MUCORMYCOSIS

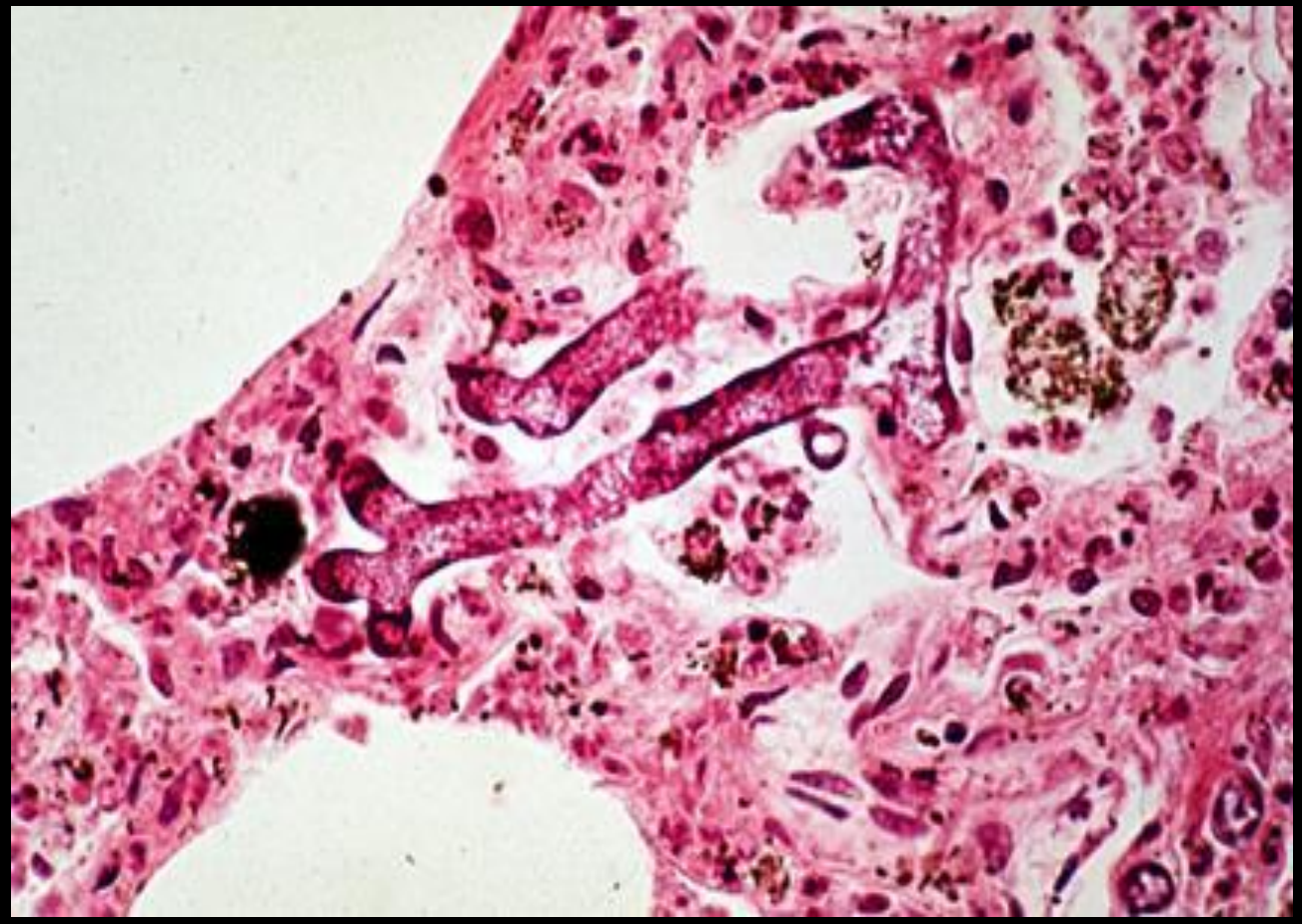
INTRODUCTION

Mucormycosis is manifested by a of different syndromes in humans, particularly in immunocompromised patients and those with diabetes mellitus. Devastating rhino-orbital-cerebral and pulmonary infections are the most common syndromes caused by these fungi.

