Management of Mucormycosis

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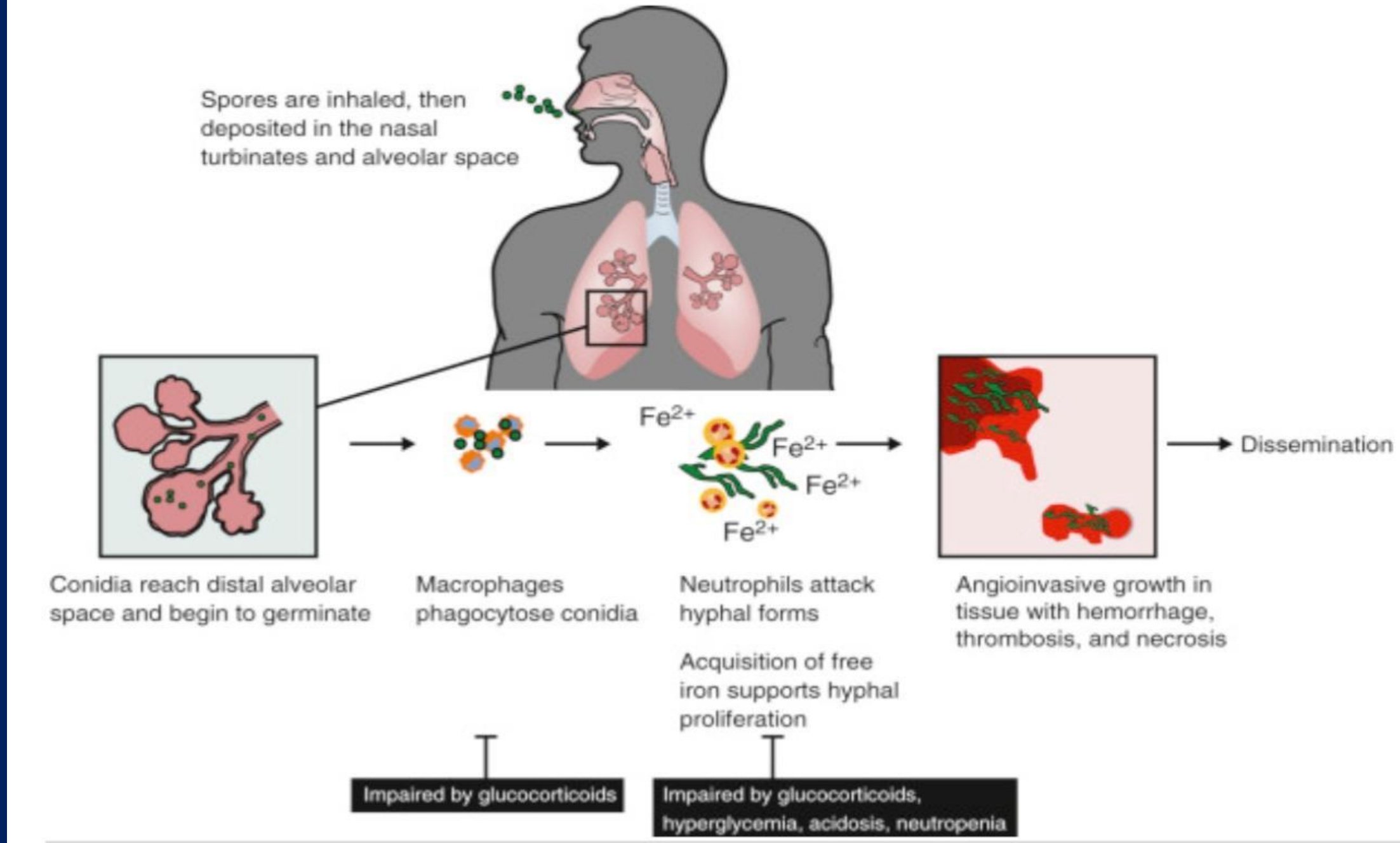
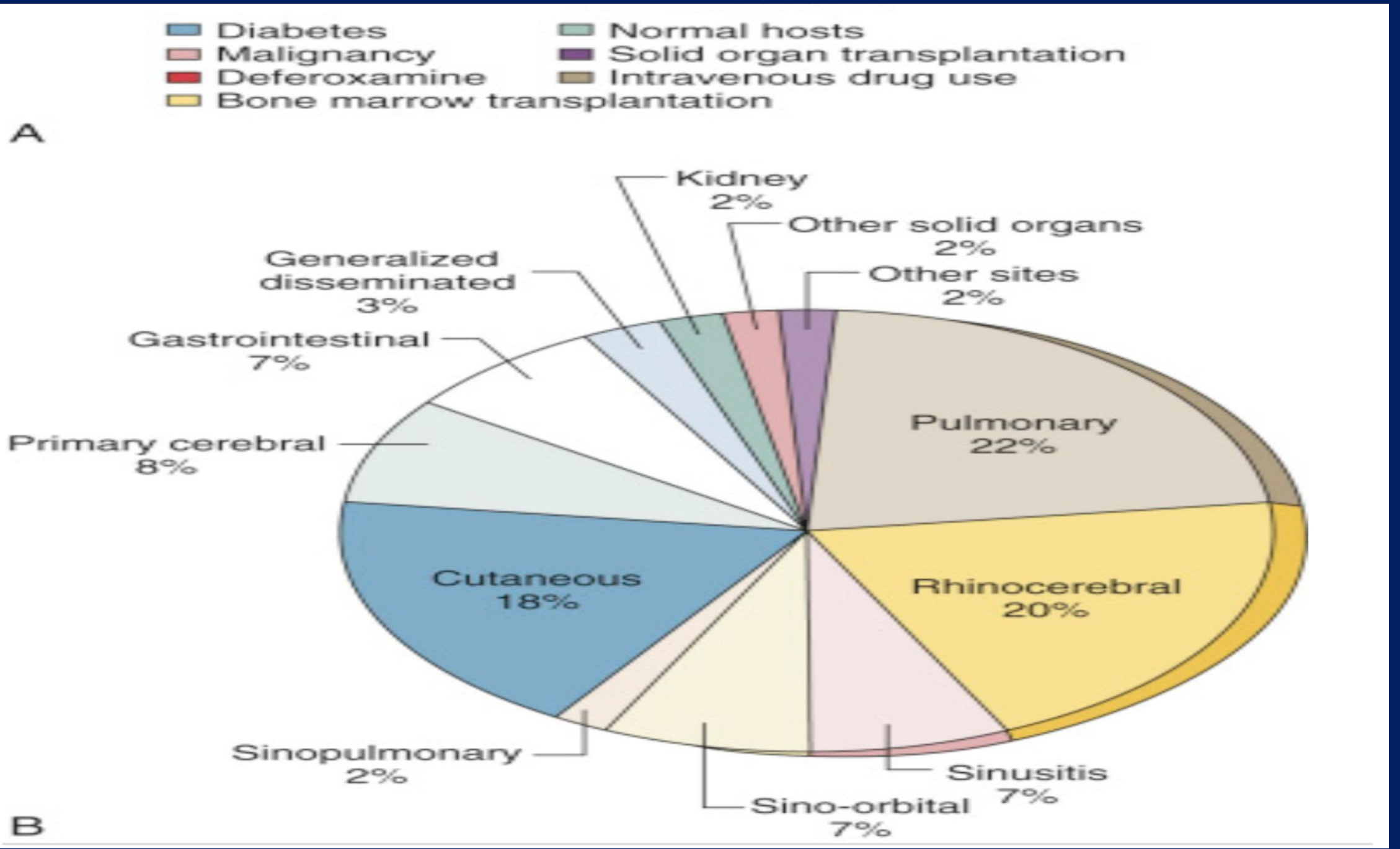

