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Fungal Diseases and COVID-19

<https://www.cdc.gov/fungal/covid-fungal.html>

Overview

Symptoms of some fungal diseases can be similar to those of [COVID-19](#), including fever, cough, and shortness of breath.¹

Laboratory testing is necessary to determine if a person has a fungal infection or COVID-19.

Some patients can have COVID-19 and a fungal infection at the same time.

Overview

People with severe COVID-19, such as those in an intensive care unit (ICU), are particularly vulnerable to bacterial and fungal infections. The most common fungal infections in patients with COVID-19 include Mucormycosis, Aspergillosis, Invasive Candidiasis.^{[1](#)–[6](#)}

These fungal co-infections are reported with increasing frequency and can be associated with severe illness and death.^{[1](#),[3](#),[4](#),[7](#),[8](#)} Awareness of the possibility of fungal co-infection is essential to reduce delays in diagnosis and treatment in order to help prevent severe illness and death from these infections.

AIRBORNE FUNGI IN TABRIZ, COMPARING AIRBORNE AND CLINICAL SAMPLES OF A. FUMIGATUS (2011), SURVEY AND LITERATURE REVIEW

[KAZEMI ABDOLHASSAN](#), [AHMADPOUR EHSSAN](#), [NAGHILI BEHROZ](#), [ZAREI MAHMOUDABADI ALI](#), [JAFARI ABBASALI*](#), [MOUSAVI AYATOLLAHI AMIN*](#) [JUNDISHAPUR JOURNAL OF MICROBIOLOGY \(JJM\)](#) [2013](#) , Volume 6 , Number 4 (S.N. 22); Page(s) 1 To 5. Paper

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Abstract: Background: Air contamination with fungal spores and the presence of these spores on respiratory tract, especially in industrialized cities with contaminated air, can play an important role on the occurrence of respiratory and coetaneous mycoses, asthma and allergic reactions. This survey was carried out to determine the prevalence of different fungal spores in the atmosphere of Tabriz district.

Objectives: The present study aimed to detect fungal air spores in Tabriz environments, and to compare the environmental samples of *Aspergillus fumigatus* with the clinical isolated samples of this fungus, due to the importance of the dangers of *A.fumigatus* for public health, particularly for the immunocompromised patients.

Materials and Methods: During this survey, the presence of air fungal spores was analyzed using settle plate and prepared culture in Sabouraud's dextrose agar. Prior identifications were performed using macroscopic characters, and direct microscopy. 262 samples were collected from different areas of the atmosphere of Tabriz district within all four seasons of the year. Fungal colonies were isolated from all air samples and identified using macroscopic and microscopic characters, and slid culture.

Results: The main isolated fungal spores from the atmosphere of Tabriz district were *Penicillium* Sp. (36.6%), *Cladosporidium* Sp. (26.8%) and *Aspergillus* Sp. (23.6%).

Conclusions: The presence of fungal spores in the atmosphere as a part of air pollution can cause significant problems for human health, particularly in the respiratory tracts.

