name	Antifungal	Reason combination not advised
Ivabradine	All triazoles except fluconazole and isavuconazole	Reduced metabolism of ivabradine and increased risk of QT prolongation
Ranolazine	All triazoles except isavuconazole	Reduced clearance of ranolazine, increasing risk of adverse events
Eplerenone	Itraconazole and voriconazole	Significant increase in AUC of eplerenone
Fentanyl	All triazoles except isavuconazole	Increased fentanyl plasma concentrations, causing potential serious respiratory depression
Apomorphine	Fluconazole	Increased risk of QT prolongation
Quetiapine	All triazoles	Increased risk of QT prolongation
Bedaquiline	All triazoles	Bedaquiline exposure increased, leading to increased risk of adverse effects, e.g. deranged LFTs and QT prolongation
Rifampicin	All triazoles	Accelerated metabolism of azole, high-dose posaconazole and fluconazole may compensate
Rifabutin	All triazoles	Accelerated metabolism of azole and dual toxicity risk
Sirolimus	All triazoles except isavuconazole	Excessive levels of sirolimus; TDM is recommended when given concomitant with triazoles
Phenytoin	All triazoles	Accelerated metabolism of azole
Carbamazepine	All triazoles except fluconazole	Accelerated metabolism of azole

Triazoles refers to fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole and not the tetraconazole oteseconazole. LFT, liver function test.

enzymes or transporters involved in the interaction. More detailed information on the metabolic pathways for specific drugs can be found at the Interactome of Drug Metabolizing Enzyme (INTEDE 2.0) (http://intede.idrblab.net) or PHARMGKB database (https://www.pharmgkb.org/).

With the continuous development of new therapeutics, online drug-interaction databases have become essential tools for screening patients' medication profiles. Both subscription and free-of-cost databases, such as the *Aspergillus Website Drug Interaction Database* (https://www.antifungalinteractions.org/), assess the possible severity of the interaction, link primary literature references, and provide general dosing or management recommendations.[2] These databases can be used to screen patient medication administration records whenever new medications are started or stopped. However, flagged DDIs and recommendations may still require expert interpretation specific to the patient population and clinical situation before doses are adjusted or alternative therapies are considered.

In this review, we examined the most prevalent antifungal DDIs encountered in distinct patient populations at risk of invasive fungal diseases, taking into consideration the specific clinical factors that contribute to the incidence of interactions. The interactions selected for discussion were based on expert input and discussions of the authors. We also examined the similarities and differences in DDI management for each risk group to identify strategies to reduce adverse events and improve the effectiveness of antifungal treatment. For decision-making in individual patients, the reader is advised to always consult the SPC, trusted drug-interactions databases, and local experts with experience in managing DDIs.[2]

Methods

The primary source for most of the information presented is publicly available on the Aspergillus website (https://www.aspergillus.org.uk/antifungal-drug-interactions/) as the *Antifungal Interactions Database*. Updates to this database are undertaken weekly by horizon scanning, ensuring that all new drugs are added once they are licensed in the UK, the EU or the USA. The SPC (from wherever the licence has been granted) was used as the initial source to add any interaction data for any new drug. In addition, published literature was searched weekly to add any additional information to the database. These papers were collated as sources for the database. Stockley's Interaction Checker was used to ensure that the database was complete and up to date. As Stockley's operates under a subscription model unavailable to non-subscribers, this source is not used as a direct reference.

The decision regarding which severity category to list for each interaction depends on the nature and magnitude of the interaction, and was classified as *severe*, *moderate*, *mild* or *unlikely*. Each category only relates to a two-way interaction and does not consider multiple drug interactions. Some interactions require only additional monitoring, some require dose adjustment, and some may need to avoid drug combination altogether. This clinical advice is reflected in the entry of each drug combination when an interaction is either documented or suspected.

Totality of antifungal drug interactions to May 2023

A summary of all the reported interactions affecting systemic antifungals, except for griseofulvin, is presented in Table 1. In terms of the frequency of severe interactions, voriconazole and itraconazole were the most prevalent, with the lowest number of interactions caused by echinocandins and terbinafine (Table 1). The tetrazole oteseconazole has only been licenced in the USA for the management of recurrent vulvovaginal candidiasis but does not bind to human cytochrome enzymes, resulting in very few documented and predicted interactions, extremely slow metabolism, and a half-life of over 130 days. Hence, information presented in subsequent sections does not pertain to oteseconazole.

Several drugs cannot be safely administered with antifungal azoles, as shown in Table 2. In most cases, the reason for not using the combination is the much higher likelihood of severe or fatal adverse reactions, and in some cases, because the other drug completely negates any antifungal activity.

