

Mucormycosis - Updates in 2025

Methee Chayakulkeeree, MD, PhD, FECMM

Division of Infectious Diseases and Tropical Medicine

Department of Medicine, Faculty of Medicine Siriraj Hospital

Mahidol University, BANGKOK, THAILAND

Disclosures

Copyright reserved by data providers and :

- No conflict of interest related to this presentation

ASIA FUNGAL
WORKING GROUP
an ISHAM working group

Mucormycosis

- Life threatening angio-invasive fungal infection primarily occurs in immunocompromised host
 - Uncontrolled diabetes, hematologic malignancies, or transplants
- Infection can also occur in immunocompetent individuals
 - Traumatic inoculation or following natural disasters
- Novel risk factor - COVID-19
- Cause thrombosis and tissue necrosis
- Very high mortality (50-100%) despite aggressive therapy

The Mucorales

R. arrhizus 33%

R. microsporus 15%

48%

Rhizopus

Mucorales

- 261 species
- 55 genera,
- 38 species cause human infections

14%

Mucor

Apophysomyces

Lichtheimia

13%

Syncephalastrum

Actinomucor

Saksenaëa

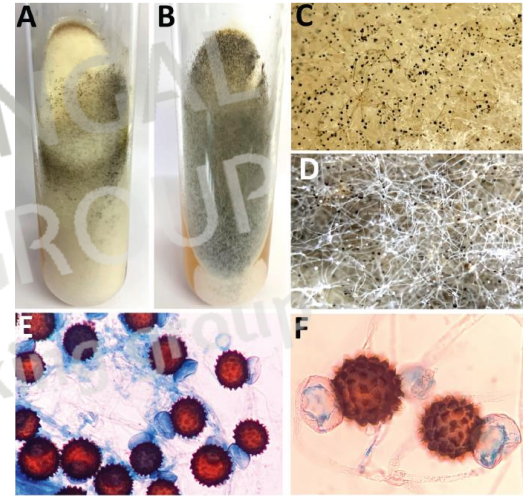
Cunninghamella

RhizoMucor

Cokeromyces

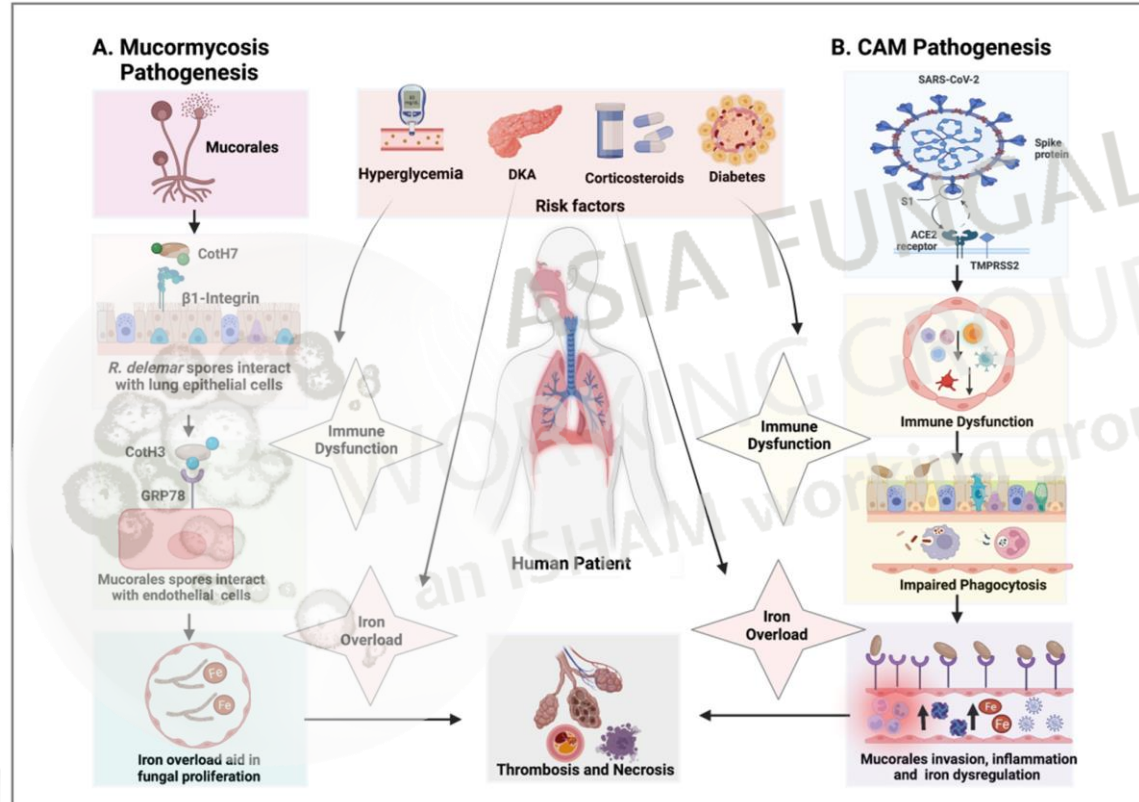
Emerging Mucormycosis caused by *Rhizopus homothallicus* in India

- *R. homothallicus* accounted for 43 (6.8%) of the 631 cases of mucormycosis
- *R. homothallicus* infection had better survival than *R. arrhizus* (mortality 9.8% vs. 39.1%)
- Low MICs for *R. homothallicus* against antifungals
 - Amphotericin B [0.03–16]
 - Itraconazole [0.03–16]
 - Posaconazole [0.03–8]
 - Isavuconazole [0.03–16]
- 18S gene sequencing and AFLP revealed distinct clustering of *R. homothallicus*

