How to mange anti-fungal resistant IFI in cancer patients

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Refractory invasive fungal infections

- (IFIs) has emerged as a significant problem in patients receiving systemic antifungals.
- Despite recent advances in both the diagnosis and prevention of IFI, the incidence of disease, treatment failure and attributable mortality remains unacceptably high.
- **There is no consensus** for the best medical or surgical management in patients with refractory IFI.
- Here, **best options for treating refractory IFI are discussed**.

Reasons for resistance to anti-fungal agents in IFD

1. Inadequate debridement

2. Not absorbtion

- Posaconazole

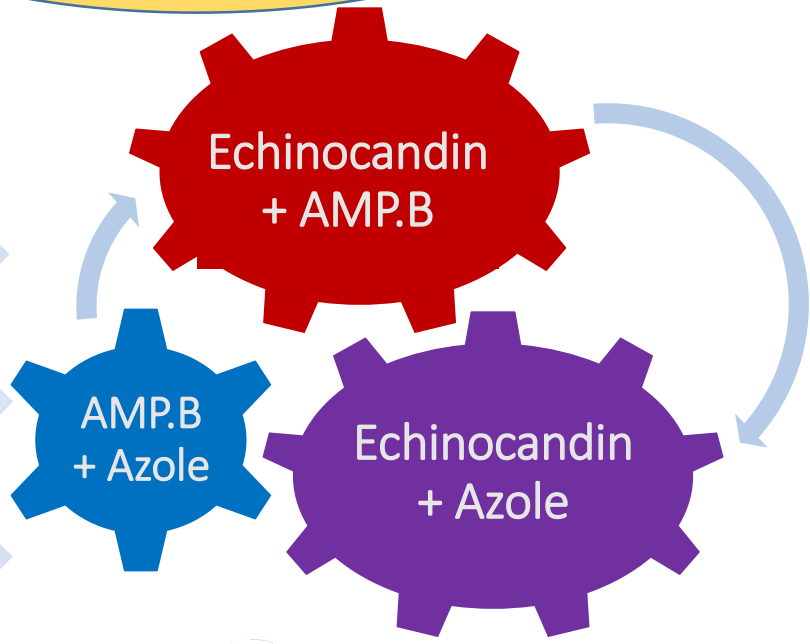
3. Too fast metabolizer

- Voriconazole

Adjusting dosages without changing therapy

4. Resistant to recent antifungal drug

- Changing to another drug class
- Increasing the dose of the drug
- Adding an antifungal agent from another class?



Resistant to recent antifungal drug

The new EUCAST categories are as follows:

- **S (Susceptible)** when there is high likelihood of clinical success using standard doses of the drug.
- **I (Susceptible, Increased exposure)** when there is high likelihood of clinical success when exposure to the agent is increased either by adjusting the dosing regimen or by physiological concentration at the site of infection.
- **R (Resistant)** when there is high likelihood of clinical failure even when there is increased exposure.

Azole resistance in *Aspergillus*

❖ **Wild-Type** *cyp51A* gene
- The most common type

MIC for Azoles < epidemiological cutoff

TR_{34}/L98H
- About 90% of isolates

Resistant to Posaconazole and Itraconazole and intermedidate to Voriconazole

TR_{46}/Y121F/T289A
- About 3-4% of isolates

Associate to Voriconazole resistance

TR_{53}
- Rare

Resistant to Itraconazole and Voriconazole

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EUCAST Susceptibility Testing of Isavuconazole: MIC Data for Contemporary Clinical Mold and Yeast Isolates

June 2019

low-level voriconazole-resistant A. fumigatus (MIC 2mg/L), or posaconazole-resistant A. fumigatus (MIC 0.5mg/L) can be **treated with Voriconazole with higher doses**, aiming to achieve higher pharmacodynamic targets compared with azole-susceptible infection.

mycoses WILEY

High-dose posaconazole for azole-resistant aspergillosis and other difficult-to-treat mould infections

2020 Feb

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

N Engl J Med 2021;385:1496-509.

Aspergillus Infections

- **Posaconazole** is approved in patients with haematological malignancies both for prophylaxis and salvage therapy and treatment of refractory IA or when intolerance to first-line agents occurs.

- Targeting high serum concentrations of POS using the tablet or IV formulation is a possible step-down option in patients with azole-resistant IA as long as the POS-MIC is <1 mg/L and for patients treated for mucormycosis with L-AmB.

