Era of Mucormycosis in Covid-19 Pandemic; Overview, Radiological Imaging and Management: Review Article

Sana Ehab Abdel-Majeed Ibrahim*, Amal Mohamed Hasan, Ahmed Abdel-Hameed Mohamed, Ahmed Awad Bessar

Department of Radiodiagnosis, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Sana Ehab Abdel-Majeed Ibrahim, **Mobile:** (+20) 01068964466, **E-Mail:** sana.ehab.rd@gmail.com

ABSTRACT

Background: Infection of the respiratory system is the main focus of the broad family of enveloped, positive-strand RNA viruses known as coronaviruses. The coronavirus that causes COVID-19 disease is a legitimate global public health threat. Mucormycosis and aspergillosis are the most typical fungal infections of the orbit. The most prevalent causative fungus for mucormycosis is a Rhizopus species, which belongs to the order Mucorales. **Objective:** Assessment of Mucormycosis in Covid-19 pandemic and its radiological diagnosis. **Methods:** We scoured medical publications and databases including PubMed, Google Scholar, and Science Direct for information on Covid-19 and Mucormycosis between May 1988 and February 2023, however, only the latest or most comprehensive study was considered. The authors also assessed the usefulness of references drawn from similar books. As a result, non-English documents have been overlooked due to a lack of resources to translate them. It was commonly recognized that scientific research did not include things like unpublished publications, oral presentations, conference abstracts, or dissertations.

Conclusion: Due to the indeterminate nature of the imaging results in mucormycosis, CT and MRI scans are better suited for preoperative planning than diagnosis. T2-weighted magnetic resonance imaging (MRI) findings can range from hyperintensity to hypointensity, and fat planes may be lost.

Keywords: Mucormycosis, Radiological diagnosis.

INTRODUCTION

The respiratory system of humans is a common target for the coronavirus family, a vast genus of enveloped, positive-strand RNA viruses. The coronavirus COVID-19 causes a potentially lethal disease that is a major public health problem around the world. Oropharyngeal and nasopharyngeal swabs are used in the diagnosis, and the results are determined by reverse transcription polymerase chain reaction. Coughing, sore throat, and shortness of breath are typical COVID-19 symptoms [(1)]. Other symptoms mentioned include dizziness, congestion, and difficulty breathing (rhinorrhea). An individual case of abrupt hyposmia or anosmia is a very unusual presentation of COVID-19. Symptoms in the upper respiratory tract are often the first ones seen in younger individuals. COVID-19 is highly linked to impairments in the senses of smell and taste [(2)]. COVID-19 causes a wide variety of neurological problems, the mechanisms of which are complex and only partially understood. The virus appears to infiltrate the central nervous system, major blood arteries, muscles, the olfactory system, and the brain, causing autoimmune neuritis, vasculitis, and encephalitis, respectively. COVID-19 may involve the PNS, however how is uncertain [(3)]. Fungi are eukaryotic organisms that can be found just about anywhere, including dead and decaying plant debris, soil, and even the air. Genetic analyses have surprisingly placed them in the animal kingdom rather than the plant kingdom. Several types of fungus, particularly those found in the orbits, can cause fatal infections in humans. Fungal taxonomy is extensive, intricate, and often misunderstood [(4)]. Vision loss isn't the only risk posed by orbital fungal infections; they also have a high mortality rate. Therefore, early diagnosis of fungal disease and the start of suitable medication is essential. The purpose of this article is to inform readers about the clinical characteristics and treatment options for the most frequent types of orbital fungal infections [(5)].Mucormycosis and aspergillosis are the most typical fungal infections of the orbit. Rhizopus species are the most prevalent causative agents of mucormycosis, which is caused by fungi belonging to the order Mucorales. Aspergillosis is caused by a fungus belonging to the genus Aspergillus, which is part of the order Eurotiales [(6)].

