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The Triple Threat of the Covid-19 Pandemic-(White, Yellow and Green Fungus)

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Abstract *- India has to prevent three deadly fungal infections Black fungus, White fungus and Yellow fungus. Designating fungus on colours generates embarrassment. Mucormycosis has been called one of the "most feared infections in all ofinfectious diseases," and now it is surging as a COVID-19-associated infection throughout India and raising fire alarm bells around the globe. The contemporary internationally rampant of COVID-19 has affected a large number of patients to fungal pneumonias,Respiratory diseaseswhich carries a risk of developing triple threat of pandemic White, Yellow and Green fungal diseases. Aspergillosis, Mucormycosis and Candida are the main cause of invasive fungal infections. COVID-associated aspergillosis (CAPA) and (COVID-19-associated mucormycosis) CAMCR cases are well registered. "Black fungus is the crossing of COVID-19 and uncontrolled Diabetic mellitus in the pandemic. Physicians are suspicious about (COVID-19-associated mucormycosis) CAMCR especially if a rhino-orbitalsare notedin COVID-19 .DM (Diabetes Mellitus) patient with COVID-19 develop On the other hand Candidiasis, are not life threatening, and is common in ICU Covid-19 patients.*

Keywords *- Coccidioides Immitis; Aspergillus fumigatus; Histoplasma capsulatum; Blastomyces dermatitidis; Cryptococcus neoformans, Candida Albicans, Pulmonary mycormycosis, Leukemia, Neutropenia, Gastrointestinal mucormycosis, Liposomal amphotericin B*

I. INTRODUCTION

COVID-19 pandemic lay out from China and affected 3 million people, and 200,000 deaths worldwide (1). This is an enveloped RNA beta coronavirus and phylogeneticallyhas affinity to n-SARS-CoV-2 (2). Fever, cough, are the primary symptoms and requires ventilation and intensive care which are associated with older age, a higher percentage of comorbidities and higher mortality (3). *Aspergillus* is the main co-infection during COVID-19 hospitalizedpatients. (4) The antagonistic feature of the SARS-CoV-2 virus is to damage the lung tissue and produce large bilateral alveolar-interstitial lesions (5). In severe COVID-19 cases, CD4+T and CD8+T cells are lower, and IL-2, IL-6, IL-10, TNF-alpha are raised (6). Coronavirus disease 2019 (COVID-19),and Aspergillus causes severe acute respiratory syndrome (7).Till May 18th, 2020, the COVID-19 has rapidly spread to 212 countries and caused more than 310,000 deaths globally (8).COVID-19 patients have alveolar damage, inflammatory exudation, with a decrease in CD4 + T and CD8 + T cells (9). The intensive care unit (ICU), ambulatory patients or patients with a longer duration of hospital stays, were more likely to develop fungal co-infections (10). Aspergillus coinfection in coronavirus disease 2019 patients has rarely been described but may be occurring among coronavirus disease 2019 patients admitted to ICUs (11). High rates of Influenza-associated invasive pulmonary Aspergillosis may not be universal (12). Candidemia is a frequent bloodstream infection worldwide, with high crude mortality rates (13). The emergence of the COVID-19 pandemic brought new challenges for healthcare workers worldwide (14,15). Therefore, candidemia could be a potential complication of patients with COVID-19 cared for in ICUs. A series of 989 patients with COVID-19 admitted to a hospital in Spain reported four cases of candidemia among 88 coinfections and superinfections (16). Bacterial(Tuberculosis.) and viral (influenza), symptoms are exhibited by Blastomycosis, coccidioidomycosis, and histoplasmosis fungal diseases (17). Yellow fungus is

curable if detected early, although the fact that it arises within the body (18).

A. Chronological record of significant events

First case of black fungus in humans reported in 1885 by Friedrich Küchenmeister (19). Fürbringer first described the Black fungus disease in the lungs in 1876 (20). Gregory first observed the rhino-orbital cerebral mucormycosis in 1943. The order Mucorales contains many species, 38 are associated with human infections (21). Mucormycosis in India were estimated to be about 70 times higher than in the rest of the world (22). *Tremellafuciformis* was first described in 1856 by English mycologist Miles Joseph Berkeley *Aspergillus* was named by Pier Antonio Micheli, an Italian priest. From 1920 to 1965, cases of disseminated aspergillus infections were implicated in the heart and CNS in addition to the sinuses and lungs.

