Mini Review

A Mini Review: Mucormycosis in Coronavirus Disease-19, Host-Iron Assimilation, and Probiotics as Novel Therapy

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Abstract

Mucormycosis is an acute fungal infection with 90% of cases in the form of rhino-orbito-cerebellar. It is an aggressive and life-threatening fungal infection causing 50% mortality in people with coronavirus disease 2019 (COVID-19). In COVID-infected patients due to, diabetic ketoacidosis, epithelial damage, ciliary dysfunction, dysfunctional phagocytic mechanism, and immunosuppression, there is impaired chemotaxis and defective intracellular killing leads to fungal spores to invade, germinate and penetrate in surrounding tissues. The use of broad-spectrum antibiotics disrupts the normal microbiomes and increases the probability of growth of Rhizopus spp. Commercially available probiotics such as *Lactobacillus, Bifidobacterium*, *Enterococcus*, *Streptococcus*, *and Saccharomyces* when administered in adequate quantities form siderophores which induces iron stress in fungus and inhibits spore germination.

Keywords: Coronavirus disease-19, iron chelators, mucormycosis, probiotics

Introduction

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused havoc globally. The second wave of COVID-19 affected world substantially with several cases of coronavirus disease associated mucormycosis. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population, while in India, prevalence of mucormycosis is estimated to be 140 per million population which is almost 80 times higher than other developing countries. A total of 45,432 cases of mucormycosis have been reported by states till July 15, 2021.[1] Most common presentation of mucormycosis included Rhino-cerebral (77.6%), cutaneous (4.3%) and pulmonary (3.0%).

Dysregulated innate immune response seen in Coronavirus infection has been associated with a wide range of opportunistic bacterial (lipopolysaccharide containing Bacteroides Fragilis and Staphylococcus aureus) and fungal infections (Aspergillus and candida are most commonly reported).[2] Various reasons reported to be facilitating the germination of mucorales spores in COVID-19 patients is hypoxia, old or new onset hyperglycemia, steroid-induced hyperglycemia, metabolic acidosis or diabetic ketoacidosis (DKA), increased serum ferritin levels, decreased phagocytic activity of white blood cells due to immunosuppression coupled with other risk factors like prolonged hospitalization with or with-out mechanical ventilators.[3,4]

Phycomycosis or zygomycosis was first described in 1885 by Paltuf,[5] and term mucormycosis is coined by Baker in 1957.[6] Mucormycosis is a angioinvasive infection caused by a group of fungi belonging to mold fungi of the genus *Rhizopus*, *Rhizomucor*, *Mucor*, *Cunninghamella,* and *Absidia* of order mucorales. *Rhizopus oryzae* (a filamentous fungus) is the most common and is responsible for almost 70% of all cases[5,6] The most important clinical condition that predispose to mucormycosis includes diabetes mellitus with or without diabetic ketoacidosis, organ transplantation, hematological and other malignancy, corticosteroids, iron overload, intravenous drug use, and malnourishment. Recently, in the Indian hospital settings,

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during COVID-19 pandemic, there is a sudden increase in the significant burden of invasive mucormycosis. It has emerged as a life-threatening complication of COVID-19. Ninety percent of cases are in the form of rhino-orbital-cerebral (ROCM).[7]

Worldwide, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population. According to a recent estimate of year 2019–2020, the prevalence of mucormycosis is 80 times higher in the Indian population in comparison with that in other developed countries.[8] Various case series have reported the development of severe opportunistic infections such as ROCM mucormycosis, pulmonary aspergillosis and mucormycosis, gastrointestinal mucormycosis, renal mucormycosis, candidiasis, etc., in patients affected with COVID-19 disease in India.[8,9] Unfortunately, despite adjunct antifungal treatment and disfiguring surgical debridement, still the overall mortality rate for mucormycosis is more than 50%.

Clearly, there is an urgent need of development of new strategies and look for alternatives to adjunctive antifungal therapy to prevent and treat mucormycosis.