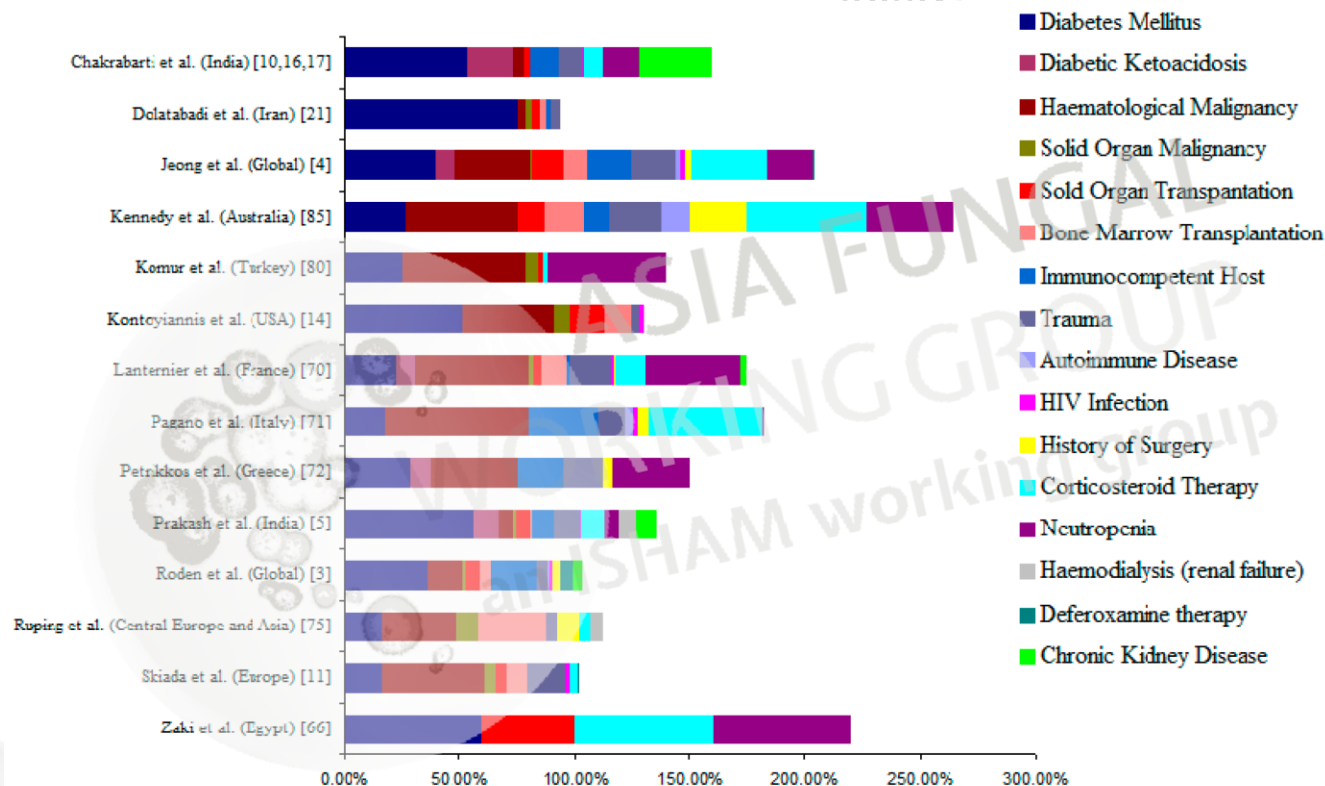


A, C, E = *R. homothallicus*
B, D, F = *R. arrhizus*

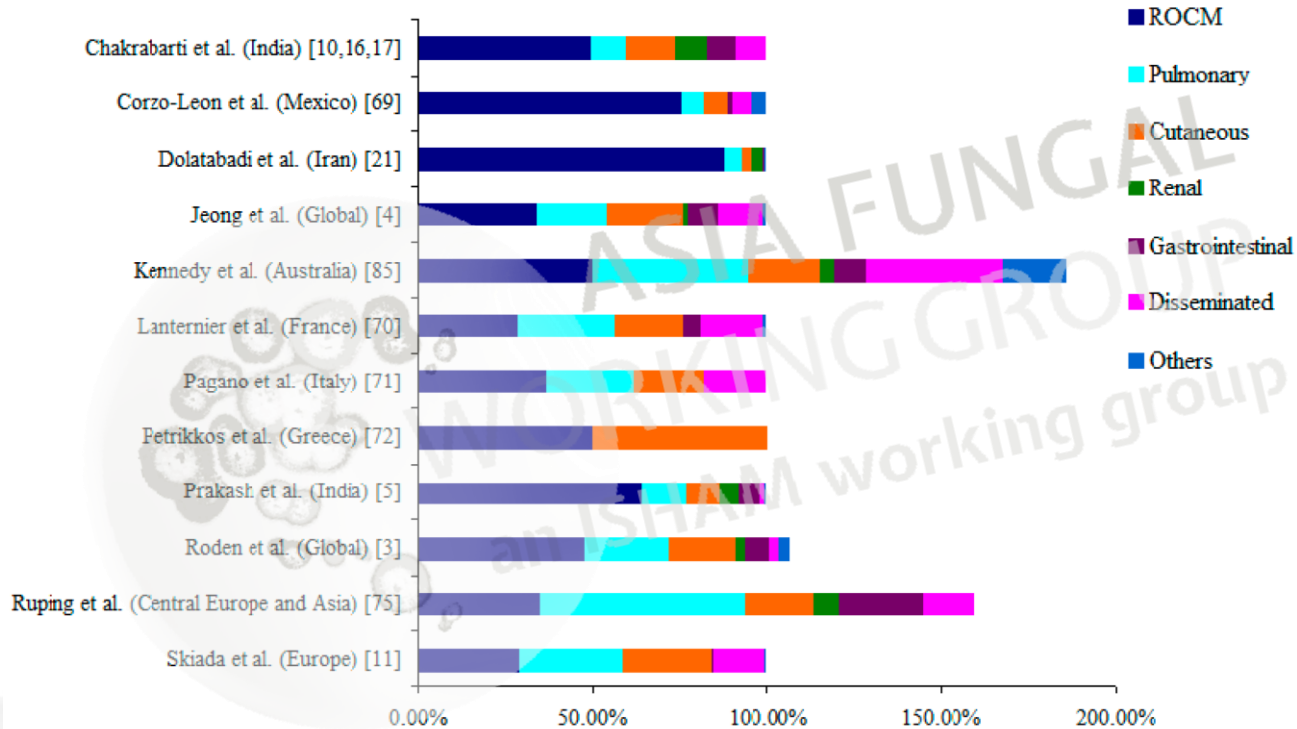
Pathogenesis



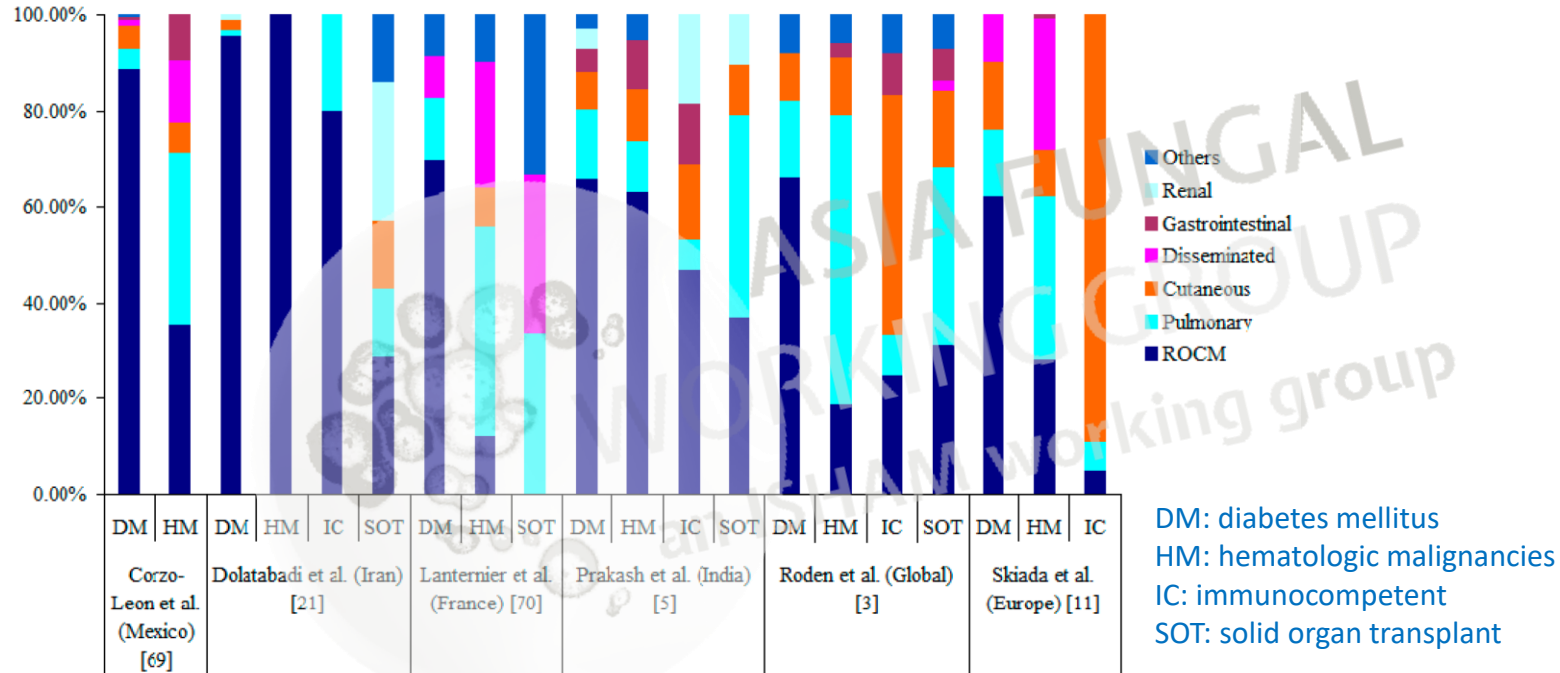
Risk Factors



Clinical Forms

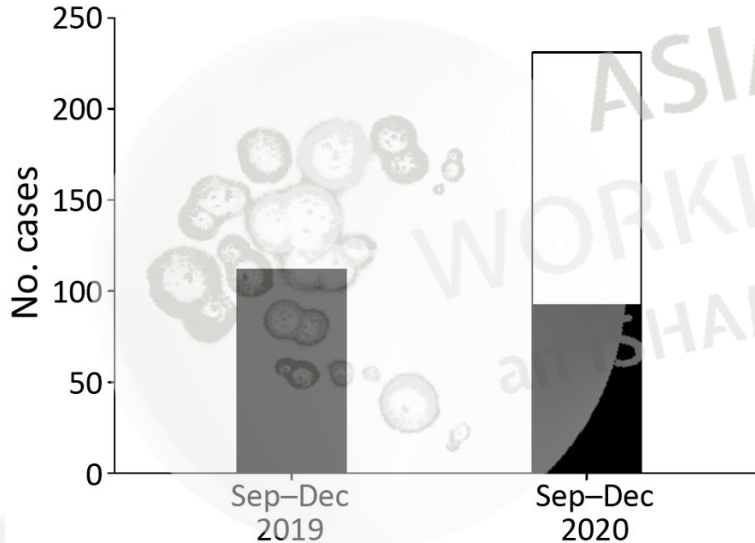


Risk Factors and Clinical Forms