Mucormycosis: Rhizopus oryzae is the leading cause of rhino-orbital-cerebral zygomycosis (ROCZ), also known as rhino-orbital-cerebral mucormycosis (ROCM), zygomycosis, phycomycosis, and orhyphomycosis (90%). Infections can also be caused by species such as Absidia corymbifera, Mucor ramosissimus, Rhizomucor pusillus, and Apophysomyces elegans, all of which belong to the order mucorales. Soil, rotting produce, animal waste, stale bread, and other organic matter are common habitats for this non-septate filamentous fungus [(1)].

Pathogenesis: The opportunistic pathogen Zygomycetes requires a compromised immune system in order to establish an infection. Primary infections of the orbit are relatively uncommon. Infection typically occurs either by spread from neighbouring paranasal sinuses or through direct traumatic injection into the orbit. Hematogenous propagation to the orbit is quite unusual. In immunocompromised hosts, they can also enter the orbit via the respiratory tract and be inhaled [(3)]. Only in a host with a weakened immune system does ROCZ develop. Diabetic patients experiencing ketoacidosis account for 60-80% of all cases. Additional risk factors include bone marrow or solid organ transplant, chemotherapy, hematologic malignancy, desferrioxamine therapy, individuals with iron excess (haemodialysis, hemochromatosis), intravenous drug usage, and neutropenia [(2)]. Since neutrophils are protected against HIV infection, the rarity of neutropenia in HIV-infected patients can be explained by this fact. The most common risk factors for developing mucormycosis in HIV patients include injecting drug use, neutropenia, and co-occurring diabetes. Because iron is essential for the growth and virulence of all zygomycota-class fungus, people with iron excess are at a higher risk of infection [(1)].

