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MUCORMYCOSIS IN COVID-19 PATIENTS: A FUNGAL DISEASE DECODED

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ABSTRACT

The year 2021 felt the brunt of the second wave of the ongoing deadly pandemic caused by the ever-emerging variants of the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which made its landfall in December 2019. Due to the lack of proper treatments to combat this disease, people heavily relied upon supportive care equipment and steroids for managing the disease progression. In this apocalyptic scenario, reports of COVID-19 patients acquiring secondary infections such as Mucormycosis, also known as the 'Black Fungus Disease', came afloat as a highly concerning threat. It caused a surge in the mortality rate observed in the COVID-19 patients. Mucormycosis can be described as a rare but fatal opportunistic fungal infection, which is notorious for its rapid spread, especially in immunocompromised hosts. Thus, rapid diagnosis, and implementation of proper treatment plans is deemed to be essential to prevent the high rates of mortality and morbidity associated with it. Recent studies have documented an alarming number of Mucormycosis cases among diabetic individuals who contracted COVID-19 and were administered with steroids to treat

the infection. This review focuses on Mucormycosis and its impact during the pandemic era in India and worldwide, the related conditions and factors, the mechanism of pathogenesis in normal and COVID-19 affected individuals, challenges posed by it, and management of this deadly disease. A significant reduction in the severity of the disease and a drop in mortality rate may be achieved by early identification, and a further investigation down the line in COVID-19 patients.

Keywords: Black fungus, COVID-19, Mucormycosis, Opportunistic fungal infection, SARS-CoV-2

INTRODUCTION

The COVID-19 pandemic has shrouded our world in endless despair and uncertainty. The coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is a β-coronavirus, first detected in the Capital city of Wuhan in the Hubei province of China on December 30, 2019 **[1, 2]**. As of 23rd July 2021, a total of 192,284,207 coronavirus-positive cases have been reported worldwide, including 4,136,518 mortalities **[3]**. The disease manifests itself to different extents in different patients. In some hosts, the infection can be asymptomatic; however in case of mild infections, it can be identified by common-flu like symptoms such as fever, cough, headache, nausea, malaise, etc. **[4, 5]**. In severe cases, however, the SARS-CoV-2 virus causes complications such as multi-organ failure, acute respiratory distress syndrome (ARDS), and septic shock **[5, 6, 7]**. During the second wave of COVID-19 infection, India experienced an unprecedented rise in Mucormycosis cases **[8, 9, 10]**. Approximately so far there have been 101 reported cases of Mucormycosis in people with COVID-19, of which 82 cases were from India and 19 from the rest of the world **[11]**. It was a prominent observation made in males (78.9%) particularly, both recovered from (about 40.6%) or active (about 59.4%) patients of COVID-19 **[11]**. As the disease progresses extremely fast, in most cases, the disease diagnosis is delayed, which exerts a huge stress on the already strained medical infrastructure and also the medicine supply chain of the country **[12]**. Through this review, we aim to provide a more or less holistic view on Mucormycosis as a COVID-19 associated secondary fungal infection, and also provide information regarding early diagnosis, management of the symptoms, and preventive measures.

MUCORMYCOSIS IN COVID-19 PATIENTS

The Disease

Patients who have been severely affected by COVID-19 exhibit a heightened immune response, primarily characterized by a paramount increase in the levels of interleukins (ILs) and cytokines such as TNF-α, and a simultaneous drop in the level of $CD4^+$ and $CD8^+$ T-cells **[5, 13, 14, 15, 16]**. Thus, due to this immune system dysregulation and rampant use of therapeutic drugs such as corticosteroids, monoclonal antibodies and broad-spectrum antibiotics, several of the severely affected patients became more susceptible to opportunistic bacterial and fungal infections such as *Pneumocystis jirovecii*-pneumonia and invasive pulmonary Aspergillosis **[15, 16]**. Mucormycosis is one such secondary, angio-invasive, opportunistic fungal infection that has plagued several countries around the world, including India **[5, 15, 17]**.

