REVIEW ARTICLE

Mucormycosis

Dimitrios P. Kontoyiannis, M.D., Sc.D.,[1] and Thomas J. Walsh, M.D.[2-4]

SUMMARY

Mucormycosis is a rapidly progressive, invasive fungal infection that affects patients who are severely immunocompromised, as well as patients with diabetes and persons with immunocompetence who have major trauma. Mucormycosis manifests in several clinical forms, including sino-orbital, rhinocerebral, sinopulmonary, gastrointestinal, cutaneous, musculoskeletal, osteoarticular, and disseminated mucormycosis, as well as single-organ disease. Although mucormycosis is often lethal, early intervention reduces mortality. Successful treatment depends on early detection and staging of the disease, timely initiation of antifungal therapy, surgical resection of infected tissue, reversal of immunodeficiencies, and correction of metabolic abnormalities. Liposomal amphotericin B is the preferred agent for initial antifungal therapy, with oral triazoles as alternative agents. Research on rapid molecular diagnostic strategies, new antifungal agents, host-directed immune augmentation, antivirulence immune therapeutics, and risk-based stratification to inform management of disease may substantially improve outcomes in patients with this highly destructive mycosis.

Author affiliations are listed at the end of the article. Dimitrios P. Kontoyiannis can be contacted at dkontoyi@mdanderson.org or at the Division of Internal Medicine, Department of Infectious Diseases, Infection Control, and Employee Health, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1460, Houston, TX 77030. Thomas J. Walsh can be contacted at tjwalsh@citdx.org.

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CME

Mucormycosis (formerly known as zygomycosis)[1] is a rapidly progressive and frequently lethal invasive fungal disease of the lungs, sinuses, orbits, and brain in immunocompromised hosts, including patients with hematologic cancers, a history of transplantation, or diabetes.[2] Among patients with immunocompetence, mucormycosis is increasingly recognized as a cause of serious necrotizing infections of traumatic wounds.[3] Recently discovered risk factors include coronavirus disease 2019 (Covid-19), chimeric antigen receptor T-cell therapy, and use of ibrutinib.[4-7] Mucormycosis manifests in several well-described clinical forms, including sino-orbital, rhinocerebral, sinopulmonary, gastrointestinal, cutaneous, musculoskeletal, osteoarticular, and disseminated mucormycosis, as well as single-organ disease.[2] The World Health Organization has designated the mucorales as high-priority pathogens, a reflection of the increasing global importance of mucormycosis.[8] Essential for successful management of mucormycosis is a multidisciplinary clinical team that consists of infectious-disease physicians, internists, pediatricians, surgeons, intensivists, hematologists, transplantation specialists, ophthalmologists, clinical microbiologists, anatomical pathologists, and diagnostic and interventional radiologists.

Among the invasive mycoses, mucormycosis is widely considered to be the most rapidly invasive and destructive. Members of the order Mucorales have angioinvasive characteristics ó related to secreted proteases, a ricinlike toxin, and affinity for endothelial cells ó that result in tissue infarction.[9,10] India has been recognized as an area of hyperendemicity for mucormycosis, and this status is thought to be attributable in part to a combination of geoclimatic factors and a high prevalence of

diabetes. The estimated disease burden in India is approximately 70 times higher than the global average, with more than 200,000 cases per year predicted in India.[11] As climate change contributes to greater frequency and severity of some natural disasters, an increase in cases of mucormycosis may occur.[12]

MYCOLOGIC FEATURES

The term mucormycosis encompasses a severe, often fatal constellation of invasive fungal diseases, first described in 1885 as mycosis mucorina, which are caused by members of the order Mucorales within the subphylum Mucormycotina.[1] Mucormycosis was previously known as zygomycosis because the causative agents belonged to the phylum Zygomycota (class Zygomycetes). However, after advances in molecular phylogenetics showed that Zygomycota was polyphyletic, the classification was revised, with the updated taxa including the class Mucormycetes and the medically important order Mucorales. As a consequence, the term zygomycosis was replaced by mucormycosis. The most commonly encountered and medically important genera are rhizopus, mucor, lichtheimia, cunninghamella, apophysomyces, and saksenaea. Several studies have shown *Cunninghamella bertholletiae* to have greater virulence than other mucormycetes and to be associated with higher mortality.[13,14]

Mucorales species are found ubiquitously in soil and decaying organic matter. The environmental form of mucorales species when they are growing in nature consists of a mycelium (a mat of hyphae) that produces sporangiospores 3 to 11 μm in diameter. These sporangiospores are inhaled into the respiratory tract, in which pulmonary alveolar macrophages (a component of innate host defenses) are efficient at eliminating them by phagocytosis.

However, in patients who are severely immunocompromised, some sporangiospores are not cleared and instead adhere to and invade respiratory epithelial cells by means of CotH surface proteins.[15] The hyphal forms that emerge from germinated sporangiospores are broad, ribbonlike, angioinvasive structures that cross tissue planes, which results in ischemia, necrosis, and hematogenous dissemination.

Mucorales species have been identified historically by phenotypic methods that assess the arrangement of sporangia, sporangiophores, and rhizoids (if present), as well as the characteristics of the sporangiospores. Broad, nonseptate (coenocytic) or sparsely septate (pauciseptate) hyphae in tissue with angioinvasion are also characteristic of mucormycosis. However, misidentification of mucormycosis on the basis of histopathological features alone may occur. In situ molecular probes, direct sequencing, and immunohistochemical and metagenomic analyses are molecular diagnostic tools that can identify mucorales species.[16]

