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Review Article

Review Article

Broad spectrum triazoles for invasive mould infections in adults: Which drug and when?

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Abstract

Invasive mould infections are an increasing cause of morbidity and mortality globally, mainly due to increasing numbers of immunocompromised individuals at risk for fungal infections. The introduction of broad spectrum triazoles, which are much better tolerated compared to conventional amphotericin B formulations, has increased survival, particularly in invasive mould infection. However, early initiation of appropriate antifungal treatment remains a major predictor of outcome in invasive mould infection, but despite significant advances in diagnosis of these diseases, early diagnosis remains a challenge. As a result, prophylaxis with mould-active triazoles is widely used for those patients at highest risk for invasive mould infection, including patients with prolonged neutropenia after induction chemotherapy for acute myeloid leukemia and patients with graft-versus-host-disease. Posaconazole is the recommended drug of choice for antimould prophylaxis in these high-risk patients. Voriconazole has its primary role in treatment of invasive aspergillosis but not in prophylaxis. Recently, isavuconazole has been introduced as an excellent alternative to voriconazole for primary treatment of invasive aspergillosis in patients with hematological malignancies. Compared to voriconazole, isavuconazole and posaconazole have broader activity against moulds and are therefore also an option for treatment of mucormycosis in the presence of intolerance or contraindications against liposomal amphotericin B.

Key words: *Aspergillus*, antifungal, targeted therapy, guidelines, Mucorales, therapeutic drug monitoring.

Introduction

Invasive mould infections (IMIs) are an increasing cause of morbidity and mortality globally, particularly in immunocompromised individuals.[1] This trend has been driven predominantly by more widespread and aggressive use of immunosuppressive therapy, increased numbers of solid organ and bone marrow transplants, and greater use of immunomodulating agents for inflammatory conditions such as rheumatoid arthritis, ulcerative colitis, and Crohn's disease.[2] While an increasing number of immunosuppressed individuals are living longer, this is often combined with more intense immunosuppression, increasing the risk of developing an IMI. Advances in medical care have also increased survival in individuals suffering from severe trauma or burns who are also at an increased risk from IMIs. Finally, in areas with high prevalence of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) and tuberculosis, fungal infections from *Aspergillus* and other moulds but also *Cryptococcus* species and *Pneumocystis jirovecii* are still common.[2,3]

Table 1. Key Pharmacokinetic Characteristics of Broad spectrum Azoles Voriconazole, Posaconazole, and Isavuconazole.[17]

	Voriconazole	Posaconazole	Isavuconazole
Dosage	2 × 6 mg/kg Day 1, 2 × 4 mg/kg starting Day 2	Suspension: 4 × 200 mg Delayed-release Tablet/ iv 2 × 300 mg (Day 1), 1 × 300 mg starting Day 2	3 × 200 mg Day 1+2; 1 × 200 mg Maintenance thereafter
po/iv	po = iv (+/-; Dosage matters!)	po < iv	po = iv
Intake	Fasting state	Fatty meals (Suspension) No influence (Delayed-release Tablet)	No influence
Half-life	6h	27–35 h	110–115 h
Oral bioavailability	96%	Suspension: variable, no data. Tablet: 54%	98%
Linear PK	No	Yes (Suspension, Tablet), No (iv)	Yes
CNS penetration	High	Low	High (Animal Model)
Renal excretion	2%	<1%	<1%
Metabolism	CYP2C19, CYP2C9, CYP3A4	UGT	CYP3A4/5

Mortality from IMIs approaches 50%, although this varies based on the site of infection, underlying risk factors for IMIs, and type of antifungal agents used for prophylaxis and treatment of infection. Antifungal prophylaxis has been associated with increased risk of IMIs caused by drug resistant moulds including *Aspergillus* spp., Mucorales, *Fusarium* spp., and *Scedosporium* spp.[4] Newer broad spectrum azoles such as voriconazole, posaconazole, itraconazole, and isavuconazole have significantly changed clinical practice and improved the prevention and treatment of IMIs. Like the first-generation triazole fluconazole, these newer agents work by disrupting ergosterol biosynthesis by inhibiting cytochrome P450-dependent 14α-lanosterol demethylation, an essential component of ergosterol production. This mechanism is similar to that of the other azoles and significantly alters the structure and function of the fungal membrane, leading to cell death.[5,6] This review will summarize pharmacokinetics of broad spectrum triazoles, focusing on voriconazole, posaconazole, and isavuconazole and discuss clinical guideline recommendations on when to use which of these triazoles.