The Pathogen

Mucormycosis is caused by the spores and filaments of Mucorales. The Mucorales are an order of fungi belonging to the class Zygomycetes **[18]**. It has been observed that 60% of the Mucormycosis cases in human beings can be attributed to a single species of Mucorales, which is *Rhizopus oryzae* **[11, 18, 19]**. They are ubiquitously present all around us in soil, decaying plant matter, and other sites **[18]**.

Classification

Based on the anatomic site infected, Mucormycosis is classified as follows: rhino-orbital, rhino-cerebral, cutaneous, gastrointestinal, pulmonary, and disseminated **[5, 20]**. Rhino-orbital mucormycosis (ROM) is the most commonly observed among them **[5, 21]**. The mortality rate of ROM patients with COVID-19 is very high, with the survival rate being just around 44.4% **[18]**.

Predisposing conditions

A rather complex interplay of several host and environmental factors, which include complications like pre-existing morbidities like diabetes mellitus (DM) and diabetic ketoacidosis (DKA), previous respiratory pathology, use of immunosuppressive therapy, the risk of hospital-acquired (nosocomial) infections, and systemic immune alterations due to COVID-19 infection itself may lead to secondary infections, being recognized increasingly based on their impact on morbidity and mortality **[8, 11, 18]**.

Compromised Immunity

The immune systems of immuno-compromised individuals cannot function efficiently to fight off this infection. Their immune systems either produce low levels of phagocytes or the phagocytes function less efficiently, and hence these individuals are more inclined to experience a more severe Mucormycosis infection **[11, 22, 23]**. Mucorales grow optimally under

hypoxic and hyperglycaemic conditions, which additionally exhibit a low pH level and high amounts of ferritins **[11]**. The acidic, high glucose-containing environment impairs the proper motility and phagocytic activity of the WBCs and along with this, the high iron levels aid the growth of the fungal cells, thus, enabling the Mucorales to thrive successfully in such immuno-compromised individuals **[11, 22]**. In contrast, patients with AIDS, however, interestingly do not seem to be at increased risk for developing Mucormycosis **[24]**. Hence, it can be stated that neutrophils, but not necessarily T-lymphocytes, are essential for inhibiting the proliferation of fungal spores.

Co-morbidities

Diabetes Mellitus (DM)

Studies show that a large proportion of COVID-19 patients who contract Mucormycosis, are already suffering from co-morbidities like DM **[11, 25, 26, 27]**.

Being home to the second largest population of individuals afflicted with DM, the prevalence of Mucormycosis in India is about 80 times more when compared to other developed countries **[11, 26]**. The recent systematic review conducted by John *et al* in April 2021, reported the findings of 41 confirmed Mucormycosis cases in people with COVID-19, of which DM was reported in 93% of cases **[11]**. This report matched with the report of an even larger case series of 101 cases of Mucormycosis (of which 95 are confirmed and 6 suspected) in COVID-19, where 80% of cases showed to have DM **[11]**. Although Europe and USA report the majority of hematological malignancy and organ transplantation cases - both of which are important risk factors with respect to Mucormycosis, India reports the largest number of Mucormycosis cases **[11]**. This is attributed to the fact that DM is the most vital and decisive risk factor. Additionally, of all the people suffering from DM in India, approximately 70% of them display the uncontrolled form of the disease, which creates the ideal hyperglycaemic condition enabling Mucormycosis to flourish prolifically **[11, 23, 28]**. Mucorales possess a ketone reductase enzyme, which enables them to survive in hyperglycaemic conditions which occur in COVID-19 patients with uncontrolled DM **[18]**. Among the diabetics, the most affected area was found to be the sinus, followed by the pulmonary areas **[8, 29]**.

Chronic diabetic patients suffering from foot ulcer conditions are prone to this infection owing to any injured skin tissue, posing as an easy entry route for this fungus **[8, 30]**.

Diabetic ketoacidosis (DKA)

During DKA, alongside an acidic environment, the increase in the quantity of

free ferric ions lends support to the growth of Mucorales **[8, 31]**. These circumstances draw convenience for the invasion and successful attachment of the hyphae of the ketone reductase enzyme-containing Mucorales inside the body **[18]**.