Spores are inhaled, then deposited in the nasal turbinates and alveolar space
Fe2+
Fe2+
Fe2+
Dissemination
Conidia reach distal alveolar space and begin to germinate
Macrophages phagocytose conidia
Neutrophils attack hyphal forms
Acquisition of free iron supports hyphal proliferation
Angioinvasive growth in tissue with hemorrhage, thrombosis, and necrosis
Impaired by glucocorticoids
Impaired by glucocorticoids, hyperglycemia, acidosis, neutropenia

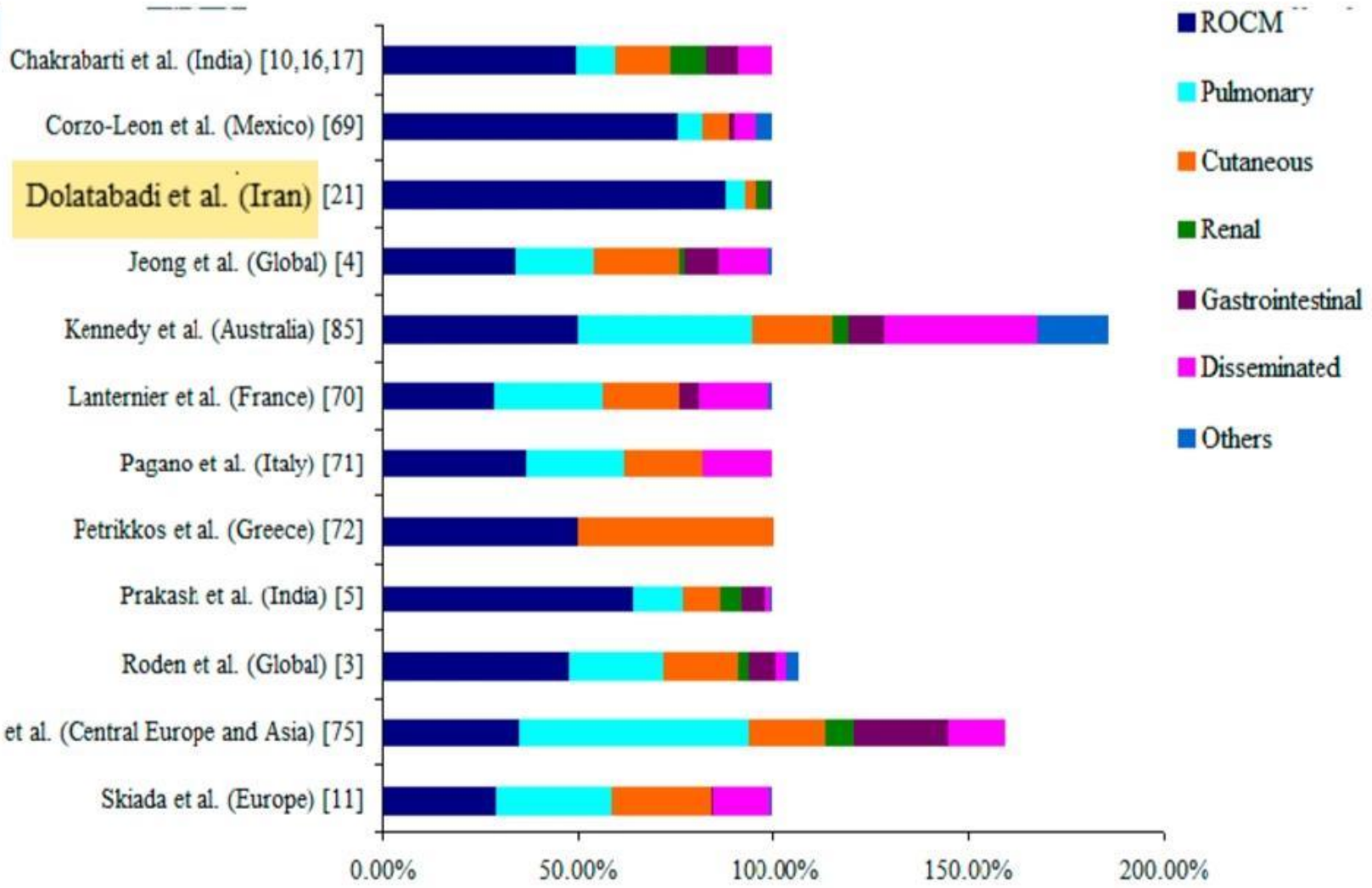
RISK FACTORS-

1. Case of concurrent or recently (<6 weeks) treated Severe COVID-19
2. **Uncontrolled diabetes mellitus**, Chronic granulomatous diseases, HIV/AIDS, or primary immunodeficiency states
3. Use of Immunosuppression by steroids (**any dose use for >3weeks or high dose >1week**), Tocilizumab, other immunomodulators, or therapy used with transplantation
4. Prolonged neutropenia
5. Trauma, Burns, IV drug abusers
6. Prolonged ICU stay
7. Post-transplant/malignancy (solid or Hemopoietic)
8. Voriconazole therapy, Deferoxamine or **other iron overloading therapy**
9. Contaminated adhesive bandages, wooden tongue depressors, adjacent building construction, and hospital linens
10. Renal failure, diarrhea, and **malnutrition** in low-birth-weight infants/even children/adults


