



Prophylaxis for Invasive Fungal Infection...Need of the Hour

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ABSTRACT

Purpose: To evaluate the existing studies on Anti-fungal prophylaxis and how it may help in controlling the post-Covid pandemic of Invasive Fungal Infection like mucormycosis.

Material & Method: Studies related to fungal infections and their treatment (prophylactic, empirical, surgical, adjunctive therapy); mainly prophylaxis.

Conclusion: The need for anti-fungal prophylaxis is very important in high-risk patients. Studies done on anti-fungal prophylaxis have given satisfactory results. Due to prolonged stay in the hospital, & use of steroids, weak immunity, patients are suffering from a post-covid pandemic of fungal infections like Mucormycosis and the use of anti-fungal prophylaxis should help in reducing infection and control the pandemic situation.

Keywords: Mucormycosis, Aspergilosis, Prophylaxis, Invasive Fungal Infection, Covid-19, Amphotericin-B.

Introduction

Invasive fungal infections (IFI) or opportunistic infections eg. Mucormycosis, Aspergilosis, Candidiasis are significant health concerns in immune-compromised patients. The main risk factors in which these infections are highly seen are Neutropenia < 500 neutrophils/ml for more than 10 days, haematological malignancies, bone marrow transplantation, prolonged (>4wks) treatment with corticosteroids, prolonged stay in ICU (>7days), chemotherapy, HIV infection, new immune-suppressive agents and malnutrition.

In the current SAR-CoV era, high numbers of these invasive fungal infections are being seen due to factors such as prolonged treatment using corticosteroids, prolonged stay in ICU and hospital, immune-suppression of the patient due to a virus, and underlying immune-compromised diseases. A rare IFI post-covid, eg. Mucormycosis being seen amongst patients on a pandemic scale, and cases are increasing by the day. A more recent outbreak of Aspergilosis (nasal) has also been noticed in India.



In this article, we reviewed the literature for anti-fungal prophylactic treatment, which may help in the control of post-Covid fungal infection pandemic, its complications and decrease the rate of disability and mortality, at the same time reducing the load on an already overburdened medical system.

What & Why Prophylactic Treatment?

Prophylaxis is a Greek word and concept which means any action taken to guard or prevent beforehand. In medical terms, it is a process which designed against the development of a specific disease by treatment or action that affects pathogenesis.

To minimize illness and disease, prophylactic treatment is a good option. Prevention of disease is Important before it gets problematic because it is cost-effective, less stressful, less invasive, easier, and faster than treating the disease.

Mucormycosis and its pandemic post-Covid

Mucormycosis is a rare invasive fungal infection, caused by exposure to mucor-mould which is commonly found in soil, manure, and decaying fruits and vegetables, and even in the nose and mucus of healthy people.

The most common causative organisms are RHIZOPUS species, others are MUCOR, APOPHYSOMYCES, LICHTHEIMIA, RHIZOMUCOR, etc. The major route of infection is inhalation; other routes are ingestion and trauma.

Mucormycosis is a life-threatening condition for people with diabetes, neutropenia, patient on long-term steroids. Severe infection in sinuses can lead to the spread to the brain. It has 6 forms: 1) Rhino cerebral 2) Pulmonary 3) Cutaneous 4) Gastrointestinal 5) Disseminate.

The few common signs seen in these patients are sinusitis, pain on the affected side of the face with swelling, Blackish discolorations on the bridge of the nose and palate area, hazy vision with pain in the eye, fever, cough, dyspnea, hemoptysis. It is also commonly known as “black fungi” because of the black appearance of the bone and soft tissue after necrosis. There is documentation of it leading to osteomyelitis. In the present covid pandemic, this rare infection is becoming a common post-covid complication. Immunosuppressant steroids used over an extended length of time in covid-19 patients, prolonged stay in hospital and ICU, pre-existing diabetes in patients, are a few reasons mucormycosis in post-covid.