Broad spectrum Triazoles

Pharmacokinetics

The pharmacokinetic profiles of these newer broad-spectrum azoles differs significantly (Table 1). The bioavailability of both voriconazole and isavuconazole, when administrated orally, are nearly equivalent and very high at 96% and 98%, respectively.[7] For posaconazole, oral administration of the delayed-release tablet formulation results in significant better oral bioavailability when compared to oral suspension, which should be administered with fatty meals to enhance absorption and optimize plasma concentrations.[8,9] The absorption and serum concentration of both the posaconazole delayed-release tablet and isavuconazole are not dependent on the timing of food intake, so can be taken with or without food.[10] Voriconazole has a significantly shorter half-life of 6 hours when compared to both posaconazole and isavuconazole, which have half-lives of 27–35 hours and 110–115 hours, respectively.[11–13] Neither voriconazole nor posaconazole in intravenous formulation demonstrate linear pharmacokinetics, while both oral posaconazole and isavuconazole do.[11–13] Voriconazole has high penetration into the central nervous system (CNS) while posaconazole penetrates the CNS poorly.[14] Isavuconazole is thought to be widely distributed in nearly all tissues, including liver, lungs, eyes, kidneys, bone, nasal mucosa, and brain, with CNS penetration is based on animal models.[15] Both voriconazole and isavuconazole are predominantly metabolized by the CYP enzyme system, with voriconazole predominantly metabolized by the CYP2C19, CYP2C9, and CYP3A4 enzymes and isavuconazole by the CYP3A4 and CYP3A5 enzymes.[11–13,16,17] Posaconazole metabolism is predominantly through the uridine diphosphate (UDP)-glucuronyltransferase (UGT) enzyme pathways.[16] Consequently, numerous pharmacokinetic drug-drug interactions of azole antifungal drugs with other coadministered agents that are metabolized over the same CYP enzymes have been described, resulting in a number of contraindications for some or all triazoles, or the necessity to decrease dosages of immunosuppressants like cyclosporine when co-administered.[16,17]

Therapeutic drug monitoring

Pharmacokinetics of broad-spectrum triazoles differ significantly, and plasma concentrations are subject to

Table 2. Therapeutic Drug Monitoring (TDM) Recommendations for Broad-Spectrum Azoles.

ECIL-6 [30,31]	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
TDM treatment	AII (efficacy)	AII (efficacy)	TDM not routinely recommended	AII (efficacy)
TDM prophylaxis	AII (toxicity)	BII (efficacy)		BII (toxicity)
Lowest target concentration (efficacy)	1–2 mg/l	Prophylaxis: 0.7 mg/l	NA	>0.5 mg/l Prophylaxis
	(>2 mg/l for severe infections, higher MICs)	Treatment: 1.0 mg/l		>1 mg/l Treatment
Upper target (toxicity)	5–6 mg/l	More studies needed	NA	HPLC <4 mg/l Bioassay <17 mg/l
TDM timepoint	Day 2–5, repeat	Suspension: Day 5–7 Tablet/iv: after Day 3	NA	Day 7–14
ECMM/ESCMID 2017[30,31]	Voriconazole	Posaconazole	Isavuconazole	Itraconazole
TDM treatment	AI	AII	CIII	AII
TDM prophylaxis	AII	CII	CIII	AII

significant inter-patient and intra-patient variability. Major factors influencing inter-patient variability (i.e., variability between patients) include genetic factors, adipositas, and metabolism, while intake procedures (with/without fatty food) and also co-medication are major factors influencing intra-patient variability (i.e., variability of plasma levels within a single patient).[18] Variability is highest for voriconazole, followed by the posaconazole oral suspension formulation, with intra- and inter-patient variability in the medium to low range for other posaconazole formulations and isavuconazole.[8,19,20] Sufficient voriconazole plasma concentrations are particularly important because of a clear exposure-response relationship with treatment failure and mortality been described in those with insufficient voriconazole plasma levels.[21–24] A probable exposure-response relationship has also been described for posaconazole,[9,25,26] while available data indicate that there is no clear exposure-response relationship for isavuconazole.[20]

Therapeutic drug monitoring (TDM) has been recommended to achieve efficacy, particularly for voriconazole but also for posaconazole oral suspension and itraconazole. Importantly, high voriconazole plasma levels have been associated with toxicity,[21,27] resulting in a small therapeutic window for voriconazole, necessitating TDM to ensure efficacy and avoid toxicity. In addition, there is also strong variability in intracellular concentrations, with *in vitro* and animal model data indicating that intracellular concentrations of posaconazole in lung epithelial cells are up to 40 times higher than in plasma.[28,29] Higher levels of tissue concentrations, compared to plasma, have also been described for isavuconazole,[15] while data for voriconazole are inconsistent.[29]

