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


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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


Mucormycosis is a difficult to diagnose rare disease with high morbidity and mortality. Diagnosis is often delayed, and disease tends to progress rapidly. Urgent surgical and medical intervention is lifesaving. Guidance on the complex multidisciplinary management has potential to improve prognosis, but approaches differ between health-care settings. From January, 2018, authors from 33 countries in all United Nations regions analysed the published evidence on mucormycosis management and provided consensus recommendations addressing differences between the regions of the world as part of the “One World One Guideline” initiative of the European Confederation of Medical Mycology (ECMM). Diagnostic management is strongly recommended to document extent of disease and is followed by strongly recommended surgical intervention. First-line treatment with high-dose liposomal amphotericin B is strongly recommended, while intravenous isavuconazole and intravenous or delayed release tablet posaconazole are recommended with moderate strength. Both triazoles are strongly recommended salvage treatments. Amphotericin B deoxycholate is recommended against, because of substantial toxicity, but may be the only option in resource limited settings. Management of mucormycosis depends on recognising disease patterns and on early diagnosis. Limited availability of contemporary treatments burdens patients in low and middle income settings. Areas of uncertainty were identified and future research directions specified.

Introduction
Suspected mucormycosis requires urgent intervention, because of the often rapidly progressive and destructive nature of the infection. Delayed initiation of therapy is associated with increased mortality. Maximising survival rates requires rapid diagnostic and therapeutic intervention, including immediate involvement of a multidisciplinary medical, surgical, radiological, and laboratory-based team. Readily available guidance is important to ensure efficient diagnosis and treatment, and to optimise patient prognosis. Optimal management depends on recognising disease patterns and the available diagnostic and therapeutic options, which differ between the regions of the world.

Currently available guidelines are limited to specific patient groups in haematology, or a specific geographical region, or require an update. Recently, several critical developments have fundamentally changed the management of this condition. These include the development of new and more widely used molecular techniques for the diagnosis of mucormycosis, the licensing of isavuconazole for treatment of mucormycosis, and the availability of new formulations of posaconazole. Moreover, previous guidelines did not include comprehensive clinical and radiological imaging, pathological and histological findings, nor did they provide details on surgery as a core element of mucormycosis management.

The European Confederation of Medical Mycology (ECMM), together with the Mycoses Study Group Education & Research Consortium (MSG ERC), issues this comprehensive guidance document to facilitate clinical decision-making, and simultaneously provides an overview of the areas of uncertainty in the field. We aimed to address limitations of previous recommendations, by engaging physicians and scientists involved in various aspects of mucormycosis management, representing the fields of microbiology, pathology, radiology, infectious diseases, surgery, paediatrics, haematology, intensive care, dermatology, and pharmacoepidemiology.

In addition, the guideline group comprises experts from all parts of the world and provides management pathways for different regional environments (panel; for further information on guideline development, systematic
Panel: How the guideline group worked

In December, 2017, experts were identified based on their publication activity in the field of mucormycosis in the previous 5 years, their involvement in patient management, and their distribution over world regions defined by the United Nations. Experts were invited to develop this guideline in January, 2018. This guideline follows the structure and definitions of previous guidelines on invasive fungal infections which are in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Appraisal of Guidelines for Research & Evaluation (AGREE) systems. The PICO (population, intervention, comparison, and outcome) approach is reflected by the tables.

Both, diagnostic assays and treatment strategies might alter patient course, and are thus regarded as interventions. First, a population is defined; then the intention or objective is stated, followed by the intervention. For such logical sequence, strength of recommendation (SOR) and quality of evidence (QOE) are provided, followed by the references on which the recommendation is based. SOR and QOE are results of two independent evaluations, thus allowing a strong recommendation even in the absence of the highest quality evidence (table 1).

Search strings used were “mucormyc* OR zygomyc*”, “cavernous sinus syndrome OR orbital apex syndrome AND etiology”, and for the epidemiological section “mucormyc* OR zygomyc*” AND (case “[Title/Abstract] OR patient [Title/Abstract] OR report [Title/Abstract]) AND (“2013/01/01”[PDat] : “2017/12/31”[PDat])

From January to February, 2018, video conferences on the methodology were held, and a video tutorial added in March, 2018. Assistance and supervision to the group were provided by the coordinators (OAC, AC). Documents were shared among the authors on a password-protected OneDrive (Microsoft Corp, Redmont WA, USA) repository, and were updated several times per day. Updates on PICO tables were written in red font, after spellcheck and formatting font colour was changed to blue for consideration by the group. Contents discussed and agreed on were changed to black font. Once all tables were finalised, a writing group (OAC, AAI, DA, SCAC, ED, BH, MH, HEJ, KL, REL, SCM, MM, ZP, DS, DCS, RW, AC) contributed the first draft, which was circulated to all participants for approval in October, 2018. Recommendations were consensus-based. If no consensus was found, majority vote was used.

