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Contemporary management and clinical outcomes of mucormycosis: A systematic review and meta-analysis of case reports ☆

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ABSTRACT

With the advent of newer antifungals, optimum treatment of mucormycosis remains to be fully elucidated. This study systematically evaluated the contemporary management and outcomes of mucormycosis. Mucormycosis cases in patients aged ≥18 years published between January 2000 and January 2017 were identified through Ovid MEDLINE and Embase. Of the 3619 articles identified, 600 (851 individual patient cases) were included in the review. Of the 851 patient cases, antifungal treatment details were available for 785. Intravenous (i.v.) amphotericin B formulations remained the most commonly prescribed first-line antifungals (760/785; 96.8%): 88.2% (670/760) were initiated as monotherapy and 11.8% (90/760) as combination antifungal therapy. Posaconazole oral suspension monotherapy was prescribed as an initial antifungal in 11 cases. It was also administered as maintenance or salvage therapy in 39 and 25 cases, respectively. Itraconazole capsule monotherapy ($n = 10$) was prescribed primarily for cutaneous disease in patients not receiving any immunosuppressive therapy. All-cause 90-day mortality was 41.0% (349/851). Initial treatment with combination antifungals did not reduce 90-day mortality compared with i.v. conventional amphotericin B or i.v. liposomal amphotericin B monotherapy [35/90 (38.9%) vs. 146/369 (39.6%) vs. 91/258 (35.3%), respectively; $P = 0.541$]. Concomitant surgical and antifungal therapy was associated with significantly lower 90-day mortality compared with treatment with antifungals alone (OR = 0.23, 95% CI 0.13–0.41; $P < 0.001$). The findings suggest that first-line antifungals with good efficacy remain an urgent unmet need. Whilst surgery is fundamental to improving survival, the clinical utility of combination antifungal therapy or posaconazole monotherapy requires further investigation.

1. Introduction

The management of mucormycosis is challenging given its aggressive nature and difficulty in diagnosing the infection [1]. In addition, the choice of antifungal therapy is limited given the reduced susceptibility of the Mucorales to many antifungal agents [2–4]. Owing to its broad-spectrum antifungal activity, traditionally amphotericin B (AmB) formulations have been the antifungal of choice for the treatment of mucormycosis [5–8]. However, with the advent of newer triazoles, specifically posaconazole and isavuconazole, clinicians now have access to a wider range of therapeutic options.

Of importance, optimal management strategies for mucormycosis and associated patient outcomes remain to be fully elucidated. Prospective clinical studies evaluating the safety and efficacy of mucormycosis treatment are scarce; only three clinical trials have been reported to date [9–11] and evidence surrounding the treatment of mucormycosis has been extrapolated primarily from case

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reports or small case series [5–8]. Roden et al. performed a comprehensive review of approaches to managing mucormycosis, but this was conducted more than 10 years ago in the absence of the newer antifungals [12]. This prompted a timely review of the current literature to generate up-to-date evidence required to support and optimise the management of this difficult-to-treat infection.

2. Methods

This was a systematic review of published case reports and case series of proven and probable mucormycosis, as defined by the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [13], in patients aged ≥18 years. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [14] were adopted to guide the undertaking and reporting of this review.

2.1. Eligibility criteria

To be included in the review, the cases must have had a description of the following: (i) infection site(s); (ii) predisposing risk factors or underlying conditions [12,15]; (iii) method(s) of diagnosis; (iv) details of antifungal therapy (including types of antifungals, dose and treatment duration) as well as surgical and/or adjunctive therapy; and (v) patient outcomes, assessed as overall 90-day mortality. Excluded from this study were poorly described cases, conference abstracts, editorials, review articles, or case series without primary or individual patient data.

2.2. Search strategies and information sources

A comprehensive search for studies involving humans published in English [16] between January 2000 and January 2017 was conducted in Ovid MEDLINE and Ovid Embase using various keywords and MeSH (Appendix A). The final search was conducted in January 2017. The reference lists in relevant articles were also searched.

2.3. Study selection

WJ implemented the search strategies and imported and merged the initial search results into the reference management software Endnote® v.X7 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA]. The titles and abstracts were screened for possible inclusion and duplicates were deleted. Two groups of investigators (SCAC & CK and WJ & WLL) then retrieved and independently assessed the full-texts of relevant articles against the inclusion criteria. Disagreements over study inclusion were resolved by consensus or, if required, by consulting MAS and DCMK as adjudicators.

2.4. Data collection process and data items

Relevant data were extracted independently by the aforementioned groups of authors using a standardised data extraction form and were verified by comparison. Information extracted included: countries in which the cases were reported; publication year; underlying conditions/predisposing risk factors; sites of infection and causative pathogens; treatment details; antifungal susceptibility data; and patient outcomes. Discrepancies were discussed and resolved by consensus; adjudicators (as above) were consulted where necessary.

2.5. Summary measures and statistical analysis

Treatment details and patient outcomes were summarised descriptively using proportions. Categorical variables were assessed using χ^2 test, whilst continuous variables were compared by the Wilcoxon–Mann–Whitney or Kruskal–Wallis test. Variables influencing 90-day mortality were identified using multivariate logistic regression. Data analysis was conducted using Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX). A *P*-value of ≤0.05 was considered statistically significant.