TDM recommendations of major guidelines are summarized in Table 2. For voriconazole, European Conference on Infections in Leukemia-6 (ECIL-6) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) guidelines (2017) give strong recommendation for voriconazole TDM for both treatment and prophylaxis and for efficacy and safety,[30,31] with the first trough level being obtained between days 2 and 5 and subsequently repeated. Similarly, there are strong recommendations for TDM when using itraconazole for treatment and prophylaxis to ensure efficacy and avoid toxicity.[30] For posaconazole there are also A recommendations for TDM in both guidelines for treatment and for achieving efficacy, with the first level being obtained between days 3, 5, and 7,[25,30] while there are only weaker recommendations for posaconazole TDM for prophylaxis, and no recommendations for posaconazole TDM to avoid toxicity.[30] For isavuconazole, it is not recommended to perform routine TDM due the likely absence of a clear exposure-response relationship and the low variability of plasma levels.

Antifungal prophylaxis

Despite important advances in the diagnosis of invasive aspergillosis (IA), including Immuno PET[32] and detection of *Aspergillus* cell wall components and *Aspergillus*-specific DNA in serum and bronchoalveolar lavage fluid (BALF),[33–37]mortality rates remain high at 30%–50%, according to epidemiologic studies.[38,39] In centers where hospital deaths undergo routine autopsy, a significant proportion of up to 50% of IA cases are still diagnosed postmortem.[40] Given the fact that autopsy rates for hospital deaths are declining throughout Europe, with rates below 15% for most European countries, IA—and in particular the fatal cases—remain underdiagnosed, and the actual mortality rate for IA is likely still above 50%.[41]

Table 3. Randomized controlled Clinical Trials on Antifungal Prophylaxis in High-risk Patients with Underlying Hematological Malignancies and Induction Chemotherapy for Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS), or with Allogeneic Stem Cell Transplantation (SCT) / Graft-versus-Host-Disease (GvHD). Bold indicates significant differences.

	AML/MDS induction Cornely NEJM 2007 ($n = 602$)[17]		Allo-SCT with GvHD Ullmann NEJM 2007 ($n = 600$)[17]		Allo-SCT Wingard Blood 2011 ($n = 600$)[17]		Allo-SCT Marks Br J Hematol 2011 ($n = 489$)[17]	
	Posa ($n = 304$)	Flu/Itra ($n = 298$)	Posa ($n = 301$)	Flu ($n = 299$)	Vori ($n = 305$)	Flu ($n = 295$)	Vori ($n = 234$)	Itra ($n = 255$)
Invasive aspergillosis	0.7% ($n = 2$)	6.7% ($n = 20$)	1.0% ($n = 3$)	5.7% ($n = 17$)	3.0% ($n = 9$)	5.8% ($n = 17$)	0.4% ($n = 1$)	2.1% ($n = 5$)
Total IFI	2.3% ($n = 7$)	8.3% ($n = 25$)	2.3% (= 7)	7.4% ($n = 22$)	7.3% ($n = 22$)	11.2% ($n = 33$)	1.3% ($n = 3$)	2.1% ($n = 5$)
Reduction in IFIs	72%		69%		35%		38%	
IFI related death / fungal free survival	2%	5%	3%	8%	78%	75%	-	-
Death all cause	16%	22%	25%	28%	81%	80%	82%	81%

Abbreviations: Flu, fluconazole; IFI, invasive fungal infection; Itra, itraconazole; Posa, posaconazole; Vori, voriconazole.

Given the high mortality rates of IA, antimould prophylaxis with broad-spectrum triazoles emerged as a strategy to prevent IA and is now widely used in hematological malignancy patients at highest risk for IA.[42,43] Two large randomized-controlled trials (RCTs) compared mould-active antifungal prophylaxis with posaconazole suspension with fluconazole/itraconazole prophylaxis. They found reductions in prevalence of invasive fungal infections (IFIs) of 72% (i.e., patients with hematological malignancies undergoing induction chemotherapy for acute leukemia[44]) and 69%, respectively (i.e., patients with graft-versus-host-disease [GVHD] after allogeneic stem cell transplantation [SCT][45]) in patients receiving posaconazole prophylaxis. Both studies reported increased overall survival in participants receiving posaconazole, and the difference in survival was significant for patients receiving induction chemotherapy for acute leukemia.[44] Two subsequent studies compared prophylaxis with voriconazole versus fluconazole[46] or itraconazole[47] in patients receiving allogeneic SCT and found nonsignificant reductions of IFI of 35% and 38%, respectively, and no change of overall survival.[48] Results of these four RCTs are summarized in Table 3.