- **It should only be used when close monitoring for AE is implemented in conjunction with TDM and when the benefits are likely to outweigh the risks.**

Safety monitoring for HD-POS

❑**The following laboratory tests should be performed twice weekly during the first 2 weeks and as long as the POS dosage is being increased**:

- **electrolytes, renal clearance, Hb, WBC diff, PLT, LFT**
- **ECG** : before the start of HD-POS as well as during treatment,

  (Posaconazole may cause QT prolongation).

  - If no laboratory abnormalities possibly related to POS are observed **the monitoring interval can be increased.**

J Antimicrob Chemother 2018; 73: 134–142

Isavuconazole susceptibility of clinical *Aspergillus fumigatus* isolates and feasibility of isavuconazole dose escalation to treat isolates with elevated MICs

- This study indicated **high-dose Isavuconazole treatment** might also be an option in patients infected with an A. fumigatus isolate with **an Isavuconazole MIC of 2mg/L**. (one 2-fold dilution step above the breakpoint)

- **High-dose Isavuconazole** treatment in azole-resistant invasive aspergillosis requires extreme caution owing to possible toxicity and drug interactions and would require intensive therapeutic drug monitoring and imaging.

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EUCAST Susceptibility Testing of Isavuconazole: MIC Data for Contemporary Clinical Mold and Yeast Isolates

❑most isolates in the studies that were resistant to Itraconazole or Posaconazole but exhibited **low Voriconazole MICs** did have a **low Isavuconazole MIC** too.

➢ **A very strong correlation was found between Isavuconazole and Voriconazole.**