Pathophysiology of Mucormycosis

Mucormycosis spores are copious in the atmosphere and ready to invade in the nose and paranasal sinuses if the environment is suitable for their growth. In general, inhaled spores and fungi form a part of normal sinonasal flora and transported to the pharynx by cilia but destroyed significantly by the immunological system in healthy patients. These spores are cleared by gut microbiomes by the generation of oxidative metabolites. In COVID-infected patients due to diabetic ketoacidosis (DKA), epithelial damage, ciliary dysfunction, dysfunctional phagocytic mechanism, and immunosuppression. There is also impaired chemotaxis and defective intracellular killing. Infection begins in the nasal turbinate's or alveoli.[10] If the spores are smaller than 10 μm, they may remain localized to the upper airways resulting in sinusitis and colonize in the distal alveolar spaces involving the pulmonary tract.[11] 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 the mucosal membranes.[12] *R. oryzae* when get exposed to neutrophils results in the upregulation of Toll-like receptor 2 and proinflammatory gene expression resulting in rapid induction of NF-kB pathway-related genes.[13]

Mucormycosis pathogenesis and iron uptake

In addition to the patient immune factor predisposing to mucormycosis, an important virulence trait of the fungus is its ability to acquire iron from the host.[14] The level of unbound serum iron in an acidic environment plays a critical predisposing factor in the growth of mucormycosis. Recent studies have proved that the level of unbound iron in serum plays major critical factor in predisposing DKA patients to mucormycosis.[15,16] The most commonly described mechanisms for iron uptake in mucormycosis include the reductive iron assimilation which involves reduction of ferric iron to ferrous form through ferric-reductase (FRE genes).[17] This reduce iron is then taken up by the fungus cells by the permease FTR1 along with the oxidation of the iron by the activity of ferroxidase (Fet3). Recent data show that the gene encoding high-affinity iron permease (FTR_1), SreA, and genes involved in the uptake of iron from heme are expressed by mucormycosis in murine model.[14] The second mechanism for iron uptake includes fungal receptors, FOB1, and FOB2 (ferrioxamine binding plasma membrane proteins), that are involved in nonreductive (iron bound siderophore complexes) iron uptake in mucormycosis.[18] Figure 1 shows the mechanism of iron uptake by mucormycosis

Another mechanism of obtaining iron from the host is through heme, stored iron stores, ferritin and transferrin. Two homologues genome of hemeoxygenase enable mucormycosis to obtain iron from host hemoglobin and explain the angioinvasive nature.[19]

Host-mucormycosis interactions

Mucormycosis infections are characterized by extensive angioinvasion that results thrombosis in vessels and subsequent tissue necrosis.[19] Ischemic necrosis of infected tissue can prevent the delivery of leukocytes and antifungal agents to the infection foci, due to which despite adjunct antifungal therapy mortality rate of mucormycosis is >50% in patients.[20] Various studies from hospitals across the country have revealed heavy

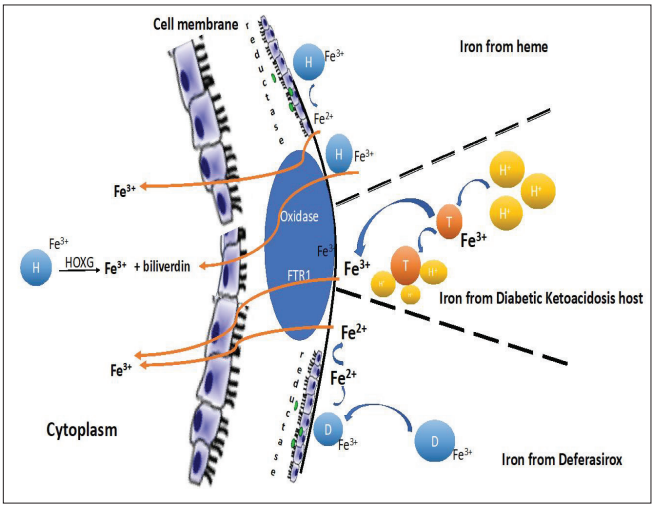

Figure 1: Mechanism of iron uptake by Mucorales during mucormycosis. (A) Heme is likely to present as source of iron as disease is angioinvasive in nature. Fungus takes up heme intracellularly or strips ferric iron from heme by action of reductase-permease system. Ferric iron is obtained by action of heme oxygenase, if heme is transported intracellularly. (B) in patients with DKA, there is proton (H+)- mediated displacement of ferric iron (Fe3+) from transferrin (T) increase the availability of iron, transported intracellularly by reductase permease system. Deferasirox (D) chelates iron from transferrin directly resulting in formation of ferrioxamine (iron-deferasirox complex). Fungus then liberates ferrous iron ferrioxamine by reduction at cell surface. Iron is transported across the cell membrane by copper oxidase -iron permease (FTR1) complex

mold spore counts even in hospital air due to predominantly hot, humid conditions in our tropical climate.[21]

