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Original Article

Mucorales: A systematic review to inform the World Health Organization priority list of fungal pathogens

C. Orla Morrissey [1,*,#], Hannah Yejin Kim [2,3,4,#], Katherine Garnham [5], Aiken Dao [2,6,7], Arunaloke Chakrabarti [8], John R. Perfect [9], Ana Alastruey-Izquierdo [10], Thomas S. Harrison [11,12], Felix Bongomin [13], Marcelo Galas[14], Siswanto Siswanto[15], Daniel Argaw Dagne[16], Felipe Roitberg[17], Valeria Gigante [18], Hatim Sati [18], Jan-Willem Alffenaar [2,3,4,†] and Justin Beardsley [2,4,19,†]

[1]Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia
[2]Infectious Diseases Institute (Sydney ID), The University of Sydney, Camperdown, New South Wales, Australia
[3]Faculty of Medicine and Health, School of Pharmacy, The University of Sydney, Camperdown, New South Wales, Australia
[4]Department of Pharmacy, Westmead Hospital, Westmead, New South Wales, Australia
[5]Department of Infectious Diseases and Microbiology, Gold Coast University Hospital, Southport, Queensland, Australia
[6]Department of Infectious Diseases, Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, Australia
[7]Orthopaedic Research and Biotechnology Unit, Children's Hospital at Westmead, Westmead, New South Wales, Australia
[8]Doodhadhari Burfani Hospital and Research Institute, Haridwar, India
[9]Division of Infectious Diseases and International Health, Duke University School of Medicine, Durham, North Carolina, USA
[10]Mycology Reference Laboratory, National Centre for Microbiology, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain
[11]Institute for Infection and Immunity, and Clinical Academic Group in Infection and Immunity, St. George's, University of London, and St. George's University Hospitals NHS Foundation Trust, London, United Kingdom
[12]MRC Centre for Medical Mycology, University of Exeter, Exeter, United Kingdom
[13]Department of Medical Microbiology and Immunology, Faculty of Medicine, Gulu University, Gulu, Uganda
[14]Antimicrobial Resistance Special Program, Communicable Diseases and Environmental Determinants of Health, Pan American Health Organization, Washington, District of Columbia, USA
[15]World Health Organization, South-East Asia Region Office, New Delhi, India
[16]Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
[17]Department of Noncommunicable Diseases, World Health Organization, Geneva, Switzerland
[18]AMR Division, World Health Organization, Geneva, Switzerland
[19]Westmead Institute for Medical Research, Westmead, New South Wales, Australia

*To whom correspondence should be addressed. C. Orla Morrissey MD, PhD, Department of Infectious Diseases, Alfred Health and Monash University, Level 2, Burnet Building, 85 Commercial Road, Melbourne, Victoria, Australia. Tel: +619076 5436. E-mail: orla.morrissey@monash.edu
[#]Shared first authorship.
[†]Shared last authorship.

Abstract

The World Health Organization, in response to the growing burden of fungal disease, established a process to develop a fungal priority pathogens list (FPPL). This systematic review aimed to evaluate the epidemiology and impact of invasive fungal disease due to Mucorales. PubMed and Web of Science were searched to identify studies published between January 1, 2011 and February 23, 2021. Studies reporting on mortality, inpatient care, complications and sequelae, antifungal susceptibility, risk factors, preventability, annual incidence, global distribution, and emergence during the study time frames were selected. Overall, 24 studies were included. Mortality rates of up to 80% were reported. Antifungal susceptibility varied across agents and species, with the minimum inhibitory concentrations lowest for amphotericin B and posaconazole. Diabetes mellitus was a common risk factor, detected in 65%–85% of patients with mucormycosis, particularly in those with rhino-orbital disease (86.9%). Breakthrough infection was detected in 13.6%–100% on azole or echinocandin antifungal prophylaxis. The reported prevalence rates were variable, with some studies reporting stable rates in the USA of 0.094–0.117/10 000 discharges between 2011 and 2014, whereas others reported an increase in Iran from 16.8% to 24% between 2011 and 2015. Carefully designed global surveillance studies, linking laboratory and clinical data, are required to develop clinical breakpoints to guide antifungal therapy and determine accurate estimates of complications and sequelae, annual incidence, trends, and global distribution. These data will provide robust estimates of disease burden to refine interventions and better inform future FPPL.

Key words: Mucorales, mucormycosis, invasive fungal disease, mortality, susceptibility, risk factors, incidence, epidemiology.

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Introduction

Mucormycosis is a life-threatening spectrum of invasive fungal disease (IFD) caused by genera of the order Mucorales.[1] Previously known as zygomycosis because infections were caused by fungi of the former phylum, Zygomycota. Following the phylogenetic reanalysis of the kingdom Fungi, the name Zygomycota has been rendered obsolete.[2,3] Diabetes mellitus was initially the most common risk factor, but as the numbers of immunosuppressed patients has increased, hematological malignancies and transplantation now predominate.[4–7] More recently, coronavirus diseases 2019 (COVID-19) has emerged as an important risk factor for mucormycosis, particularly in India.[8] This has highlighted the need to improve our understanding of the pathogenesis of mucormycosis.

The most commonly reported pathogens causing mucormycosis are *Rhizopus* species (spp.), *Mucor* spp., *Lichtheimia* spp. (formerly from the genera *Absidia* and *Mycocladus*), *Rhizomucor* spp., *Cunninghamella* spp., *Apophysomyces* spp., and *Saksenaea* spp. The different species vary in their geographical distribution.[4,9] Given that a large number of species cause human disease and have a limited capacity to grow on culture medium, experienced and expert mycologists are required for identification.

People with diabetes mellitus typically present with rhino-orbital-cerebral mucormycosis, whereas pulmonary mucormycosis predominates in immunosuppressed patients (i.e., neutropenic, with graft-versus-host diseases [GVHD]).[4,10] Cutaneous and soft-tissue mucormycosis are most commonly seen in immunocompetent patients, usually following a traumatic injury.[11] Primary gastrointestinal mucormycosis is rare, but it is the most common clinical manifestation in neonates.[12,13] The mainstay of treatment is surgical debridement of necrotic tissue and a lipid formulation of amphotericin B, which may not be readily available in low- and middle-income countries (LMICs). Moreover, amphotericin B, even in its lipid form, is associated with significant adverse events. These factors likely contribute to the ongoing high mortality rates seen with mucormycosis (23%–90.9%).[14,15]

Given the ongoing high mortality rates seen with IFD due to Mucorales, the aim of this systematic review was to evaluate Mucorales against a set of criteria: mortality, inpatient care, complications and sequelae, antifungal susceptibility, risk factors, preventability, annual incidence, global distribution, and emergence in the 10 years from 2011. The generated data identified knowledge gaps for Mucorales, informing the fungal priority pathogens list (FFPL) of the World Health Organization (WHO).

Methods

Study design

A systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[16]

Inclusion and exclusion criteria

Studies were included if they reported data on: (a) adults and/or pediatric populations; (b) Mucorales; (c) invasive infections; (d) at least 1 criterion (e.g., mortality, inpatient care, complications/sequelae, antifungal susceptibility, risk factors, preventability, annual incidence, global distribution, and emergence in the previous 10 years); (e) retrospective or prospective observational studies, randomized controlled trials, epidemiological or surveillance studies; and (f) were published between January 1, 2011 to February 23, 2021. Studies were excluded if they reported on/were: (a) animals and/or plants; (b) bacteria, viruses, and/or parasites; (c) other fungi or criteria only; (d) included <10 mucormycosis cases or Mucorales isolates (total from all genera); (e) novel antifungals in pre-clinical studies or early-phase trials or unlicensed antifungals only; (f) *in vitro* resistance mechanisms only; (g) case reports, conference abstracts, or reviews; (h) not in English; and (i) outside the study time frames.

