ANTI FUNGAL TREATMENT IN COVID 19

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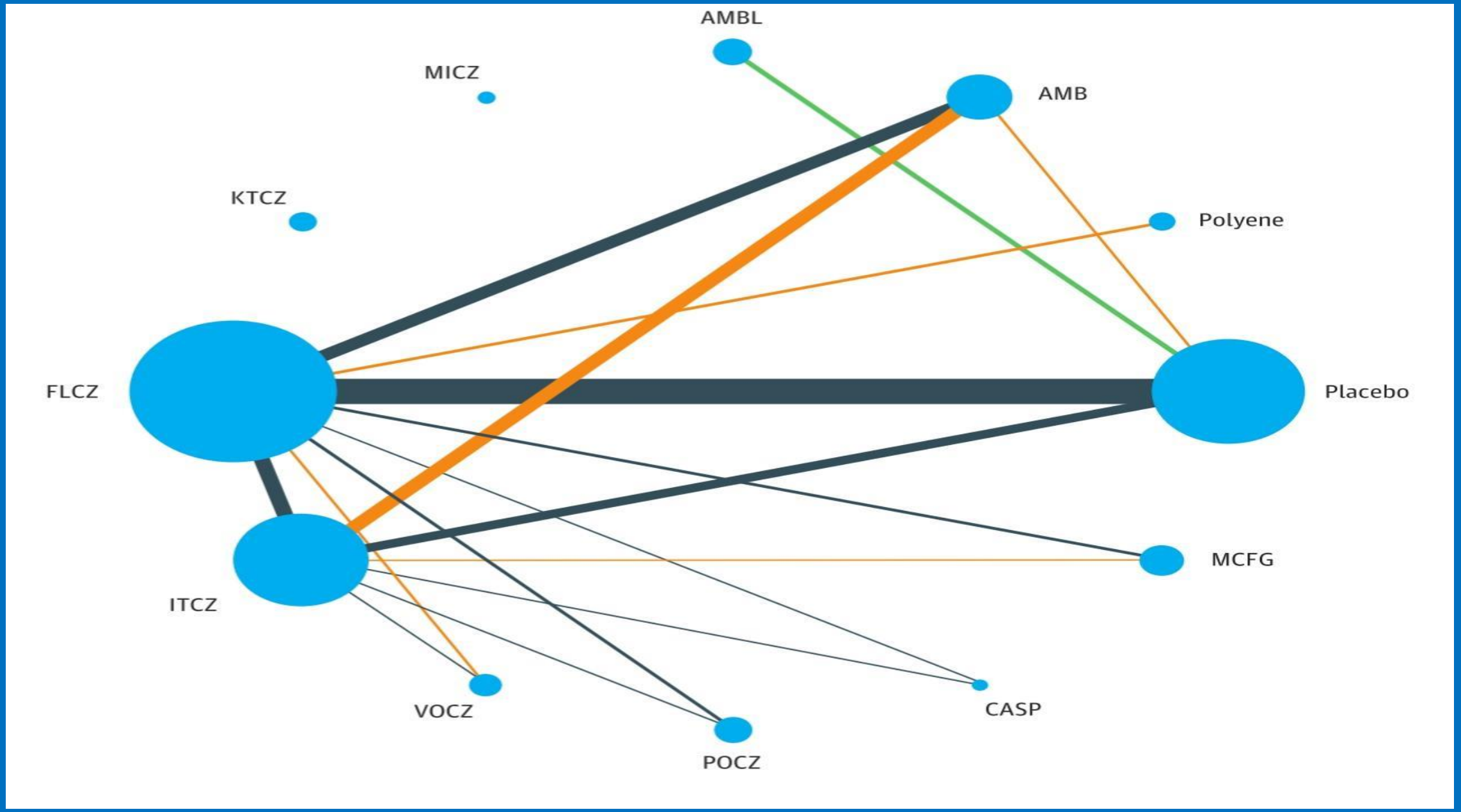
AMBL
MICZ
AMB
KTCZ
Polyene
FLCZ
Placebo
MCFG
ITCZ
VOCZ
CASP
POCZ

ORIGINAL ARTICLE

Occurrence of Invasive Pulmonary Fungal Infections in Patients with Severe COVID-19 Admitted to the ICU

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Risk factors:

- Immunosuppression by steroids
- Prolonged ICU stay
- Voriconazole therapy
- Use antibiotics/antifungals

Table 3: Prevention of rhino-orbito-cerebral mucormycosis in the setting of COVID-19

