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Letter to the Editor

Mucormycosis in COVID-19, host-iron assimilation: Probiotics can be novel therapy

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Dear Sir,

Coronavirus-2 (SARS CoV-2) has caused havoc globally with 16,57,72,430 confirmed cases of COVID-19, and 34,37,545 deaths in the past 1 year. It causes disease ranging from mild fever with respiratory and or gastrointestinal symptoms to life-threatening pneumonia with hypoxia, post COVID-19 sepsis, and other complications. There is a dysregulated innate immune response, characterized by cytokine storm, ciliary dysfunction, thrombo-inflammation, microvascular coagulation, and exhaustion of immune response. Patients admitted and subjected to various emergency procedures, mechanical ventilation, prolonged hospital stay, and breaches in asepsis may have opportunistic secondary infection with bacteria and fungus.

Pre-existing disease, such as diabetes mellitus, previous respiratory pathologies, use of broad-spectrum antibiotics, high doses of corticosteroids, anti-IL-6 inhibiting strategies, and systemic immune alterations in COVID-19, affects the gut microbiome.

In Indian hospital settings, COVID-19-associated invasive mucormycosis (*Rhizopus oryzae,* a filamentous fungus), has emerged as a life-threatening complication recently. Mucormycosis is mainly acquired by the inhalation of spores and transported to the pharynx by cilia. In COVID-infected patients due to epithelium damage, ciliary dysfunction and immunosuppression infection begins in the nasal turbinates or alveoli. Once the fungus colonizes the nose and paranasal sinuses, the infection spreads along vascular structures and invades the base of the skull (eroding bones), disseminating to the central nervous system or disseminates in the body. Mucor sporangiospores are also capable of secreting several toxins or proteases which may further destroy the endothelial cells in mucosal membranes.[1]

An important virulence trait of the fungus is its ability to acquire iron from the host.

The level of unbound serum iron in an acidic environment plays a critical predisposing factor in the growth of mucormycosis. In COVID-19 patients with uncontrolled diabetes and diabetic ketoacidosis (DKA) with blood pH 7.3–6.8, there is temporarily disruption of transferrin capacity to bind iron. Recent studies have proved that the level of unbound iron in serum plays major critical factor in predisposing DKA patients to mucormycosis.[2,3] Increase in serum concentration of iron and ferritin levels can cause insulin resistance and dysfunction of β cells of the pancreases. This excess endogenous free iron is taken up efficiently by the fungus through siderophores, and iron permeases, further enhancing their growth and virulence. This way DKA abolishes an important host defense mechanism by decreasing pH and increasing free serum iron levels.[4]

In animal models of DKA, iron chelators deferiprone and deferasirox protected mice from mucormycosis. Deferoxamine obtained from the bacteria streptomyces pilosus, acts as a siderophore, worsened mucormycosis by stimulating its growth.

While deferasirox and deferiprone did not allow mucormycosis to take up iron and did not support its growth *in vitro*. Deferasirox proved effective in iron-chelating from *R. oryzae* and has cidal activity against mucormycosis. Deferasirox proved significant improvement in survival of mice infected with *mucormycosis* in DKA or neutropenia, with comparable to that of liposomal amphotericin B.[5]

In COVID-19 with its associated related opportunistic infections, probiotics supplements could be pivotal in maintaining an optimal immune system. Probiotics are live microorganisms and when consumed or administered in adequate quantities, confer multiple health benefits to the host. Bacteria from the genera *Lactobacillus, Bifidobacterium*, *Enterococcus*, *Streptococcus*, *and Saccharomyces* are used commonly as probiotics in various food supplements.

Epithelial cells of immune cells express multiple series of pattern recognition receptors which include Toll-like receptors (TLRs). These TLRs interact with

pathogen-associated molecular patterns from fungus and initiate appropriate signaling pathways that express different genes and produce subsequent immune mediators.

Probiotics used as nutritional supplements may play a key role in maintaining the internal immune homeostasis, with their ability to modulate gut microbiota. They have the ability to affect the redox status by their antioxidative potential in the gut lumen.

Probiotics have indirect antioxidant mechanism by reducing the bioavailability of metals such as iron which, have been indicated to limit pathogen growth through iron chelation and anti-microbial metabolite production.[6] *Enterococcus* and *Bacillus* isolate *SB10*, *JC13* and *IFM22* have been found to produce maximum siderophores ranging from 65% to 90% at an optimum pH 7. They have significant iron-chelating ability. They are non-hemolytic in nature and show excellent tolerance to acid and bile salts. Most of these strains are highly resistant to all the antibiotics tested. In addition, they have antimicrobial activity against *Staphylococcus aureus*, *Klebsiella,* and *Escherichia coli.*[7] Another commercially available *Lactobacillus (L.) rhamnosus R0011*, *Streptococcus thermophilus 821,* and *Saccharomyces boulardii* as singular treatment or in combination has significant iron chelation ability. Ferrichrome is a siderophore which is obtained from *Lactobacillus casei* ATCC334 (*L. casei*). They are found to have a high antioxidants activity by acting as iron-chelating agents. This strategy of limiting iron availability can also be a major universal host defense against mucormycosis in particular as mucormycosis grows poorly in serum with less iron.[8]

The role of iron chelators in mucormycosis requires further elaboration. In view of the urgency of the situation the concept that probiotics strains with higher iron-reducing and iron-chelating ability, could provide an effective strategy to combat the virulence of mucormycosis needs to be looked into. In addition, these probiotics might help stabilize the altered gut microbiota which affects the immune response of the body.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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