Search strategy

We conducted a comprehensive search for studies published in English using the PubMed and Web of Science Core Collection databases between January 1, 2011 and February 23, 2021. On PubMed, the search was optimized using medical subject headings (MeSH) and/or keyword terms in the title/abstract for Mucorales and the inclusion/exclusion criteria. For Mucorales, exclusion terms for environmental sources (e.g., NOT plants) were used to focus the search results. On the Web of Science, MeSH terms are not available, and therefore topic, title, or abstract searches were used. The final searches used can be found in the supplementary material.

PubMed and related databases are underpinned by a standardized taxonomy database. Thus, using a species name as a search term retrieves articles with obsolete or updated nomenclature. Hence, this search using the Mucorales term retrieved articles utilizing either Mucorales or Zygomycetes.[17]

Study selection

The final search results from each PubMed and Web of Science Core Collection databases were imported into the reference manager, Endnote™, and the online systematic review software, Covidence® (Veritas Health Innovation, Australia), and duplicates were removed. The remaining articles underwent title and abstract screening using the inclusion/exclusion criteria, and no reasons were provided for excluding articles at this step. Then, full text screening was performed to determine eligible articles for inclusion with the reasons for excluding any articles recorded (Fig. 1). The title/abstract screening and full text screenings were performed independently by two reviewers (H.Y.K. and C.O.M.) in Covidence®. Any discrepancies were resolved by a third reviewer (J.W.A.). Any additional articles identified from the references of the included articles were added.

Data extraction

Data from the final set of eligible articles were extracted into an Excel database for each relevant criterion by one of the screening reviewers (C.O.M.) and were independently checked for accuracy by the other reviewers (H.Y.K., K.G., and A.D.).

Risk of bias assessment

The risk of bias assessment was independently performed by two reviewers (H.Y.K. and C.O.M.) for the included studies (Table 1 and Supplementary Table 1). The risk of bias tool for randomized trials version 2 (ROB 2) and the risk of bias tool for non-randomized studies (RoBANS) were used in this

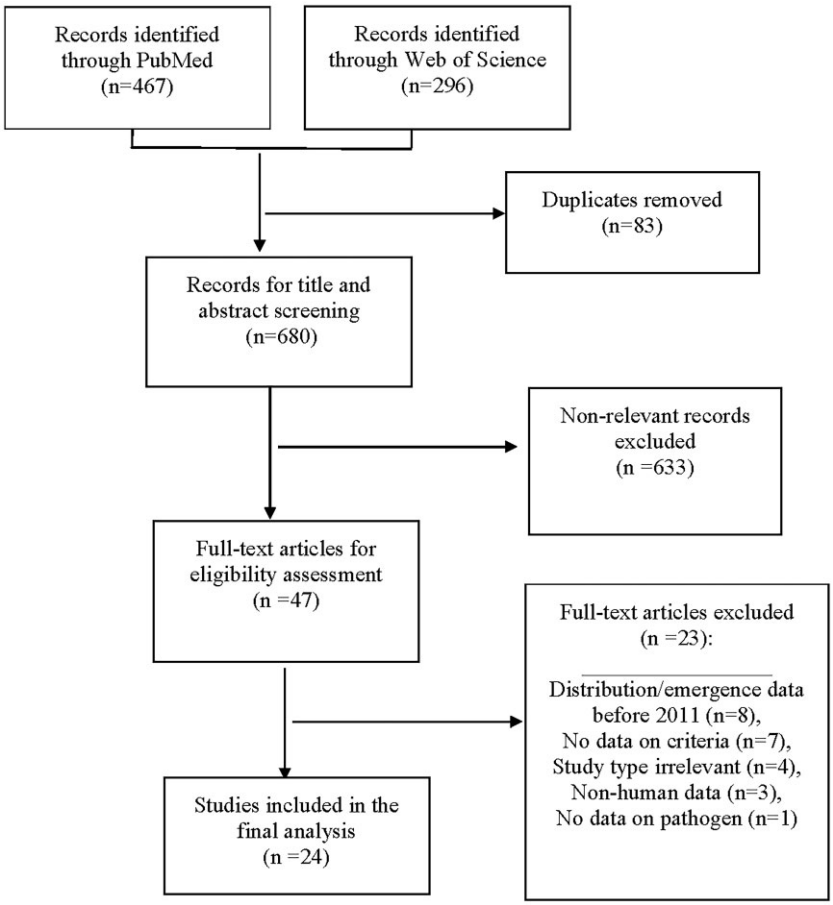

Figure 1. Flow diagram for the selection of studies included in the systematic review of Mucorales. Based on Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement.

Table 1. Overall risk of bias for included studies.

Author	Publication year	Risk	Reference
Alastruey-Izquierdo et al.	2018	High	[91]
Arendrup et al.	2015	High	[92]
Bonifaz et al.	2014	High	[23]
Bonifaz et al.	2021	High	[32]
Bonifaz et al.	2021	High	[35]
Caramalho et al.	2015	High	[30]
Chakrabarti et al.	2019	High	[24]
Chowdhary et al.	2014	High	[29]
Dolatabadi et al.	2018	High	[33]
Espinel-Ingroff et al.	2015	High	[49]
Kontoyiannis et al.	2016	High	[14]
Lee et al.	2020	High	[22]
Legrand et al.	2016	High	[20]
Manesh et al.	2019	High	[21]
Marty et al.	2016	Low	[36]
Millon et al.	2016	High	[34]
Ozenci et al.	2019	High	[93]
Pana et al.	2016	High	[31]
Patel et al.	2020	High	[26]
Pfaller et al.	2018	High	[27]
Prakash et al.	2019	High	[6]
Salmanton-Garcia et al.	2020	High	[25]
Van den Nest et al.	2021	High	[15]
Wagner et al.	2019	High	[28]

assessment.[18,19] For the overall risk, using ROB 2 tool, the studies were rated low, high, or with some concerns. Using RoBANS tool, the studies were rated as low, high, or unclear risk.

This systematic review was intended to inform on specific criteria; therefore, we used each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, or analysis in that particular study. With this approach, studies classified as unclear or high overall risk were still considered for analysis.

Data synthesis

The extracted data on the outcome criteria were quantitatively (e.g., proportions [%], mean, median, range) or qualitatively analyzed depending on the amount and nature of the data and tabulated. (Tables 2–8 and Supplementary Tables 1–3).

Results

Study selection

Between January 1, 2011 and February 23, 2021, 467 and 296 articles were identified in PubMed and World of Science Core Collection databases, respectively. After excluding the duplicated and non-relevant articles, 47 articles underwent full-text screening, of which 24 studies were included in the final analysis. Eight studies were excluded because they contained data

Table 2. Mortality associated with invasive fungal disease due to Mucorales.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description (%)	Number of patients	Mortality type (*n*/*N* (%))
Bonifaz et al.[23]	2014	Retrospective cohort study	Multi-center	January 1985–December 2012	Mexico	Tertiary	Children with mucormycosis ROC (77.27%), primary cutaneous, pulmonary	22	Death: 16/22 (72.7%)
Bonifaz et al.[32]	2021	Retrospective cohort study	Single-center	January 1985–December 2019	Mexico	Tertiary	Pediatric patients with mucormycosis ROC (75.9%), primary cutaneous (8.41%), pulmonary (7.47%)	214	Overall: 46/111 (41.4%)
Bonifaz et al.[35]	2021	Retrospective cohort study	Single-center	January 1985–December 2019	Mexico	Tertiary	Adults and children Primary cutaneous* ($n = 18$), secondary# cutaneous ($n = 97$)	115	Mortality: Primary cutaneous: 9/18 (50%) Secondary: 42/97 (43.3%)
Chakrabarti et al.[24]	2019	Prospective cohort study	Multi-center	April 2016–September 2017	India	Tertiary	Adult patients in ICU ROC ($n = 29$), pulmonary ($n = 17$)	398	Overall 42-day: 64.8% Overall 84-day: 65.8%
Chowdhary et al.[29]	2014	Antifungal susceptibility study	Multi-center	2004–2013	India	Tertiary	Pulmonary ($n = 39$), ROC ($n = 15$), cutaneous/subcutaneous ($n = 13$), disseminated ($n = 4$)	71	28/54 (51.8%)
Dolatabadi et al.[33]	2018	Retrospective cohort study	Multi-center	2008–2014	Iran	Provincial	Adults and children sinuses (86%)	208	Mortality: 11/41 (26.8%)
Kontoyiannis et al.[14]	2016	Retrospective cohort study	Multi-center	Janary 2005–June 2014	USA	Teaching and non-teaching hospital	Patients with mucormycosis-related hospitalization. USA hospital-based database covering more than 560 participating hospitals and 104 million patients	555	Discharge death rate: 130/555 (23%)
Lee et al.[22]	2020	Retrospective cohort study	Single-center	January 2011–August 2018	South Korea	Tertiary	Adult patients with hematological diseases	27	6-week mortality: 6/26 (23.1%) 12-week mortality: 7/26 (26.9%)
Legrand et al.[20]	2016	Retrospective/period A: October 2013–January 2015 Prospective/period B: January 2015–February 2016	Multi-center	October 2013–February 2016	France	Tertiary	Adult burns patients with invasive wound mucormycosis: >20% total body surface area	77	Period A: 4/5 (80%) Period B: 1/3 (33.3%)