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, which results in generation of more nontransferrin bound iron by glycation of apotransferrin.[22] A study by Momeni *et al*. states that there is significant correlation between increase serum ferritin level and diabetes mellitus.[23] Increasing concentration of iron and ferritin levels could cause resistance to insulin and dysfunction of β-cells of pancreases. Hyperinsulinemia due to resistance to insulin may be responsible for increasing serum ferritin.[24] This excess endogenous free iron is efficiently taken up by the fungus through sidephores or iron permeases, further enhancing their growth and virulence. Diabetic ketoacidosis abolishes an important host defence mechanism by decreasing pH and increasing free serum iron levels that permits the growth of mucormycosis.[25]

Entry of mucormycosis through a glucose-regulated protein (GRP78) presents on endothelial cells with damage to endothelial cells has been observed. GRP78 receptors are also known as BiP/HSPA5, discovered as cellular protein mainly present in the endoplasmic reticulum, and induced by glucose starvation.[26] Elevated concentration of iron and glucose during DKA along with increased expression of GRP78 in the sinus, lungs, and brains in diabetic rats supports the occurrence of mucormycosis.[27]

Gut microbiomes *in vitro* antifungal activity

The human gut microbiota consists of approximately 10[14] resident micro-organisms which include bacteria, viruses, and fungi. The most prominent are phyla *Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes*[28] while the colon harbors high density of bacteria from the family *Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae, and Ruminococcaceae*.[29] Table 1 lists bacterial genus, species, and their products which exhibit antifungal activity.[30-39]

These commensal microbiota in symbiosis with each other play a key role in various host physiological functions, including dietary digestion, modulation of immune response by inflammatory cytokines, and development and function of innate and adaptive immune system. Gut microbiomes inhibit the growth of other microorganisms by competing for nutrients, production of siderophores, production of antimicrobials, and enzymes. Gut macrophages are located in close proximity to the intestinal microbiota and develop a unique phenotype called "inflammation energy" in which they do not produce pro-inflammatory cytokines in response to microbial stimuli such as Toll-like receptors (TLR) ligands, a set of microbes associated molecular patterns.[40] Gut microbiota plays an important role in the development of $CD4^+$ T-cells both within and outside the intestine and regulate the balance of pro-inflammatory responses by controlling their differentiation into Th1 cells (T-helper subtype cells) critical for the host defense against intracellular microbial infection and cytokines production.[41] Due to broad-spectrum antibiotics uses in COVID-19, there is change in composition of the microbiota, and in few previous studies, it has been reported that it took at least 40 days for microbiota to revert back to their pretreatment status.[42,43] In COVID-19 with its associated related opportunistic infections, a healthy gut microbiome could be pivotal in maintaining an optimal immune system and response.

Probiotics as Novel Treatment

Probiotics are defined as live microorganisms which when consumed or administered in adequate quantities, confer multiple health benefits to the host. Bacteria belonging to the genera *Lactobacillus, Bifidobacterium*, *Enterococcus*, *Streptococcus*, *and Saccharomyces* have often been used as probiotics in food supplements.[44] Figure 2 illustrating various known mechanisms of action of probiotics on microorganisms.

Epithelial cells or immune cells express multiple series of pattern recognition receptors which include TLRs.[45] These TLRs interact with pathogen-associated molecular patterns from fungus and initiate appropriate signalling pathways that express different genes and produce subsequent immune mediators, which help the hosts to counteract various pathogenic infections.[46] Probiotic used as nutritional supplements may play a key role in maintaining the internal immune homeostasis, with their ability to modulate gut microbiota. They have ability to affect the redox status by their anti-oxidative potential in the gut lumen.[47]

Probiotics as iron-chelators

In many animal disease models, probiotics decrease cytotoxic damage and downregulate inflammatory pathways. Probiotics have indirect antioxidant mechanism by reducing bioavailability

Table 1: Gut microbiomes and their products with exhibit antifungal activity

Bacterial genus	Bacterial species	Antifungal molecule	References
Streptococcus	*S. viridians group*	Peptides	30, 31
Clostridium	Clostridium butyricum	-	32
Bacillus	*Bacillus mesentricus*	Chitin degrading enzymes, and inhibition of formation of dense hyphal mats	33
Lactobacillus	*L. acidophilus* *Lactobacillus* spp. *L. rhamnosus*	Block adhesion and nutrition depletion	34, 35
Enterococcus	*E. faecalis*	-	31, 36
Brevibacterium	*B. linens*	Methanethiol	37
Pseudomonas	*P. aeruginosa*	Dihydroaeruginoic acid, Pyocyanin, 1-hydroxyphenazine	38, 39