Diabetes
Malignancy
Deferoxamine
Bone marrow transplantation
Normal hosts
Solid organ transplantation
Intravenous drug use
A
Kidney
2%
Other solid organs
2%
Other sites
2%
Generalized
disseminated
3%
Gastrointestinal
7%
Primary cerebral
8%
Pulmonary
22%
Cutaneous
18%
Rhinocerebral
20%
Sinopulmonary
2%
Sinusitis
7%
Sino-orbital
7%
B

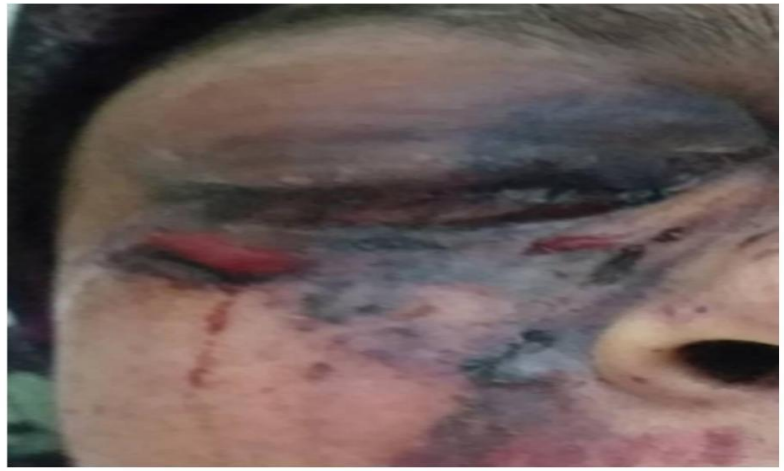
Clinical forms of mucormycosis reported from different studies across the globe

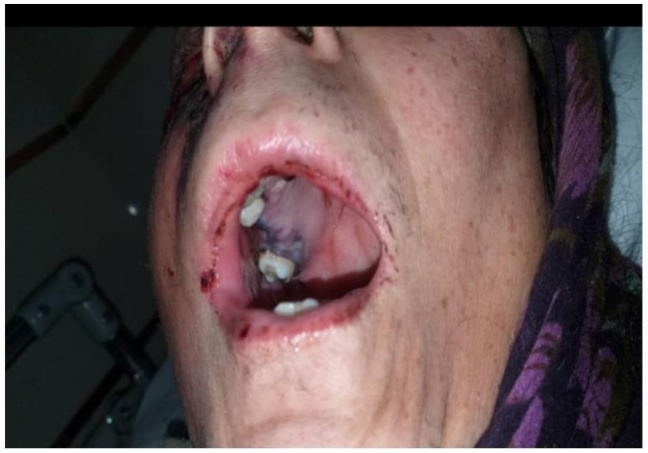
- ROCM is the most common form.
- A meta-analysis of mucormycosis cases revealed that **Rhizopus** species was often associated with ROCM form of the disease