Real-life data have confirmed that posaconazole prophylaxis is highly effective in preventing IFIs in patients with underlying hematological malignancies at high risk for fungal infections.[26,43] Posaconazole may even have a long-term effect when used in the setting of induction/salvage chemotherapy of acute myeloid leukemia, preventing development of IA after subsequent allogeneic SCT.[49]

As a consequence, posaconazole prophylaxis is now an AI recommendation for patients with induction chemotherapy for acute myeloid leukemia and patients with GVHD. In fact, all three major guidelines, namely, the ECIL-5,[50] the ESCMID/ECMM guideline (2017),[31] and the Infectious Diseases Society of America (IDSA) guideline (2016)[51] all unequivocally give an AI recommendation for posaconazole in those settings. Recommendations are summarized in Table 4. Recommendations are less unanimous in the setting of allogeneic SCT before engraftment, where posaconazole is recommended as the agent of choice in ESCMID/ECMM and IDSA guidelines, while ECIL-5 guidelines prefer voriconazole or itraconazole in those at high risk and fluconazole in those at low risk.[31,50,51] Despite the guidelines favoring posaconazole, there might still be a role for less-expensive voriconazole in certain settings of antifungal prophylaxis in hospitalized patients in settings that do regular therapeutic drug monitoring, in particular as an alternative in patients with allogeneic SCT before engraftment and also as primary agent for prophylaxis in lung transplant recipients.[31] Isavuconazole is well tolerated and has very good activity against *Aspergillus* spp.,[52] but studies are missing evaluating the drug for antifungal prophylaxis. Itraconazole, having shown inferior performance versus the comparators, may still be an alternative for low resource settings in lower risk patients.

While antimould prophylaxis is successful in reducing the burden of IA in high-risk patients by about 70%, it is important to consider that cases of breakthrough IA do occur.[1,8,26,44,53,54] Diagnosis of these breakthrough cases is particularly challenging because sensitivities of available diagnostic tests (including polymerase chain reaction [PCR] and culture) decrease significantly in the presence of antimould prophylaxis.[55–57] For example, sensitivity of BALF galactomannan (GM) testing with the recommended 1.0 ODI cutoff has been shown to decrease from 81% in patients without antimould prophylaxis to 52% in those with antimould prophylaxis. As a result, a lower cutoff for GM testing from BALF (i.e., > 0.5 ODI cutoff, which was

Table 4. Recommendations for Antifungal Prophylaxis in Patients with Hematological Malignancies.

	Posaconazole tablet/ oral solution	Voriconazole	Itraconazole	Fluconazole	Micafungin / Caspofingin
			Acute (Myeloid) Leukemia (AML) & prolonged neutropenia		
ECIL 5 AML[50]	AI	BII	BI	BI	CII
ESCMID/ECMM 2017[30,31]	AI	CII	DII	-[#]	CII
IDSA 2016*[50]	AI	AII	AII	-	CIII
			Allogeneic stem cell transplantation (SCT) until engraftment		
ECIL 5 HSCT Pre-engraftment high-risk[50]	BII	BI	BI	AIII against[$]	CI
ESCMID/ECMM 2017[30,31]	BII	CI	DI	-[#]	CI
IDSA 2016*[50]	AI	AII	AII	-	CIII
ECIL 5 HSCT pre-engraftment low risk[50]	BII	BI	BI	AI	BI (Micafungin)
			Graft versus Host Disease (GvHD)		
ECIL 5[50]	AI	BI	BI	AIII against	CII (Micafungin)
ESCMID/ECMM 2017[50]	AI	CII	CII	-	CIII (Micafungin)
IDSA 2016[50]	AI	AII	AI	-	-

*During prolonged neutropenia for those who are at high risk for IA (both AML and HSCT without GvHD).
[#]BI if given together with nebulized liposomal Amphotericin B.
[$]BIII if given together with nebulized liposomal Amphotericin B.

associated with 71% sensitivity in the presence of antimould prophylaxis) has been recommended.[34–36,58,59] An algorithm for GM testing that takes into account ongoing antimould prophylaxis, as well as neutrophil status (sensitivity of serum GM testing is significantly reduced in non-neutropenic patients[53,60–62]), is displayed in Figure 1. In addition, combination of multiple biomarkers for IA from blood and BALF has been shown to increase sensitivity for diagnosing breakthrough IA, with only marginal impacts on specificity; many of these combinations include GM from BALF and serum, *Aspergillus* PCR from BALF, and the *Aspergillus*-specific lateral flow device test.[34,57,63–67] Novel biomarkers, including triacetylfusarine C from BALF and urine, immunologic biomarkers from blood and BALF, and GM from urine (normalized to urine concentration) have emerged as candidate biomarkers for combination with established biomarkers for diagnosing breakthrough IA.[37,54,67–70]

Treatment of invasive aspergillosis

The newer generation triazoles, particularly voriconazole and isavuconazole, have offered an appealing alternative to the use of lipid and liposomal formulations of amphotericin B and other antifungal agents for the treatment of IA.