MYCOLOGY

The genera in the order Mucorales cause most human infection. These organisms are ubiquitous in nature and can be found on decaying vegetation and in the soil. These fungi grow rapidly and release large numbers of spores that can become airborne. Because the agents of mucormycosis are common in the environment, they are relatively frequent contaminants in the clinical microbiology laboratory.

The hyphae of the Mucorales are distinct and allow for a presumptive identification from clinical specimens. The hyphae are broad (5 to 15 micron diameter), irregularly branched, and have rare septations .This is in contrast with the hyphae of ascomycetous molds, such as *Aspergillus*, which are narrower (2 to 5 micron diameter), exhibit regular branching, and have many septations



PATHOGENESIS –

Rhizopus organisms have an enzyme, ketone reductase, which allows them to thrive in high glucose, acidic conditions.

Serum from healthy individuals inhibits growth of *Rhizopus*, whereas serum from I individuals in diabetic ketoacidosis stimulates growth.

Rhino-orbital-cerebral and pulmonary mucormycosis are acquired by the inhalation of spores. In healthy individuals, cilia transport these spores to the pharynx and they are cleared through the gastrointestinal tract. In susceptible individuals, infection usually begins in the nasal turbinates or the alveoli .The agents of mucormycosis are angioinvasive; thus, infarction of infected tissues is a hallmark of invasive disease

Deferoxamine and iron overload — Deferoxamine, which chelates both iron and aluminum, increases the risk of mucormycosis by enhancing growth and pathogenicity.

The deferoxamine-iron chelate, called feroxamine, is a siderophore for the species *Rhizopus*, increasing iron uptake by the fungus, which stimulates fungal growth and leads to tissue invasion.

Iron overload itself may predispose to mucormycosis in the absence of deferoxamine therapy. In addition, individuals with diabetic ketoacidosis have elevated concentrations of free iron in their serum, which supports the growth of *Rhizopus oryzae* at an acidic, but not at an alkaline, pH

Deferoxamine was once used commonly as an aluminum chelator in patients with renal failure; however, aluminum excess is rarely seen today. Currently, patients at risk for deferoxamine-associated mucormycosis are those who have received multiple blood transfusions and are treated with this chelating agent for iron overload. The majority of patients with deferoxamine-associated infection present with disseminated disease that is rapidly fatal, with a mortality rate that approaches 90 percent Deferoxamine was once used commonly as an aluminum chelator in patients with renal failure; however, aluminum excess is rarely seen today. Currently, patients at risk for deferoxamine-associated mucormycosis are those who have received multiple blood transfusions and are treated with this chelating agent for iron overload. The majority of patients with deferoxamine-associated infection present with disseminated disease that is rapidly fatal, with a mortality rate that approaches 90 percent .

RISK FACTORS

- Diabetes mellitus, particularly with ketoacidosis
- Treatment with glucocorticoids
- Hematologic malignancies
- Hematopoietic cell transplantation
- Solid organ transplantation
- Treatment with deferoxamine
- Iron overload
- AIDS
- Injection drug use
- Trauma/burns
- Malnutrition

EPIDEMIOLOGY

— The incidence of mucormycosis is difficult to estimate since it is not a reportable disease and the risk varies widely in different populations. A review of 929 cases of mucormycosis that were reported between 1940 and 2003 noted that diabetes mellitus was the most common risk factor, found in 36 percent of cases, followed by hematologic malignancies (17 percent) and solid organ or hematopoietic cell transplantation (12 percent) [5]. In some patients, mucormycosis was the diabetes-defining illness. In a later study of 101 patients diagnosed with mucormycosis between 2005 and 2007 in France, hematologic malignancy was the most common risk factor, occurring in 50 percent of patients, followed by diabetes in 23 percent and trauma in 18 percent of cases [34].