Table 3. Key triazole drug interactions in paediatrics

Therapeutic area	Antifungal	Concomitant drugs, interactions and effects
Antimicrobial agents	All triazoles	Erythromycin, clarithromycin: ↓ metabolism, ↑ exposure, ↑ drug effects Isoniazid, rifampicin, rifabutin:[a] complex metabolic interactions
Anticancer agents	All triazoles	Vinca-alkaloids:[a] ↓ metabolism/efflux, ↑ neurotoxicity; various anticancer agents, tyrosine and protein kinase inhibitors:[b] ↓ metabolism/efflux, ↑ exposure/↑ toxicity
Systemic steroids	All triazoles	All steroids: ↓ metabolism, ↑ exposure, ↑ drug effects
Inhaled steroids	Itraconazole	Inhaled steroids: ↓systemic metabolism, ↑systemic exposure, ↑ drug effects
Bronchodilators	Fluconazole	Theophylline: ↓metabolism, ↑exposure, ↑ drug effects
Immunosuppressants	All triazoles	Calcineurin/mTOR inhibitors:[b] ↓ metabolism/efflux, ↑exposure, ↑ drug effects
Sedatives	All triazoles	Benzodiazepines: ↓ metabolism, ↑ exposure, ↑ drug effects
Opioids	All triazoles	All opioids: ↓ metabolism, ↑ exposure, ↑ drug effects
Analgesics	Voriconazole	Ibuprofen: ↓ metabolism, ↑exposure, ↑ drug effects
Antiemetics	All triazoles	Ondansetron: ↓ metabolism, ↑exposure, ↑ QTc
Antacids	Fluconazole and voriconazole	PPIs: ↓ metabolism, ↑exposure, ↑ drug effects
Anticonvulsants	All triazoles	Phenobarbital, phenytoin, carbamazepine:[a] complex metabolic interactions
Cardiac agents	All triazoles	Ca channel blockers, digoxin: ↓metabolism, ↑exposure, ↑ drug effects Fluconazole and sildenafil: ↓metabolism, ↑exposure, ↑ drug effects

[a]Avoid combination.
[b]Use combination with care or seek expert advice.

Special DDI considerations in children

Similar to adults, triazole antifungals are an important component of the paediatric antifungal armamentarium. While all agents are utilized for the prevention and/or treatment of invasive fungal diseases in infants, children and adolescents, their approval status for indications in paediatric patient populations varies. None of the mould-active antifungal triazoles have been approved for critically ill neonates and are rarely used in practice.[8,9] DDIs with triazole antifungals that are of concern in children are shown in Table 3. Otherwise, the discussion of problematic DDIs can be assumed to be a similar concern for children and adults. Notably, because of the inherently greater PK variability of antifungals in paediatric patients, TDM is routinely recommended for all mould-active triazoles. Liposomal amphotericin B and echinocandins are alternatives for prevention and prophylaxis if triazoles cannot be administered.[2]

Interactions with anti-infective agents

β-Lactams

Flucloxacillin, a penicillin β-lactam antibiotic, is used to treat infections caused by susceptible Gram-positive organisms, such as *Staphylococcus aureus*. Flucloxacillin activates the pregnane X receptor (PXR), which can induce the expression of CYP450 and UGT enzymes, and P-gP transporters.[10] Flucloxacillin markedly decreases the plasma exposure of voriconazole and, to lesser degree, posaconazole.[10] Case reports of patients who required treatment for bacteraemia and fungaemia where flucloxacillin and voriconazole were given concomitantly have reported subtherapeutic voriconazole exposures. We recommend close surveillance with TDM when both drugs are used together, and to consider a pre-emptive dose increase of voriconazole. Moreover, caution is warranted when combining flucloxacillin with isavuconazole, as this interaction might occur with all triazoles. Interactions with fluconazole, which undergoes less extensive CYP450-mediated metabolism, are less likely than those with voriconazole.

Antiviral therapy

Similar observations of subtherapeutic triazole exposures have been reported for letermovir, a new antiviral agent that is increasingly used to prevent cytomegalovirus (CMV) infection.[11] Subtherapeutic voriconazole levels are likely, with fewer effects expected with itraconazole and isavuconazole. Letermovir does not induce the clearance of posaconazole.

Invasive fungal infections (IFIs) are common in patients with HIV infection, especially those with AIDS.[12] Efavirenz and tenofovir disoproxil fumarate are used as first-line HIV medications. Studies have shown that the administration of efavirenz when given with voriconazole significantly reduces the levels of voriconazole, which can lead to treatment failure (Table 4).[13–15] This interaction is attributed to efavirenz inducing the activity of CYP3A4 enzymes, while voriconazole inhibits CYP3A4. This combination is contraindicated; however, if necessary, the dose of voriconazole should be increased while reducing the dose of efavirenz.[16] Only minor interactions are anticipated with the new antiretroviral agent lenacapavir, which does not necessitate dosing adjustment.

The combination of voriconazole and antihepaciviral products (ombitasvir, paritaprevir and ritonavir) may decrease serum concentrations of voriconazole.[16] This interaction is severe, and concomitant use should generally be avoided, unless the patient-specific benefit/risk ratio is justifiable. Close monitoring and consideration of alternative treatment options is necessary.

Ritonavir is a potent irreversible inhibitor of CYP3A4/5 and is routinely used to block the metabolism of partner drugs that otherwise would be extensively metabolized through CYP3A4/5.[17] While some studies have reported near-complete recovery of CYP3A4 metabolic activity after 3 days of stopping ritonavir, other studies have reported more prolonged suppression after drug washout.[18]

Ritonavir has been used in combination with nirmatrelvir to treat mild COVID-19. There are inconsistent data and reports regarding DDIs, with some suggesting a decrease in the serum concentration of voriconazole, whereas other reports indicate an increase in voriconazole serum exposures. The prescribing information for voriconazole advises against the concomitant use of high-dose ritonavir and voriconazole, and caution is recommended when using lower doses of ritonavir with voriconazole (Table 4).[16] However, the emergency-use authorization fact sheet for nirmatrelvir/ritonavir suggests avoiding coadministration with voriconazole,[19] even though NIH COVID-19 treatment guidelines permit using the combination with close monitoring.[20]