Keyword(s): FUNGI, SPORES, FUNGAL, TABRIZ, ASPERGILLUS FUMIGATUS

Figure 2. Gel Electrophoresis of PCR Products Using Degenerate Primers

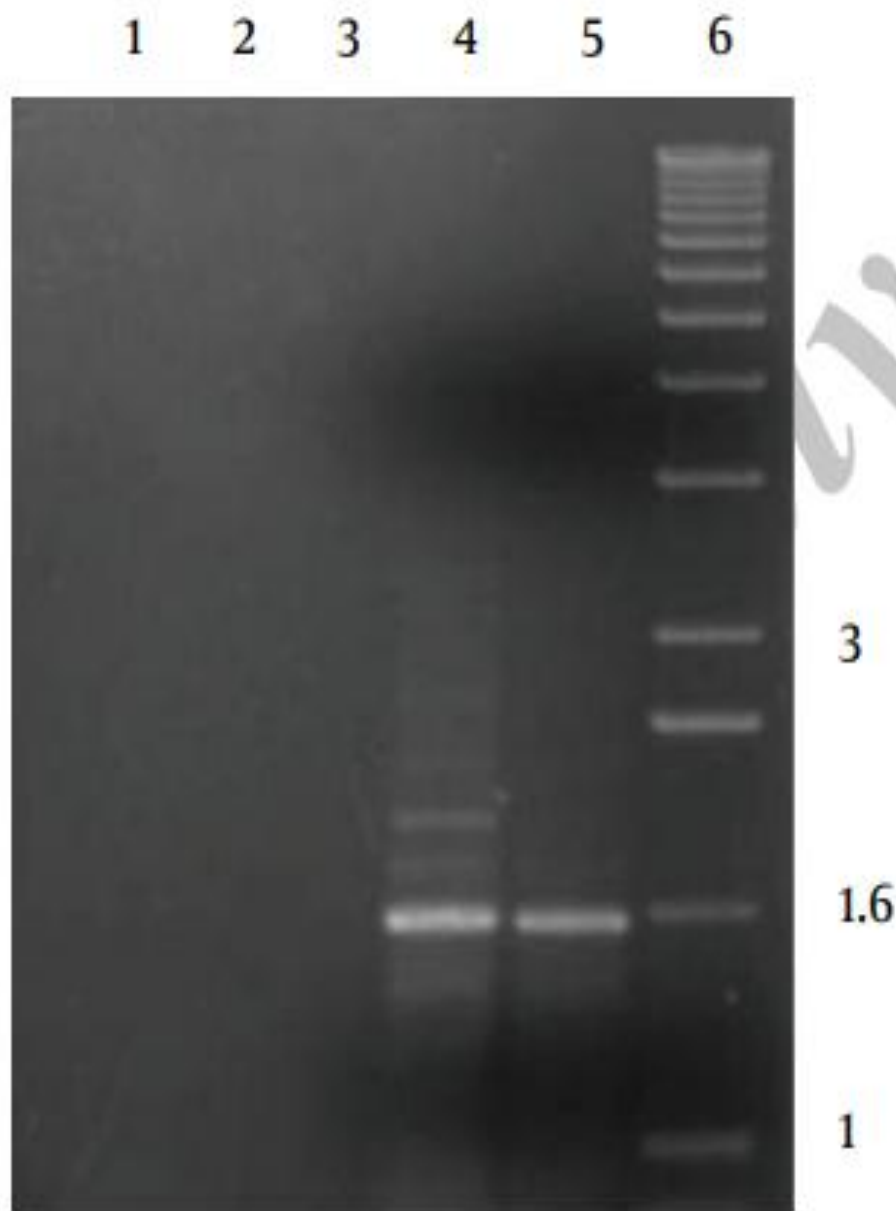


Table 1. Colony Count and Percentage of the Identified Fungi

| Fungi | Percentage | Colony Count |
|---------------------------|------------|--------------|
| <i>Penicillium Sp.</i> | 39.6 | 104 |
| <i>Cladosporidium Sp.</i> | 26.8 | 70 |
| <i>Aspergillus Sp.</i> | 23.6 | 62 |
| <i>Tichoderma Sp.</i> | 5.1 | 14 |
| Yeast | 2.8 | 4 |
| <i>Chrysosporium Sp.</i> | 0.7 | 2 |
| <i>Fusarium Sp.</i> | 0.7 | 2 |
| <i>Alternaria Sp.</i> | 0.7 | 2 |
| <i>Acremonium Sp.</i> | 0.7 | 2 |
| Total | 100 | 262 |

5. Discussion

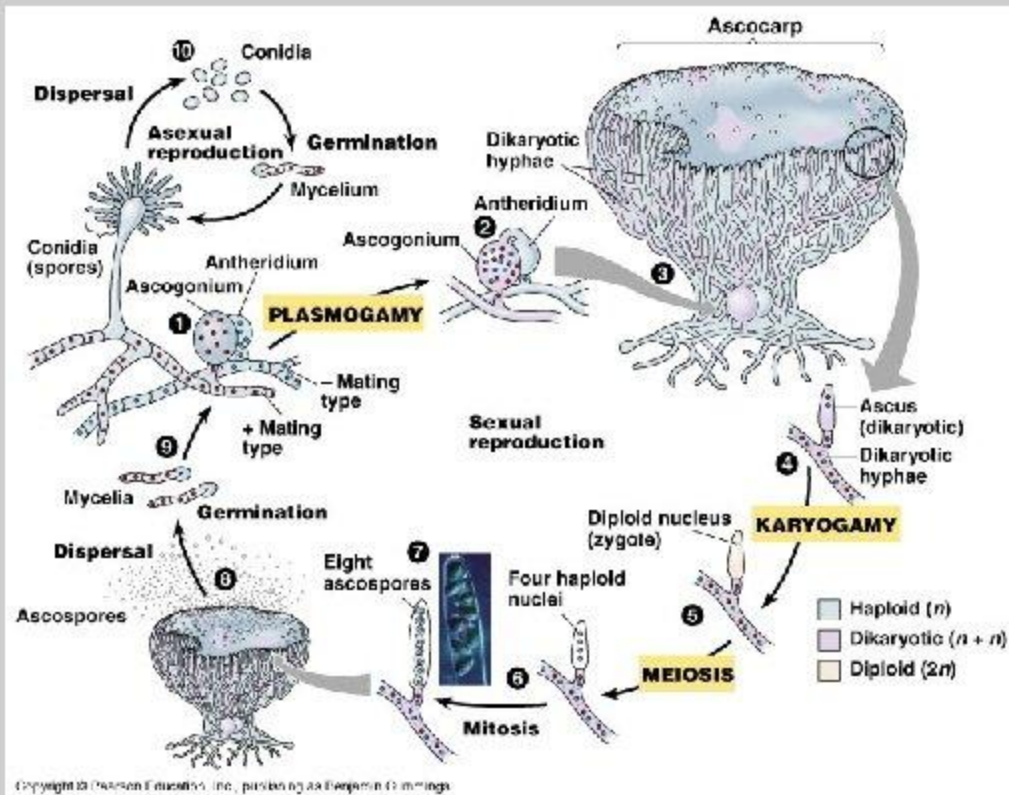
Fungi can both degrade the organic materials and structures of their colonies, and contribute to the appearance of symptoms and diseases in the inhabitants of contaminated homes, hospitals, factories, etc. (8, 9). Citizens in city environments are not only at risk of harm to their health through environmental degradation as a result of the worsening air pollution problems such as fungal spores, but are also constantly threatened by emerging and recurring asthma, rhinitis, bronchopulmonary disorders, mycoses and hypersensitivity pneumonitis eni