More than 15 years ago Herbrecht and colleagues investigated voriconazole and amphotericin B for the primary treatment of IA in patients with hematologic diseases. In this study, 144 patients were randomized to receive intravenous voriconazole versus 133 patients randomized to receive intravenous amphotericin B deoxycholate given at doses of 1–1.5 mg per kilogram daily. The primary outcome was a complete or partial response to therapy. At week 12, 52.8% of patients in the voriconazole group met the primary outcome (complete response 20.8% and partial response 31.9%) versus 31.6% in the amphotericin group (complete response 16.5% and partial response 15.0%) (95% confidence interval [CI] 10.4–32.9) At 12 weeks the survival rate was 70.8% in the voriconazole group versus 57.9% in the amphotericin group (95% CI 0.40–0.88). In addition, those in the voriconazole group had fewer drug-related adverse events than those in the amphotericin group (343 vs. 421 events, respectively), although visual disturbances such as blurred vision, altered visual and color perception, and photophobia were common in those receiving voriconazole, occurring in 44.8% of patients.[71]

More than a decade later, the SECURE trial randomized 527 patients with invasive mould disease to receive either isavuconazole ($n = 263$) or voriconazole ($n = 264$). The majority of patients in both the isavuconazole and voriconazole groups had a hematologic malignancy (82% and 86%, respectively). *Aspergillus* spp. were identified as the primary pathogen in approximately 30% of patients in both groups. The primary endpoint was all-cause mortality starting from the first dose of the study drug to 42 days. At 42 days all-cause mortality was 19% in the isavuconazole group versus 20% in the voriconazole group (95% CI −7.8–5.7), showing isavuconazole to be noninferior to voriconazole. Drug-related adverse events were lower in the isavuconazole group compared to the voriconazole