Table 4. Interactions of triazole antifungal drugs with anti-infective agents

Interacting drug	Potential severity of interaction					Antifungal modification	Interacting drug modification
	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole		
Efavirenz	+	+++	+++	++	+++	Consider less interacting azole Increase the dose of voriconazole to 400 mg every 12 h	Reduce efavirenz to 300 mg daily
Ritonavir	–	++	+++	++	+++	Consider amphotericin if applicable	Can use in combination with nirmatrelvir Use other anti-HCV medications
Rifampin	++	+++	+++	++	+++	Consider amphotericin B if applicable High-dose posaconazole (600–800 mg daily) may be sufficient	
Praziquantel	++	++	++	++	++	Consider amphotericin B if applicable	Consider albendazole if applicable
Artemether/lumefantrine	+	++	++	++	–	Favours isavuconazole	
Bedaquiline	+++	+++	+++	+++	+++	Avoid for more than a few days	

+++ strong severity; ++ moderate severity; + mild severity; – no interaction identified.

Antimycobacterial therapy

Coinfections with fungi and TB or non-tuberculous mycobacteria can occur in patients with airway anomalies or immunosuppression.[21] Managing both conditions can be challenging owing to the potential DDIs. Rifampicin and rifabutin are contraindicated in patients taking voriconazole and itraconazole because rifampicin significantly reduces the levels of both triazoles (Table 4).[22,23] Increasing the dose of either triazole does not adequately restore appropriate serum concentrations, leading to an increased risk of treatment failure.[24] The induction of accelerated triazole metabolism takes approximately 3 weeks to abate after stopping rifampicin. In contrast, higher doses of posaconazole (i.e. 600–800 mg daily) have been used successfully with rifampicin, with TDM to ensure adequate posaconazole concentrations.[25] Coadministration of voriconazole with ethambutol has been reported to increase the risk of ethambutol-associated optic neuropathy.[26] Alternative agents or transitioning to a less potent CYP3A4 inhibitor antifungal, such as isavuconazole, are possible alternative strategies. For the treatment of non-tuberculous mycobacterial infections, first-line oral drugs such as clarithromycin, quinolones and clofazimine are recommended. However, concomitant use of these drugs with voriconazole can potentially lead to DDIs, highlighting the need for close monitoring.[27] Azithromycin, which does not inhibit CYP3A4, may be alternatively used for some non-tuberculous mycobacterial infections instead of clarithromycin.[28] DDIs with rifampicin are also likely when IFI coexists with other infections where rifampicin is needed, such as brucellosis, prosthetic joint and valve infections.

Bedaquiline, a diarylquinoline agent used in the treatment of TB, is a CYP3A4 substrate that can cause a dose-dependent prolongation of the QT interval.[29] While no studies assessing the combined QT-prolonging effect of both bedaquiline and azoles have been conducted except with ketoconazole, both classes of medications are associated with QT prolongation risk.[30] Therefore, it is advised to avoid this combination, especially when used with azoles that are strong CYP3A4 inhibitors and in patients with underlying QT prolongation risk factors.[30] If the benefit outweighs the risk, regular QTc monitoring is advised, with the therapy duration not exceeding 14 days.[31] Posaconazole, should be avoided during bedaquiline therapy. While the QT-prolonging effects of posaconazole alone are not substantially greater than other triazoles,[32] a case report documented a patient with multiple Torsade de Pointes episodes, which was partially attributed to posaconazole therapy.[33]

Isavuconazole is a moderate CYP3A4 inhibitor that shortens the QT interval. Given its efficacy in the treatment of invasive aspergillosis, exploring the safety of isavuconazole in patients who require bedaquiline for the treatment of MDR-TB is promising.[34]

Antiparasitic therapy

DDIs have also been observed between azoles and other antiparasitic agents; however, clinical data on these interactions are limited. Studies have shown that ketoconazole administration can increase the levels of praziquantel (Table 4).[35] Similarly, the interactions between azoles and antimalarials have been described in PK studies. The coadministration of ketoconazole and artemether/lumefantrine resulted in increased levels of antimalarials (Table 4).[36,37] Close monitoring for QTc prolongation is crucial. Isavuconazole, a moderate CYP3A4 inhibitor, has a comparatively low risk of toxicity and may be a safer option. Similarly, for prophylaxis, atovaquone/proguanil, mefloquine and chloroquine, when given with strong CYP3A4 inhibitors, have an increased risk of toxicity.[38–40] In these cases, it may be more appropriate to consider prophylaxis with doxycycline or tafenoquine or switch to isavuconazole to minimize potential adverse effects.

Table 5. Key triazole antifungal/respiratory drug interactions

	Potential severity of interaction						
Interacting drug	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Antifungal modification	Interacting drug modification
Prednisolone/ prednisone	+	+	++	+	–	None	Reduce prednisolone/ prednisone dose by 30% with voriconazole
Methylprednisolone	++	++	++	++	++	None	Reduce methylprednisolone dose by 50%–60%
Dexamethasone	++	++	++	++	++	None	Reduce dexamethasone dose by 50%–60%, or observe for adverse corticosteroid adverse effects
Fluticasone	++	++	++	+	–	None	Reduce fluticasone dose by 50%, as exposure increased
Budesonide (inhaled)	+	++	++	++	++	None	Reduce budesonide dose by 50%, as exposure increased
Mometasone	+	+	+	+	–	None	Caution advised with longer term dual usage
Ivacaftor	++	+++	+++	+++	++	None	Use ivacaftor, one tablet twice a week, except with fluconazole and isavuconazole when once a day
Elexacaftor	++	+++	+++	+++	++	None	Use elexacaftor 2 tablets once daily twice weekly, except isavuconazole and fluconazole using two tablets alternating with one tablet daily
Tezacaftor/ivacaftor	++	+++	+++	+++	++	None	Use tezacaftor/ivacaftor single tablet every 3–4 days, except fluconazole and isavuconazole when ivacaftor single tablet taken daily and a tezacaftor every alternate day

+++ strong severity; ++ moderate severity; + mild severity; – no interaction identified.

