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IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

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IA-Primary therapy

- Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h

  oral therapy 200–300 mg every 12 h or weight

  based dosing on a mg/kg basis
- Monitor plasma voriconazole level (variable PK)

Patterson et al. CID 2016

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Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Primary IA-Alternative therapy

- Liposomal AmB (3–5 mg/kg/day IV)
- Isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily

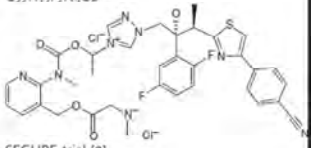
Salvage

- ABLC (5 mg/kg/day IV)
- Caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter)
- Micafungin (100–150 mg/day IV)
- Posaconazole
- Itraconazole suspension

Patterson et al. CID 2016

Isavuconazole

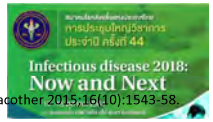
Box 1. Drug summary.

Drug name (generic)	Isavuconazole
Phase	US: Approved for the treatment of invasive aspergillosis and mucormycosis in adults
Indications	Treatment of invasive aspergillosis and invasive mucormycosis
Pharmacology description/ mechanism of action	Potent inhibitor of ergosterol biosynthesis by inhibition of 14α-demethylase, resulting in the disruption of fungal membrane structure and function
Routes of administration	IV and oral (hard gelatin capsule)
Chemical structure [7]	$C_{35}H_{35}F_2N_8OS$ 
Pivotal trials	SECURE trial [9] VITAL trial [71,73,75] ACTIVE trial (http://clinicaltrials.gov/show/NCT00413218)

-ISA had good activity against **Candida yeasts, non-Candida yeasts** (Trichosporon, Rhodotorula, Saccharomyces), **Aspergillus species, non-Aspergillus moulds (including Mucor), dimorphic fungi, Cryptococcus neoformans**, and **dematiaceous fungi.**

-Isavuconazole iv. had no β-cyclodextrin component.
-Isavuconazole oral displays excellent bioavailability (roughly 98%) after oral administration without any clinically relevant food effects.

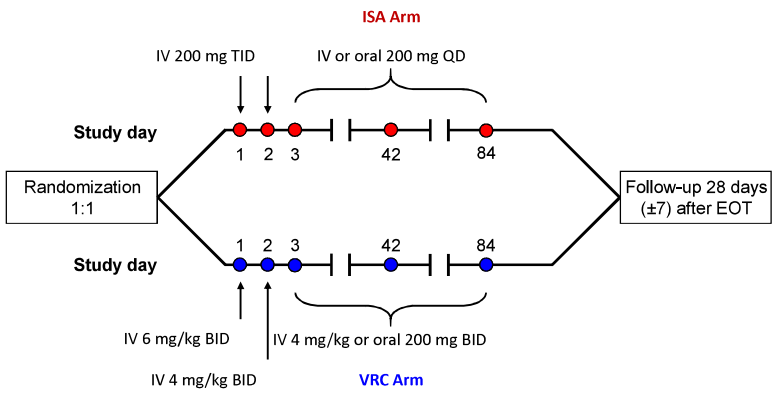
Chitasombat M. N. & Kontoyiannis D. P. Expert Opin Pharmacother 2015;16(10):1543-58.



SECURE Trial (Isavuconazole)

Lancet 2016; 387: 760–69

Study design



ACM was assessed on Days 42 and 84; overall response was assessed by the DRC on Days 42, 84, and EOT.
The maximum duration of therapy was 84 days
Patients were stratified by geographic region, allogeneic BMT/HSCT, and uncontrolled malignancy status

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SECURE Trial (Isavuconazole)

A Phase 3, Randomized, Double-blind, Non-inferiority Trial to Evaluate Efficacy and Safety of Isavuconazole versus Voriconazole in Patients with Invasive Mold Disease (SECURE): Outcomes in Neutropenic Patients

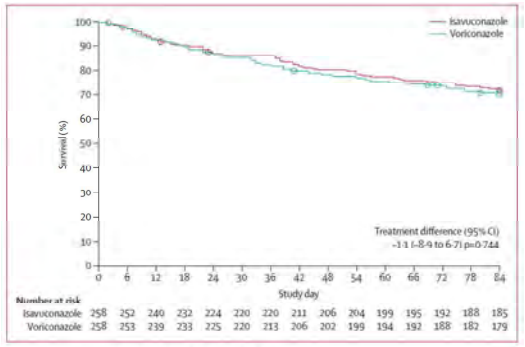

Figure 2: Survival from first dose of study drug to day 84
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Lancet 2016; 387: 760–69

Table 2. Primary and secondary outcome data from the SECURE trial for various subsets of patients.