Malignancy and hematopoietic cell transplantation –

Among patients with malignancy, hematologic malignancies are much more frequently associated with mucormycosis than are solid tumors .However, even in patients with hematologic malignancies, mucormycosis appears to occur in less than 1 percent of patients. Among hematopoietic cell transplant (HCT) recipients, the reported incidence has ranged from 0.1 to 2 percent, with the highest incidence in patients with graft-versus-host disease.

Reports from several countries have noted an increase in mucormycosis in patients with hematologic malignancies .Most of these patients had undergone HCT, many had graft-versus-host disease, and almost all were on voriconazole for prophylaxis or treatment. A case-control study in a population of patients with hematologic malignancies compared patients with mucormycosis to those who had no fungal infection; voriconazole prophylaxis was an independent risk factor for mucormycosis

Although the possible causes of the increase in mucormycosis in patients with hematologic malignancies continue to be debated, reasons that have been proposed include selection of the agents of mucormycosis caused by voriconazole use, increasing use and intensity of immunosuppressive agents, and a decrease in invasive aspergillosis-related mortality following HCT, resulting in the emergence of rare fungi during the late post-transplant period

Solid organ transplantation

— In a multicenter prospective study of invasive fungal infections in transplant recipients in the United States between 2001 and 2006, the 12-month cumulative incidence of mucormycosis was less than 1 percent among solid organ transplant recipients; only 2 percent of invasive fungal infections in such patients were caused by the agents of mucormycosis .Among solid organ transplant recipients, risk factors for mucormycosis include renal transplantation, renal failure, diabetes, and prior voriconazole or caspofungin use

Diabetes

As noted above, diabetes is a common predisposing condition,. Diabetes appears to be more likely than other conditions to predispose to rhino-cerebral infection. The number of reported cases of mucormycosis in diabetic patients in the United States has declined since the 1990s, a trend that has not been noted in France or in developing countries. One hypothesis that has been suggested to explain the decline in the United States is the widespread use of statins, which have inhibitory activity in vitro against a wide range of the agents of mucormycosis

Health care-associated

Skin was the most common site of infection (in 57 percent), followed by the gastrointestinal tract (15 percent). Portals of entry included surgery, catheters (especially intravascular catheters), and adhesive tape. Outbreaks and clusters have been associated with adhesive bandages, wooden tongue depressors, adjacent building construction, and hospital linens .A survey found that Mucorales could be cultured from 47 percent of hospital linen at several cancer and transplant centers

Coronavirus disease 2019-associated

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There have been case reports of mucormycosis in patients diagnosed with coronavirus disease 2019 (COVID-19), but the relationship of these two infections is unclear. Some of the infections of mucormycosis were diagnosed several days to a couple weeks after being admitted for COVID-19, and it seems reasonable to assume that the mucormycosis (rhinocerebral and pulmonary in these cases) was a secondary infection arising in a critically-ill patient on steroids. Other case reports describe patients who were diagnosed with rhinocerebral mucormycosis and COVID-19 simultaneously ,and one patient who was diagnosed with gastric mucormycosis five days after admission for COVID-19 treated with both steroids and tocilizumab

One review of case reports of mucormycosis in patients with COVID-19 included 101 cases, 80 percent of whom had pre-existing diabetes mellitus, and 76 percent of whom had received glucocorticoids for the treatment of COVID-19 .The majority of cases were from India; the reasons for this are unknown. Almost 90 percent of cases involved the nose and sinuses, and overall mortality was 31 percent. Clinicians should be aware of the potential for rhinocerebral mucormycosis as a complication of COVID-19, especially in patients with underlying diabetes mellitus.

CLINICAL PRESENTATION

Mucormycosis is characterized by infarction and necrosis of host tissues that results from invasion of the vasculature by hyphae. The pace is usually fast, but there are rare descriptions of infections with an indolent course .