Received: 08/01/2023
Accepted: 10/03/2023

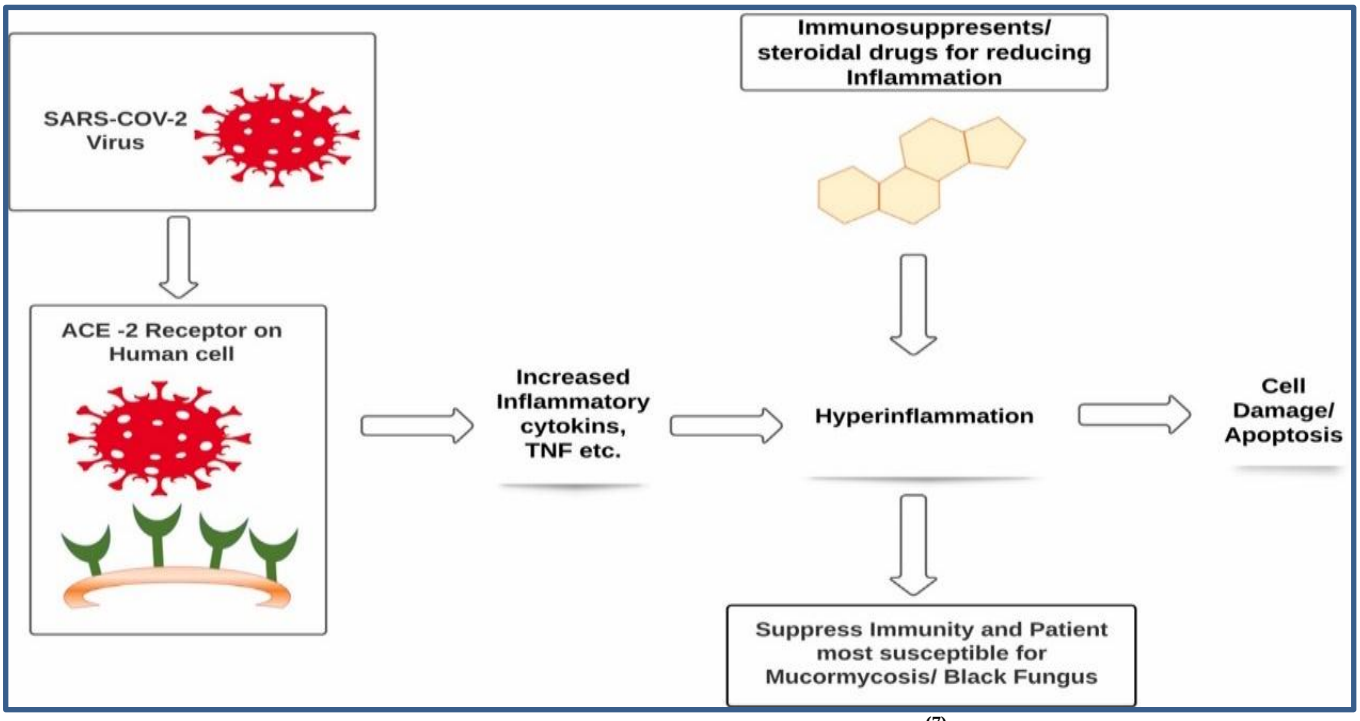

Figure (1): Pathogenesis of Mucormycosis [7].

Chelating therapy is an additional risk concern since these fungi can use the iron-desferrioxamine combination for their own growth. Deferoxamine, even in the absence of iron overload, has been proven to increase mucormycosis. Fungi are able to acquire more iron because the acidotic environment of diabetic ketoacidosis causes phagocytic dysfunction and lowers the blood's iron-binding capacity [4].

ROCZ can develop after a periorbital burn if the mucocutaneous barrier is compromised and broad-spectrum antibiotics are used to treat the infection. Infection is likely to occur after a traumatic inoculation with spores in wounds that have been exposed to water, soil, or debris [6].

The invasive fungal illness mucormycosis, in particular, has been shown to increase in frequency after natural catastrophes. Fungal infections are thought to result from a combination of factors, including an increase in environmental concentration, the displacement of fungi from their normal habitats, and subsequent interaction with injured humans [8].

Morbidity and death rates rise after natural disasters because of factors like population dislocation, poor sanitation, and hygiene practises that weaken the immune system [5].

Clinical Features:

Nasal mucosal ulceration, crusting, and necrosis, together with fever, sinusitis, nasal discharge, epistaxis, orbital and periorbital discomfort, are early indications of ROCZ. Mucormycosis is characterised by the development of a black eschar across the skin, nasal mucosa, or palate, however this development is usually quite late and highly variable. This is due to vascular thrombosis and the subsequent tissue necrosis it causes [2].

Common ophthalmic manifestations include blurred vision, drooping eyelids, swelling around the orbit, and sometimes even total external ophthalmoplegia. In addition to these symptoms, ophthalmic patients may also experience ptosis, chemosis, congestion, internal ophthalmoplegia, and corneal anaesthesia. Causes of sudden blindness include blockage of blood flow to the central retina, clot formation in the posterior ciliary arteries, infarction of the optic nerve's intraorbital branch, and direct fungal invasion of the optic nerve or optic chiasm's intracranial branch [1].

In rare cases, ROCZ might manifest as a symptom-free orbital apex syndrome devoid of orbital cellulitis. It is possible for an infection to move from the orbit to the brain via the cribriform plate and the apex of the orbit. Fungal meningitis, mycotic abscess, cerebral infarction, intracranial aneurysm/hemorrhage, and mortality can all result from an infection in the cavernous sinus or the cavernous section of the carotid artery [4].

Hemiplegia, cavernous sinus thrombosis, and periorbital necrosis, are all indicators of a worse prognosis. It is possible for periorbital mucormycosis to spread deeply into the subcutaneous fat, skeletal muscle, and fascia layers beneath the skin. Significant morbidity and mortality may result from necrotizing fasciitis caused by cutaneous zygomycosis [5].

Investigations:

Diagnosis of ROCZ requires a high level of suspicion. When a case is suspected, it is important to check the nasal and oral mucosa and send samples for microbiological analysis. Fungal hyphae in potassium hydroxide (KOH) mounts are organised in a nonseptate fashion [8].