In November, 2018, a 4-week public consultation phase ensued. Comments received were evaluated, and either dismissed or used to change the manuscript, resulting in a final author review in December, 2018. 51 scientific societies from 33 countries reviewed and endorsed the guidance document.

Epidemiology of mucormycosis

Patient populations

As medical science advances, the patient populations most at risk for mucormycosis expand accordingly. In the mid-20th century, diabetes evolved as a major risk factor for mucormycosis, while in more recent years, underlying malignancy emerged as another important risk factor due to the increasing number of patients undergoing chemotherapy or cancer immunotherapy. Furthermore, with more solid organ and haematopoietic stem-cell transplantations (HSCT) being performed, increasing numbers of cases have also been reported in these patient groups. At the same time, diabetes continues to changeably with zygomycosis. The latter term referred to infections caused by fungi of the former phylum Zygomycota (comprising Mucorales, Entomophthorales, and others), which became obsolete with phylogenetic reanalysis of the kingdom Fungi. Today, mucormycosis describes infections caused by fungi of the order Mucorales. The most frequently reported pathogens in mucormycosis are Rhizopus spp, Mucor spp, and Lichtheimia spp (formerly of the genera Absidia and Mycoclada), followed by Rhizomucor spp, Cunninghamella spp, Apophysomyces spp, and Saksenaea spp. Lichtheimia spp were identified as the major cause of mucormycosis in a single hospital in Spain, indicating geographical variation and the need to know local epidemiology.

Clinical manifestations of mucormycosis

For further information on clinical manifestations, see appendix p 6.

In immunocompromised patients, the main route of infection seems to be through inhalation of sporangiospores causing pulmonary infection. Pulmonary mucormycosis typically develops in patients with profound neutropenia, and graft-versus-host disease, whereas diabetic patients typically present with rhino-orbital disease. Prolonged fever is seen in most patients, although some patients might be asymptomatic. Radiological findings often vary in configuration, size, number, and distribution of lesions; typical examples are given below. Pulmonary mucormycosis can spread...
Cutaneous and rhino-orbito-cerebral mucormycosis

(A) Extensive primary cutaneous mucormycosis of the left leg due to *Apophysomyces variabilis*, after a car accident. (B) Erythematous skin, ptosis, palpebral oedema, limited ocular motility, and right maxillary pain, 6 days after symptom onset in uncontrolled diabetes. (C) Proptosis, palpebral oedema, and cavernous sinus syndrome, 7 days after symptom onset in uncontrolled diabetes. (D) Necrotic, purulent palatal ulcer and cavernous sinus syndrome, 8 days after symptom onset in uncontrolled diabetes. (E) Rhinocerebral mucormycosis in a female child, 2 years old with acute lymphoblastic leukaemia and lethal outcome. (F) 52-year-old man with persistent tissue necrosis, dry ulcers, and eschars 7 days after symptom onset in uncontrolled diabetes. (G) Black eschar as typical skin lesion in mucormycosis; one of several lesions on the right forehead, ear and diaphragm into the abdomen.

Cutaneous and soft-tissue mucormycosis are the most common forms of mucormycosis in immunocompetent patients, primarily after skin disruption due to traumatic injury (eg from natural disasters, motor vehicle accidents, improvised explosive devices in theatres of war, or iatrogenic sources), surgery, or burns.30–32 Abscesses, skin swelling, necrosis, dry ulcers, and eschars are characteristic presentations (figure 1A and G).33,34 For further information on cutaneous and soft-tissue mucormycosis, see appendix p 6.
Rhino-orbital-cerebral mucormycosis typically develops in patients with diabetes, whereas such patients very rarely develop lung infection. It has been described in haematology patients, too. Rhino-orbital-cerebral infection usually originates from the paranasal sinuses, with bone destruction and subsequent invasion of the orbit, eye, and brain. Unilateral facial oedema, proptosis, and palatal or palpebral fistula developing into necrosis may be present (figure 1B, F).

For further information on rhino-orbital-cerebral mucormycosis see appendix p 6.

Primary gastrointestinal disease is a rare manifestation of mucormycosis that can present with symptoms similar to other common gastrointestinal diseases. However, gastrointestinal mucormycosis is the most common manifestation of mucormycosis in neonates, where it carries a high mortality.
For further information on gastrointestinal mucormycosis, see appendix p 6.