3. Results

3.1. Study inclusion and selection

A total of 3619 articles were identified in the initial search, of which 600 (comprising 851 individual patient cases) were included. Appendix B lists the articles included in the review. Details of patient characteristics, underlying conditions/risk factors, disease manifestations and causative pathogens have been described recently [17].

3.2. Treatment modalities

Treatment data were reported for 815 of the 851 cases. Antifungal therapy in combination with surgery was the most commonly prescribed treatment (476/815; 58.4%). Treatment with antifungal or surgery alone was employed in 227/815 (27.9%) and 30/815 (3.7%) cases, respectively. Adjunctive therapy was administered in addition to antifungals and/or surgical therapy in 82/815 cases (10.1%). In the remaining 36/851 cases (4.4%), death was documented prior to treatment initiation, primarily in patients with disseminated ($n = 15$) or pulmonary disease ($n = 14$).

3.2.1. Antifungals

3.2.1.1. Initial therapy. Use of antifungal therapy was described in 785 cases. Intravenous (i.v.) AmB was the most commonly administered first-line antifungal (760/785 cases; 96.8%). Antifungal prescribed in the remaining 25/785 cases included posaconazole oral suspension ($n = 11$), posaconazole modified-release (MR) tablet ($n = 1$), itraconazole capsules ($n = 10$) and topical AmB ($n = 3$). Table 1 summarises the details of initial antifungal therapy.

Of the 760 cases reporting the use of i.v. AmB, conventional amphotericin B (C-AmB) was prescribed in 390 cases (51.3%), whilst liposomal amphotericin B (L-AmB) was administered in 316 cases (41.6%). The i.v. AmB formulations prescribed in the remaining 54/760 cases included: amphotericin B lipid complex (ABLC) ($n = 49$) and amphotericin B colloidal dispersion ($n = 5$). Notably, C-AmB was prescribed mainly in Asian and African countries, whilst lipid-based AmB (predominantly L-AmB) has replaced C-AmB over the years in Europe, North and South America, Australia and New Zealand (Fig. 1). Irrespective of disease manifestations, the median [interquartile range (IQR)] dose of C-AmB prescribed was 1 (0.7–1) mg/kg/day ($P = 0.258$), whilst that of lipid-based AmB was 5 (3–5) mg/kg/day ($P = 0.744$).

Of note, i.v. AmB was primarily initiated as monotherapy (670/760; 88.2%). In the remaining 90/760 cases (11.8%) it was administered in combination with other antifungals. Of the 90 cases employing initial combination antifungal therapy, i.v. AmB was concurrently administered with another antifungal agent in 82 cases, including an echinocandin [$n = 39$; caspofungin ($n = 21$), micafungin ($n = 17$) and unspecified echinocandin ($n = 1$)], posaconazole oral suspension ($n = 32$), itraconazole ($n = 10$), or posaconazole MR tablet ($n = 1$). In the remaining 8/90 cases, i.v. AmB was concomitantly given with posaconazole oral suspension and an echinocandin (caspofungin in 6 cases and micafungin in 2 cases).

3.2.1.2. Salvage antifungal therapy. Use of salvage therapy following unsatisfactory clinical response to initial antifungals was reported in 63 cases; the median (IQR) time to initiation was 11 (5–20) days post-commencement of initial treatment. Of the 63 cases,

Table 1
Initial antifungal therapy and treatment outcomes amongst various mucormycosis disease manifestations[a].

Disease manifestation	Initial antifungals	Daily dose [median (IQR) or otherwise specified]	Duration of therapy (days) [median (IQR) or otherwise specified]	Surgery (*n*)	Underlying immunosuppression (*n*)[b]	90-day mortality (*n*)
Rhino-orbito-cerebral (*n* = 274)	C-AmB (*n* = 146)	1 (0.7–1) mg/kg	21 (8–43)	114	34	55
	Lipid AmB (*n* = 93)	5 (3–5) mg/kg	34 (14–57)	77	48	31
	POS suspension (*n* = 2)	N/A	N/A	2	1	0
	ITR capsule (*n* = 1)	300 mg	N/A	1	0	0
	Combination therapy (*n* = 31)	N/A	28 (12–56)	27	16	10
	C-AmB eye drop (*n* = 1)	0.15%	42	0	0	0
Pulmonary (*n* = 158)	C-AmB (*n* = 60)	1 (1–1) mg/kg	7 (14–34)	23	27	27
	Lipid AmB (*n* = 72)	5 (3–5) mg/kg	25 (13–46)	31	55	28
	POS suspension (*n* = 2)	800 mg	N/A	0	1	0
	ITR capsule (*n* = 1)	600 mg	150	1	1	0
	Combination therapy (*n* = 22)	N/A	21 (13–29)	9	15	8
	C-AmB lung instillation (*n* = 1)	10 mg/week	7 weeks	1	0	0
Cutaneous (*n* = 177)	C-AmB (*n* = 84)	1 (0.7–1) mg/kg	21 (10–42)	72	23	22
	Lipid AmB (*n* = 69)	5 (3–5) mg/kg	21 (14–30)	60	26	19
	POS suspension (*n* = 4)	800 mg	N/A	4	2	0
	POS MR tablet (*n* = 1)	300 mg	42	1	0	0
	ITR capsule (*n* = 7)	400 mg	49 (28–60)	4	1	0
	Combination therapy (*n* = 12)	N/A	14 (10–21)	12	5	4
Disseminated (*n* = 92)	C-AmB (*n* = 38)	1 (1–1) mg/kg	8 (5–40)	18	28	25
	Lipid AmB (*n* = 40)	5 (4–7) mg/kg	31 (12–58)	17	33	22
	POS suspension (*n* = 2)	800 mg	N/A	2	1	1
	ITR capsule (*n* = 1)	600 mg	17	0	1	1
	Combination therapy (*n* = 10)	N/A	35 (6–180)	8	7	5
	Intrathecal C-AmB (*n* = 1)	N/A	N/A	1	0	1
Gastrointestinal (*n* = 64)	C-AmB (*n* = 30)	1 (0.7–1) mg/kg	22 (7–49) days	21	16	14
	Lipid AmB (*n* = 21)	5 (4–5) mg/kg	38 (24–47) days	15	15	8
	POS suspension (*n* = 1)	N/A	N/A	1	0	0
	Combination therapy (*n* = 12)	N/A	N/A	10	8	7
Others (*n* = 20)[c]	C-AmB (*n* = 11)	1 (0.6–1) mg/kg	19 (4–42)	7	3	3
	Lipid AmB (*n* = 6)	N/A	N/A	6	2	3
	Combination therapy (*n* = 3)	N/A	N/A	3	2	1

