Review Article

Medley of Fungal Infections, and developing Antifungal Resistance: Post COVID

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Abstract

The Covid 19 pandemic has brought a paradigm shift in the incidence of fungal infection. S COV 2 is an RNA virus that causes a serious infection and is associated with many adverse effects involving different organs and systems during its pathogenic cycle in human. Immunocompromised status due to Covid infection especially in vulnerable groups like the elderly and patients with many Co morbidities; and also due to systemic steroid usage in the treatment of the Covid 19 infection has increased the incidence of invasive fungal infection. The most often encountered invasive fungal infection in Covid 19 infected patients and post Covid period are seen due to mucormycosis, aspergillosis, candidiasis. Other infection which are also in increasing trend are caused by pneumocystis Jiroveci, Histoplasma Sp., Cryptococcus Sp. etc. We have made a systematic review from more than 20 articles to know about the most commonly encountered opportunistic fungal infection Post Covid 19 period, the shift in the epidemiology of this fungal infection from the Pre Covid-era, Clinical features, diagnosis and treatment. Also, we stressed about the anti-fungal resistance encountered in the commonly used drugs belonging to the azole group and ecchinocandins etc.

Key Words: Covid 19, fungal infection, aspergillosis, mucormycosis, invasive candidiasis, Voriconazole, isuvaconasole, posaconazole, amohotericin B.

Introduction

Fungal infections, also known as mycoses, have historically been one of the most overlooked diseases in medical history. Despite their prevalence and potential to cause inflammation, irritation, and discomfort, these conditions were often neglected by the medical profession. Today, fungal infections remain a significant medical concern, impacting nearly 1,000,000 individuals worldwide.[1] The emergence of the COVID-19 pandemic has further exacerbated this situation, as the viral respiratory disease increases the susceptibility of patients to potentially life-threatening secondary fungal infections, especially in intensive care units (ICUs). In COVID-19 sufferers, invasive fungal infections like invasive mycosis, aspergillosis, cryptococcosis, and Candida are more

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common. The prolonged hospitalization periods, along with conditions such as lymphopenia, leucopenia, and a systemic hyper-inflammatory reaction, create an environment conducive to fungal growth in COVID-19 patients. Essential antifungal treatments are required to mitigate the associated comorbidities and mortality caused by these fungal infections. However, the susceptibility of fungal species to antifungal treatments has decreased and become less predictable.[1]

Epidemiology

Over 2900 papers were identified through literature searches, and a meticulous analysis focused on 434 papers containing incidence, prevalence, or proportion data. The findings suggest that approximately 4.1% of the Indian population, an estimated 57,251,328 out of 13,19,400 individuals, suffer from serious fungal diseases. Notable prevalence figures (in million) include recurrent vulvovaginal candidiasis at 24.3, allergic bronchopulmonary aspergillosis at 2.0, tinea capitis in school-age children at 25, severe asthma with fungal sensitization at 1.36, chronic pulmonary aspergillosis at 1.74, and chronic fungal rhinosinusitis at 1.5. Additionally, the annual incidence rates of pneumocystis pneumonia (58,400), invasive aspergillosis (2,50,900), mucormycosis (1,95,000), esophageal candidiasis in HIV (2,60,000), candidiasis (1,80,000), fungal keratitis (10,17,100), and cryptococcal meningitis (11,500) were determined.[2]

A prospective observational study conducted at AIIMS, New Delhi, spanning from April 2017 to December 2018, aimed to investigate invasive fungal infections (IFI). The study involved 3300 patients suspected of IFI, with 253 in the population proven to have fungal infections. In this mixed cohort, invasive aspergillosis emerged as the most common IFI at 40.7% (103/253), followed by mucormycosis at 24.5% (62/253). These findings align with studies in the hematological patient population, but they contrast with reports where invasive candidiasis is identified as the most common IFI. Diabetes mellitus (23.7%) and hematological malignancies (19.8%) were prevalent predisposing conditions, with chronic kidney disease (CKD) at 34.4% and pulmonary manifestations at 30.8% among other predisposing factors.[3]

Shift of trend of fungal infection during Covid.

