Diagnosis

- **The capability of diagnosing mucormycosis depends on the availability of imaging techniques, trained personnel, and mycological and histological investigations.**
- **Patients with suspected mucormycosis should be referred immediately to a facility with the highest care level.**
- In case of any delay, management should be initiated following this guidance document.
- If all diagnostic options are available, one should follow the management pathway depicted in recommendations.

Imaging

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- **In patients with haematological malignancy and suspected pulmonary mucormycosis, pulmonary CT scan is recommended for the detection of the reversed halo sign, an area of ground glass opacity surrounded by a ring of consolidation on thoracic CT, or vessel occlusion on CT pulmonary angiography.**
- **In diabetic patients with facial pain, sinusitis, proptosis, ophthalmoplegia, or newly diagnosed amaurosis, or both, cranial CT or MRI is strongly recommended to determine if sinusitis is present.**
- **If sinusitis is diagnosed, endoscopy is strongly recommended to diagnose mucormycosis.**
- If disease of the eye or brain is suspected, MRI should be conducted in lieu of a CT scan due to substantially greater sensitivity.

- **If mucormycosis is a potential diagnosis, biopsy is strongly recommended.**
- Once mucormycosis has been proven in a patient with underlying malignancy, cranial, thoracic, and abdominal imaging studies to determine the extent of disease are recommended with moderate strength.

- **In view of the rapid progress of mucormycosis, weekly CT scans are strongly recommended, particularly in unstable patients.**

Histopathology in mucormycosis

- Mucormycosis is usually suspected based on results of direct microscopy of clinical specimens, preferably stained with fluorescent brighteners calcofluor white (Sigma Aldrich, St Louis, MO, USA) or blankophor (Tanatax Chemicals, Ede, The Netherlands).
- **To confirm an infection, non-pigmented hyphae showing tissue invasion must be shown in tissue sections stained with haematoxylin-eosin (HE), periodic acid-Schiff stain (PAS), or Grocott-Gomori's methenamine-silver stain (GMS), or both.**

- **Histopathologically, Mucorales hyphae have a variable width of 6–16 μm, but may be up to 25 μm, and are non-septate or pauci-septate.**
- In tissue, the hyphae appear ribbon-like with an irregular pattern of branching (figure 4A–C).57
- Hyphae can artefactually seem to have septae because tissue can fold over itself during processing, which can create artificial lines that can be confused with septations.

- Similarly, the historically described 90° branching angle of Mucorales in tissue, versus 45° branching angle of septate moulds, can be difficult to identify in tissue due to interstitial pressures exerted on the fungi by the tissue and alterations in tissue architecture during processing.
- **Thus the wider and irregular (ribbon-like) nature of the hyphae are more reliable distinguishing characteristics than septations and angle of branching.**

- The lesions of mucormycosis are characteristic but nonspecific.

- **In acute lesions, haemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils (in non-neutropenic hosts), and perineural invasion are characteristic features**
- whereas, in chronic lesions, a pyogranulomatous inflammation with presence of giant cells, and sometimes hyphae covered by the Splendore-Hoeppli phenomenon which describes deeply eosinophilic material surrounding the pathogen, are seen .

- **Obtaining a diagnosis of mucormycosis on histomorphological basis is challenging, and the most common cause for incorrect morphological diagnosis is the misidentification of Mucorales as *Aspergillus* spp.**
- **The application of immunohistochemistry with commercially available monoclonal antibodies or PCR techniques on either fresh or formalin-fixed paraffin-embedded tissue have been shown to be highly specific,** although a variation in sensitivity has been reported, in addition, these tests might not be widely available.

Recommendations

- **Hyphae of Mucorales can be distinguished from septate hyaline moulds due to their greater width and irregular pattern of branching.**

- However, there are no data available to describe the accuracy of distinguishing Mucorales from other moulds based on these characteristics.

- **Therefore, it is strongly recommended to confirm the diagnosis of mucormycosis in tissue by culture or by application of molecular or in-situ identification techniques, at centres where such assays are available .**

Culture and microscopy

- *Recommendations*

- **Culture of specimens is strongly recommended for genus and species identification, and for antifungal susceptibility testing.**

- Homogenisation of tissue should be avoided before culturing.