B. COVID Unleashes the 'Lurking Scourge'

Yeast species association to the Candida genus locating numerous mucosal surfaces, like skin and the respiratory, digestive, and urinary tracts (23, 24). Lengthened ICU stays, continuous use of catheters, and indiscriminate use of broad-spectrum antibiotics, excessive use of steroids to COVID-19 patients results to develop IYIs.(Invasive yeast infections) *Aspergillus fumigatus* is increasingly recognized as an important cause offungal infections in sick COVID-19 patients (25)."Black fungus is the crossing of COVID-19 and uncontrolled Diabetic mellitus in the pandemic. DM (Diabetes Mellitus) patients with COVID-19 develop craniofacial pain without bump. Offensive smelling nasal extravasate with headache and foul halitosis in a diabetic and COVID-19 patient should be considered exceedingly distrustful of mucormycosis.

C. Fungal pneumonias can resemble COVID-19

Coccidioidomycosis, histoplasmosis, and blastomycosis,etc fungal diseases, produce fever, cough, and shortness of breath, complimentary to COVID-19 and bacterial pneumonias (26). People are infected by inhaling fungal spores in the air. Physicians have to consider fungal pneumonias as a cause of respiratory illness, especially if COVID-19 test is negative. It is predominant to note that these fungal diseases occur at the same time as COVID-19 (27, 28). Pneumonia is the leading infectious cause of death in developed countries.

D. Respiratory diseases caused by Fungi

Diabetes mellitus, chronic alcoholism, leukaemia, treatment with corticosteroids and immunosuppressive drugs and radiotherapy are the pre disposing factors. Tissue damage, necrosis and the elimination of a normal bacterial flora by antibiotics, may also facilitate fungal infection. Allergic reactions to fungi may cause bronchial asthma (*Aspergillus fumigatus*),Allergic alveolitis, etc.

E. A perfect tempest in Covid-19-associated Fungal diseases

a) Pulmonary aspergillosis--(Green fungus)

1) A cause of "destroyed lung syndrome"

Aspergillus species constitute the second most common cause of hospital-acquired fungal infections after Candida. It is found wherever organic debris occurs, especially in soil, decomposing plant matter, household dust, building materials, some foods and water. It is almost impossible to avoid the daily inhalation of Aspergillus spores. "It's fairly uncommon, but still life threatening," Aspergillosis is a disease caused by Aspergillus, a common mold that lives indoors and outdoors. "Invasive Pulmonary Aspergillosis-mimicking Tuberculosis". "Chronic fibrosing pulmonary aspergillosis: a cause of 'destroyed lung' syndrome"

Respiratory diseases caused by *Aspergillus fumigatus*

Allergic Bronchopulmonary Aspergillosis (ABPA) - causes shortness of breath, coughing and wheezing.

Invasive Aspergillosis - People with weakened immune systems like cancer patients and AIDS patients are more likely to get invasive aspergillosis. If invasive aspergillosis goes untreated, it can lead to infectious pneumonia.

Aspergilloma - People with tuberculosis are more likely to get Aspergilloma. Exposure to the fungus can develop a fungus growth called a fungus ball.

Chronic pulmonary aspergillosis - People with lung diseases, such as tuberculosis, chronic obstructive pulmonary disease (COPD), are at risk of Chronic pulmonary aspergillosis.

F. Respiratory diseases caused by Candida auris (The new superbug)

Occasionally in debilitated subject's oral thrush extends into the respiratory tract to involve the bronchi or lungs. Candida infection may be a secondary invader of lungs, wherepre-existing disease is present (eg T.B or cancer).Candida pneumonia is a rare infection of the lungs, with the majority of cases occurring secondary to haematological dissemination of *Candida* organisms from a distant site, usually the gastrointestinal tract or skin (29)*Candida auris* enters the bloodstream and causing serious invasive infections. This yeast often resistant to antifungal drugs, and difficult to treat. Ambulatory, post-covid patients with corticosteroid therapy,central venous catheter, or other lines or tubes entering their body, or have previously received antibiotics or antifungal medications, appear to be at highest risk of infection with this yeast.