Table 2. Continued

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description (%)	Number of patients	Mortality type (*n*/*N* (%))
Manesh et al.[21]	2019	Retrospective cohort study	Single-center	September 2005–September 2015	India	Tertiary	Patients with culture proven mucormycosis Paranasal sinuses (73.9%), MSK (15.2%)	184	Overall mortality: 57/184 (30.97%) Mortality in patients with hematological conditions:16/28 (57.14%)
Marty et al.[36]	2016	Single-arm open-label trial with matched case-control analysis	Multi-center	April 2008–June 2013	USA, Germany, France, Russia, Belgium, India, Israel, Czech Republic, Brazil, Thailand, Lebanon, and Switzerland	Tertiary	Adult patients with mucormycosis Pulmonary only (27%), pulmonary and other organs (32%), non-pulmonary disease (41%)	37 in the single-arm open-label trial33 amphotericin B-treated matched controls	Isavuconazole Day-42 crude all-cause mortality primary treatment: 7/21 (33%) Day-42 crude all-cause mortality refractory group: 5/11 (45%) Day-42 crude all-cause mortality intolerant to other antifungal agents: 2/5 (40%) Day-84 crude all-cause mortality primary treatment: 9/21 (43%) Day-84 crude all-cause mortality refractory group: 5/11 (45%) Day-84 crude all-cause mortality intolerant to other antifungal agents: 2/5 (40%) Weighted all-cause mortality: 33% (13.2–53.5%) Amphotericin B Day-42 crude all-cause mortality primary treatment: 13/33 (39%) Weighted all-cause mortality: 41% (20.2%–62.3%)

Table 2. Continued

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description (%)	Number of patients	Mortality type (*n*/*N* (%))
Millon et al.[34]	2016	Retrospective cohort study	Multi-center	January 2012–December 2014	France	Tertiary	Adult patients Pulmonary ($n = 17$), disseminated ($n = 14$), ROC ($n = 8$), cutaneous ($n = 4$), GIT ($n = 1$)	44	Mortality Day 28: 27/44 (61%) Mortality Day 84: 32/44 (72%)
Pana et al.[31]	2016	Retrospective review of prospectively collected cases	Multi-center	2005–2014	15 countries (54 in European and 9 in non-European countries)	Not stated	Pediatric patients Disseminated (38.1%), pulmonary (19%), skin and soft tissue (19%), paranasal sinuses/sino-orbital (15.8%), ROC (7.5%)	63	Crude mortality, overall: 21 (33.3%)
Patel et al.[26]	2020	Prospective cohort study	Multi-center	January 1, 2016–September 30, 2017	India	Tertiary	Adults with proven mucormycosis ROC (67.7%), pulmonary (13.3%), cutaneous (1.0.5%), other (8.5%)	485	90-day mortality: 242/465 (52.0%)
Prakash et al.[6]	2019	Prospective cohort study	Multi-center	January 2013–December 2015	India	Tertiary	Children and adults with mucormycosis ROC (63.9%), pulmonary (12.9%), cutaneous (9.5%), GIT (6.4%), renal (5.4%), other (1.8%)	388	Overall: 129/276 (46.7%)
Salmanton-Garcia et al.[25]	2020	Retrospective review of prospectively collected cases	Multi-center	1997–2019	Multiple: mostly from India ($n = 30$, 16.1%), the United States ($n = 24$, 12.9%), Spain ($n = 21$, 11.3%), and Germany ($n = 19$, 10.2%)	Not stated	Adults and children with mucormycosis Disseminated (18.2%), eye (9.1%)	22	Day 42: 7/22 (31.8%) Overall: 11/22 (50%) Attributable: 8/11 (72.7%)
Van den Nest et al.[15]	2021	Retrospective cohort study	Single-center	January 2009–August 2017	Austria	Tertiary	Children and adults with invasive or localized filamentous fungi Pulmonary ($n = 11$), disseminated ($n = 4$), heart ($n = 2$), CNS ($n = 1$)	18	30-day mortality: 9/11 (81.8%; 95% CI 55.8%–97.2%) 90-day mortality: 10/11 (90.9%; 95% CI 66.7%–99.5%)

n/*N*, number that died/number included in study; ROC, rhino-orbital-cerebral; ICU, intensive care unit; USA, United States of America; MSK, musculoskeletal system; GIT, gastrointestinal tract; CI, confidence interval; CNS, central nervous system.
^Infection sites tabulated if identified for mucormycosis in the study
∗Primary cutaneous: face (44.4%), leg (33.3%); forearm (11.1%), simultaneous thorax and leg (5.5%), and ear and neck (5.5%).
#Secondary cutaneous: face (65.9%), nose and palate (20.6%), gum and palate (11.4%), ear and neck (1.03%), disseminated (1.03%), and organs affected as part of disseminated disease: soft tissue and wounds ($n = 4$), stomach ($n = 1$).

Table 3. Duration of inpatient stay associated with invasive fungal disease due to Mucorales.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Length of stay (days)
Kontoyiannis et al.[14]	2016	Retrospective cohort study	Multi-center	January 2005–June 2014	USA	Teaching and non-teaching hospital	Patients with mucormycosis-related hospitalization. USA hospital-based database covering more than 560 participating hospitals and 104 million patients.	555	Median (range) 17 (1–259)
Patel et al.[26]	2020	Prospective cohort study	Multi-center	January 1, 2016–September 30, 2017	India	Tertiary	Adults with proven mucormycosis.	485	Overall, median (IQR) 16 (6–32)

USA, United States of America; IQR, interquartile range.

Table 4. Complications and sequelae associated with invasive fungal disease due to Mucorales.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Complications and sequelae
Legrand et al.[20]	2016	Retrospective/period A: October 2013–January 2015 Prospective/period B: January 2015–February 2016	Multi-center	October 2013–February 2016	France	Tertiary	Adult burns patients	77	More patients with positive circulating (blood) cmDNA required RRT (62% vs. 18%; $P = .01$) and developed septic shock (87% vs. 32%; $P = .004$) c/w cmDNA negative patients. In-hospital mortality was higher in patients with IWM/cmDNA positivity (62% vs. 25%; $P = .03$).
Kontoyiannis et al.[14]	2016	Retrospective cohort study	Multi-center	January 2005–June 2014	USA	Teaching and non-teaching hospital	Patients with mucormycosis-related hospitalization. USA hospital-based database covering >560 hospitals and 104 million patients.	555	Readmission: 1-month 168/555 (30%) 3-month 206/555 (37%)

cmDNA, circulating Mucorales DNA; RRT, renal replacement therapy; IWM, invasive wound mucormycosis; USA, United States of America.

from prior to 2011 only (Fig. 1). A flow diagram outlining the process of study selection is shown in Figure 1.