- **Incubation at 30°C and 37°C separately is strongly recommended .**

- Direct microscopy with fluorescent brighteners from clinical specimens is strongly recommended mainly focusing on septation, branching angle, and hyphal width.

Susceptibility testing

- **The use of standard methods for antifungal susceptibility testing to guide antifungal treatment in Mucorales is marginally supported and may be clinically useful in cases of treatment failure.**
- However, we strongly recommend the use of these methods primarily to establish epidemiological knowledge in the field.
- **Currently, commercial methods such as E-test are recommended for use in mucormycosis with marginal strength only.**

Molecular-based methods for direct detection

- **Currently, in the absence of a standardised test, the use of molecular methods on both fresh clinical material and paraffin sections for the diagnosis of mucormycosis is moderately supported.**

- Fresh material is preferred over paraffin-embedded tissue because formalin damages DNA.
- **Detection of DNA in serum as well as in other body fluids is very promising but because of lack of standardization supported with moderate strength only.**

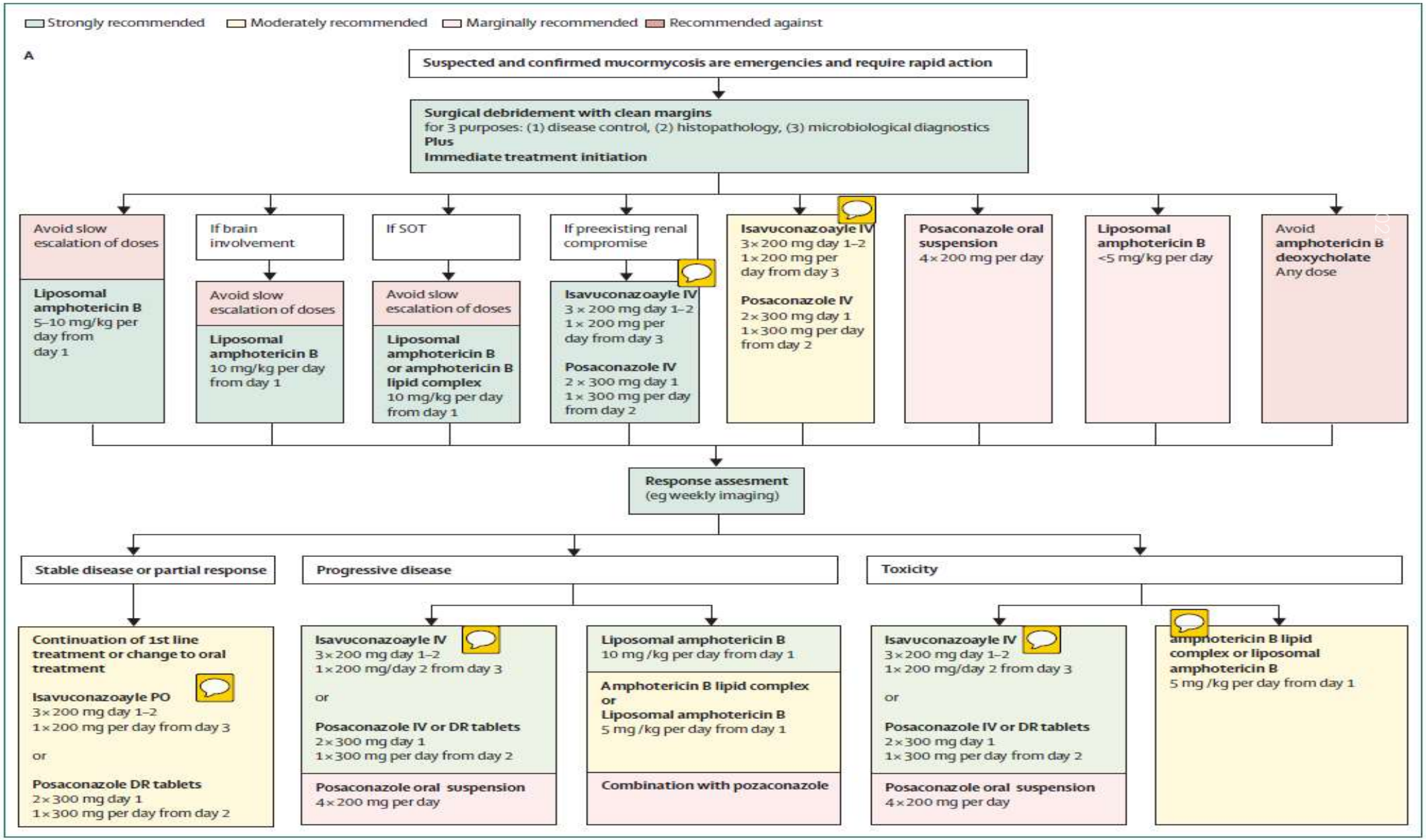
Genus and species identification

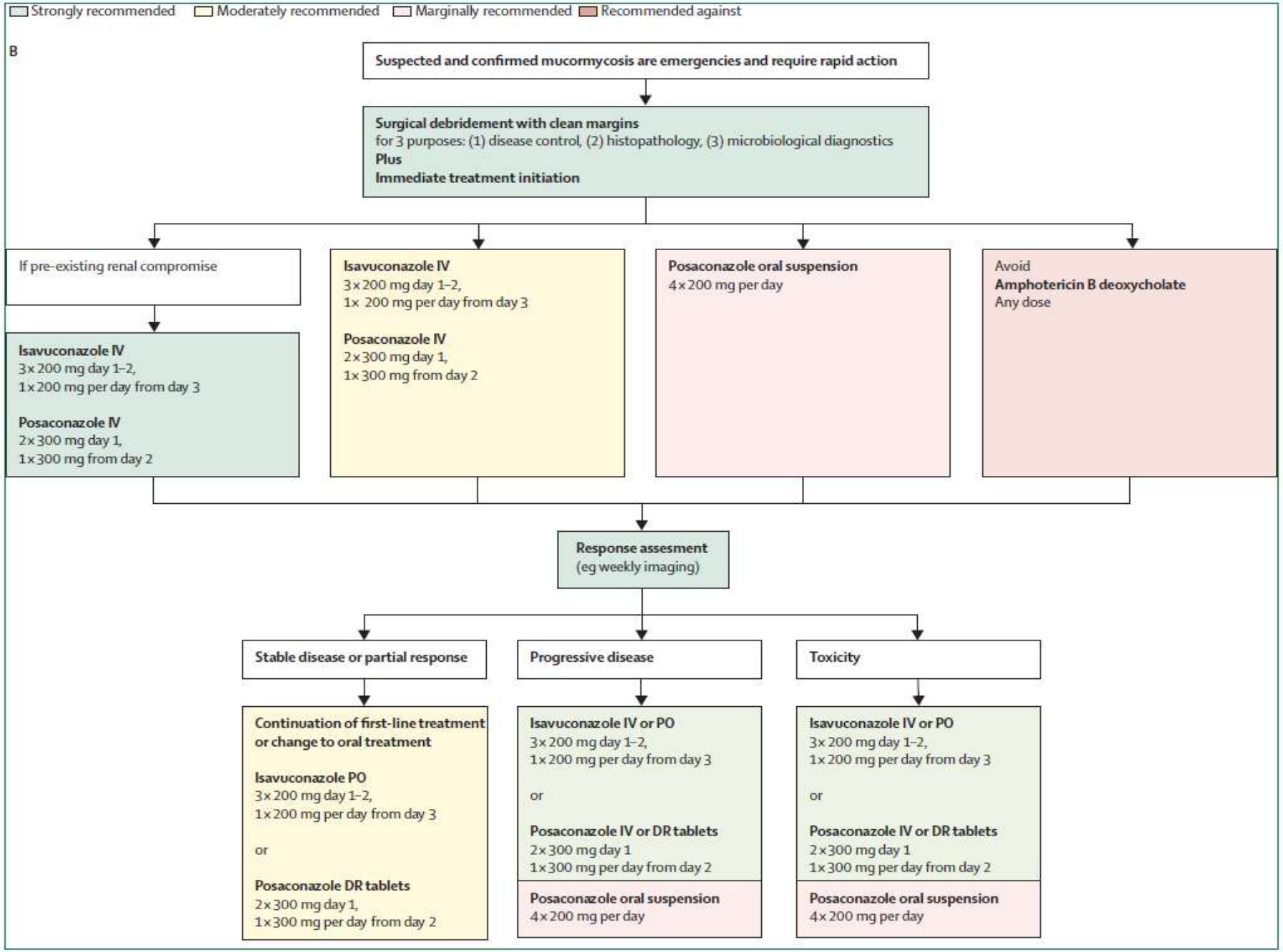
- **Although some genera, such as Cunninghamella, can be associated with an increased mortality rate in patients and have been shown to be more virulent in experimental models,**
- there is currently sparse evidence that identification of the causative Mucorales to the genus or species level, or both, could guide the choice of the antifungal treatment.

