

## Epidemiological Alert: COVID-19 associated Mucormycosis

11 June 2021

Given the potential increase in cases of COVID-19 associated mucormycosis (CAM) in the Region of the Americas, the Pan American Health Organization / World Health Organization (PAHO/WHO) recommends that Member States prepare health services in order to minimize morbidity and mortality due to CAM.

### Introduction

In recent months, an increase in reports of cases of COVID-19 associated Mucormycosis (CAM) has been observed mainly in people with underlying diseases, such as diabetes mellitus (DM), diabetic ketoacidosis, or on steroids. In these patients, the most frequent clinical manifestation is rhino-orbital mucormycosis, followed by rhino-orbital-cerebral mucormycosis, which present as secondary infections and occur after SARS CoV-2 infection.<sup>1,2</sup>

Globally, the highest number of cases has been reported in India, where it is estimated that there are more than 4,000 people with CAM.<sup>3</sup>

In a retrospective multicenter study conducted in India<sup>4</sup> between September to December 2020, it was found that among 287 patients with mucormycosis, 187 (65.2%) had CAM; with a prevalence of 0.27% among hospitalized patients with COVID-19. When comparing the period under study with the same period in 2019, a 2.1-fold increase in mucormycosis was observed.

Regarding the characteristics of the 187 patients with CAM, 80.2% were male, 32.6% had COVID-19 as the only underlying disease, 78.7% were treated with gluco-corticosteroids for COVID-19, 60.4% had diabetes mellitus, 62.6% had rhino-orbital mucormycosis, and 23.5% had rhino-orbital-cerebral mucormycosis.

Mucormycosis (previously called zygomycosis) is the term used to name invasive fungal infections (IFI) caused by saprophytic environmental fungi, belonging to the subphylum *Mucoromycotina*, order *Mucorales*. Among the most frequent genera are *Rhizopus* and *Mucor*; and less frequently *Lichtheimia*, *Saksenaeca*, *Rhizomucor*, *Apophysomyces*, and *Cunninghamella* (*Nucci M*, *Engelhardt M*, *Hamed K*. *Mucormycosis in South America: A review of 143 reported cases*. *Mycoses*. 2019 Sep;62(9):730-738. doi: 10.1111/myc.12958. Epub 2019 Jul 11. PMID: 31192488; PMID: PMC6852100).

The infection is acquired by the implantation of the spores of the fungus in the oral, nasal, and conjunctival mucosa, by inhalation, or by ingestion of contaminated food, since they quickly colonize foods rich in simple carbohydrates.

Mucormycosis is characterized by infarction and necrosis of the host's tissues, which results from the invasion of the vessels by the hyphae. The clinical presentations of mucormycosis can be: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated.

It can be described as "black fungus," because it makes infected tissues turn black. The fatality rate is estimated at 40-80% (Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, et al; Mucormycosis ECMM MSG Global Guideline Writing Group. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis*. 2019 Dec;19(12):e405-e421. doi: 10.1016/S1473-3099(19)30312-3. Epub 2019 Nov 5. PMID: 31699664).

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Additionally, cases have been described in Brazil<sup>5</sup>, Chile<sup>6</sup>, Honduras<sup>7</sup>, Mexico<sup>89</sup>, Paraguay<sup>10</sup>, the United States of America<sup>11,12,13</sup> Uruguay<sup>14</sup>, Italy<sup>15</sup> and United Kingdom.<sup>16</sup>

## Cases reported in the Americas

Below is a summary table of the cases reported in the Americas, for which information is available (**Table 1**).

As of 9 June 2021, 7 countries in the Region of the Americas have reported to PAHO/WHO or published the detection of CAM cases.

**Table 1.** Description of cases of COVID-19 associated mucormycosis in the Americas (9 June 2021)

Age (year-olds)	Sex	Underlying diseases / Comorbidities	Clinical Presentation - Mucormycosis	Status*
24	Female	Diabetes mellitus Rhinosinusitis, Severe diabetic ketoacidosis, Severe metabolic acidosis, Atypical pneumonia	Rhino-orbital	Deceased
35	Male	Uncontrolled type 2 diabetes mellitus	Rhino-orbito-cerebral	Deceased
52	Female	Overweight, Smoking	Rhino-orbital	On going
35	Male	Uncontrolled diabetes, obesity	Rhino-orbito-cerebral	On going
68	Male	Diabetes mellitus, Arterial hypertension, Dyslipidemia, Mycosis of the external auditory canal treated.	Rhino-orbital	On going
51	Female	Diabetes mellitus, Chronic renal insufficiency	Rhino-orbital	Deceased
67	Male	Diabetes mellitus	Pulmonary	On going
33	Female	Uncontrolled diabetes, Arterial hypertension, Asthma	Rhino-orbito-cerebral	Deceased
49	Male	Immune system compromise	Pulmonary	Deceased
60	Male	Uncontrolled diabetes, Arterial hypertension, Asthma	Rhino-orbital	Deceased
70	Male	Heart disease, Arterial hypertension	Rhino-orbito-cerebral	On going
61	Male	Heart disease, Lung transplantation, Lung transplantation	Pulmonary	Deceased
74	Female	Arterial hypertension, Diabetes mellitus	Rhino-orbital	Deceased
45	Female	Arterial hypertension, Diabetes mellitus	Rhino-orbital	On going
51	Female	Diabetic type 2 IR, poorly compensated, chronic hypertensive, obese (BMI over 30), severe COVID-19 pneumonia, severe acute respiratory failure, severe acute respiratory failure.	Rhino-orbital	Deceased
56	Male	Arterial hypertension, Asthma	Rhino-orbital	On going