Interactions with corticosteroids and therapies used for respiratory medicine

The use of inhaled corticosteroids (ICSs) with or without a long-acting β agonist (LABA) combination (ICS/LABA) for both asthma and COPD underpins the current recommended treatment approach within national and international guidelines.[41,42] Physicians rarely consider these ubiquitous inhaled medications as victims or perpetrators of systemic drug interactions. All oral triazoles, except possibly isavuconazole and the tetrazole oteseconazole, increased the blood levels of the LABA salmeterol following oral inhalation, owing to CYP3A4 inhibition (Table 5).[43] Combined azole/salmeterol therapy can increase the risk of irregular heart rhythm in susceptible populations via QT prolongation.[44] Although there are fewer significant triazole interactions with formoterol and arformoterol, caution is still warranted with these combinations.

Many DDIs between triazoles and inhaled or systemic corticosteroids have been reported. Allergic bronchopulmonary aspergillosis (ABPA) may require long-term therapy with oral prednisone and antifungals, as well as continued maintenance of inhaled steroids and β-2 agonist regimens. However, the coadministration of triazoles with ICSs in patients with asthma or COPD increases the risk of excess steroid exposure.

Both itraconazole and voriconazole significantly increased the systemic absorption of fluticasone into the bloodstream (Table 5).[44,45] Gilchrist *et al.*[46] examined the risk of adrenal axis suppression in patients with cystic fibrosis (CF) undergoing concomitant itraconazole and inhaled fluticasone treatment. Adrenal insufficiency was analysed using the synthetic adrenocorticotropic hormone (ACTH) (synacthen) test in matched cohorts of 12 patients with CF receiving inhaled fluticasone alone with or without itraconazole. Serum concentrations of itraconazole were documented as therapeutic in both the cohorts. All 12 patients who received itraconazole with inhaled fluticasone exhibited abnormal synacthen test results, and 10/12 (83%) showed hypothalamic–pituitary axis (HPA) axis suppression. HPA suppression was severe in two patients, with a peak cortisol level of <75 nmol/L, and three additional patients had moderately severe suppression, with a peak cortisol

level of <250 nmol/L. In contrast, only 2/12 receiving fluticasone alone showed HPA suppression (both mild). The median (range) basal cortisol levels were significantly lower in patients who received itraconazole and inhaled fluticasone. Neither itraconazole nor fluticasone dose correlated with the degree of adrenal suppression. A similar, but less marked, interaction was expected with budesonide and beclomethasone. As ciclesonide has a very low potential to produce systemic adverse effects, any interaction risk with itraconazole, voriconazole and posaconazole is not expected to be clinically significant, but could boost local airway steroid concentrations.

Concomitant triazole therapy also increased the exposure to both methylprednisolone and dexamethasone, resulting in the suppression of endogenous cortisol secretion (Table 5). The PK interaction between methylprednisolone, steroids and itraconazole is likely related to the inhibition of hepatic CYP3A4 activity by itraconazole.[47,48] Voriconazole demonstrates moderate inhibition of prednisolone metabolism, resulting in a ∼30% increase in the AUC. Consequently, reduction of oral prednisolone dose by 30% is recommended.[49] There is little change to the AUC of prednisolone when administered with isavuconazole, indicating the absence of a clinically relevant interaction between these two agents.[50]

TDM has been necessary to ensure the safety and efficacy of itraconazole, voriconazole and posaconazole in patients with chronic pulmonary fungal diseases.[51,52] However, routine TDM may be less important for isavuconazole, which exhibits more a predictable PK profile versus voriconazole and posaconazole and a lower propensity for severe drug interactions.[53] However, some intra- and inter-patient variability has been reported, especially in critically ill patients.[54,55]

Patients with CF are often receiving novel CF transmembrane conductance regulator (CFTR) therapies (e.g. elexacaftor/tezacaftor/ivacaftor), which are metabolized by the CYP P450 (CYP) pathway. Dosing modifications are recommended for patients started on potent CYP3A4 inhibitors during elexacaftor/tezacaftor/ivacaftor treatment owing to potential 7-fold increase in drug exposures when administered with potent CYP3A4 inhibitors (Table 5).[56,57] In general, evening doses are suspended, using CFTR to reduce the risk of excessive drug exposure. Next-generation CFTR modulator therapies under development are expected to provide increased activity with reduced DDI risk.[57]

Drug interactions in intensive care, anaesthesia and cardiology

DDIs are of particular concern in ICUs. Patients admitted to the ICU are at increased risk of DDIs owing to the complexity of pharmacotherapy, the large number of medications, disease severity and organ failure. Administration of antifungals for therapeutic and prophylactic purposes is virtually constant in patients admitted to the ICU for several reasons. Triazoles are frequently used to prevent or treat *Aspergillus* or Mucorales spp. infections. High-consequence interactions in intensive care include antistaphylococcal penicillins (discussed previously), sedation and cardiovascular drugs.[58,59]