COVID-19-associated pulmonary aspergillosis

Scientists are still learning about [aspergillosis](#) (infections caused by the fungus *Aspergillus*) in people with severe COVID-19. In the past, scientists thought aspergillosis occurred almost entirely in people with severely weakened immune systems. However, aspergillosis has been [increasingly reported](#) in patients without weakened immune systems but who have severe respiratory infections caused by viruses, including influenza. Several recent reports describe COVID-19-associated pulmonary aspergillosis (CAPA).[1,3,6,9,10-14](#)

C. Ascomycota - Life cycle

1. Dikaryotic growth
2. Fruiting body: ascocarp
3. Fertile layer with asci
4. Eight ascospores per ascus (sac)
5. Asexual reproduction via conidia



COVID-19-associated pulmonary aspergillosis

Available information indicates that CAPA: usually occurs in patients with severe COVID-19 (e.g., patients on ventilators in ICUs)^{[1](#),[6](#),[11-14](#)} can be difficult to diagnose because patients often have non-specific symptoms and testing typically requires a specimen from deep in the lungs^{[11](#), [14](#)} can cause severe illness and death^{[8](#),[9](#),[11-14](#)}

COVID-19-associated pulmonary aspergillosis

Clinicians should consider the possibility of aspergillosis in patients with severe COVID-19 who have worsening respiratory function or sepsis, even if they do not have classical risk factors for aspergillosis.^{[16](#)}

Testing for CAPA usually involves obtaining specimens from patients' lower respiratory tract, which are tested for *Aspergillus* galactomannan antigen and fungal culture.

Invasive aspergillosis¹

Usually occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to an *Aspergillus* infection.

However, the symptoms of invasive aspergillosis in the lungs include:

Fever

Chest pain

Cough

Coughing up blood

Shortness of breath

Other symptoms can develop if the infection spreads from the lungs to other parts of the body.

Treatment

First-line treatment for invasive aspergillosis is voriconazole. Alternative treatments include lipid amphotericin formulations, posaconazole, isavuconazole, itraconazole, caspofungin, and micafungin. Prophylaxis against aspergillosis is recommended during prolonged neutropenia for patients who are at high risk for aspergillosis, allogeneic stem cell transplant patients with graft versus host disease, lung transplant recipients, and certain other solid organ transplant recipients under certain conditions.

For more detailed recommendations on treatment and prophylaxis, please refer to the Infectious Diseases Society of America's [Practice Guidelines for the Diagnosis and Management of Aspergillosis](#)external icon.

Antifungal resistance

Even with antifungal treatment, aspergillosis can cause death in more than half of infected patients with weakened immune systems. *Aspergillus fumigatus* (*A. fumigatus*) that is [resistant to all azole](#) antifungal medications, including voriconazole, itraconazole, and posaconazole, is emerging in the U.S. [1](#) [2](#) [3](#) making infections with this strain even harder to treat.

Some *A. fumigatus* strains carry resistance markers that have been associated with environmental fungicide use rather than a patient's previous exposure to antifungals. Healthcare professionals and public health officials should be aware that resistant infections are possible even in patients not previously treated with these medications. Most U.S. laboratories do not have the capability to test for antifungal-resistance in *A. fumigatus*.