G. COVID-19-Associated Black Fungus

a) An Underestimated Complexity

Black fungus is Mucormycosis. It causes chest pain, unilateral pain of the face, toothache, discoloration over the nose, and breathlessness. Delay in treatment can be exceptionally alarming. Black fungus is a rare, but aggressive fungal infection. Black fungus cases are more

in hot tropical countries because the environment is ideal for these spores present in the air to grow. Our breath makesthe mask moist, which becomes a potentially sound place for the fungus to grow. "Black fungus is the crossing of COVID-19 and uncontrolled Diabetic mellitus in the pandemic. COVID-associated aspergillosis (CAPA) and (COVID-19-associatedmucormycosis) CAMCR cases are well registered. Physicians are suspicious about (COVID-19-associated mucor mucormycosis) CAMCR especially if rhino-orbital or rhino-cerebral presentations are noted in severely ill patient with COVID-19 and Diabetes Mellitus.DM (Diabetes Mellitus) patients with COVID-19 develop craniofacial pain without bump. Offensive smelling nasal extravasate with headache and foul halitosis in a diabetic and COVID-19 patient should be considered exceedingly distrustful of mucormycosis. Black fungus spreads to the eyes and causes blindness. In the brain causes headache and seizures.

b) Increased spread of White Fungus during COVID-19 pandemic--

White fungus cases are less compared to black fungus. Symptoms are similar to Covid's –cough, headache, breathlessness and chest pain. White fungal infection caused by a yeas called Candida. Covid-19 patients are vulnerable to white fungus as it affects the lungs and symptoms are similar that of coronavirus.*Tremela fuciformis* is commonly known as snow fungus, snow ear, silver ear fungus, and white jelly mushroom. White fungus infection can spread very easily in the lungs, kidneys, intestines, stomach, and private organs. Immune-mediated pathways subsidize to the pathogenesis COVID-19-associated candidiasis (CAC). The single-cell analyses of Broncho alveolar lavages from critically ill patients with COVID-19 showed an abundance of monocyte-derived macrophages (30) An increased peripheral neutrophil-to-lymphocyte ratio was also observed in severe cases of COVID-19. (31) The increased cells may contribute to tissue damage and the severity of disease. (32)

c) Increased spread of Yellow Fungus during COVID-19 pandemic-

Mucor septicus produces Yellow fungus infection. Yellow fungal infection initiatesinternally. It is more serious and deadly than black fungus and white fungus.

d) Does immunity restore susceptibility to invasive fungal Infections?

1. Hypo immunity patients are more susceptible to infection.
2. Diabetes reduces immune response.
3. Hyperglycaemia in acidic environment particularly in diabetic ketoacidosis boost up the rapid growth
4. Steroids escalate blood sugar levels and decline the immune response of the body.
5. Patients on immunosuppressant
6. Patients suffering from malignancies
7. Patients with iron overdose
8. Malnourished, trauma, and burn people.
9. People who have spent a long time under intensive care units (ICU)
10. People who undergo an organ transplant recently, suffering from immune complications or low WBCs counts.
11. People depend on extensive antibacterial use.
12. Patients suffering from kidney damage or put on dialysis.

e) Immunity to Cryptococcus neoformans

Cryptococcus neoformans is an invasive fungus that causes cryptococcosis.*Cryptococcus* neoformans produce polysaccharide capsules, which inhibits phagocytosis. This helps to escape from the opsonic effect of complement and antibodies.Fungi are known to make molecules similar to those of our own immune system. Antibodies against fungi and yeasts may be found in the sera of many apparently normal people, as well as in those who have overt infections. In the presence of clinical fungal infections e.g. due to Aspergillus fumigatus, the amount of antibody may be so great as to be readily demonstrable by precipitin tests. Although there is considerable evidence to implicate such antibodies in the pathogenic effects of pulmonary fungal infections, there is no evidence that they hinder their spread once infection is established