AmB, amphotericin B; IQR, interquartile range; C-AmB, conventional amphotericin B; POS, posaconazole; ITR, itraconazole; MR, modified release; N/A, not available.
[a] Lipid AmB included liposomal AmB, AmB lipid complex and AmB colloidal dispersion; combination therapy included an AmB formulation, posaconazole suspension and/or an echinocandin.
[b] Underlying immunosuppression included patients with underlying haematological malignancies, recipients of haematopoietic stem cell or solid-organ transplantation, and use of cancer chemotherapy, immunosuppressants or biologics.
[c] Others included mucormycosis affecting the kidneys (*n* = 11), ear (*n* = 3), parotid glands (*n* = 3), lymph nodes (*n* = 1), uterus (*n* = 1) and heart (*n* = 1).

36 reported addition of another antifungal to the initial antifungal therapy. These included posaconazole oral suspension (*n* = 24), i.v. posaconazole (*n* = 1), itraconazole capsules (*n* = 2), an echinocandin [*n* = 8; caspofungin (*n* = 6) and micafungin (*n* = 2)] and concurrent posaconazole oral suspension and micafungin (*n* = 1). Intravenous lipid-based AmB preparations were administered as a substitute for initial C-AmB (13/63) or posaconazole oral suspension monotherapy (2/63). In the remaining 12 cases, i.v. AmB therapy was continued at higher doses. Despite salvage therapy, death was documented in 23/63 cases (36.5%) at 90 days.

3.2.1.3. Maintenance antifungal therapy. A total of 54 patients received maintenance antifungals after completing a median (IQR) of 35 (25–58) days of initial antifungal therapy. Posaconazole oral suspension was the most commonly prescribed (*n* = 40), followed by itraconazole capsules (*n* = 13) and posaconazole MR tablets (*n* = 1). The median (IQR) duration of maintenance therapy was 56 (32–90) days. One case of recurrent infection was reported during posaconazole suspension maintenance therapy. The patient's antifungal therapy was subsequently switched to isavuconazole capsules. The patient completed 29 weeks of isavuconazole therapy; clinical improvement was observed after 19 weeks.

3.2.1.4. Adverse events. Adverse events associated with initial antifungal therapy were mainly observed in patients receiving i.v. AmB therapy (Table 2). These were more common amongst patients prescribed C-AmB (86/390; 22.1%) compared with those receiving lipid-based AmB preparations (49/370; 13.2%) ($P = 0.008$). The median (IQR) duration of therapy with lipid-based AmB preparations was also significantly longer than that of C-AmB [28 (14–49) days vs. 18.5 (7–42) days; $P = 0.017$].

3.2.1.5. In vitro antifungal susceptibility. Antifungal susceptibility testing was performed in 40 cases. Minimum inhibitory concentrations (MICs) were determined using the Clinical and Laboratory Standards Institute (CLSI) (*n* = 16) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) (*n* = 8) broth microdilution method. Use of Etest® or Sensititre® YeastOne® was reported in seven and two cases, respectively. In the remaining seven cases the method was not described. Notably, the geometric mean MIC of AmB was observed to be the lowest for *Mucor* spp. (0.09 μg/mL) and highest for *Cunninghamella* spp. (1 μg/mL), whilst that of posaconazole was reported to be lowest for *Lichtheimia* spp. (0.33 μg/mL) and highest for *Rhizopus* spp. (1.5 μg/mL). The MIC