Risk of bias

The overall risk of bias for each study is presented in Table 1. Of the included studies, 23/24 (95.8%) were classified as having a high risk of bias in the domains used for classification (study design, data collection, or data analysis). This high-risk classification was most commonly due to a lack of information in the studies on measures used to mitigate selection bias (17/24 [70.8%]), account for confounding variables (19/24 [79.2%]), or failures to report all outcome data (19/24 [79.2%]). The details of the risk of bias assessment for each domain can be found in the supplementary material (Supplementary Table 1).

Analysis of the criteria

Mortality

A total of 17 (70.8%) studies reported on mortality using different metrics (Table 2). Mortality rates in adult-only populations ranged from 23% to 80% (Table 2).[14,20] Manesh et al. reported higher mortality rates in patients with hematological diseases as compared with the overall cohort (57.14% vs. 30.97%) (Table 2).[21] While not completely comparable, a South Korean single-center study reported lower mortal-

Table 5. Susceptibility testing of Mucorales to azole antifungal agents.

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Arendrup et al.[92]	EUCAST and CLSI	Not stated	*Lichtheimia corymbifera* ($n = 12$) EUCAST (Day 2) (mg/l): Range 1–4 MIC_{50} 2 CLSI (Day 2) (mg/l): Range 1–2 MIC_{50} 1 *Rhizopus microsporus* ($n = 26$) EUCAST (Day 2) (mg/l): Range 1–8 MIC_{50} 4 CLSI (Day 2) (mg/l): Range 0.125–1 MIC_{50} 0.5	Not done	*Lichtheimia corymbifera* ($n = 12$) EUCAST (Day 2) (mg/l): Range 0.125–0.5 MIC_{50} 0.25 CLSI (Day 2) (mg/l): Range 0.125–0.5 MIC_{50} 0.25 *Rhizopus microsporus* ($n = 26$) EUCAST (Day 2) (mg/l): Range 0.5–>16 MIC_{50} 2 CLSI (Day 2) (mg/l): Range 0.06–0.5 MIC_{50} 0.25	*Lichtheimia corymbifera* ($n = 12$) EUCAST (Day 2) (mg/l): Range >16 MIC_{50} >6 CLSI (Day 2) (mg/l): Range 16–>16 MIC_{50} 16 *Rhizopus microsporus* ($n = 26$) EUCAST (Day 2) (mg/l): Range 16–>16 MIC_{50} >16 CLSI (Day 2) (mg/l): Range 2–16 MIC_{50} 8

Table 5. Continued

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Caramalho et al.[30]	EUCAST *E*-test	Not tested	Not tested	Not tested	*Lichtheimia corymbifera* ($n = 41$) EUCAST (mg/l): Range 0.5–2.0 GM MIC 1.06 MIC_{50} 1.0 MIC_{90} 2.00 *E*-test (mg/l): Range 0.032–64.0 GM MIC 1.96 MIC_{50} 0.25 MIC_{90} 0.75 *Rhizopus arrhizus* ($n = 29$) EUCAST (mg/l): Range 0.5–32.0 GM MIC 2.98 MIC_{50} 2.0 MIC_{90} 4.00 *E*-test (mg/l): Range 0.064–64.0 GM MIC 12.15 MIC_{50} 1.0 MIC_{90} 64.00 *Rhizopus microsporus* ($n = 23$) EUCAST (mg/l): Range 0.5–4.0 GM MIC 1.85 MIC_{50} 2.0 MIC_{90} 4.0 *E*-test (mg/l): Range 0.25–64.0 GM MIC 5.4; MIC_{50} 2.0 MIC_{90} 64.00 *Mucor circinelloides* ($n = 16$) EUCAST (mg/l): Range 0.5–32.0 GM MIC 4.9 MIC_{50} 2.0 MIC_{90} 32.00 *E*-test (mg/l): Range 0.064–64.0 GM MIC 21.7 MIC_{50} 4.0 MIC_{90} 64.00	Not tested

Table 5. Continued

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Chowdhary et al.[29]	CLSI	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range 64–>64 GM 64 MIC_{50} 64 MIC_{90} 64 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range 64–>64 GM 64 MIC_{50} 64 MIC_{90} 64 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range 64 GM 64 MIC_{50} 64 MIC_{90} 64 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range 64 GM 64 MIC_{50} 64 MIC_{90} 64	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range 0.25–16 GM 1.5 MIC_{50} 1.5 MIC_{90} 8 *Rhizopuus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range 0.5–4 GM 0.96 MIC_{50} 1 MIC_{90} 3.2 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range 0.125–4 GM 1.2 MIC_{50} 1 MIC_{90} 2 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range 0.125–8 GM 1.45 MIC_{50} 1 MIC_{90} 8	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range 0.125–16 GM 2.75 MIC_{50} 5 MIC_{90} 16 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range 0.125–16 GM 1.2 MIC_{50} 1 MIC_{90} 16 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range 0.06–16 GM 0.95 MIC_{50} 1 MIC_{90} 8 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range 0.125–16 GM 0.46 MIC_{50} 0.25 MIC_{90} 16	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range 0.125–4 GM 0.51 MIC_{50} 0.5 MIC_{90} 1 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range 0.125–0.5 GM 0.31 MIC_{50} 0.25 MIC_{90} 0.5 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range 0.06–4 GM 0.34 MIC_{50} 0.25 MIC_{90} 0.5 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range 0.06–1 GM 0.43 MIC_{50} 0.5 MIC_{90} 1	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range 4–16 GM 10.08 MIC_{50} 16 MIC_{90} 16 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range 4–16 GM 6.65 MIC_{50} 8 MIC_{90} 8 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range 1–16 GM 7.3 MIC_{50} 8 MIC_{90} 16 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range 4–16 GM 9.18 MIC_{50} 8 MIC_{90} 16

Table 5. Continued

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Espinel-Ingroff et al.[49]	CLSI M38-A2, ECV	Not done	Not done	*Lichtheimia corymbifera* ($n = 93$) (μg/ml) MIC range 0.06–8 MIC mode 0.25 *Mucor circinelloides* ($n = 49$) (μg/ml) MIC range 0.25–16 MIC mode 4 *Rhizopus arrhizus* ($n = 215$) (μg/ml) MIC range 0.06–16 MIC mode 0.5 *Rhizopus microsporus* ($n = 74$) (μg/ml) MIC range 0.25–32 MIC mode 1	*Lichtheimia corymbifera* ($n = 112$) (μg/ml) MIC range 0.06–4 MIC mode 0.5 ECV (≥95%) 1 (1.8) ECV (≥97.5%) 2 (0.9) *Mucor circinelloides* ($n = 120$) (μg/ml) MIC range 0.06–16 MIC mode 1 ECV (≥95%) 4 (5) ECV (≥97.5%) 4 (5) *Rhizopus arrhizus* ($n = 349$) (μg/ml) MIC range 0.03–32 MIC mode 0.5 ECV (≥95%) 1 (10.9) ECV (≥97.5%) 2 (3.2) *Rhizopus microsporus* ($n = 137$) (μg/ml) MIC range 0.06–16 MIC mode 0.5 ECV (≥95%) 1 (5.1) ECV (≥97.5%) 2 (2.2)	Not done