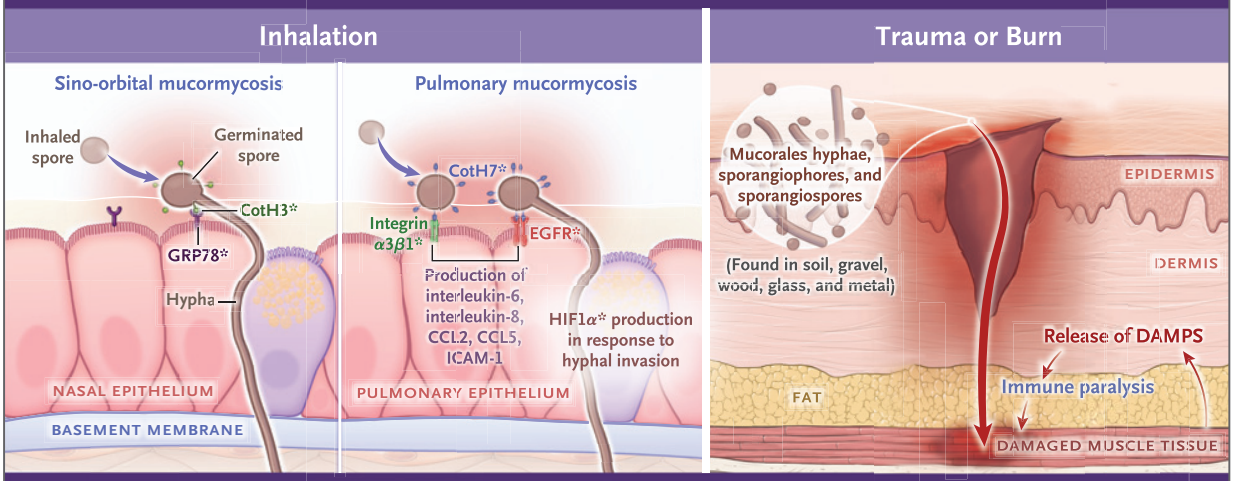
HOST DEFENSES AND PATHOGENESIS

The complex and robust innate immune response to the sporangiospores of mucorales species prevents development of mucormycosis in persons with immunocompetence.[17] The mucociliary clearance mechanisms of pseudostratified columnar respiratory epithelial cells are mechanical barriers that remove sporangiospores. Invasion of alveolar epithelial cells by mucorales fungi induces transcriptional activation of epithelial proinflammatory cytokines, chemokines, and adhesion molecules (Fig. 1A). Pulmonary alveolar macrophages provide another line of innate host defenses by means of phagocytosis and destruction of sporangiospores in phagolysosomes. Intracellular swelling of sporangiospores (a critical step in pathogenesis) is further inhibited by iron deprivation.[18]

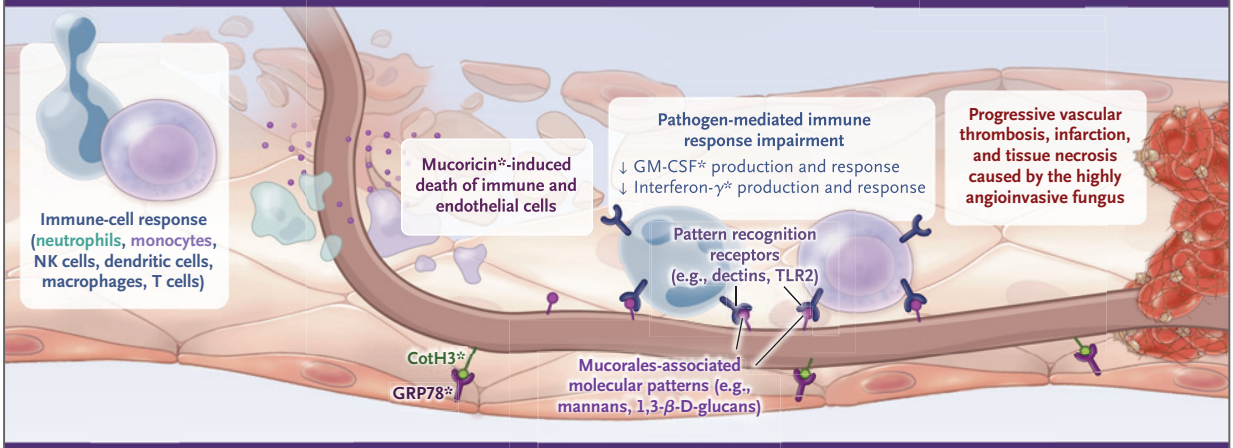
Neutrophils are the first-line innate host defense against mucorales hyphae (Fig. 1B) through reactive oxygen species and nonoxidative mechanisms, including actions of cationic antimicrobial peptides.[19] Recognition of hyphae by pattern recognition receptors such as toll-like receptor 2 activates neutrophils and induces the release of proinflammatory cytokines. Interferon-γ, granulocyteñmacrophage colony-stimulating factor (GM-CSF), tumor necrosis factor α, and interleukin-8 further augment neutrophil function in response to hyphae.

In patients who are immunocompromised, mucormycosis develops as the result of quantitative or qualitative defects in phagocytic activity caused by neutropenia and functional defects in macrophages, neutrophils, and lymphocytes, including natural killer cells. Glucocorticoids impair

A Modes of Mucorales Infection



B Endovascular Pathogenesis



C Factors in the Tissue Microenvironment That Promote Mucorales Invasion

High glucose levels and low pH levels (diabetic acidosis, treatment of Covid-19 with glucocorticoids, other metabolic disorders with acidemia)	Increased CotH3* expression on mucorales spores Increased GRP78* expression on host endothelial cells Increased available free iron* Increased growth of mucorales
Immunometabolic factors (low serum albumin or malnutrition)	Increased unbound oxidized fatty acids Decreased serum antifungal activity Increased mucoricin* and adhesin expression by mucorales
Neutropenia, monocytopenia, or use of glucocorticoids	Impaired phagocytosis of mucorales and subsequent dissemination of pathogen Functional impairment of neutrophils, macrophages, and monocytes Cytokine deficiencies (GM-CSF*, interferon-γ*) Immune-cell exhaustion mediated by checkpoint molecules such as PD-1* and PDL-1*
Iron-overload conditions	Increased available free iron* Increased growth of mucorales
Severe trauma or burns	Release of DAMPs Immune paralysis Proteolysis of immune receptors — Impaired chemotaxis Defective regulation of lysosomal pH — Decreased Th17 cells

Figure 1 (facing page). Pathogenesis of Mucormycosis, Host Defenses, and Potential Future Therapeutic Targets.