- Judicious and supervised use of systemic corticosteroids in compliance with the current preferred practice guidelines
- Judicious and supervised use of tocilizumab in compliance with the current preferred practice guidelines
- Aggressive monitoring and control of diabetes mellitus
- Strict aseptic precautions while administering oxygen (sterile water for the humidifier, daily change of the sterilized humidifier and the tubes)
- Personal and environmental hygiene
- Betadine mouth gargle (not nasal drops)
- Barrier mask covering the nose and mouth
- Consider prophylactic oral Posaconazole in high-risk patients (>3 weeks of mechanical ventilation, >3 weeks of supplemental oxygen, >3 weeks of systemic corticosteroids, uncontrolled diabetes mellitus with or without ketoacidosis, prior history of chronic sinusitis, and co-morbidities with immunosuppression)

RESEARCH Open Access

Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study

Stefan Hatzl[1,2†], Alexander C. Reisinger[1†], Florian Posch[3], Juergen Prattes[4], Martin Stradner[5], Stefan Pilz[6], Philipp Eller[1], Michael Schoerghuber[7], Wolfgang Toller[7], Gregor Gorkiewicz[8], Philipp Metnitz[8], Martin Rief[8], Florian Prüller[9], Alexander R. Rosenkranz[10], Thomas Valentin[5], Robert Krause[4*], Martin Hoenigl[4,11†] and Gernot Schilcher[1†]

Abstract

Background: Coronavirus disease 19 (COVID-19)-associated pulmonary aspergillosis (CAPA) emerged as important fungal complications in patients with COVID-19-associated severe acute respiratory failure (ARF). Whether mould active antifungal prophylaxis (MAFP) can prevent CAPA remains elusive so far.

Methods: In this observational study, we included all consecutive patients admitted to intensive care units with COVID-19-associated ARF between September 1, 2020, and May 1, 2021. We compared patients with versus without antifungal prophylaxis with respect to CAPA incidence (primary outcome) and mortality (secondary outcome). Propensity score adjustment was performed to account for any imbalances in baseline characteristics. CAPA cases were classified according to European Confederation of Medical Mycology (ECMM)/International Society of Human and Animal Mycoses (ISHAM) consensus criteria.

Results: We included 132 patients, of whom 75 (57%) received antifungal prophylaxis (98% posaconazole). Ten CAPA cases were diagnosed, after a median of 6 days following ICU admission. Of those, 9 CAPA cases were recorded in the non-prophylaxis group and one in the prophylaxis group, respectively. However, no difference in 30-day ICU mortality could be observed. Thirty-day CAPA incidence estimates were 1.4% (95% CI 0.2–9.7) in the MAFP group and 17.5% (95% CI 9.6–31.4) in the group without MAFP ($p = 0.002$). The respective subdistributional hazard ratio (sHR) for CAPA incidence comparing the MAFP versus no MAFP group was of 0.08 (95% CI 0.01–0.63; $p = 0.017$).

Conclusion: In ICU patients with COVID-19 ARF, antifungal prophylaxis was associated with significantly reduced CAPA incidence, but this did not translate into improved survival. Randomized controlled trials are warranted to evaluate the efficacy and safety of MAFP with respect to CAPA incidence and clinical outcomes.

Keywords: ICU, CAPA, COVID-19-associated aspergillosis, Posaconazole, Mould prophylaxis

Invasive Aspergillosis

ECIL-6 recommendations for first-line treatment of invasive aspergillosis

Voriconazole	AI	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	AI	As effective as voriconazole and better tolerated
Liposomal amphotericin	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination vorico + anidulafungin	C I	
Other combinations	C III	

Posaconazole

- Posaconazole is highly active in vitro against Aspergillus spp
- Posaconazole initially was available only as an oral suspension and required administration in divided doses, 2 times to 4 times per day, and suffered from poor absorption.
- A delayed-release oral tablet and an IV formulation since have been developed substantial improving serum drug levels.
- Posaconazole achieves high levels in peripheral tissues, such as lung, kidneys, liver, and heart, and there are limited data regarding penetration into the CNS

Invasive Aspergillosis

- Aspergillus fumigatus resistance is caused most commonly .

- Resistance may develop following long durations of therapy, particularly in those with chronic cavitary disease, although de novo resistance also may be found, particularly in regions using azoles on agricultural products

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- The management of patients infected with azole-resistant infection is :
- lipid AmB products and combination therapy with an azole or echinocandin

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- **Voriconazole** is the treatment of choice in most patients; isavuconazole, **posaconazole**, and **L-AmB** are important alternative agents.

