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## Forschungsmittel

Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Immunic, Janssen, Medicines Company, Melinta, Merck/MSD, Octapharma, Pfizer, Scynexis

## Beratung zu Studiendesign, DRC oder DSMB

Actelion, Allecra, Amplyx, Astellas, Basilea, Biosys, Cidara, Da Volterra, Entasis, F2G, Gilead, Matinas, MedPace, Menarini, Merck/MSD, Mylan, Nabriva, Noxxon, Octapharma, Paratek, Pfizer, PSI, Roche Diagnostics, Scynexis, Shionogi

## Vortragshonorare

Al-Jazeera Pharmaceuticals, Astellas, Gilead, Grupo Biotoscana, Merck/MSD, Pfizer





- **Overcome limitations of “continentalism” in guidelines**
- **Guidance for diagnosis and management stratified by high and low resource settings**
- **Utilize global network of ECMM Academy and ECMM Excellence Centers**
- **Orphan diseases guidance from all disciplines involved in IFI management**
- **Professionals from all UN regions contribute their expertise**
- **2019 ISHAM joined**
- **2020 ASM joined**

# Clinical Practice Guideline – Rare Yeasts

*(no Candida, but Geotrichum, Kodamea, Malassezia, Pseudozyma, Rhodotorula, Saccharomyces, Saprochaete, Sporobolomyces, Trichosporon)*

## Guideline Coordinators

Infectious Diseases:	Sharon Chen, FECMM, Sydney, Australia	<b>Oceania</b>
Infectious Diseases:	Arnaldo Colombo, Sao Paolo, Brazil	<b>America, Latin</b>
Microbiology:	Nelesh Govender, Joh...burg, South Africa	<b>Africa</b>
Microbiology:	John Perfect, Durham, United States	<b>America, US</b>

# Guideline Definition of Contributorship and Authorship

**Authors** are individuals who meet the [ICMJE](#) requirements for authorship.

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## **Added criteria for the purpose of this Guideline Initiative:**

5. Responsiveness throughout the guideline process.
6. Received training on the ECMM guideline process → <https://www.youtube.com/watch?v=1siIWTWHwdg>
7. Responsiveness to submit ICMJE Conflict of Interest form

**Contributors** are individuals who do not meet all six requirements for authorship but have contributed significantly to the work.

# Search Strings

# Literature Access – OneDrive: <https://1drv.ms/f/s!AtfwuPuvjUJI3WC-YMa7xJwg855m>



Archive  
Sa um 13:30



Fusarium  
15. Feb



Lomentospora  
15. Feb



Penicillium  
15. Feb



Phaeohyphomycetes  
15. Feb



Rasamsonia  
15. Feb



Scedosporium  
15. Feb



Schizophyllum and othe...  
15. Feb



Scopulariopsis  
15. Feb



Talaromyces other than...  
15. Feb



ECMM Rare Moulds Gui...  
vor 3 Min

# Guideline Methodology – Two Independent Evaluations

1. Strength of Recommendation = SoR
2. Quality of Evidence = QoE

→ Allows strong recommendations in the absence of highest quality of evidence.

Examples:

Population	Intention	Intervention	SoR	QoE	Reference	Comment
People on planes	Jump off a burning plane	Use parachutes	A	III	No reference found.	
Patient with fever	Diagnose fungaemia	Take blood cultures	A	IIu	Acme WJFD 2002	



# Guideline Methodology – Strength of Recommendation

Grade of Recommendation	Definition
<b>Grade A</b>	The guideline group <b><u>strongly</u></b> supports a recommendation for use
<b>Grade B</b>	The guideline group <b><u>moderately</u></b> supports a recommendation for use
<b>Grade C</b>	The guideline group <b><u>marginally</u></b> supports a recommendation for use
<b>Grade D</b>	The guideline group supports a recommendation <b><u>against</u></b> use

# Guideline Methodology – Quality of Evidence

Level of Evidence	Definition
<b>Level I</b>	Evidence from at least 1 properly designed randomized, controlled trial
<b>Level II</b>	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
<b>Level III</b>	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

# Guideline Methodology – Source of Level II Evidence

Added Index	Source of Level II Evidence
<b>r</b>	Meta-analysis or systematic review of RCT
<b>t</b>	Transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation
<b>h</b>	Comparator group: historical control
<b>u</b>	Uncontrolled trials
<b>a</b>	For published abstract presented at an international symposium or meeting

# Guideline Methodology – Colour Code

**Black** is information the group agreed on

**Blue** is Coordinator colour for **NEW** information the group did not yet agree on

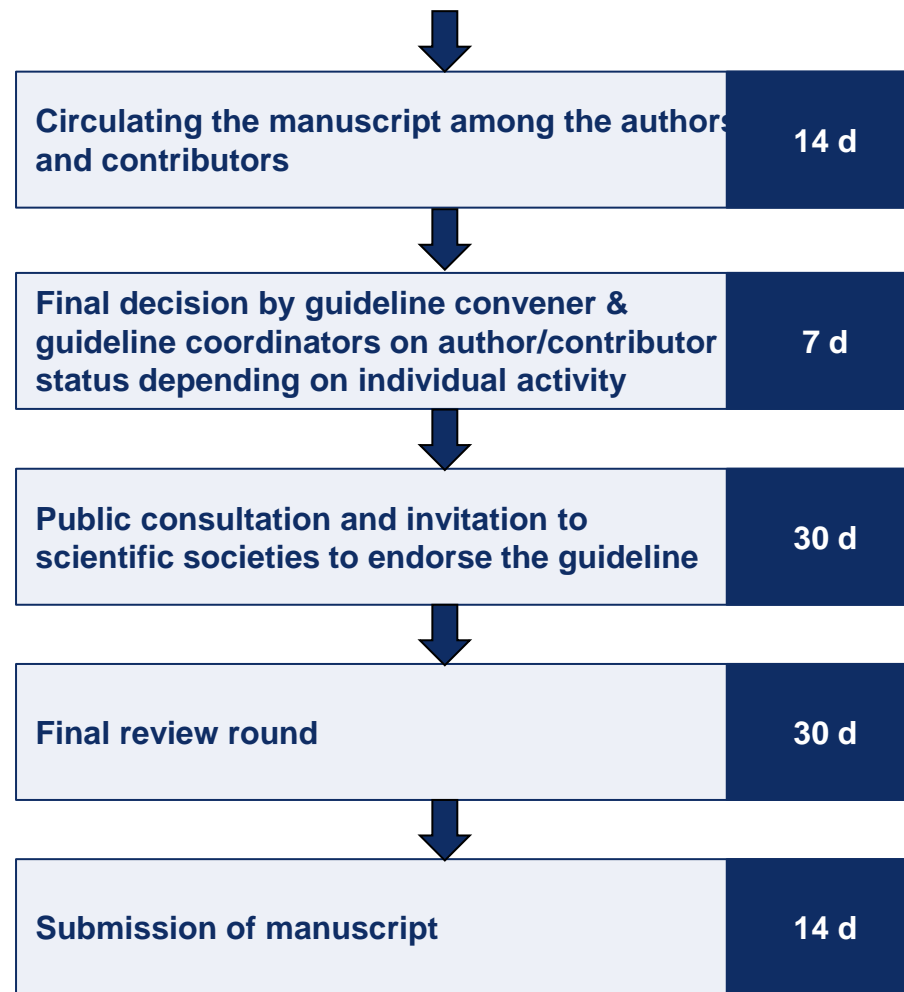
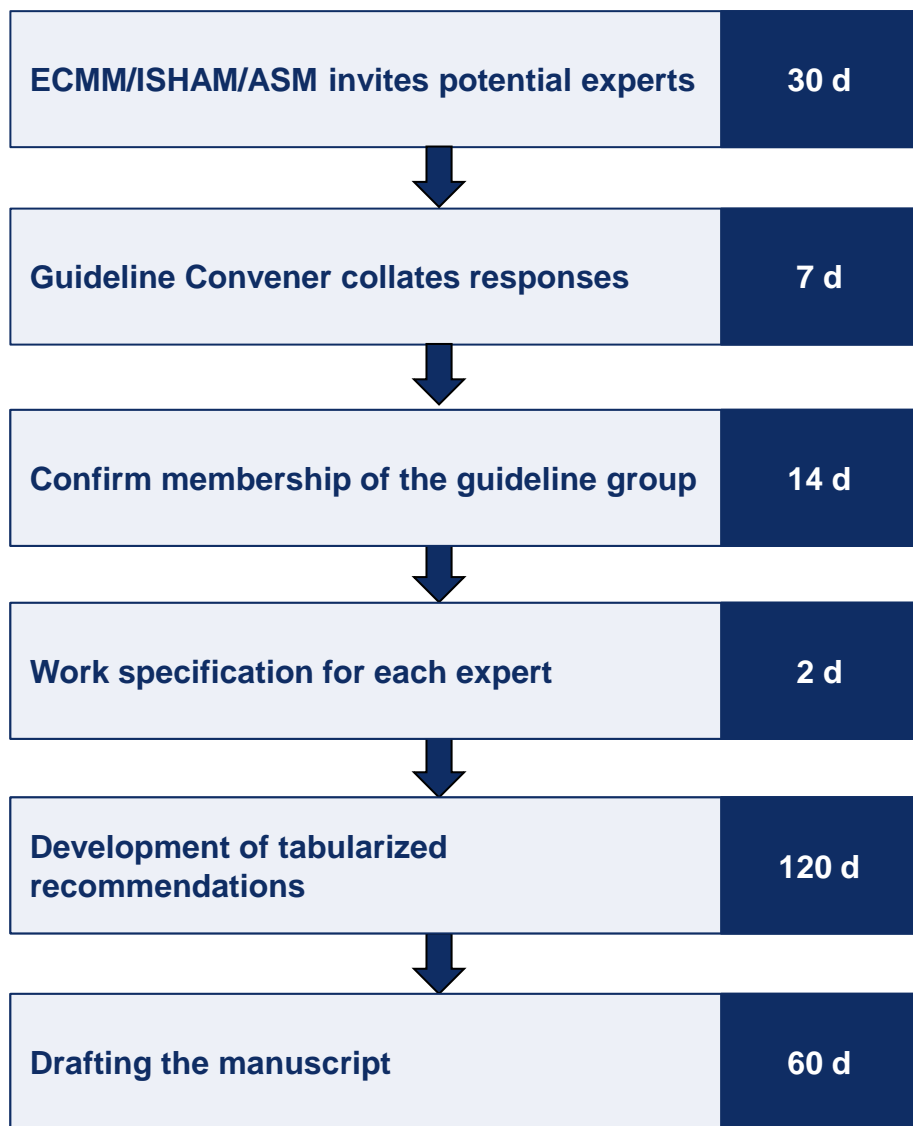
**Red** is Author colour that **YOU** should use