Mucorales sporangiospores released into the air from sporangia are inhaled, and the sporangiospore coat protein CotH3 binds to glucose-regulated protein 78 (GRP78) on the pseudostratified columnar epithelial cells of the upper respiratory tract, where the sporangiospores may germinate into hyphae to invade nasal airways and sinuses (Panel A). Sporangiospores, by means of another coat adhesin (CotH7), also bind to epidermal growth factor receptor (EGFR) and integrin $\alpha 3\beta 1$ receptor on pulmonary alveolar epithelial cells of the lower respiratory tract, which triggers a downstream transcriptional response involving cytokines (interleukin-6 and interleukin-8), chemokines (CCL2 and CCL5), and intercellular adhesion molecule 1 (ICAM-1). Hyphal invasion also triggers production of hypoxia-inducible factor 1α (HIF1α) and release of proinflammatory cytokines. In wound-related mucormycosis, traumatic inoculation of fungal elements (found on the surfaces of rocks, wood, glass, and metal) into damaged tissue allows for the development of infection in a host with immune paralysis due to trauma. The release of endogenous host-derived molecules known as damage-associated molecular patterns (DAMPs) reduces phagocytosis, impairs chemotaxis, and induces immune paralysis. Mucoricin released by the invading hyphae induces death of immune and endothelial cells, which results in tissue necrosis and accelerates endovascular thrombosis, ischemia, and infarction (Panel B). Polymorphonuclear neutrophils and monocytes recognize early germinated sporangiospores by means of pattern recognition receptors (e.g., toll-like receptor 2 [TLR2]) that detect mucorales-associated molecular patterns (e.g., 1,3-β-D-glucans exposed on hyphal structures). Intrinsic host colony-stimulating factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) and interferon-γ further contribute to augmentation of innate host defenses against the invading hyphae, which in turn dampen immune responses. Factors in the tissue microenvironment that increase susceptibility to mucorales invasion are listed with the predominant mechanisms associated (Panel C). Asterisks indicate potential future therapeutic targets. Covid-19 denotes coronavirus disease 2019, NK natural killer, PD-1 programmed cell death protein 1, PD-L1 programmed death ligand 1, Th1 type 1 helper T, Th2 type 2 helper T, and Th17 type 17 helper T.

both neutrophil and macrophage host responses against mucorales species. Hyperglycemia and metabolic acidosis in patients with diabetes permit proliferation of hyphae and impair phagocytic oxidative and nonoxidative host responses. Hypoalbuminemia also contributes to progression of mucormycosis; free fatty acids bound to albumin restrict mucorales growth, but hypoalbuminemia allows oxidation of unbound free fatty acids and increases the expression of mucorales virulence genes.[20]

Angioinvasion, thrombosis, and tissue infarction are pathophysiological and clinical hallmarks of mucormycosis. The CotH spore coat proteins of rhizopus differentially bind to host receptors glucose-regulated protein 78 (GRP78) on nasal epithelial cells and integrin $\alpha 3\beta 1$ on alveolar epithelial cells.[19,21] The CotH3 protein of invading hyphae binds to the endothelial receptor GRP78, a process that allows for angioinvasion and thrombosis. Mucoricin, a 17-kD ricin-like toxin, also contributes to cellular injury and tissue necrosis.[10] CotH3 and GRP78 are up-regulated by metabolic acidosis as a pivotal event in the angioinvasive pathogenesis of rhinocerebral mucormycosis (Fig. 1A). In children with inherited disorders of metabolism, such as methylmalonic aciduria, metabolic acidosis alone is sufficient to induce mucormycosis. Metabolic acidosis in patients with poorly controlled type 1 diabetes may be the basis for a higher risk of mucormycosis among patients with type 1 diabetes than among those with type 2 diabetes. Glycemic and acidemic control in patients with diabetes reduces the risk of mucormycosis.

Iron metabolism also has a key role in the pathogenesis of mucormycosis and in host defenses in patients with diabetes.[18,19] Mucorales species are dependent on the acquisition of free ionic iron from infected hosts. Metabolic acidosis decreases the affinity of transferrin and ferritin for iron, which results in the availability of more free iron. Increased glycosylation of transferrin and ferritin that results from poorly controlled diabetes also increases the availability of free iron. The effect of excess available iron was observed in patients with disseminated mucormycosis who received deferoxamine for hemochromatosis and other iron-overload conditions.[19]

In patients with blast injuries, burns, and other major trauma who were previously healthy, mucormycosis may develop in the context of immune paralysis (Fig. 1A). Investigation of the mechanisms of immune paralysis in such patients showed that functional neutropenia occurs when mediators released from the damaged tissue create a tissue microenvironment that causes local neutrophil dysfunction and immune dysregulation (Fig. 1C).[3,22]

Table 1. Risk Factors for Mucormycosis and Clinical Manifestations of Disease.*

Clinical Form	Common Risk Factors	Symptoms	Clinical Features and Findings on Diagnostic Imaging	Comments
Sino-orbital[26,27]	Diabetes Hematologic cancers Hematopoietic-cell transplantation Solid-organ transplantation Severe aplastic anemia Covid-19 Prolonged use of high-dose glucocorticoids	Congestion Localized sinus pain Odontogenic pain in cases of maxillary-sinus infection Nasal discharge Headache	Infection of nasal turbinates: ulcerations, eschars Maxillary-sinus infection: palatal ischemia or necrosis and involvement of the molars and premolars Ethmoid-sinus infection: hyposmia or anosmia; extension through the lamina papyracea bone into the orbit with entrapment of the medial rectus muscle and other extraocular muscles and progression to orbital apex syndrome	Sphenoidal mucormycosis may manifest with referred pain in the vertex of the skull. Sino-orbital mucormycosis is a medical and surgical emergency. Early examination and reexamination with imaging and otolaryngologic evaluation are important.
Rhinocerebral[26,27]	Diabetes Hematologic cancers Hematopoietic-cell transplantation Solid-organ transplantation Severe aplastic anemia Covid-19 Prolonged use of high-dose glucocorticoids	Diplopia related to cranial nerve deficits Seizures	Focal neurologic deficits Extension from ethmoid sinuses and frontal sinuses into veins draining into the cavernous sinus, with damage to cranial nerves III, IV, V1, V2, and VI and the internal carotid artery	Frontal sinus mucormycosis may be complicated by direct extension into frontal lobes, which is indicated by meningeal enhancement of tissue invasion. Rhinocerebral mucormycosis is a medical and surgical emergency. Early examination and reexamination with imaging and otolaryngologic evaluation are important.
Sinopulmonary[28-31]	Hematopoietic-cell transplantation Solid-organ transplantation Severe aplastic anemia Covid-19 Prolonged use of high-dose glucocorticoids	Cough Dyspnea Pleuritic pain	Persistent fever refractory to empirical antibacterial therapy Hemoptysis Multiple pulmonary nodules with the halo sign or reversed halo sign on CT scan Intrathoracic extension of disease into the pleura, ribs, diaphragm, mediastinum, and pericardium	Angioinvasive properties lead to necrotizing pneumonia with pulmonary infarction and hemorrhage. Tracheobronchitis, bronchial obstruction, severe or fatal hemoptysis, and cavitary fungus ball are rare manifestations. The presence of a reversed halo sign is more highly suggestive of pulmonary mucormycosis than the conventional halo sign, which is associated with pulmonary aspergillosis and infection with other angioinvasive molds in patients with hematologic cancer.
Cutaneous and musculoskeletal[3,32-34]	Trauma Burns Blast injuries Severe natural disasters (e.g., tornadoes, tsunamis, floods, earthquakes) Premature birth Immunosuppression	Local pain at the site of injury	Cutaneous ulcerations Brown-black eschars with firm, woody consistency and deep necrotizing extension into fascia, tendon, and muscle	This form occurs in infants who are born prematurely and exposed to contaminated bed linens; it also occurs in patients who are immunocompromised, especially during neutropenia, as the result of cutaneous inoculation from soil or plant sources. CT scans, MRI, and surgical exploration typically show that the degree of subcutaneous infection is much deeper and more extensive than what can be detected on physical examination. The differential diagnosis includes cutaneous aspergillosis, fusariosis, and ecthyma gangrenosum caused by *Pseudomonas aeruginosa* and other gram-negative bacilli.