- **Combination** therapy can be used in select patients with more **extensive** infection and in those with significant and **ongoing immunosuppression**.

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Journal of Antimicrobial Chemotherapy

Article Navigation

When to change treatment of acute invasive aspergillosis: an expert viewpoint

Monica A Slavin ✉, Yee-Chun Chen, Catherine Cordonnier, Oliver A Cornely, Manuel Cuenca-Estrella, J Peter Donnelly, Andreas H Groll, Olivier Lortholary, Francisco M Marty, Marcio Nucci ... Show more
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- Voriconazole
- liposomal amphotericin B
- Isavuconazole
- Posaconazole
- Voriconazole plus anidulafungin have been studied for primary therapy of acute IA
- Caspofungin, posaconazole, micafungin and caspofungin plus other antifungals have been studied as salvage therapy

Table 2. Reasons for changing first-line antifungal treatment

Days since initiation of therapy	Clinical and diagnostic findings compared with baseline
At any time	Identification of a pathogen resistant to primary antifungal therapy
8 to 14	On the basis of changes in GM: (i) Serum: The serum GM index has not fallen by either 1 unit or to <0.5 units based on measurements taken at least 7 days apart (ii) BAL: Positive GM from BAL in a patient with a previous BAL test that did not meet the definition of positive (too low or entirely negative) without regard for the interval of time between samples. Note that there is not a definition for rising GM index values from BAL as these values are subject to sampling error *Or* Clinical deterioration consistent with persisting or progressive invasive fungal disease with no other identifiable aetiology *Or* New distinct site of infection detected clinically or radiologically
≥15	Any of the above criteria *Or* Progression of original lesions on CT (or other imaging) based on >25% growth of initial lesions in the context of no change in immune status