**Green** is information to the group

Coordinators turns red into blue for discussion, and after agreement (or sometimes voting) into black.

# Fusarium Diagnosis – Microbiology – Serology

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Any	To diagnose	Galactomannan in serum	B	Ilu	Nucci PLoS ONE 2014	83% sensitivity, 67% specificity, 73% serum GM pos. before 1 <sup>st</sup> clinical manifestation
Any	To diagnose	BDG in serum	C	Ila	Nucci Mycoses 2019	For 2 tests >80 pg/ml, 90% sensitivity and 61% specificity, high NPV, low PPV
Hematologic with fever	To diagnose	Galactomannan in serum to distinguish aspergillosis and fusariosis	D	II	Nucci CMI 2018	GM pos 89% in IA, 73% in fusariosis
Any with GM pos. fusariosis	To monitor response	Repeat galactomannan in serum	A	II	Nucci PLoS ONE 2014	GM correlated with outcome
Clinical isolates <i>Fusarium</i> spp.	To rule out Fusariosis	Aspergillus-specific Lateral Flow Device Test	C	III	Thornton CVI 2008 Hoeningl JCM 2014	LFD highly specific, results negative in samples from patients with invasive fusariosis



**Total: 328 Days**



**2019 Mucormycosis (with MSG-ERC)**

**2020 CAPA (adapted methodology)**

**2021 Rare Moulds**

**Rare Yeasts**

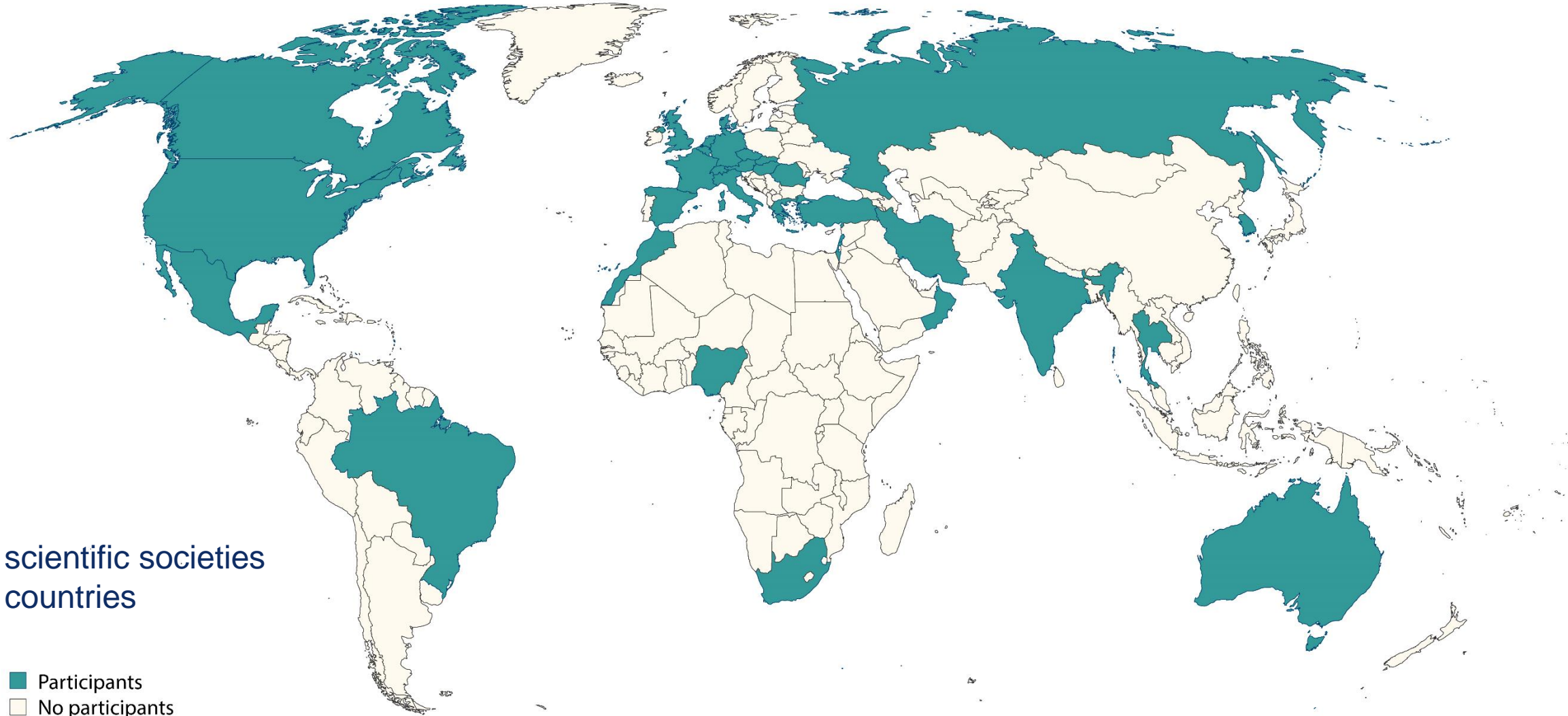
**Endemic Mycoses**

**Cryptococcosis**

**2022 Candida**

**Aspergillus**

**2023 tbd**



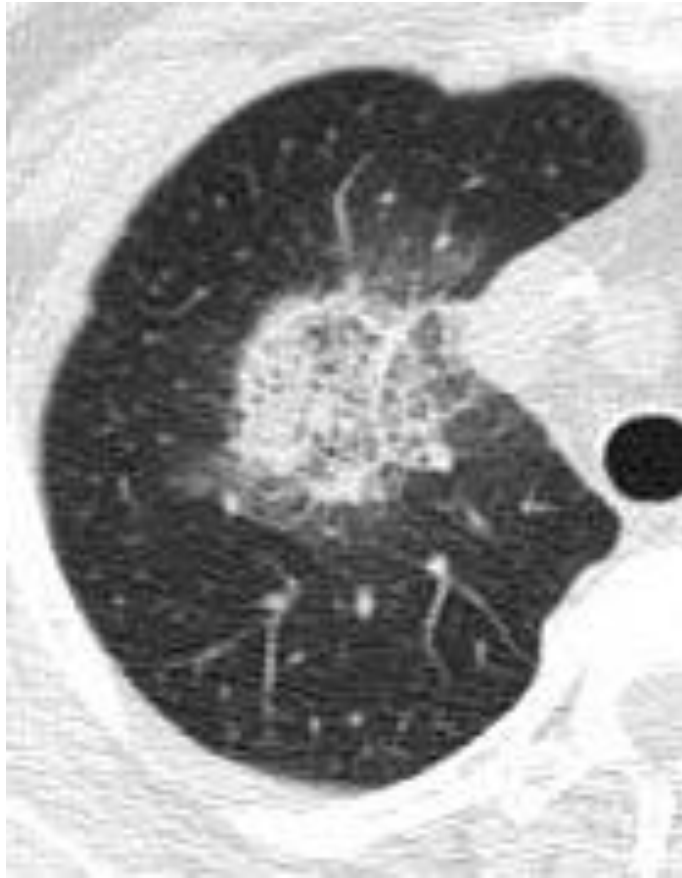
51 scientific societies  
33 countries

- Participants
- No participants





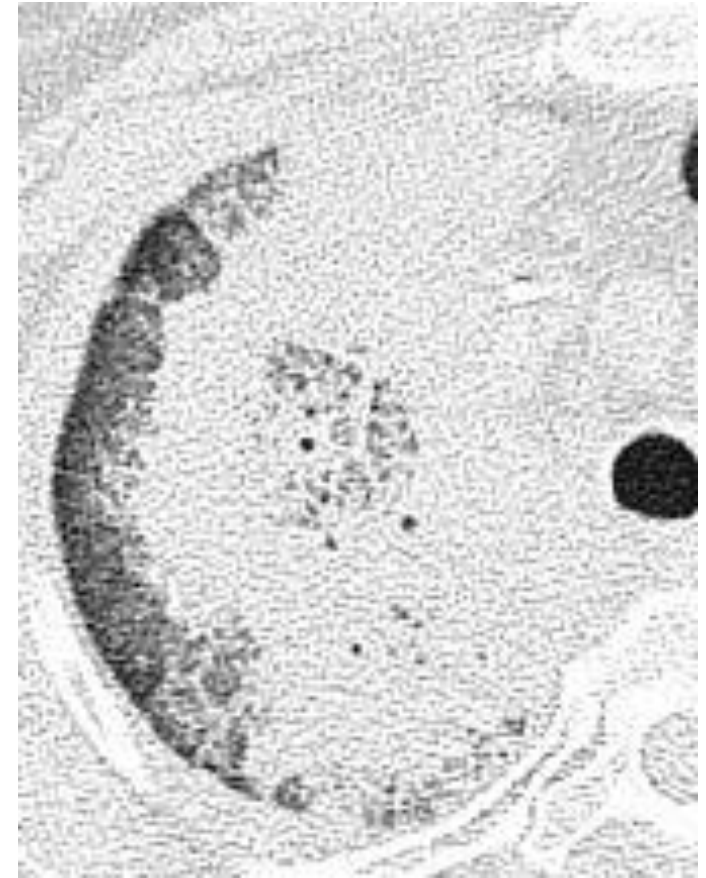
# Mucormycosis – Inverse Halo Sign



d1



d8



d15



**A. Mucorales hyphae are 6-  $\geq$ 16  $\mu$ m broad, ribbon-like, pauci-septate, branch irregularly**

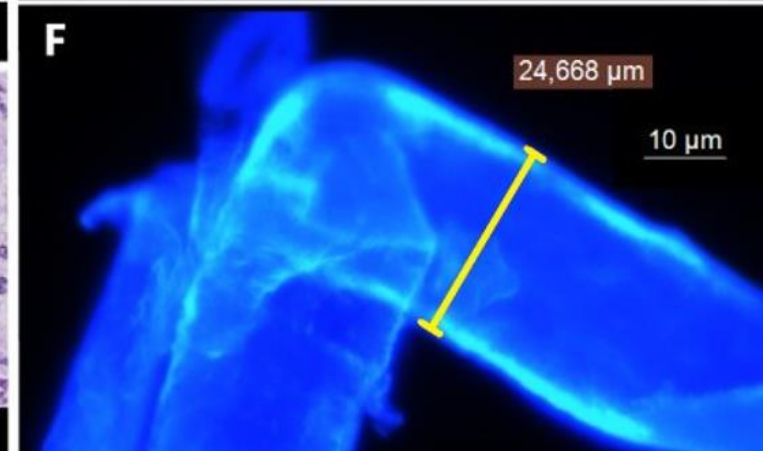
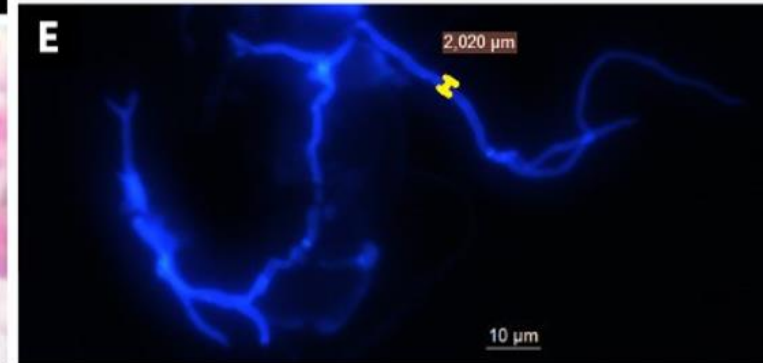
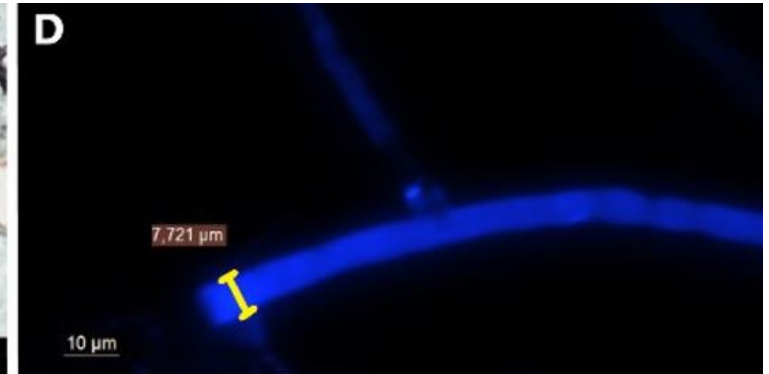
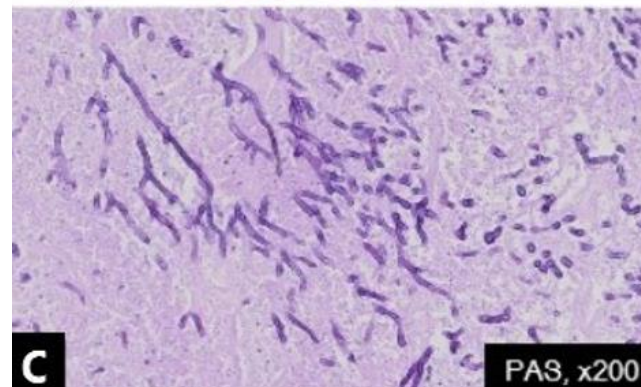
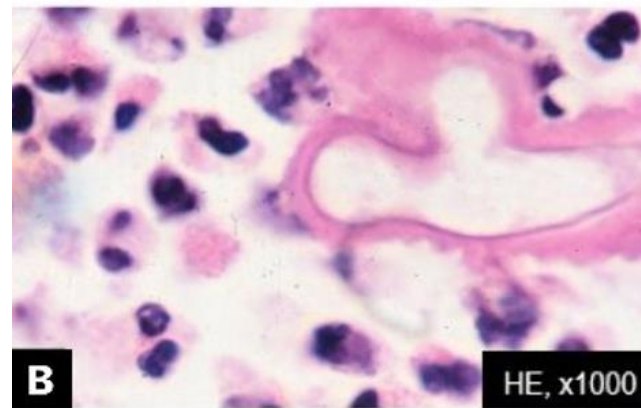
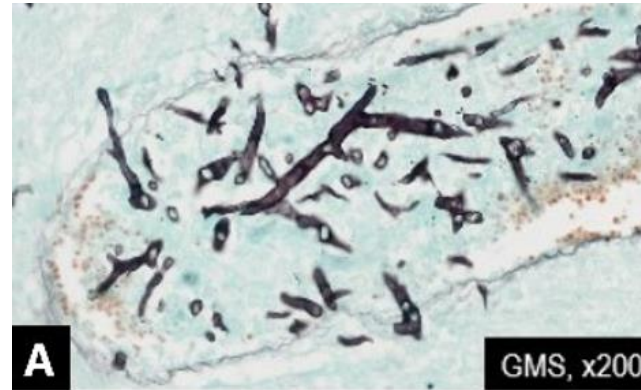
**B. Hyphal structure covered with Splendore-Hoepli phenomenon: eosinophilic material likely represents antigen-antibody complexes. First described by Splendore (1908), by Hoepli (1932)**