If resistant aspergillosis is suspected in a hospital that lacks immediate access to testing, clinicians should consult their local health department to inquire how to access testing. Further research is needed to determine the prevalence of this resistance.

Select regional labs in the [AR Lab Network](#) perform screening to monitor and track the emergence of [azole-resistant *A. fumigatus*](#) in the United States. Testing is available to all states. For more information on antifungal resistance, please see CDC [Antifungal Resistance page](#).

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**IDENTIFICATION, ISOLATION, CLONING AND SEQUENCING OF
FLUCONAZOLE RESISTANCE GENE IN ASPERGILLUS FUMIGATUS.**
[PHARMACEUTICAL SCIENCES](#) [SUMMER 2008](#) , [Volume -](#)
[, Number 2](#); Page(s): 27 - 35.

Abstract: Objectives: Development of azole resistance in opportunistic fungi is the most problematic reason in immunocompromised patients and at present time, there is an increased awareness of the morbidity and mortality associated with fungal infections caused by resistant fungi to imidazole. This research was carried out for cloning and sequencing of Fluconazole resistance gene.

Methods: Using genomic DNA of *Aspergillus fumigatus* (ATCC strain 90254) a primary 800 bp PCR product and then a secondary 1750 bp inverse PCR product were obtained. The 1750 bp PCR product was gel purified and cloned into *E. coli* using the suitable plasmid. Plasmid was extracted from transformed *E. coli* and the presence of expected insert into plasmid, was confirmed by digestion of plasmid using *Eco* R1 restriction enzyme. Also southern analysis using standard protocol was carried out for investigation of gene expression.

Results: Gel purified 1750 bp band was sequenced and after deletion of extra nucleotides from both side of residue a 1703 bp motif submitted at NCBI gene bank with accession No.: AY848856.

Conclusion: In conclusion considering (resistant to fluconazole) *A. fumigatus* resistance gene to this compound was cloned and sequenced successfully in our lab. Since *A. fumigatus* is increasingly resistant to the widely used fluconazole, we emphasize for future additional studies for expression of this gene and its mRNA transcription to understand the effective and inhibitor factors for expression of gene.

Keyword(s): FLUCONAZOLE RESISTANCE, GENE, SEQUENCING, ASPERGILLUS FUMIGATUS

Aspergillosis Statistics

How common is aspergillosis?

Because aspergillosis is not a reportable infection in the United States, the exact number of cases is difficult to determine. Milder, allergic forms of aspergillosis are more common than the invasive form of the infection. Allergic bronchopulmonary aspergillosis (ABPA) likely affects between 1 and 15% of cystic fibrosis patients.¹ One study calculated that **2.5% of adults who have asthma also have ABPA, which is approximately 4.8 million people worldwide.**² Of these **4.8 million people who have ABPA, an estimated 400,000 also have chronic pulmonary aspergillosis (CPA).**² **Another 1.2 million people are estimated to have CPA after having tuberculosis,**³ and over 70,000 people are estimated to have CPA as a complication of sarcoidosis.⁴

Invasive aspergillosis is uncommon and occurs primarily in immunocompromised people. The first population-based incidence estimates for invasive aspergillosis were obtained from laboratory surveillance conducted in the San Francisco Bay Area during 1992-1993 and suggested a yearly rate of 1 to 2 cases of aspergillosis per 100,000 population.⁵ However, the epidemiology of invasive *Aspergillus* infections has likely shifted since this time due to the increasing number of solid organ and stem cell transplant recipients and newer immunosuppressive agents. The number of hospitalizations related to invasive aspergillosis in the United States increased an average of **3% per year during 2000-2013.**⁶ **Nearly 15,000 aspergillosis-associated hospitalizations occurred in the United States in 2014, at an estimated cost of \$1.2 billion.**⁷

Prospective surveillance among transplant recipients performed during 2001-2006 found that invasive aspergillosis was the most common type of fungal infection among stem cell transplant recipients⁸ and was the second-most common type of fungal infection among solid organ transplant recipients.⁹ **In a broad US healthcare network of intensive care unit autopsy studies, aspergillosis was one of the top four most common diagnoses that likely lead to death.**¹⁰

Aspergillosis outbreaks: Although most cases of aspergillosis are sporadic (not part of an outbreak), outbreaks of invasive aspergillosis occasionally occur in hospitalized patients. Invasive aspergillosis outbreaks are often found to be associated with hospital construction or renovation, which can increase the amount of airborne *Aspergillus*, resulting in respiratory infections or surgical site infections in high-risk patients.^{12,13} Outbreaks of primary cutaneous aspergillosis and central nervous system aspergillosis in association with the use of contaminated medical devices have also been described.^{14, 15} The incubation period for aspergillosis is unclear and likely varies depending on the dose of *Aspergillus* and the host immune response.