f) Immunity to Histoplasma capsulatum

Histoplasma capsulatum is an obligate intracellular pathogen that evades macrophage killing by entering the cell via CR3 and then altering the normal pathway of the phagosome maturation, in parallel to the strategies of intracellular bacteria such as Mycobacterium tuberculosis (33) Differential recognition of *H. capsulatum* by macrophages and DCs may trigger unique signaling cascades. (34) The cells recognize Pathogen-Associated Molecular Patterns (PAMPs) present in fungal surface like galactomannan and β-1,3-glucan among others, through Pathogen-Recognition Receptors (PRR) such as Toll-like receptors (specially TLR-1,−3,−4, and-6), the C-type lectin receptor-Dectin-1 (35) Aspergillus recognition leads to the generation of proinflammatory cytokines like IL-1α, IL1β, TNF-α, IL-8 and MIP-1α by activation of the NFkB and inflammasome pathways (36,37) Granulomas are a sign for control of infections and are composed of macrophages and giant multinucleated cells that contain cryptococcal cells, as well as CD4+ T-cells (38) Macrophages also infiltrate microbial infection sites in response to various inflammatory signals (39) Proinflammatory cytokines (e.g., interferon-γ (IFN-γ)) guide the polarization of M1 macrophages, whereas Interleukin (IL)-4 mediates the development of M2 phenotypes (40)

g) Immunity to Candida albicans

Animals can be immunized actively and are then resistant to disseminated candidiasis. Human sera often contain IgG antibodies that can clump Candida albicans, in-vitro and may be candidacidal. The basis of resistance to Candidiasis is complex and incompletely understood (41). *Candida albicans* conceal the beta glucans of their cell wall which would otherwise be efficiently recognized by host dectin-1 underneath an external coat of mannan, a molecule which

is considerably less immune-reactive. The cutaneous fungal infections are self-limiting and recovery is associated with certain limited resistance to reinfection. Resistance is apparently based on cell mediated immunity since patients develop DTH reactions, fungal antigens and occurrence of chronic infections associated with lack of these reactions. T-cell immunity is also implicated in resistance to other fungal infections. Since resistance can sometimes be transferred with immune T-cells. It is presumed that T-cells release lymphokines which activate macrophages to produce the destruction of the fungi. In respiratory mycosis, spectra of disease activity somewhat similar to the spectrum of activity in leprosy can be seen.

h) Immunity to Blastomyces dermatitidis

The principle host defence mechanisms against *B. dermatitidis* have not been clearly defined. The fungal cells activate the complement system by both classical and alternate pathways and antibodies directed against a glucan component of the cell wall have been identified.

i) Immunity to Coccidioides immitis

Following recovery from primary infection with Coccidioides immitis there usually is immunity to reinfection. Macrophages also infiltrate microbial infection sites in response to various inflammatory signals.Proinflammatory cytokines (e.g., interferon-γ (IFN-γ)) guide the polarization of M1 macrophages, whereas interleukin (IL)-4 mediates the development of M2 phenotypes

II. SERODIAGNOSIS OF FUNGAL DISEASES

A. Biotechnology for Molecular Diagnosis of Aspergillosis (Green fungus)

Diagnosis of Aspergillosis rests most securely on demonstration of hyphal fragments in tissue biopsies by methenamine-silver stain The hyphae have a tendency to branch repeatedly. In aspergilloma, fungus may be difficult to find in sputum. In invasive aspergillosis, sputum smear is often negative. The most reliable method for the diagnosis of acute invasive aspergillosis is the examination of stained tissue sections. The histological section can be stained with hematoxylin and eosin(H&E) and Gomorimethenamine silver(GMS) and examined for characteristic hyphae. An ELISA technique was introduced using a rat anti-GM monoclonal antibodies,EB-A2, which recognizes 1---5 BetaD-Galactiofuranoside side chains of the GM molecule. This sandwich ELISA technique is used in current commercially available GM assay for the diagnosis of IA.(42) Unfortunately, the GM assay has decreased sensitivity in the setting of a patient receiving Aspergillus antifungals, although specificity for detection does not change (43) These assays are more sensitive than Enzyme immunoassays and latex agglutination techniques. Radiological manifestations include nodular shadows, patchy infiltrates, cavitating lesions are the common findings on the chest radiograph. Computed tomography (CT) scan is useful in the evaluation of non-specific infiltrates in immunocompromised patients. It is imperative to achieve an early diagnosis in order to avoid the development of longstanding complications and to reduce the mortality rates as much as possible. The ' halo sign' on CT is now regarded as an early indicator of invasive pulmonary Aspergillosis (44).