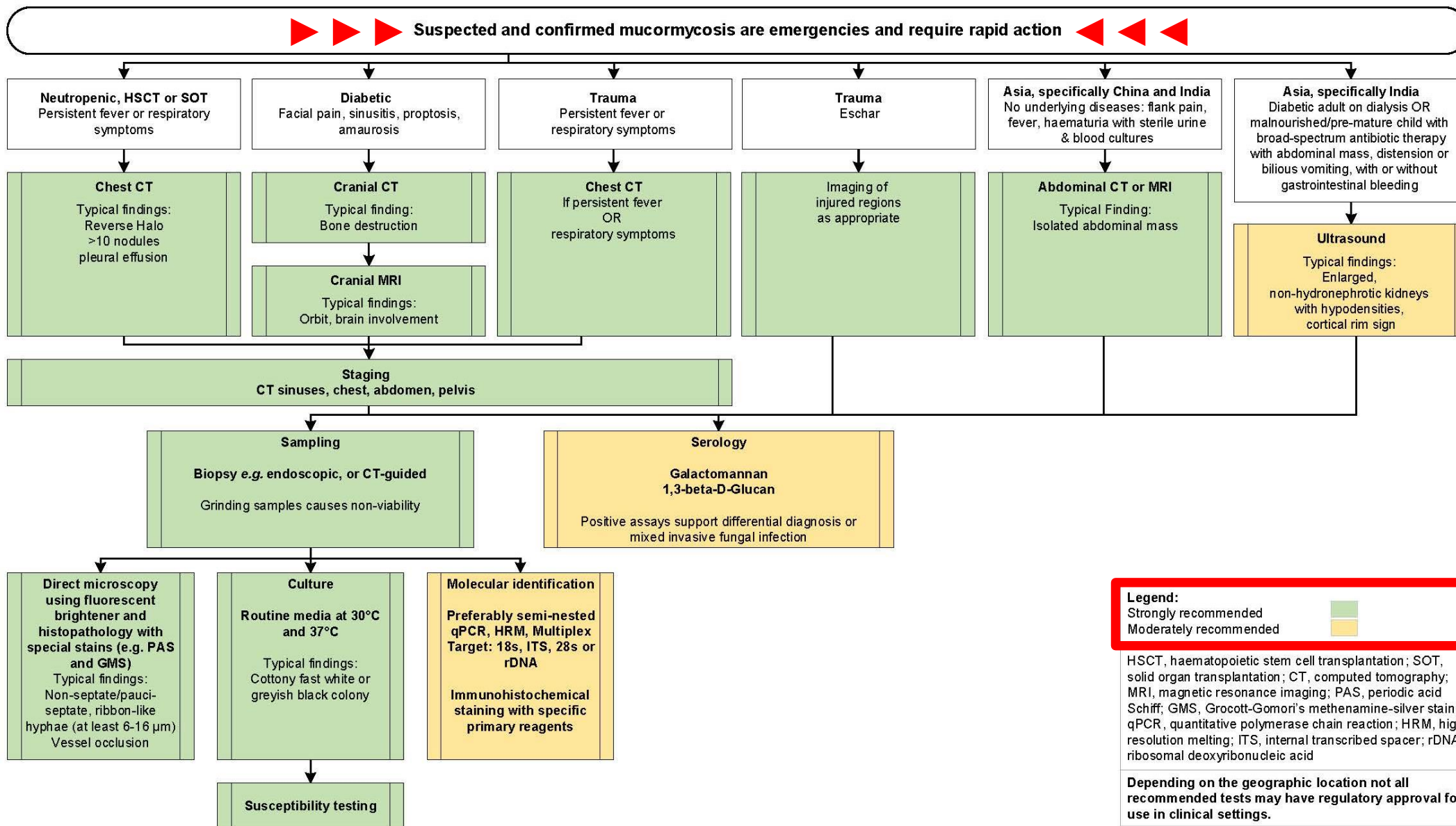
**C. *Aspergillus* hyphae 3-5  $\mu$ m wide, regularly septate, dichotomous branching**

