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1 Mucormycosis treatment: recommendations, latest advances, and perspectives.

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20

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25

26 **Abstract**

27

28 Mucormycosis are life-threatening fungal infections especially affecting immunocompromised or
29 diabetic patients. Despite treatment, mortality remains high (from 32 to 70% according to organ
30 involvement). This review provides an update on mucormycosis management. The latest
31 recommendations strongly recommend as first-line therapy the use of liposomal amphotericin B (\geq
32 5mg/kg) combined with surgery whenever possible. Isavuconazole and intravenous or delayed-
33 release tablet forms of posaconazole have remained second-line. Many molecules are currently in
34 development to fight against invasive fungal diseases but few have demonstrated efficacy against
35 *Mucorales*. Despite *in vitro* efficacy, combinations of treatment have failed to demonstrate
36 superiority versus monotherapy. Adjuvant therapies are particularly complex to evaluate without
37 prospective randomized controlled studies which are complex to perform due to low incidence rate
38 and high mortality of mucormycosis. Perspectives are nonetheless encouraging. New approaches
39 assessing relationships between host, fungi, and antifungal drugs, and new routes of administration
40 such as aerosols could improve mucormycosis treatment.

41

42

43

44 **Keywords**

45

46 *Mucorales*, antifungal drugs, nebulization, polyenes, azoles, prophylaxis

47

48

49 Introduction

50 Mucormycosis are life-threatening invasive fungal diseases (IFD) due to fungi belonging to
51 *Mucorales* order [1]. Mucormycosis lead to many clinical manifestations, ranging from localized to
52 disseminated infection. Pulmonary or disseminated diseases are commonly found in
53 immunosuppressed patients (hematological malignancy, hematopoietic stem cell transplantation),
54 rhino-orbito-cerebral form in diabetic patients, and cutaneous forms in patients having trauma [2].
55 Other localizations (gastrointestinal, endocarditis, osteoarticular or isolated cerebral infections) are
56 less frequent. Treatment is based on surgery when possible, correction of underlying factors, and
57 aggressive antifungal drug therapy [3]. In contrast to other fungi, few molecules are active.
58 Amphotericin B (AmB), posaconazole (PSZ), and isavuconazole (ISZ) have shown *in vitro* efficacy while
59 voriconazole (VCZ) and echinocandins are inefficient [4,5]. The reference method for antifungal
60 susceptibility testing (AST) is broth microdilution method with the methodology of the European
61 Committee for Antimicrobial Susceptibility Testing (EUCAST) [6] or the Clinical and Laboratory
62 Standards Institute (CLSI) [7]. However, a major concern with AST is the lack of clinical breakpoints.
63 Prognosis remains poor, mortality ranging from 32 to 70%, and is linked to underlying diseases and
64 clinical forms [2]. Therapeutic improvement is therefore mandatory [8]. The aim of this review is to
65 focus on latest recommendations, advances and perspectives on mucormycosis treatment.

66

67 Recent and new antifungal drugs

68 Current recommendations

69 The European Conference on Infections in Leukemia (ECIL) published mucormycosis
70 treatment guidelines in 2017 [9] and the European Confederation of Medical Mycology (ECMM)
71 provided an update in 2019 [10]. Both societies strongly recommend liposomal Amphotericin B (L-
72 AmB) for first-line treatment in adults (A II) (Table 1). Another lipid formulation, Amphotericin B lipid
73 complex (ABLCL) could be used in mucormycosis but without central nervous system (CNS)
74 involvement according to the ECIL (B II) [9]. For neonates and pediatric population, L-AmB and ABLCL
75 were strongly recommended as first-line treatment (A II) [10].

76 One issue to be addressed is the dose regimen of L-AmB. The ECMM recommends 5-10
77 mg/kg and 10 mg/kg in the event of CNS involvement [10]. In a prospective pilot study (Ambizyo),
78 high doses of L-AmB were tested as first-line treatment of mucormycosis [11]. Response rate was
79 43% (12/28) in patients who received ≥ 7.5 mg/kg/day during the first week compared with 0% (0/5)
80 in patients who did not. A high dose of L-AmB (10mg/kg), combined with surgery in 71% of cases, led
81 to an overall response rate of 36% at week 4 and 45% at week 12. Compared to another study using
82 L-AmB ≥ 5 mg/kg in mucormycosis treatment, response was similar at week 4 (36% vs 40%) but was
83 better at week 12 (45% vs 35%) [12]. Mortality rates were equivalent at week 12 (38% vs 42%). A
84 major side effect with L-AmB high dose was creatinine level doubling in 40% of patients.