Resistant to Posaconazole

- **Probability resistant to Itraconazole**

Voriconazole probability a better choice

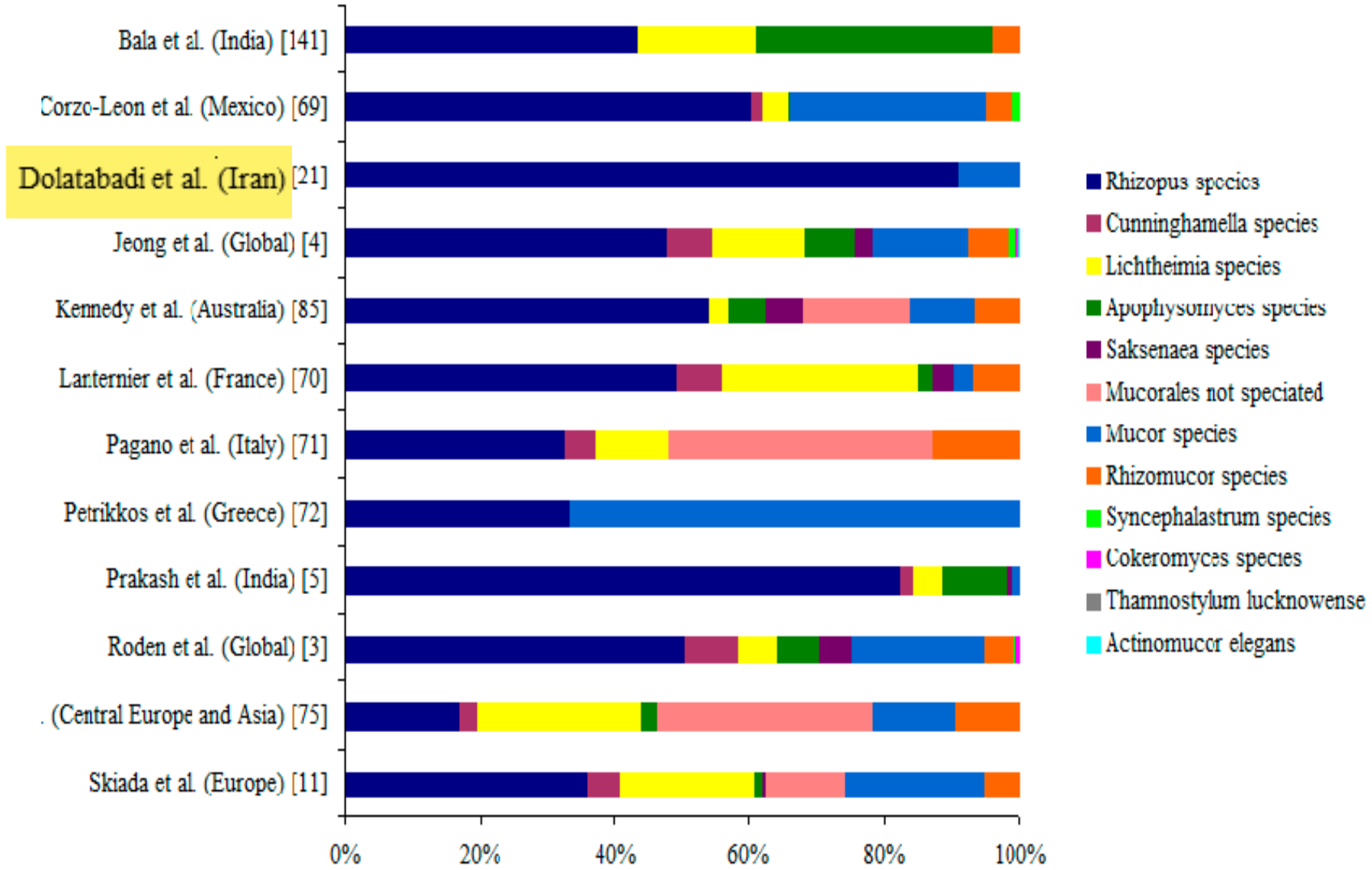
Resistant to Isavuconazole

- **Probability resistant to Voriconazole**

Posaconazole probability a better choice

Causative agents of mucormycosis

- **Rhizopus sp.** is the most common cause of mucormycosis in Iran.
- Beyond that, infections due to **Mucor sp.** are common.



In vitro antifungal drug resistance profiles of clinically relevant members of the Mucorales (Mucoromycota) especially with the newer triazoles (2021)

Journal of Fungi

- In agreement with previous studies, the most active antifungal drug for all Mucorales was **Amphotericin B,** with MICs within the range 0.125-5.
- Conversely, MICs for **Voriconazole** against all species tested were high, (MIC >16-32)

- For **Isavuconazole**, only 25% of isolates had MICs of less than 2 mg/L and for species of **Mucor and Rhizomucor**, MICs were significantly higher (with the range of between **2-16, ECV=2).**
- **MIC50 and MIC90** values with **Isavuconazole** were **2** (**Rhizopus** spp.) and **4 doubling dilutions higher** (**Mucor spp., L. corymbifera**) when compared to **posaconazole**

- The **Itraconazole** MICs for **Mucor spp., Rhizopus spp**. were significantly **higher** than those observed with **L. corymbifera, Apophysomyces.** (**MIC 90 >16** versus **MIC 90 = 1**).

- For **Posaconazole,** most of the isolates had MIC of less than 2 mg/L (**MIC= 0.125 - >16, ECV=2**).

- So, after LAMP-B, Posaconazole is a good option for refractory disease and salvage therapy.

❑ In **Iran** due to the prevalence of **Rhizopus and Mucor sp**. **Itraconazole** is not a good choice for mucormycosis treatment but in **India** due to the prevalence of **Apophysomyces**, Itraconazole may be an alternative option.

Posaconazole & Mucorales isolates

- There is **higher MICs for Mucorales isolates** compared to A fumigatus, it seems reasonable to pursue higher than normal POS serum concentrations for the treatment of mucormycosis as long as this is not associated with toxicity.
- Posaconazole-oral suspension has been used as salvage therapy for mucormycosis with a success rate of approximately 60%-80%.
- when the **Ctrough concentration is 1.5 mg/L**, increasing the dose **from 300 mg once daily to 300 mg twice daily** can be expected to lead to a **serum concentration of 3 mg/L.**
- **For safety reasons, It is advised to increase the dose with no more than 200 mg per step.**

❑In conclusion, targeting **high serum concentrations of POS** using the tablet or IV formulation is **a possible step-down option** for patients treated for **mucormycosis with L-AmB.**

- **Adverse effects of high serum concentrations of POS:** diarrhea and nausea (most common), prolonged QT interval in ECG, elevations in hepatic enzymes, hypokalaemia, Hyponatremia, hypertension, thrombocytopenia, anemia, neutropenia, hyperbilirubinemia, renal failure

❑ It should only be used when **close monitoring** for adverse events is implemented in conjunction with **TDM** and when the benefits are likely to outweigh the risks.

Combination antifungal therapy:

- **There are no convincing data to support any form of combination antifungal therapy**.

- In vitro studies and in vivo animal model investigations have shown evidence of synergism between Polyenes (low dose, not high dose) and Echinocandins for R.oryzae (due to the small amount of glucan on the cell wall of this fungus).