Numerous studies have indicated that individuals with COVID-19 are more prone to co-infections or superinfections. In January 2020, just before the global spread of COVID-19, Chen et al. reported a fungal coinfection rate of 2%, with 2 out of 99 patients being infected with Candida albicans and Candida glabrata.4 Yang et al. reported a higher rate of 5.17%, with three out of 52 patients being infected with Aspergillus flavus, Aspergillus fumigatus, or Candida albicans.[5]

Subsequently, in February 2020, Zhu et al. found that co-infection was present in 94.2% of COVID-19 patients, of which 91.8% had bacterial coinfections, including Streptococcus pneumonia, Klebsiella pneumonia, and Haemophilus influenza. Additionally, 23.3% of patients experienced fungal co-infections. Notably, patients with more severe COVID-19 illness exhibited a higher incidence of fungal coinfections, with rates of 23.3% for aspergillosis, 2.5% for mucormycosis, 0.8% for candida, and 0.4% for cryptococcosis.[6]

COVID-19-associated Pulmonary Aspergillosis (CAPA) necessitates long-term treatment in the intensive care unit (ICU) due to its high mortality rate.7 In France, 33% of COVID-19 patients in the ICU were affected by CAPA, while in Germany, it impacted up to 26% of patients.8,9 However, Kula et al. reported a lower prevalence of invasive mold disease from CAPA, approximately 2%, based on a systematic review of post-mortem studies involving autopsies of COVID-19 patients, highlighting the possibility of overdiagnosis of CAPA.[10]

Before the COVID-19 pandemic, the estimated prevalence of mucormycosis in India ranged from as low as 0.02 to 9.5 cases per 100,000 population. However, the country witnessed a concerning surge in the number of mucormycosis cases during the COVID-19 pandemic.

Classification of mycoses

Based on site it is classified into superficial, Subcutaneous or systemic (deep) mycoses.

Epidemiological it is classified into endemic and oppurtunistic[11].

Morphological it is classified into yeast which includes Candda, Cryptococcus, Trichosporon; mold which include Aspergillus, Mucor, dinorphic fungi which include Histoplasma coccidioses, Blastomyces.[11]

Superficial and cutaneous mycoses

This classification encompasses various infections and their corresponding causative agents: Black Piedra (Piedra Hortae), manifested by small firm black nodules involving the hair shaft[11]; White Piedra (Trichosporon Beigelii) which Presents with soft, friable, beige nodules at the distal ends of the hair shaft[11]; Pityriasis Versicolor (Malassezia Furfur) which is the most prevalent superficial mycosis, characterized by hyperpigmentation or hypopigmentation of the skin on the neck, shoulders, chest, and back. It involves the superficial keratin layer[11]; Tinea Nigra (Horta Werneckii). It presents with brown to black patches on the palms of hands and the soles of feet.[11]

Cutaneous mycoses can be classified as either dermatophytes or dermatomycoses. Dermatophytes which is caused by agents belonging to the genera Epidermophyton, Microsporum and Trichophyton[11] and Dermatomycoses refers to cutaneous infections caused by other fungi, with Candida species being the most common among them.[11]

Subcutaneous mycoses

Subcutaneous mycoses can be broadly categorized into three types: Chromoblastomycosis, Mycetoma, and Sporotrichosis. These conditions typically arise from the traumatic inoculation of etiological fungi into the subcutaneous skin.[11]

Chromoblastomycosis, presents with verrucous skin lesions. Common causes of which include Fonsecaea pedrosoi, Fonsecaea compacta, Cladosporium carrionii, and Phialophora verrucosa.[11]

Mycetoma is characterised by suppurative granulomatous subcutaneous mycosis. It involves the destruction of contiguous bone, tendon, and muscle, often accompanied by the presence of draining sinus tracts.[11] It is classified into eumycetoma and actinomycetoma. Pseudallescheria boydii is the most common cause of eumycetoma, while Nocardia brasiliensis is the most common cause of actinomycetoma.[11]

Sporotrichosis is caused by Sporothrix schenckii. Involves the subcutaneous tissue at the point of traumatic inoculation.[11]

In these subcutaneous mycoses, the clinical presentation varies, and histological examinations often reveal distinctive features such as muriform cells or copper penny bodies.[11]

Deep mycosis

Caused by primary pathogen and opportunistic pathogen. Primary establishes infection in normal host whereas opportunistic infection requires a compromised host to establish infection(Cancer, AIDS etc.[11]

Primary deep mycosis

Primary deep mycoses are characterized by asymptomatic or clinically mild infections that occur in normal, immunocompetent individuals. However, exposure to a high inoculation of organisms can lead to life-threatening progression or the reactivation of latent infections.[11]

An example of a primary deep mycosis is Coccidioidomycosis immitis. In this infection, the inhaled fungal spores are transformed into spherules in the lungs[11]. While most cases of Coccidioidomycosis are occult or mild, some patients may experience progressive pulmonary infection that can disseminate to the brain, bones, and other sites. Coccidioidomycosis meningitis, a severe manifestation, requires lifelong treatment due to its potentially life-threatening nature[11].

Primary pulmonary coccidioidomycosis typically manifests with symptoms such as fever, cough, pleuritic chest pain, night sweats, fatigue, and a lack of improvement with antibiotic treatment[11]. This condition arises from the inhalation of spores of Coccidioides immitis, leading to respiratory symptoms and systemic involvement[11].