Midazolam is used for sedation in ICU patients, and it is extensively metabolized by CYP3A4 enzymes (Table 3). The psychomotor effects of oral midazolam were profoundly increased by coadministration with voriconazole. However, voriconazole only weakly affected the clearance of small IV doses of midazolam. If midazolam cannot be avoided, the midazolam dose can be reduced by 75% and the frequency can be reduced if necessary. If a single IV or oral dose is administered, clinicians should expect risk for prolonged sedation. In addition, itraconazole and posaconazole are likely to increase the concentration of sublingual midazolam; therefore, concomitant IV use of triazoles should be avoided. Isavuconazole and fluconazole are less likely to be associated with midazolam interactions.[60] Diazepam has only a weak interaction (∼15%) with voriconazole and itraconazole. Although not extensively studied, voriconazole likely increases the plasma concentrations of other benzodiazepines metabolized by CYP3A4, leading to a prolonged sedative effect. No significant interactions have been reported with concomitant propofol, etomidate, ketamine or suxamethonium.

There were no significant interactions between the triazoles and diamorphine or tramadol. Profound and potentially life-threatening DDIs of all triazoles are predictable with fentanyl and alfentanil; although the interaction is less marked with isavuconazole. However, significant prolongation of the effect was observed with methadone and all triazoles. Moderate interactions with prolonged sedation were observed with buprenorphine and oxycodone (mild interactions with posaconazole and both drugs).

Of note, voriconazole may inhibit the metabolization of ibuprofen by CYP2C9, and dose reductions of ibuprofen are recommended (Table 3).[61]

H2-receptor antagonists and proton-pump inhibitors (PPIs) are substrates and/or inhibitors of several CYP enzymes, which predict interactions with triazoles.[62] Although no effects of cimetidine and ranitidine on voriconazole exposure have been reported,[63] coadministration of fluconazole and voriconazole led to detectable increases in the exposure to omeprazole (Table 3).[64,65] Similar observations have been made for pantoprazole, lansoprazole and rabeprazole.[66] These drugs have been used in the past as CYP2C19 inhibitors to boost voriconazole serum concentrations. The antiemetic 5-HT3-receptor antagonist ondansetron is metabolized by several CYP enzymes,[62] and triazole coadministration is expected to lead to increased exposure and amplification of its effects,[67] including dual effects on prolongation of the QT interval, except for isavuconazole, which shortens the QT interval.[68,69]

There are numerous interactions between triazoles and agents used to treat cardiac diseases (Table 6). Triazoles may increase the plasma concentration of calcium channel blockers metabolized by CYP3A4 (verapamil, diltiazem, nifedipine, nicardipine and felodipine). Frequent monitoring of adverse reactions is recommended, and a dose reduction of calcium channel blockers may be required. Itraconazole increases digoxin concentrations; plasma concentrations should be checked.[70–72] Amiodarone alters the pharmacokinetics and, in some cases, the pharmacodynamics of several clinically important drugs. Amiodarone is also CYP3A4 substrate; coadministration of triazoles will increase serum concentrations of amiodarone and associated risk of QT prolongation. There is only one isolated report of cardiac arrest in a patient being treated in an ICU for an ischaemic stroke associated with atrial fibrillation, who received IV itraconazole while on IV amiodarone.[73] Nontheless, amiodarone is used in treatment of ventricular arrhythmia and uniformly delays repolarization in all layers of the myocardial wall, which theoretically reduces transmural heterogeneity and the risk of reentrant arrhythmias.[74] However, in an analysis of FDA adverse event reporting system (FAERS) data, amiodarone was one of the two drugs most commonly associated with drug-induced Torsades de Pointes likely reflecting its use in high-risk populations.[75] Concurrent use of amiodarone with potent CYP3A4 inhibitors or fluconazole should be avoided if possible, while use of isavuconazole should be undertaken carefully with frequent ECG monitoring and possible dose reduction of amiodarone. Although amphotericin B is sometimes substituted for triazoles because of QT prolongation concerns, electrolyte disturbances associated with amphotericin B therapy may also increase risk of arrhythmias. Symptoms include dizziness, lightheadedness, palpitations, irregular heartbeat, shortness of breath or fainting.[76,77] Potassium and magnesium levels should be monitored and corrected.

Sildenafil is metabolized by CYP3A isoenzymes and used to treat pulmonary hypertension. When given to infants in combination with fluconazole at treatment doses (12 mg/kg/day), dose reductions by 60% are suggested by physiologically based PK models (Table 6).[78] In adult males on long-term triazole therapy, single doses of sildenafil, tadalafil, vardenafil or avanafil for erectile dysfunction are likely to result in prolonged action (priapism), with less impact predicted for fluconazole and isavuconazole clearance.[78]