Table 5. Continued

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Pfaller et al.*[27]	CLSI	Not done	*Lichtheimia* spp. ($n = 22$) (μg/ml) MIC range 1–16 MIC_{50} 4 MIC_{90} 8 *Mucor* spp. ($n = 69$) (μg/ml) MIC range 0.5–32 MIC_{50} 8 MIC_{90} 32 *Rhizomucor pusillus* ($n = 14$) (μg/ml) MIC range 0.5–8 MIC_{50} 2 MIC_{90} 8 *Rhizopus* spp. ($n = 161$) (μg/ml) MIC range 0.25–32 MIC_{50} 2 MIC_{90} 8 *Syncephalastrum* spp. ($n = 11$) MIC range 0.5–32 MIC_{50} ≥16 MIC_{90} ≥16	*Lichtheimia* spp. ($n = 9$) (μg/ml) MIC range 1–16 *Mucor* spp. ($n = 23$) (μg/ml) MIC range 1–3 MIC_{50} 4 MIC_{90} 32 *Rhizomucor pusillus* ($n = 4$) (μg/ml) MIC range 0.5–1 *Rhizopus* spp. ($n = 52$) (μg/ml) MIC range 0.12–32 MIC_{50} 1 MIC_{90} 4 *Syncephalastrum* spp. ($n = 3$) MIC range 1–4	*Lichtheimia* spp. ($n = 20$) (μg/ml) MIC range 0.25–2 MIC_{50} 0.5 MIC_{90} 1 *Mucor* spp. ($n = 52$) (μg/ml) MIC range 0.5–4 MIC_{50} 1 MIC_{90} 2 *Rhizomucor pusillus* ($n = 13$) (μg/ml) MIC range 0.25–1 MIC_{50} 0.25 MIC_{90} 0.5 *Rhizopus* spp. ($n = 115$) (μg/ml) MIC range 0.06–32 MIC_{50} 0.5 MIC_{90} 1 *Syncephalastrum* spp. ($n = 8$) MIC range 0.25–4	*Lichtheimia* spp. ($n = 12$) (μg/ml) MIC range 16–32 MIC_{50} 16 MIC_{90} 32 *Mucor* spp. ($n = 33$) (μg/ml) MIC range 16–32 MIC_{50} 32 MIC_{90} 32 *Rhizomucor pusillus* ($n = 7$) MIC range 4–16 *Rhizopus* spp. ($n = 72$) (μg/ml) MIC range 0.06–32 MIC_{50} 8 MIC_{90} 16 *Syncephalastrum* spp. ($n = 6$) MIC range 4–32
Wagner et al.[28]	EUCAST	Not done	*Mucor circinelloides* ($n = 14$) (mg/l) Range 2–8 GM MIC 5.1 MIC_{50} 4 *Mucor indicus* ($n = 10$) (mg/l) Range >8 GM MIC 16.0 MIC_{50} >8 *Mucor lusitanicus* ($n = 13$) (mg/l) Range 4–8 GM MIC 13.6 MIC_{50} >8	*Mucor circinelloides* ($n = 14$) (mg/l) Range 0.5–8 GM MIC 3.1 MIC_{50} 4 *Mucor indicus* ($n = 10$) (mg/l) GM MIC 13.0 MIC_{50} 8 Range 2–8 *Mucor lusitanicus* ($n = 13$) (mg/l) Range 2–8 GM MIC 12.3 MIC_{50} 8	*Mucor circinelloides* ($n = 14$) (mg/l) Range 0.125–4 GM MIC 0.6 MIC_{50} 0.5 *Mucor indicus* ($n = 10$) (mg/l) GM MIC 2.8 MIC_{50} 1 Range 0.25–8 *Mucor lusitanicus* ($n = 13$) (mg/l) Range 1–8 GM MIC 9.4 MIC_{50} 8	Not done Not done

Susceptibility results are presented in this table if at least 10 isolates of any Mucorales pathogen were tested. The exception was the study of Pfaller et al.* where for some species <10 isolates were tested against itraconazole, posaconazole, and voriconazole but were included for comparison with isavuconazole MIC values.
Data are reported as they appear in source documents.
MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; CLSI, Clinical and Laboratory Standards Institute; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; GM, geometric mean; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; ECV (%), calculated statistical epidemiological cutoff values in μg/ml (% of MIC above the ECV, or non-wild type).

ity rates in their hematology population (23.1%–26.9%) (Table 2).[21,22] In the pediatric populations, mortality rates as high as 72.7% were detected (Table 2).[23] Chakrabarti et al. reported that overall 42-day and 84-day mortality rates were 64.8% and 65.8%, respectively, in patients with mucormycosis admitted to the intensive care unit (ICU) (Table 2).[24] Only one (4.2%) study reported on attributable mortality rates (72.7%) (Table 2).[25]

Inpatient care

Only two (8.3%) studies reported on the hospital length of stay for patients with invasive mucormycosis (Table 3). The median hospital length of stay was similar (17 and 16 days, respectively) (Table 3).[14,26] However, one study reported a vast range (1–259 days) (Table 3).[14]

Complications and sequelae

Only a small number of studies reported on complications and sequelae (two [8.3%]) (Table 4). Legrand et al. observed that a greater proportion of burn patients who tested positive for circulating Mucorales DNA (cmDNA) required renal replacement therapy (RRT) (62% vs. 18%; $P = .01$) and developed septic shock (87% vs. 32%; $P = .004$) compared with those who tested negative for cmDNA (Table 4).[20] Higher in-hospital mortality was also observed in the cmDNA-positive patients compared with those who were cmDNA-negative (62% vs. 25%; $P = .03$) (Table 4).[20] Kontoyiannis et al. reported 30%–37% readmission rates within 3 months of discharge in patients with mucormycosis in the United States of America (USA) (Table 4).[14]

Antifungal susceptibility testing

Six (25%) studies reported on the antifungal drug susceptibility of Mucorales. The details of the study methods can be found in Supplementary Table 2. Drug susceptibility results for azole and other antifungal drugs are presented in Tables 5 and 6. Susceptibility to isavuconazole was variable, and higher MIC values for *Mucor* spp. (geometric mean [GM] 5–16 mg/l/MIC_{90} of 32 mg/l) compared with *Rhizopus* spp. (GM 1–1.5 mg/l/MIC_{90} of 2–8 mg/l) were described (Table 5).[27,28] Itraconazole MIC values were also higher for *Mucor* spp. (GM 3–13 mg/l/MIC_{90} of 32 mg/l) compared with *Rhizopus* spp. (GM 0.95–2.75 mg/l/MIC_{90} of 4–16 mg/l) (Table 5).[27,29]

Posaconazole MIC results were uniformly lower than for other antifungal agents, with values reported for *Mucor* spp. (GM 0.6–9.4 mg/l/MIC_{90} of 2 mg/l), *Rhizopus* spp. (GM 0.31–0.51 mg/l/MIC_{90} of 0.5–1 mg/l) and *Lichtheimia* spp. (GM 1.06–1.96 mg/l/MIC_{90} of 0.75–2 mg/l) (Table 5).[27,30] Voriconazole MIC values for Mucorales were high (GM 7–10 mg/l/MIC_{90} of 8–32 mg/l), which was predictable given the innate resistance of Mucorales to this agent (Table 5).[27,29]

For the echinocandins, including anidulafungin, caspofungin, and micafungin, MIC_{90} values were >8 mg/l for all tested Mucorales isolates, including *Rhizopus* spp. and *Syncephalastrum racemosum* (Table 6).[29] Mucorales isolates demonstrated low MIC values to amphotericin B with GM MIC of ≤0.1 mg/l and MIC_{90} of ≤0.5 mg/l reported for *Rhizopus* spp., *Mucor* spp., and *S. racemosum*, respectively (Table 6).[28,29] Due to the disparate results generated by the *E*-test and European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology (overall agreement was 75.1%), Caramalho et al. did not recommend the *E*-test for antifungal susceptibility testing of Mucorales.[30]

Risk factors and preventive measures

One (4.2%) study reported that a high proportion (81%) of patients with mucormycosis had neutropenia (absolute neutrophil count of <500/mm^3) at diagnosis (Table 7). Diabetes mellitus was a common predisposing factor, observed in up to 65%–85% of patients with mucormycosis, particularly those with rhino-orbital disease (86.9%).[21,26] In addition, diabetes mellitus was determined to be a risk factor for poor outcome (odds ratio [OR] 2.3, 95% confidence interval [CI] 1–6.2; $P = .07$) (Table 7).[21] Trauma was a predisposing factor for cutaneous mucormycosis, which was observed in 53% of this patient group (Table 7).[26]