Coccidioidal meningitis is primarily observed in immunosuppressed patients and those in the second or third trimester of pregnancy. Symptoms of coccidioidal meningitis include persistent headache, lethargy, and confusion. Immunocompromised individuals are particularly susceptible to severe forms of the infection[11].

Histoplasmosis, caused by the inhalation of conidia of Histoplasma capsulatum, can lead to life-threatening complications. Dissemination to the hilum and mediastinal lymph nodes, spleen, bone, and brain can occur[11]. The pathogenesis involves the intracellular growth of the pathogen within macrophages, triggering a granulomatous reaction in tissues. This can lead to reactivation and the dissemination of the fungus to other organs[11].

There are different types of histoplasmosis are Acute Pulmonary Histoplasmosis which involves initial respiratory symptoms[11], Chronic Cavitary Pulmonary Histoplasmosis which is typically seen in smokers with structural lung disease. Presents with productive cough, dyspnea, low-grade fever, night sweats, and weight loss[11]. Progressive Disseminated Histoplasmosis. It occurs in immunocompromised individuals and presents with shock and coagulopathy[11]. Fibrosing Mediastinitis, a rare complication involving fibrous tissue formation in the mediastinum[11].

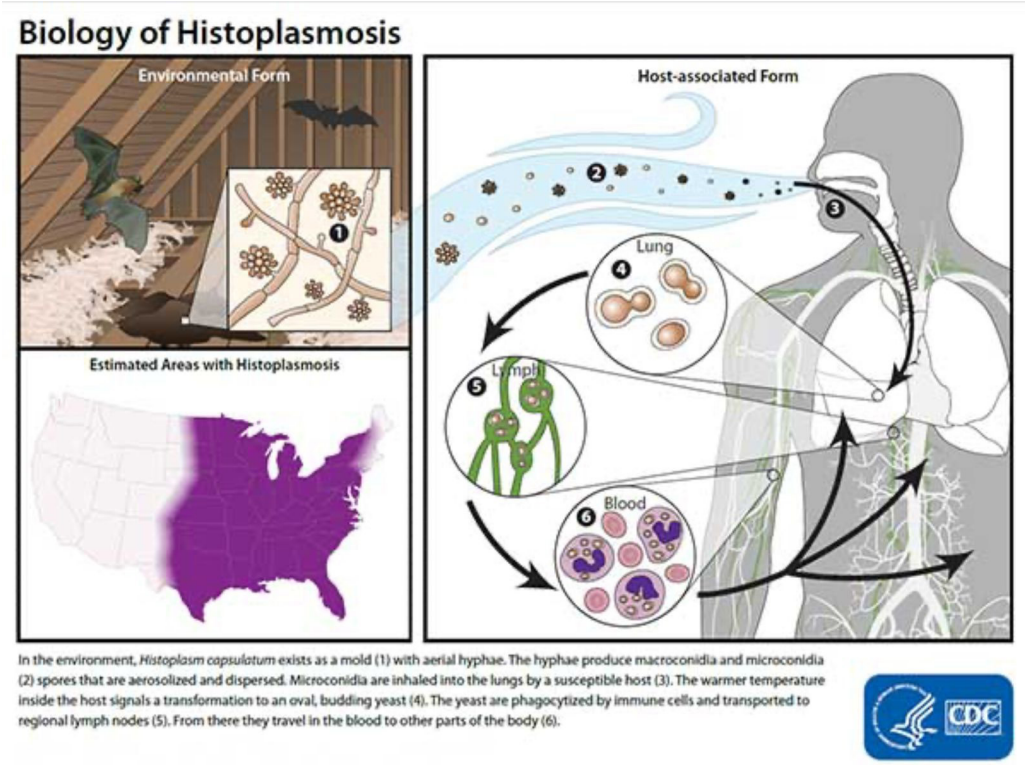


Fig 1: The epidemiology and pathogenesis of histoplasmosis[12]

Blastomycosis is a primary pulmonary infection caused by Blastomyces dermatitidis in the blastoconidial phase, leading to primary pulmonary infection[11]. The transmission occurs through the inhalation of conidia. Pulmonary blastomycosis can exhibit various clinical presentations, including asymptomatic cases or those presenting with flu-like symptoms, acute pneumonia, or chronic pneumonia.[11]

Notably, the severity of blastomycosis tends to increase in specific populations such as diabetics, immunosuppressed individuals, and those with multilobular pneumonia. Diabetics and immunocompromised individuals are particularly vulnerable to more severe manifestations of the infection, underscoring the importance of considering underlying health conditions when assessing the potential impact of blastomycosis[11].