Deaths due to aspergillosis

Allergic forms of aspergillosis such as allergic bronchopulmonary aspergillosis (ABPA) and allergic *Aspergillus* sinusitis are generally not life-threatening.

In contrast, although invasive aspergillosis is uncommon, it is a serious infection and can be a major cause of mortality in immunocompromised patients.

For example, a large prospective study found that the one-year survival for people who had **invasive aspergillosis was 59% among solid organ transplant recipients¹⁰ and 25% among stem cell transplant recipients.⁸** In a systematic review of intensive care unit autopsy studies, aspergillosis was one of the top four most common diagnoses that likely lead to death.¹¹

Mucormycosis

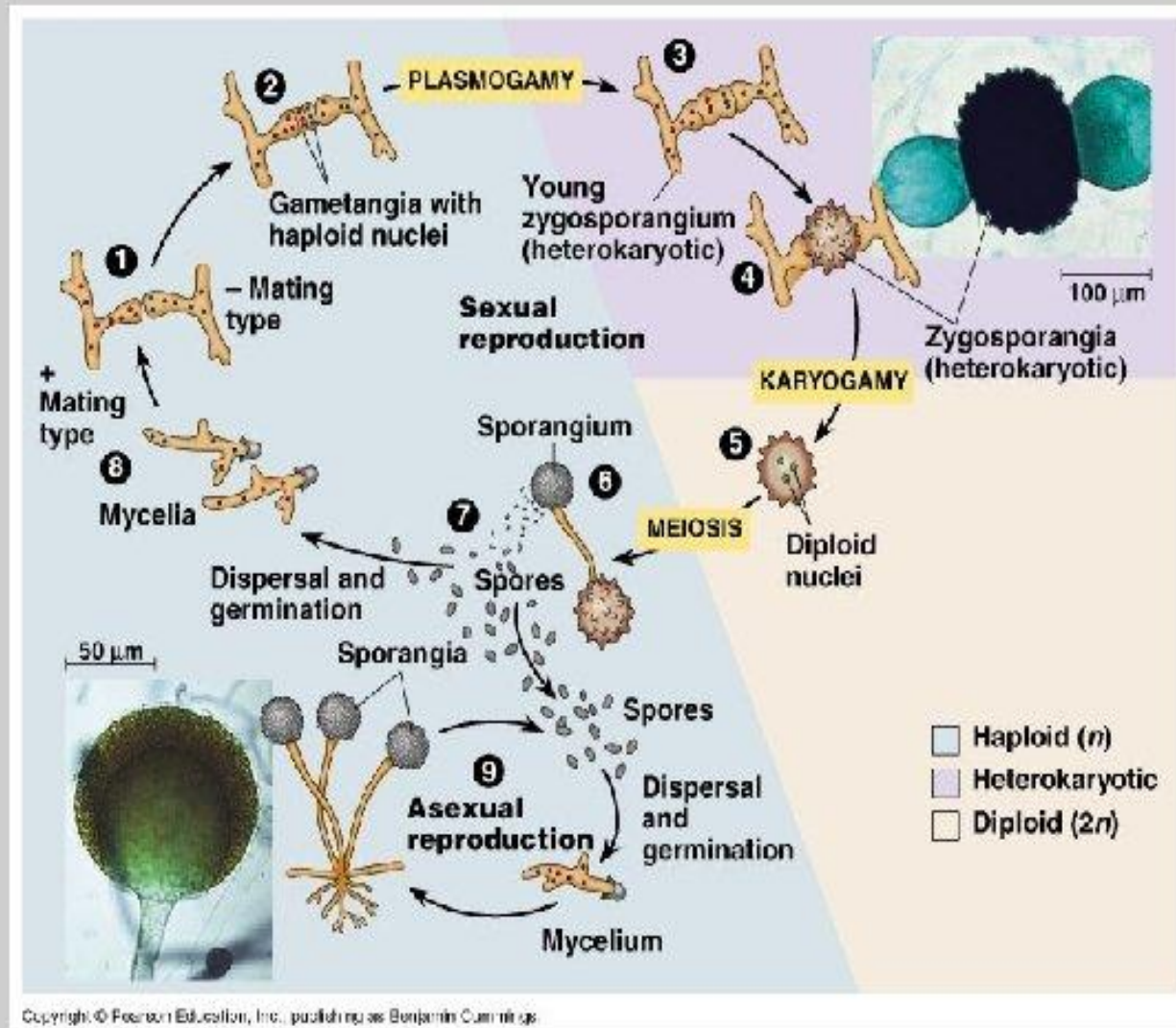
Mucormycosis (previously called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These molds live throughout the environment.