85 The ECMM recommended dose should not be slowly increased over several days but a full
86 dose must be given from the first day of daily treatment [10].

87 ISZ per os (PO) or intravenous (IV), PSZ delayed-release (DR) tablets or IV forms have been
88 recommended with moderate strength (B II) and PSZ oral suspension have been marginally

89 recommended (C II) [10]. Moreover, the ECMM strongly discouraged the use of AmB deoxycholate
90 (AmBd) (D II).

91 Treatment should be started as soon as possible, as delayed AmB therapy is linked to
92 increased mortality [13]. Moreover, it must be continued until complete response on imaging and
93 permanent reversal of immunosuppression [10]. Treatment duration necessary to treat
94 mucormycosis is unknown and further studies are needed to better determine it. To facilitate
95 treatment in stable disease, ISZ PO or PSZ DR tablets are strongly recommended. Time between
96 induction phase with AmB and introduction of azoles depends on clinical and imaging responses.
97 Some authors recommend at least 3 weeks of induction with parenteral AmB [14].

98 The ECMM has addressed recommendations concerning prophylaxis (Table 2). In neutropenic
99 or GvHD, PSZ DR tablets or IV form are moderately supported (B II, B III) and PSZ oral suspension
100 marginally recommended (C II) while ISZ is marginally supported in neutropenic patients (C II).
101 Finally, in solid organ transplant (SOT) recipients, PSZ and ISZ are marginally recommended in
102 prophylaxis (C III, C II).

103

104 Recent drugs

105 ISZ, a new azole, was approved in the United States and in Europe in 2015 for the treatment
106 of mucormycosis [3,15]. ISZ is available in oral and IV formulations, and presents some advantages:
107 linear pharmacokinetics, few interactions with cytochrome P450 isoenzymes leading to few drug-
108 drug interactions, QT decrease, no nephrotoxic cyclodextrin in the IV formulation (different from
109 posaconazole IV form), no need for dose adjustment in kidney or liver failure and in obesity, and
110 excellent oral bioavailability with no food requirements [3]. Although ISZ has shown higher minimal
111 inhibitory concentrations (MIC) than posaconazole [16], it is demonstrably as effective as AmB to
112 decrease fungal burden and to improve survival in a neutropenic mouse model of mucormycosis
113 [17]. ISZ was tested in VITAL study, a phase 3, single-arm, open-label, non-comparative study. This
114 study assessed safety and efficacy of ISZ in the treatment of mucormycosis [18]. Case-control analysis
115 with historic controls treated with AmB included in the Fungiscope registry showed similar survival
116 benefit. However, some biases are noticeable. A total of 21 patients treated with ISZ were compared
117 to 33 matched controls who had received AmB. AmB was administered through AmBd formulation in
118 7 controls. This formulation is appreciably less efficient than the liposomal one. Other drawbacks
119 could be emphasized in the use of ISZ. Breakthrough *Mucorales* infections in patients receiving ISZ
120 have been reported [19]. Moreover, some authors have shown in *Drosophila* model of mucormycosis
121 that preexposure to ISZ enhances the virulence of *Mucorales* [20,21]. In a large study including 147
122 patients, ISZ prophylaxis was less effective than VCZ or PSZ against IFD. Two patients who received
123 ISZ as prophylaxis presented mucormycosis [22]. Although ISZ seems to be less hepatotoxic than
124 other mould-active azoles and present a better tolerance profile than L-AmB [23], the ECMM
125 recommends only moderately ISZ as first-line treatment [10].