Opportunistic fungal infection

Candida, with Candida albicans as the most common causative agent, is primarily recognized as the most prevalent opportunistic infection. The infection is classified into superficial and deep candidiasis.[11]

Superficial Candidiasis involves the epidermal and mucosal surfaces, affecting areas such as the oral cavity, pharynx, esophagus, intestine, urinary bladder, and vagina.[11]

Deep Candidiasis extends beyond superficial areas to involve internal organs like the kidneys, liver, heart, and others.[11]

Clinical manifestations of invasive candidiasis are often non-specific, with specific lesions observed in chronic disseminated candidiasis (CDC) and ocular candidiasis[11]. CDC is a form of invasive fungal infection that primarily affects the liver and spleen, typically manifesting as small, target-like abscesses referred to as "bull's-eyes"[11] These abscesses can be visualized through ultrasound, computed tomography, or magnetic resonance imaging. This condition is commonly observed in patients with acute leukemia undergoing chemotherapy[11].

Candida auris is an emerging pathogen causing nosocomial infections and is recognized as a significant global health concern. First identified as a novel Candida species in 2009, it has been isolated in 35 countries, excluding Antarctica. The clinical presentation of Candida auris infection resembles that of other Candida species[11]. It has been found in various body sites, leading to conditions such as bloodstream infections (fungemia), myocarditis, urinary tract infections, surgical wound infections, burn infections, skin abscesses (associated with catheter insertion), otitis, meningitis, and bone infections. The versatility of Candida auris in causing infections across diverse body sites underscores its clinical significance and challenges in treatment.[11]

Aspergillosis

Invasive aspergillosis is most commonly associated with the lungs and the paranasal sinuses. This fungal infection may extend beyond the lungs to disseminate into other organs such as the brain, kidneys, liver, heart, and bones. The types of aspergillosis include: Aspergilloma, Allergic Bronchopulmonary Aspergillosis (ABPA), Chronic Pulmonary Aspergillosis, Invasive Aspergillosis[11].

Zygomycosis

Zygomycosis, caused by fungi such as Rhizopus, Rhizomucor, Absidia, Mucor species, and other members of the zygomycete class, can result in invasive sinopulmonary infections. Mucormycosis, a particularly life-threatening form of zygomycosis, is associated with rhinocerebral syndrome.[11]

Major risk factors for mucormycosis include uncontrolled diabetes mellitus with or without ketoacidosis, as well as other forms of metabolic acidosis and immunocompromised conditions[11]. In cases of mucormycosis, the intracranial spread of the fungus is rapid and progressive. This spread can occur through direct extension across bone structures such as the cribriform plate/ethmoid or walls of the frontal and sphenoid sinuses. Additionally, angioinvasion of the walls of arteries and veins may occur, leading to microvascular thrombosis, occlusion, and infarction[11].

Fig 2: Clinical features of mucormycosis[13]

Mucormycosis affecting the bone marrow may facilitate fungal growth by damaging the endothelial lining of vessels, resulting in vascular insufficiency. This process can lead to bony necrosis and fungal osteomyelitis. The swift progression and potential complications of mucormycosis highlight the importance of early diagnosis and targeted intervention, especially in individuals with predisposing risk factors.[14]

Cryptococcosis

Cryptococcosis is indeed an opportunistic fungal infection that commonly affects individuals with compromised immune systems. The fungus responsible for cryptococcosis is Cryptococcus neoformans. While pneumonia and meningitis are two common manifestations, the infection can also affect other organs.[11]

Phaeohyphomycoses

Phaeohyphomycosis refers to infections caused by brown and black pigmented fungi, impacting the skin, superficial tissues, and even deeper organs like the brain. These infections are uncommon,

life-threatening, and typically occur in individuals with compromised immune systems. Early diagnosis and appropriate antifungal treatment, often involving surgery, are critical due to the severity of these infections.[15]

Hyalohyphomycosis

Hyalohyphomycosis is an infection caused by various saprophytic fungi characterized by hyaline hyphae elements. One example is Fusarium spp., known to infect immunocompromised patients, leading to conditions such as pneumonia, fungemia, and disseminated infection with associated cutaneous lesions. This type of infection is particularly prevalent in individuals with neutropenia, emphasizing the importance of understanding and managing these fungal infections, especially in immunocompromised populations.[15]