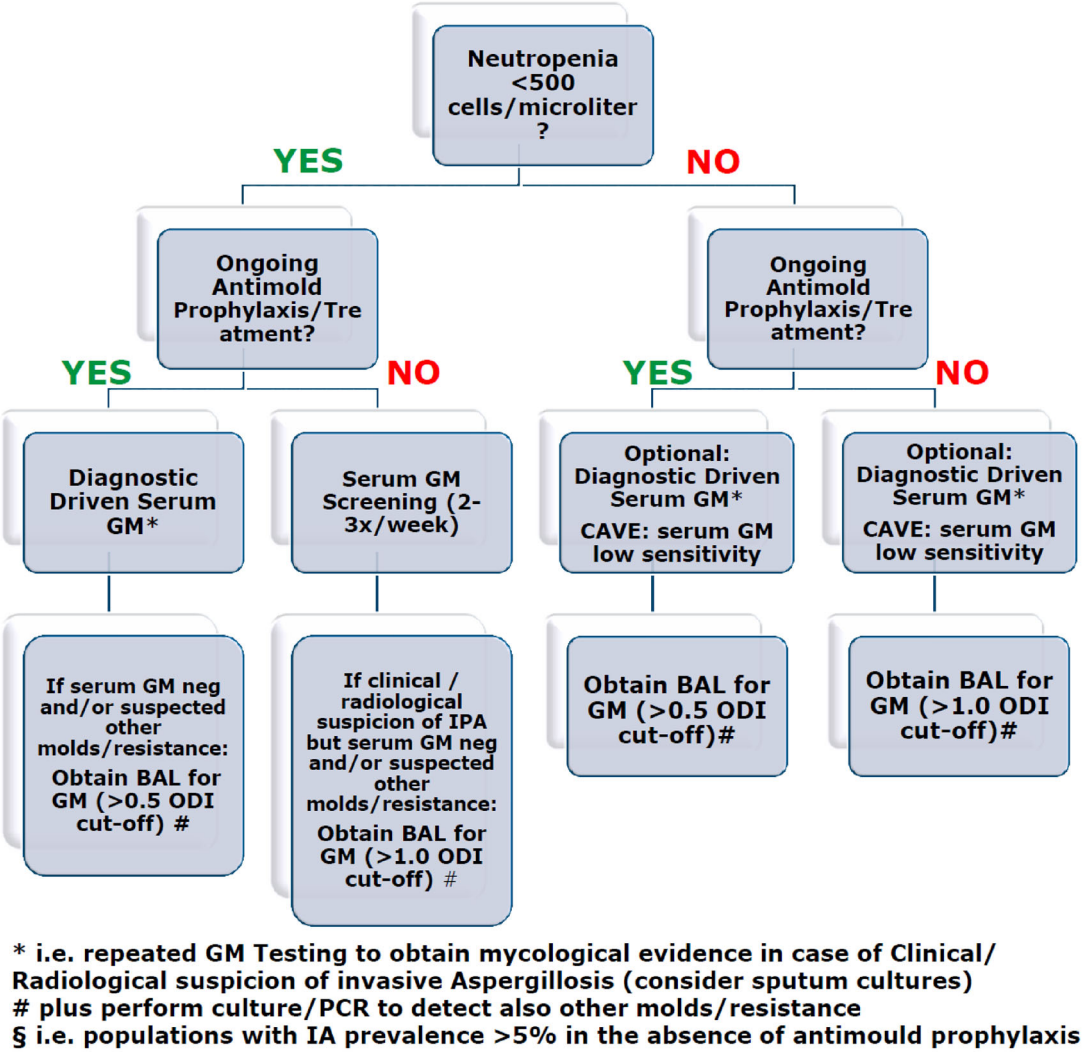

Figure 1. Galactomannan (GM) Testing from Serum and bronchoalveolar lavage (BAL) for Invasive Pulmonary Aspergillosis (IPA) in High Risk Patients. § Adapted from.[99] This Figure is reproduced in color in the online version of *Medical Mycology*.

group (42% vs. 60%, respectively; $P < .001$), including a lower frequency of liver toxicity with isavuconazole compared to voriconazole (2% vs. 10%, respectively) and fewer ocular disorders in those that took isavuconazole compared to voriconazole. The numbers needed to treat with isavuconazole to avoid adverse events was 14 for liver toxicity, 9 for ocular disorders, and 11 for skin toxicity. Furthermore, permanent drug discontinuation was lower for isavuconazole than voriconazole (8% vs. 14%, respectively).[72]

An open-label trial investigating the use of posaconazole monotherapy for the treatment of IA in patients refractory or intolerant to other antifungal agents compared response rates to antifungal therapy in 107 patients who received posaconazole oral suspension (800 mg/day in divided doses) versus 86 external control patients with refractory IA. The two groups were similar in demographics and disease characteristics and around 80% of patients in both groups had hematologic malignancy. Overall response to treatment was 42% in the posaconazole group versus 26% for control subjects (95% CI 150–11.04; $P = .006$).[73] Another study compared response to salvage antifungal therapy in 53 patients who received posaconazole 800 mg/day in divided doses and compared their response rates to 52 control patients who received lipid formulation of amphotericin B (LPD/AMB) 7.5 mg/kg daily and 38 other control patients who received a combination of caspofungin plus LPD/AMB. A favorable response was deemed if there was significant improvement or complete resolution of IA at 12 weeks. Patient characteristics were similar between the two groups, and over 90% of patients in both groups had hematologic malignancy. A favorable response occurred in 40% of patients in the posaconazole group compared to 8% of patients in the LPD/AMB group and 11% of patients in the combination group ($P < .002$). At 12 months 40% of

Table 5. Recommendations for Targeted Treatment of Invasive Aspergillosis in Patients with and without Hematological Malignancies.

Targeted treatment of invasive (pulmonary) aspergillosis in hematological malignancy patients				
	Isavuconazole	Voriconazole	Itraconazole	Liposomal Amphotericin B
ECIL 6[50]	AI	AI	CIII	BI
ESCMID 2017[50]	AI - AII	AI - AII	CII - CIII	BII
IDSA 2016[50]	AII	AI	-	AII
Salvage treatment for IA: switch to another drug class				
	Liposomal Amphotericin B	Voriconazole	Itraconazole	Posaconazole
ECIL 6[50]	BII	BII	CIII	BII
ESCMID 2017[50]	BII	AII	CII	BII

patients died in the posaconazole group compared to 65% in the LPD/AMB group and 68% in the combination group ($P < .008$).[74]

Thus, in patients with hematologic malignancies, voriconazole appears to be more effective for the treatment of IA compared to Amphotericin B and offers improved survival as well as fewer adverse drug-related events, although visual disturbances with voriconazole are common. Isavuconazole has been shown to be equally efficacious to voriconazole in prolonging survival, but unlike voriconazole, isavuconazole doesn't result in visual disturbances and may be better tolerated, overall. Posaconazole has been shown to be an option for salvage therapy in the treatment of IA.