B. Biotechnology for Molecular Diagnosis of Mucormycosis (Black fungus)

1. Direct microscopy of clinical specimens and culture is strongly recommended for identification of mucormycosis.
2. Histopathology may allow differentiation of mucormycosis from aspergillosis
3. Microscopicy estimates morphology, branching and septation. For the species recognition direct microscopy is not useful
4. Grinding of specimens should therefore be avoided (45)
5. Standardized appraisals are available for the detection of fungus-specific antigens
6. CT lesions are expressive for invasive fungal disease
7. The 1,3-b-D-glucan is a common component of the cell wall of fungi
8. Detection of antigen and Mucorales-specific T cells.
1. Fungus T cells were detected by an enzyme-- linked immunospot (ELISpot) assay.
9. Molecular-based methods for direct detection -PCR that targets the 18S ribosomal DNA of Mucorales was evaluated on fresh tissue specimens
10. The semi-nested PCR as described was also evaluated on formalin-fixed paraffin-embedded tissue specimens
2. Mucorales PCR was positive in 22 of 27 tissue specimens from patients with a haematological malignancy
3. The failure to amplify specific DNA might result from fungal DNA concentrations below detection limits. (46)

C. Biotechnology for Molecular Diagnosis of white fungus

Early diagnosis of fungal infection is critical to effective treatment. Traditional approaches to diagnosis include direct microscopic examination of clinical samples, histopathology,culture and serology.(47)Positive cultures from normally sterile sites support the diagnosis, but cultures must be interpreted with caution to rule out contamination with endogenous flora. The detection of *candida* in patients with bladder catheters in place most likely represents colonization. In patients without foreign bodies in the urinary tract, however, significant candiduria may be a marker of obstruction, DM or other serious conditions. Isolation of *Candida albicans* from sputum and other respiratory specimens is common but rarely associated with pulmonary infection. In CNS infection, isolation of *Candida* from CSF is diagnostic, but the concentration of the organisms may be very low, so repeat testing and submission of a large volume of CSF per sample may be needed to establish the diagnosis. When associated with signs of tissue damage or inflammation, this may provide reliable detection of infection. Diagnosis

of oropharyngeal, esophageal, or vulvovaginal Candidiasis may be made on the basis of clinical appearance and risk factors. Conformation may be established by the wet mount of gram stain examination or scrapings from the affected sites.

D. Management of Green Fungus, White Fungus and Yellow Fungus

The management protocol includes a multidisciplinary approach for salvaging patients of

Green fungus, White fungus and Yellow fungus

E. Basic principles in the management of Triple fungal infections

1. High index of suspicion,
2. Expedating early prompt clinical and laboratory diagnosis, risk stratification for severity of the diseases
3. Timely initiation of an effective antifungal therapy (monotherapy or combination therapy)
4. Aggressive surgical debridement of necrotic lesions along with antifungal therapy
5. Reverse of risk factors and immunosuppression
6. Control of the underlying medical condition

a) First line therapies

1. Surgical debridement
2. Antifungal therapy
3. Control of underlying conditions
4. Hyperbaric oxygen

b) Second line therapies

1. Combination therapies

1) Surgical debridement:

1. Surgical debridement is the treatment of choice to halt the progress and control of infection.
2. Immediate aggressive surgical debridement of necrotic tissue should take place and plays a critical for salvaging patients of cutaneous mucormycosis.
3. It is usually used in combination with antifungal therapy

2) Antifungal therapies:

A. Amphotericin B

1. It is the drug of choice for the Triple fungal infections
2. Lipid formulations of amphotericin B (liposomal AMB, LAMB; and AMB lipid complex, ABLC) are the preferred first line drugs as they have better therapeutic index and better safety profile than the Conventional amphotericin B deoxycholate
3. Treatment should be initiated within first 5 days at the earliest
4. Recommended dose is intravenous 5mg/kg which could be incremented on an individual basis
5. High dose L-AMB was associated with increased nephrotoxicity and electrolyte derangements.
6. The duration of treatment varies with the clinical picture and is subjective to the clinical and radiological response

B. Azoles

1. Isavuconazole: It is approved for the treatment of mucormycosis when amphotericin B is not feasible. It is available in both intravenous and oral formulations and it is administered with a loading dose of 200 mg three times a day for two days and 200 mg daily thereafter.