126 Regarding central nervous system (CNS) infections, treatment is based on L-AmB due to
127 clinical experience and *in vitro* data [24]. It has been demonstrated that ISZ penetrates the blood-
128 brain barrier in animal models [25], while AmB displays limited penetration. Concentration of ISZ in
129 the necrotic center of brain abscess has been shown low, but concentration in inflammatory brain
130 tissue surrounding the abscess was adequate, equivalent to predicted plasma concentration [26]. A

131 recent retrospective study has shown that ISZ is effective in *Mucorales* CNS infections [27]. This result
132 has to be confirmed with larger studies.

133 IV and DR tablets of PSZ were recently developed and lead to better bioavailability and drug
134 exposure than previous oral solution [28–30]. This increased drug exposure has been related to
135 increased PSZ efficiency [31]. Moreover, DR tablets lead to less variability in absorption and
136 compared to oral suspension are not affected by food [32]. Due to higher serum level, suspension DR
137 tablets and IV forms are moderately recommended while oral suspension is only marginally
138 recommended by the ECMM as first-line treatment [10]. There is no safety concern compared to oral
139 suspension for the two new forms, since there is no correlation between serum level and safety [29–
140 32]. However, IV form is solubilized in cyclodextrin and may lead to renal issues [31]. In a matched-
141 paired analysis of patients treated for invasive mucormycosis, new formulations of PSZ were
142 evaluated [33]. The authors showed that PSZ new formulations are as effective as AmB as first-line
143 treatment and as oral suspension in salvage therapy. However, these results should be interpreted
144 with caution. Numerous biases can be noted such as small sample size, retrospective design,
145 heterogeneity of infectious sites, lack of drug monitoring, and pre-exposure to other antifungal
146 drugs.

147 Routine therapeutic drug monitoring (TDM) is strongly recommended for patients treated by
148 PSZ [10]. Serum trough PSZ concentrations of 1 mg/L or higher are recommended. However, there is
149 currently no conclusive evidence for routine TDM with ISZ. It could be useful in case of suspected
150 toxicity, treatment failure, drug interactions, obesity, or after a switch from IV to PO therapy [10].

151

152 New drugs

153 Some new antifungal drugs are under clinical evaluation include Rezafungin, SCY-078,
154 orolofim, and encochleated amphotericin B [34]. Rezafungin, a new echinocandin has not been
155 tested against *Mucorales*. SCY-078, member of a new glucan synthase inhibitor subclass is poorly
156 or not active against *Mucorales* [35]. Olorofim is a member of the orotomides, a new antifungal
157 class inhibiting dihydroorotate dehydrogenase (DHODH), a key enzyme in pyrimidine
158 biosynthesis. It is also poorly active against *Mucorales* [36]. Encochleated amphotericin B is a
159 new oral formulation of amphotericin B [34]. It has been shown to be well-tolerated, and is
160 currently tested for cryptococcosis treatment in developing countries (clinical trial
161 NCT04031833). No studies on *Mucorales* efficacy are available.

162 Other antifungal drugs with activity against *Mucorales* are being developed. VT-1161 is a
163 novel inhibitor of the fungal CYP 51 with *in vitro* activity against *Mucorales*. VT-1161 used as curative
164 or prophylactic treatment has prolonged survival of neutropenic mice in *R. arrhizus* models [37,38].
165 SCH 42427 a broad-spectrum triazole was found to be effective in a murine model [39]. APX001A
166 (Fosmanogepix) (formerly E1210) is an antifungal agent targeting protein Gwt1. Gwt1 is a surface
167 protein of the glycosylphosphatidylinositol post-translational modification pathway. Although MICs
168 against *Mucorales* are high [40,41], several authors have shown that APX001A is as effective as AmB
169 to protect mice in a *R. delamar* model [3,42]. Finally, PC1244 a new long-acting fungicidal azole, has
170 shown antifungal activity against *Mucorales* with MICs from 0.25 to 2 mg/L [43] but has not been
171 tested *in vivo*. Among antibiotics, colistin has presented modest *in vitro* and *in vivo* activity against
172 *Mucorales* [44].