Osteoarticular[33]	Severe trauma Blast injuries Intravenous drug use Immunosuppression	Local pain at the site of injury Tenderness Erythema Limited range of motion	Tenderness with overlying cellulitis Lytic bone destruction at the site of direct or hematogenous inoculation	Infection of bone and joints may occur as a result of direct traumatic inoculation after severe trauma, blast injuries, or intravenous drug use. Osteoarticular mucormycosis also occurs in patients who are immunocompromised by means of direct extension from infected foci or hematogenous dissemination. In view of the broad differential diagnosis, which includes cancer and several other infectious entities, bone biopsy and cultures are indicated.
Gastrointestinal[35-37]	Premature birth Severe malnutrition Immunosuppression Pica	Abdominal pain Nausea Vomiting Hematemesis Abdominal tenderness Hematochezia Melena Abdominal distension	Gastrointestinal hemorrhage, obstruction, perforation, or infarction Intraabdominal dissemination	Gastrointestinal mucormycosis should be distinguished from gastrointestinal basidiobolomycosis. Patients who are immunocompromised may become infected after ingesting contaminated food or herbal medicinal products containing mucorales species. This form is commonly diagnosed post mortem.
Disseminated[38]	Hematologic cancers Hematopoietic-cell transplantation Solid-organ transplantation Severe aplastic anemia Endocarditis (may be associated with illicit drug use)	Focal seizures	Focal neurologic deficits arising from involvement of the central nervous system	Involvement of the central nervous system is common. Other affected sites (alone or in combination with other organs) may include the lungs, spleen, kidneys, and thyroid. Dissemination most commonly arises from the lung but may also arise from a cutaneous lesion.
Early manifestations	High pretest probability that mucormycosis will develop	Diplopia	Periorbital cellulitis Focal palatal necrosis Necrotic wounds (consistent with angioinvasion)	These early sentinel clinical manifestations call for urgent assessment.

* CT denotes computed tomography.
Sino-orbital mucormycosis and rhinocerebral mucormycosis are the most common manifestations in patients with diabetes, especially those with type 1 diabetes or poorly controlled diabetes with ketoacidosis.
Sino-orbital mucormycosis and rhinocerebral mucormycosis are the most common manifestations of coronavirus disease 2019 (Covid-19) associated mucormycosis.
In addition to the lungs, any single organ may also be infected through either cryptic hematogenous dissemination or traumatic inoculation.
Basidiobolomycosis is an indolent, chronic granulomatous fungal disease that causes constriction and obstruction of the intestinal tract; treatment, which is usually triazole-based, has been successful with itraconazole.

EPIDEMIOLOGIC FEATURES AND RISK FACTORS

Because mucormycosis is not a reportable disease, the exact incidence or prevalence is unknown. An older population-based study of mucormycosis in San Francisco showed an estimated incidence of 1.7 cases per 1 million population.[23] However, other studies have shown regional differences and an increase in the incidence over time.[5,11,24] Moreover, retrospective data from January 2005 through June 2014 show a substantial clinical and economic burden from mucormycosis-related hospitalizations in the United States, with a prevalence of 0.12 per 10,000 discharges, high costs (an average of $112,419 per stay), long stays (median, 17 days), and high in-hospital mortality (23%).[24] Important risk factors for mucormycosis include diabetes, hematologic cancers, allogeneic hematopoietic-cell transplantation, severe graft-versus-host disease, solid-organ transplantation, prolonged use of high-dose glucocorticoids, low birth weight, metabolic acidosis, iron-overload states, injection-drug use, and severe malnutrition (Table 1).[2,25-42]

Several reports from India indicated an increase in the incidence of Covid-19ñassociated mucormycosis in late 2020 and early 2021, and the incidence reached a peak of more than 51,000 cases in 2021.[4,5] Covid-19ñassociated mucormycosis typically manifests as sino-orbital and rhinocerebral disease in patients with poorly controlled diabetes with hyperglycemia, ketoacidosis, and an elevated glycated hemoglobin level. Covid-19ñ associated mucormycosis may reflect the deleterious convergence of critical host and environmental factors, including poorly controlled diabetes, use of glucocorticoids to control the pulmonary inflammatory response to severe acute respiratory syndrome coronavirus 2, and possibly Covid-19ñ induced dysimmunoregulation.[42]

Nosocomial and home environmental sources of mucorales species also increase the risk of mucormycosis.[34,43] Contaminated air-handling systems, arm boards used with intravenous tubing, plants, and hospital construction have been implicated as sources of nosocomial mucormycosis, as have bed linens contaminated with sporangiospores.[34] Linens have also been considered to be the source of cutaneous mucormycosis in low-birth-weight infants in neonatal intensive care units.