\* At the time of publication

**Source:** Data received from the International Health Regulations (IHR) National Focal Points of Brazil, Chile, Honduras, Paraguay, and Uruguay; information published by Mexico and the United States of America and reproduced by PAHO/WHO.

## Guidance for national authorities

**The Pan American Health Organization / World Health Organization (PAHO/WHO) recommends considering clinical suspicion of mucormycosis as a medical emergency.**

**Due to the progression and destructive nature of the infection, rapid diagnostic and therapeutic intervention is required. This intervention should be multidisciplinary, involving clinicians, surgeons, radiologists, and the microbiologists.**

The Pan American Health Organization / World Health Organization (PAHO/WHO) urges Member States to prepare health services to increase clinical suspicion of mucormycosis in patients with COVID-19, especially those with diabetes mellitus, treatment with corticosteroids or other immunosuppressants, in order to perform a thorough clinical evaluation, originate an early diagnosis and initiate appropriate treatment of suspected cases of COVID-19-associated mucormycosis.

### Diagnosis

The suspicion of mucormycosis is fundamental to proceed with the correct procedure and complementary examinations. Generally, mucormycosis should be suspected in patients with diabetes mellitus (DM), especially those with diabetic ketoacidosis, acquired immunodeficiency syndrome, iatrogenic immunosuppression, oncohematological patients (mainly allogeneic bone marrow transplants) and solid organ transplant recipients. The current epidemiological situation incorporates patients with COVID-19 into this list.

Radiologic studies: magnetic resonance imaging of the paranasal sinuses, with cerebral contrast study, for rhino-orbito-cerebral mucormycosis (ROCM); simple computed tomography of the thorax, for pulmonary mucormycosis.

Histopathological diagnosis: biopsy of the affected tissues is the most critical form for diagnosis. To confirm the infection, tissue invasion of unseptated hyphae should be observed in tissue sections stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS) or Grocott-Gomori methenamine-silver (GMS), or both.

Microbiological diagnosis:

**In the case of biopsy processing, biopsies should not be homogenized in a mortar. Unseptate or coenocytic filamentous fungi are very fragile and break easily, which makes microscopic visualization difficult and affects culture yield.**

Microscopic examination: Microscopic examination is essential for an early diagnosis of mucormycosis. It can be performed fresh or calcofluor white (40x) and Giemsa staining (100x). Cenocytic (not septate), broad (6-16 µm), branched (usually at 90° angle) hyphae are observed.

Culture: Mucorales usually grow on culture media commonly used in mycology: Sabouraud glucose or honey agar and Brain and Heart Infusion agar (BHI); incubation at 28°C and 35-37°C. Unseptate fungi are fast developing (24-48h).

Other media that can be used to favor fructification are potato glucose agar and malt extract; and particularly Czapek agar, for *Saksenaea* and *Apophysomyces*.

General characteristics of colonies: cottony, white or grayish black.

Identification and antifungal susceptibility testing: identification to genus and species level improves the epidemiological understanding of mucormycosis. Identification can be performed by micro- and macromorphology, MALDI-TOF (depending on the database used) and molecular biology techniques (e.g., PCR + sequencing). Treatment guidance is based on direct microscopic examination and culture, regardless of identification to genus and species level.

Antifungal sensitivity testing is not routinely performed and is clinically useful only in cases where treatment failure is observed, although therapeutic failure is multifactorial. The determination of MIC mainly allows establishing epidemiological knowledge and is usually performed in the national reference laboratory.

Detection of galactomannan and  $\beta$ -D-Glucan: both tests are negative.

## **Treatment**

Treatment requires surgical debridement, antifungal treatment and, if possible, stabilization of risk factors.

First choice, induction phase, approximately 3 weeks: amphotericin B in lipid formulations 5 mg/kg or, in case of intolerance to amphotericin B, isavuconazole, loading dose 372 mg/iv or vo/d for 6 doses, followed by 372 mg/iv or vo/d.

Consolidation phase: isavuconazole, loading dose, 372 mg/iv or vo c/8 h for 6 doses, followed by 372 mg/iv or vo/d, until clinical improvement or posaconazole tablets, 300 mg/d. Serum level of > 1  $\mu$ g/ml should be achieved (PAHO/WHO Treatment of Infectious Diseases 2020-2022 Eighth Edition, available at: <https://bit.ly/3irdeWs>).

It is recommended that the healthcare professional be informed and look for the advised of experts for detailed management regarding the complications and management of COVID-19.

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- <sup>5</sup> Report by the **Brazil** International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.
- <sup>6</sup> Report by the **Chile** International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.
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