**D-F. Sizes and branching angles for Mucorales and *Aspergillus* stained by Calcofluor White**

**Confirm diagnosis by culture or molecular techniques!**

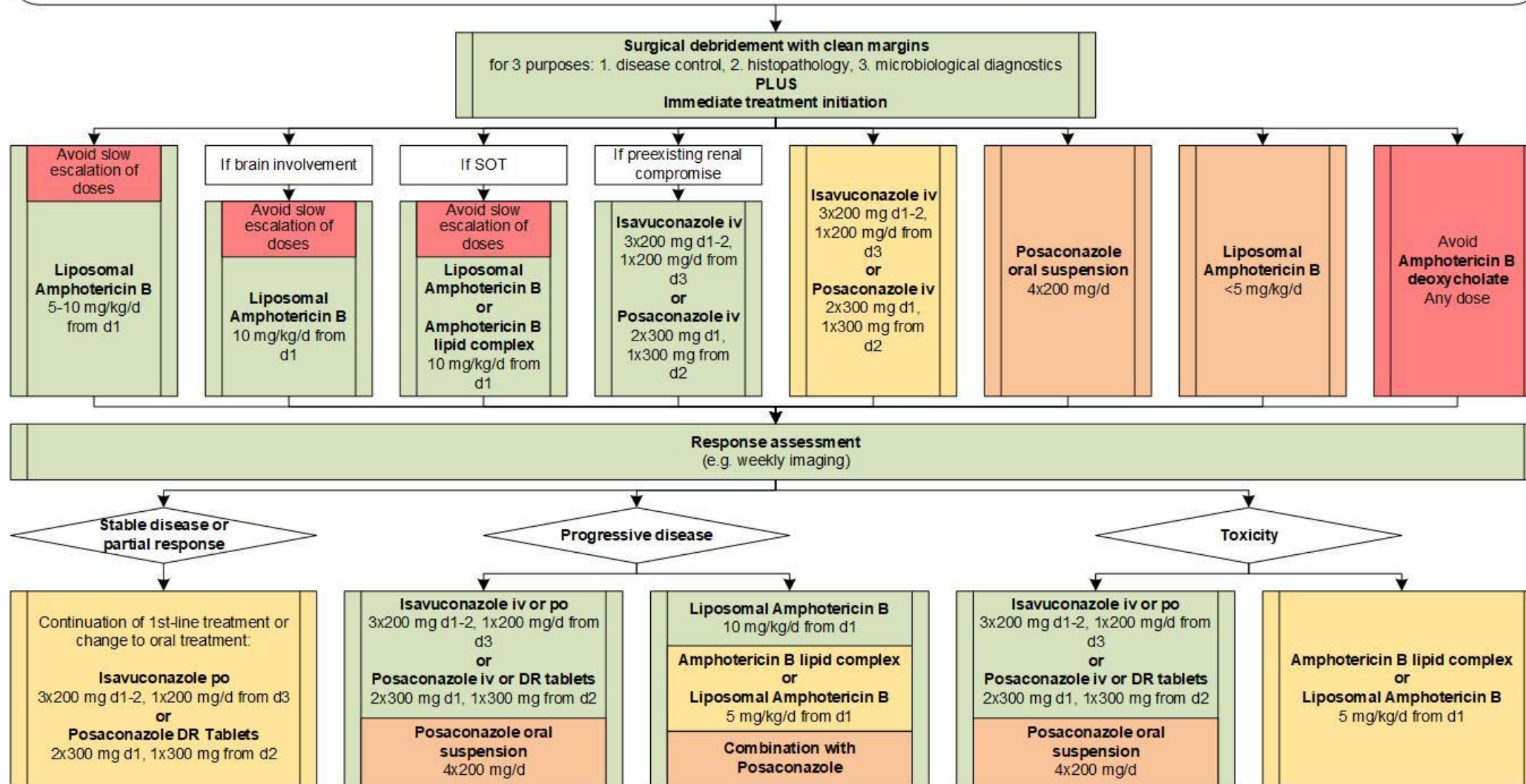
Images A-C courtesy of Henrik E. Jensen  
Images D-F courtesy of Ana Alastruey-Izquierdo