Other co-morbidities

It has been seen in clinical and experimental data, rather clearly, that persons having impaired phagocytic function or lacking phagocytes due to some co-morbidities like neutropenia are at a higher risk of Mucormycosis **[24]**. This is because mononuclear and polymorphonuclear (PMN) phagocytes of normal hosts destroy Mucorales by the generation of cationic peptides, defensins and oxidative metabolites **[24]**.

It has been observed that hosts susceptible to this fungal infection suffer from characteristic abnormal physiological conditions like hematologic malignancies **[32]**. Individuals with hematological malignancies were susceptible to contracting Mucormycosis during the neutropenia phase of the infection **[33]**. Chemotherapy and the usage of voriconazole used in the treatment of Aspergillosis can contribute to the presence of Mucormycosis in hematological malignancies **[34]**. Mucormycosis was also observed to be more common in individuals with acute leukemia than other types of cancers **[8, 35, 36]**. Prevention of Mucormycosis in patients with hematological malignancies can be prevented by avoiding environmental exposure **[37]**. The treatment strategies may include surgery, antifungal treatment, and reversal of neutropenia **[8, 38]**.

Transplantation therapies, like stem cell transplantation, have also been identified as risk factors for Mucormycosis **[8, 39]**. The incidence of the condition, however, varies based on the type of organs that are being transplanted. The vulnerability of the recipients of transplantation therapies towards Mucormycosis is owed to the administration of immunosuppressants and high doses of steroids **[40]**.

Corticosteroid treatment

COVID-19 infection is often treated by administering heavy doses of steroids (corticosteroids), as its use provides relief from inflammation in the lungs and may play a role in curbing the damages incurred in the body during the course of the cytokine storm **[24]**.

Mucormycosis occurs in those who have undergone a prolonged corticosteroid treatment **[18]**. The review by John *et al* conducted in April 2021 reported the findings of 41 confirmed Mucormycosis cases in people with COVID-19, of whom 88% were receiving corticosteroids **[11]**. This report was re-iterated with studies on an even larger case series of 101 cases of Mucormycosis (of which 95 are confirmed

and 6 suspected) in COVID-19, where more than two-third (76.3%) received a course of corticosteroids **[11]**.

Use of steroids leads to inflammation and reduction in the production of white blood cells (WBCs) and T-helper cells, making it suitable for invasion of foreign substances, and complete corrosion of the immune system of the host cell, thus making COVID-19 patients more vulnerable to such secondary fungal infections **[18]**. Besides this, these steroids may trigger the uncontrolled release of sugar in the blood, enabling the growth of Mucorales and their proliferation and invasion at a rapid rate **[25, 41]**.

Antibiotic treatment

Widespread use of broad-spectrum antibiotics was also observed, with as many 72% of patients being administered these drugs, often with no underlying evidence of infection **[11].**

Antibody treatment

The use of monoclonal antibodies to treat COVID-19 may also be seen as a reason for the occurrence of co-infections like Mucormycosis **[42]**.

Prolonged hospital stay

8% of patients were said to have had secondary bacterial or fungal infections during their hospital admission for COVID-19 treatment, as reported in a recent review **[11]**. Immense use of oxygen masks and ventilators increase susceptibility to contracting Mucormycosis.

Virulence factors of the pathogen

Besides host factors that predispose patients to this fungus, Mucorales possess certain virulence factors. One such trait is demonstrated by its ability to take up iron from the host **[24]**. Iron is an essential element for cell growth and development, contributing to various vital processes of the cell **[24]**. Therefore, skilled pathogens like Mucorales make use of multiple processes in their quest to obtain iron from the host. Suggested data from recent sources shed light upon the fact that the quantity of available, unbound iron in serum plays a critical factor in turning patients with DKA susceptible to Mucormycosis contraction **[24]**.

However, in mammalian hosts, iron is found bound to host iron-binding proteins such as transferrin, lactoferrin, and ferritin **[24]**. This sequestration averts the toxic effect of free iron that would otherwise be used by the pathogens. Limiting iron availability proves to be an important strategy in major universal host defense mechanisms against microbes and against Mucorales in particular because, in the absence of exogenous iron, *R. oryzae*is observed to grow poorly in normal serum **[24]**.

Transmission

The fungal pathogen enters the host via the nostril, and spreads further to the paranasal sinuses and lungs, the common targets for this fungal disease. The infection eventually makes its way to intra-orbital and intracranial regions of the body, accentuated by the viral infection of COVID-19, which provides a perfect environment for the growth and development of Mucorales.