- **By contrast, identification to the species level is of importance for improved epidemiological knowledge of the disease.**
- In particular, the clinical picture can be different depending on the species.
- Moreover, species identification is valuable for investigation of health care-associated mucormycosis and outbreaks.

- Recommendations

- **Identification to the genus and species level is strongly supported for improved epidemiological understanding of mucormycosis.**
- Guiding treatment by identification to the genus level is supported with marginal strength.
- **Molecular identification is strongly supported and preferred over morphology.**
- Because the best technique for molecular identification, internal transcribed spacer (ITS) sequencing is strongly supported.
- Matrix assisted laser desorption ionisation time of flight (MALDI-TOF) identification is moderately supported because it relies mainly on in-house databases, and many laboratories do not have that capacity.


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
Response assesment
(eg weekly imaging)
Stable disease or partial response
Continuation of 1st line treatment or change to oral treatment
Isavuconazoayle PO
3×200 mg day 1–2
1×200 mg per day from day 3
or
Posaconazole DR tablets
2×300 mg day 1
1×300 mg per day from day 2
Progressive disease
Isavuconazoayle IV
3×200 mg day 1–2
1×200 mg/day 2 from day 3
or
Posaconazole IV or DR tablets
2×300 mg day 1
1×300 mg per day from day 2
Posaconazole oral suspension
4×200 mg per day
Liposomal amphotericin B
10 mg /kg per day from day 1
Amphotericin B lipid complex
or
Liposomal amphotericin B
5 mg /kg per day from day 1
Combination with pozaconazole
Toxicity
Isavuconazoayle IV
3×200 mg day 1–2
1×200 mg/day 2 from day 3
or
Posaconazole IV or DR tablets
2×300 mg day 1
1×300 mg per day from day 2
Posaconazole oral suspension
4×200 mg per day
amphotericin B lipid complex or liposomal amphotericin B