Treatment plan of Mucormycosis consists:

- a. **Antifungal Therapy:** Liposomal and lipid complex of AMPHOTERICINE B-[5-7.5mg/kg/d]; AMPHOTERICINE DEOXYCHOLATE-1-1.5mg/kg/d; ISAVUCONAZOLE; POSACONAZOLE.
- b. **Combination Therapy:** LIPOSOMAL AMPHOTERICINE B WITH POSACONAZOLE; LIPOSOMAL AMPHOTERICINE B WITH ECHINOCANDINS.
- c. **Surgical Intervention:** complete removal of necrotic bone and soft tissue of involved area.
- d. **Adjunctive Therapy:** hyperbaric oxygen

How to avoid IFI like MUCORMYCOSIS- Preventions and Precautions?

“PREVENTION IS BETTER THAN CURE”- **Desiderius Erasmus** (1500AD)

- Always consider and control the underlying diseases like diabetes and neutropenia.
- During stay in hospital, proper nursing care under aseptic conditions.
- Patients educated about personal hygiene before discharge.



- Oral hygiene
- Post-Covid- personal hygiene, nasal endoscopy for evaluation of any sign of infection, wearing mask and face shield to avoid dirt and pollution, regular cleaning or changing of mask.

Prophylaxis for Fungal Infection-Discussion

There are numerous studies done on the prophylaxis of MUCORMYCOSIS, ASPERGILLOSIS and other fungal infections.

The drugs used for prophylaxis are: FLUCONAZOLE, ITRACONAZOLE, POSACONAZOLE, CAPSOFUNGIN, VORICONAZOLE, ISAVUCONAZOLE.

According to some authors, Mucorales like Histoplasma remain dormant in immunocompetent patients but become active due to immunosuppression and lead to disease.^{1,11,12} Experiments done on mice to prevent reactivation in LICHTHEIMIA CORYMBIFERA by giving LIPOSOMAL AMPHOTERICIN-B were found effective.^{1,14} Reduction of overall mortality by using prophylaxis with FLUCONAZOLE is also observed in the recipients of stem cell transplantation significantly.^{2,15} Patients suffering from ACUTE MYELOGENOUS LEUKAMIA or MYELOYDPLASTIC SYNDROME whom are undergoing remission induction chemotherapy cycles and patients receiving immunosuppressives for the graft-vs-host disease were given prophylaxis with POSACONAZOLE.^{2,16,17} In two placebo-controlled studies, a total of 656 recipients of bone marrow transplants, were given FLUCONAZOLE (400mg/day) as prophylaxis which resulted in reducing the incidence of proven systemic fungal infection from 17 to 4.5%.^{8,9,20} Low doses of AMPHOTERICIN B in HSCT (HEMATOPOIETIC STEM CELL TRANSPLANTATION) and BMT (BONE MARROW TRANSPLANTATION) recipients were given but it was ineffective.^{4,20,21,22,23} whereas the trial evaluating prophylaxis of lipid formulation shows benefit in neutropenic patients with hematologic malignancy [with or without HSCT (HEMATOPOIETIC STEM CELL TRANSPLANTATION) or BMT (BONE MARROW TRANSPLANTATION)].^{4,24,25,26} Similarly, prophylaxis with aerosolized ABLC and FLUCONAZOLE in HSCT recipients developed a breakthrough IFI [mean duration of treatment 59 days post-HSCT (HEMATOPOIETIC STEM CELL TRANSPLANTATION)].^{4,27} Prophylactic regimen in SOT (SOLID ORGAN TRANSPORT) patients with lipid formulation of AMPHOTERICINE B show a low incidence of IFI.^{4,28,29,30,39}

Data on ITRACONAZOLE prophylaxis is conflicting. In one meta-analysis, ITRACONAZOLE (solution formulation) prophylaxis prevented IFI including invasive aspergillosis compared with controls (i.e. no treatment, placebo, oral polyenes, fluconazole) but overall mortality was not reduced.³¹ The result of prophylactic therapy in SOT (SOLID ORGAN TRANSPORT) recipients with ITRACONAZOLE showed good results.^{32,33} The efficacy of POSACONAZOLE was demonstrated in two randomised trials.^{34,35}