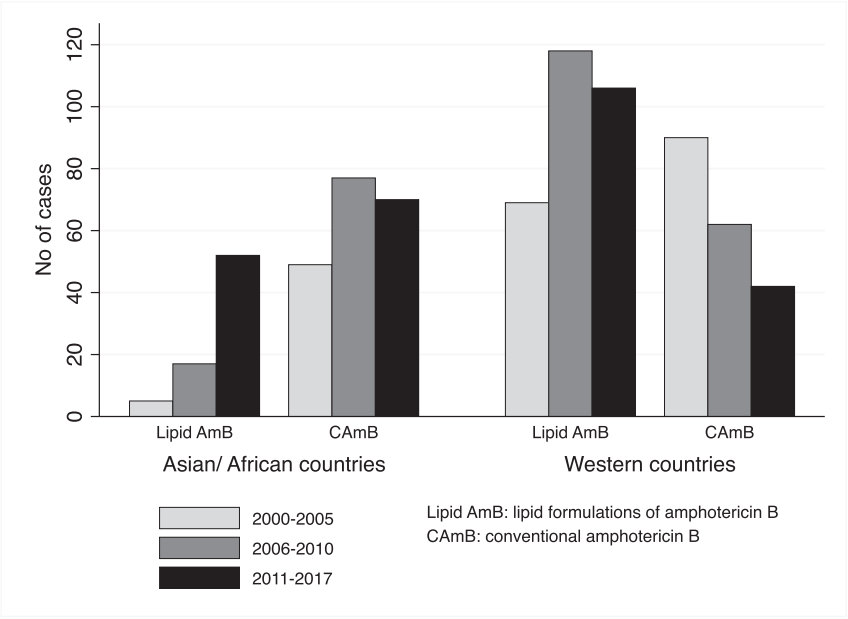

Fig. 1. Number of cases of intravenous lipid-based amphotericin B and conventional amphotericin B prescribed over time. Western countries included Europe, North/South America and Australia/New Zealand.

Table 2
Adverse events associated with initial antifungal therapy.

Initial antifungal	Daily dose [median (IQR)]	Duration of therapy [median (IQR)]	Adverse events
C-AmB ($n=86$)	1 (0.7–1) mg/kg	11.5 (7–33.5) days	Renal toxicity ($n=67$) Infusion reactions ($n=8$) Hypokalaemia ($n=5$) Unspecified intolerance ($n=6$)
L-AmB ($n=38$)	5 (5–10) mg/kg	27 (14–65.5) days	Renal toxicity ($n=32$) Hypokalaemia ($n=5$) Anaphylaxis ($n=1$)
ABLC ($n=10$)	5 (5–10) mg/kg	30 (14–90) days	Renal toxicity ($n=6$) Infusion reaction ($n=3$) Hypokalaemia ($n=1$)
ABCD ($n=1$)	6 mg/kg	8 days	Renal toxicity
Itraconazole capsule ($n=1$)	600 mg	30 days	Diarrhoea
Posaconazole tablet ($n=1$)	300 mg	42 days	Nausea/vomiting

IQR, interquartile range; C-AmB, conventional amphotericin B; L-AmB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion.

distributions of AmB, itraconazole and posaconazole for various Mucorales pathogens are summarised in Table 3.

3.2.2. Adjunctive therapy

The details of adjunctive therapies are summarised in Table 4. Use of colony-stimulating factors was observed in 26 cases, of which 23 were administered in patients with underlying haematological malignancies. Whilst 20 cases reported the use of hyperbaric oxygen (O_2) therapy, neither the chamber pressure nor treatment duration was consistently described. Deferasirox was administered in seven cases, although it was prematurely terminated in two cases following renal toxicity. Topically administered AmB (including AmB wound irrigation, nebulised AmB, AmB impregnated bone cement and/or local instillation of AmB solution) in conjunction with systemic antifungals and/or surgery was also reported (Table 5).

3.3. Patient outcomes

Of the 851 cases, death was observed in 349 (41.0%), occurring at a median (IQR) of 19 (8.5–35) days post-presentation. Whilst improvement in 90-day mortality was observed over the years, this difference was not statistically significant: 107/240 (44.6%) between 2000 and 2005; 128/305 (42.0%) between 2006 and 2010; and 114/306 (37.3%) between 2011 and 2017 ($P=0.205$). Notably, initial treatment with combination antifungals did not appear to statistically improve the 90-day mortality compared with i.v. C-AmB or i.v. L-AmB monotherapy [35/90 (38.9%) vs. 146/369 (39.6%) vs. 91/258 (35.3%), respectively; $P=0.541$]. Surgery in addition to antifungal therapy, however, was associated with significantly lower 90-day mortality compared with treatment with antifungals alone [144/476 (30.3%) vs. 131/226 (58.0%); $P < 0.001$]. Of note, when surgery was performed in the absence of antifungal therapy, the 90-day mortality was determined to be 63.3% (19/30).

Factors influencing 90-day mortality are summarised in Table 6. Previous haematopoietic stem cell transplantation was the only underlying condition associated with increased mortality at 90 days [odds ratio (OR) = 3.77, 95% confidence interval (CI) 1.37–10.37; $P=0.010$]. Disease manifestation was not an independent predictor of 90-day mortality. Although by univariate analysis *Cunninghamella* infection was an independent predictor of 90-day mortality compared with infections caused by *Rhizopus* (OR = 3.58, 95% CI 1.52–8.40; $P=0.003$), it was not associated with increased mortality in the multivariate analysis. However, it is interesting to note

Table 3
Minimum inhibitory concentration (MIC) distributions of amphotericin B (AmB), itraconazole (ITR) and posaconazole (POS) for various Mucorales organisms.