5 mg /kg per day from day 1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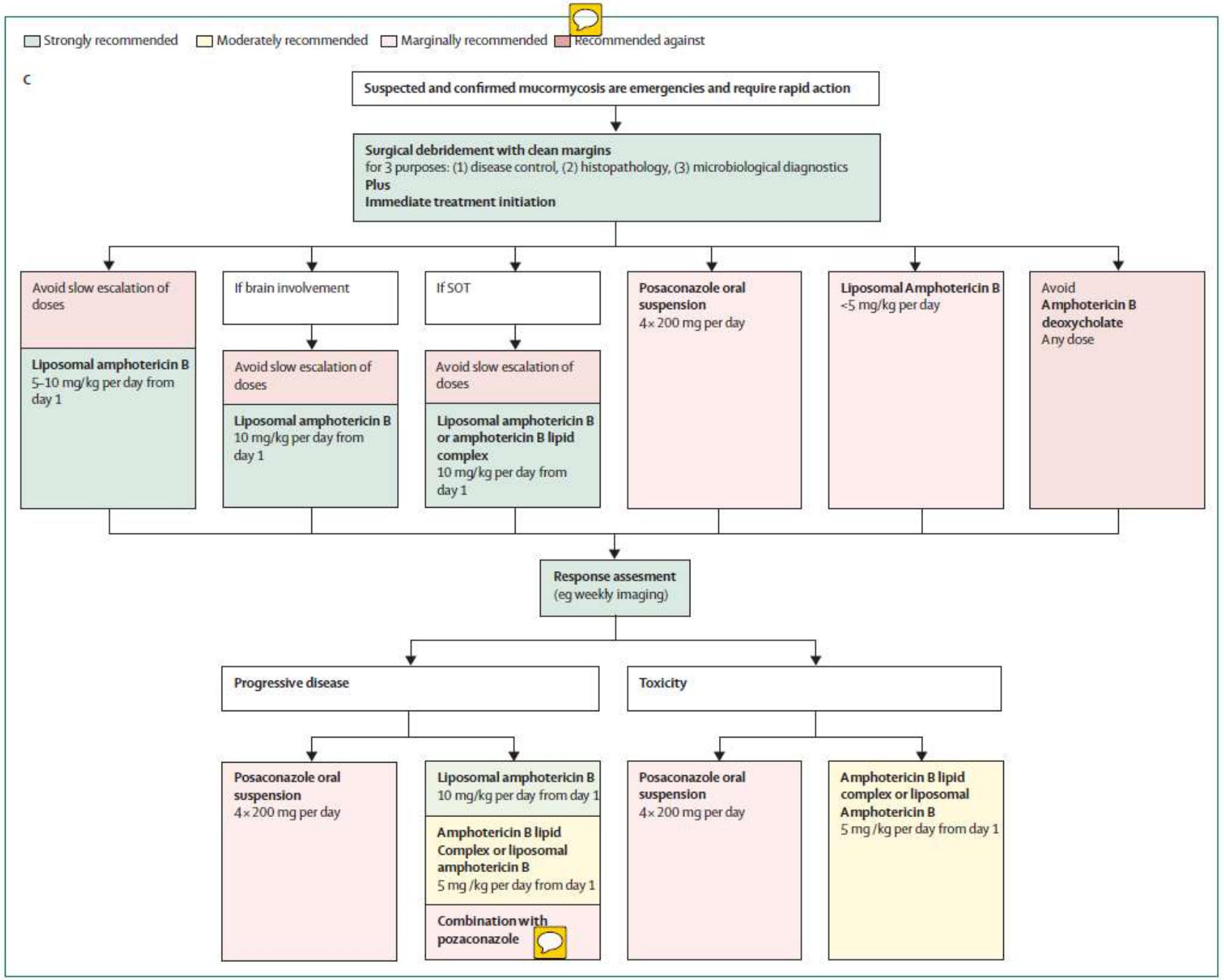
Plus
Immediate treatment initiation
If pre-existing renal compromise
Isavuconazole IV
3×200 mg day 1–2,
1×200 mg per day from day 3
Posaconazole IV
2×300 mg day 1,
1×300 mg from day 2
Isavuconazole IV
3×200 mg day 1–2,
1× 200 mg per day from day 3
Posaconazole IV
2×300 mg day 1,
1×300 mg from day 2
Posaconazole oral suspension
4×200 mg per day
Avoid
Amphotericin B deoxycholate
Any dose
Response assesment
(eg weekly imaging)
Stable disease or partial response
Progressive disease
Toxicity
Continuation of first-line treatment or change to oral treatment
Isavuconazole PO
3×200 mg day 1–2,
1×200 mg per day from day 3
or
Posaconazole DR tablets
2×300 mg day 1,
1×300 mg per day from day 2
Isavuconazole IV or PO
3×200 mg day 1–2,
1×200 mg per day from day 3
or
Posaconazole IV or DR tablets
2×300 mg day 1
1×300 mg per day from day 2
Posaconazole oral suspension
4×200 mg per day
Isavuconazole IV or PO
3×200 mg day 1–2,
1×200 mg per day from day 3
or
Posaconazole IV or DR tablets
2×300 mg day 1
1×300 mg per day from day 2
Posaconazole oral suspension
4×200 mg per day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Avoid slow escalation of doses
Liposomal amphotericin B or amphotericin B lipid complex
10 mg/kg per day from day 1
Posaconazole oral suspension
4×200 mg per day
Liposomal Amphotericin B
<5 mg/kg per day
Avoid
Amphotericin B deoxycholate
Any dose
Response assesment
(eg weekly imaging)
Progressive disease
Toxicity
Posaconazole oral suspension
4×200 mg per day
Liposomal amphotericin B
10 mg/kg per day from day 1
Amphotericin B lipid Complex or liposomal amphotericin B
5 mg /kg per day from day 1
Combination with pozaconazole
Posaconazole oral suspension
4×200 mg per day
Amphotericin B lipid complex or liposomal Amphotericin B
5 mg /kg per day from day 1

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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.