COVID-19-Associated Mucormycosis (CAM)

- 0.27% in hospitalized COVID-19 patients in India (2.1-fold rise)



Species

Rhizopus arrhizus

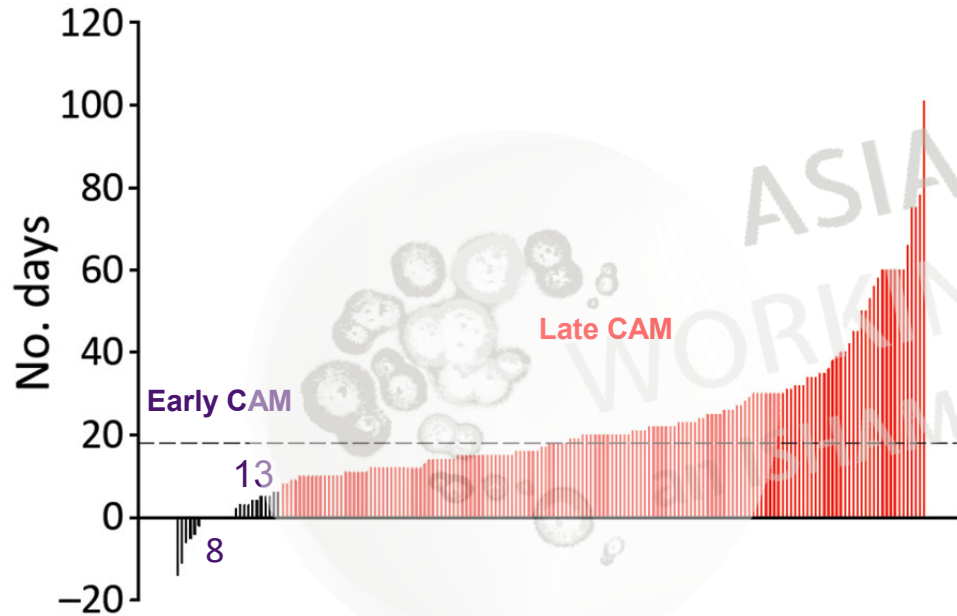
Rhizomucor pusillus

Apophysomyces variabilis

Lichtheimia corymbifera

Others

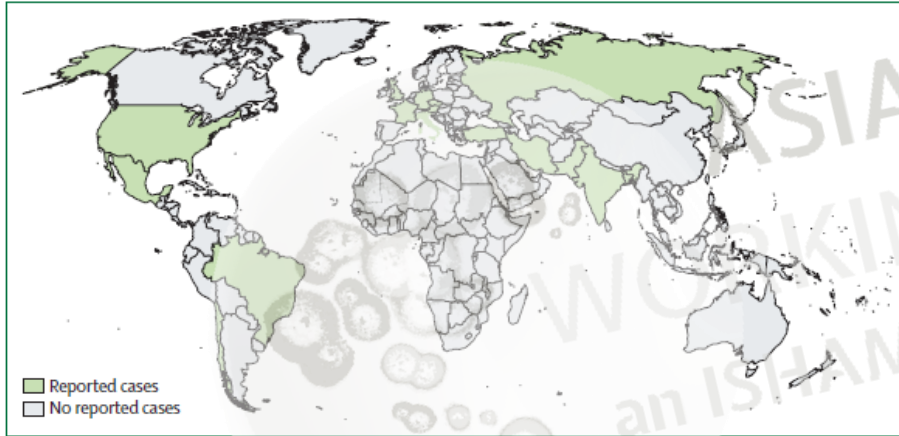
Onset of COVID-19-Associated Mucormycosis