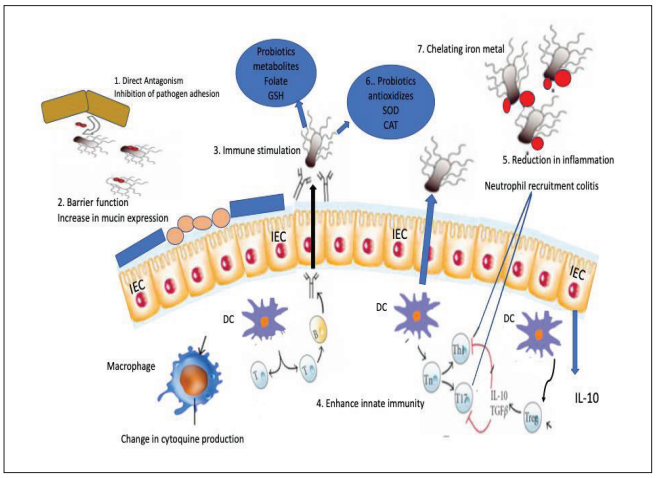

Figure 2: Schematic diagram illustrating known mechanism of action of probiotics on microorganism. (1) direct antagonism, inhibition of pathogen adhesion, (2) barrier function by increase in mucin expression, (3) immune stimulation, (4) enhance innate immunity (5) reduction in inflammation, thus altering intestinal properties for colonization, (6) increase level of host antioxidant metabolites (7) chelate metal iron

of metals such as iron which have been indicated to limit pathogen growth through iron chelation and anti-microbial metabolite production.[17] *Enterococcus* and *Bacillus* isolates *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 nonhemolytic in nature and shown excellent tolerance to acid and bile salts. Most of these strains are highly resistance to all the antibiotics tested.[48,49] In addition, they have antimicrobial activity against *S. aureus*, *Klebsiella,* and *Escherichia coli*.[50,51] Another commercially available *lactobacillus (L.) rhamnosus R0011*, *Streptococcus thermophilus 821,* and *Saccharomyces boulardii* as singular treatment or in combination has significant iron chelation ability.[52] Ferrichrome is a siderophore which are derived from *Lactobacillus casei* ATCC334 (*Lacticaseibacillus casei*). They are found to possess a high antioxidants activity by acting as iron-chelating agent.[53] The factors and mechanism responsible for metal ion chelation by probiotic bacteria's are not well understood, but it is revealed that transition metal ion inhibit enzyme-catalyzed phosphatase easter displacement and produce peroxyl and alkoxyl radicals by the decomposition of hydroperoxides.[54] This strategy of limiting iron availability can also be a major universal host defence against mucormycosis in particular as mucormycosis grows poorly in serum with less iron.[19]

Iron chelators and mucormycosis

In animal models of DKA, iron chelators deferiprone and deferasirox protected mice from mucormycosis. *Deferoxamine* obtained from the bacteria streptomyces pilosus, strips ferric iron from transferrin, acts as a siderophore. It attaches itself with Rhizopus through inducible receptors, and then iron is transported intracellularly by and active reduction of ferric form into more soluble ferrous form, which worsened mucormycosis by stimulating it growth and worsen the survival of animals with mucormycosis.[55] While in contrast with other iron chelators *Deferasirox* and *Deferiprone* did not allow mucormycosis to take up iron and did not support its growth *in vitro*. Deferasirox proved effective in chelating iron from *R. Oryzae* and has cidal activity against *mucormycosis*. Deferasirox significantly improved survival of diabetic ketoacidotic or neutropenic mice with *mucormycosis,* with comparable to that of liposomal amphotericin B.[55]

Conclusion

Increasing number of mucormycosis in the Indian population followed COVID-19 is a dangerous intersection of trinity of high dose corticosteroid use, diabetes, and opportunistic fungal infection. 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 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. The role of probiotics and iron chelators as supporting treatment along with other major antifungal therapy in mucormycosis requires further elaboration and clinical trials.

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Conflicts of interest

There are no conflicts of interest.

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