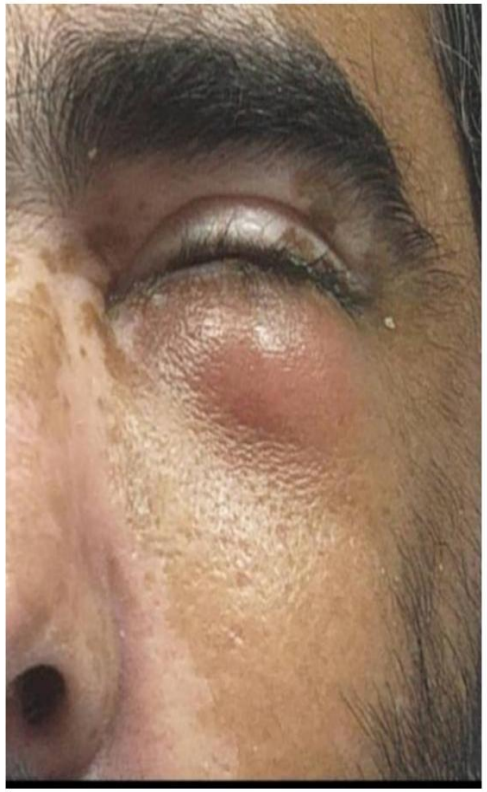


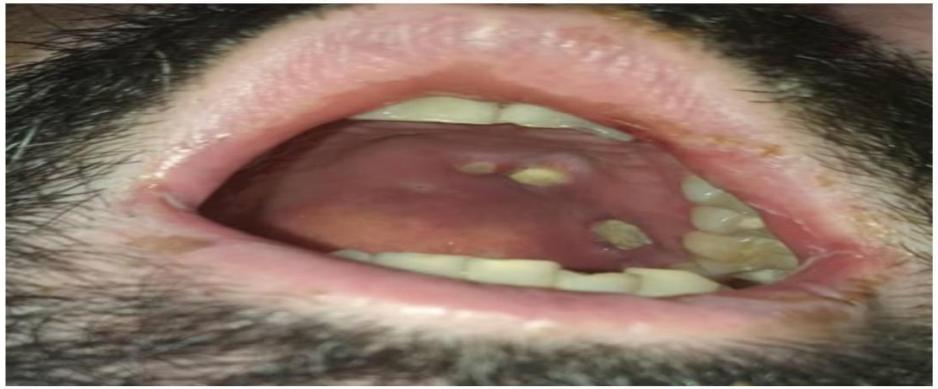
1. Rhino-orbito-cerebral mucormycosis (ROCM)	Nasal stuffiness, foul smell, epistaxis, nasal discharge, unilateral facial oedema, diplopia, proptosis, pain and redness around eyes and/or nose, loss of vision, restriction of eye movements, palatal or palpebral fistula, blackish discolouration over bridge of nose/palate, prolonged Fever, headache, toothache, loosening of teeth, jaw involvement, altered mental status
2. Cutaneous and soft tissue mucormycosis	Erythema, induration, then black eschar at trauma/puncture site, muscle pain with deeper involvement
3. Pulmonary mucormycosis	Refractory fever on broad-spectrum antibiotics, non-productive cough, progressive dyspnea, pleuritic chest pain
4. Gastrointestinal mucormycosis	Fever, bleeding per anus, masslike lesions, then perforation of gut
5. Mucormycosis of bones and joints	Local pain and tenderness, cellulitis, fever is rare
6. Disseminated mucormycosis	Symptoms vary as per site of involvement, mostly associated with pneumonia