Author	Study	All-cause mortality at day 42				Overall successful response	
		ITT population		mITT population		mITT population	
		ISA	VRC	ISA	VRC	ISA	VRC
Maertens *et al.* [9]	SECURE trial (n = 516)	n = 258 18.6%	n = 258 20.2%	n = 143 19.6%	n = 129 23.3%	n = 143 35.0%	n = 129 36.4%
Kontoyiannis *et al.* [76]	Invasive aspergillosis (n = 231)	NA	NA	n = 123 19%	n = 108 22%	n = 123 35%	n = 108 39%
Raad *et al.* [87]	Pulmonary invasive mould disease (n = 412)	n = 200 17%	n = 212 21%	n = 116 18%	n = 107 24%	n = 116 37%	n = 107 36%
Patterson *et al.* [77]	Patients with neutropenia (n = 338)	n = 163 21%	n = 175 21%	n = 88 25%	n = 73 23%	n = 88 39%	n = 73 40%
	versus patients without neutropenia (n = 178)	n = 95 15%	n = 83 18%	n = 55 11%	n = 56 23%	n = 55 29%	n = 56 32%
Ullmann *et al.* [68]	Patients with uncontrolled malignancy (n = 178, mITT)	n = 173 21%	n = 187 22%	n = 89 26%	n = 89 25%	n = 89 36%	n = 89 34%
	versus patients without uncontrolled malignancy (n = 94, mITT)	n = 85 13%	n = 71 15%	n = 54 9%	n = 40 20%	n = 54 33%	n = 40 43%
Marr *et al.* [67]	Patients with hematologic malignancies (n = 433)	n = 211 NA	n = 222 NA	n = 112 22%	n = 105 24%	n = 112 39%	n = 105 34%
	Allogeneic HSCT (n = 56)	NA	NA	n = 30 27%	n = 26 27%	n = 30 27%	n = 26 27%
	Uncontrolled malignancy (n = 171)	NA	NA	n = 85 26%	n = 86 26%	n = 85 37%	n = 86 34%
	Neutropenic (n = 47)	NA	NA	n = 82 24%	n = 70 23%	n = 82 40%	n = 70 40%
	Acute myeloid leukemia (n = 102)	NA	NA	n = 50 18%	n = 52 15%	n = 50 36%	n = 52 48%
	Acute lymphocytic leukemia and other conditions (n = 115)	NA	NA	n = 62 26%	n = 53 32%	n = 62 42%	n = 53 21%

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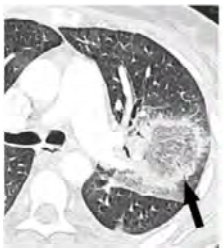
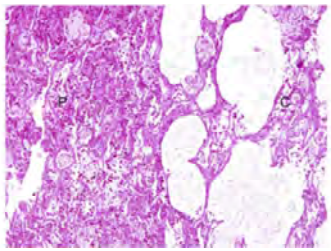
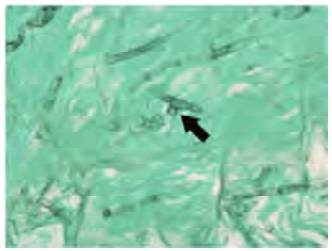
Invasive Mucormycosis

Georgiadou *et al.*, CID 2011

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Treatment of Mucormycosis

Table 9. ECIL-6 recommendations for first-line therapy of mucormycosis.

	Grade	Comments
Management includes antifungal therapy, surgery and control of underlying conditions	A II	Multidisciplinary approach is required
Antifungal therapy		
Amphotericin B deoxycholate	C II	
Liposomal amphotericin B	B II	Daily dose: 5 mg/kg. Liposomal amphotericin B should be preferred in CNS infection and/or renal failure
Amphotericin B lipid complex	B II	
Amphotericin B colloidal dispersion	C II	
Posaconazole	C III	No data to support its use as first-line treatment. Alternative when amphotericin B formulations are absolutely contraindicated.
Combination therapy	C III	
Control of underlying condition	A II	Includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy
Surgery		
Rhino-orbito-cerebral infection	A II	
Soft tissue infection	A II	
Localized pulmonary lesion	B III	
Disseminated infection	C III	Surgery should be considered on a case by case basis, using a multi-disciplinary approach
Hyperbaric oxygen	C III	

haematologica | 2017; 102(3)

Treatment of Mucormycosis

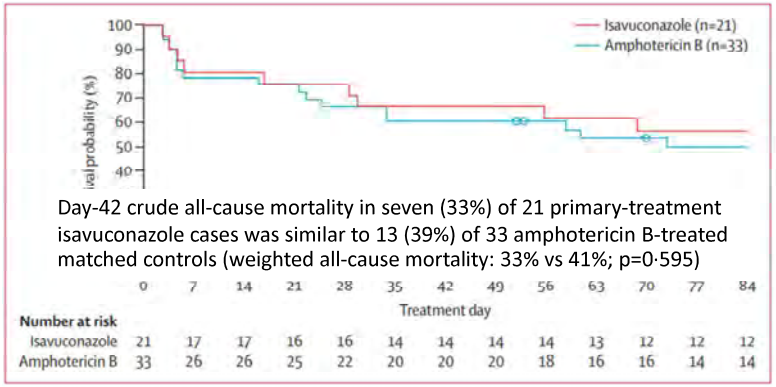
Table 10. ECIL-6 recommendations for salvage and maintenance therapy of mucormycosis.