POSACONAZOLE was superior to other azoles in the prevention of IFI and improving survival in hematologic malignancies and chemotherapy-induced neutropenic patients.³⁴ This antifungal drug was also effective in preventing aspergillosis in HSCT (HEMATOPOIETIC STEM CELL TRANSPLANTATION) recipients with GVHD (GRAFT vs HOST DISEASE) in comparison with FLUCONAZOLE.³⁵

CASPOFUNGIN is also as effective as itraconazole for antifungal prophylaxis in patients with hematologic malignancies.^{4,37} If we talk about ANIDULAFUNGIN no data is present as anti-fungal prophylaxis. MICAFUNGIN has also been reported in prophylaxis with a good success rate in HSCT (HEMATOPOIETIC STEM CELL TRANSPLANTATION) patients.^{4,37,38}

Lower doses of VORICONAZOLE are recommended for antifungal prophylaxis after allogenic HSCT (HEMATOPOIETIC STEM CELL TRANSPLANTATION). ISAVUCONAZOLE is one option for antifungal prophylaxis and approved by both Europe and the USA in the treatment of invasive aspergillosis and mucormycosis. In liver transplantation, after evaluating which of the recipients are at high risk of invasive fungal infection and would benefit from prophylaxis, The Infectious Diseases **Society of America** guidelines^{5,36} recommend fluconazole, 200–400 mg daily, or liposomal amphotericin B, 1–2mg/kg daily, for 7–14 days post-transplantation.

ECMM2019		Grade
Primary		
Neutropenic	Posaconazole DR tablet (300 mg b. i. d day 1,300 mg/d from day 2)	B II
GvHD	Posaconazole IV(300 mg b.i.d day1,300 mg/d from day2)	B III
	Posaconazole oral suspension (200 mg t.i.d)	CII
Neutropenic	Isavuconazole PO or IV (200mg t.i.d day 1-2,200mg/d from day 3; or 200 mg/d from day1)	CII
SOT	Isavuconazole PO/IV (200mg t.i.d day 1-2, 200mg/d from day 3; or 200 mg/d from day 1)	CII
	Posaconazole IV (300mg b.i.d day 1, 300mg/d from day 2)	C III
	Posaconazole oral suspension (200mg t.i.d)	C III
All induction chemotherapy	Liposomal Amphotericin B	DI
Neutropenic or GvHD	Fluconazole, itraconazole, voriconazole	DII
Secondary		
	Last effective drug in the same patient	AIII
SOT: solid organ transplantation. DR: delayed-release. IV: intravenous. PO: per os. GvHD: graft versus host disease. b.i.d: twice a day. t.i.d: three times a day.		

Table 1: Prophylaxis recommendation from European Confederation of Medical Mycology (ECMM) (2019), adapted from Cornely et al.2019.⁴

Advantages of Anti-Fungal Prophylaxis

- Activation of IFI suppression
- Less severity in cases if infection occur.
- No secondary surgeries
- Decrease in mortality and disability due to IFI

Disadvantages of Anti-Fungal Prophylaxis

- Selection of resistant strains²⁹
- Drug-related toxicity^{29,30}



Why Anti-Fungal prophylaxis should be considered in patient Post-Covid?

Conclusion: The aforementioned gives abroad an idea of how anti-fungal prophylaxis can suppress the activation of IFI like MUCORMYCOSIS and could also help in reduction in the severity of infection. we are already suffering a severe COVID-19 pandemic and with the use of anti-fungal prophylaxis, we might slow or stop the second post-Covid pandemic of Fungal Infection including MUCORMYCOSIS, ASPERGILLOSIS, CANDIDIASIS, which will certainly help in controlling disability and mortality due to IFI.

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