Genus	Antifungal (no. of cases)	No. of isolates with MIC (μg/mL) of:												Geometric mean MIC (μg/mL)
		<0.06	0.125	0.25	0.38	0.5	0.75	1	2	4	8	12	>16	
Rhizopus	AmB ($n=15$)	2	2			4		3	3				1	0.57
	ITR ($n=9$)							1	1	2	1		4	6.86
	POS ($n=11$)			2		1		2	2	3	1			1.5
Mucor	AmB ($n=6$)		2	1		1		1		1				0.09
	ITR ($n=4$)					1				2		1		3.13
	POS ($n=4$)		1					2			1			1
Rhizomucor	AmB ($n=3$)		1	1	1									
	ITR ($n=3$)		1		1								1	
	POS ($n=1$)				1									
Lichtheimia	AmB ($n=6$)	1	3			1		1						0.18
	ITR ($n=4$)			1		1			1			1		1.19
	POS ($n=4$)			2	1	1								0.33
Cunninghamella	AmB ($n=5$)					2		2		1				1
	ITR ($n=5$)					1	1	2			1			1.25
	POS ($n=3$)			1		1		1						
Saksenaea complex	AmB ($n=1$)										1			
	ITR ($n=1$)					1								
	POS ($n=1$)					1								
Apophysomyces	AmB ($n=3$)	1		1						1				
	ITR ($n=1$)		1											
	POS ($n=3$)	2				1								
Actinomucor	AmB ($n=1$)			1										
	ITR ($n=1$)			1										
	POS ($n=1$)		1											

Table 4
Details of adjunctive therapies administered in the management of various manifestations of mucormycosis.

	Hyperbaric O_2 ($n=20$)	G-CSF ($n=19$)	GM-CSF ($n=7$)	Deferasirox ($n=7$)	IFNγ ($n=1$)
Disease manifestations	Rhino-orbito-cerebral ($n=8$) Cutaneous ($n=11$) Disseminated ($n=1$)	Rhino-orbito-cerebral ($n=7$) Pulmonary ($n=4$) Cutaneous ($n=2$) Disseminated ($n=5$) Gastrointestinal ($n=1$)	Rhino-orbito-cerebral ($n=3$) Pulmonary ($n=2$) Cutaneous ($n=1$) Gastrointestinal ($n=1$)	Rhino-orbito-cerebral ($n=5$) Pulmonary ($n=1$) Cutaneous ($n=1$)	Gastrointestinal ($n=1$)
Dosing regimen	N/A	5 μg/kg/day	150–500 μg/day	15–20 mg/kg/day	0.1 mg three times weekly in combination with a single dose of 250 mg nivolumab
Duration of therapy [median (IQR)]	13 (5–23) sessions	11 (6–34) days	18 (7–210) days	6 (3–8) days	5 doses
Adverse events	Barotrauma ($n=1$)	None	None	Renal toxicity ($n=2$)	None
90-day mortality (n)	2	8	1	3	0

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFNγ, interferon-gamma; N/A, not available.

that infection due to *Mucor* spp. was associated with significantly lower 90-day mortality (OR = 0.41, 95% CI 0.18–0.92; $P = 0.030$). Concurrent surgical and antifungal therapy was associated with lower 90-day mortality compared with treatment with antifungal alone (OR = 0.23, 95% CI 0.13–0.41; $P < 0.001$).

4. Discussion

To our knowledge, this is the most comprehensive systematic review to date investigating the management strategies and outcomes of mucormycosis, a critical therapeutic area that is relatively evidence-poor. This review has provided important insights into the clinical utility of the newer antifungals such as posaconazole in the management of mucormycosis. Pivotal data associated with adjunctive therapy are presented. Furthermore, the treatment outcomes and clinical variables influencing 90-day mortality across various disease manifestations were investigated.

This review suggests that i.v. AmB remains the antifungal of choice in the management of mucormycosis. C-AmB was the most commonly used formulation in Asian and African countries. Although we were unable to determine the reasons behind this observation, the high cost of lipid-based preparations may have partly influenced the choice of AmB formulations in these regions. Renal toxicity was common in patients receiving C-AmB. Although pre-emptive hydration may potentially mitigate renal toxicity and electrolyte imbalances associated with C-AmB [18], its use was not described in the cases reported.

The findings suggested that compared with i.v. C-AmB, i.v. lipid-based AmB therapy enabled a significantly longer treatment duration, potentially due to its better safety profile [19]. In addition, the availability of the less nephrotoxic lipid-based AmB preparations has facilitated the use of high-dose AmB, particularly in the management of mucormycosis with central nervous system (CNS) involvement [5–8]. In the current study, 57 patients received high-dose i.v. L-AmB (6–15 mg/kg/day), albeit in non-CNS diseases. Notably, compared with patients receiving 5 mg/kg/day of i.v. L-AmB, those who received higher doses had a higher 90-day mortality, although not statistically significant [22/57 (38.6%) vs. 29/93 (31.2%); $P = 0.352$]. In addition, renal toxicity was more common following administration of higher-dose i.v. L-AmB [15/57 (26.3%) vs. 12/93 (12.9%); $P = 0.038$]. Indeed, previous pharmacokinetic data had suggested that administration of i.v. L-AmB above 10 mg/kg/day did

Table 5
Various approaches to topical administration of conventional amphotericin B (C-AmB), liposomal amphotericin B (L-AmB) and/or amphotericin B lipid complex (ABLC).