	Grade	Comments
Salvage therapy		
Management includes antifungal therapy, control of underlying disease and surgery	A II	
Posaconazole	B II	
Combination of lipid amphotericin B and caspofungin	B III	
Combination of lipid amphotericin B and posaconazole	B III	
Maintenance therapy		
Posaconazole	B III	Overlap of a few days with first-line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated[a]

[a]Both comments apply to the oral solution but may not apply to the solid oral formulation.

haematologica | 2017; 102(3)

Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis



Day-42 crude all-cause mortality in seven (33%) of 21 primary-treatment isavuconazole cases was similar to 13 (39%) of 33 amphotericin B-treated matched controls (weighted all-cause mortality: 33% vs 41%; p=0·595)

Figure 2: **Kaplan-Meier analysis of patients who received isavuconazole as primary treatment (VITAL) compared with amphotericin B-treated matched controls (FungiScope)**
Hazard ratio (HR) and 95% CI are calculated from a Cox model without covariates. Patients were censored on the day of their last known survival status, represented by the circles.

Lancet Infect Dis 2016;16:828–37

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Fusariosis

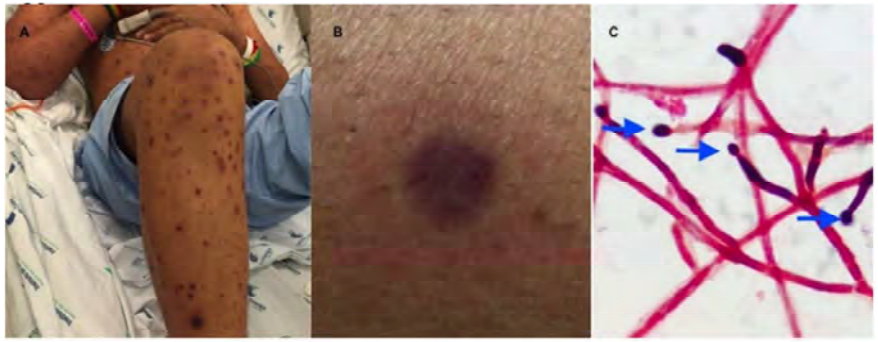

Figure S2. Patient with acute myeloid leukemia that developed disseminated fusariosis after induction chemotherapy
(A) large number of erythematous papular and necrotic lesions at different stages of evolution highlighted on the right lower limb. (B) target lesion showing central necrosis surrounded by an erythematous base. (C) Gram staining from positive blood cultures (1000X): Gram positive hyphae and adventitious sporulation (blue arrows) from blood culture with *Fusarium solani*.

Lancet Infect Dis. 2017 Nov;17(11):e344-e356.

Treatment of Fusariosis and Scedosporiosis

		Primary	Alternative
Fusariosis	Targeted therapy	Liposomal amphotericin B: 3-5 mg/kg daily (as alternative, amphotericin B lipid complex 5 mg/kg daily); or intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for 2 doses, then 300 mg (4 mg/kg)[S8-10]	Intravenous posaconazole: 300 mg every 12 h on day 1, then 300 mg daily; or intravenous isavuconazole: 200 mg every 8 h for 2 days, then 200 mg daily[S8-10]
Scedosporiosis	Targeted therapy	Intravenous voriconazole: 400 mg (6 mg/kg) loading dose twice daily for 2 doses, then 300 mg (4 mg/kg)[S10]	Intravenous posaconazole: 300 mg every 12 h on day 1, then 300 mg daily; or intravenous isavuconazole for intolerance or salvage therapy[S10]

Lancet Infect Dis. 2017 Nov;17(11):e344-e356.

New agent/formulation

	Benefit	Precaution
Posaconazole iv.	Early achievement of steady-state plasma levels	B-cyclodextrin component – avoid use in patient with low GFR
Posaconazole tablet (delayed release)	-Improving the absorption profile (pH-sensitive polymers to release in the duodenum) -Once-daily dosing	-No division/crushing of the tablet, feeding via gastric tube -Should not be administered with strong inducers or inhibitors of CYP3A4
Isavuconazole iv.	-Broad spectrum azole -No B-cyclodextrin component-safe to use in patient with low GFR -QT shortening effect -Potentially fewer drug-drug interactions	Should not be administered with strong inducers or inhibitors of CYP3A4
Isavuconazole po.	-Predictable, linear pharmacokinetics with no relevant food effect	Should not be administered with strong inducers or inhibitors of CYP3A4

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