Early CAM – DKA more often
Late CAM – Hypoxemia and steroids

Median day 18

Global Distribution of COVID-19-Associated Mucormycosis



Reports of 80 cases from 18 countries

The Perfect Storm Triad

- ARDS from SARS-CoV-2
- Corticosteroid
- Uncontrolled DM (most common)

COVID-19 – only underlying disease in 32.6% of CAM (no other co-morbidities)

Rhinocerebral mucormycosis > 50%

Scenario: A 84-Year-Old Woman

- Diagnosed with COVID-19 pneumonia, diabetes mellitus
- Received remdesivir and high dose corticosteroid (prednisolone 50 mg/day for 3 weeks)
- Painful and erythematous swelling at left eyelid and cheek
- Tissue biopsy was obtained from left sinus
- Histopathology revealed broad non-septate hyphae
- **Culture grew *Rhizopus* spp.**

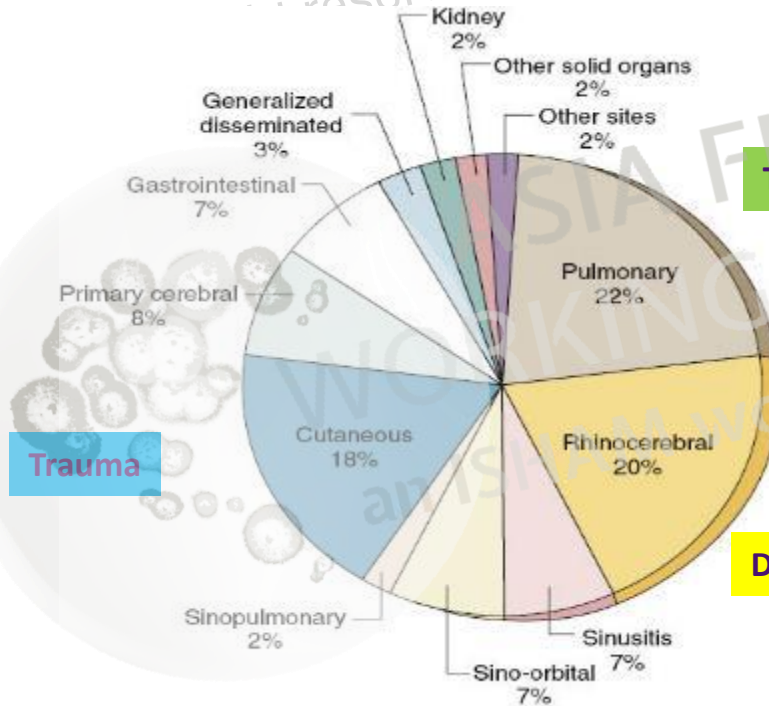


- **Diagnosis: COVID-19 –associated mucormycosis**
- **Treatment:**
 - Liposomal amphotericin B due to acute kidney injury

Risk Factors of Mold Infections

<i>A. fumigatus</i> and Other Molds	Shared Risk Factors for IMI	Unique for Mucormycosis
Primary immunodeficiency - Genetic defects in NADPH oxidase complex (CGD) - CADR9 deficiency	Defects in number or function of phagocytes in - Hematological malignancy and transplant recipients - Prolonged, persistent neutropenia - High doses of corticosteroids - Aplastic anemia	Primary immunodeficiency - Acquired STAT1 function - Papillon–Lefevre syndrome
Acquired immune defects Influenza-associated aspergillosis (IAPA)	Immune deactivation induced by bacterial sepsis Severe fever with thrombocytopenia syndrome (SFTS) Immunosuppression related to ibrutinib and other small-molecule kinase inhibitors (SMKIs) COVID-19-associated aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM)	Metabolic disorders - Poorly controlled DM - Diabetic ketoacidosis (DKA) - Other forms of acidosis - Acquired iron overload; - Deferoxamine therapy - Malnutrition
		Trauma and burns

Mucormycosis Manifestations

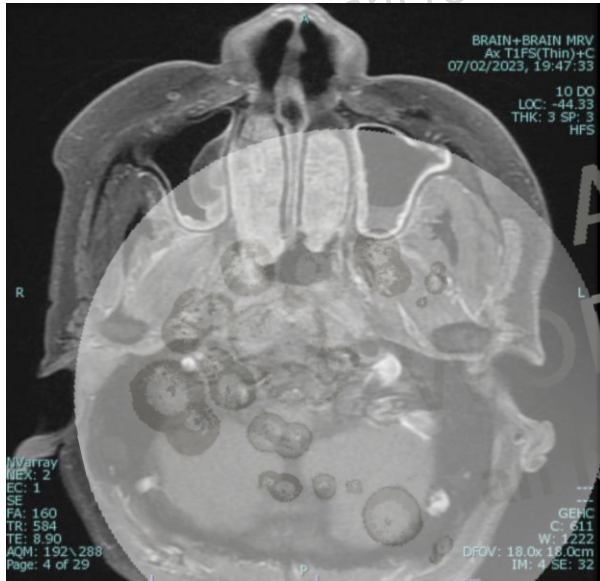


Transplants

Trauma

Diabetes mellitus

Rhino-Orbito-Cerebral Mucormycosis



Histopathology

Clinical Information:

40/M DM with extensive sinonasal necrosis

Pathologic Diagnosis

A) Labeled as "Right inferior turbinate", excision:

&

B) Labeled as "Right anterior ethmoid", excision:

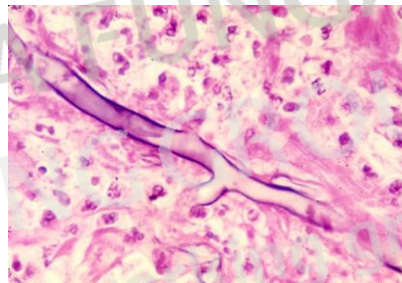
&

C) Labeled as "left anterior ethmoid", excision:

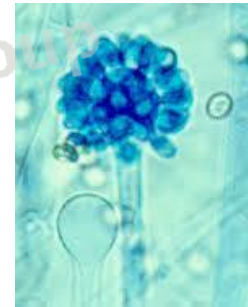
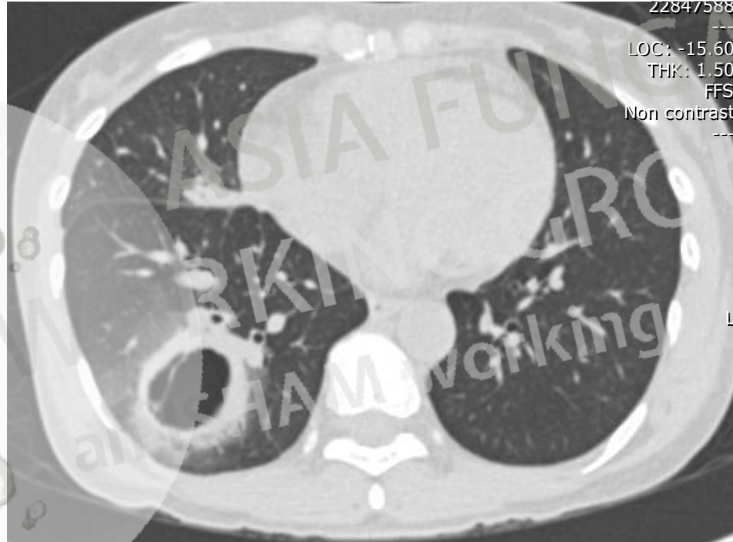
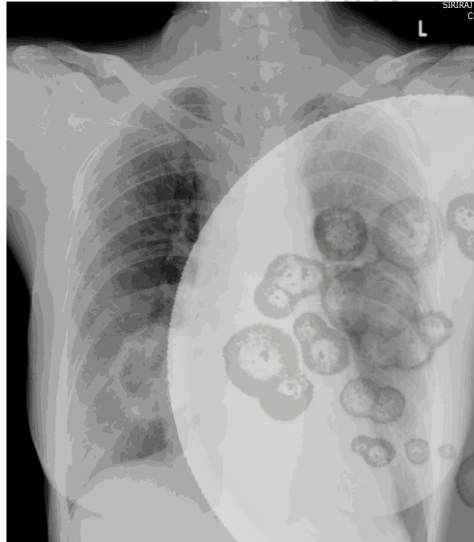
&

D) Labeled as "right middle turbinate", excision:

- **Invasive fungal necrotizing rhinosinusitis**; morphologically favoring mucormycosis, involving all four sites; *see comment*



Pulmonary Mucormycosis in a Kidney Transplant Recipient



Cunninghamella bertholletiae

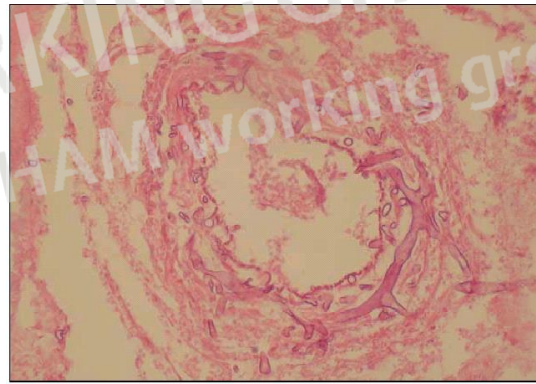
Tornado “Joplin” and Cutaneous Mucormycosis

- Large amount of soil particles disseminated by the tornado, the fungus was able to penetrate the open wounds of tornado victims
- Necrotizing soft tissue fungal infection
- Total 15 confirmed cases with 4 death
- Organism identified as *Apophysomyces trapeziformis*



Cutaneous Mucormycosis

- Multifocal cutaneous mucormycosis in a tsunami survivor from Sri Lanka
 - An Australian man injured in the tsunami with soft-tissue injuries
 - Cultures grew *Apophysomyces elegans*



Diagnosis

- Histopathology : H&E, PAS, GMS
- Culture from clinical specimens
 - Conventional identification
 - MALDI-TOF MS
 - Sequencing
- Blood cultures usually negative
- Antigen tests are not available – research area

Need high index of suspicion

- Prolonged acidosis such as poorly controlled diabetics
- Renal failure, immunosuppressed patients, deferoxamine therapy
- Presence of multiple (> 10) macronodules on chest CT
- Presence of pleural effusion
- “Reverse halo sign”



Culture and Susceptibility Testing

- *Mucor circinelloides* shows high MIC against posaconazole
- *Rhizopus* and *Cunninghamella* shows high MIC against amphotericin B
- Some *Apophysomyces* isolates have also increased MIC against amphotericin B

Molecular Diagnostic Tests

- Panfungal PCR
 - Target : ITS, 18S rRNA, 28SrRNA gene
 - Non-blood, nonstool specimens
 - Fresh specimen **better** than formalin-fixed paraffin-embedded (FFPE) tissues
 - High yield if fungal elements seen in tissue
- Mucorales PCR
 - Not FDA-approved
 - Serum, respiratory specimen (e.g. BAL), tissue including FFPE
 - Serum - sensitivity 85.2%, specificity 89.8%
 - BAL - overall sensitivity 72.7%, specificity 98.6%,
 - for immunocompromised, sensitivity 97-100%, specificity 95.7-97.9%
- Metagenomic next-generation sequencing (mNGS)
 - Plasma microbial cell-free NGS for non-*Aspergillus* mold – sensitivity 79% (*Aspergillus* 31%) with a PPV of 72.6%
 - Up to 14 days preceding clinical invasive mold infection diagnosis

Therapeutic Approach to Mucormycosis

- Multimodal approach (equally important)
 - **Antifungal agents**
 - Liposomal amphotericin B
 - Maintenance: posaconazole, isavuconazole
 - **Surgical debridement**
 - **Correction of the underlying condition predisposing the patient to the disease**
 - Control DM
 - Corticosteroids should be discontinued
 - Other immunosuppressive drugs should be tapered as much as possible