173

174 New therapeutic approaches

175 New approaches have recently emerged regarding relationship between fungus, antifungal
176 agent, and host [45]. For example, some authors have emphasized the capacity of PSZ to accumulate
177 within leukocyte membrane due to its lipophilic properties. Cells from HL-60 leukemia cell line
178 differentiated to neutrophil-like phenotype have been loaded with PSZ and used in an aspergillosis
179 mouse model to deliver PSZ directly to the infectious site [46]. However, this new approach has not
180 been tested in a *Mucorales* model. Bioengineering has made great improvement, especially in
181 genetically modified cytotoxic T-cells. These modified cells can specifically target beta-glucan of
182 fungus cell wall [47]. However, this approach has only been tested in an aspergillosis model.

183 Recently, a *Mucorales* peptide named CoH3 was found to be linked to mucormycosis
184 endothelial invasion by binding the endothelial cell receptor GRP78. Authors generated antibodies
185 against CoH3 to prevent endothelial invasion. Anti-CoH3 antibodies protected neutropenic and
186 diabetic mice from mucormycosis and acted synergistically with antifungal drugs [48]. Moreover,
187 other authors have shown that blocking GRP78 cell receptor by GRP78-specific immune serum may
188 protect diabetic mice from mucormycosis [49]. This peptide-receptor interaction may be a new
189 therapeutic way of research.

190

191 New concepts may guide antifungal prophylaxis.

192 Several authors have hypothesized that *Mucorales*, such as *Histoplasma sp* or *Cryptococcus*
193 *sp*, can remain latent in immunocompetent patients and lead to active disease when a patient
194 becomes immunosuppressed [50,51]. Authors have shown that *Mucorales* spores might remain
195 dormant in cutaneous granulomatous lesions in an immunocompetent rabbit model [52] and inside
196 innate granuloma in a Zebrafish model [51]. In the event of immunodepression, spores were
197 reactivated. In a murine model of latent mucormycosis, L-AmB was effective to prevent reactivation
198 in *Lichtheimia corymbifera* colonized mice [53]. This concept must be verified in human to evaluate if
199 decolonization of patients before immunosuppression could reduce the risk of reactivation.

200

201 **Combinations**

202 Combination are not currently recommended for first-line therapy due to lack of evidence of
203 their efficacy (C II, C III) (Table 1) [54]. They could nonetheless represent a major way of increasing
204 antifungal treatment efficacy [55].

205 Combinations of antifungal agents have been largely tested *in vitro*. Most combinations were
206 indifferent, except for AmB + caspofungin (CAS), PSZ + CAS and ISZ + CAS which were synergistic [55–
207 57]. For azoles + echinocandins, few *in vivo* studies have been performed, showing lack of synergy
208 [58,59]. Among AmB + echinocandins, more data are available *in vivo*. *In vitro* data have been
209 confirmed in a ketoacidotic mouse model where L-AmB and echinocandins (micafungin and
210 anidulafungin) appeared synergistic [60]. Combination of L-AmB and echinocandins prolonged
211 survival and decreased fungal burden of mice in an IV model of *Rhizopus arrhizus* infection. These
212 data were confirmed with ABLC + caspofungin in a ketoacidotic mouse model with improvement of

213 survival but without fungal clearance in organs [61]. Case reports of combinations have been
214 published and five retrospective clinical studies have been performed on antifungal combinations.
215 AmB + CAS and/or PSZ combinations have been evaluated. Four of the five studies showed
216 indifference [62–65] and one showed synergy [66]. However, the latter included only rhino-orbito-
217 cerebral forms and a small number of patients.

218 Some non-antifungal agents combined with antifungals drugs have shown interesting
219 synergy. Iron chelators have shown high synergy with antifungal drugs *in vitro* and *in vivo* [59,67,68],
220 but this has not been confirmed in patients [12]. Calcineurin inhibitors (cyclosporine A and
221 tacrolimus), which have immunosuppressive effects, have shown synergy with AmB, PSZ or ISZ *in*
222 *vitro* and *in vivo* [69–71]. Other agents such as MGCD290 (a Hos2 Histone Deacetylase Inhibitor), not
223 yet FDA-approved, have shown synergy *in vitro* with PSZ [72]. Although lovastatin has shown synergy
224 *in vitro* and *in vivo* with voriconazole [73], the latter is known to enhance *Mucorales* virulence [21].
225 Ciprofloxacin and fluconazole have shown synergy in mouse models [74], while miltefosine and
226 azoles, and rifampicine and AmB have presented synergistic effects *in vitro* on $\leq 50\%$ [75] and 56 to
227 83 % [76,77] of tested strains respectively.