Cases of isolated renal mucormycosis in immunocompetent hosts are extremely rare, but have been reported from China and India.43–48 For further information on renal and abdominal mucormycosis, see appendix p 7.

Mortality

All-cause mortality rates for mucormycosis range from 40% to 80% with varying rates depending on underlying conditions and sites of infection.12,13,41–43 The highest survival rates are reported in patients with a healthy immune status and those without comorbidities. The poorest prognosis is observed in patients with haematological malignancies and HSCT recipients13 and in patients with extensive burns.12 Disseminated disease, especially to the CNS is often associated with mortality rates higher than 80%.12 Conversely, lower mortality is seen with localised sinus or skin infection, where earlier tissue-based diagnosis is often feasible and surgical debridement may result in cure. Mortality is also high in neonates and other

Figure 3: Radiographic signs of mucormycosis

Four imaging signs can suggest pulmonary mucormycosis in an appropriate clinical setting. (A) Halo sign on CT, a ring of ground glass opacity surrounding a nodular infiltrate, which pathophysiologically represents a region of ischaemia, and which is also typical of invasive pulmonary aspergillosis (arrow). (D & B) Reversed halo sign on CT, also known as inverso halo or atoll sign, an area of ground glass opacity surrounded by a ring of consolidation (arrow). (E) Hypodense sign on MRI, T1 weighted, a central hypodensity in a lung consolidation or nodule, corresponding to a central area of necrosis caused by vascular obstruction with secondary lung infarction and sequestration. Magnetic resonance imaging shows pulmonary nodule with central hypodensity in right upper lobe (arrow), corresponding to a central area of necrosis caused by vascular obstruction with secondary lung infarct and sequestration. (C) Vascular occlusion sign on CT angiography, defined as interrupted vessel at the border of a focal lesion without depiction of the vessel inside the lesion or peripheral to the lesion (arrow). Particularly aggressive forms of mucormycosis are F. Contiguous spread on CT, presence of a mass or consolidation exhibiting invasion of adjacent organs by traversing tissue planes, including the diaphragm, chest wall, pleura, and spleen. (G) Typical rapidly progressive pulmonary mucormycosis on CT, associated with clinical deterioration. Day 8 and Day 15 CT scans showing a reversed halo sign. Images A, C, D, and E courtesy of Bruno Hochhegger, images B, F, and G courtesy of University Hospital Cologne.

For further information on gastrointestinal mucormycosis, see appendix p 6.

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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 figure 2.

For further information on diagnosing mucormycosis, see appendix p. 7.

Imaging

Radiographical signs suggestive of pulmonary mucormycosis are shown in figure 3. For further information on imaging see appendix p. 7.

Recommendations

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 (appendix p. 7).

Histopathology in mucormycosis

Evidence

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 (Tanon 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 (PAS) or G rocott's methenamine-silver stain (PAS), x 1000. The eosinophilic material likely represents antigen-antibody complexes. First described by Splendore in 1908, and by Hoeppli in 1932. (C) Typical hyphal morphology in aspergillosis lesions (PAS, x 200). Aspergillus hyphae are 3–5 µm wide, regularly septated, with dichotomous branching. (D–F) Sizes and branching angles for Mucorales and aspergillus stained by calcofluor-white. D and F correspond to Rhizopus arrhizus and E to Aspergillus fumigatus. Measurements correspond to the size of the white lines; hyphal diameter were performed with the Leica software LAS-AF and are expressed in µm. Diagnosis needs to be confirmed by culture, molecular techniques, or both. Images A–C courtesy of Henrik E Jensen and images D–F courtesy of Ana Alastruey-Izquierdo.