Pathogenesis

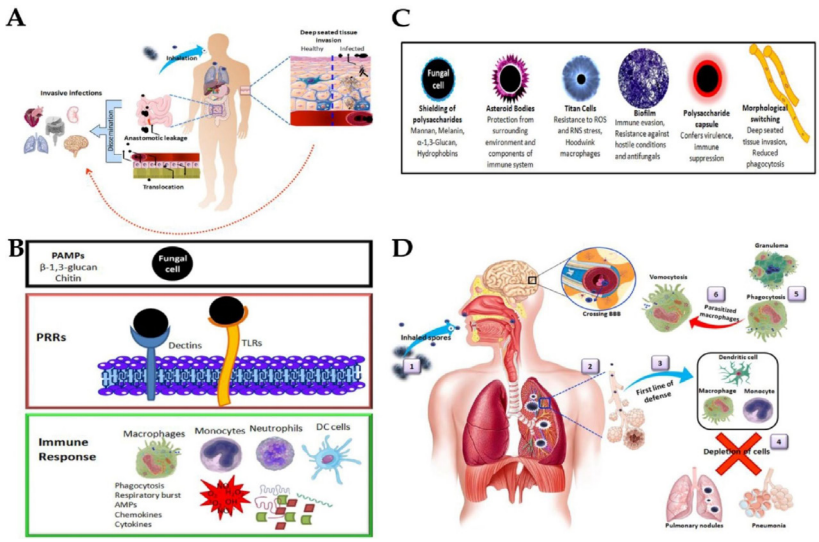


Fig 3: Pathogenesis of fungal infection[16]

A. Routes of invasion of fungal pathogens. B. Pathogen recognition and response in host immune system. C.Morphological modulation of fungal cells for immune evasion. D. Pulmonary transmission and pathogenesis of invasive fungal infections. 1. Inhalation of spores or conidia; 2. Entry into alveoli; 3. Eliciting first line of defense; 4. Depletion of phagocytic cells leads to disease progression as pulmonary nodules and pneumonia; 5. Macrophages phagocytise the fungal cells or encapsulate and form granuloma; 6. Fungal cells parasitize the macrophages that lead to vomocytosis of intact fungi and circulation into bloodstream and crossing blood brain barrier to cause systemic infections.[16]

Diagnosis

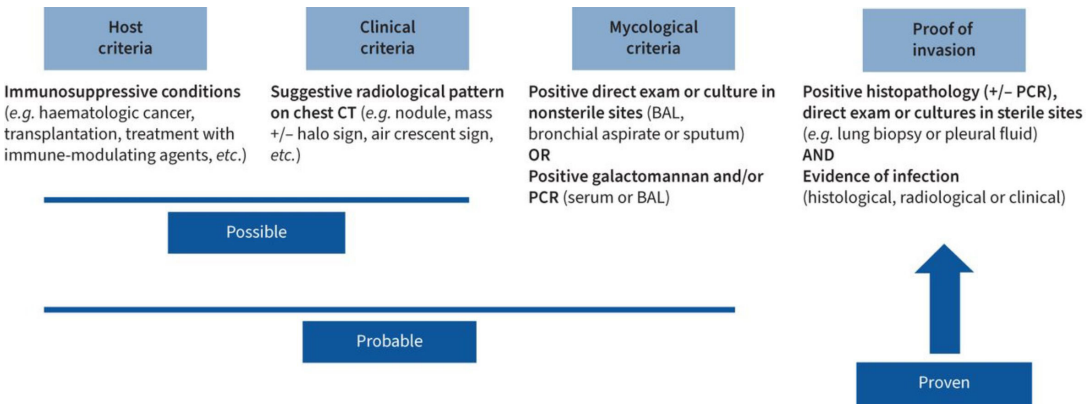


Fig. 4 Diagnosis of Invasive pulmonary aspergillosis[17]

Table 1: Characteristics of nonculture commercialised diagnostic tests for invasive pulmonary aspergillosis[17]

Target	Spectrum of detection	Type of sample
Galactomannan	All Aspergillus species (specific)#	Serum, BAL
(1→3)-β-d- Glucan	All Aspergillus species (not specific) +	Serum
***Aspergillus* DNA**	Most relevant Aspergillus species	BAL, other respiratory samples, serum
	Most relevant Aspergillus species,	
	Cyp 51 Amutations (L98H, TR34, T289A, Y121F)	
	Aspergillus fumigatus, Cyp51A mutations	
	(L98H, TR34)	
	Aspergillus species, Cyp51A (TR34, TR46)	

Treatment of Aspergillus infection

Three AF drug classes are currently licensed for the treatment of aspergillosis (table 3): the polyenes (amphotericin B formulations), the triazoles (voriconazole, posaconazole, isavuconazole, itraconazole) and the echinocandins (anidulafungin, caspofungin, micafungin)[17]

Therapeutic approaches

Invasive Pulmonary Aspergillosis *(IPA)*

AF therapy should be initiated promptly when IPA is suspected. When a bronchoscopy is planned, AF therapy should be started after the procedure whenever possible, but should not be delayed by more than 24 h. Triazoles (voriconazole, isavuconazole or posaconazole) should be privileged for proven or probable IPA and liposomal amphotericin B for possible IPA to ensure broad coverage including the Mucorales and azole-resistant *Aspergillus* species.[17]

Table 2: Treatment of invasive aspergillosis [18]