As a result of these studies and others, the ESCMID 2017 and ECIL-6 both recommend voriconazole and isavuconazole as the preferred agents for the treatment of IA in patients with hematologic malignancies (AI–AII recommendation and A1 recommendation, respectively).[30,31] ESCMID 2017 gives "moderate" support for the use of liposomal amphotericin B (BII recommendation) and the ECIL-6 a BI grade for liposomal amphotericin B and BII grade for amphotericin B lipid complex. Neither the ESCMID 2017 nor ECIL-6 favor the use of itraconazole for IA (CII–CIII and CIII recommendation, respectively). The Infections Diseases Society of America (IDSA) recommends voriconazole as first-line treatment for IA (AI recommendation) with liposomal amphotericin B and isavuconazole as alternative options (AII recommendation).[51] ESCMID recommends against combination antifungal therapy for primary treatment of IA,[31] while the IDSA gives combination treatment with voriconazole and an echinocandin a weak recommendation.[51] For salvage therapy for IA, posaconazole is given a BII grade by both the ESCMID and ECIL-6 and is recommended by the IDSA (AII recommendation). Voriconazole remains the treatment of choice for central nervous system aspergillosis.[14,75] In addition, the ESCMID 2017 guidelines recommend voriconazole as first-line treatment of IA in patients without hematologic malignancies (AIII recommendation). Recommendations are summarized in Table 5.

Treatment of mucormycosis and other mould infections

The newer generation triazoles provide much needed options for the treatment of non-*Aspergillus* IMIs. While lipid and liposomal formulations of amphotericin B significantly improved tolerability and reduced toxicity when compared to the deoxycholate formulation, infusion, and renal toxicity remain problematic.[76] This is particularly true when considering the higher doses and prolonged courses required to treat infections from particular moulds, such as Mucorales. The mix of activity and tolerability provided by newer generation triazoles has revolutionized the treatment of IMIs, particularly in the highly immunocompromised transplant populations.

Mucomycosis, the second most common IMI, nearly always requires surgery along with adjunctive medical therapy. Variation in susceptibility to antifungals occurs between different species of Mucorales. For example, *Rhizopus* and *Cunninghamella* spp. often have relatively higher minimal inhibitory concentrations (MICs) to amphotericin, and *Mucor* spp. often have higher MICs to posaconazole than other Mucorales.[77] However, there is not yet enough evidence to recommend that these differences should be used to guide treatment.

ESCMID 2013 and ECIL-6 guidelines for the medical management of invasive mucormycosis recommend liposomal amphotericin B as first line therapy (AII and BII recommendations, respectively).[30] These guidelines recommend the use of liposomal amphotericin at 5 mg/kg daily dose as induction therapy. While in murine models, high dose liposomal amphotericin (10 mg/kg daily dose) outperformed amphotericin deoxycholate,[78] pilot studies in humans have not yet been able to demonstrate a mortality benefit.[79] Higher rates of toxicity were also seen with these higher doses, with 40% of the individuals doubling their creatinine, most of whom normalized at the end of therapy.[79] Posaconazole has demonstrated good efficacy in the salvage treatment of mucormycosis, with response rates ranging around 60%.[80,81] Based on this, posaconazole can be recommended for both salvage (when patients are not tolerating amphotericin) and the maintenance phase of therapy.[30] In the setting of

cutaneous mucormycosis, clinicians are also experimenting with posaconazole as first line medical therapy, but this should only be attempted in select cases.[82] A matched case control study performed by the Fungiscope group found no significant difference in survival between amphotericin B and isavuconazole for the treatment of Mucorales infection.[83] The amphotericin group in this study included individuals who received posaconazole after induction therapy with amphotericin B. This matched case control study has resulted in FDA approval of isavuconazole for treatment of Mucormycoses, and updated guidelines are needed to define the role of isavuconazole for Mucorales infection (the current versions of the guidelines were published before the study results were available). A new guideline on mucormycosis is currently in development under the leadership of the ECMM and involving experts from around the world (all United Nations regions represented) and all involved medical specialties and expected to be published in early 2019.

While the issue of which triazole to use is not fully settled, the option of alternative active agents allows the ability to change if toxicities limit the use of one drug. In particular, the Qtc prolongation seen with posaconazole is not seen with isavuconazole, which may be a safe option for patients with prolonged QT interval who cannot be prescribed any of the other triazoles. Sufficient data are not yet available to recommend either isavuconazole or posaconazole over the other for salvage therapy for mucomycosis. Finally, limited data exist for the use of combination therapy of a polyene and triazole for mucormycosis. The best evidence comes from a retrospective case series of 32 individuals with mucormycosis and either hematologic malignancies or aplastic anemia in whom posaconazole was added to amphotericin therapy.[84] In the majority of cases, posaconazole was added due to lack of response to amphotericin. The addition of posaconazole led to a response in 56% of individuals, similar to what has been seen when posaconazole is used as salvage therapy.