Figure 4: Hyphal morphology in mucormycosis and aspergillosis

(A) Typical hyphal morphology in mucormycosis lesions (GMS, x 200). Mucorales hyphae are at least 6–16 µm wide, ribbon-like, pauci-septate, and branch irregularly. (B) Hyphal structure covered with Splendore-Hoeppli phenomenon (HE, x 1000). The eosinophilic material likely represents antigen-antibody complexes. First described by Splendore in 1908, and by Hoeppli in 1932. (C) Typical hyphal morphology in aspergillosis lesions (PAS, x 200). Aspergillus hyphae are 3–5 µm wide, regularly septated, with dichotomous branching. (D–F) Sizes and branching angles for Mucorales and aspergillus stained by calcofluor-white. D and F correspond to Rhizopus arrhizus and E to Aspergillus fumigatus. Measurements correspond to the size of the white lines; hyphal diameter were performed with the Leica software LAS-AF and are expressed in µm. Diagnosis needs to be confirmed by culture, molecular techniques, or both. Images A–C courtesy of Henrik E Jensen and images D–F courtesy of Ana Alastruey-Izquierdo.
stain (GMS), or both.\(^{27,28}\) 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 (figure 4A–C).\(^{27,62}\) 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, may 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 non-specific.\(^{29–41}\) In acute lesions, haemorrhagic infarction, coagulation necrosis, angiinvasion, infiltration by neutrophils (in non-neutropenic hosts), and perineural invasion are characteristic features;\(^{39}\) whereas, in chronic lesions, a pyogranulomatous inflammation with presence of giant cells, and sometimes hyphae covered by the Splendore-Hoeppli phenomenon,\(^{39,44}\) which describes deeply eosinophilic material surrounding the pathogen, are seen (figure A–C).\(^{39,41,46–48}\) 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 (figure A–C).\(^{39}\) The application of immunohistochemistry with commercially available monoclonal antibodies\(^{46–50}\)

### Table: The lesions of mucormycosis are characteristic but non-specific.

<table>
<thead>
<tr>
<th>A</th>
<th>Suspected and confirmed mucormycosis are emergencies and require rapid action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical debridement with clean margins</strong></td>
<td>for 3 purposes: (1) disease control, (2) histopathology, (3) microbiological diagnostics</td>
</tr>
<tr>
<td><strong>Immediate treatment initiation</strong></td>
<td>Plus</td>
</tr>
</tbody>
</table>

- **Stable disease or partial response**
  - **Continuation of 1st line treatment or change to oral treatment**
    - Isavuconazole PO
      - 3 x 200 mg day 1–2
      - 1 x 200 mg per day from day 3
    - or
    - Posaconazole IV or DR tablets
      - 2 x 300 mg day 1
      - 1 x 300 mg per day from day 2
  - Posaconazole oral suspension
    - 4 x 200 mg per day

- **Progressive disease**
  - Isavuconazole IV
    - 3 x 200 mg day 1–2
    - 1 x 200 mg per day from day 3
  - or
  - Posaconazole IV or DR tablets
    - 2 x 300 mg day 1
    - 1 x 300 mg per day from day 2
  - Posaconazole oral suspension
    - 4 x 200 mg per day

- **Toxicity**
  - If preexisting renal compromise
    - Isavuconazole IV
      - 3 x 200 mg day 1–2
      - 1 x 200 mg per day from day 3
    - or
    - Posaconazole IV or DR tablets
      - 2 x 300 mg day 1
      - 1 x 300 mg per day from day 2
  - Liposomal amphotericin B
    - 5 mg/kg per day from day 1
  - Avoid
    - Amphotericin B lipid complex or liposomal amphotericin B
    - 5 mg/kg per day from day 1

### Figure 5 (Continues on next page)
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 (appendix p 9).

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 (appendix p 9).

For further information on antigen biomarkers, see appendix p 10.

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 (appendix p 11). Direct microscopy with fluorescent brighteners from clinical specimens is strongly recommended mainly focusing on septation, branching angle, and hyphal width.

(Figure 5 continues on next page)
For further information on culture and microscopy, see appendix p 10.

Susceptibility testing
For further information on susceptibility testing, see appendix p 11–12.

Recommendations
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 (appendix p 11).

Molecular-based methods for direct detection
For further information on molecular-based methods, see appendix p 13.

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 standardisation supported with moderate strength only (appendix p 13).

Genus and species identification

Evidence

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.

For further information on genus and species identification, see appendix p 14–15.

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 (appendix p 15).

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 pathways detailed in figure 5A and appendix p 25. If local or regional capabilities differ, less comprehensive pathways need to be followed; examples are given in figure 5B, C, and appendix p 26.

Surgical treatment for mucormycosis

For further information on surgical treatment, see appendix p 16.

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 (appendix p 16).

Drug treatment for mucormycosis

Prophylaxis

For further information on prophylaxis, see appendix p 18.

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

For further information on secondary prophylaxis, see appendix p 18.

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

For further information on fever-driven treatment, see appendix p 19.

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

For further information on fever-driven treatment, see appendix p 19.

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 deoxylcholate has been the drug of choice for decades. It is effective, but its use is limited by its substantial toxicity, specifically in the doses and treatment durations needed for mucormycosis. The use of amphotericin B deoxylcholate should be restricted to settings in which there is no other antifungal therapy available.