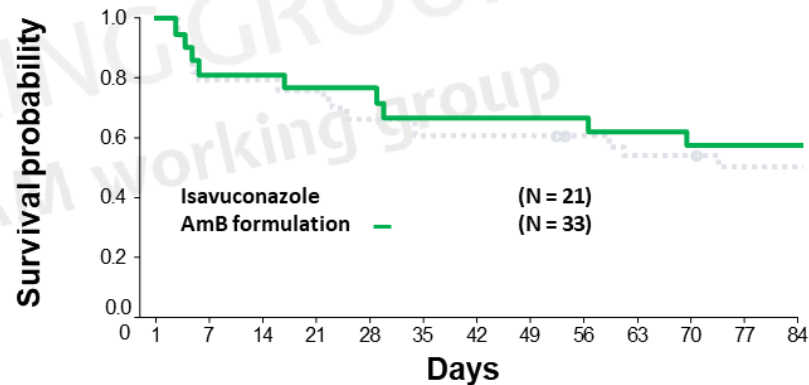
VITAL Study: Isavuconazole

Open-label global trial in patients with rare fungi including 37 mucormycosis

- Overall response rate: 54% (11% PR, 43% SD)
- Compared with historical control from FungiScope study
- No difference in 6-week mortality (33% vs. 41%)

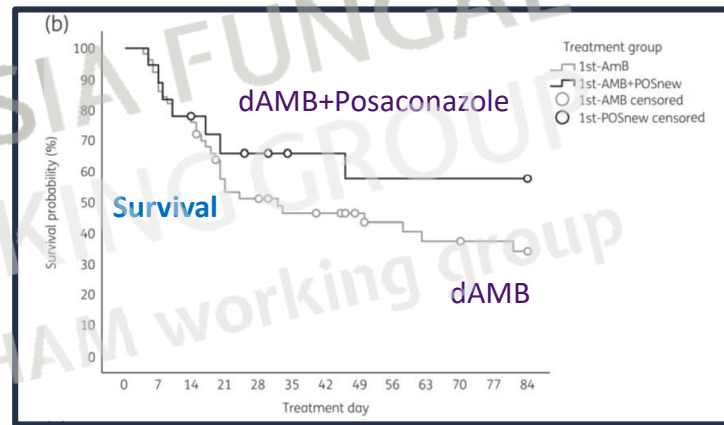
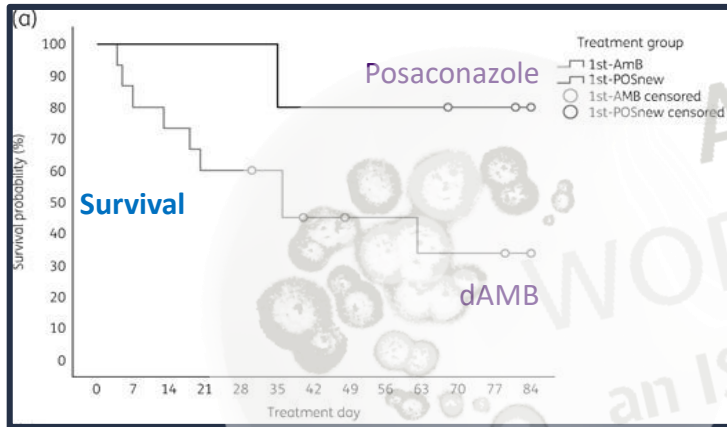
Case matching criteria:

- ✓ Severe disease (CNS involvement or disseminated)
- ✓ Hematologic malignancy
- ✓ Surgery (resection or debridement)



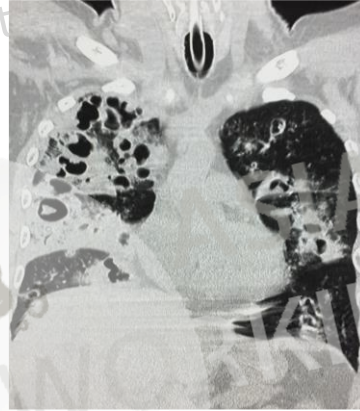
Posaconazole DR Tablet: MoveOn Study

Case-matched analysis from Fungiscope registry ; Treatment within 14 days



Day 42 all-cause mortality of patients receiving posaconazole new formulations was lower compared with controls
[20.0% (n=1/5) in 1st-POSnew versus 53.3% (n=8/15) in 1st-AMB; 33.3% (n=6/18) in 1st-AMB+POSnew versus 52.0% (n=26/50) in 1st-AMB]

A 44-Year-Old Man - Car Accident



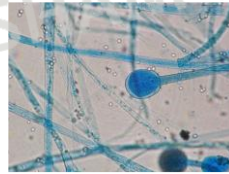
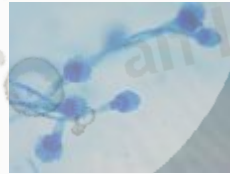
- Multiple air-filled cavities
- Intracavitary segmental consolidation in apical and posterior segments of RUL
- Scattered multi-focal consolidations in all segments of both lungs

Tracheal aspirates

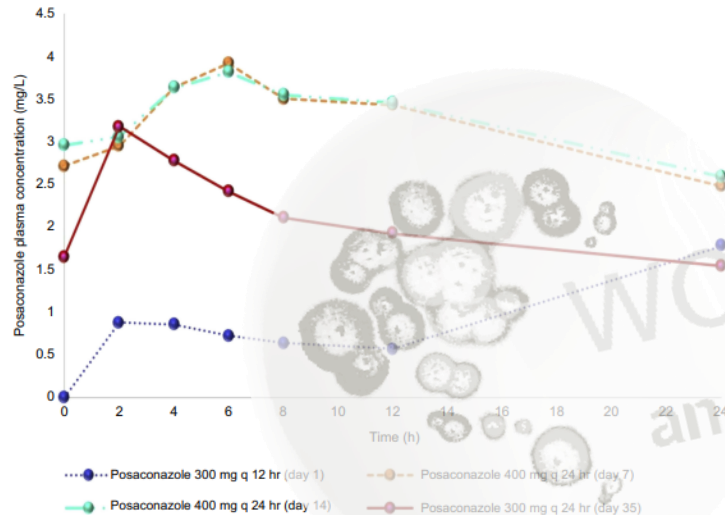
- *Aspergillus* galactomannan > 6

Cultures:

- *Aspergillus flavus*
- *Aspergillus fumigatus*
- *Rhizopus microsporus*
- *Lichtheimia corymbifera*



PK/PD Target in Mucormycosis



Loading dose:
 BID on day 1
 (Patients 13 years of age and older)

Maintenance dose:
 QD starting on day 2
 (Patients 13 years of age and older)

300 mg (three 100 mg delayed-release tablets) twice a day on the first day.