[Ibrahim, A.S. et al. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob. Agents Chemother. 2008, 52, 1556–1558.]

Polyenes + Echinocandins

- In one retrospective study among diabetic patients with **ROCM**, the combination of AMB + Echinocandin was **successful in 6 of 7 treated** patients compared with only 7 of 22 patients treated with ABLC monotherapy.

[Reed, C,et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin. Infect. Dis. 2008, 47, 364–371.]

- A, single-institution study of **106 HM** patients with mucormycosis **failed to show any benefit** from combination treatment, compared to AMB monotherapy.

[Kyvernitakis, A, et al. Initial use of combination treatment does not impact early survival of 106 patients with hematologic malignancies and mucormycosis: A propensity score analysis. Clin. Microbiol. Infect. 2016, 22, 811e1–811e8]

AMB + Triazole

- Data on the efficacy of the AMB + Triazole combination for the treatment of mucormycosis are contradictory.
- In vitro studies have shown synergy for the combination of a polyene and posaconazole, but in vivo studies in murine models showed no benefit.

Ghady Haidar, MD and Nina Singh, MD. How We Approach Combination Antifungal Therapy for Invasive Aspergillosis and Mucormycosis in Transplant Recipients (Transplantation 2018;102: 1815–1823

- According to a recent retrospective study by Patel et al., **no survival benefit was observed** with the use of **posaconazole/L-AMB** combination in **287 patients** with **ROCM** that 187 (65.2%) had COVID-19–associated mucormycosis.

Patel A, et al. A multicenter observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect 2020;26:944. e9-944.e15.

- The modest existing pre-clinical and clinical data do not support the use of combination therapy, with the possible **exception of CNS** mucormycosis, where a combination of high-dose LAMB and posaconazole or isavuconazole might be considered. ?

- **32** Patients with **hematologic malignancies** and proven IM treated with a combination of LipAmB+POS (between 2007 and 2012) due to lack of response to antifungal monotherapy.
- After a median follow up **of three months**, **clinical improvement was observed in 18 patients (56%)**: 11 (34%) complete and 7 (22%) partial responses. Stable disease was demonstrated in 5 patients (16%). Nine patients (28%) did not respond to treatment and died of progressive IM.
- **Due to the low number of cases at multivariate analysis, no parameters were identified as being significant.**

[Herbrecht, R; et al. Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematologic diseases. Haematologica 2013, 98, e127–e130

Adjunctive Therapies

- **Hyperbaric oxygen** therapy after surgical debridement
- **Iron chelators** without xenosiderophore activity (eg, deferasirox)
- **Topical amphotericin** in refractory sino-orbital mucormycosis
- **Statins** (invitro activity against mucorals in combination with voriconazole or AMP-B)
- **Immune-augmentation strategies** :
  - ✓**Granulocyte (macrophage) colony-stimulating factor or interferon-γ**
  - ✓**Granulocyte transfusion**
  - ✓**Check point inhibitors (Anti-PD-1): nivolumab** (case report)

Adjunctive therapy recommendations for treatment of invasive mucormycosis from European Conference on Infections in Leukemia 6 (ECIL-6) (2017) and European Confederation of Medical Mycology (ECMM) (2019)

ECIL-6 2017		ECMM 2019	
Adjunctive therapy			
Against use of deferasirox	AII	Deferasirox (other than haematology)	C II
		Deferasirox (haematology)	D II
		Deferoxamine	D II
Hyperbaric oxygen	C III	Exposure to 100% hyperbaric oxygen (haematology)	C II
		Exposure to 100% hyperbaric oxygen (diabetes)	B II
Hematopoietic growth factor if neutropenia	A II	G-CSF (haematology, ongoing neutropenia)	B II
		Granulocyte transfusion (haematology, ongoing neutropenia)	C II
		Granulocyte transfusion + IFNγ1b (haematology, ongoing neutropenia)	C III
		GM-CSF (diabetes)	C III
		Adoptive immunotherapy, T cells generated in response to *R. arrhizus* antigens	C III
		Nivolumab + interferon-γ	C III

Invasive candidiasis

- **Invasive candidiasis** is widely recognized as a major cause of morbidity and mortality in the health-care environment.
- Candida strains that are resistant to first-line antifungals are increasingly being recognized, and usually correlates with high azole and/or echinocandin background usage in hospitals .