3) Adjunctive therapies

1. Used to reverse immunosuppression
2. Granulocyte (macrophage) colonystimulating factor or interferon-γ have been tried
3. Deferasirox,ironchelator have proved to be beneficial in ketoacidosis and ketoacidosis
4. Hyperbaric oxygen(increased oxygen pressure)treatment improve the functionality of neutrophils which inhibits fungal growth and improves the rate of wound healing especially in diabetics.

The yellow fungus can be treated with Amphotericin-B injections. The white Fungus can be treated with Anti-Fungus drugs.

F. Invasive Pulmonary Aspergillosis-

Possible interactions with other drugs must be considered before Azoles are prescribed. In addition, plasma azole concentrations vary substantially from one patient to another, and many authorities recommend monitoring levels to ensure that drug concentrations are adequate, but not excessive, especially withIitraconazole and voriconazole.Initial IV administration is preferred for acute invasive aspergillosis and oral administration for all other diseases that require anti-fungaltherapy.(48) Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction that requires treatment with oral corticosteroids. Inhaled steroids are not effective (49) Few studies have evaluated treatment options for chronic pulmonary aspergillosis (CPA), where long-term oral itraconazole or voriconazole remain the treatment of choice. (50).

G. Growing resistance to antifungal drugs 'a global issue'

Resistance may be encountered in the antifungal drug-exposed or drug-naive patients and is particularly

challenging when it concerns mycoses with acquired resistance that cannot be predicted from the species identification itself (51). Antifungal drugs treatment develops resistance to some species of fungi. Aspergillus is resistant to fluconazol. When dosages of antifungal drugs are too low, or even when antifungal drugs are used improperly to treat sick people, the antifungal treatment develops resistance (52, 53). People exposed to agriculture fungicides develop resistance to fungal diseases. Antibiotics, which include antifungal drugs contribute to antifungal resistance in *Candida.* Antibiotics can reduce useful and dreadful germs in the gut, which constitute positive environment for *Candida* growth (54). The three major groups of antifungal drugs in clinical use are , azoles, polyenes, and allylamine/thiocarbamates. These antifungal drugs inhibits the synthesis of ergosterol. Ergosterol is the chief chemical substance of cell membrane of fungi. White Fungus, *Candida auris*, resistant to azoles, polyenes, and allyl amine/thiocarbamates. (55) Patients with *Candida. auris* strains,are. Resistance to the common antifungal drug fluconazole.DNA information shows that the antifungal resistance genes in drug fluconazole.DNA information shows that the antifungal resistance genes in *Candida. auris* are analogus to *Candida. albicans.*

H. Amalgamation of drugs in India

Viruses suppress immunity after viral infection. For instance, Post-Covid-19 suppressed the immunity for great number of patients. Indescriminate use of corticoids in turn affects health and reduces the immunity. End result is the resistance of Green, White, and Yellow fungal drugs. This situation aggravated by prescribing a cocktail of drugs to patients with even mild Covid in India. It may or may not be true, but the widespread use of cocktails of drugs, could absolutely subsidize to mucormycosis cases. The home use of long term oxygen, corticosteroids, invited invasive mucor infection. Histopathology shows yeast cells and mycelial forms, epithelial disruption with organisms invading through mucosal cells, and submucosal inflammation and mucosal candidiasis. Deep tissue candidiasis shows organisms invading and disrupting infected tissue. Antibody detection has played a limited role in diagnosis

III. CONCLUSION

Black fungus, is one of the "most formidable infections in all of infectious diseases," and now it is surging as a COVID-19-associated infection at full length in India and giving warning signals around the globe.Uncontrolled diabetes is a focal point in accelerating mucormycosis. Similarly,yellow fungus and white fungus are spreading alarm among people.*Mucor septicus* produces Yellow fungus infection. Yellow fungal infection initiates internally. It is more serious and deadly than black fungus and white fungus. COVID-19 patients are treated with broad-spectrum antibacterial drugs, and excessive corticoid therapy. As a result, the risk of infection with *Candida* species may significantly increase. The Triple threat of the Covid-19 Pandemic- (White, Yellow and Green Fungus) patients showed the declaration of inflammatory cytokines, and impaired cell-mediated immune response with decreased CD4 + T and CD8 + T cell counts, indicating its vulnerabilty to fungal co-infection.

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