Hematopoietic stem cell transplantation (HSCT) (OR 13.66, 95% CI 1.88–98.6) in pediatric patients, the presence of comorbid conditions such as chronic kidney disease, cardiovascular, pulmonary, or lung disease (adjusted hazard ratio [HR] 1.52, 95% CI 1.15–2.02; $P = .06$) and corticosteroid therapy (OR 2.33, 95% CI 0.925–5.46; $P = .073$) were risk factors for mortality in patients with mucormycosis (Table 7).[6,26,31]

Three (12.5%) studies reported break-through mucormycosis in 13.6%–100% of patients on triazoles or echinocandin prophylaxis; but, overall, the number of patients was small (<30 patients across all studies) (Supplementary Table 3).[22,24,25]

Annual incidence

Three (12.5%) studies reported on the annual incidence of mucormycosis.[22,23,32] Bonifaz et al. estimated the annual incidence rates to be 0.14–0.4/10 000 patient/day in children living in Mexico between 2011 and 2019 (Table 8).[23,32] A single-center study conducted in South Korea reported that the number of new cases of mucormycosis ranged from 1 to 4/year, which represents 1.7%–5.5% of all invasive mould infections identified annually ($n = 72$–116).[22]

Current global distribution

Mucorales are environmentally ubiquitous and globally distributed, with known but poorly defined geographic variability. Studies have reported mucormycosis cases in various regions, including the USA, Mexico, Iran, Austria, and South Korea (Table 8).[14,15,22,32,33] The estimated prevalence of mucormycosis-related hospitalizations in the USA ranged from 0.094 to 0.117/10 000 discharges between 2011 and 2014 (Table 8).[14] The prevalence of mucormycosis as a proportion of all IFD in South Korea and Austria ranged from 3.9% to 13.7% between 2011 and 2018 (Table 8).[15,22,33]

Trends in IFD due to Mucorales, 2011–2021

The trends are variable, with some studies reporting consistent rates and others reporting an increase over time. Kontoyiannis et al. reported that the prevalence of mucormycosis-related hospitalization remained relatively consistent (0.094–0.117 per 10 000 discharges) between 2011 and 2014 (Table 8).[14] In contrast, Dolatabadi et al. reported an increase in mucormycosis cases in adults and children in Iran from 16.8% in 2011 to 24% in 2015 (Table 8).[33] New mucormycosis cases in pediatric patients in Mexico fluctuated between 0.28 and 0.32/10 000 patients/days during 2011–2016, with a sudden decline in 2017 (0.14/10 000 patients/days).[32] This was followed by an increase to 0.4/10 000 patients/days in 2019.[32] A relatively stable trend was reported during the time

Table 6. Susceptibility testing of Mucorales to other antifungal agents.

Author	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Natamycin
Arendrup et al.[92]	EUCAST and CLSI	Not done	Not done	Not done	*Lichtheimia corymbifera* ($n = 12$) EUCAST (Day 2) (mg/l): Range ≤0.03–0.25 MIC_{50} 0.125 CLSI (Day 2) (mg/l): Range ≤0.03–0.125 MIC_{50} ≤0.03 ECV (≥95%) 1 (2.9) ECV (≥97.5%) 2 (0.7) *Rhizopus microsporus* ($n = 26$) EUCAST (Day 2) (mg/l): Range 0.25–1 MIC_{50} 0.5 CLSI (Day 2) (mg/l): Range ≤0.03–0.25 MIC_{50} 0.125 ECV (≥95%) 2 (2.1) ECV (≥97.5%) 2 (2.1)	Not done

Table 6. Continued

Author	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Natamycin
Caramalho et al.[30]	EUCAST *E*-test	Not tested	Not tested	Not tested	*Lichtheimia corymbifera* ($n = 41$) EUCAST (mg/l): Range 0.125–2.0 GM MIC 0.66 MIC_{50} 0.5 MIC_{90} 1.00 *E*-test (mg/l): Range 0.002–2.0 GM MIC 0.43 MIC_{50} 0.25 MIC_{90} 1.00 *Rhizopus arrrhizus* ($n = 29$) EUCAST (mg/l): Range 0.25–32.0 GM MIC 1.87 MIC_{50} 1.0 MIC_{90} 1.00 *E*-test (mg/l): Range 0.002–64.0 GM MIC 11.7 MIC_{50} 2.0 MIC_{90} 64.00 *Rhizopus microsporus* ($n = 23$) EUCAST (mg/l): Range 0.5–2.0 GM MIC 0.8 MIC_{50} 1.0 MIC_{90} 1.00 *E*-test (mg/l): Range 0.064–64.0 GM MIC 4.19 MIC_{50} 0.5 MIC_{90} 6.00 *Mucor circinelloides* ($n = 16$) EUCAST (mg/l): Range 0.125–1.0 GM MIC 0.48 MIC_{50} 0.5 MIC_{90} 1.00 *E*-test (mg/l): Range 0.016–64.0 GM MIC 4.56 MIC_{50} 0.13 MIC_{90} 32.00	Not tested

Table 6. Continued

Author	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Natamycin
Chowdhary et al.[29]	CLSI	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MI_{C90} >8 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range >8 GM >8 MIC_{50} >8 MIC_{90} >8	*Rhizopus arrhizus var. delemar* ($n = 25$) (μg/ml) Range 0.03–0.25 GM 0.05 MIC_{50} 0.03 MIC_{90} 0.2 *Rhizopus arrhizus var. arrhizus* ($n = 15$) (μg/ml) Range 0.03–0.125 GM 0.045 MIC_{50} 0.03 MIC_{90} 0.125 *Rhizopus microsporus* ($n = 17$) (μg/ml) Range 0.03–1 GM 0.0 MIC_{50} 0.06 MIC_{90} 0.5 *Syncephalastrum racemosum* ($n = 11$) (μg/ml) Range 0.03–0.125 GM 0.047 MIC_{50} 0.06 MIC_{90} 0.06 Mucorales above breakpoint (≥1 μg/ml) 2 (2.5%)	

Table 6. Continued

Author	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Natamycin
Espinel-Ingroff et al.[49]	CLSI M38-A2	Not done	Not done	Not done	*Lichtheimia corymbifera* ($n = 136$) (μg/ml) MIC range 0.06–16 MIC mode 0.5 *Mucor circinelloides* ($n = 123$) (μg/ml) MIC range 0.03–4 MIC mode 0.25 *Rhizopus arrhizus* ($n = 257$) (μg/ml) MIC range 0.03–4 MIC mode 1 *Rhizopus microsporus* ($n = 146$) (μg/ml) MIC range 0.06–4 MIC mode 0.5	Not done
Wagner et al.[28]	EUCAST	Not done	Not done	Not done	*Mucor circinelloides* ($n = 14$) (mg/l) Range ≤0.03–0.5 GM MIC 0.1 MIC_{50} 0.125 *Mucor indicus* ($n = 10$) (mg/l) Range ≤0.03–0.125 GM MIC 0.04 MIC_{50} 0.03 *Mucor lusitanicus* ($n = 13$) (mg/l) Range ≤0.03–0.25 GM MIC 0.08 MIC_{50} 0.06	*Mucor circinelloides* ($n = 14$) (mg/l) Range 1–4 GM MIC 1.9 MIC_{50} 2 *Mucor indicus* ($n = 10$) (mg/l) Range 2–4 GM MIC 2.5 MIC_{50} 2 *Mucor lusitanicus* ($n = 13$) (mg/l) Range 1–4 GM MIC 2.5 MIC_{50} 2

Susceptibility results are presented in this table if at least 10 isolates of any Mucorales pathogen were tested.
Data are reported as they appear in source documents.
MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; CLSI, Clinical and Laboratory Standards Institute; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; GM, geometric mean; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; ECV (%): calculated statistical epidemiological cutoff values in μg/ml (% of MIC above the ECV, or non-wild type).