Mucormycosis mainly affects people who have health problems or take medicines that lower the body's ability to fight germs and sickness.

It most commonly affects the sinuses or the lungs after inhaling fungal spores from the air. It can also occur on the skin after a cut, burn, or other type of skin injury.

B. Zygomycota

1. No dikaryotic growth
2. Both sexual and asexual sporangia



Why Deadly 'Black Fungus' Is Ravaging

COVID Patients in India

Standard treatments such as steroids, as well as illnesses such as diabetes, make the fungal infection worse [@Scientific American](#)

COVID-19-associated mucormycosis

COVID-19–associated mucormycosis is less common than other COVID-19–associated fungal infections²⁴, but emerging reports from India highlight the importance of considering this infection. Some medications used to treat severe COVID-19, including high-dose corticosteroids and tocilizumab, might predispose patients with COVID-19 to mucormycosis.

Mucormycosis has been reported in patients with severe COVID-19 infection who lacked other classical mucormycosis risk factors, such as diabetes, conditions or medications that weaken the immune system, and cancer.^{25, 26}

Early diagnosis and treatment are key to improving outcomes for patients with COVID-19–associated mucormycosis. Clinicians should consider the possibility of mucormycosis in patients with severe COVID-19 even when patients lack classical risk factors for this disease.

Biomarkers for diagnosing invasive aspergillosis, such as beta-d-glucan and galactomannan, are typically negative in patients with mucormycosis. The treatment for mucormycosis frequently involves aggressive surgical intervention and treatment with antifungals, including amphotericin B, posaconazole, or isavuconazole.

Voriconazole is not recommended for treating mucormycosis.²⁷

Symptoms of Mucormycosis

The symptoms of mucormycosis depend on where in the body the fungus is growing. [1,4](#)

Symptoms of **rhinocerebral (sinus and brain) mucormycosis** include:

One-sided facial swelling

Headache

Nasal or sinus congestion

Black lesions on nasal bridge or upper inside of mouth that quickly become more severe
Fever

Disseminated mucormycosis typically occurs in people who are already sick from other medical conditions, so it can be difficult to know which symptoms are related to mucormycosis.

Patients with disseminated infection in the brain can develop mental status changes or coma.

Treatment

Early recognition, diagnosis, and prompt administration of appropriate antifungal treatment are important for improving outcomes for patients with mucormycosis. [2](#)

Amphotericin B, posaconazole, and isavuconazole are active against most mucormycetes.

Lipid formulations of amphotericin B are often used as first-line treatment.

Medications active against *Aspergillus* such as voriconazole are not active against mucormycetes, and there is some evidence to suggest that pre-exposure to voriconazole may be associated with increased incidence of mucormycosis in some patients. [26,27](#)

In addition, surgical debridement or resection of infected tissue is often necessary, particularly for rhinocerebral, cutaneous, and gastrointestinal infections. [2,4](#) Control of the underlying immunocompromising condition should be attempted when possible. [2](#) The efficacy of other treatments such as hyperbaric oxygen therapy is uncertain but have been useful in certain situations. [28](#)

How common is mucormycosis?

Mucormycosis is rare, but the exact number of cases is difficult to determine because no national surveillance exists in the United States. Population-based incidence estimates for mucormycosis were obtained from laboratory surveillance in the San Francisco Bay Area during 1992–1993 and suggested a yearly rate of **1.7 cases per 1 million** population. ¹

Prospective surveillance among 16,808 transplant recipients performed in 23 institutions during 2001–2006 found that mucormycosis was the third most common type of invasive fungal infection in **stem cell transplant recipients** and accounted **for 8% of all invasive fungal infections** (77 mucormycete cases occurred among 983 stem cell transplant recipients who developed any fungal infection). ^{2,3} Among solid organ transplant recipients, **mucormycosis accounted for 2% of all invasive fungal infections** (28 mucormycete cases occurred among 1,208 solid organ transplant recipients who developed any fungal infection). ^{3,4}

The number of cases varied widely across participating institutions.

Mucormycosis outbreaks

Healthcare providers who are concerned about an unusual number of new cases should contact their state or local public health agency.

Although most cases of mucormycosis are sporadic (not part of an outbreak), outbreaks of mucormycosis have occurred. In healthcare settings, it can be difficult to determine whether mucormycosis is healthcare-associated or whether the infections were acquired somewhere else.