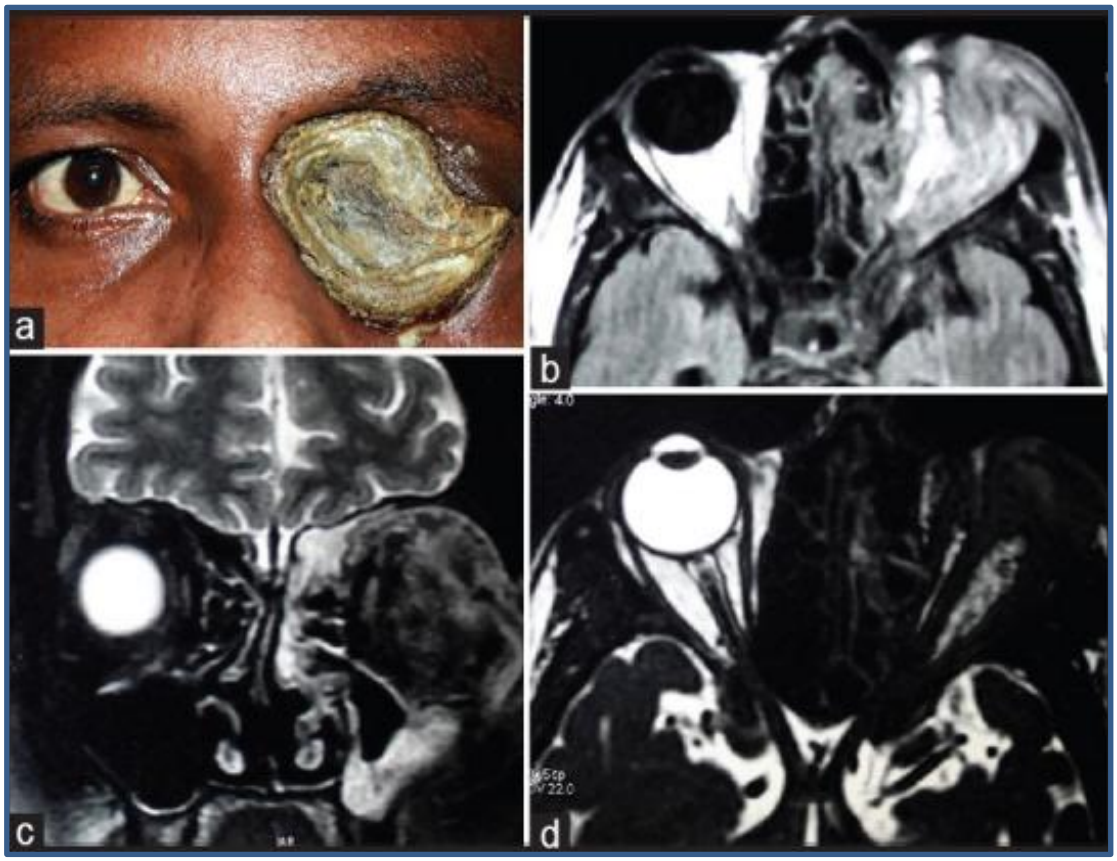

Figure (2): (a) Eschar covering the left periocular skin, as seen in a clinical picture. Ocular structures and eyelids blend., (b) Magnetic resonance imaging (MRI) scan with a T1-weighted axial section through the orbital midpoint. The mass in the left orbit is difficult to characterize since it is isointense. Superior orbital fissure and cavernous sinus extension is observed, (c) The maxillary sinus and orbit as shown on a T2 weighted coronal slice. The maxillary sinus mucosa has become thickened and opaque. Extraconal and intraconal space are filled by a diffuse, hypo- to iso-intense mass. The globe is unrecognisable, (d) Scanning the orbit with a T2 weighted image. The muscles surrounding the eyes have grown. Mixed intraconal and extraconal signal strength suggests a poorly defined mass invading orbital structures and fat [(9)].

It is important to take your time and get as much tissue as possible for the biopsy, but if the results are negative or unclear, you may have to do it again. A little piece of the biopsied tissue must also be cultured. Culture can be done on any portion of the removed tissue, even necrotic mucosa or surgically debrided tissue [(9)].