300 mg (three 100 mg delayed-release tablets) once a day starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Dose 1: 100, 100, 100

Dose 2: 100, 100, 100

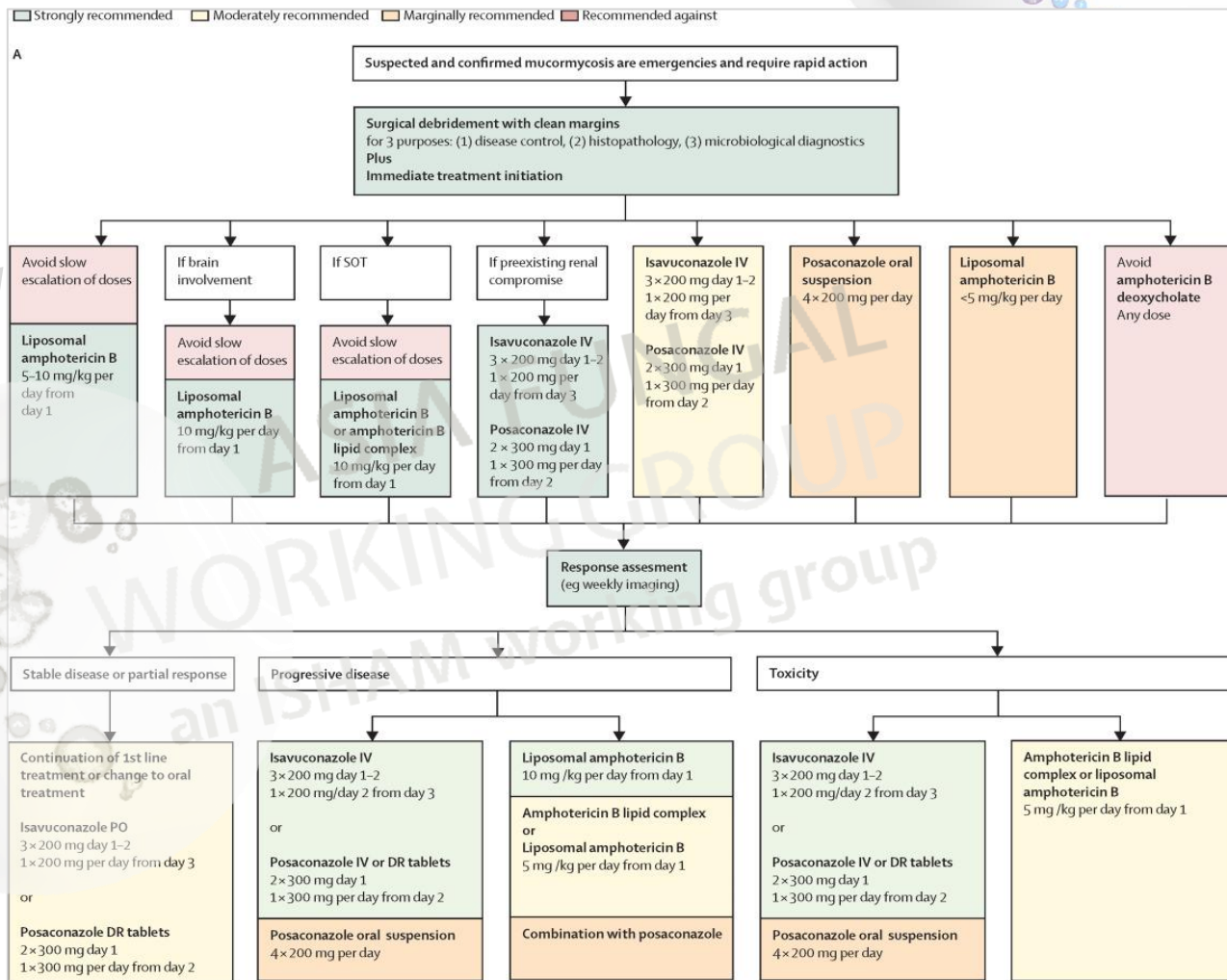
Tablets not actual size.

Fungal culture	MIC of posaconazole (mg/L)	Target of AUC/MIC ratio	AUC ₀₋₁₂ /MIC ratio		AUC ₀₋₂₄ /MIC ratio			
			300 mg q 12 hrs (day 1)		400 mg q 24 hrs (day 7)	400 mg q 24 hrs (day 14)	300 mg q 24 hrs (day 35)	
Aspergillosis	<i>A. fumigatus</i>	0.01	815.15	1,630.30	7,618.43	7,746.44	4,923.02	
	<i>A. flavus</i>	0.12	67.93	135.86	634.87	645.54	410.25	
Mucormycosis	<i>R. microsporus</i>	0.25	32.61	65.21	304.74	309.86	196.92	
	<i>L. corymbifera</i>	0.25	32.61	65.21	304.74	309.86	196.92	

Abbreviations: MIC, minimum fungicidal inhibitory concentration; AUC/MIC ratio, area under concentration-time curve over minimum fungicidal inhibitory concentration (MIC); AUC₀₋₁₂, area under concentration-time curve from 0 to 12 hrs; AUC₀₋₂₄, area under concentration-time curve from 0 to 24 hrs.

Global Guideline Recommendation

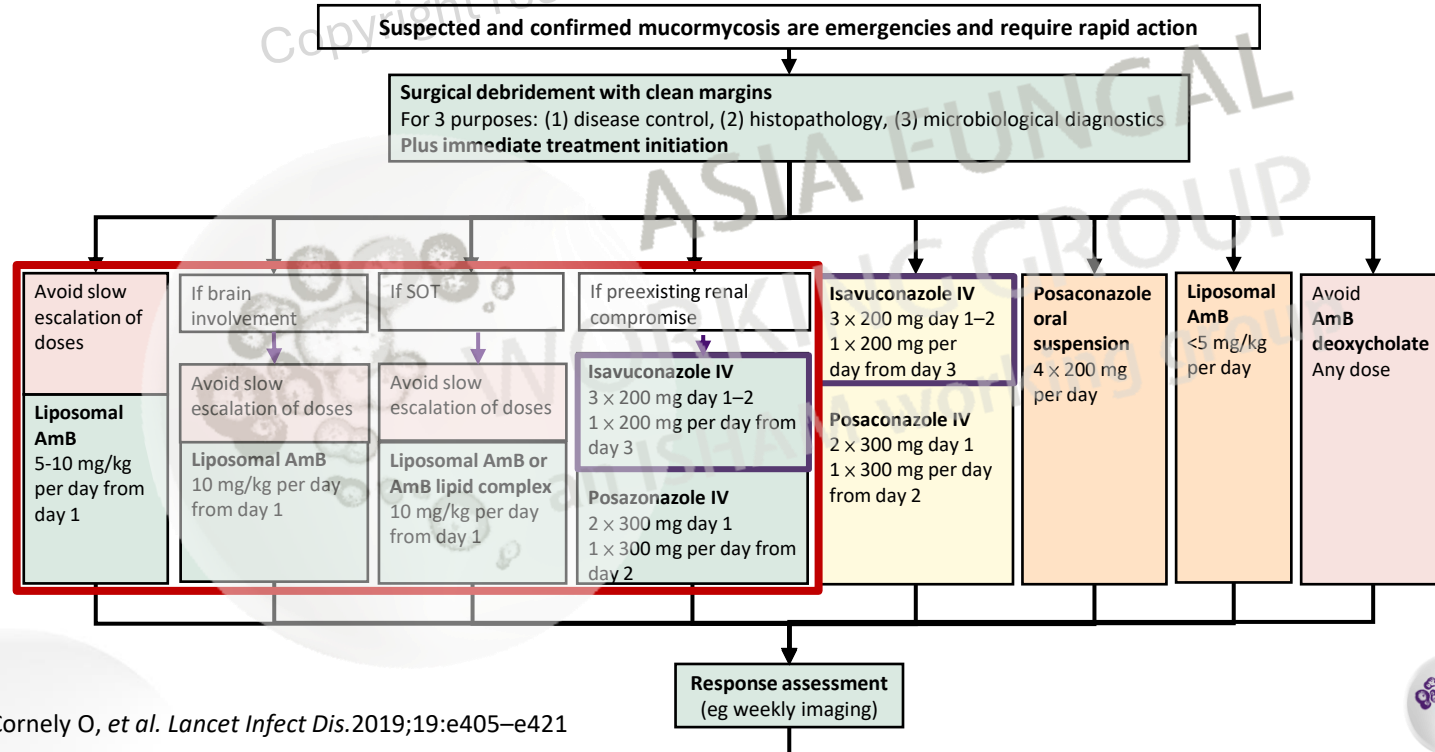
When **all treatment** modalities and anti-fungal drugs are **available**.