Some examples of sources implicated in healthcare-associated mucormycosis outbreaks include adhesive bandages, wooden tongue depressors, **hospital linens**, negative pressure rooms, water leaks, **poor air filtration, non-sterile medical devices, and building construction.** [7-14](#)

Community-onset outbreaks have been associated with trauma sustained during natural disasters. [15](#)

Deaths due to mucormycosis

Mucormycosis is frequently a life-threatening infection. A review of published mucormycosis cases found an overall all-cause mortality rate of 54%.⁸

The mortality rate varied depending on underlying patient condition, type of fungus, and body site affected (for example, the mortality rate was 46% among people with sinus infections, 76% for pulmonary infections, and 96% for disseminated mucormycosis).⁸

The perfect storm

COVID-19 Resource Center

Breaking news and emerging research on the COVID-19 pandemic.

The combination of COVID-19, corticosteroid therapy and diabetes creates the perfect storm in which mucormycosis takes roots and thrives. Corticosteroids are a life-saving treatment used to reduce the dysregulated immune response observed in patients with COVID-19. However, **they increase the blood sugar level, and fungi enjoy the sugar**, Natarajan said. Hyperglycemia in patients with diabetes creates an even more favorable environment.

“Diabetes affects many people in India and, due to the weakened immune system, predisposes to more severe COVID-19 infection, which is typically treated with corticosteroids. With this combination of dysfunctional immune system — that is, a common denominator of COVID-19 and **diabetes — plus the use of corticosteroids, the risk of mucormycosis increases exponentially,**” Natarajan said.

In addition, COVID-19 damages and weakens the superior respiratory tract and the eye, increasing susceptibility to fungal infection. Another contributing factor is the use of antibiotics, also commonly prescribed in patients with COVID-19 to fight secondary infections, he said.

Increased spread of *Candida auris* during COVID-19 pandemic

Candida auris is an emerging fungus that can cause outbreaks of severe infections in healthcare facilities. In the United States, it has most commonly spread in long-term care facilities caring for people with severe medical conditions. However, since the start of the COVID-19 pandemic, outbreaks of *C. auris* have been reported in COVID-19 units of acute care hospitals.

These outbreaks may be related to changes in routine infection control practices during the COVID-19 pandemic, including limited availability of gloves and gowns, or reuse of these items, and changes in cleaning and disinfection practices.

New *C. auris* cases without links to known cases or healthcare abroad have been identified recently in multiple states, suggesting an increase in undetected transmission. Screening for *C. auris* colonization, an important part of containment efforts, has been more limited as resources of healthcare facilities and health departments have been diverted to respond to COVID-19.

Invasive candidiasis in patients with COVID-19

Invasive candidiasis in patients with COVID-19

Patients hospitalized for COVID-19 are at risk for healthcare-associated infections (HAIs), including [candidemia](#), or bloodstream infections caused by *Candida*.^{7,17-19} Fungal infections resistant to antifungal treatment have also been described in patients with severe COVID-19.^{19,20} Early diagnosis and monitoring for *Candida* infections and antifungal resistant infections (e.g., *C. auris*, azole-resistant *Aspergillus*) are key to reducing death from COVID-19 in patients with severe COVID-19 fungal co-infections.

Fungal pneumonias can resemble COVID-19

Other fungal diseases, such as histoplasmosis, Valley fever (coccidioidomycosis), and blastomycosis, can cause fever, cough, and shortness of breath, similar to COVID-19 and bacterial pneumonias.^{[21](#)}

These fungi live in soil. People become infected by breathing in fungi present in the air. Clinicians should consider fungal pneumonias as a possible cause of respiratory illness, particularly if COVID-19 testing is negative. It is important to note that these fungal diseases can occur at the same time as COVID-19.^{[22](#),[23](#)}

Miscellaneous

[Invasive pulmonary fusariosis in an immunocompetent critically ill patient with severe COVID-19.](#)