In patients who are immunocompromised, gastrointestinal mucormycosis develops after ingestion of sporangiospores in herbal remedies, homeopathic medicines, food, and substances consumed in the context of pica.[35,36] Gastrointestinal mucormycosis also occurs in low-birth-weight infants[37] and is associated with high mortality ó close to 100% ó in this population as a result of gastrointestinal perforation and intraabdominal dissemination.

The profile of infection differs between neonates and older children.[37] Whereas older children with persistent neutropenia, a history of transplantation, rare metabolic disorders, or type 1 diabetes are at risk for sino-orbital, rhinocerebral, and pulmonary mucormycosis, infants have a significantly greater risk of cutaneous or gastrointestinal mucormycosis than older children, and mortality associated with mucormycosis is significantly higher among infants.

CLINICAL MANIFESTATIONS

The clinical manifestations of mucormycosis include sino-orbital, rhinocerebral, sinopulmonary, cutaneous, musculoskeletal, gastrointestinal, osteoarticular, disseminated, and single-organ disease and are driven by angioinvasive and infarctive properties (Table 1).[26-42] The various forms of mucormycosis appear to have a predilection for hosts with specific characteristics. Sino-orbital and rhinocerebral disease are the most common manifestations in patients with diabetes, whereas sinopulmonary and disseminated mucormycosis are more common in patients with severe immunosuppression. In addition, some mucorales species have a predilection toward specific clinical manifestations; for example, *Apophysomyces elegans* and *Saksenaea vasiformis* are common causes of mucormycosis in the context of combat-wound and storm-associated cutaneous and musculoskeletal trauma.[3,12,13,32,33]

DIAGNOSIS

Early diagnosis and initiation of antifungal therapy significantly reduce mortality among patients with mucormycosis and hematologic cancers,

from approximately 80% to 40%.[44] Accurate diagnosis of mucormycosis begins at the bedside with evaluation of symptoms and signs in patients at high risk (Table 1 and Fig. 2). Although early symptoms and physical findings in patients with mucormycosis are often nonspecific, they carry important diagnostic significance in patient populations with high risk.[26-33,38]

Periorbital cellulitis, diplopia, focal palatal necrosis, and necrotic wounds in patients at high risk should cause serious concern for mucormycosis and lead to prompt assessment (Fig. 2). Maintaining a high index of suspicion for mucormycosis in such patients can be the impetus for obtaining fluids and tissues for diagnostic analysis, ordering imaging procedures, initiating antifungal therapy, requesting surgical assessment, reversing immunodeficiencies, and correcting metabolic abnormalities.

The staging of mucormycosis, which has critical implications for treatment and outcomes, depends on a comprehensive examination, diagnostic imaging, and laboratory-confirmed diagnosis (Table 2). For suspected sino-orbital disease, staging includes diagnostic imaging (computed tomography [CT]) of the paranasal sinuses and chest, as well as endoscopic examination of nasal turbinates with brush biopsy of ulcerations and necrotic eschars (Table 1). In sino-orbital or sinus mucormycosis, CT and magnetic resonance imaging (MRI) scans of the sinuses or head may be unremarkable during early phases of disease, which underscores the need for close monitoring by physical examination, repeat imaging, and follow-up endoscopy.[26,27] For patients in whom pulmonary lesions are suspected, bronchoalveolar lavage, preferably with biopsy, should be per-

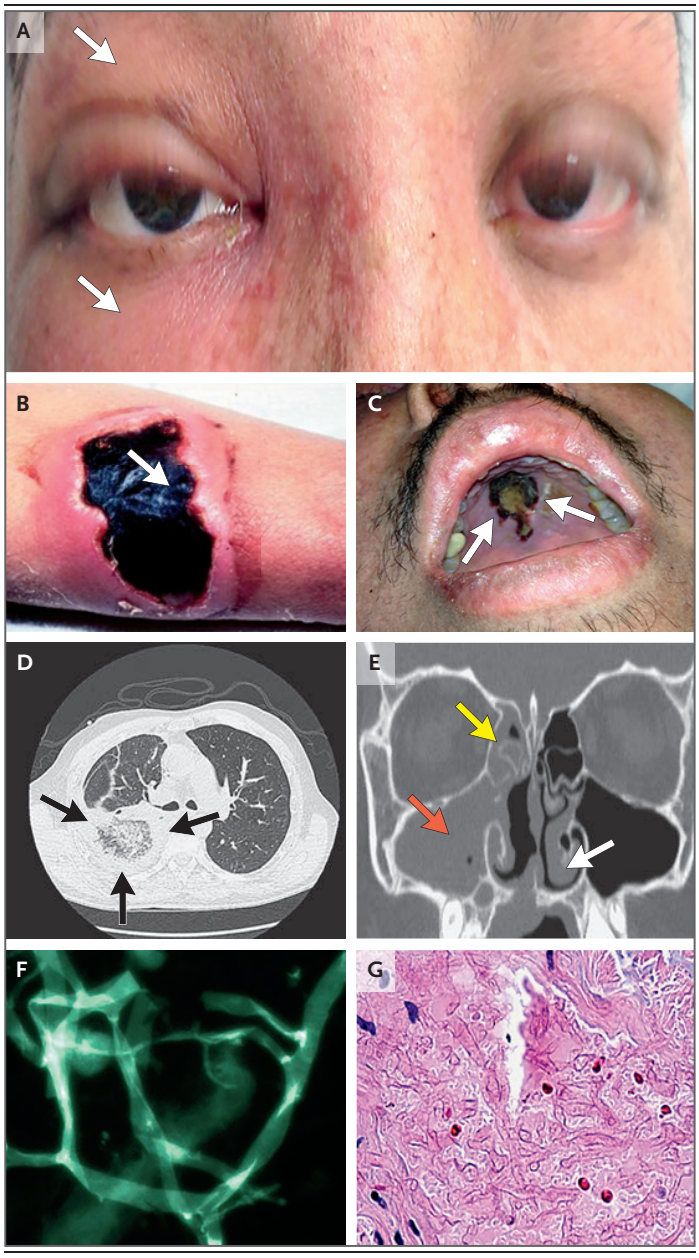


Figure 2. Direct Examination and CT Imaging in Mucormycosis.