Treatment approaches to mucormycosis

- **The ability to treat mucormycosis effectively depends on the availability of the surgical techniques and antifungal drugs discussed below.**
- If all treatment options are available one should follow the management.
- If local or regional capabilities differ, less comprehensive pathways need to be followed;

Surgical treatment for mucormycosis

- ***Recommendations*—The guideline group strongly supports an early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment.**
- **Resection or debridement should be repeated as required**

Drug treatment for mucormycosis

- Recommendations—

- **In neutropenic patients or those with graft versus host disease, primary prophylaxis with posaconazole delayed release tablets is recommended with moderate strength, and prophylaxis with oral suspension is recommended with marginal strength to prevent mucormycosis.**
- Secondary prophylaxis

- Recommendations—
- **In immunosuppressed patients with previous diagnosis of mucormycosis, surgical resection and continuation or restart of the last drug effective in that patient is strongly recommended.**
- Fever-driven treatment
- Recommendations—
- **The guideline group recommends against initiation of treatment for mucormycosis when fever of unknown origin is the sole evidence of infection.**
- Diagnosis-driven treatment
- Recommendations—
- **In any immunocompromised patient with suspected mucormycosis, immediate treatment initiation is strongly recommended.**
- Every attempt to attain a diagnosis should be made at the time of initiation of therapy, but should not delay therapy.

First-line antifungal monotherapy

- Evidence—In several case series, the use of liposomal amphotericin B successfully treated mucormycosis with various organ involvement patterns.
- Daily doses ranged from 1 mg/kg per day to 10 mg/kg per day.
- Recipients of increased doses tended to have increased response rates.
- **Patients receiving 10 mg/kg per day had substantial serum creatinine increases that were mostly reversible.**
- Doses higher than 10 mg/kg per day did not result in higher blood concentrations.
- In CNS involvement, animal models and the above observations support use of liposomal amphotericin B at 10 mg/kg per
- day.

- In the absence of CNS involvement, amphotericin B lipid complex 5 mg/kg per day has been used successfully.
- In kidney transplant recipients, amphotericin B lipid complex 10 mg/kg per day has been given.
- Amphotericin B deoxycholate has been the drug of choicefor decades.
- It is effective, but its use is limited by its substantial toxicity, specifically in the doses and treatment durations needed for mucormycosis .
- Use of amphotericin B deoxycholate should be restricted to settings in which there is no other antifungal therapy available

	Intention	Intervention	SOR	QOE	Reference
Any	To cure and to increase survival rates	Amphotericin B, any formulation, escalation to full dose over days	D	IIu	Chamilos[3] (N=70, give full daily dose from day 1)
Any	To cure and to increase survival rates	Amphotericin B, liposomal, 5–10 mg/kg per day	A	IIu	Gleissner[144] (N=16, haematology); Pagano[109] (N=5); Cornely[106] (N=4); Pagano[105] (N=44); Rüping[67] (N=21); Shoham[50] (N=28); Skiada[17] (N=130); Lanternier[104] (N=34, 18 haematology, six diabetic); Kyvernitakis[108] (N=41); Stanzani[107] (N=97, increased renal toxicity with cyclosporine)
CNS involvement	To cure	Amphotericin B, liposomal, 10 mg/kg per day, initial 28 days	A	III	Ibrahim[112] (Animal); Lanternier[104] (N=9)
SOT adults	To cure	Amphotericin B, lipid formulation; dose not given	A	IIh	Singh[145] (N=25); Sun[146] (N=14); Lanternier[147] (N=3)
SOT adults	To cure	Amphotericin B, lipid complex; 10 mg/kg per day	A	III	Forrest[114] (N=6, 3 of 6 died)
Any, without CNS involvement	To cure	Amphotericin B, lipid complex; 5 mg/kg per day	B	IIu	Larkin[113] (N=10); Ibrahim[112] (animal); Skiada[17] (N=7)
Haematological malignancy	To cure	Amphotericin B, liposomal; 1–<5 mg/kg per day ± surgery	C	III	Nosari[110] (N=13, 8 of 13 treated, 5/8 died); Li[148] (N=7, 2 of 7 died)
Any	To cure	Isavuconazole PO or IV; 3 × 200 mg day 1–2, 1 × 200 mg/d from day 3	B	IIh	Marty[49] (N=21, 11 haematology, 4 diabetes, overall mortality comparable to amphotericin B formulations)
Any	To cure	Posaconazole DR tablet or intravenously 2 × 300 mg day 1, 1 × 300 mg from day 2	B	IItu	Duarte;[122] Maertens;[124] Cornely;[123] Cornely[125] (higher trough levels than oral suspension, intravenous bridging when oral dosing not feasible)
Any	To cure	Posaconazole oral suspension; 4 × 200 mg/day or 2 × 400 mg/day	C	IIu	Rüping[67] (N=8); Skiada[17] (N=17); Dannaoui[149] (animal, emphasises preference of amphotericin B, liposomal)
Any	To cure	Amphotericin B, deoxycholate, any dose (if alternative therapy available)	D	IIt	Walsh[116] (renal toxicity); Pagano[109] (N=9); Roden[11] (N=532); Ullmann[115] (renal toxicity); Chakrabarti[66] (N=10); Skiada1[17] (N=21)
Orbital mucormycosis	To cure	Retrobulbar injection of amphotericin B deoxycholate in addition to systemic therapy	D	III	Hirabayashi[50] (N=1, post-injection inflammatory response, risk for acute compartment syndrome)