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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.110,112 As a result, isavuconazole has been licensed in the USA for first-line treatment of mucormycosis.113 By contrast with other mould-active azoles, isavuconazole is less hepatotoxic although it can result in shortening the QTc interval.114–116 Posaconazole azoles, isavuconazole is less hepatotoxic although it can result in shortening the QTc interval.114–116 Posaconazole tablet with improved exposure122,123 and an intravenous availability led to the development of a delayed release infusion formulation (table 2).124,125

### 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.117,118 Results from some patient series are promising.119–121 However, a historical control study122 and a propensity score analysis failed to show benefits of double and triple antifungal combinations in patients with haematological malignancy.123 In trauma patients, specifically in blast injury, more than one mould species can cause mixed

<table>
<thead>
<tr>
<th>Intention</th>
<th>Intervention</th>
<th>SOR</th>
<th>QOE</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Any</td>
<td>To cure and to increase survival rates</td>
<td>Amphotericin B, any formulation, escalation to full dose over days</td>
<td>D</td>
<td>III</td>
</tr>
<tr>
<td>Any</td>
<td>To cure and to increase survival rates</td>
<td>Amphotericin B, liposomal, 5–10 mg/kg per day</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>To cure</td>
<td>Amphotericin B, liposomal, 10 mg/kg per day, initial 28 days</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>SOT adults</td>
<td>To cure</td>
<td>Amphotericin B, lipid formulation, dose not given</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>SOT adults</td>
<td>To cure</td>
<td>Amphotericin B, lipid complex, 10 mg/kg per day</td>
<td>A</td>
<td>III</td>
</tr>
<tr>
<td>Any, without CNS involvement</td>
<td>To cure</td>
<td>Amphotericin B, lipid complex, 5 mg/kg per day</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>To cure</td>
<td>Amphotericin B, liposomal, 1–5 mg/kg per day surgery</td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Isavuconazole PO or IV; 1 × 200 mg/day 1–2, 1 × 200 mg/d from day 3</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Posaconazole DR tablet or intravenously 2 × 300 mg day 1, 1 × 300 mg from day 2</td>
<td>B</td>
<td>III</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Posaconazole oral suspension; 4 × 200 mg/day or 2 × 400 mg/day</td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Amphotericin B, deoxycholate, any dose (if alternative therapy available)</td>
<td>D</td>
<td>III</td>
</tr>
<tr>
<td>Orbital mucormycosis</td>
<td>To cure</td>
<td>Retrobulbar injection of amphotericin B deoxycholate in addition to systemic therapy</td>
<td>D</td>
<td>III</td>
</tr>
</tbody>
</table>


**Table 2:** Recommendations on first-line antifungal monotherapy for mucormycosis by population type.
infection warranting empirical combination therapy with liposomal amphotericin B and either posaconazole or voriconazole.\textsuperscript{25,26} 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.

For further information on first-line combination therapy, see appendix p 19.

**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.\textsuperscript{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 trials\textsuperscript{113,134} and in case series.\textsuperscript{12,115} Liposomal amphotericin B was effective as salvage treatment,\textsuperscript{109} as was amphotericin B lipid complex,\textsuperscript{111,114} and amphotericin B colloidal dispersion.\textsuperscript{117}

**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 lipid-based amphotericin B formulations with strong to moderate strength.

For further information on salvage treatment, see appendix p 20.

**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.\textsuperscript{109} Across several posaconazole oral suspension studies, treatment duration ranged from 1 week to almost 3 years, mean duration was approximately 6 months.\textsuperscript{111,113,114,118,139} The wide range reflects the pattern of organs involved, with competing risks from underlying conditions. Late relapse in long-term survivors have been documented (appendix p 21).

**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 (appendix p 21).

Therapeutic drug monitoring in mucormycosis (appendix p 22), specific considerations on treatment of mucormycosis in children (appendix p 23), adjunctive treatments for mucormycosis (appendix p 27), intensive care and critically ill patients with mucormycosis (appendix p 29), health economics (appendix p 29), and future directions (appendix p 30) are available in the appendix where indicated.

**Treatment pathways for mucormycosis**

The proposed treatment algorithms for adult (appendix p 25; figure 5) and for paediatric patients (appendix p 25) 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.\textsuperscript{112,117,141,142} The drug of choice is liposomal amphotericin B.\textsuperscript{121,129} 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 of isavuconazole or posaconazole can be considered.\textsuperscript{111,115}

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.\textsuperscript{111}

**Contributors**

OAC and AC coordinated the work of the authors and guided the development of the guideline. OAC, AC, AA1, DA, SCAC, ED, BH, MH, HEJ, XL, REL, SCM, MMc, 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.

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