Table 6. Key triazole antifungal and cardiac/anticoagulant drug interactions

Interacting drug	Potential severity of interaction					Antifungal modification	Interacting drug modification
	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole		
Digoxin	–	+++	+	–	++	Avoid itraconazole, if possible	Monitor digoxin levels on isavuconazole, or reduce dose by 30%
Ivabradine	++	+++	+++	+++	++	Avoid combination all, except fluconazole and isavuconazole	Starting dose of 2.5 mg BD and if resting heart rate is >70 bpm, with monitoring of heart rate
Verapamil	+	++	++	++	++	Avoid, if possible, for different reasons	Use alternative, if possible; if used, monitor for side effects.
Sotalol	++	–	++	++	–	Caution with fluconazole, voriconazole and posaconazole	Risk of QT prolongation
Flecainide	+	–	+	+	–	Triazoles can modestly increase exposure	ECG monitoring recommended
Propafenone	+	+	+	+	++	Triazoles can modestly increase exposure	ECG monitoring recommend
Ranolazine	+++	+++	+++	+++	++	Avoid combination	Avoid combination
Amiodarone	++	++	+	+	–	Caution with fluconazole and itraconazole	None
Calcium channel blockers	+	++	++	++	++	No alteration	Consider alternatives; if used, monitor BP and for fluid retention
Atorvastatin and simvastatin	++	+++	+++	+++	++	Switch to rosuvastatin, pravastatin or fluvastatin	Reduce dose to 25%–30%
Eplerenone	++	+++	+++	++	++	Avoid itraconazole and voriconazole	Maximum dose of 25 mg, less if possible with isavuconazole and posaconazole
Bosentan	+++	++	++	+++	+++	Avoid isavuconazole (low levels); fluconazole and voriconazole (bosentan toxicity)	Monitor LFTs on bosentan, possibly avoid dose escalation with posaconazole and itraconazole
Macitentan	++	++	++	++	–	Consider isavuconazole	Monitor LFTs
Ticagrelor	+	+++	+++	++	–	Avoid itraconazole and voriconazole, consider isavuconazole	Carefully monitor for side effects
Sildenafil	+++	+++	+++	+++	++	Avoid combination or consider isavuconazole	Reduce sildenafil dose to once daily
Warfarin	+++	++++	++++	+++	+++	All triazoles will increase the anticoagulant effects of warfarin	Monitor for increased anticoagulant effects (e.g. INR, bleeding) and decrease anticoagulant if antifungal is discontinued

Continued

Table 6. *Continued*

Interacting drug	Potential severity of interaction					Antifungal modification	Interacting drug modification
	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole		
Edoxaban	++	++	+	++	+		Monitor for signs of bleeding or anaemia and/or thrombosis and coagulation tests advised by manufacturer
Rivaroxaban	++	+++	+++	+++	+		
Apixaban	++	+++	+++	+++	+		
Dabigatran	++	+++	+	++	++		

+++ strong severity; ++ moderate severity; + mild severity; – no interaction identified. INR, international normalized ratio; bpm, beats per minute; BP, blood pressure; LFT, liver function test.

Drug interactions with immunosuppressive therapies used in transplantation

TDM is recommended to ensure the safety and efficacy of itraconazole, voriconazole and posaconazole in transplant populations.[51,52] There is less of a consensus on the need for routine TDM for isavuconazole, which exhibits a more predictable PK profile versus voriconazole and posaconazole and a lower propensity for severe drug interactions.[53] However, some intra- and inter-patient variability has been reported, especially in critically ill patients.[54,55] Generally, serum trough concentrations of triazoles should monitored between 5–7 days after initiation of therapy, especially for itraconazole and voriconazole.

All triazoles strongly inhibit the metabolism of calcineurin inhibitors (tacrolimus and ciclosporine) and the mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, by inhibiting CYP450 3A4 and P-gP, although at different potency.[49] Because of the magnitude of this interaction, the concomitant use of sirolimus and posaconazole or voriconazole is contraindicated in the manufacturer's labelling.[61,79] Kubiak *et al*.[80] reported that combinations of sirolimus and posaconazole were well tolerated, with an initial 30%–50% sirolimus dose reduction and close monitoring of sirolimus trough levels. Reduction in tacrolimus dose and TDM is essential for monitoring and accurate dose adjustment of immunosuppressive therapies in patients receiving antifungal triazoles, particularly when triazoles are newly started, the dose is adjusted or discontinued.[81,82] The recommendations for initial empirical dosage adjustment of immunosuppressants when used as combination with triazoles are shown in Table 7. Increased doses of immunosuppressants are also necessary when triazoles are stopped, but at variable intervals after stopping, depending on the tissue half-life of the triazole and mechanism of the interaction. Checking of serial calcineurin levels up to 3 weeks is recommended.

In contrast, only minor (<50%) increases in exposure have been reported with concomitant use of mycophenolate mofetil and triazoles.[16,49,84] Interestingly, several-fold increased systemic steroid exposure after concomitant use of voriconazole with non-absorbable oral steroids has been reported in the context of topical treatment of intestinal graft-versus-host disease (GVHD).[85]

Triazole antifungals are frequently used for prophylaxis or treatment of invasive fungal disease in solid organ transplants. Lung transplant recipients, in particular, are at risk for *Aspergillus* infection because of direct graft exposure of environmental fungi and moulds, decreased cough reflex, airway ischaemia and higher immunosuppression levels compared with other solid organ transplants.[86] Triazole DDIs with calcineurin inhibitors are similar to those encountered in other transplant populations. Alternative prophylaxis or treatment approaches (i.e. inhaled liposomal amphotericin B, IV echinocandins) have not been shown as monotherapy to provide the same protection as triazoles. The availability of non-interacting triazoles or novel antifungals without CYP3A4 interactions may improve the safety and efficacy of antifungal prophylaxis and treatment in this highly vulnerable population.