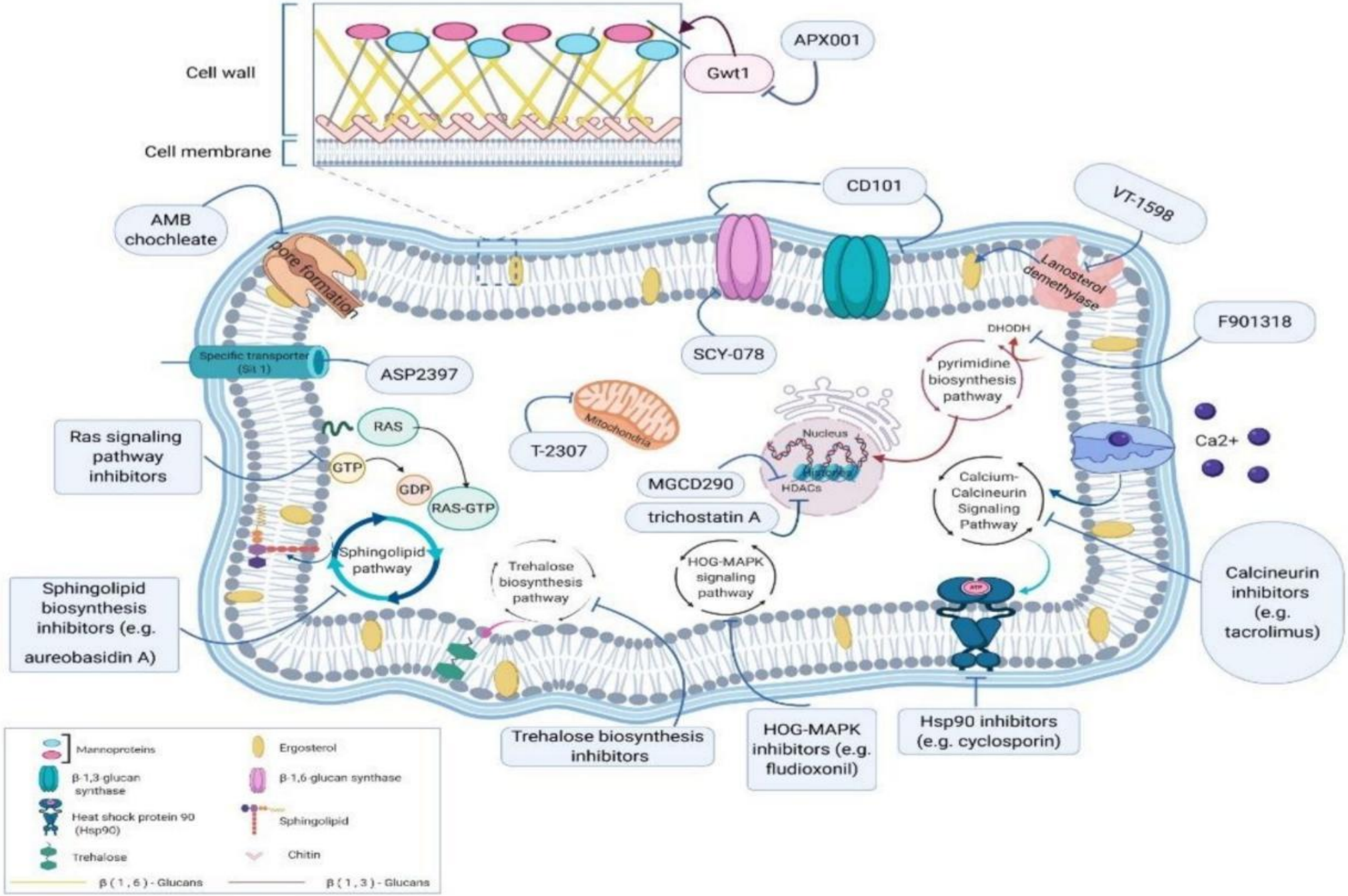
pathogens

MDPI

Review

Nanomaterial-Based Antifungal Therapies to Combat Fungal Diseases Aspergillosis, Coccidioidomycosis, Mucormycosis, and Candidiasis

Angel León-Buitimea [1,2,†], Javier A. Garza-Cervantes [1,2,†], Diana Y. Gallegos-Alvarado [1], Macario Osorio-Concepción [1,2] and José Ruben Morones-Ramírez [1,2,*]


Cell wall
Cell membrane
Gwt1
APX001
AMB chochleate
pore formation
CD101
VT-1598
Lanosterol demethylase
F901318
DHODH
pyrimidine biosynthesis pathway
SCY-078
Specific transporter (Sit 1)
ASP2397
Ras signaling pathway inhibitors
RAS
GTP
GDP
RAS-GTP
T-2307
Mitochondria
Nucleus
HDACs
MGCD290
trichostatin A
Ca2+
Calcium-Calcineurin Signaling Pathway
Sphingolipid pathway
Sphingolipid biosynthesis inhibitors (e.g. aureobasidin A)
Trehalose biosynthesis pathway
HOG-MAPK signaling pathway
Calcineurin inhibitors (e.g. tacrolimus)
Trehalose biosynthesis inhibitors
HOG-MAPK inhibitors (e.g. fludioxonil)
Hsp90 inhibitors (e.g. cyclosporin)
Mannoproteins
β-1,3 glucan synthase
Heat shock protein 90 (Hsp90)
Trehalose
β (1,6) - Glucans
Ergosterol
β-1,6 glucan synthase
Sphingolipid
Chitin
β (1,3) - Glucans

Mucormycosis

- Mucorales are intrinsically resistant to :
- Fluconazole
- Itraconazole
- Voriconazole
- Echinocandins
- Flucytosine

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Journal de Mycologie Médicale
Volume 30, Issue 3, September 2020, 101007