228 Randomized, placebo-controlled clinical trials are needed to determine combination therapy
229 efficacy [78]. Added toxicity, drug interactions, and cost-benefit balance of combinations remain
230 unclear [10].

231

232 **Adjunctive treatment**

233 Current recommendations

234 The ECMM and the ECIL-6 strongly recommend surgery and control of underlying disease
235 including management of ketoacidosis and hyperglycemia in diabetic patients, modulation of
236 corticosteroids and immunosuppressive drugs, and reduction of neutropenia duration using
237 hematopoietic growth factor if possible (A II, AII) (Table 3) [9,10]. Granulocyte colony-stimulating
238 factor (G CSF) and hyperbaric oxygen are moderately recommended in case of neutropenia and in
239 diabetic patients respectively (B II), while iron chelators are strongly discouraged.

240

241 Surgery

242 Surgery remains easier to perform in rhino-orbital or cutaneous localizations than in cerebral,
243 pulmonary or disseminated disease. Surgery is precluded in critical ill patients [79]. In patients with
244 unifocal pulmonary mucormycosis, lobectomy or pneumonectomy have provided benefit [80].
245 However, in case of multifocal or close to great vessels lesions, benefit is less established and surgery
246 is most complicated to perform. In rhino-orbito-cerebral forms, surgery is strongly linked to
247 treatment outcome [81,82]. In a clinico-epidemiological review over 10 years, surgery was performed
248 in 65.2 % of 184 patients but only in 21.4 % of hematological patients [83]. Surgical debridement in
249 combination with medical therapy was associated with a better outcome than medical therapy only.
250 Attention must be paid to the fact that only retrospective studies and epidemiological data are
251 available. However, the benefits of surgery are presumed and is highly recommended whenever
252 possible (A II) [10].

253

254 Adjunctive therapies

255 Adjunctive therapy is used to reverse immunosuppression. Granulocyte (macrophage)
256 colony-stimulating factor (G(M)-CSF) or interferon- γ increases the activity of granulocytes against
257 *Mucorales* such as hyphae damage [84,85]. However, several authors have shown that G-CSF or GM-
258 CSF did not improve antifungal activity of PSZ or L-AmB in a neutropenic murine model [86,87].
259 Clinical data on this topic are very poor and few cases are published [88–91]. Clear benefit has yet to
260 be established.

261 Iron chelators have been tested in adjunctive therapy as means of reducing iron availability
262 and thereby inhibiting fungal growth. Deferoxamine, an iron chelator, has been associated with
263 increased mucormycosis incidence. Deferoxamine acts as a xenosiderophore, whereas the two other
264 iron chelators, deferiprone and deferasirox, do not [92]. Ibrahim *et al.* have shown that deferiprone
265 protected diabetic mice from mucormycosis [93]. Deferasirox shared the same effect in diabetic and
266 neutropenic mice and acted synergistically with AmB [67]. Triple therapy using L-AmB, micafungin,
267 and deferasirox was also found to be effective [94]. Moreover, deferasirox increased PSZ activity in a
268 neutropenic mouse model [59]. These promising results led to a clinical study assessing deferasirox +
269 LAmB efficacy [12]. However, patients with mucormycosis treated with deferasirox + L-AmB had a
270 higher mortality rate at 90 days than patients treated with L-AmB alone. However, patients treated
271 with deferasirox had more active malignancy, neutropenia and corticosteroid therapy compared to
272 the placebo group. Population imbalance between deferasirox and placebo groups did not allow for
273 clear conclusions. Unlike iron chelators, zinc chelators have not shown synergy with AmB and have
274 shown poor synergy with PSZ [95].