Anticonvulsants

Phenobarbital, phenytoin and carbamazepine are classical enzyme inducers, and all triazoles may inhibit their metabolism through inhibition of CYP P450, so that their combination should be avoided (Tables 2 and 3).[62,87] Fortunately, the impact of these interactions has become less prominent following the advent of levetiracetam, a well-tolerated anticonvulsant that is virtually free of interactions.[83]

Oncological chemotherapy and antiemetics

Aprepitant, an antiemetic and neurokinin-1 receptor antagonist, is a substrate and inhibitor of CYP3A4, 1A2 and 2C19, and all triazoles may increase the AUC of aprepitant. However, the clinical significance of this increase is unclear as the drug is well tolerated over a wide dosage range, but liver function tests should be monitored.[62]

Triazoles are among the most common drugs involved in clinically relevant DDIs in paediatric and adult cancer patients.[88] All triazoles may lead to decreased CYP-mediated metabolism and decreased P-gP-mediated efflux of vinca alkaloids (vincristine, vinblastine, vinorelbine and vindesine), resulting in potentially life-threatening increases in their neurotoxicity.[62,89] Therefore, coadministration of triazoles during vinca alkaloid-based chemotherapy regimens should be avoided whenever possible. Triazoles may affect the pharmacokinetics of cyclophosphamide through differential inhibition of hepatic CYP isoenzymes, leading to decreased conversion into the active metabolite but also increased toxicity.[62,90,91] Further interactions between azoles and ifosfamide, methotrexate, busulfan, anthracyclines, epipodophyllotoxins, irinotecan, taxanes and tyrosine- and protein-kinase inhibitors can be expected from the inhibitory effects of azoles on P-gP and several CYP isoenzymes, and the use of triazoles during times of administration of these and other agents should be avoided.[62,92] Of note, this does not exclude their use in drug-free periods if chemotherapy is administered in cycles.

Newer targeted therapies used for haematological malignancies

Progress in deciphering the molecular pathogenesis of acute and chronic leukaemia has enabled the development of precision medicine approaches. New targeted drugs, either administered as single agents or in combination with conventional chemotherapy or with drugs targeting epigenetic or other oncogenic signalling pathways, have greatly improved the outcomes of patients with AML and ALL (Table 8).[93–95]

However, most targeted agents introduced for the treatment of AML and ALL are small-molecule kinase inhibitors with a narrow therapeutic index that undergo extensive metabolism through CYP3A4.[98] As many of the patients receiving these targeted therapies requiring prophylaxis or

Table 7. Significant drug interactions of azoles with immunosuppressants used in transplantation

Interacting drug	Potential severity of interaction					Antifungal modification	Interacting drug modification
	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole		
Ciclosporin	+++	+++	++	+++	+	None	Reduce dose by 50%–66% for voriconazole and itraconazole, 25% for posaconazole, no dosage adjustment may be required for isavuconazole. Close monitoring of ciclosporin exposure is recommended
Tacrolimus	+++	+++	+++	+++	++	Preferably avoid fluconazole and itraconazole	With posaconazole and voriconazole, reduce dose by 66%; with isavuconazole, reduce dose by 20%
Sirolimus	+++	+++	++++	+++	++	Avoid voriconazole; combinations of posaconazole with sirolimus have been well tolerated with 30%–50% initial dose reduction of sirolimus[83]	Monitor sirolimus levels with isavuconazole and expect to reduce the dose by ∼50%
Everolimus	+++	+++	+++	+++	++	Avoid all triazoles except isavuconazole	Reduce everolimus dose to 5 or 2.5 mg with isavuconazole
Mycophenolate	–	–	–	–	+	None	Monitor for possible adverse events of mycophenolate

+++ strong severity; ++ moderate severity; + mild severity; – no interaction identified.

treatment with mould-active azoles (e.g. posaconazole or voriconazole),[99] DDIs are a common problem that can result in overexposure of the targeted therapy and unanticipated toxicity and treatment interruptions.

Coadministration of the FLT3-inhibitor midostaurin with posaconazole is particularly challenging (Table 8). Midostaurin is extensively metabolized by CYP3A4, resulting in two pharmacologically active metabolites (CGP52421 and CGP62221) that are reversible and time-dependent inhibitors and inducers of CYP3A4 *in vitro*. Coadministration of the strong CYP3A4 inhibitor ketoconazole resulted in a 5.4-fold increased exposure to midostaurin at steady state.[100] However, it remains unclear whether (serious) adverse events can be directly linked to DDIs.

GVHD is a potentially fatal complication of allogeneic HSCT. Acute GVHD is the main complication during the first months after transplantation, while chronic GVHD accounts for a significant long-term fraction of mortality, morbidity and reduced quality of life in patients. Acute GVHD is treated first with glucocorticoids, but patients who are glucocorticoid-refractory have a dismal long-term prognosis, with only 5%–30% overall survival. Approximately 50%–60% of patients with chronic GVHD require secondary treatment within 2 years of initial systemic treatment with corticosteroids. Following recent advances in understanding the pathophysiology of both acute and chronic GVHD, two small molecules have recently been approved for treatment of steroid-refractory cases of GVHD: ruxolitinib, a Janus kinase-2 (JAK-2) inhibitor (also used for the management of myeloproliferative disorders such as primary myelofibrosis)[101] and ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor (also used in the treatment of indolent lymphoproliferative diseases).[102]

Several approaches have been proposed for dealing with these drug interactions:[103]