IV=intravenous. PO=per os (taken orally). SOR=strength of recommendation. QOE=quality of evidence. N=number of individuals. SOT=solid organ transplantation. DR=delayed release.

Table 2: **Recommendations on first-line antifungal monotherapy for mucormycosis by population type**

- The efficacy of isavuconazole was similar to an external matched control group treated with amphotericin B formulations.

- This limited size study enrolled 21 patients with isavuconazole first-line treatment, and compared efficacy results to 33 matched patients from the FungiScope registry.
- As a result, isavuconazole has been licenced in the USA for first-line treatment of mucormycosis.
- By contrast with other mould-active azoles, isavuconazole is less hepatotoxic although it can result in shortening the QTc interval.
- Posaconazole oral suspension has been used successfully in first-line treatment.
- Recently, concerns about its oral bioavailability led to the development of a delayed release tablet with improved exposure and an intravenous infusion formulation

- *Recommendations—*
- First-line treatment with liposomal amphotericin B 5–10 mg/kg per day is strongly supported across all patterns of organ involvement.
- If substantial renal toxicity develops, the dose can be reduced as necessary, but doses below 5 mg/kg per day are recommended with marginal strength only.
- Doses should not be slowly increased over several days; rather, the full daily dose should be given from the first treatment day.
- Amphotericin B lipid complex 5 mg/kg per day is recommended with moderate strength for patients without CNS involvement.
- Use of amphotericin B deoxycholate is discouraged whenever alternatives are available.
- Isavuconazole is recommended with moderate strength for the first-line treatment of mucormycosis.
- The group marginally supports use of posaconazole oral suspension, and moderately supportsposaconazole delayed release tablets and infusion for firstline treatment

First-line antifungal combination therapy

- *Evidence*—In animal models, some antifungal combinations have shown the potential to improve cure and survival rates with no antagonism noted.
- Results from some patient series are promising.
- However, a historical control study55 and a propensity score analysis failed to show benefits of double and triple antifungal combinations in patients with haematological malignancy.
- 108 In trauma patients, specifically in blast injury, more than one mould species can cause mixed infection warranting empirical combination therapy with liposomal amphotericin B and either posaconazole or voriconazole.
- The downsides of combination therapy are unclear aside from potential added toxicity, drug interactions, and cost.

- *Recommendations—*
- There are no definitive data to guide the use of antifungal combination therapy.
- Limited data support combinations of polyenes and azoles or polyenes plus echinocandins.
- Combination therapy can be rationally given due to lack of enhanced toxicity with possible but unproven benefit; however, data are too limited to support this beyond a marginal recommendation.