Sino-orbital mucormycosis is associated with right periorbital cellulitis (Panel A, arrows) and ophthalmoplegia. Cutaneous mucormycosis is characterized by blackened, raised eschars (Panel B, arrow). Lesions due to palatal mucormycosis are shown (Panel C, arrows). In pulmonary mucormycosis, a large reversed halo sign (Panel D, arrows) in the right lower lobe is characterized by a pulmonary infiltrate with a central ground-glass opacity that is circumscribed by denser air-space opacities. (Photo used with permission from Dr. Genovefa Papanicolaou.) Examples of imaging results in mucormycosis of the right maxillary sinus (Panel E, red arrow), right ethmoid sinus (yellow arrow), and left nasal turbinates (white arrow) are shown. Direct examination of sinus aspirate under fluorescence microscopy with calcofluor staining shows broad, ribbonlike hyphae with nondichotomous right-angled branching typical of rhizopus (Panel F). Histopathological analysis of infected tissue with periodic acid Schiff staining also shows broad, ribbonlike hyphae with nondichotomous right-angled branching (Panel G).

Table 2. Laboratory Tools for Diagnosis of Mucormycosis.*

Laboratory Method	Description
Direct examination[45,46]	On direct microscopic examination of a wet mount with potassium hydroxide or fluorescence staining, such as calcofluor or Blankophor, mucorales species typically have ribbonlike, nonseptated (coenocytic) or sparsely septated hyphae that are broad (7 to 15 μm in diameter) with nondichotomous branching. These features help narrow the differential diagnosis by ruling out infection with other pathogenic molds, including *Aspergillus* spp., *Fusarium* spp., and *Scedosporium* spp., which typically appear as slender, dichotomously branching, septated hyphae.
Culture[45-47]	Mucorales species typically grow rapidly to fill the petri dish as a floccose colony on Sabouraud s glucose agar at 25 to 37 C. Recovery of organisms may be enhanced by culturing at 37 C. *Lichtheimia corymbifera* (formerly known as *Absidia corymbifera*) and the most frequently encountered *Rhizopus* spp. and *Mucor* spp. have microscopically distinctive patterns of sporangiophores, sporangia, sporangiospores, and rhizoids (if present). *Cunninghamella* spp. have characteristic denticles and sporangiola instead of sporangiospores.
Antifungal susceptibility testing[48]	Because there are currently no established interpretive breakpoints by which to assess susceptibility, the value of minimum inhibitory concentrations in the management of mucormycosis is limited. Data from in vitro, preclinical animal models and clinical correlation indicate that echinocandins, flucytosine, fluconazole, itraconazole, and voriconazole are not active against mucorales species. Amphotericin B, isavuconazole, and posaconazole are active against the medically important mucorales species in vivo and clinically.
Histopathological analysis[49-51]	Detection of the characteristic ribbonlike, nonseptated or sparsely septate hyphae of the mucorales species in tissue samples with periodic acid Schiff and Grocott Gomori methenamine silver stains unequivocally establishes a diagnosis of mucormycosis in the corresponding site. Delays in time to detection may result from formalin fixation, paraffin embedding, sectioning, and staining. Immunohistochemical techniques and fluorescence in situ hybridization further establish a microbiologic diagnosis.
MALDI-TOF MS[52,53]	Recovery of an organism allows rapid molecular identification by MALDI-TOF MS. The informatics database of the MALDI-TOF MS instrument allows clinical laboratories to identify a wide range of medically important mucorales species.
Nucleic acid amplification testing[54-58]	Molecular detection of mucormycosis may be performed with whole blood or BAL fluid. Quantitive PCR assays with primer probe sets that target the 18S ribosomal RNA have been shown to have the ability to detect *Rhizopus arrhizus*, *Mucor circinelloides*, *L. corymbifera*, and *Cunninghamella bertholletiae* in BAL fluid, plasma, and serum. Nucleic acid amplification assays that are commercially available in Europe, as well as proprietary assays, detect circulating mucorales DNA from BAL fluid, serum, and whole blood. Analysis of cell-free DNA from plasma or serum with the use of a PCR assay offers a new strategy that improves analytical sensitivity over that obtained with traditional whole-blood extractions.
Metagenomic analysis[59,60]	The usefulness of metagenomic analysis of cell-free DNA for the diagnosis of mucormycosis is not well defined. In a recent prospective, multicenter, observational study that involved patients with suspected pneumonia who were immunocompromised and underwent bronchoscopy for evaluation of pneumonic infiltrates of unknown cause, the use of plasma microbial cell-free DNA sequencing significantly increased diagnostic yield as compared with standard-care testing. Among the six fungal pathogens detected only by metagenomic sequencing, two mucorales species were identified.

* BAL denotes bronchoalveolar lavage, MALDI-TOF MS matrix-assisted laser desorption ionization time-of-flight mass spectrometry, and PCR polymerase chain reaction.

formed when possible. For pleural lesions, a percutaneous needle aspirate may be diagnostic.

Definitive diagnosis of mucormycosis depends on direct examination of clinical specimens, culture of tissue or bronchoalveolar lavage fluid, and histopathological analysis (Table 2). Although availability is limited in many centers, matrix-assisted laser desorption ionizationñtime-of-flight mass spectrometry, nucleic acid amplification testing, and metagenomic analysis (Table 2) are emerging tools for the early diagnosis of mucormycosis.[45-60]

TREATMENT

The burden of infection, occurrence of dissemination, timeliness of diagnosis, and reversibility of underlying immunodeficiencies are important factors in outcomes and in the assessment of treatment strategies. Successful treatment of mu-

cormycosis depends on five pillars of intervention: early detection and staging of the disease, timely initiation of antifungal therapy, surgical resection of infected tissue, reversal of immunodeficiencies, and correction of metabolic abnormalities (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

ANTIFUNGAL THERAPY

Randomized, controlled trials involving patients with mucormycosis are lacking because of the rarity and tremendous heterogeneity of the disease.[61] Amphotericin B is the primary antifungal agent used for the treatment of mucormycosis.[61] Although prospective, randomized, clinical trials of amphotericin B as compared with placebo are also lacking, the cumulative body of data from animal models, case series, registries, and prospective single-group studies support the use of amphotericin B as primary treatment.[61-65]