✓**(MDR)** Candida sp.: strains that are resistant to two antifungal drug classe.s

✓ **(XDR)** Candida sp.: strains that are resistant to ≥3 antifungal drug classes.

Amphotericin B

- Elevated MICs have been reported for some Aspergillus species including **A. flavus, A. terreus and A. nidulans**.
- **In contrast, the in vitro activity of amphotericin B against species of Candida is mostly uniform**.
- Amphotericin B has limited clinical activity against **Candida lusitaniae** although the MICs are comparable to those for the other Candida spp.
- This is due to a higher mutational rate and less fungicidal activity when exposed to amphotericin B.

Echinocandins

- **The in vitro activity of the Echinocandins against Candida species is not uniform.**
- The species more frequently associated with human infections include C. albicans, C. dubliniensis, C. glabrata, C. parapsilosis, C. tropicalis and C. krusei, of which all **but C. parapsilosis** exhibit low MIC values.
- The **C. parapsilosis wildtype** populations were classified as **intermediate** for anidulafungin and micafungin.
- **As there is a high degree of cross-resistance between the three Echinocandins**, isolates categorized as Anidulafungin and Micafungin susceptible can be regarded as susceptible to Caspofungin until drug-specific breakpoints are available for Caspofungin.

Azoles

- **The activity in vitro of Fluconazole against species of Candida is not uniform**.
- Candida albicans, C. dubliniensis, C. parapsilosis and C. tropicalis tend to have relatively low MICs, whereas **the MICs for C. glabrata tend to be higher.**
- In addition, **C. krusei is inherently resistant to fluconazole**.

❖ The wild type population of C. glabrata was classified as **Intermediate for fluconazole**. In cases where fluconazole is the only available antifungal agent for treating C. glabrata infections the use of a higher dosage may be requiered.

Candida auris

- All ***Candida auris*** isolates should **undergo antifungal susceptibility testing** according to CLSI guidelines.
- Although *C. auris* is commonly **multidrug resistant**, levels of antifungal resistance can vary widely across isolates.
- There are currently no established *C. auris*-specific susceptibility breakpoints.
- Correlation between microbiologic breakpoints and clinical outcomes is not known at this time.

EUCAST breakpoints for Candida species

Antifungal agent	Candida albicans			Candida dubliniensis		Candida glabrata		Candida krusei		Candida parapsilosis		Candida tropicalis	
	S ≤	R >	ATU	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B[b]	1	1		*1*	*1*	1	1	1	1	1	1	1	1
Anidulafungin[b,c]	0.03	0.03				0.06	0.06	0.06	0.06	4	4	0.06	0.06
Fluconazole[d]	2	4		*2*	*4*	*0.001*[e]	*16*	—	—	2	4	2	4
Itraconazole[b]	0.06	0.06		*0.06*	*0.06*	IE[f]	IE[f]	IE[f]	IE[f]	0.125	0.125	0.125	0.125
Micafungin[b,c]	0.016	0.016	*0.03*[g]			0.03	0.03	IE[h]	IE[h]	*2*	2	IE[h]	IE[e]
Posaconazole[b]	0.06	0.06		*0.06*	*0.06*	IE[f]	IE[f]	IE[f]	IE[f]	0.06	0.06	0.06	0.06
Voriconazole[i]	0.06[j]	0.25[j]		*0.06*[j]	*0.25*[j]	IE	IE	IE	IE	0.125[j]	0.25[j]	0.125[j]	0.25[j]

IE: insufficient evidence that the organism or group is a good target for therapy with the agent.

- Based on these MIC breakpoints, many isolates are resistant to multiple classes of drugs.
- This information should be considered as a general guide and **not as definitive breakpoints for resistance.**

- **A finding of an elevated (MIC) for an antifungal drug should not necessarily preclude its use, especially if the use of other antifungal drugs for the patient has been ineffective.**

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June 2019

- A good and highly significant correlation was also observed **between Isavuconazole and Fluconazole** for C. albicans, C. glabrata, and C. tropicalis **but not for C. parapsilosis**

- **The strongest correlation overall was found for Isavuconazole and Voriconazole .**

- A significant correlation was observed between Isavuconazole and Voriconazole MICs for all Candida species, **although it was weak for C. krusei, and C. parapsilosis.**

- Acquired Isavuconazole resistance was infrequent, except in A. terreus, C. glabrata, and C. tropicalis, and, when present, was associated with cross-resistance to other azoles.

Thanks!