Antifungal salvage treatment

Evidence—In general, there are two drug-related reasons for treatment failures, refractory mucormycosis or toxicity of first-line regimens—ie, intolerance to a drug. For amphotericin B formulations, particularly renal toxicity can be a limiting factor, while for the azole class hepatic toxicity has the highest prevalence. Toxicity can be caused by previous antifungals, or expected due to pre-existing organ damage. Only two drug classes have proven efficacy in mucormycosis, thus salvage treatment mostly means switching to the other class. Isavuconazole salvage

treatment was successful in both clinical scenarios, refractory disease, and intolerance or toxicity.49,132 In Europe, isavuconazole is licenced for salvage treatment of mucormycosis only. Posaconazole treatment with oral suspension achieved cure in two non-randomised clinical trials133,134 and in case series.17,135 Liposomal amphotericin B was effective as salvage treatment,109 as was amphotericin B lipid complex,113,136 and amphotericin B colloidal dispersion

- *Recommendations—*
- Isavuconazole is strongly supported as salvage treatment. Posaconazole delayed release tablets or infusions are strongly supported for salvage treatment, and when available should be preferred over posaconazole oral suspension, which in turn is marginally supported for salvage treatment.
- In cases of primary treatment failure with isavuconazole or posaconazole, the guideline group supports recommendations for all three lipidbased amphotericin B formulations with strong to moderate strength.

Treatment duration for mucormycosis

- *Treatment duration for mucormycosis Evidence—*
- The duration of therapy necessary to treat mucormycosis is unknown.
- In general, weeks to months of therapy are given.
- If immune defect is resolved—eg diabetes is controlled, neutropenia definitively resolved, immunosuppression can be tapered or stopped, therapy can be continued until resolution of signs and symptoms of infection, and substantial radiographical improvement.

- Median duration of isavuconazole first-line or salvage treatment was 84 days intravenous or oral route or both. Across several posaconazole oral suspension studies,
- treatment duration ranged from 1 week to almost 3 years, mean duration was approximately 6 months .
- The wide range reflects the pattern of organs involved, with competing risks from underlying conditions. Late relapse in long-term survivors have been documented

- *Recommendations—*
- The guideline group strongly supports treatment until permanent reversal of immunosuppression
- and complete response on imaging, which might be difficult to determine because of scarring and postoperative changes.
- Treatment duration is a personalised decision.
- There is moderate support for intravenous treatment until stable disease is achieved.
- When switching to oral treatment, use of isavuconazole or posaconazole delayed release tablets is strongly supported.
- Posaconazole oral suspension can be used, but is marginally supported, especially when formulations with higher exposure are available.
- Therapeutic drug monitoring in mucormycosis ,specific considerations on treatment of mucormycosis in children, adjunctive treatments for mucormycosis, intensive care and crtically ill patients with mucormycosis ,health economics, and future directions are available in the appendix where indicated.

Treatment pathways for mucormycosis

- The proposed treatment algorithms for adult and for paediatric patients are based on case series, retrospective studies, and expert opinion.
- Large, randomised controlled trials investigating efficacy of treatment regimens are lacking.
- Surgical debridement should be performed whenever feasible in parallel to antifungal treatment.
- The drug of choiceis liposomal amphotericin B.
- In case of renal failure, posaconazole or isavuconazole were shown to be effective.
- If a patient is intolerant to liposomal amphotericin B, its dose can be reduced, but should stay ≥5 mg/kg bodyweight.
- In case of extensive disease, rapid progression, or poor general condition, the addition ofisavuconazole or posaconazole can be considered.
- Treatment should be continued until resolution of initially indicative findings on imaging and reconstitution of host immune system.
- Isavuconazole or posaconazole may be administered as maintenance therapy.

Contributors

- OAC and AC coordinated the work of the authors and guided the development of the guideline.
- OAC, AC, AAI, DA, SCAC, ED, BH, MH, HEJ, KL, REL, SCM, MMe, ZP, DS, DCS, and RW wrote the initial manuscript draft.
- All authors contributed to the literature review, compilation of data tables and interpretation and assessment of recommendations.
- All authors participated in review and revisions, approved the final manuscript, and are 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.

Declaration of interests

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- SAA reports grants from Pfizer. SCAC reports grants from MSD Australia.
- MH reports reports personal fees from Basilea, Merck,Practitioner Network; and grants and personal fees from Gilead.
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