LIPID FORMULATIONS OF AMPHOTERICIN B

Liposomal amphotericin B is preferred over amphotericin B deoxycholate because liposomal amphotericin B has less nephrotoxicity than amphotericin B deoxycholate. However, amphotericin B deoxycholate may be the only formulation of amphotericin B available in resource-limited environments. Preclinical and clinical studies of lipid formulations of amphotericin B as compared with amphotericin B deoxycholate have shown that the efficacy of lipid formulations is similar to that of amphotericin B deoxycholate but that lipid formulations have a more favorable safety profile for early treatment of invasive mycoses.[61,66] The most widely used range of doses of liposomal amphotericin B is 5.0 to 7.5 mg per kilogram of body weight per day.[44,61,64] These doses are higher than those typically used for initial treatment of invasive pulmonary aspergillosis (approximately 3 mg per kilogram per day), but they are consistent with doses shown to have efficacy in preclinical models and are compatible with the higher minimum inhibitory concentrations of amphotericin B for mucorales species than for aspergillus. High-dose liposomal amphotericin B (10 mg per kilogram per day) led to a higher risk of nephrotoxic effects than lower doses and was not associated with any apparent improvement in therapeutic outcome.[65] Despite the availability of liposomal amphotericin B, the risk of death from mucormycosis remains unacceptably high among patients with profound immunosuppression,[67] especially in the context of breakthrough infection during treatment with antifungal agents that have activity against mucorales species.[68]

ANTIFUNGAL TRIAZOLES

The only antifungal triazole licensed for primary treatment of mucormycosis is isavuconazole, on the basis of preclinical studies and a single-group, open-label, observational study (Isavuconazole in the Treatment of Renally Impaired Aspergillosis and Rare Fungi [VITAL]).[69] In that study, the responses were compared with those among matched controls from the FungiScope case registry who were treated with liposomal amphotericin B. Isavuconazole is an appropriate alternative to liposomal amphotericin B, especially for extended treatment and for the treatment of patients for whom amphotericin B is not an option because of dose-limiting nephrotoxicity.

In two studies that evaluated the use of posaconazole as salvage therapy, patients received a previous suspension formulation of posaconazole administered in divided doses that totalled 800 mg per day. Among a total of 24 patients with mucormycosis, overall success (defined as a complete or partial response) was 79%.[70] A retrospective study of posaconazole for treatment of refractory mucormycosis in 91 patients showed overall success of 61%.[71] Posaconazole is now administered principally as an extended-release tablet or an intravenous formulation.

COMBINATION THERAPY

Clinical data from studies of combination antifungal therapy are limited.[72,73] A retrospective study that used a propensity-score analysis to evaluate combination therapy for the treatment of mucormycosis in patients with hematologic cancers did not show clinical benefit.[73]

DURATION OF TREATMENT

The duration of treatment of mucormycosis should be individualized for each patient, according to the stage of the infection, response to antifungal therapy, surgical removal of infected tissue, recovery from immune impairment, and the treatment plan for the underlying disease. Therapeutic objectives that define clinical end points of

treatment include near normalization of diagnostic imaging, epithelialization of sinus tissue detected on endoscopic examination, and negative follow-up cultures and biopsies of the infected site, as well as recovery from immune impairment. Because relapse of mucormycosis may occur, particularly during periods of repeated cycles of immunosuppression, patients with hematologic cancers who have mucormycosis should receive further long-term secondary prophylaxis with a triazole active against mucorales species, along with careful monitoring if their fungal disease is assessed to be stable.

SURGICAL RESECTION

Surgery has an important role in selected cases. Effective management of mucormycosis calls for multidisciplinary surgical expertise, including that of general, otolaryngologic, ophthalmic, thoracic, orthopedic, and plastic surgeons, depending on the site of infection. Minimally invasive procedures are useful in some patients with limited forms of rhinosinusitis. Complete resection of myocutaneous lesions is indicated to prevent further local extension and hematogenous dissemination. For management of sino-orbital and craniofacial infection, an individual assessment of the extent of disease is indicated. A study in India involving 2826 patients with Covid-19 and sino-orbital-cerebral mucormycosis showed that surgical debridement was beneficial only in early stages of disease.[27] Use of intraoperative staging with specimens processed for fluorescence microscopy or surgical pathological analysis helps to accurately define surgical margins and prevent local recurrence.[74] Because of angioinvasive infarction and the lack of tissue bioavailability of systemic antifungal agents, advanced stages of pulmonary, sino-orbital, cerebral, and myocutaneous mucormycosis are largely surgically treated diseases.

ADJUNCTIVE THERAPEUTICS AND REVERSAL OF UNDERLYING CONDITIONS

Correction of metabolic acidosis and hyperglycemia in patients with diabetes is critical for successful outcomes in cases of sino-orbital or rhinocerebral mucormycosis. Doses of glucocorticoids should be rapidly reduced to the lowest possible effective dose. Recovery from neutropenia is paramount for successful outcomes in mucormycosis. Administration of recombinant human granulocyte colony-stimulating factor or recombinant human GM-CSF shortens the duration of neutropenia and augments phagocytic function. Granulocyte transfusions may be beneficial in stabilizing the disease in selected patients in whom recovery from neutropenia is pending.[75] Hyperbaric oxygen may be beneficial in the management of selected cases of sino-orbital and rhinocerebral mucormycosis in patients with diabetes, as well as cases of isolated myocutaneous mucormycosis.[76,77]

NEW DIRECTIONS FOR IMPROVING OUTCOMES

Variables that influence outcomes in mucormycosis include the stage or location of disease, early diagnosis of invasive disease, timely initiation of antifungal therapy, surgical resection of tissue with medically intractable infection, occurrence of relapsed leukemia, allogeneic hematopoietic-cell transplantation, dissemination of infection, the involvement of the central nervous system, and reversal of immunodeficiencies, which involves remission of underlying hematologic cancers when present.[78] The future research agenda in mucormycosis will be driven by exciting new developments in early diagnosis, new antifungal compounds, virulence targets, and host-directed immune adjunctive therapy (Table 3).[79-93] Laboratory diagnosis of mucormycosis may be improved by expanded availability and use of new culture-independent techniques and tools, including polymerase-chain-reaction analysis of cell-free DNA,[91] metagenomic analysis,[92] new antigen assays, and point-of-care devices, such as loop-mediated isothermal amplification assays.[80]