Route of administration	Details
Nasal/sinus irrigation ($n=11$)	C-AmB irrigation solution was administered as nasal wash ($n=5$) or sinus irrigation ($n=6$). The dosing regimens, however, were described only in four cases, whereby C-AmB was administered two to three times daily for up to 21 days. The concentration of C-AmB when administered as a sinus irrigation ($n=1$) was 1 mg/mL, whilst that of nasal irrigation ($n=3$) was lower (0.1 mg/mL in two cases and 0.01 mg/mL in the other case).
Cerebral instillation ($n=3$)	C-AmB was administered intrathecally ($n=2$) or directly to the brain ventricle via an Ommaya reservoir ($n=1$) in three cases of mucormycosis with cerebral involvement. Of the two intrathecal C-AmB, treatment details were described in one (0.5 mg C-AmB administered once daily); however, treatment was discontinued after 7 days due to altered state of consciousness. When administered via the Ommaya reservoir, 0.5 mg C-AmB was given every second day for 80 days, throughout which no treatment-related adverse effects were reported.
Intraocular ($n=2$)	Intraocular AmB was prescribed for the treatment mucormycosis keratitis and endophthalmitis: For the management of Mucorales keratitis, C-AmB 0.15% eyedrops were administered over 6 weeks (every 1 h for 1 week, every 2 h for another 1 week, every 4 h for 2 weeks, and then tapered over another 2 weeks). In addition, prednisolone 0.5% eyedrops were concurrently administered 3 weeks post-initiation of AmB eyedrops. For the management of Mucorales endophthalmitis, AmB 0.005 mg in 0.1 mL of water for injection was injected intravitreally as a single dose in addition to endoscopic sinus surgery and a 10-week course of intravenous L-AmB. Resolution of the corneal infiltrates and endophthalmitis was reported following completion of treatment.
Inhaled/nebulised ($n=7$)	Details of nebulised AmB were described in five cases: four cases reported the use of C-AmB (daily doses of 10 mg in one case, 25 mg in two cases and 160 mg in the other case), whilst ABLC (50 mg daily) was used in one case. No treatment-related adverse events were documented.
Lung instillation ($n=3$)	C-AmB was instilled to the lungs via flexible bronchoscopy. The dosing regimens included 10 mg weekly for 7 weeks, 20 mg twice weekly or 25 mg daily for 5 weeks.
Wound irrigation ($n=5$)	C-AmB solution was used as wound irrigation in the management of cutaneous mucormycosis post-surgical debridement. The concentrations of C-AmB solutions, however, were reported only in two cases (0.05 mg/mL and 2.5 mg/mL). Drying effects on the skin limited the utility of the irrigation solution.
Bone cement ($n=3$)	Following surgical resection of infected bone in three cases of osteomyelitis, AmB impregnated in polymethylmethacrylate cement was fixated to the post-surgical space. The dose was reported in two cases (400 mg in one case and 500 mg in the other case).
Intraperitoneal instillation ($n=1$)	C-AmB (12 mg/L) was administered daily for a total of 40 days in one case of abdominal mucormycosis.

Table 6
Univariate and multivariate logistic regression of clinical variables influencing 90-day mortality[a].

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
No underlying conditions	0.51 (0.35–0.74)	<0.001	0.98 (0.37–2.58)	0.966
Diabetes mellitus	0.74 (0.56–0.99)	0.039	1.46 (0.72–2.97)	0.295
Haematological malignancy	2.91 (2.15–3.93)	<0.001	1.12 (0.40–3.10)	0.834
Haematopoietic stem cell transplantation	3.73 (2.31–6.04)	<0.001	3.77 (1.37–10.37)	0.010
Solid-organ transplantation	0.69 (0.46–1.05)	0.084	1.66 (0.63–4.31)	0.303
Major trauma	0.54 (0.33–0.89)	0.016	1.66 (0.67–4.14)	0.276
Minor trauma	0.87 (0.54–1.39)	0.556	2.02 (0.83–4.88)	0.121
Liver disease	1.73 (0.80–3.75)	0.161	0.38 (0.06–2.46)	0.309
Use of cancer chemotherapy	1.94 (1.35–2.78)	<0.001	1.56 (0.60–4.03)	0.363
Use of corticosteroids	1.42 (1.05–1.90)	0.021	0.95 (0.49–1.83)	0.873
Neutropenia	2.46 (1.73–3.48)	<0.001	1.46 (0.58–3.69)	0.425
Use of biologics	1.56 (0.92–2.65)	0.102	2.63 (0.98–7.05)	0.054
Use of renal replacement therapy	2.38 (1.08–5.27)	0.032	3.66 (0.89–14.99)	0.072
Disease manifestation	Compared with rhino-orbito-cerebral disease	<0.001		0.082
Pulmonary	1.46 (0.99–2.15)	0.059	1.10 (0.53–2.30)	0.794
Cutaneous	0.58 (0.39–0.88)	0.010	0.99 (0.47–2.09)	0.982
Disseminated	3.30 (2.07–5.26)	<0.001	2.33 (1.02–5.29)	0.044
Gastrointestinal	1.67 (0.99–2.82)	0.054	2.85 (0.97–8.34)	0.057
Mucorales organisms	Compared with *Rhizopus*	0.014		0.022
Mucor	0.70 (0.39–1.27)	0.242	0.41 (0.18–0.92)	0.030
Rhizomucor	0.84 (0.38–1.88)	0.674	0.37 (0.12–1.14)	0.084
Lichtheimia	0.63 (0.34–1.17)	0.144	0.65 (0.30–1.41)	0.275
Cunninghamella	3.58 (1.52–8.40)	0.003	1.51 (0.54–4.23)	0.434
Saksenaea complex	1.30 (0.41–4.17)	0.659	3.27 (0.86–12.46)	0.082
Apophysomyces	0.96 (0.46–2.01)	0.910	1.62 (0.60–4.37)	0.344
Treatment modality	Compared with antifungal alone	<0.001		<0.001
Surgery	0.88 (0.24–3.28)	0.851	0.47 (0.09–2.44)	0.372
Antifungal and surgery	0.28 (0.17–0.43)	<0.001	0.23 (0.13–0.41)	<0.001
Antifungal and adjunctive therapy	0.44 (0.09–2.05)	0.297	0.38 (0.06–2.31)	0.293
Antifungal and surgery and adjunctive therapy	0.11 (0.04–0.28)	<0.001	0.07 (0.02–0.20)	<0.001