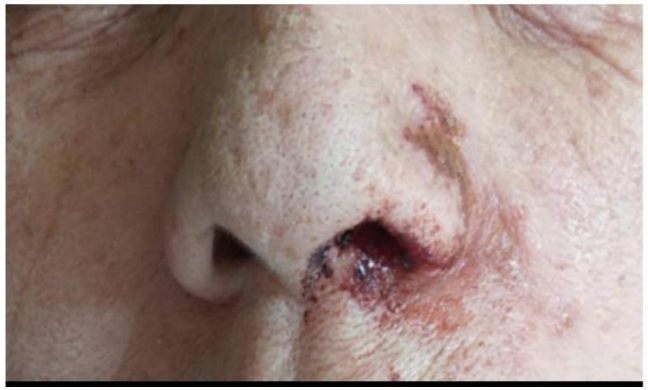
Mucormycosis



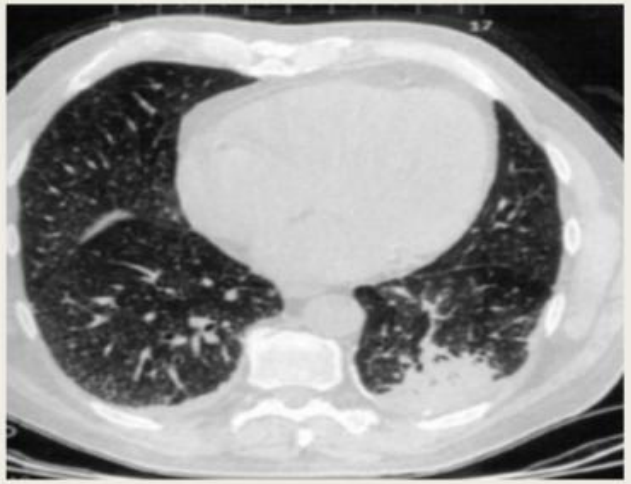


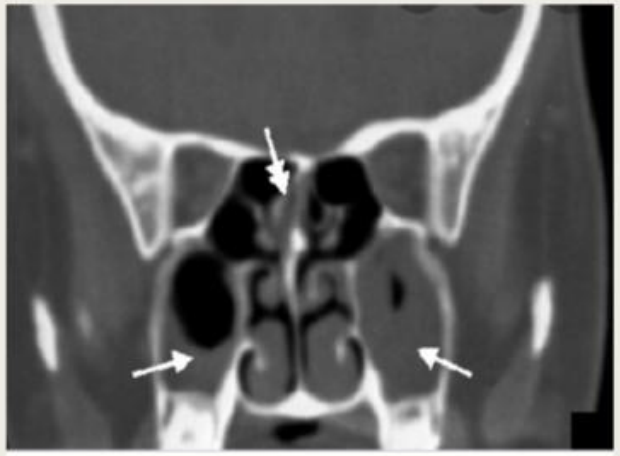


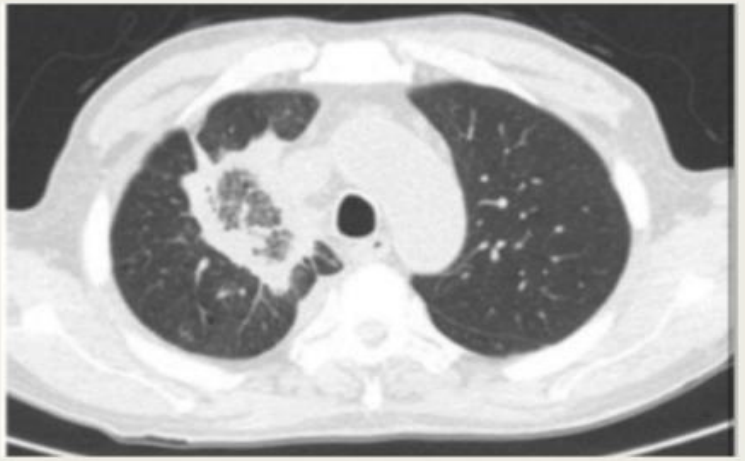


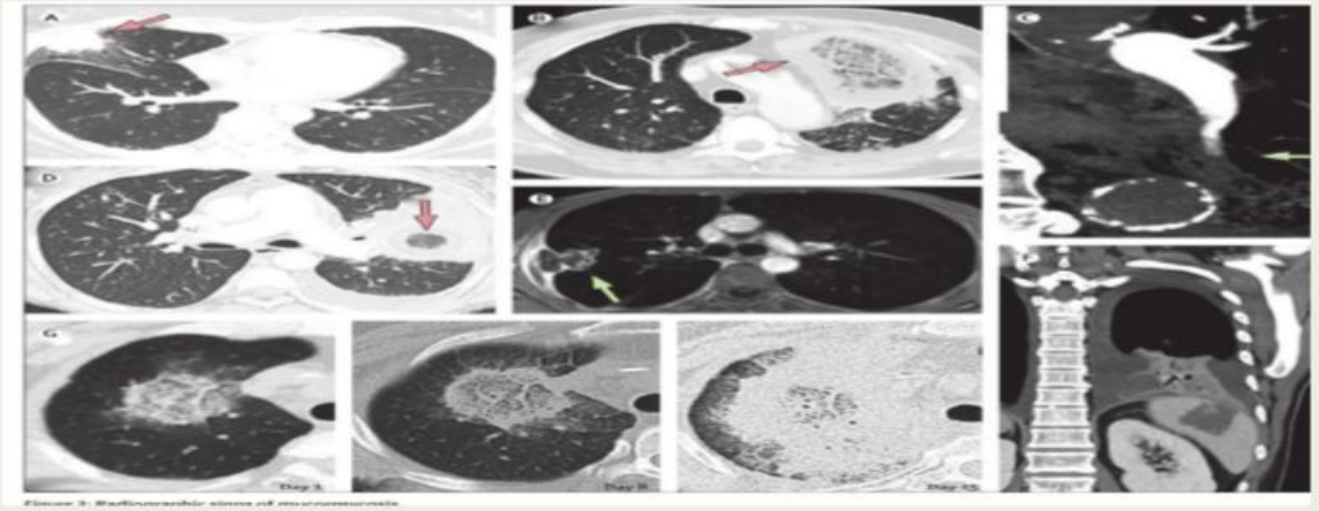


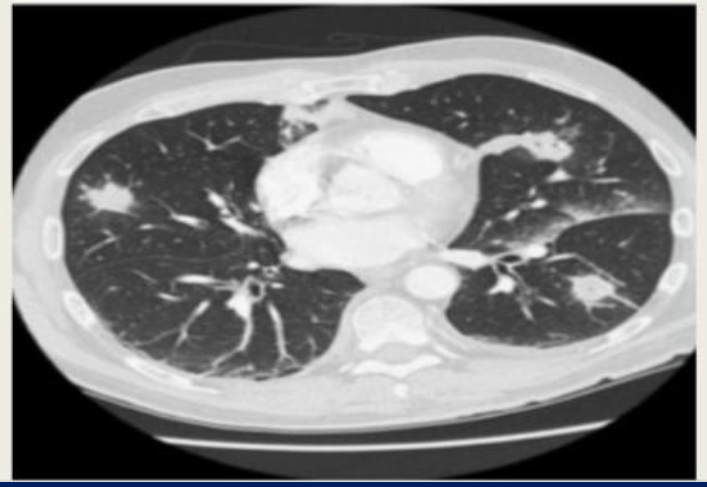
Sinopulmonary Mucormycosis











Patterns of IFI in practice

Clinical Infectious Diseases

MAJOR ARTICLE

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

EORTC/MSG Consensus Group definitions:

Proven IFI	Probable IF	Possible IFI
Histological or culture evidence (in sterile material)	Host factors (neutropenia, immunosuppressants) + **Mycological criteria** (direct - cytology, culture of non sterile material - or indirect tests - GM or βDG) + Clinical criteria (+CT/MRI, FBS, retinal)	Host factors + **Clinical criteria**

Mucormycosis

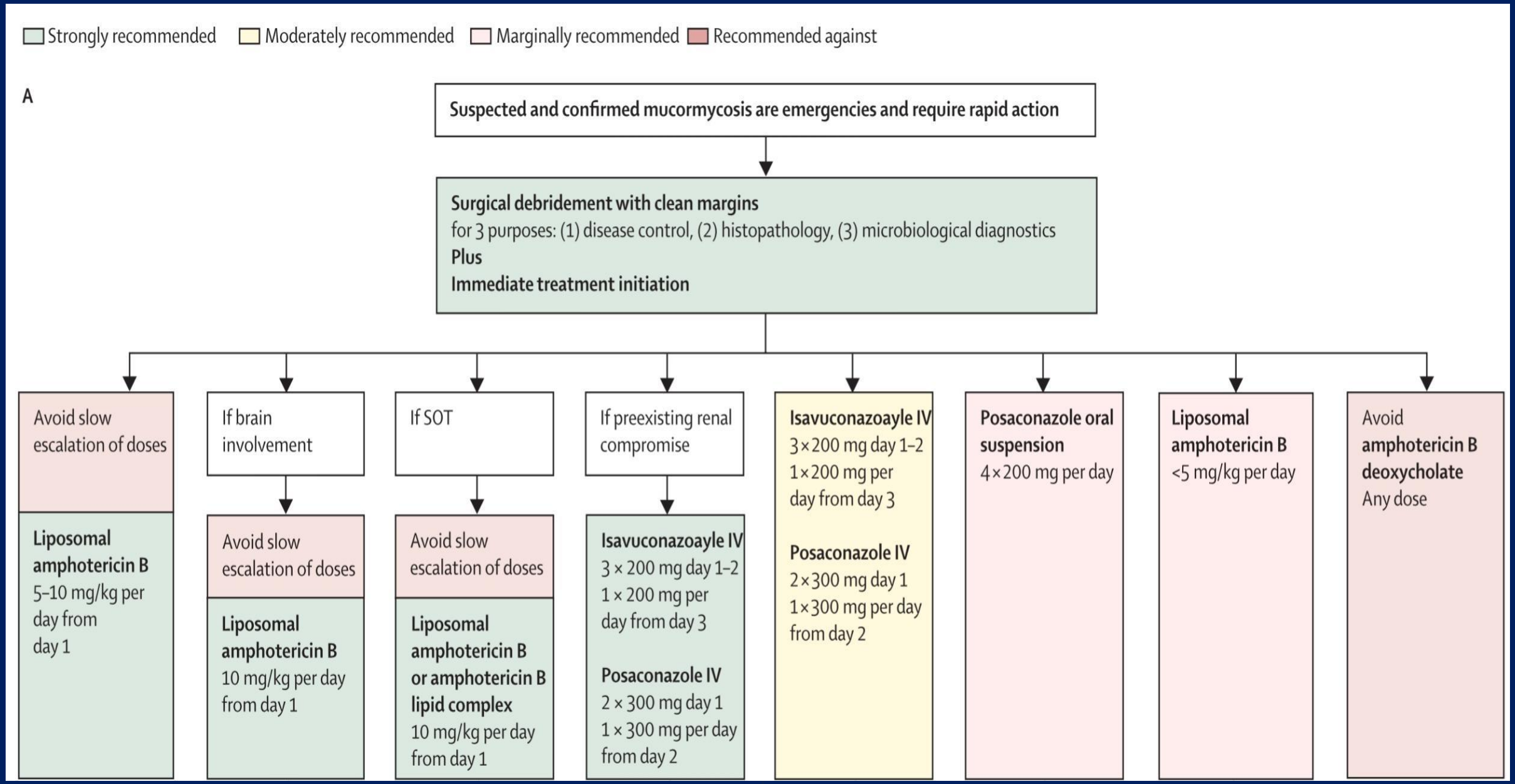
- Mucorales are intrinsically resistant to :
- Fluconazole
- Itraconazole
- Voriconazole
- Echinocandins
- Flucytosine