275 Hyperbaric oxygen treatment has been shown to deploy direct antimicrobial activity. It exerts
276 a synergistic effect with antimicrobial agents, and enhances cellular immune system and tissue repair
277 in some infectious diseases [96]. In a mucormycosis mouse model, addition of hyperbaric oxygen to
278 AmB did not improve survival [97]. However, in this model, mice were neither immunosuppressed
279 nor diabetic and infection was performed by IV route. In a review of 28 published cases, authors
280 showed that while hyperbaric oxygen improved survival in diabetic patients, it was ineffective in
281 neutropenic patients [98]. However, hyperbaric oxygen treatment failure may be underestimated
282 due to publication bias. Up until now, there has been no randomized study with control group to
283 evaluate efficacy of hyperbaric oxygen so far.

284

285 **New routes of administration**

286 Nebulized antifungal agents may be a new way of research to improve mucormycosis
287 therapy. The pulmonary aerosolization of antifungal agents can theoretically increase their
288 concentration at the infectious site, which could improve efficacy while limiting their systemic
289 exposure and toxicity. [99]. Administration of L-AmB aerosol was evaluated in a neutropenic mouse
290 model of *R. arrhizus* pulmonary infection [100]. The authors showed that aerosolized L-AmB is
291 effective as a means of decreasing fungal burden and improving survival when administered from
292 day 1 to 5 after infection compared to placebo. However, aerosolized L-AmB was not compared to
293 systemic L-AmB. More animal studies are needed to assess aerosols efficacy alone and in

294 combination with systemic treatment. Few human cases of mucormycosis treated with AmB aerosols
295 are reported in the literature [101–105]. AmBd has been the most used formulation. Dosage of
296 nebulized AmBd ranges from 6 mg three times a day to 30 mg twice a week, in combination with
297 AmB systemic treatment and surgical treatment. ABLC has also been used in *Rhizomucor sp* infection
298 treatment (50 mg twice daily) [105].

299 Topical AmB has been used in a few clinical cases [106–108], particularly in burned patients
300 [109]. It has been employed in different forms: washes [110], 5% sulfamylon–amphotericin B (2
301 µg/ml) dressings [111], daily topical infusions through dressings (50 mg L-AmB diluted in 1L of sterile
302 water) [112], soaks [113] or gauze soaked in 0.2 % AmB solution [114]. Nystatin cream was used in
303 one case report [115]. AmB nanoemulsion was developed to use AmB as topical route of
304 administration, but it has not been tested on *Mucorales* [116,117]. Other authors have developed
305 nanoemulsions containing surfactant to mechanically disrupt microbial membranes. For example,
306 nanoemulsion NB-201, containing refined soybean oil, water, glycerol, EDTA, Tween 20, and the
307 surfactant benzalkonium chloride has shown *in vitro* activity against *Mucorales* [118].

308 Other routes of administration for AmB are anecdotal: eye drop in *Mucorales* keratitis [119],
309 oral administration in gastrointestinal mucormycosis [120], intradiaphyseal incorporation cement
310 beads in osteomyelitis [121], intrathecal administration in cerebral abscess [122], percutaneous
311 injection in cutaneous lesions [123].

312

313 **Conclusion**

314 Mucormycosis treatment recommendations were recently updated by the ECMM. L-AmB
315 remains the first-line drug in mucormycosis therapy. ISZ and new PSZ formulations have been added
316 to the guidelines but remain in second-line treatment following L-AmB due to some remaining issues.
317 Few anti-*Mucorales* drugs are currently under development. Moreover, evidence for adjunctive
318 therapies is scarce and doubts on their effectiveness persist due to a lack of randomized prospective
319 controlled studies. They are particularly complex to implement in a context of low incidence disease.
320 Few advances have been made on mucormycosis treatment. However, empowering new concepts
321 and new routes of administration to fight this devastating disease appear promising and are to be
322 encouraged.

323

324

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327

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329

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721 Table 1: Recommendations for treatment of invasive mucormycosis from European Conference on
 722 Infections in Leukemia 6 (ECIL-6) (2017) and European Confederation of Medical Mycology (ECMM)
 723 (2019), adapted from [9,10].