	Voriconazole	Isuvaconazole	Posaconasole	Liposomal amphotericin B	Caspofungin	Anidulafungin
Dosage	IV: 6mg/ kg Q12x 2, 4mg/kg Q12 starting Day 2 PO: 200mg Q12 h	IV: 200 mg Q8hrX 48hr 200mg daily starting day 3 PO: 200mg Q8 h for 48 hr, 200 mg daily starting Day 3	IV: 300mg Q12x 24 hr, 300mg daily starting Day 2 Delayed release: 300mg daily starting Day 2 Oral suspension: 200mg TID	IV: 3 mg/kg/ day	70mg daily on day1, 50 mg daily starting Day 2	200 mg daily on day 1, 100mg daiky on day 2

Chronic Pulmonary Aspergillosis

Oral triazoles are the cornerstone of CPA treatment. Itraconazole may be used as first-line therapy because of its low cost and good safety profile]. Voriconazole (or posaconazole) can be administered for more severe disease]. Isavuconazole can be used in case of toxicity or drug–drug interactions[17]. Patients with long-term triazole therapy should have regular dermatologic control (every 6 months) for the early detection of skin cancer. Echinocandin therapy may be considered in case of intolerance or resistance to triazoles]. Rezafungin (administered only once a week) or the novel oral beta-glucan synthase inhibitor ibrexafungerp may represent interesting alternative treatments.[17]

Candidiasis

Table 3: Tests approved for the diagnosis of invasive candidiasis.[19]

Test.	Diagnostic Time	Sensitivity Value		Specificity	Notes
Culture Testing	2-4 days	Positive	21-71%.	N/A	Allows susceptibility
T2Candida	3-5h	Positive	91%.	99%	Approved For detection of C. Albicans, C. Parasilopsis, C. Krusei, C. and C. glabrata
ß-D-glucan1h (Fungi tell).	≥80 ng/dl.	92%.	81%.		Can be positive other fungal Infection
ß-D-glucan + Procalcitonin	≥80ng/L 1h ng/mL.	<0.2	96%	98%	Can be positive in Other fungal Infection

Treatment of candidiasis[20]