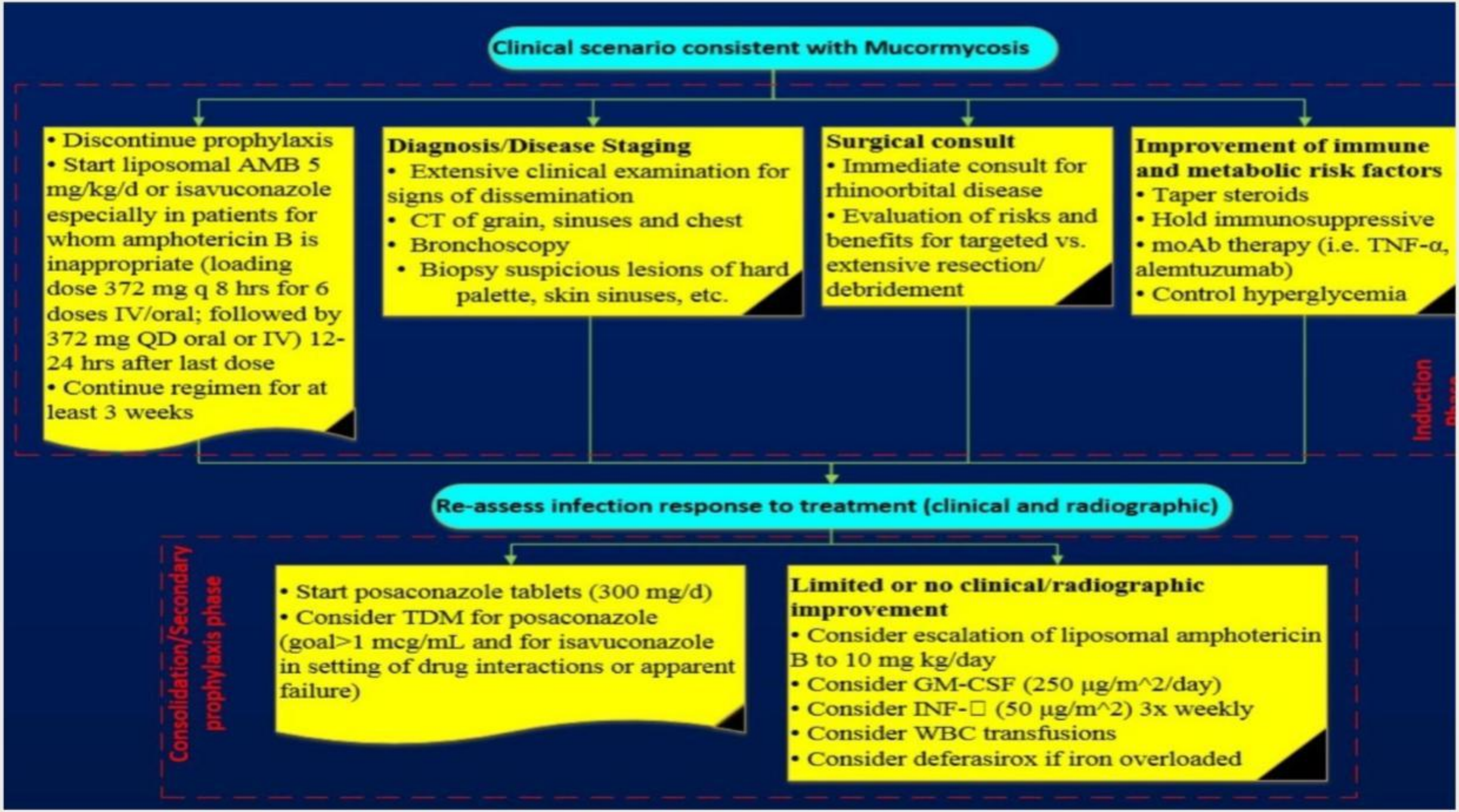
Infect Dis Clin N Am 35 (2021) 415–434

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


Strongly recommended
Moderately recommended
Marginally recommended
Recommended against
A
Suspected and confirmed mucormycosis are emergencies and require rapid action
Surgical debridement with clean margins
for 3 purposes: (1) disease control, (2) histopathology, (3) microbiological diagnostics
Plus
Immediate treatment initiation
Avoid slow escalation of doses
Liposomal amphotericin B
5–10 mg/kg per day from day 1
If brain involvement
Avoid slow escalation of doses
Liposomal amphotericin B
10 mg/kg per day from day 1
If SOT
Avoid slow escalation of doses
Liposomal amphotericin B or amphotericin B lipid complex
10 mg/kg per day from day 1
If preexisting renal compromise
Isavuconazoayle IV
3 × 200 mg day 1–2
1 × 200 mg per day from day 3
Posaconazole IV
2 × 300 mg day 1
1 × 300 mg per day from day 2
Isavuconazoayle IV
3×200 mg day 1–2
1×200 mg per day from day 3
Posaconazole IV
2×300 mg day 1
1×300 mg per day from day 2
Posaconazole oral suspension
4×200 mg per day
Liposomal amphotericin B
<5 mg/kg per day
Avoid amphotericin B deoxycholate
Any dose