The fungal hyphae and spores can also enter the host via consumption of contaminated food or through open wounds which the host may possess **[5, 8, 11, 43, 44]**.

It may be speculated that during the COVID-19 pandemic, many post-COVID-patients contracted Mucormycosis mainly due to prolonged hospitalization or through the use of contaminated medical equipment such as mechanical ventilators **[8, 11, 45]**.

Mechanism of Pathogenesis

Infection with the Mucormycosis pathogen usually takes place via invasion of the blood vessels, resulting in thrombosis and infarction of the concerned tissue **[8]**. When the endothelial cells come in proximal contact with the spores of the fungus, angio-invasion occurs **[8]**. Enhanced interaction with the receptors of these cells gives rise to in-cell damage and fungal spread **[8, 46]**. In comparatively healthier people, the fungi often get eradicated by the polymorphonuclear (PMN)-phagocytes, and hence fungal growth is usually observed in individuals with defects in this mechanism **[8]** Additionally, Mucorales sometimes demonstrate resistance to these mechanisms making them more virulent.

Signs and Symptoms

The potential to invade multiple systems in the body resulting in a myriad of clinical symptoms that progress rapidly is demonstrated by Mucormycosis in COVID-19 patients **(Table 1)**.

Table 1: Characteristics of COVID-19 disease, complicated by Mucormycosis. Source 1 (S1): Singh *et al*. [11]; Source 2 (S2): Honavar *et al*. [25]

Case Report in each country	• **India-82%** • **USA-9%** • **Iran, UK, France, Italy, Brazil, Turkey, Mexico, Austria-Percentage negligible in each country**	**Highest number of cases was reported from India**
Age Range	• **22-86**	-
Sex	• **Male-80%** • **Female-20%**	**The comorbidity was observed in males more often.**
Risk factors	• **Hyperglycemia at presentation** • **Malignancy** • **Post transpalant**	-
Hyperglycemia at presentation	• **Pre-existing DM-80%** • **New-onset Diabetes mellitus/hyperglycemia-2%** • **Presented with DKA (Diabetic Ketoacidosis)-15%**	**Majorly Type 2 diabetes observed.**
COVID-19 Treatment	• **Steroid-76%** • **Tocilizumab-4%** • **Remdesivir-21%**	**Very few cases received all three drugs, most of them received a combination of two or just one of them.**
Mucormycosis cases	• **Confirmed-95%** • **Suspected-5%**	**Confirmation indicates both microbiological and histopathological diagnosis.**
Localisation of Mucormycosis	• **Nasal/Sinus-89%** • **Rhino-orbital- 57%** • **Rhino-orbito-cerebral-22.2%** • **Bone involvement-15%** • **Pulmonary- 8%** • **Gastrointestinal- 1%** • **Cutaneous-1%**	**There appears to have an overlap between) Nasal/Sinus only and Rhino-orbital variety.**

As this disease can affect different parts of the host body such as the nose, central nervous system (CNS), gastrointestinal tract (GIT), heart and the kidneys, the patient afflicted with Mucormycosis can exhibit a wide range of symptoms **[5, 11]**. These may include prolonged high fever, cough, headache, sinus congestion, nausea and shortness of breath which are similar to the symptoms of COVID-19 infection **[8]**. Other symptoms include black lesions in and around the nose and the top of the mouth, blackish or blood-tinged nasal discharge, unilateral facial swelling accompanied with numbness, amaurosis, skin lesions, abscess and necrosis of tissues, chest pain, and hemoptysis **[11, 12]**. Direct invasion with marked tissue necrosis of adjacent structures is common in Mucormycosis **[11, 12]**. It is succeeded by

fast progression and angio-invasion of the pathogen from the nasal and sinus mucosa into the orbit and brain **[18, 19]**. This is known as the rhino-orbital movement, and it progresses rapidly. Some cases have reported extensive orbital infections which progress into the optic canal and superior orbital fissure **[18]**. It causes severe paralysis of the eye muscles, dysfunction of the optic and cranial nerves, vision loss and a permanently dilated pupil **(Figure 1)[18]**. Orbital cellulitis was also observed with cases manifesting decreases in visual acuity, a hindrance to extraocular movement and severe pain **[18]**. Some case studies have also displayed symptoms like conjunctival hyperemia, complete loss of vision, and ptosis **[18]**. Some rare cases have shown retino-choroiditis, followed by retinoschisis **[18]**.