Table 7. Risk factors for and outcomes of invasive fungal disease due to Mucorales.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Risk factors
Lee et al.[22]	2020	Retrospective cohort study	Single-center	January 2011–Aug 2018	South Korea	Tertiary	Adult patients with hematological diseases	27	21/26 (81%) of patients with mucormycosis had neutropenia (ANC < 500/mm^3) at diagnosis Mean duration of neutropenia: 14.6 days (SD 6.7)
Manesh et al.[21]	2019	Retrospective cohort study	Single-center	September 2005–September 2015	India	Tertiary	Patients with culture proven mucormycosis	184	DM was the most common predisposing factor: (65%, $n = 120$) DM was a risk factor for poor outcome: OR 2.3 (95% CI 1–6.2); $P = .07$
Pana et al.[31]	2016	Retrospective review of prospectively collected cases	Multi-center	2005–2014	15 countries (54 European and 9 non-European)	Not stated	Pediatric patients	63	On multivariate analysis, risk factors for mortality: hemopoietic stem cell transplant: OR 13.66 (95% CI 1.88–98.6) Antifungal therapy only OR 2.3 (9.5% CI 0.5–10.6) Disseminated disease OR 4.2 (95% CI 0.9–18.5)
Patel et al.[26]	2020	Prospective cohort study	Multi-center	January 1, 2016–September 30, 2017	India	Tertiary	Adults with proven mucormycosis	485	71%–85% of patients with mucormycosis had DM. 53% of patients with cutaneous mucormycosis experienced prior trauma. Risk factor for mortality: Presence of a co-morbid illness: Adjusted HR 1.52 (95% CI 1.15–2.02) $P = .06$
Prakash et al.[6]	2019	Prospective cohort study	Multi-center	January 2013–December 2015	India	Tertiary	Children and adults with mucormycosis	388	Independent risk factor for mortality: Corticosteroid therapy OR 2.33 (95% CI 0.925–5.46); $P = .073$ Gastrointestinal mucormycosis OR 18.70 (95% CI 2.38–147.32); $P = .005$ Pulmonary mucormycosis OR 3.03 (95% CI 1.236–7.447); $P = .15$

ANC, absolute neutrophil count; SD, standard deviation; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; HR, hazard ratio.

Table 8. Annual incidence, current global distribtion, and trends (2011–2021) in invasvie fungal disease due to Mucorales.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Number of patients	Incidence/prevalence and trend
Bonifaz et al.[32]	2021	Retrospective cohort study	Single-center	January 1985–December 2019	Mexico	Tertiary	Pediatric patients with mucormycosis	214	Annual incidence 2012: 0.28/10 000 patients/days 2013: 0.28/10 000 patients/days 2014: 0.32/10 000 patients/days 2015: 0.25/10 000 patients/days 2016: 0.32/10 000 patients/days 2017: 0.14/10 000 patients/days 2018: 0.28/10 000 patients/days 2019 0.4/10 000 patients/days
Dolatabadi et al.[33]	2018	Retrospective cohort study	Multi-center	2008–2014	Iran	Provincial	Adults and children (median age of 50)	208	2011: 35/208 (16.8%) 2012: 47/208 (22.6%) 2015: 50/208 (24.0%)
Kontoyiannis et al.[14]	2016	Retrospective cohort study	Multi-center	January 2005–June 2014	USA	Teaching and non-teaching hospital	Patients with mucormycosis-related hospitalizations. USA hospital-based database covering more than 560 participating hospitals and 104 million patients.	555	555 cases/47 131 360 population: 0.094–0.117/10 000 discharges during 2011–2014 No clear trend in prevalence across study time frame
Lee et al.[22]	2020	Retrospective cohort study	Single-center	January 2011–August 2018	South Korea	Tertiary	Adult patients with hematological diseases	27	2011: 3/26 (11.5%) 2012: 4/26 (15.4%) 2013: 2/26 (7.7%) 2014: 2/26 (7.7%) 2015: 3/26 (11.5%) 2016: 4/26 (15.4%) 2017: 4/26 (15.4%) To August 2018 4/26 (15.4%) 2–4 new mucormycosis cases/year out of 72–116 new IMD cases/year (1.7–5.5%)
Van den Nest et al.[15]	2021	Retrospective cohort study	Single-center	January 2009–August 2017	Austria	Tertiary	Children and adults with invasive or localized filamentous fungi	18	2/14 (14.3%) 2/13 (15.4%) No change (2013 vs. 2017)

USA, United States of America.

frame of 2011–2018 in small single-center studies conducted in both South Korea and Austria (Table 8).[15,22]

Discussion

This systematic review evaluated the epidemiology, susceptibility profile, and outcomes of IFD due to Mucorales. Overall, the data are limited, with most (95.8%) studies classified as having a high risk of bias. Despite this, it is clear that IFD due to Mucorales is critically important as they demonstrate a limited susceptibility to the currently available agents and are associated with high mortality rates.

Mortality rates were variable, but they were reported as very high in some studies.[15,20,23,24,34] Comparison between studies is challenging as different patient groups were examined using different metrics. Some studies described just mortality[33,35] and others reported overall mortality.[6,21,32] Further studies examined overall or all-cause mortality at particular time-points (e.g., 30-day, 90-day, 6-week, and 12-week).[15,22,24–26,34,36] In order to compare mortality rates in specific patient groups across different institutions or regions (e.g., LMICs vs. high-income countries [HICs]), and importantly, over time (for trends) the same metrics should be used. Recently, randomized trials have used 6-week and 12-week all-cause mortality. So, these two metrics should be adopted to report mortality in future studies.[37,38] Only one study reported on attributable mortality.[25] It is often difficult to determine the relative contributions of the IFD and other factors to mortality, but it is an important outcome to ascertain as it is indicative of disease burden. Attributable mortality is variously defined, ranging from investigators' opinions to more specific definitions such as death directly due to IFD, death due to another cause but had active IFD at the time of death, or death with a failure to respond to antifungal therapy (i.e., stable or progressive IFD at the time of death).[39,40] A consensus definition is required, which should then be applied across all future studies. Such a step will allow for the comparison of the burden of IFD due to Mucorales across different patient groups and regions (LMICs vs. HICs) over time and to determine the relative efficacy of different antifungal therapies.

The hallmarks of mucormycosis are angioinvasion, tissue necrosis, and rapid spread. Thus, early surgical debridement down to normal, well-perfused tissue is required, along with antifungal therapy, to optimize survival.[4,41] The need for extensive surgical debridement may result in significant facial disfigurement, exenteration, visual loss (in the setting of rhino-orbital-cerebral mucormycosis), limited exercise tolerance (due to lobectomy or pneumonectomy), and limb amputation. Such complications may lead to stigmatization, inability to work, and poverty, especially in LMICs. Thus, mucormycosis is a disease of public health importance.[42,43] Yet, no such data was available for reporting in this systematic review. While case reports/series exist,[44–46] to get an accurate assessment of the complications/sequelae of mucormycosis to determine its burden and economic impact, all future cohort studies should report on these parameters.