1. Administer both the small molecule and antifungal agent at the recommended dosage, together with close monitoring of adverse events. As such, both drugs were administered as previously described in the registration studies. Indeed, a *post hoc* analysis of the RATIFY study cautioned for increased plasma concentrations of midostaurin when coadministered with strong CYP3A4 inhibitors *without midostaurin dose adjustment*, but also showed a balanced safety and efficacy profile (with a median relative dose intensity of midostaurin of >94% of the intended dose).[104]
2. An empirical dose reduction of the small molecule during coadministration with a strong CYP3A4 inhibitor was supported by the PK data. For instance, physiologically based PK modelling supports a venetoclax dose reduction of at least 50% and 75% when coadministered with moderate and strong CYP3A4 inhibitors, respectively, maintaining venetoclax exposure between those at the therapeutic dose of 400 mg once daily and the established maximal dose of 1200 mg once

Table 8. Triazole drug interactions with targeted therapies used for AML, ALL and transplantation

Therapy	Approved dose	Strong CYP3A4 inhibitor[a]	Moderate CYP3A4 inhibitor[b]	Strong CYP3A4 inducer[c]
Venetoclax	400–600 mg q24h	Dose adjustment (75% reduction venetoclax)	Dose adjustment (50% reduction venetoclax)	Avoid
Midostaurin	50 mg q12h	Consider alternative antifungal or careful monitoring; some have advocated 50% dose reduction to 25 mg q12h of midostaurin and careful monitoring	No action required	Avoid
Gilteritinib	120 mg q24h	Consider alternative antifungal or careful monitoring	No action required	Avoid
Ivosidenib	500 mg q24h	Dose adjustment (50% reduction of ivosidenib); Ivosidenib also induces the metabolism of triazole antifungals; higher triazole doses have been recommended[d]	Alternative drug or careful monitoring	Avoid
Enasidenib	100 mg q24h	No action required	No action required	No action required
Glasdegib	100 mg q24h	Consider alternative antifungal	Consider alternative antifungal	Avoid
Ruxolitinib	10 mg q12h	For patients undergoing treatment of GVHD, monitor closely, consider dose reduction to 5 mg q12h	Monitor carefully and consider dose reduction	Monitor therapy and increase dose if needed
Ibrutinib	420 mg q24h (CLL/WM/cGVHD) 560 mg q24h (MCL)	Reduce dose of ibrutinib to 70 mg q24h or 140 mg every other day	Reduce dose to 140 mg q24h	Avoid
Acalabrutinib	100 mg q12h	Avoid; for short-term therapy it is recommended to stop acalabrutinib for 7 days	No dose adjustment; monitor patients carefully for adverse reactions	Avoid
Zanubrutinib	160 mg q12h	Reduce zanubrutinib dose by 75% to 80 mg q24h	Reduce dose by 50% to 80 mg q12h	Avoid

Recommendations from the manufacturer's Summary of Product Characteristics, and Megías-Vericat *et al.*[96] MCL, mantle cell lymphoma; WM, Waldström's macroglobinaemia; cGVHD, chronic GVHD.
[a]Strong inhibitors: voriconazole, posaconazole, itraconazole.
[b]Moderate inhibitors: fluconazole, isavuconazole.
[c]Strong CYP3A4 inducers: rifampicin.
[d]Concomitant administration of ivosidenib and voriconazole or posaconazole reduced triazole exposures.[97]

daily.[105] These dose modifications were already employed in the pivotal VIALE-A study without any impact on response rates and time of remission.[106] Limited supportive PK data of coadministration are also available for ibrutinib[107] and ruxolitinib[108] but are missing for most other drugs. Of note, there is always the risk of underdosing the antineoplastic drug in cases of non-compliance or sudden cessation of antifungal therapy.

3. Switch to another antifungal agent. Alternative approaches include the use of a weaker inhibitor of CYP3A4 (e.g. fluconazole or isavuconazole), off-label use of a polyene or echinocandin (albeit with their specific toxicities and shortcomings) or relying on a pre-emptive approach using sensitive imaging and blood surrogate markers of fungal disease.

Obviously, there is no perfect approach. While awaiting the availability of novel agents with fewer drug interactions [e.g. gilteritinib in FLT3-mutated AML and antifungals with few interactions (e.g. rezafungin)], the best solution may be to advance TDM of the targeted chemotherapy agents to allow for more individualized dosing adjustment (both parent drug and its metabolites).[109] Although not widely available (yet) and reference ranges remain to be determined, TDM will most likely become a very important tool to individualize the multidisciplinary approach of patients with aggressive leukaemia and those with steroid-refractory GVHD.

Conclusions

The management of DDIs with antifungals in patients receiving complex therapies for infection, transplant, respiratory diseases and/or chemotherapy for haematological malignancies is crucial to ensure optimal patient outcomes. Healthcare providers must be aware of potential drug interactions before initiating therapy and consider alternative treatment options if significant interactions are anticipated. Screening medication profiles with computerized drug databases is a critical first step for identifying interactions. A thorough understanding of the nature of the PK interaction of the perpetrator and victim drug, and potential clinical consequences of altered drug exposures determine how empirical dosing adjustments and TDM should be used to reduce risks to the patient. Ultimately the management of PK DDIs requires a multidisciplinary approach, with regular and redundant checks and careful consideration of alternative treatment options. By implementing these strategies, healthcare providers can ensure the safe and effective use of triazole antifungals in patients receiving complex therapies for various medical conditions.

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