Cycloheximide-free Sabouraud's agar is utilised for the culturing process. Positive culture results are not conclusive, however, because mucorales are a common laboratory contaminant and can be generated from healthy mucosal surfaces. Arterial wall invasion by fungal hyphae is seen histopathologically in cases of thrombosing arteritis. Generally speaking, veins are spared [(1)]. Widespread tissue death with bleeding, abscess formation with core tissue death, acute inflammatory exudates, and hyphal elements invading the periphery of the body are all possible findings. Not to be confused with septations, poorly preserved hyphae often take on a "crinkled cellophane" appearance due to their wrinkling and gnarling [(9)].

A tissue sample can also be analysed with immunohistochemistry, in situ hybridization, or polymerase chain reaction (PCR) for fungal DNA to determine the presence or absence of the causal culprit. Although culture and microscopy are the gold standards for diagnosing fungal infections, identifying the precise species involved can be challenging, making PCR an invaluable tool [(4)].

The speed of PCR is its greatest benefit. Compared to the minimum of 4-5 days required for a report on the results of a histopathological examination of biopsy specimens, the combined use of automated DNA extraction and real-time PCR only takes around 2 to 4 hours [(9)].

Imaging:

Due to the possibility of modest and nonspecific imaging results, CT and MRI scans are best used for preoperative planning rather than diagnosis. Evidence of sinusitis, mucosal thickness, bone necrosis involving the pterygoid and infratemporal fossa, and thrombosis of the superior ophthalmic vein can be shown on a CT scan [(3)].

Hypodense masses with enhanced periphery characterize the appearance of intracerebral fungus (ring abscess). T2-weighted magnetic resonance imaging (MRI) findings can range from hyperintensity to hypointensity, and fat planes may be lost [(8)].

The fludeoxyglucose positron emission tomography (PET)/computed tomography (CT) scan is becoming an important technique for diagnosing ROCZ and gauging therapy efficacy. However, serial PET/CT scans may not be cost-effective for patient treatment [6].

Management:

The mortality rate from ROCZ is significantly higher than 50%. Without delay, therapy should be started as though it were an emergency. A multidisciplinary strategy is recommended for the management of ROCZ. A doctor who specialises in infectious diseases must be involved in the patient's care. Early identification, reversal of predisposing variables, extensive local debridement of necrotic tissues, development of sufficient sinus drainage, and systemic antifungals are essential for effective treatment of mucormycosis [9].

Antifungals:

Orbital fungal infections can be treated with a number of different antifungal medications. Most of these compounds exert their effects by blocking the production of ergosterol or by disrupting the structure of this crucial component of fungal cell membranes [10].

Amphotericin B and its derivatives are the most often used polyene antifungal drugs, and ketoconazole, clotrimazole (imidazoles), fluconazole, voriconazole, and posaconazole are the most widely used azole antifungal agents to treat invasive infections (triazoles). New antifungal drugs known as echinocandins appeared around the turn of the century. Caspofungin is one member of this new class, and it showed impressive efficacy against the fungal pathogens Candida and Aspergillus [11].

Intravenous amphotericin B:

After an initial test dose of 1 mg, the dosage of amphotericin B is gradually increased from 0.7 to 1 mg/kg intravenously to a cumulative dose of 2 to 4 g over the course of weeks to months. Amphotericin B's most common adverse reactions are temperature elevation, chills, headache, muscle pain, loss of appetite, general malaise, low potassium levels, and vomiting. One of the most concerning adverse effects is nephrotoxicity [12].

It is OK to have levels of 50 mg/dl for blood urea nitrogen and 3.0 mg/dl for creatinine. If the maximum is reached, the dosage is administered on alternate days. If the readings are still above 50 mg/dl and 3.0 mg/dl, the dosage and administration schedule should be adjusted downward. Involving an expert in infectious diseases in patient care is always recommended [13].