Variable isavuconazole MIC values across genera and species have been observed herein. *Mucor* spp. demonstrated higher isavuconazole MIC values than *Rhizopus* spp. (MIC_{90}: 32 and 2–8 mg/l).[27] The isavuconazole GM MIC values for *M. circinelloides* were lower than for *M. indicus* (5.1 vs. 16 μg/ml).[28] To date, routine susceptibility testing has not been recommended. However, as isavuconazole is now recommended as an alternative first-line treatment for mucormycosis, our data would indicate that susceptibility testing should be performed when isavuconazole is being considered as a first-line treatment.[47] Amphotericin B demonstrated low MIC values, justifying its ongoing use as the first-line treatment of mucormycosis.[47] Posaconazole also demonstrated low MIC values. The new formulations of posaconazole (modified-release tablets and intravenous) have been compared with amphotericin B alone or in combination in a matched-paired analysis of patients treated for invasive mucormycosis (MoveOn Study).[48] Higher favorable response rates to posaconazole were seen as compared with the combination of amphotericin B and posaconazole (4/5 [80%] vs. 5/18 [27.8%]).[48] While the MoveOn study has several limitations, including small numbers and treatment heterogeneity, and further data are required, it indicates that the new formulations of posaconazole are acceptable alternatives to amphotericin B as first-line therapy, especially in those with underlying renal failure.[47]

Espinel-Ingroff et al. have developed epidemiological cutoff values (ECV) for posaconazole, amphotericin B, and itraconazole for 10 Mucorales species.[49] The ECV vary according to antifungal agent and species but indicates whether a particular isolate is a wild-type or not and assist in guiding antifungal selection.[49,50] However, as they are not correlated to clinical outcome, the ECV provides no guarantee of a favorable response to the selected antifungal agent.[51] Lamoth et al. performed antifungal susceptibility testing on non-*Aspergillus* moulds isolated from 39 patients who had proven or probable IFD (19 with mucormycosis) and compared the MIC results with responses to therapy.[52,53] The lower the MIC value of the first-line drug, the greater the chance of successful treatment (86% when MIC $\leq$0.5 μg/ml vs. 20% when MIC >4 μg/ml).[52] Amphotericin B was used as first-line treatment in 10 patients (8 with mucormycosis), and the 6-week favorable response was significantly greater in those with a pathogen that had a MIC value $\leq$0.5 μg/ml compared with >0.5 μg/ml (83% vs. 0%; $P = .05$).[52] More broadly, we currently lack clinical break-points for Mucorales. These are critical to selecting appropriate antifungal therapy to improve outcomes, determining resistance mechanisms and rates, and evaluating new antifungal agents. To develop clinical breakpoints, it is critical that mycologists collaborate at a global level and test all Mucorales isolates, and systematically collect the associated clinical data for correlation.

Specific risk factors include prolonged neutropenia, poorly-controlled diabetes mellitus, high-dose corticosteroid therapy, allogeneic HSCT, iron overload, deferoxamine therapy, major trauma, and prior voriconazole and/or caspofungin use.[6,21,22,24–26,31,54] Diabetes mellitus and ketoacidosis are particular risk factors for rhino-orbital-cerebral disease. Mucormycosis related to diabetes mellitus is more common in Asia, particularly India, as compared with Western countries (46% vs. 36%).[55] The risk factors identified herein, along with suggestive clinical features, should prompt an early and aggressive diagnostic approach.[47]

Break-through infections in patients on voriconazole have been described.[56–60] Previous use of voriconazole, caspofungin, or both in solid-organ transplant (SOT) recipients was significantly associated with break-through mucormycosis (OR 4.41; $P = .033$).[61] The emergence of mucormycosis on voriconazole may be coincidental, as it occurred around the same time as high-risk immunosuppressed populations

expanded. Voriconazole has no activity against Mucorales; widespread use in expanding high-risk populations may have accelerated the increasing incidence.[62] Of note, mucormycosis has occurred in patients on posaconazole or isavuconazole.[63,64] These antifungal agents have activity against Mucorales. Others have demonstrated that the virulence of Mucorales increases after voriconazole exposure.[65] Comparison over time and between studies is difficult as different metrics were used and a denominator was not always included. Similar to mortality, a standard metric that includes a well-defined denominator needs to be used to determine the actual influence of any risk factor over time.

There are conflicting data on the trends in the prevalence of mucormycosis. From 2011 to 2021, the trends in the USA, South Korea, and Austria were stable, but in Iran, the rates increased from 16.8% in 2011 to 24% in 2015.[14,15,22,33] Bitar et al. showed that the incidence increased from 0.7/million in 1997 to 1.2/million in 2006 ($P < .001$) in France, whereas a more contemporary surveillance study, also from France, showed stable rates between 2012 and 2018.[66,67] Going forward, global surveillance studies need to incorporate accurate assessments of prevalence so we can confidently determine the actual trends over time and across regions. Such data will better guide the development and implementation of interventions to minimize the burden of mucormycosis.

After we performed this systematic review, an increasing number of mucormycosis cases were reported in India during the second wave of COVID-19 infections. By June 7, 2021, around 28 252 cases of mucormycosis had been recorded by the Indian Health Ministry.[68] Since then, cases have been reported in South America, Mexico, the USA, the UK, Iran, and parts of Europe.[69–75] Thus, it has become a global threat. Several factors led to the emergence of COVID-associated mucormycosis (CAM), including uncontrolled diabetes mellitus, other underlying co-morbidities, poor glycemic control, uncontrolled use of high-dose corticosteroids, and pre-existing respiratory diseases.[69,76,77] COVID-19 itself, which caused (in some cases) a cytokine storm requiring treatment with immunosuppressants (e.g., dexamethasone, tocilizumab) and decreased T-helper cell numbers and potentially function, is also likely to have contributed.[78–80] Prolonged hospital stays, mechanical ventilation, pulmonary endothelial damage, the use of non-sterile industrial oxygen, and the re-use of oxygen masks may also have contributed.[74,81–84] Rhino-orbital mucormycosis was the most common clinical manifestation of CAM, and the mean time interval between COVID-19 and ROM diagnosis was 14.4 ± 4.3 days.[85] Most patients required radical debridement of the sinuses, resulting in significant facial disfigurement.[68,86,87] Mortality was high, up to 100% in non-prevalent countries, due to delays in recognition and diagnosis and the limited resources available during the COVID-19 pandemic.[88–90] Indeed, CAM has highlighted the current lack of knowledge about mucormycosis (in general). This has hampered early diagnosis and treatment, contributing to poorer outcomes. High-quality basic science, surveillance, and clinical epidemiological studies are urgently required, as is the development of novel diagnostic tests and antifungal agents for treatment.

One of the limitations of the present systematic review was the difference in the patient populations studied. Some studies examined very specific patient populations (e.g., burn patients). This heterogeneity makes it difficult to extrapolate specific findings more generally. Thus, it may be difficult to draw any firm conclusions regarding any of the specific criteria. Other limitations include the study time frame (2011–2021). This may have resulted in a failure to include all relevant and important studies, which may have affected the findings. The exclusion of conference abstracts and studies that were not in English may have also biased the findings.

Conclusion

Mucorales are significant fungal pathogens associated with high mortality, innate resistance to voriconazole, and variable susceptibility to the remaining mould-active triazoles. Carefully designed global surveillance studies, linking laboratory and clinical data, are required to evaluate morbidity outcomes and generate more consistent data on incidence and prevalence rates in various regions to better understand the distribution of and trends for Mucorales.

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Author contributions

Catherine Orla Morrissey (Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing), Hannah Yejin Kim (Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing), Katherine Garnham (Data curation, Formal analysis, Writing – review & editing), Aiken Dao (Data curation, Formal analysis, Writing – review & editing), Arunaloke Chakrabarti (Conceptualization, Formal analysis, Writing – review & editing), John R. Perfect (Conceptualization, Formal analysis, Writing – review & editing), Ana Alastruey-Izquierdo (Conceptualization, Formal analysis, Writing – review & editing), Thomas S. Harrison (Conceptualization, Formal analysis, Writing – review & editing), Felix Bongomin (Formal analysis, Writing – review & editing), Marcelo Galas (Formal analysis, Writing – review & editing), Siswanto Siswanto (Formal analysis, Writing – review & editing), Daniel Argaw Dagne (Formal analysis, Writing – review & editing), Felipe Roitberg (Formal analysis, Writing – review & editing), Valeria Gigante (Formal analysis, Project administration, Writing – review & editing), Hatim Sati (Conceptualization, Formal analysis, Methodology, Writing – review & editing), Jan-Willem Alffenaar (Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & edit-

ing), and Justin Beardsley (Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing).

Supplementary material

Supplementary material is available at *Medical Mycology* online.

Declaration of interest

This manuscript has been prepared in a personal capacity by the authors and reflects their views. The views expressed must not be attributed to the WHO, its Secretariat or its member states. Ana Alastruey-Izquierdo has given educational talks on behalf of Gilead Sciences and Pfizer. The other authors have no conflicts of interest to declare.

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