OR, odds ratio; CI, confidence interval.
[a] Complete details of demographic data and underlying conditions are presented in [17].

not result in higher exposure [20]. Findings from a recent prospective study also showed that the use of ≥7.5 mg/kg/day of i.v. L-AmB did not confer an additional survival benefit [11]. Therefore, the clinical utility of high-dose i.v. L-AmB as identified in the current review remains debatable and requires further investigation.

Owing to its good safety profile [21,22] and in vitro activity against the Mucorales [23–25], posaconazole is an attractive alternative for the management of mucormycosis. Patient outcomes associated with posaconazole therapy in the current study were favourable. Amongst the 11 patients receiving posaconazole oral suspension monotherapy, death was observed in one patient with disseminated disease (Table 1). Similarly, only one case of recurrent infection was reported during posaconazole oral suspension maintenance therapy. The dose of posaconazole oral suspension reported in these patients was 800 mg daily, although use of therapeutic drug monitoring to guide posaconazole dosing was not described. Thus, we were unable to ascertain whether the observed negative outcomes were due to a subtherapeutic posaconazole trough plasma concentration (C_{min}).

Given the higher resultant posaconazole C_{min} (>1 mg/L), the more recent posaconazole MR tablet [26] or i.v. posaconazole formulation [21] may be a useful alternative to posaconazole oral suspension. However, clinical data supporting the use of these newer formulations in the management of mucormycosis remain scarce. In the current study, whilst no deaths were observed in patients receiving posaconazole MR tablet, it is worth noting that it was prescribed for the management of cutaneous mucormycosis. Similarly, despite clinical improvement, use of i.v. posaconazole salvage therapy (in combination with i.v. L-AmB and caspofungin) was described only in one patient for the management of rhino-orbital-cerebral mucormycosis. Further studies are required to investigate the role of these newer posaconazole formulations.

The current review suggests that itraconazole capsules in combination with surgical debridement may afford favourable outcomes in the management of cutaneous disease in patients who are not receiving immunosuppressants or cancer chemotherapy. Consistent with previous reports [23–25], this review demonstrated that itraconazole exhibits some in vitro activity against the Mucorales, albeit variable. However, there is currently insufficient evidence to support the use of itraconazole as a primary therapy for mucormycosis owing to concern regarding variability in oral absorption and bioavailability [8]. The recently approved itraconazole capsule formulations [27] may potentially overcome these limitations, although the clinical efficacy of this novel formulation in the management of mucormycosis is yet to be established.

Despite their negligible in vitro activity against the Mucorales [2–4], echinocandins, when used in combination with lipid-based AmB, have been associated with a survival benefit in a murine mucormycosis model [28]. The clinical benefit of concomitant i.v. ABLC and caspofungin therapy in the management of rhino-orbital-cerebral mucormycosis has been reported in a small retrospective study [29]. However, this study was performed primarily in patients with diabetes mellitus, and the outcomes of this combination therapy were only evaluated in six patients. A more recent propensity score analysis of 106 patients with mucormycosis and haematological malignancy suggested a lack of survival benefit amongst patients receiving initial combination antifungal therapy comprising i.v. L-AmB, posaconazole and an echinocandin (OR = 0.8, 95% CI 0.3–2.4; $P = 0.69$) [30]. Similarly, the current data suggested that i.v. AmB in combination with an echinocandin and/or posaconazole oral suspension did not offer any survival advantage over i.v. AmB monotherapy, although we were unable to exclude the possibility that these combination therapies were initiated in more severe diseases with poorer prognosis. Importantly, no clinical study has evaluated the efficacy of i.v. AmB and posaconazole combination therapy, although the findings from an animal study suggested a lack of survival benefit [31].

Data supporting the clinical use of adjunctive therapies in the management of mucormycosis remain limited and we were unable to fully evaluate their therapeutic role owing to the small number of reports. Moreover, the treatment details (including dosing regimen and duration of therapy) in the reported cases were not consistently presented. The safety and clinical efficacy of such therapies for managing mucormycosis has only been evaluated for deferasirox (DEFEAT Mucor study) [10]. Although limited by the small sample size and a heterogeneous study population, findings from the DEFEAT Mucor study suggested that 90-day mortality was higher in patients treated with deferasirox. In the current review, nearly one-half of the patients receiving deferasirox therapy (3/7) were dead within 90 days; all 3 patients had underlying haematological malignancies. In addition, renal toxicity was observed in two patients. Hence, without further safety and efficacy further data, its use should not be routinely recommended.