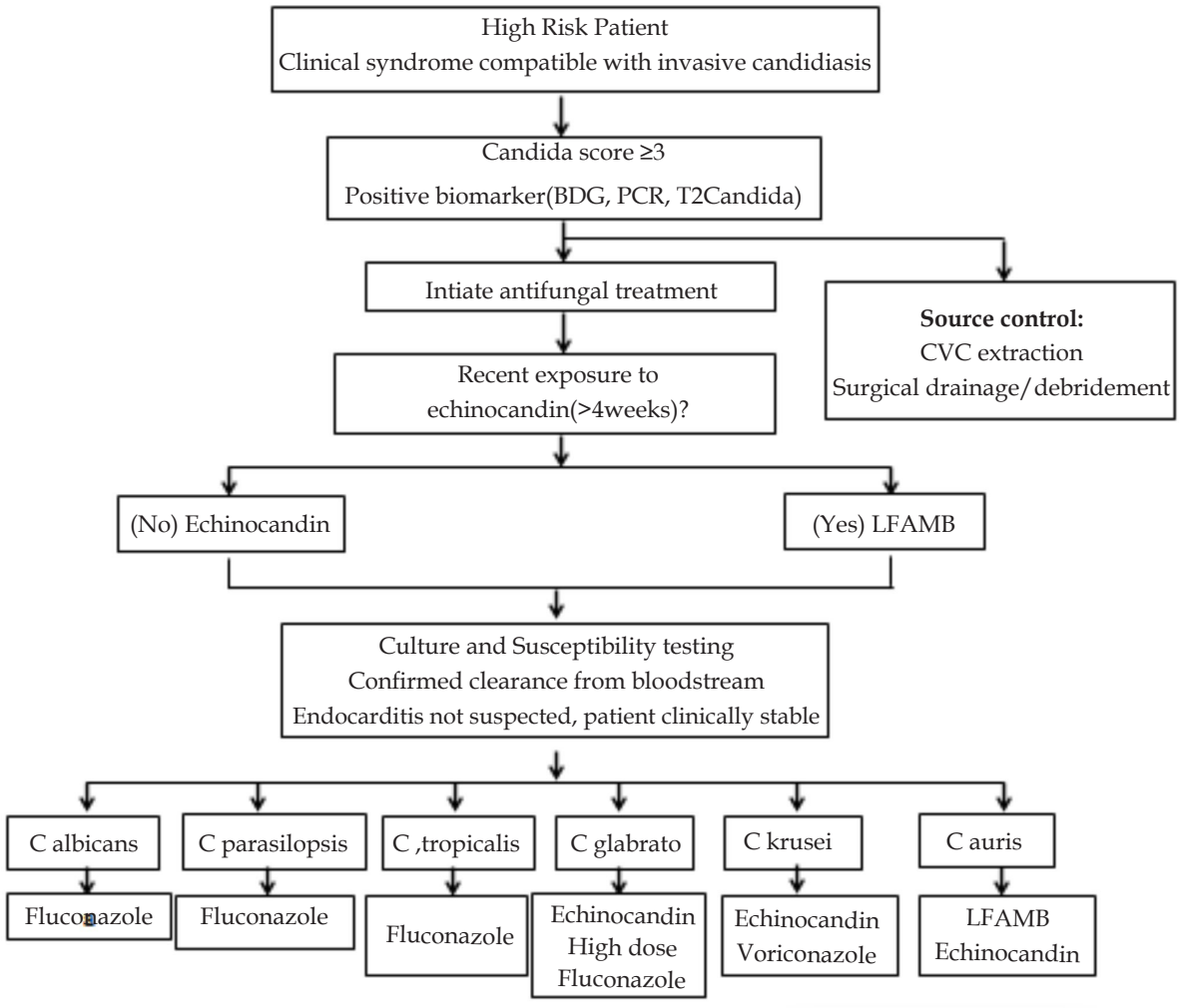


Table 4: Antifungal treatment and common adult dosage for Candidiasis.[21]

Treatment	Dosage
Fluconazole	Treating oral thrush is 50-100 mg once Daily for 7-14 days. The typical dose for Treating Vulvovaginal candidiasis is 150 Mg as a single dose.
Itraconazole	The typical dose for treating oral thrush is 200 mg once daily for 7-14 day. The typicalDose for treating Vulvovaginal candidiasis Is 100 mg twice daily for 7-14 Days.
Terbinafine	Treatment for Dermatophyte infections Caused by candida is 250 mg once daily.
Nystatin	Treatment for Dermatophyte infections 100,000 million units/g -1 million units/g Of cream or ointment applied to the Affected area noce or twice daily.

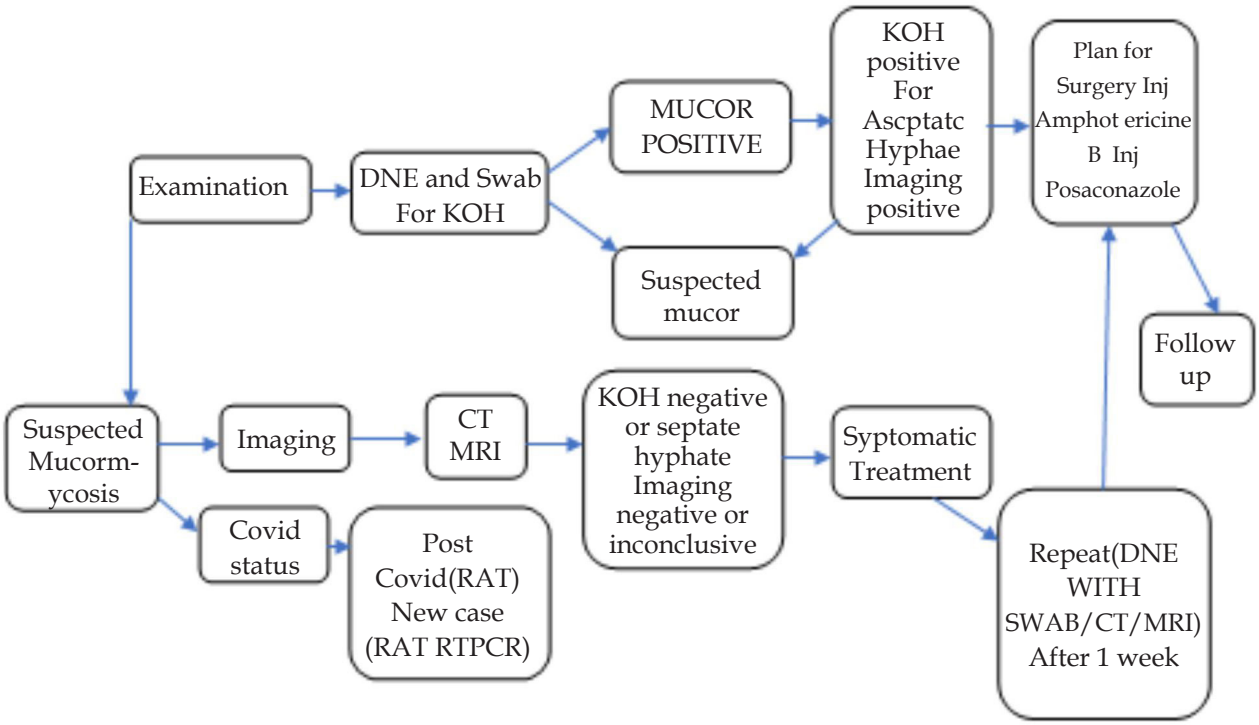
Table 5 : Therapeutic option for treatment of invasive candidiasis[22]