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[Thana Thongsricome¹, Talerngsak Kanjanabuch^{1,2,3}, Nopparat Maeboonruen³, Preeyarat Pavatung², Pisut Katavetin^{1,3}, Somchai Eiam-Ong¹](#)
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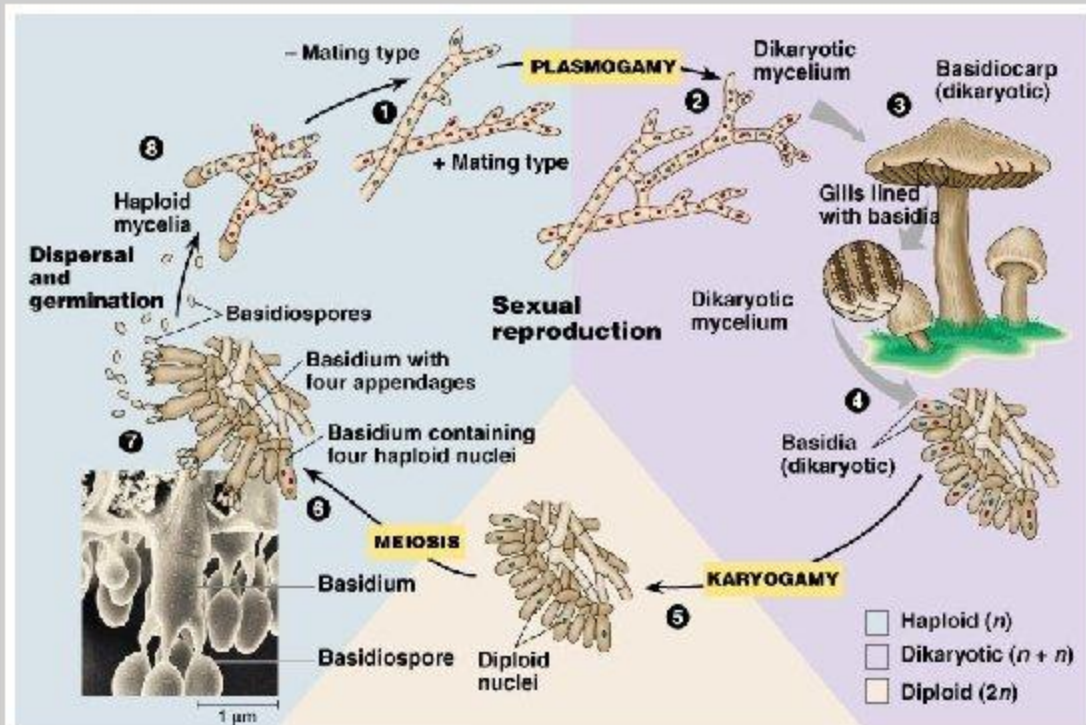
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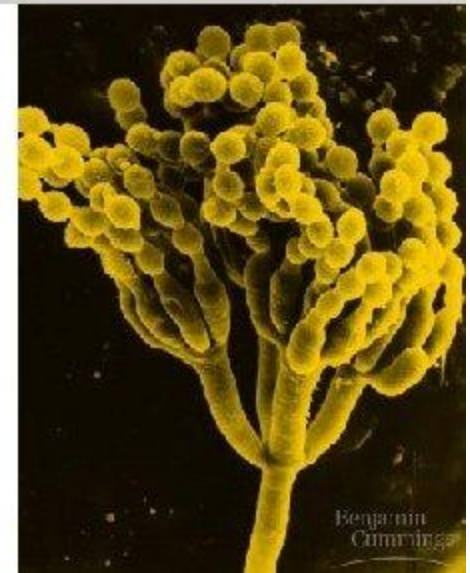
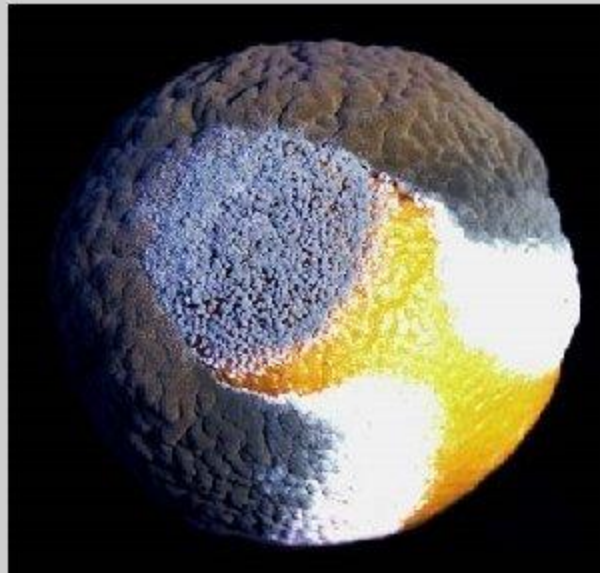
D. Basidiomycota - Life cycle

1. Dikaryotic growth
2. Fruiting body: basidiocarp
3. Fertile layer on gills with basidia (“clubs”)
4. Four spores per basidium
5. Asexual reproduction is rare



E. Deuteromycota - “fungi imperfecti”

1. Not a true phylum (not a natural group): polyphyletic
2. Fungi with no known sexual reproduction
3. Asexual reproduction by conidia



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Fungal Diseases and COVID-19