Liposomal amphotericin B:

It has been suggested that the newer, less toxic amphotericin B preparations (amphotericin B lipid complex and liposomal amphotericin B) are more effective against ROCM. They have recently become the standard treatment for ROCM. Amphotericin B's improved potency is likely due to liposomal encapsulation, which improves the drug's distribution to fungal cells, infected tissues, and phagocytes [14].

Instead, there is a reduction in renal delivery. Liposomal amphotericin B should be administered at a dose of 5 mg/kg/day, with a cap of 10 mg/kg/day for central nervous system infections. Complete and partial response rates are between 32% and 100%, and overall mortality is between 5% and 61% [9].

Surgery and local debridement:

The necrotic orbital tissues and sinuses must be extensively excised locally in order to reduce the fungal burden. Ischemia brought on by mucor arteritis and thrombophlebitis reduces bleeding from infected tissue. Therefore, the degree of surgical resection required can be gauged by debriding tissues to the point of bleeding [15]. In many instances, repeated surgical debridement is required. Additional serial imaging studies are required to prove that the infection has spread beyond the initial treatment area and that further surgery is required. There is widespread agreement amongst experts that exenteration could save lives in cases of severe fungal infections [16].

If there is active inflammation in the orbit and one or both eyes are affected, then exenteration must be performed. Even if the infection has spread intracranially, exenteration may aid by reducing the volume of the fungus. Surgical debridement guided by frozen sections may help prevent the need for radical exenteration [17].

Topical amphotericin B:

Amphotericin B (1 mg/ml) can be delivered more effectively to the infected region by irrigating and packing the affected orbit and paranasal sinuses. In one patient with ROCM, intravenous amphotericin B was administered in conjunction with intraconal injections of amphotericin B (1 mg/ml) for 9 days, with the desired result of preventing diabetic ketoacidosis and the subsequent need for exenteration [9].

Exenteration was prevented in the vast majority of studies that detailed intraorbital infusions of amphotericin B (concentration 0.25-1.25 mg/ml; volume 1-15 ml; frequency 1-4 times daily; period 5 days to 4 weeks) [18].

Hyperbaric oxygen:

It is unclear what part hyperbaric oxygen should play in treating mucormycosis. A combination of factors is postulated as the mechanism of action. Oxygenation is increased, which reduces acidosis and stimulates phagocytic activity. Some research suggests that hyperbaric oxygen can boost amphotericin B's efficacy [19]. Hyperbaric oxygen therapy has showed some promise in the treatment of ROCM with cerebral extension in some studies. After three days of hyperbaric oxygen at 2 atmospheres absolute for 2

hours every 12 hours, the patient will transfer to daily treatments of 2 hours in duration. The overall number of treatments will depend on the patient's reaction. Unfortunately, it's not cheap, easy to use, or widely accessible [(20)].

Newer modalities:

Antifungal medication posaconazole can be taken orally. In patients with refractory mycosis, it can be used in conjunction with liposomal amphotericin B. Those who are allergic to amphotericin B also have a viable option in this drug. If a patient responds well to amphotericin B, posaconazole can be used as an oral step-down medication. Posaconazole is effective, but not as a first-line treatment [(21)].

The echinocandin caspofungin has been proven to be effective against R. oryzae. When used in conjunction with polyenes, it has been demonstrated to improve survival in patients with ROCM. Granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-stimulating factor (GM-CSF), and interferon- are only some of the immune augmentation techniques proposed for mucormycosis [(22)].

CONCLUSION

Due to the indeterminate nature of the imaging results in mucormycosis, CT and MRI scans are better suited for preoperative planning than diagnosis. T2-weighted magnetic resonance imaging (MRI) findings can range from hyperintensity to hypointensity, and fat planes may be lost.

Sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Werthman A (2021):** Mucormycosis with orbital compartment syndrome in a patient with COVID-19. The American Journal of Emergency Medicine, 42: 264-65.
2. **Alekseyev K, Didenko L, Chaudhry B (2021):** Rhinocerebral mucormycosis and COVID-19 pneumonia. Journal of Medical Cases, 12 (3): 85-89.
3. **Ravani S, Agrawal G, Leuva P *et al.* (2021):** Rise of the phoenix: Mucormycosis in COVID-19 times. Indian Journal of Ophthalmology, 69 (6): 1563-67.
4. **Singh A, Singh R, Joshi S *et al.* (2021):** Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes & Metabolic Syndrome, 15 (4): 102146. doi: 10.1016/j.dsx.2021.05.019.
5. **Azhar A, Khan W, Khan P *et al.* (2022):** Mucormycosis and COVID-19 pandemic: Clinical and diagnostic approach. Journal of Infection and Public Health, 15 (4): 466-479.
6. **Mahalaxmi I, Jayaramayya K, Venkatesan D *et al.* (2021):** Mucormycosis: An opportunistic pathogen during COVID-19. Environmental Research, 201: 111643. doi: 10.1016/j.envres.2021.111643.
7. **Choudhary N, Jain A, Soni R *et al.* (2021):** Mucormycosis: A deadly black fungus infection among COVID-19 patients in India. Clinical Epidemiology and Global Health, 12: 100900. doi: 10.1016/j.cegh.2021.100900
8. **Mehta S, Pandey A (2020):** Rhino-orbital mucormycosis associated with COVID-19. Cureus, 12 (9): e10726. doi: 10.7759/cureus.10726.
9. **Mukherjee B, Raichura N, Alam M (2016):** Fungal infections of the orbit. Indian Journal of Ophthalmology, 64 (5): 337-45.
10. **Herrick E, Hashmi M (2023):** Antifungal Ergosterol Synthesis Inhibitors. In: StatPearls. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK551581/
11. **Johnson M, Perfect J (2010):** Use of Antifungal Combination Therapy: Agents, Order, and Timing. Curr Fungal Infect Rep., 4 (2): 87-95.
12. **Noor A, Preuss C (2023):** Amphotericin B. In: StatPearls. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK482327/
13. **Shahbaz H, Gupta M (2023):** Creatinine Clearance. In: StatPearls. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK544228/
14. **Hamill R (2013):** Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs, 73 (9): 919–934.
15. **Erma A, Singh V, Jindal N *et al.* (2013):** Necrosis of maxilla, nasal, and frontal bone secondary to extensive rhino-cerebral mucormycosis. Natl J Maxillofac Surg., 4 (2): 249-51.
16. **Wouthuyzen-Bakker M, Löwik C, Ploegmakers J *et al.* (2020):** A Second Surgical Debridement for Acute Periprosthetic Joint Infections Should Not Be Discarded. The Journal of Arthroplasty, 35 (8): 2204–2209.
17. **Mukherjee B, Raichura N, Alam M (2016):** Fungal infections of the orbit. Indian J Ophthalmol., 64 (5): 337-45.
18. **Shabana R, Eldesouky M, Elbedewy H (2022):** Exenterate or Not: A Simple Proposed Management Algorithm for Mucormycosis During the Era of COVID-19 in a Tertiary Eye Care Center in Egypt. Clin Ophthalmol., 16: 1933-1940.
19. **Ferguson B, Mitchell T, Moon R *et al.* (1988):** Adjunctive hyperbaric oxygen for treatment of rhinocerebral mucormycosis. Reviews of Infectious Diseases, 10 (3): 551–559.
20. **Hadanny A, Rittblat M, Bitterman M *et al.* (2020):** Hyperbaric oxygen therapy improves neurocognitive functions of post-stroke patients - a retrospective analysis. Restorative Neurology and Neuroscience, 38 (1): 93–107.
21. **Anderson A, McManus D, Perreault S *et al.* (2017):** Combination liposomal amphotericin B, posaconazole and oral amphotericin B for treatment of gastrointestinal Mucorales in an immunocompromised patient. Med Mycol Case Rep., 17: 11-13.
22. **Ballinger M, Paine R, Serezani C *et al.* (2006):** Role of granulocyte macrophage colony-stimulating factor during gram-negative lung infection with Pseudomonas aeruginosa. American Journal of Respiratory Cell and Molecular Biology, 34 (6): 766–774.