Evidence for the use of hyperbaric O_2 therapy was extrapolated from in vitro data, which demonstrated fungal growth inhibition and enhanced AmB fungicidal activity at an O_2 pressure of 1800 mmHg [32]. Furthermore, hyperbaric O_2 has also been shown to promote the release of growth factors and to improve angiogenesis and wound healing [33]. Although the overall 90-day survival in patients receiving hyperbaric O_2 therapy in this review was 90%, it is worth noting that it was primarily administered to patients with no underlying immunosuppression (14/20; 70.0%). In addition, hyperbaric O_2 therapy may have been initiated in patients who have already responded to antifungal therapies. Therefore, well designed, prospective clinical studies are required to determine the efficacy of hyperbaric O_2 therapy before it can be routinely recommended for the management of mucormycosis.

In the current review, use of topical AmB in the management of various manifestations of mucormycosis was also observed. However, data supporting the use of this approach are lacking given the inadequate description of the drug concentrations used, the methods of preparation, as well as the stability, safety and efficacy of these topical formulations.

Importantly, this review indicated that there has been no significant improvement in mucormycosis-associated mortality in recent years despite the advent of newer antifungals. The overall 90-day mortality (41.0%) was comparable with that reported previously (44–46%) [12,34,35]. The difficulties in establishing early diagnosis and treatment initiation as well as complex underlying conditions (including immunosuppression) in these patient populations may have contributed to the observed high mortality [36]. Indeed, delaying administration of antifungals by >6 days has been associated with a two-fold increase in mucormycosis-associated 90-day mortality [37]. However, we were unable to ascertain whether the mortality observed in the current review was influenced by a delay in treatment, given that the time to treatment initiation was not uniformly reported. Furthermore, although reversal of predisposing factors is critical in the management of mucormycosis [36], this was not regularly reported in the cases included in this review and thus could not be evaluated.

Nevertheless, concurrent antifungal and surgical therapy was independently associated with improved 90-day mortality. Furthermore, although we have noted improved outcomes amongst patients receiving adjunctive therapies, the small number of cases limits the interpretation of this observation. Of importance, the reported duration of antifungal therapy for mucormycosis remained inconsistent and was often tailored individually according to disease manifestations and patient response [5,7,8]. In the current review, it was observed that patients who were alive at 90 days had received antifungals for a median (IQR) of 30 (20–56) days.

Roden et al. previously reported that *Cunninghamella* infections were associated with a 2.8-fold higher mortality (95% CI 1.11–6.96; $P = 0.029$) compared with those due to *Rhizopus* spp. [12]. Further, experimental data have demonstrated that *Cunninghamella* spp. are more virulent than *Rhizopus* spp. [38]. In the current study, we also observed higher 90-day mortality amongst patients with *Cunninghamella* disease, although this was noted only in the univariate analysis. Conversely, infections caused by *Mucor* spp. were associated with significantly lower 90-day mortality. Whilst we were unable to determine the reasons behind this observation, much lower geometric MICs of AmB were noted for *Mucor* spp. compared with those for other genera, consistent with previous studies [23–25].

Notably, interpretative clinical breakpoints to assign susceptibility/resistance of Mucorales against various antifungals and to correlate MICs with clinical outcome are yet to be established [23]. The current review also indicates considerable variability in the methodology used for MIC determination. More recently, Espinel-Ingroff et al. reported epidemiologic cut-off values (ECVs) of AmB, itraconazole and posaconazole for several Mucorales organisms [23]. ECVs may be useful in guiding the surveillance of emerging resistance or isolates with reduced susceptibility to antifungals [23], although there is a need for standardisation of the in vitro antifungal susceptibility testing methods to aid interpretation of the results [39].

4.1. Strength and weakness

This systematic review is the most recent and comprehensive overview of evidence related to the clinical outcomes and therapeutic advances in the management of mucormycosis. The cases included in the current work were assessed for inclusion using stringent criteria. However, the potential influence of publication bias impacting the findings cannot be excluded given that published case reports often describe observations of uncommon/unique conditions [40]. In addition, treatment details, patient outcomes and duration of follow-up were not uniformly reported amongst the cases identified in the current study, and cases with missing information were excluded from the analysis.

4.2. Practice and research implications

The current review suggests that first-line therapies with acceptable efficacy and toxicity remain an urgent unmet need. Despite a lower rate of renal toxicity, i.v. lipid-based AmB formulations, which are generally more costly, did not appear to confer any survival advantage over i.v. C-AmB. However, the former were associated with fewer adverse effects. Similarly, initial therapy with combination antifungals (including posaconazole oral suspension and/or an echinocandin) did not result in statistically significant lower mortality compared with initial treatment with AmB monotherapy. Further studies are required to generate more robust evidence before the use of combination therapy can be recommended. Indeed, surgery was fundamental to improving survival and must be accessible to all patients. Itraconazole capsules may be a useful alternative in the management of cutaneous mucormycosis in patients without underlying immunosuppression. Although use of posaconazole oral suspension as salvage or maintenance therapy appears to afford favourable outcomes, the efficacy of posaconazole MR tablet or injection particularly when use as monotherapy remains to be determined. Studies are required to determine the clinical utility of isavuconazole given the dearth of data available. Likewise, the safety and efficacy of adjunctive therapies in the management of mucormycosis also require further evaluation with well designed, adequately powered studies.

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Competing interests

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Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.01.002.

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