	ECIL-6 2017	Grade	ECMM 2019	Grade
<i>First-line antifungal therapy</i>				
Liposomal amphotericin B	5mg/kg	B II	5-10 mg/kg For CNS involvement: 10 mg/kg	A II A III
Amphotericin B lipid complex	without CNS involvement	B II	Any without CNS involvement SOT: 10 mg/kg	B II A III
Amphotericin B deoxycholate		C II		D II
Posaconazole		C III	DR tablet or IV: 300 mg b.i.d, day 1; 300 mg/d from day 2 Oral suspension (4 x 200 mg or 2 x 400 mg)	B II C II
Isavuconazole			200 mg t.i.d, day 1 -2 ; 200 mg/d from day 3	B II
Combination therapy		C III	Liposomal amphotericin B + caspofungin and/or posaconazole	C II - C III
<i>Control of underlying conditions</i>				
Diabetes	Control of diabetes	A II	Control of hyperglycaemia and Ketoacidosis	A III
Immuno-suppression	Discontinuation/tapering of steroids, reduction of immunosuppressive therapy	A II	Rapidly taper glucocorticosteroid dose to discontinue, if feasible, or reduce dose to minimum required	A II
<i>Surgery</i>				
	Rhino-orbito-cerebral infection	A II	Repeated surgery in addition to antifungal treatment	A II
	Soft tissue infection	A II		
	Localized pulmonary lesion	B III		
	Disseminated infection	C III		

SOT: solid organ transplantation. CNS: central nervous system. DR: delayed-release. IV: intravenous. b.i.d: twice a day. t.i.d: three times a day.

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726 Table 2: Prophylaxis recommendation from European Confederation of Medical Mycology (ECMM)
 727 (2019), adapted from [10].

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ECMM 2019			Grade
Primary	Neutropenic, GvHD	Posaconazole DR tablet (300 mg b.i.d day1, 300 mg/d from day2)	B II
		Posaconazole IV (300 mg b.i.d day1, 300 mg/d from day2)	B III
		Posaconazole oral suspension (200 mg t.i.d)	C II
	Neutropenic	Isavuconazole PO or IV (200 mg t.i.d day1-2, 200 mg/d from day3; or 200 mg/d from day1)	C II
	SOT	Isavuconazole PO/IV (200 mg t.i.d day1-2, 200 mg/d from day3; or 200 mg/d from day1)	C II
		Posaconazole IV (300 mg b.i.d day1, 300 mg/d from day2)	C III
		Posaconazole oral suspension (200 mg t.i.d)	C III
	All induction chemotherapy	Liposomal amphotericin B	D I
	Neutropenic or GvHD	Fluconazole, itraconazole, voriconazole	D II
	Secondary	Last effective drug in the same patient	A III

SOT: solid organ transplantation. DR: delayed-release. IV: intravenous. PO: per os. GvHD: graft versus host disease. d: day. b.i.d: twice a day. t.i.d: three times a day.

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731 Table 3: Adjunctive therapy recommendations for treatment of invasive mucormycosis from
 732 European Conference on Infections in Leukemia 6 (ECIL-6) (2017) and European Confederation of
 733 Medical Mycology (ECMM) (2019), adapted from [9,10].

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ECIL-6 2017		ECMM 2019	
Adjunctive therapy			
Against use of deferasirox	All	Deferasirox (other than haematology)	C II
		Deferasirox (haematology)	D II
		Deferoxamine	D II
Hyperbaric oxygen	C III	Exposure to 100% hyperbaric oxygen (haematology)	C II
		Exposure to 100% hyperbaric oxygen (diabetes)	B II
Hematopoietic growth factor if neutropenia	A II	G-CSF (haematology, ongoing neutropenia)	B II
		Granulocyte transfusion (haematology, ongoing neutropenia)	C II
		Granulocyte transfusion + IFN γ 1b (haematology, ongoing neutropenia)	C III
		GM-CSF (diabetes)	C III
		Adoptive immunotherapy, T cells generated in response to <i>R. arrhizus</i> antigens	C III
		Nivolumab + interferon- γ	C III

G-CSF: granulocyte colony stimulating factor. GM-CSF: granulocyte macrophage colony stimulating factor.

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