Invasive fusariosis, most commonly seen as a complication of intensive chemotherapy or in the post-transplant setting, continues to have a high mortality rate. However, survival rates have been increasing in more recent years, mainly due to the introduction of voriconazole, which was associated with higher survival rates compared to amphotericin B formulations.[85] While differences in susceptibility exist among *Fusarium* spp., guidelines currently recommend voriconazole as the initial treatment for all fusariosis (AII recommendation).[86–88] However, recent reports have also demonstrated activity of posaconazole against *Fusarium,*[89] and it should be considered an option for salvage therapy. *In vitro* MICs to isavuconazole appear to be slightly higher.[90]

Scedosporium spp. are another group of opportunistic invasive mou. *Scedosporium apiospermum* (sexual telomorph *Pseudollescheria boydii*) causes disease in individuals with immunocompromising conditions, cystic fibrosis, as well immunocompetent individuals exposed to brackish water (e.g., near drownings). In all situations, the recommended agent for medical therapy is voriconazole (AII recommendation).[91] Case reports have demonstrated activity of posaconazole,[92] but the evidence remains limited. *Scedosporium prolificans* infections can be much harder to manage given resistance of this organism to most of the available antifungals. After surgery has been performed to reduce the fungal burden, voriconazole is currently the recommended agent for lung, skin and soft tissue, bone, central nervous system, and disseminated infections (AII or BII recommendations).[91] However, the MIC to voriconazole is often very high (>16 μg/ml),[90] and multiple case reports have demonstrated improved responses with the addition of terbinafine.[93–95] Again, only limited data exist for isavuconazole for *S. prolificans* treatment, but MICs appear higher than for voriconazole.[90]

While IFIs, including IA, continue to cause significant morbidity and mortality globally, newer broad-spectrum triazoles offer more efficacious and better-tolerated treatment options to amphotericin B and other older antifungal agents.

Posaconazole prophylaxis is highly efficacious in preventing IFIs in patients with hematologic malignancies and is recommended as prophylaxis for patients after induction chemotherapy for acute myeloid leukemia and in patients with GVHD by ESCMID, ECIL-5, and the IDSA. Voriconazole may still have a role as prophylaxis in certain settings, such as in hospitalized patients in settings that perform regular therapeutic drug monitoring, and it is a less costly option than posaconazole.

Voriconazole and isavuconazole are recommended by ESCMID and ECIL-6 as first-line treatment for IA in patients with hematologic malignancies. Both options appear more efficacious than amphotericin B and are better tolerated, although isavuconazole has the added benefit of not causing the visual disturbances that are common with voriconazole use. The IDSA recommends voriconazole as first-line treatment for IA with liposomal amphotericin B and isavuconazole as alternative options. Posaconazole has shown efficacy for salvage therapy for IA and is a recommended option by all three guideline groups.

Liposomal amphotericin B is the recommended first-line therapy for the treatment of invasive mucormycosis by ESCMID and ECIL-6 with posaconazole being an option for salvage therapy. A recent study indicates that isavuconazole may be an alternative to posaconazole for salvage therapy or in case of intolerance to liposomal Amphotericin B, and updated guidelines are currently being developed that will define the role of isavuconazole for mucormycosis. Voriconazole is recommended for the treatment of invasive *Fusarium* spp. and *Scedosporium* spp. infections, with posaconazole being an option for salvage therapy for the treatment of invasive fusariosis.

Broad-spectrum triazoles have markedly improved our ability to prevent and treat IMIs. However, the available agents in this class still have limitations, including major drug-drug interactions resulting from their status as substrates and inhibitors of the cytochrome P450 system.[20] This is a major concern, as IMIs

most commonly develop in individuals with complex medical conditions, requiring multiple co-medications. Genetic polymorphisms, particularly in CYP2C9, CYP2C19, and CYP3A5 can further affect drug efficacy and safety. Several triazole derivatives have been developed by manipulating metal binding group of the azole to limit binding against mammalian CYP enzymes while maximizing potency again the fungal CYP51 target.[96] Optimization of the antifungal backbone has also led to an increased half-life and potency for these compounds.[97] One of these compounds, VT-1598, has potent activity against the endemic mycoses (*Coccidioides*, *Histoplasma*, and *Blastomyces)*, and its efficacy against central nervous system *Coccidioides* infection led to orphan drug designation by the US Food and Drug Administration. Another of these compounds, VT-1129, has demonstrated high levels of in vitro efficacy against *Cryptococcus*.[98]

In addition to newer agents, there are also newer formulations of existing triazoles coming down the pipeline. Using nanotechonology, Mayne Pharmaceuticals has engineered a new form of super bioavailable itraconazole (SUBA-itraconazole), although clinical studies are mainly focusing on its anticancer properties.[97]

In summary, new technology and rational drug design are continuing to improve the potency and tolerability of this class of antifungals, and they will likely remain a mainstay in our armamentarium against IMIs for years to come.

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