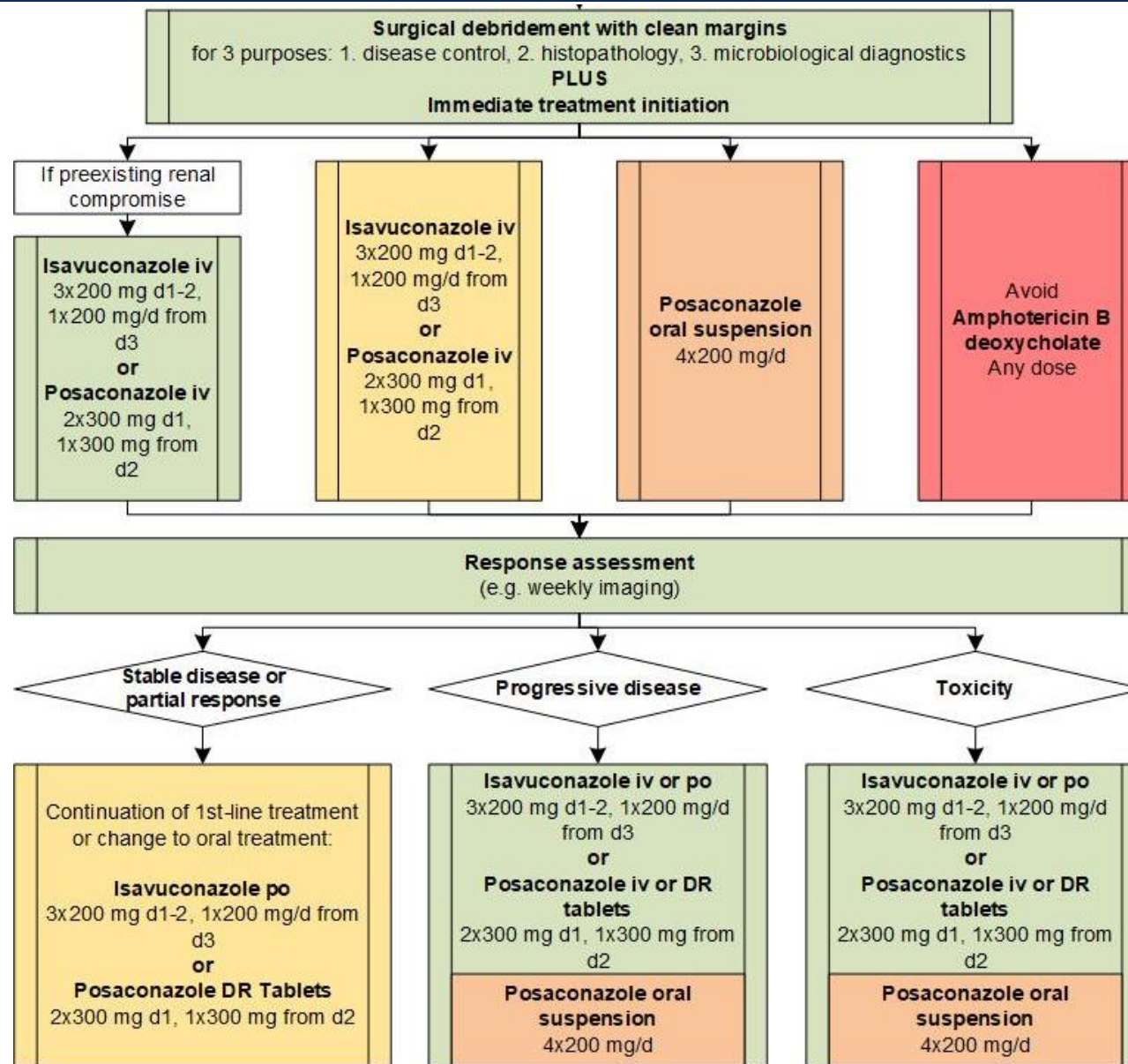


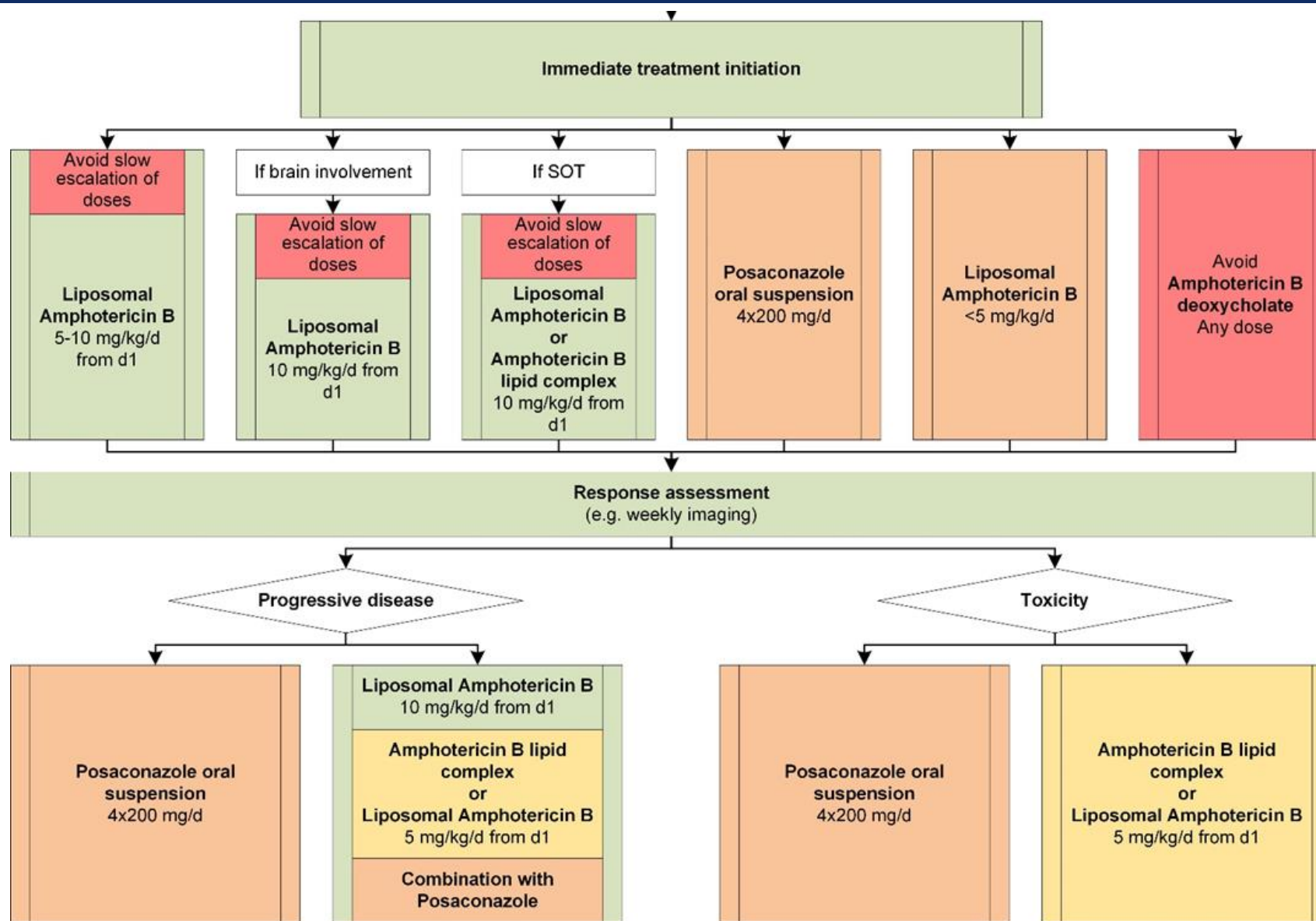
▶▶▶ Suspected and confirmed mucormycosis are emergencies and require rapid action ◀◀◀





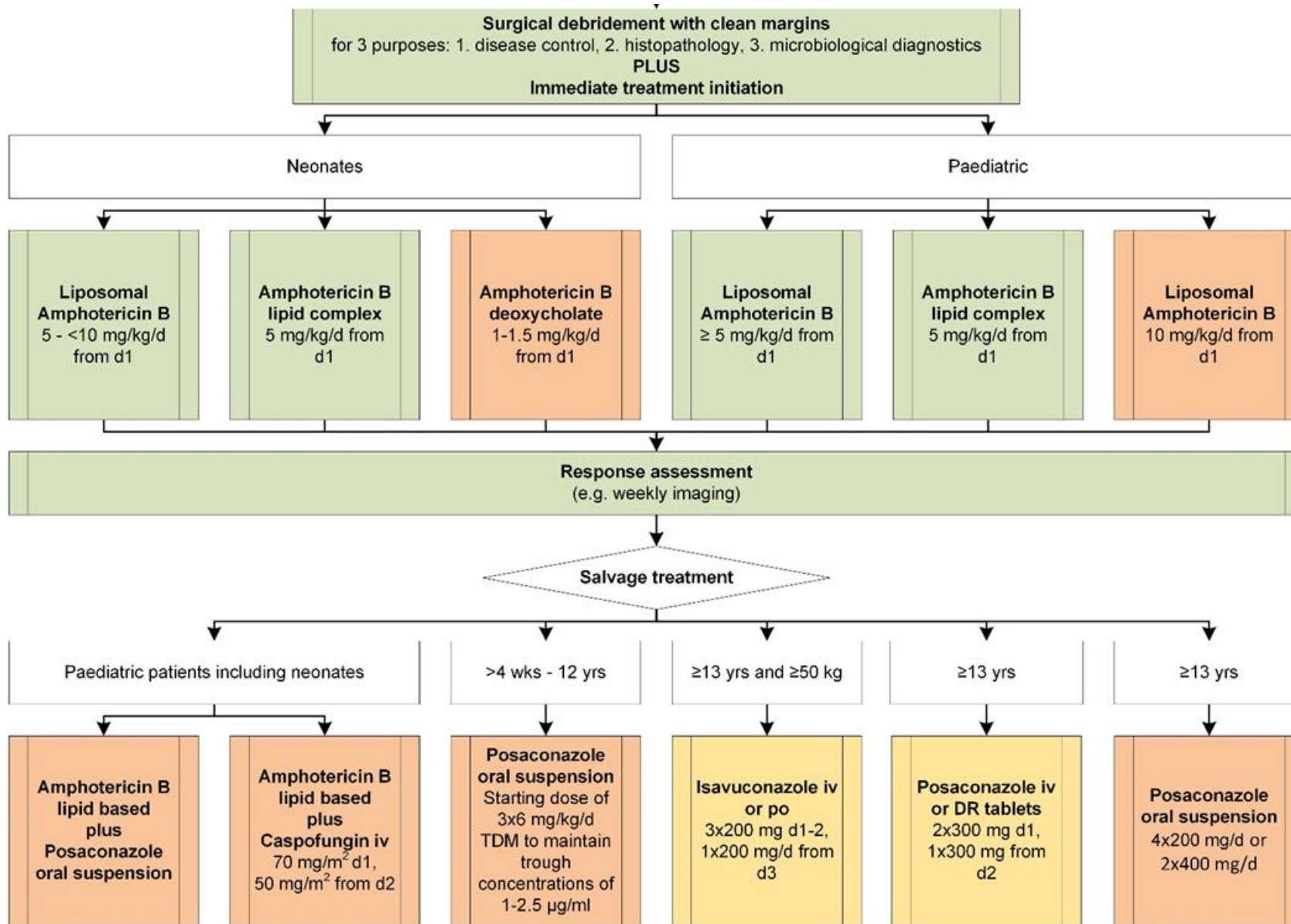
# Mucormycosis “No L-AmB Available” Treatment Path Adults