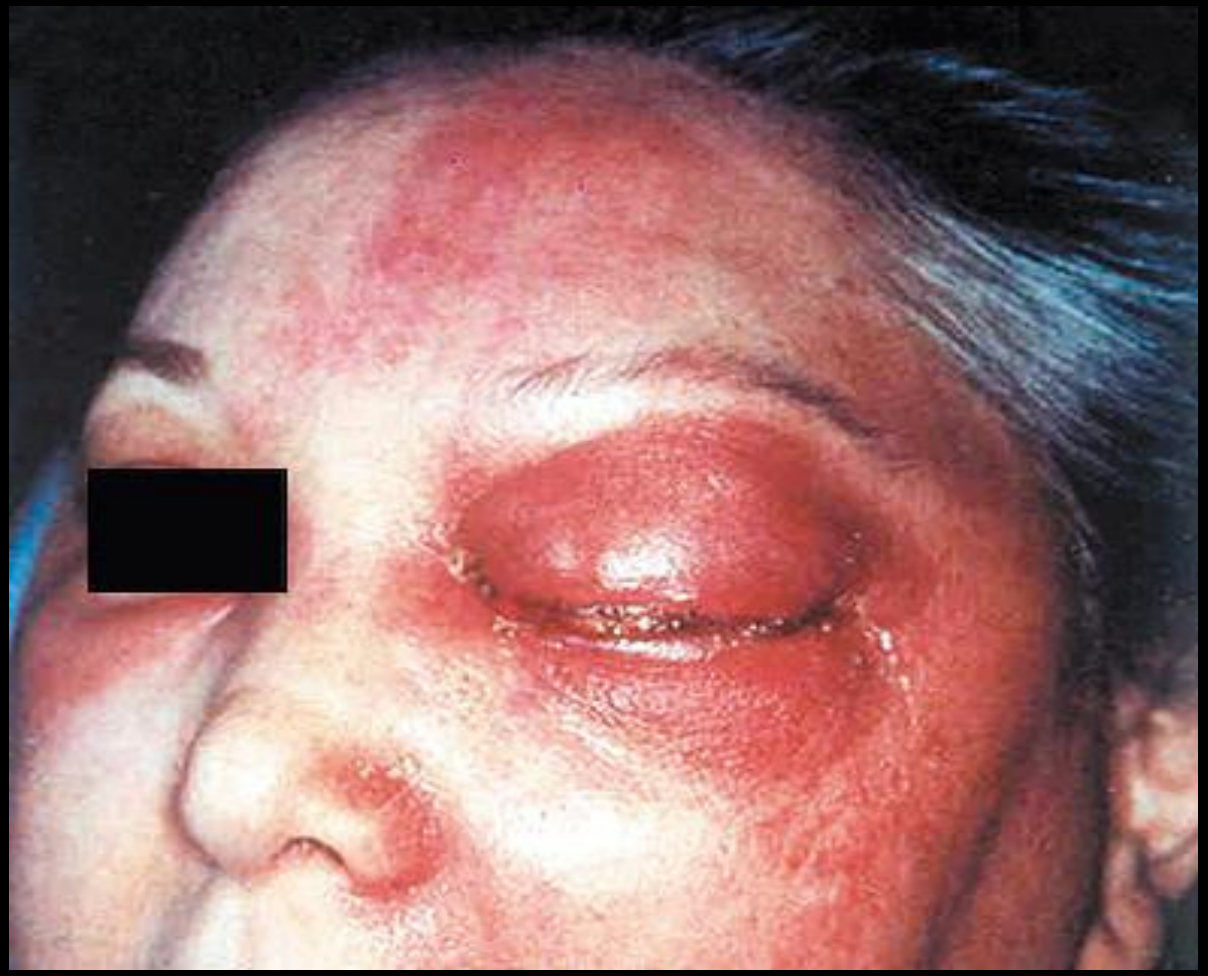
Rhino-orbital-cerebral mucormycosis

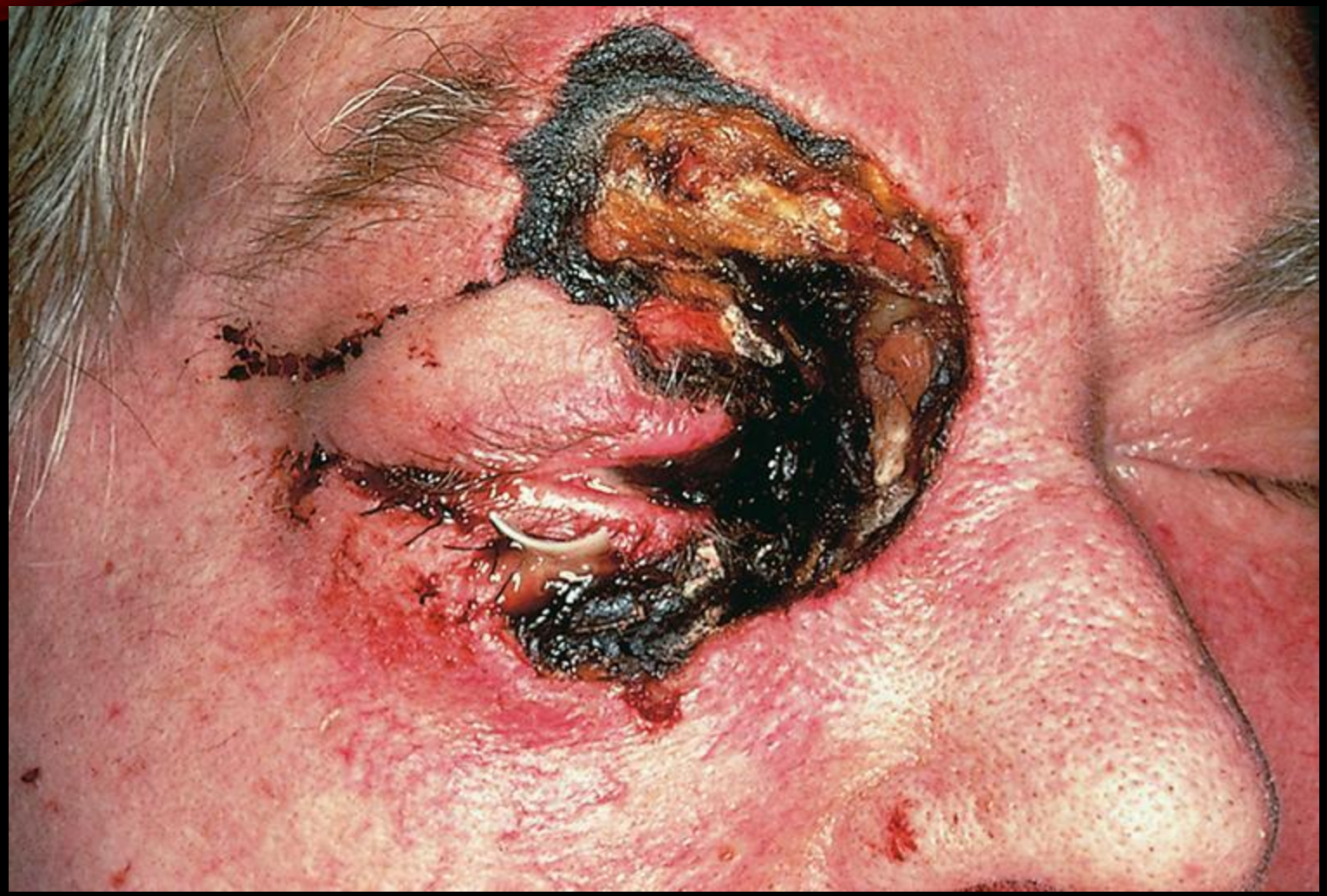
The most common clinical presentation of mucormycosis is rhino-orbital-cerebral infection, which is presumed to start with inhalation of spores into the paranasal sinuses of a susceptible host.
Hyperglycemia, usually with an associated metabolic acidosis, is the most common underlying condition.

A review of 179 cases of rhino-orbital-cerebral mucormycosis found that 126 (70 percent) of the patients had diabetes mellitus and that most had ketoacidosis at the time of presentationThere are rare reports of rhino-orbital-cerebral mucormycosis in the absence of any apparent risk factors .