General review

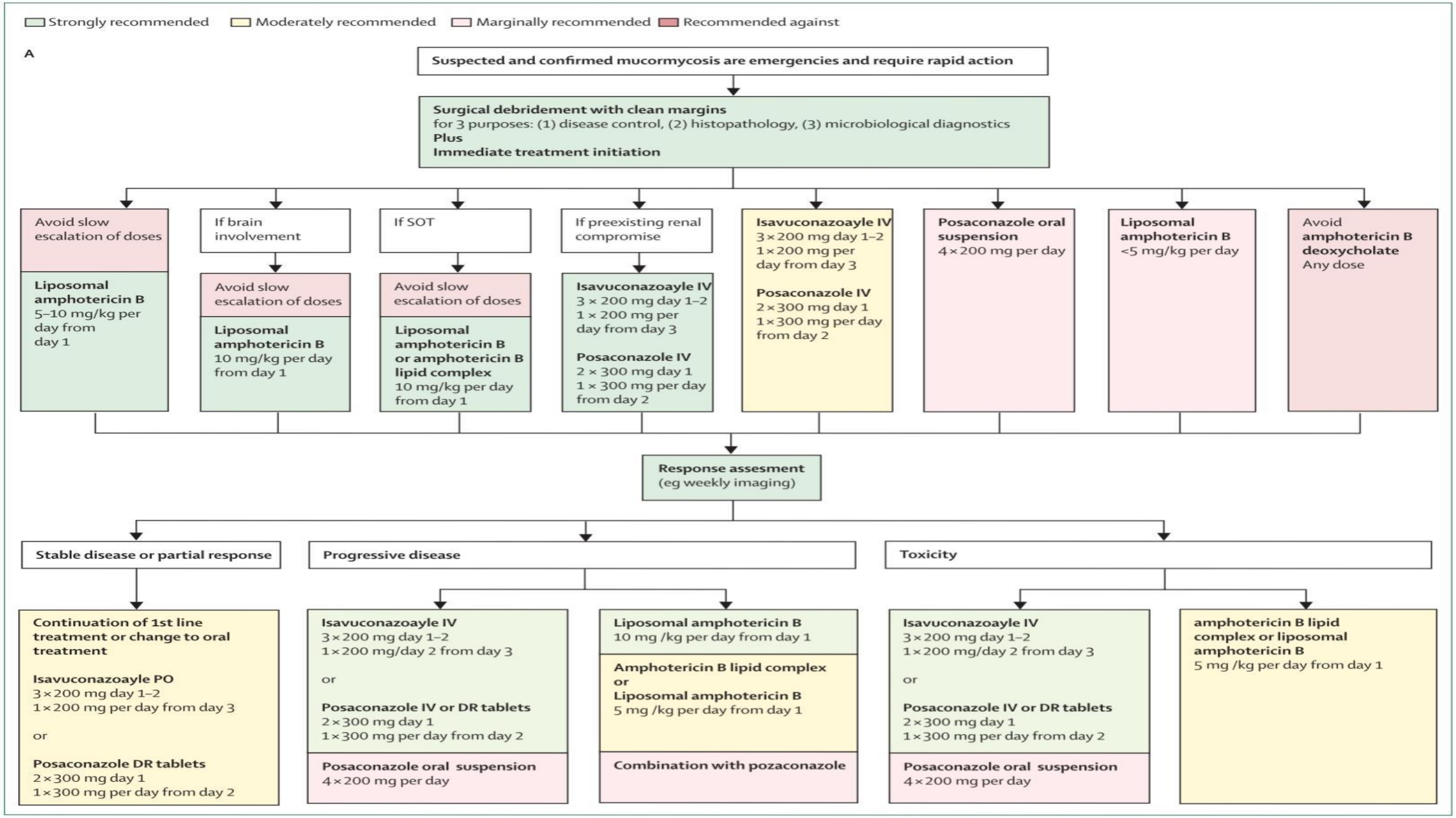
Mucormycosis treatment: Recommendations, latest advances, and perspectives

K. Brunet [a, b, c] ... B. Rammaert [a, b, d]

Review

Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium

Oliver A Cornely, Ana Alastruey-Izquierdo, Dorothee Arenz, Sharon C A Chen, Eric Dannaoui, Bruno Hochhegger, Martin Hoenigl, Henrik E Jensen, Katrien Lagrou, Russell E Lewis, Sibylle C Mellinghoff, Mervyn Mer, Zoi D Pana, Danila Seidel, Donald C Sheppard, Roger Wahba, Murat Akova, Alexandre Alanio, Abdullah M S Al-Hatmi, Sevtap Arikan-Akdagli, Hamid Badali, Ronen Ben-Ami, Alexandro Bonifaz, Stéphane Bretagne, Elio Castagnola, Methee Chayakulkeeree, Arnaldo L Colombo, Dora E Corzo-León, Lubos Drgona, Andreas H Groll, Jesus Guinea, Claus-Peter Heussel, Ashraf S Ibrahim, Souha S Kanj, Nikolay Klimko, Michaela Lackner, Frederic Lamoth, Fanny Lanternier, Cornelia Lass-Floerl, Dong-Gun Lee, Thomas Lehrnbecher, Badre E Lmimouni, Mihai Mares, Georg Maschmeyer, Jacques F Meis, Joseph Meletiadis, C Orla Morrissey, Marcio Nucci, Rita Oladele, Livio Pagano, Alessandro Pasqualotto, Atul Patel, Zdenek Racil, Malcolm Richardson, Emmanuel Roilides, Markus Ruhnke, Seyedmojtaba Seyedmousavi, Neeraj Sidharthan, Nina Singh, János Sinko, Anna Skiada, Monica Slavin, Rajeev Soman, Brad Spellberg, William Steinbach, Ban Hock Tan, Andrew J Ullmann, Jörg J Vehreschild, Maria J G T Vehreschild, Thomas J Walsh, P Lewis White, Nathan P Wiederhold, Theoklis Zaoutis, Arunaloke Chakrabarti, for the Mucormycosis ECMM MSG Global Guideline Writing Group