# Mucormycosis “All Options Available” Treatment Path Children



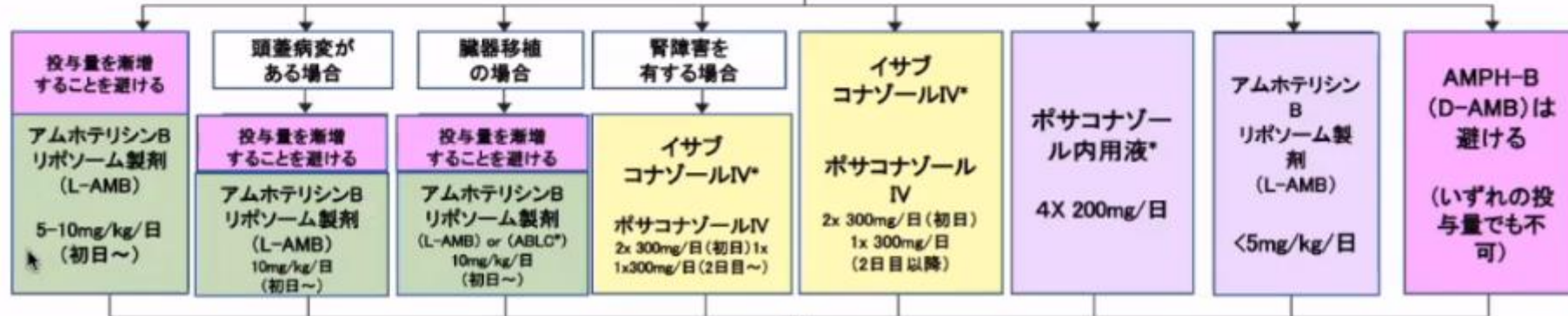
# Global GLで推奨されるムーコル症の治療

- 強い推奨
- 中等度推奨
- 弱い推奨
- 推奨せず

ムーコル症の確定診断(疑い例含む)は緊急事態で早期の対応が必要

外科的デブリードマン

目的(1)病巣のコントロール、(2)病理組織学的診断、(3)微生物学診断+初期治療開始



治療効果の判定  
(例:毎週の画像検査等)