The infection usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache, and sinus pain. All of the sinuses become involved, and spread to contiguous structures, such as the palate, orbit, and brain, usually progresses rapidly over the course of a few days. However, there have been some reports of rhino-orbital-cerebral mucormycosis with an indolent course that progresses over the course of weeks

The hallmarks of spread beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars, destruction of the turbinates, perinasal swelling, and erythema and cyanosis of the facial skin overlying the involved sinuses and/or orbit. A black eschar, which results from necrosis of tissues after vascular invasion by the fungus, may be visible in the nasal mucosa, palate, or skin overlying the orbit





Signs of orbital involvement include periorbital edema, proptosis, and blindness. Facial numbness is frequent and results from infarction of sensory branches of the fifth cranial nerve. Spread of the infection from the ethmoid sinus to the frontal lobe results in obtundation. Spread from the sphenoid sinuses to the adjacent cavernous sinus can result in cranial nerve palsies, thrombosis of the sinus, and involvement of the carotid artery. Hematogenous spread to other organs is rare unless the patient has an underlying hematologic malignancy with neutropenia.

A review of 208 cases of rhino-orbital-cerebral mucormycosis published in the literature between 1970 and 1993 found the following frequency of symptoms and signs:

- Fever – 44 percent
- Nasal ulceration or necrosis – 38 percent
- Periorbital or facial swelling – 34 percent
- Decreased vision – 30 percent
- Ophthalmoplegia – 29 percent
- Sinusitis – 26 percent
- Headache – 25 percent

Pulmonary mucormycosis —

Pulmonary mucormycosis is a rapidly progressive infection that occurs after inhalation of spores into the bronchioles and alveoli.

Pneumonia with infarction and necrosis results, and the infection can spread to contiguous structures, such as the mediastinum and heart ,or disseminate hematogenously to other organs .

Most patients have fever with hemoptysis that can sometimes be massive]. The most common underlying conditions have been hematologic malignancies, treatment with glucocorticoids or deferoxamine, and solid organ transplantation; pulmonary infection is less common than rhino-orbital-cerebral infection in diabetics

Gastrointestinal mucormycosis — Although unusual, mucormycosis of the gastrointestinal tract may occur as the result of ingestion of sporesThe ileum and esophagus were rare sites of involvement. The underlying diseases of patients with gastrointestinal mucormycosis have been diabetes mellitus, solid organ transplantation, treatment with glucocorticoids, and prematurity and/or malnutrition in infants]. Patients present with abdominal pain and hematemesis. The gastrointestinal lesions are necrotic ulcers that can lead to perforation and peritonitis. Bowel infarctions and hemorrhagic shock can result from gastrointestinal mucormycosis ,and the prognosis for all patients is poor.

Cutaneous mucormycosis –

Infection of the skin and soft tissues with the agents of mucormycosis usually results from inoculation of the spores into the dermis. Thus, cutaneous mucormycosis is almost always associated with trauma or wounds. The entry of the fungi into the dermis can result from seemingly innocuous insults, such as the entry site for an intravenous catheter, spider bites, and insulin injection sites. Infection has also been associated with contaminated traumatic wounds, dressings and splints, burns, and surgical sites

When infection is associated with relatively minor breaks in the skin, the host usually has some underlying disease, such as diabetes mellitus, organ transplantation, neutropenia, or severe prematurity. Infections associated with major trauma or contaminated dressings have been found in otherwise immunocompetent patients . severe prematurity. Infections associated with major trauma or contaminated dressings have been found in otherwise immunocompetent patients

Cutaneous mucormycosis usually appears as a single, painful, indurated area of cellulitis that develops into an ecthyma-like lesion. Patients who have suffered trauma with an open wound that was contaminated with spores can develop rapidly progressive tissue necrosis, reflecting the presence of ischemic infarction. Dissemination and deep tissue involvement are unusual complications of cutaneous mucormycosis

Disseminated disease –

Disseminated mucormycosis is rare and occurs most commonly in severely immunocompromised patients, burn patients, premature infants, and individuals who have received deferoxamine.The mortality rate in patients with disseminated mucormycosis was 96 percent.