Augmentation of innate host defenses with multifunctional immunomodulatory agents, including recombinant human GM-CSF, interleukin-7, and other recombinant immunomodulators, may be beneficial in patients with trauma-related immune paralysis and radiation- or chemotherapy-induced neutropenia, contexts in which wound and mucocutaneous healing are important. Small-molecule inhibition of hypoxia-inducible factor 1α, inhibition of epidermal growth factor receptor signaling by gefitinib, and use of inhibitors of programmed death ligand 1 and programmed cell death protein 1 may also be viable therapeutic strategies.[81-83] In addition, adjustment of nasal microbiota may provide defense against colonizing mucorales species.[84]

Table 3. Future Directions in Mucormycosis Research.*

Epidemiology	Performance of national and multinational prospective, population-based studies to investigate the incidence of mucormycosis and regional differences in disease Development of multicenter registries of mucormycosis cases to characterize evolving patient-specific risk factors, including diabetes, hematologic cancer, transplantation, trauma, receipt of critical care, and age, as well as outcomes Characterization of immunogenetic risk factors
Laboratory diagnosis	Development of new culture-independent biomarkers with the use of mucorales-specific PCR, cell-free DNA, metagenomics, and volatolomics Further characterization of existing molecular biomarkers for early detection of mucormycosis and correlation of fungal burden with outcome Development of point-of-care diagnostic tools for mucormycosis
Treatment	Development of biomarkers and functional imaging techniques (e.g., PET-CT) for determination of intensity and duration of antifungal therapy Development of new first-in-class antifungal agents Exploration of combination antifungal therapy Harnessing of host-directed immune therapeutics against mucormycosis Development of antivirulence-based therapeutics Elucidation of the effects of metabolic control on risk of mucormycosis and outcomes Characterization of the mechanisms of hyperbaric oxygen therapy and its potential role in treatment of mucormycosis Clarification of the timing and extent of surgery Assessment of the role of local administration (by nebulization or retrobulbar or topical application) of antifungal agents Development of new regulatory pathways and adaptive clinical trials
Outcomes	Definition of the role of diagnostic imaging and biomarkers in outcomes Delineation of the role of coexisting conditions in risk stratification for outcomes Incorporation of patient-reported outcomes into clinical-trial assessments of outcomes Incorporation of desirability-of-outcome ranking into clinical-trial end points

* PET denotes positron-emission tomography.

Several small-molecule antifungal agents have been shown to have in vitro and in vivo activity against mucormycetes and mucormycosis in preclinical studies.[79,85-87] These agents include SCY-247, fosmanogepix, and MAT2203 (an oral nanoparticle amphotericin B formulation). SCY-247, which is a triterpenoid molecule that inhibits synthesis of 1,3-β-D-glucan, has antifungal activity against experimental murine mucormycosis alone and in combination with liposomal amphotericin B. Fosmanogepix is an *N*-phosphonooxymethyl prodrug that is metabolized to the active manogepix molecule, which inhibits Gwt1, the fungal enzyme required for inositol acylation of glycosylphosphatidylinositol anchors.[79] Fosmanogepix has also been shown to have activity in the treatment of experimental murine pulmonary mucormycosis.[85] Similarly, the orally administered lipid nanoparticle MAT2203 has in vivo activity in the neutropenic mouse model of pulmonary mucormycosis.[86] Further investigation of the heritable RNA interference epimutations that result in resistance to antifungal drugs in mucorales species may offer new approaches to understanding the pathogenesis of mucormycosis and combatting the broad antifungal drug resistance of those fungi.[93] As new antineoplastic agents are introduced, complex drugñdrug interactions between established and newer antifungal agents will require a personalized approach for each patient.[87]

In cases of mucormycotic wound infection, topical therapy may be beneficial. Dakin s solution (0.025% sodium hypochlorite) is recommended for topical treatment of mucormycotic combat wounds,[88] but therapeutic advances may be possible with new clinically relevant murine models of musculocutaneous mucormycosis and blast injury.[89]

Alternative approaches that target virulence factors of the mucormycetes may also lead to important therapeutic advances. Polyclonal antibodies that target CotH3 proteins protect neutropenic and diabetic ketoacidotic mice from mucormycosis.[90] Polyclonal antibodies against mucoricin prolong survival in mice with experimental mucormycosis.[10]

The future promises to bring combinatorial strategies of early detection in conjunction with

KEY POINTS

MUCORMYCOSIS

- Mucormycosis is a rapidly progressive and often lethal invasive fungal infection that affects patients who are severely immunocompromised, as well as patients with diabetes and persons with immunocompetence who have major trauma.
- Mucormycosis manifests in several clinical forms, including sino-orbital, rhinocerebral, sinopulmonary, gastrointestinal, cutaneous, musculoskeletal, osteoarticular, and disseminated mucormycosis, as well as single-organ disease.
- A high index of suspicion in the appropriate clinical context and subsequent microbiologic or histopathological confirmation are necessary for early intervention, which reduces mortality.
- Successful treatment depends on five pillars of intervention: early detection and staging of the disease, timely initiation of antifungal therapy, surgical resection of infected tissue, reversal of immunodeficiencies, and correction of metabolic abnormalities.
- Liposomal amphotericin B is the preferred agent for initial antifungal therapy. Oral triazoles (i.e., isavuconazole and posaconazole) are alternative agents, especially for step-down therapy.
- Research on rapid molecular diagnostic strategies, new antifungal agents, host-directed immune augmentation, antivirulence immune therapeutics, and risk-based stratification to inform management of disease may substantially improve outcomes in patients with this highly destructive mycosis.

the use of antivirulence, antifungal, and immunomodulatory agents, all in concert with efforts to reverse underlying immunodeficiencies and metabolic abnormalities.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

[1] Department of Infectious Diseases, Infection Control, and Employee Health, University of Texas M.D. Anderson Cancer Center, Houston; [2] Center for Innovative Therapeutics and Diagnostics, Richmond, VA; [3] Department of Medicine, University of Maryland School of Medicine, Baltimore; [4] Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore.

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