Being a highly invasive disease, its symptoms progress rapidly, and hence, Mucormycosis is associated with high morbidity levels **[5, 11, 12**]. However, these fungi rarely cause pathological manifestations in immunocompetent individuals due to the presence of a robust immune system in them. When the spores of Mucorales enter immunocompetent individuals, neutrophils are deployed by the body's immune system to eliminate them, and thus the individual successfully staves off the infection **[5, 11]**.

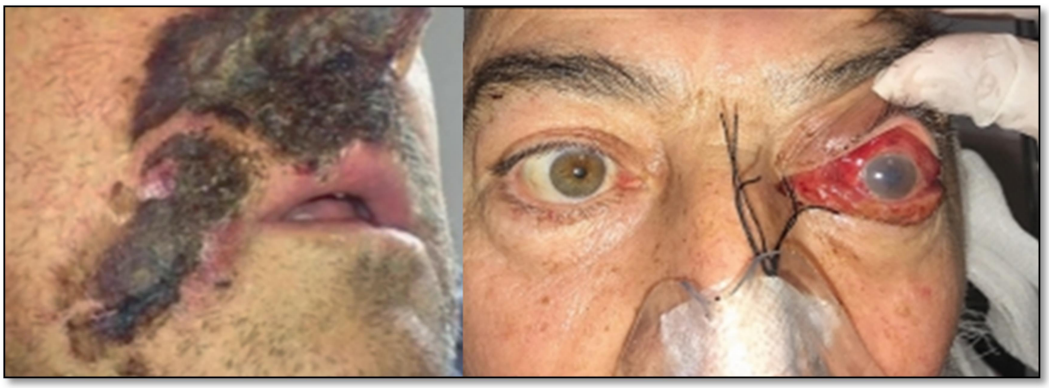

Figure 1: Physical manifestation of Mucormycosis as observed in clinical patients. Source 1 (S1): Cornely *et al.* [12]; Source 2 (S2): Bayram *et al.* [18]; Source 3 (S3): Werthman-Ehrenreich *et al.* [26]

Diagnosis

Detection of Mucormycosis witnesses several approaches, whilst all of them approaching the same goal: the detection of the broad, aseptate hyphae, which branches at right angles under KOH mounts **[18, 26]**. They are stained with the commonly available fungal stain lactophenol cotton blue (LPCB) **[18]**. This helps to visualize the aseptate hyphae, as well as the sporangiospores **[18]**. The Grocott-Gomori methenamine silver stain best shows the hyphae in infected tissues **[18]**. Periodic acid-Schiff, and hematoxylinand eosin

stains are used to check the presence of pathological changes in tissues, including acute suppurative inflammation with focal areas of granulomatous inflammation and angio-invasion by hyphae with consequent thrombosis and infarction **[18]**.

Other methods can be immune-histochemical investigations, detection of fungal DNA by PCR reactions, and diagnosis of the infected tissue by *in situ* hybridization **[18]**.

To gauge the extent of the spread of the disease, CT/MRI of the sinuses, orbit, or brain may also be done according to requirements **[18] (Figure 2).**

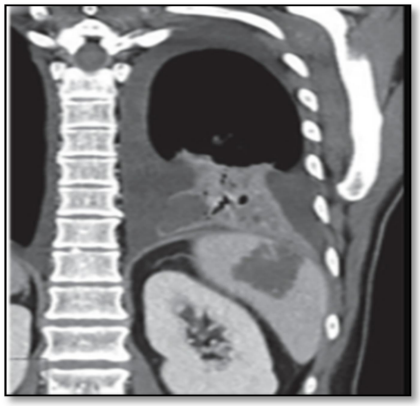

Figure 2: Particularly aggressive form of Mucormycosis, as observed through radiographic imaging techniques such as computed tomography (CT). Source 1 (S1): Cornely *et al*. [12]