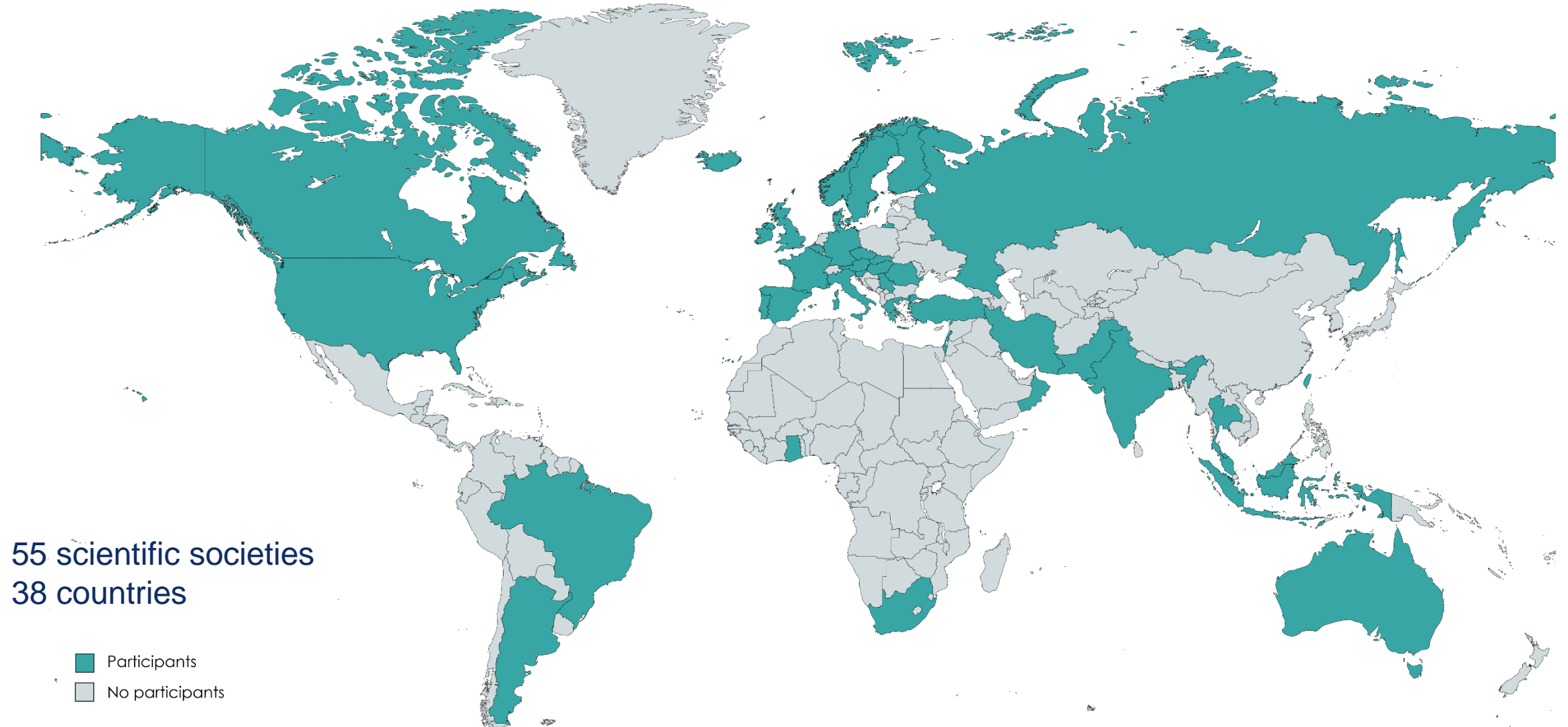
\*: 我が国では未発売

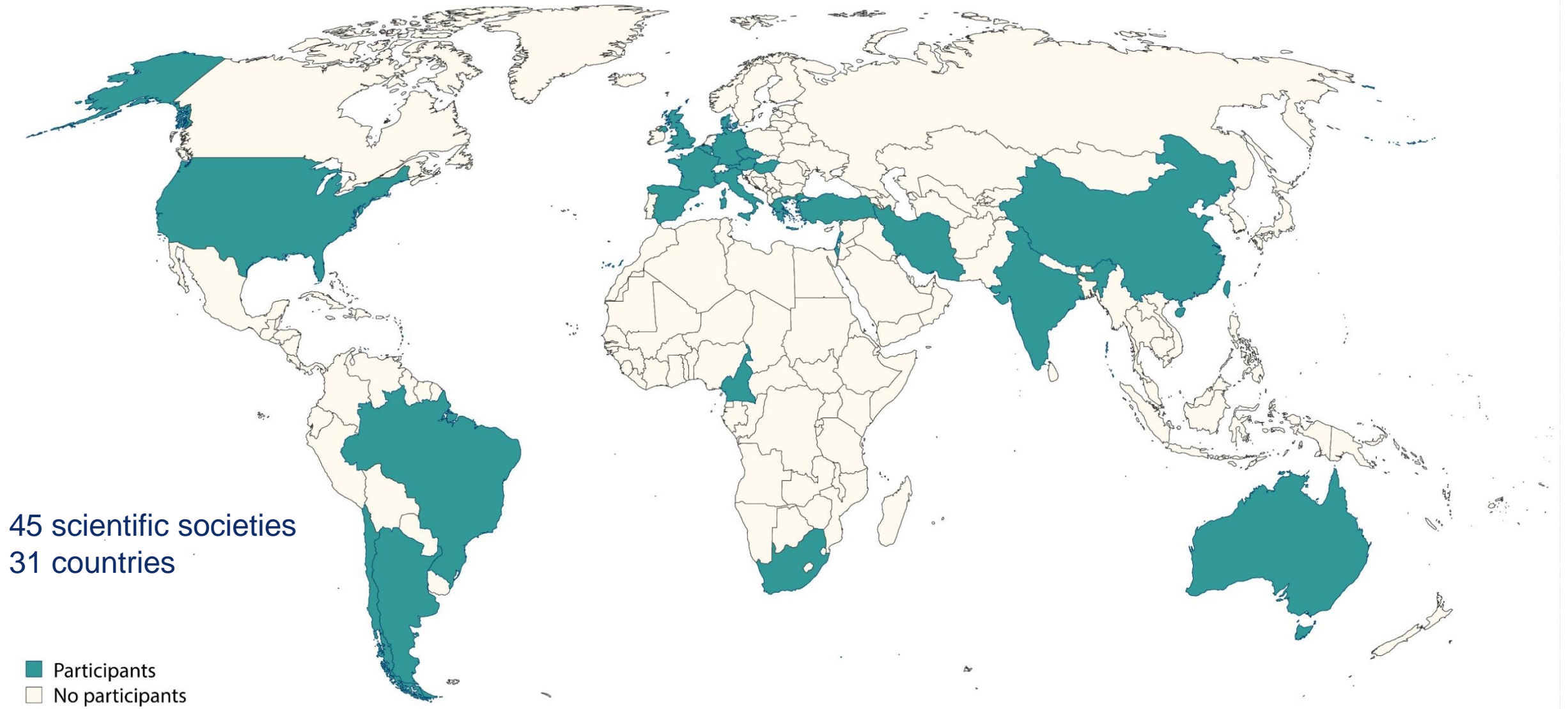


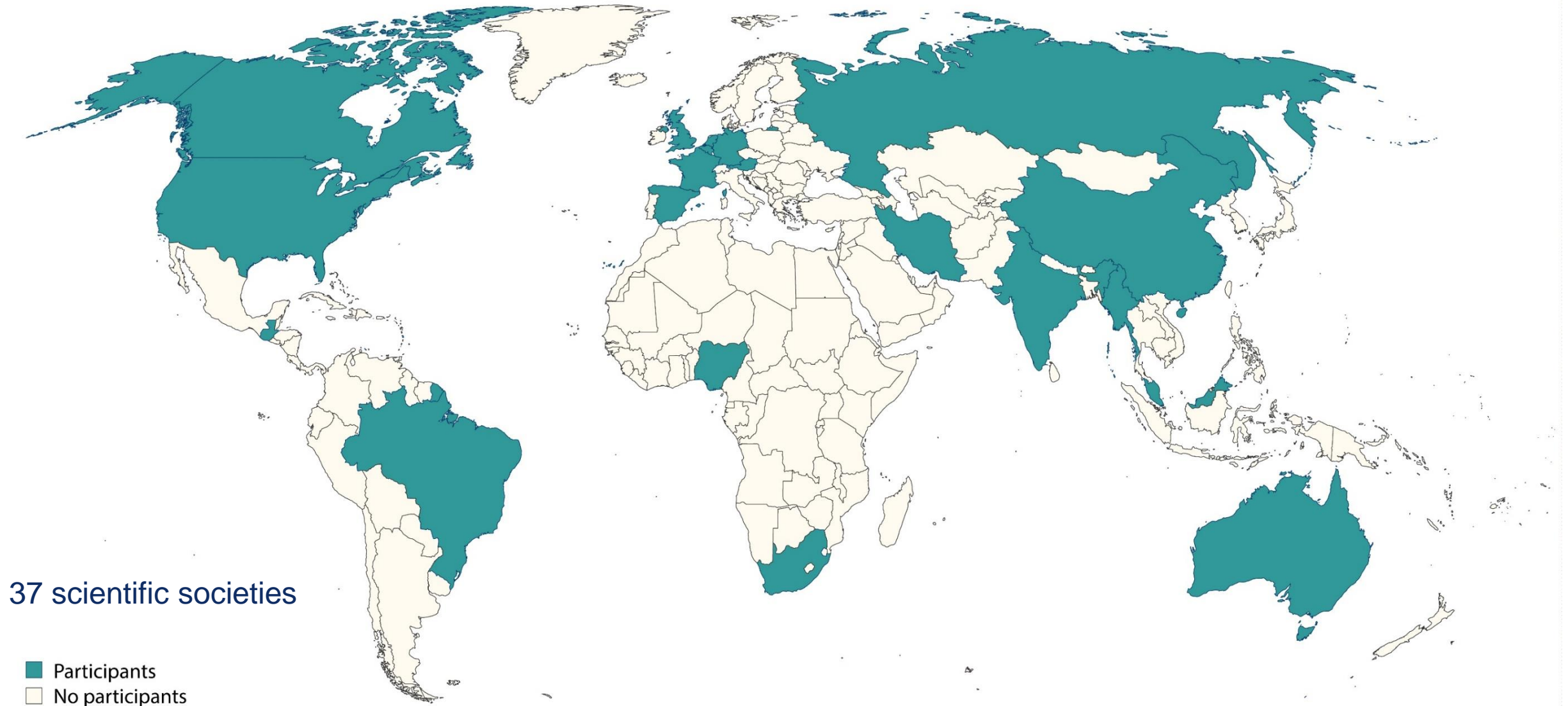
Cornely OA, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation

Medical Mycology in cooperation with the Mycoses study group education and Research consortium. Lancet Infect Dis, 2019









37 scientific societies

- Participants
- No participants



**EQUAL Mucormycosis Score 2018: An ECMM Score Derived From Current Guidelines to Measure QUALity of Mucormycosis Management**

Cornely OA<sup>1,2</sup>, Koehler P<sup>1,2</sup>, Mellinghoff SC<sup>1,2</sup>

<sup>1</sup>Department I for Internal Medicine, Excellence Center for Medical Mycology (ECMM), University of Cologne, Germany; <sup>2</sup>CECAD Cluster of Excellence, University of Cologne, Germany  
DOI: 10.4126/FRL01-006407808

## Background

The EQUAL Mucormycosis Score 2018 weighs and aggregates factors for ideal management of mucormycosis.

EQUAL Scores reflect the strongest recommendations from current guidelines. The Score Cards are a quick reference to measure guideline adherence and to support antifungal stewardship.

Maximum Score	In case of isolate	In case of biopsy	In case of isolate and biopsy
Diagnosis	11	13	16
Treatment		8	
Follow-up		6	
Total	25	27	30

## References

1. Cornely et al. *Clin Microbiol Infect* 2014; 2. Tacke et al. *Mycoses* 2014; 4. Koehler et al. *Infect Dis Clin N Am* 2015; 3. Tissot et al. *Haematol* 2017.



## EQUAL Mucormycosis Score 2018

Category	Item	Score	
Diagnosis	Neutropenia >10d or alloHSCT → Mould active prophylaxis	3	
	72-96h of persistent fever → Chest CT	3	
	Inversed halo	2	
	– CT/MR staging: Head, neck, abdomen		
	– Inversed halo → BAL		
	– Direct microscopy, preferably using optical brighteners		1
	– Culture		1
	– Fungal PCR (pan, <i>Aspergillus</i> , Mucorales)	1	
	1st line Treatment	Microbiological test results negative → Biopsy	2
		– Tissue culture	
– Histopathology			
– Molecular-based tests on fresh clinical material or embedded tissue		1	
Isolate grows → Identification to species level and susceptibility testing		2	
Follow-up	Surgical debridement	2	
	with microscopically clear resection margins	1	
	L-AmB ≥5 mg/kg/d or	3	
	Isavuconazole with TDM or posaconazole with TDM	2	
Follow-up	Control of risk factors: Neutropenia, hyperglycaemia, ketoacidosis, corticosteroids	2	
	CT scan on day 7	2	
	CT scan on day 14	2	
	Weekly CT scan until improvement	2	





- **Weigh and aggregate recommendations for ideal clinical management of invasive fungal diseases**
- **A useful tool for**
  - **Measuring guideline adherence**
  - **Antifungal stewardship**
  - **Facilitate clinical decision-making**
- **Providing an easy-to-follow algorithm, currently 22 languages:**
  - **Albanian, Azerbaijani, Bulgarian, Chinese, Czech, Dutch, English, French, German, Greek, Hungarian, Italian, Kurdish, Persian, Polish, Portuguese, Romanian, Russian, Serbo-Croatian, Spanish, Swedish, Turkish**
  - **Under development: Arabic, Japanese**