Clinical scenario consistent with Mucormycosis
• Discontinue prophylaxis
• Start liposomal AMB 5 mg/kg/d or isavuconazole especially in patients for whom amphotericin B is inappropriate (loading dose 372 mg q 8 hrs for 6 doses IV/oral; followed by 372 mg QD oral or IV) 12-24 hrs after last dose
• Continue regimen for at least 3 weeks
Diagnosis/Disease Staging
• Extensive clinical examination for signs of dissemination
• CT of grain, sinuses and chest
• Bronchoscopy
• Biopsy suspicious lesions of hard palette, skin sinuses, etc.
Surgical consult
• Immediate consult for rhinoorbital disease
• Evaluation of risks and benefits for targeted vs. extensive resection/ debridement
Improvement of immune and metabolic risk factors
• Taper steroids
• Hold immunosuppressive
• moAb therapy (i.e. TNF-α, alemtuzumab)
• Control hyperglycemia
Induction phase
Re-assess infection response to treatment (clinical and radiographic)
Consolidation/Secondary prophylaxis phase
• Start posaconazole tablets (300 mg/d)
• Consider TDM for posaconazole (goal>1 mcg/mL and for isavuconazole in setting of drug interactions or apparent failure)
Limited or no clinical/radiographic improvement
• Consider escalation of liposomal amphotericin B to 10 mg kg/day
• Consider GM-CSF (250 µg/m^2/day)
• Consider INF-□ (50 µg/m^2) 3x weekly
• Consider WBC transfusions
• Consider deferasirox if iron overloaded

ECMM/ISHAM recommendations for clinical management of COVID-19 associated mucormycosis in low- and middle-income countries

1. Diabetes control
2. Reduce steroids
3. Discontinue immuno-modulaters

Extensive surgical debridement (If eye involved, exenteration of eye; in lung, if localized or one lobe involved)

Medical therapy (maintain adequate hydration; put PICC or CVC)

Liposomal/lipid amphotericin B
5mg/kg/d for 3-6 weeks
1. Infuse 500ml of normal saline before and after infusion of amphotericin B
2. In 200ml 5% dextrose over 2-3h
3. No slow escalation
4. In CNS infection, dose can increase to 10mg/kg/d
5. Monitor RFT, potassium & magnesium level

Lipid amphotericin B Not available

Amphotericin B deoxycholate – 1-1.5mg/kg/d for 3-6 weeks
1. Infuse 500ml of normal saline before and after infusion of amphotericin BIn 5% dextrose slow infusion for 6-8 hours
2. Pre-medication to avoid infusion reaction
3. No slow escalation
4. Monitor RFT, potassium & magnesium level

Polyene not available or intolerant to polyene

Isavuconazole inj – 200mg tid on day 1-2 & 200mg/d from day 3 for 3-6 weeks
OR
Posaconazole inj – 300mg bid on day 1 & then 300mg/d for 3-6 weeks
(Monitor trough level after 3-5 days)

Polyene/Isavuconazole/ posaconazole not available

Itraconazole – 200mg tid for
- Injection preferable, suspension is the next choice before tablet
- Stop proton-pump inhibitor, H2 blockers when tablet used
- SUBA may itraconazole can reduce absorption issues.
- Consume along with food
- TDM after 5 days is recommended

Stable disease after 3-6 weeks

Isavuconazole tab – 200mg tid on day 1-2 & then 200mg/d for 3-6 months
OR
Posaconazole tab – 300mg bid on day 1 & then 300mg/d for 3-6 months
(Posaconazole trough level after 3-5 days recommended)

Progressive disease clinically & radiologically

If on amphotericin B

Raise the dose of amphotericin B **OR** Isavuconazole tab – 200mg tid on day 1-2 & then 200mg/d for 3-6 months **OR** Posaconazole tab – 300mg bid on day 1 & then 300mg/d for 3-6 months
(Monitor posaconazole trough level after 3-5 days)