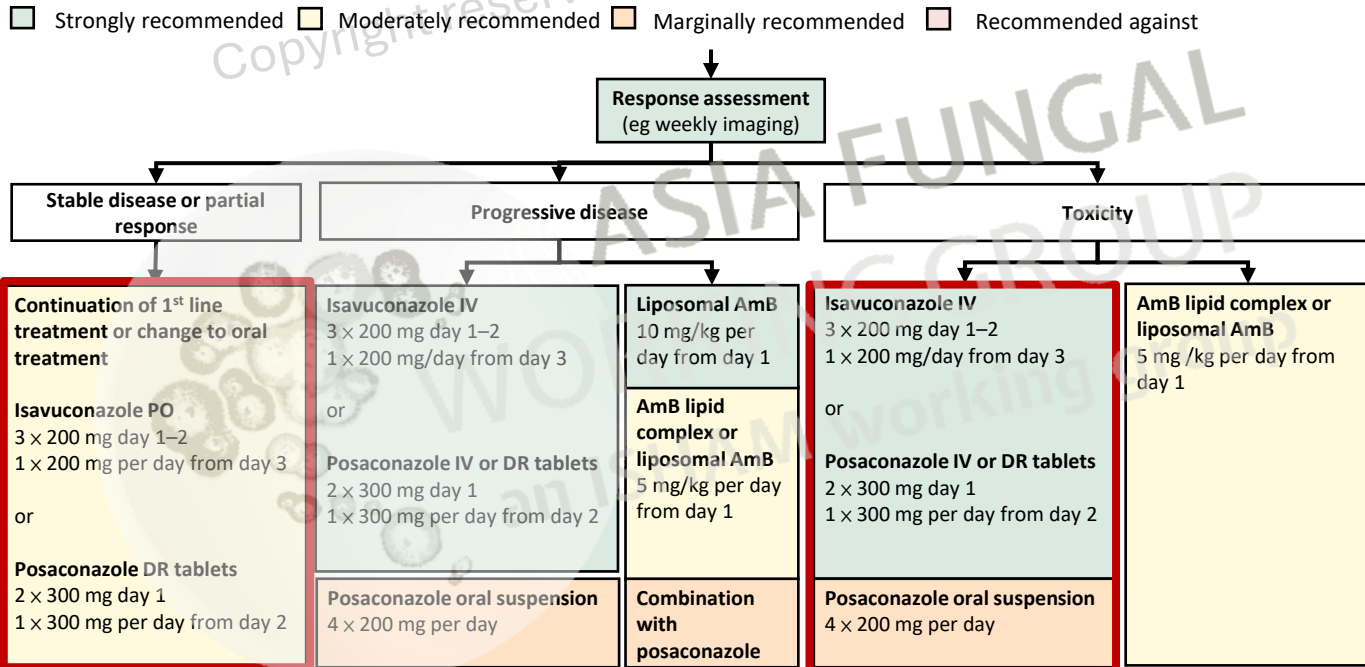
Optimal treatment pathways for mucormycosis in adults
Depending on the geographical location not all recommended treatments may have regulatory approval for use in clinical settings. (A) When all treatment modalities and antifungal drugs are available, (B) when amphotericin B lipid formulations are not available, and (C) when isavuconazole and posaconazole IV and delayed release tablets are not available. IV=intravenous. PO=per os (taken orally). SOT=solid organ transplantation. DR=delayed release.

ECMM-MSG-ERC guidelines: Treatment pathway for mucormycosis in adults

Strongly recommended
 Moderately recommended
 Marginally recommended
 Recommended against



ECMM-MSG-ERC guidelines: Treatment pathway for mucormycosis in adults



Treatment Duration

- No definite answer, normally several weeks to months
- Depending on several factors
 - Underlying condition: control of DM and DKA, managing immunosuppression, neutropenia
 - Surgical debridement
- Antifungal therapy can be continued until clinical resolution of infection with radiographic improvement

Long-Term Survival

- Prospective cohort study - 26 sites in India
- Total 686 patients
 - 101 deaths (14.7%) within 1 year with median survival 230 days
 - 64.3% occurred early, i.e. during hospitalization
- Independent predictors of mortality
 - Orbit involvement (HR 2.0)
 - Intracranial/cerebral involvement (HR 2.6)
 - ICU admission (HR 6.4)
 - Poor glycaemic control (HR 2.3)
 - Other comorbidities (HR 1.6)
- Factors of lower mortality
 - Combination antifungal therapy (HR 0.2)
 - Receipt of surgical treatment (HR 0.1)

New Antifungal Agents

Under investigation

- Encochleated amphotericin B
- Oteseconazole (a tetrazole)
- Fosmanogepix

Thank you

Methee Chayakulkeeree, MD, PhD, FECMM

Division of Infectious Diseases and Tropical Medicine

Department of Medicine, Faculty of Medicine Siriraj Hospital

Mahidol University, BANGKOK, THAILAND