Treatment

The key to combating Mucormycosis as a co-infection with regard to COVID-19 has to be its early detection and immediate treatment. Proper diagnosis and extent of the spread of the fungus must be analysed, and subsequently the patient must be put on antifungal therapy. High-dose liposomal amphotericin B is started immediately after diagnosis, while isavuconazole and delayed-release tablet posaconazole can be combined along with it **[12, 47]**. Both triazoles are strongly recommended salvage treatments. Amphotericin B deoxycholate should be avoided as it is highly toxic to the kidney; instead liposomal amphotericin B must be used due to its reduced toxicity **[12, 25]**. The latter can hence be used for a longer treatment plan, as it have a lesser effect on the already affected kidneys **[18, 26, 27]**.

However, treatment with antifungals is a genuine problem in India right now as low-income families may not be able to afford it owing to its expensive nature.

A lot of options are unavailable for antifungal therapy, and most of these pricey medicines are quite inaccessible for the low-income families in developing countries like India. A lot of research work

must therefore be undertaken in future to find out more combinatorial approaches of applying antifungals to treat the disease **[48]**.

Furthermore, only antifungal treatment may not be enough to treat the invasive tissue damage due to vascular thrombosis and ischemic necrosis barrier; it may require intense debridement and even surgery along with drainage of the paranasal sinuses, in extreme cases, to curb the further spread of the fungus **[18, 27, 47]**.

The diagnostic and therapeutic approaches for Mucormycosis in COVID-19 patients are summarized in the following flowchart **(Figure 3)**:

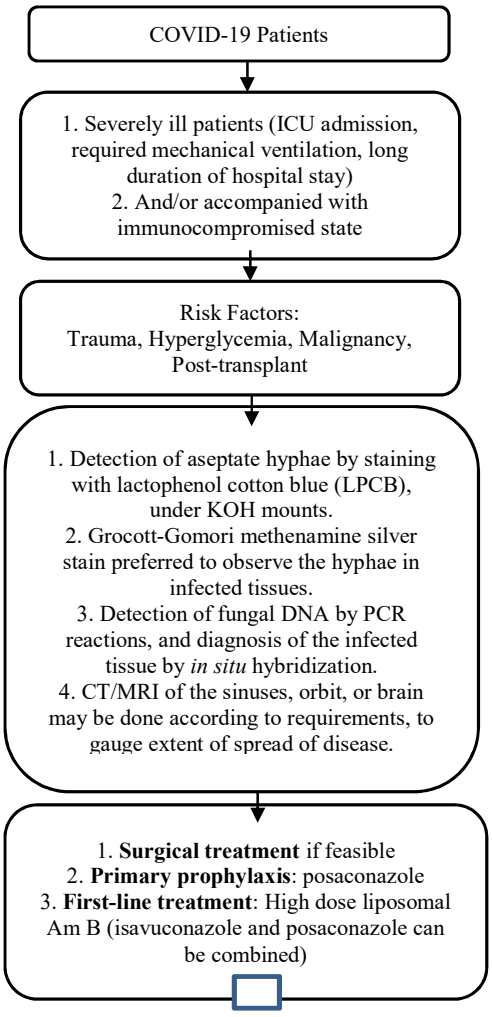

Figure 3: Diagnostic and therapeutic pathway for invasive Mucormycosis co infection in COVID-19 patients Source 1 (S1): Bhatt *et al.* [5]; Source 2 (S2): Bayram *et al.* [18]

Prevention

During the entire course of COVID-19 treatment, the ailment of the co-morbid patients must be managed, and kept under control, using necessary medications such as insulin or other applicable therapies. The

causative fungal pathogen is airborne and it mainly affects paranasal sinuses, orbit, and the brain, and therefore mechanical ventilators which are to be used by COVID-19 patients must be properly sanitized, and a controlled set-up must be maintained. A sterile environment must be maintained so that artificial ventilation, surgery, or any other anthropogenic actions do not lead up to contraction of this fatal infection. Steroidal treatment administered to COVID-19 patients must be done carefully. Healthcare officials should strongly recommend combinatorial approaches to treat the SARS-CoV-2 virus before finally resorting to steroids.

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CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest.

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