If on azole

Consider adding polyene; TDM, dose adjustment, drug-drug interaction with azole

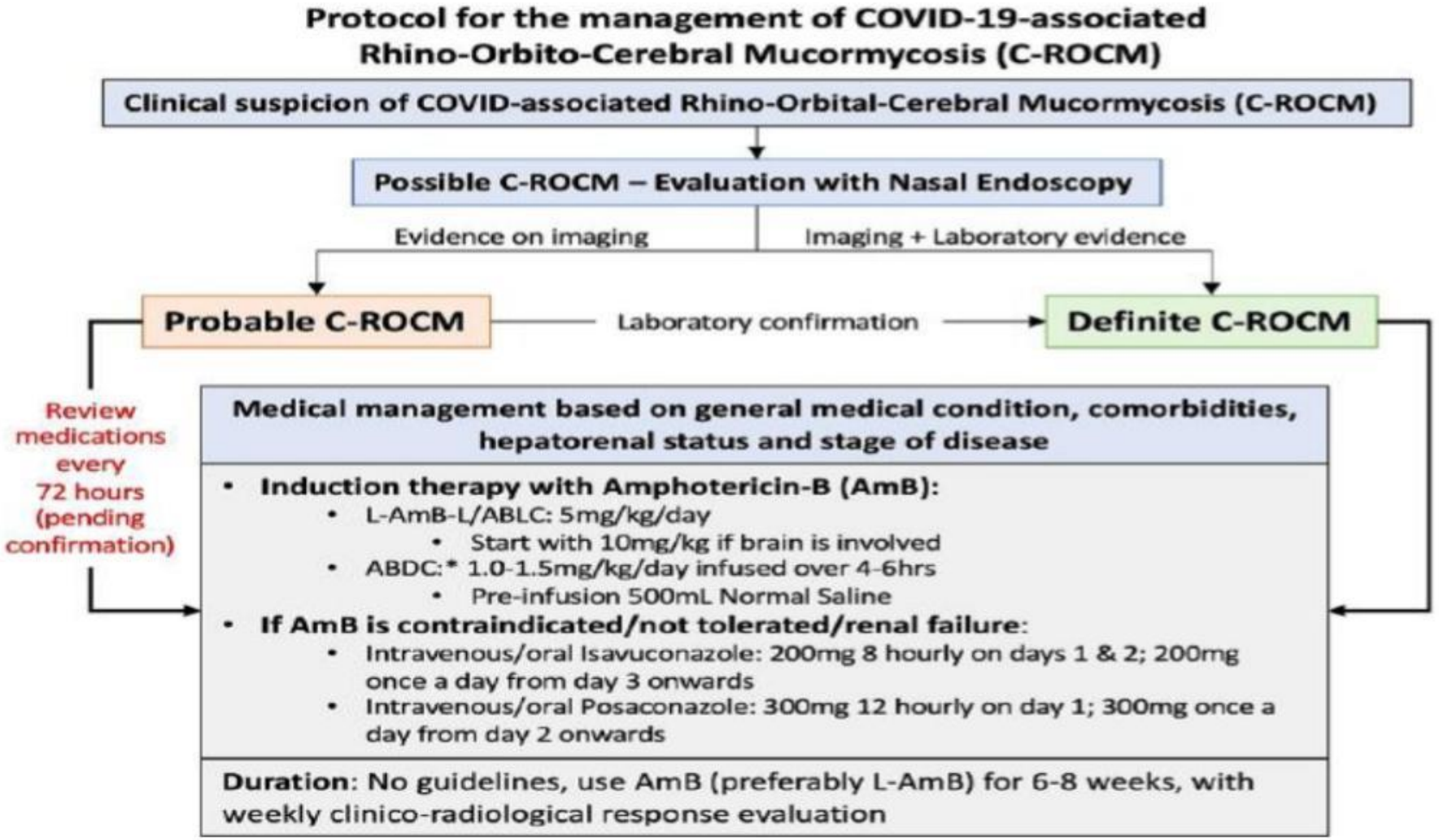
Toxicity

1. Shift to azoles, if the patient is on polyene
2. Shift to isavuconazole, if drug interaction with posaconazole

Mycoses, Volume: 64, Issue: 9, Pages: 1028-1037, First published: 16 June 2021, DOI: (10.1111/myc.13335)

COVID-19-associated mucormycosis: An updated systematic review of literature

Rimesh Pal et al. Mycoses. 2021 Dec.

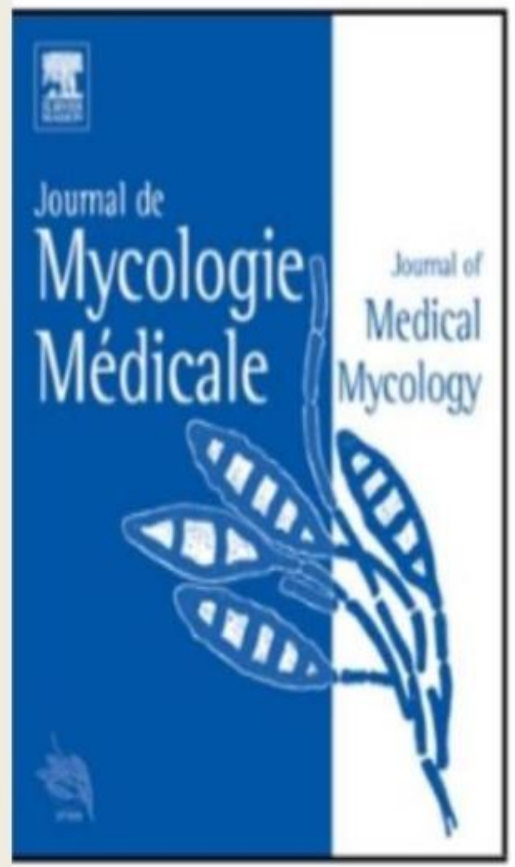


Journal de Mycologie Médicale
Volume 30, Issue 3, September 2020, 101007

General review

Mucormycosis treatment: Recommendations, latest advances, and perspectives

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



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

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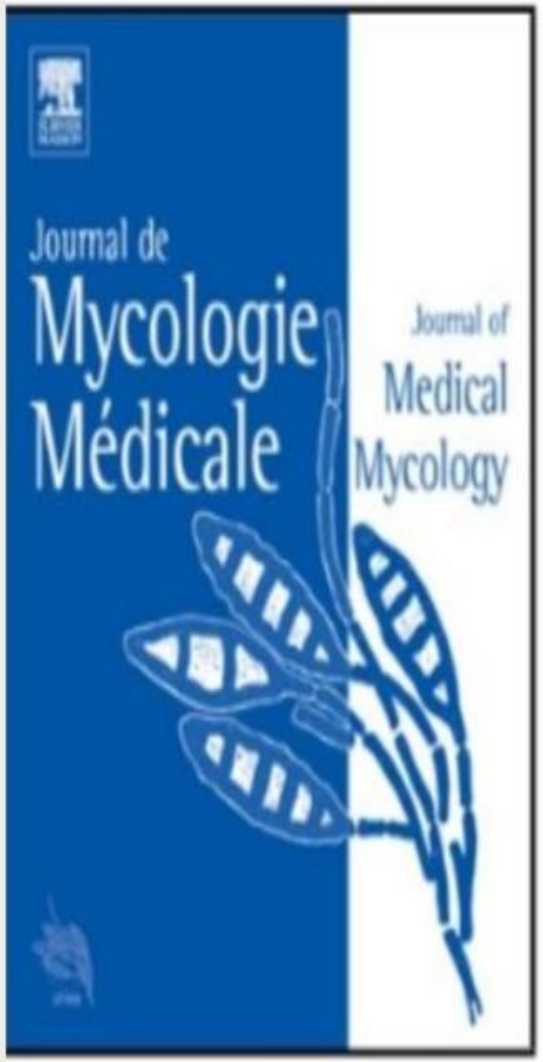
- **Clinical data do not support the use of combination therapy, with the possible exception of CNS mucormycosis, where a combination of high-dose LAMB and posaconazole or isavuconazole might be considered.**

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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Thank You!