(Figure 5 continues on next page)

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

Management includes: -Antifungal therapy -Control of underlying disease -Surgery	AII
Posaconazole	B II
Combination of lipid amphotericin B and caspofungin	B III
Combination of lipid amphotericin B and posaconazole	B III

Journal of *Fungi*

MDPI

Review

Therapy of Mucormycosis

Nikolaos V. Sipsas [1], Maria N. Gamaletsou [1], Amalia Anastasopoulou [1] and Dimitrios P. Kontoyiannis [2,*]

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[2] Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

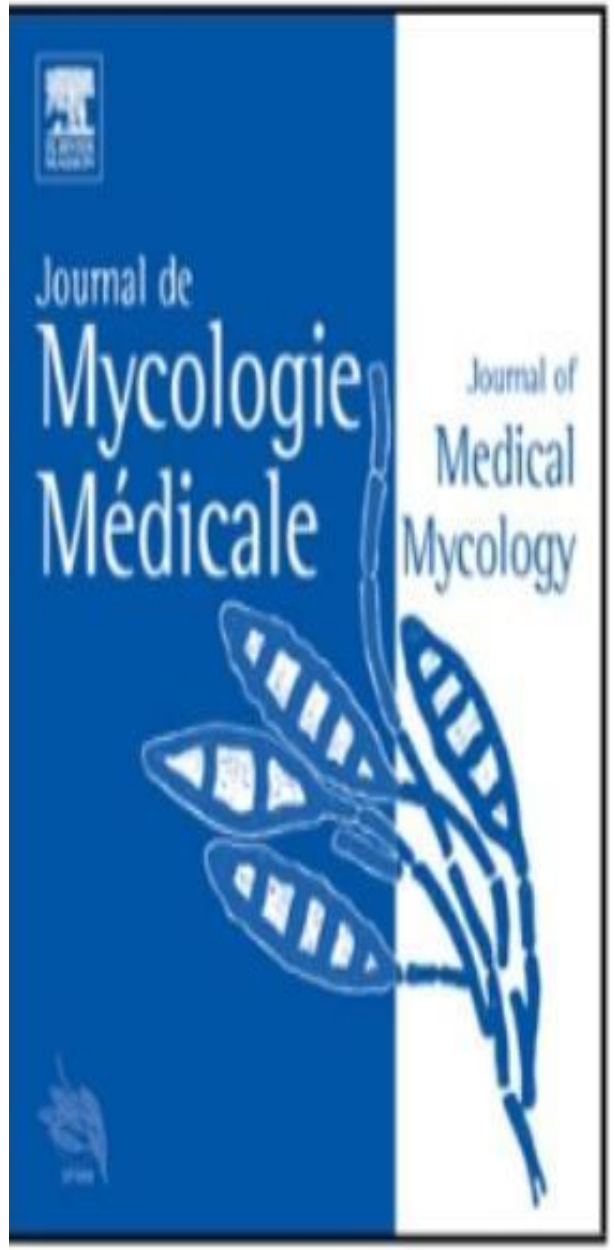
* Correspondence: dkontoyi@mdanderson.org; Tel.: +1+713-792-6237

- **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.**

J. Fungi 2018, 4

- **Combination are not currently recommended for first-line therapy due to lack evidence of their efficacy.**

- **Combinations of antifungal agents have been largely tested in vitro. Most combinations were indifferent, except for AmB + caspofungin (CAS), PSZ + CAS and ISZ + CAS which were synergistic**



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- **Combination** antifungal therapy is typically used by many physicians in an attemptto maximize treatment of this devastating disease, especially in patients with profound immunosuppression that cannot be reverted

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- Despite a paucity of data, many experts support the use of combination therapy with L-AmB and posaconazole, given the potential clinical benefit and the lack of evidence for antagonism between the drugs.

- Echinocandins have also been used in combination with AmB despite their lack of activity against Mucorales.

- The clinical experience using combination therapy with echinocandins and AmB is limited to small retrospective series and case reports.

Thank You!