Therapy	Regimen	Comments
Primary Caspofungin	70mg as a loading dose, then 50mg/day	
Micafungin	100-150mg/day	No difference in clinical outcome between 100 and 150 mg/day
Anidulafungin	200mg as a loading dose f/b 100mg/day	
Liposomal amphotericin B	3mg/kg/day IV 400-800mg/day	Monitor renal function
Fluconazole		Increasing echinocandins are preferred for induction therapy
Voriconazole	6mg/kg Iv Q12hrx 2 doses followed by 4mg/kg IV Q12hr IV, oral therapy 200mg Q12hr	Therapeutic drug monitoring should be considered with dosage adjustment to keep trough concentration >1mg/l and 6mg/l

CoNsolodation therapy Fluconazole	400-800mg/day	Switch to fluconazole when patient is hemodynamically stable
Voriconazole	6mg/kg IV Q12 hr X2 doses, followed by 4 mg/kg Q12 IV; oral therapy 200mg Q12hr	Therapeutic drug monitoring should be considered with dosage adjustment to keep trough concentration >1mg/l and 6mg/l; Consider for patients with candida kruse I and candida glabrata

Mucormycosis

Diagnostic protocol[23]



The preliminary diagnostic tools used are DNE (diagnostic nasal endoscopy) with or without biopsy followed by nasal swab for KOH mount and the radiological investigations included CT scan and MRI.

MRI is the gold standard investigation for the diagnosis of Mucormycosis.

Table 6: Treatment of Mucormycosis[21]

Treatment	Dosage
Amphotericin B	1 mg/kg/day to 2 mg/kg/day. Amphotericin B can be given Intravenously (into a vein) or be given Formulation.
Isavuconazole	200 mg three times daily.
Posaconzole	The typical adult dose is 200 mg to 400 Mg once or twice daily.

Antifungal resistance

Currently, only a small number of antifungal drug types exist, so resistance can severely limit treatment options. Some types of fungi, like *Candida auris*, can become resistant to all the antifungal drugs normally used to treat these infections.[21]

Some species of fungi are naturally resistant to certain types of antifungal drugs. For example, the drug fluconazole does not work against infections caused by the fungus Aspergillus.[21]

Antifungal resistance is a complex process and depends on multiple host and microbial factors. Host immune status is a critical factor, as fungistatic drug must work synergistically to control and clear an infection. Patient with severe immune dysfunction are more likely to fail therapy, as the antifungal drug must combat the infection without the benefit of immune response. The presence of indwelling catheters, artificial heart valves, and other surgical devices may also contribute to refractory infections, as the infecting organisms attach to these objects and establish biofilms that resist drug action. [21]

Hülle cells, a thick-walled fungal spore formation seen in association with itraconazole resistance aspergillosis case as shown in Figure 3. The formation of Hülle cells in association with antifungal resistance needs to be investigated further to confirm the resistance character of the spores to corresponding antifungal.[21]

Improve treatment outcomes. Antifungal medications are often prescribed for extended periods of time, leading to the selection of resistant strains of fungi. Hülle cells, a thick-walled fungal spore formation seen in association with itraconazole resistance aspergillosis case as shown in Figure 3. The formation of Hülle cells in association with antifungal resistance needs to be investigated further to confirm the resistance character of the spores to corresponding antifungal.[21]

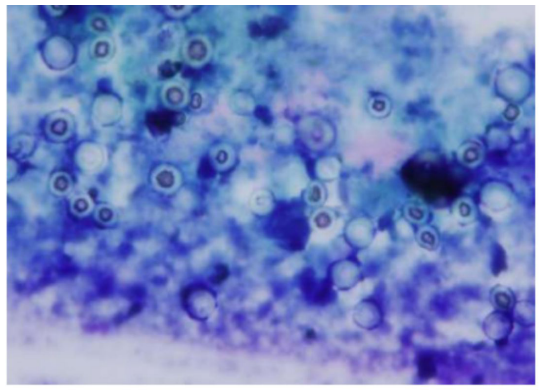


Fig. 5: Imprint cytology from Aspergilloma after the treatment with itraconazole showed numerous Hülle cells with thick protective wall formation.[21]

Voriconazole, isavuconazole, and Posaconazole are commonly used for the treatment of invasive fungal infections, including infections caused by Aspergillus species. Studies have shown that posaconazole, isavuconazole, and voriconazole have high potency against Aspergillus species and has demonstrated excellent in vitro activity against both itraconazole-sensitive and itraconazole-resistant strains. This suggests that posaconazole, isavuconazole, and voriconazole may be a better choice for the treatment of Aspergillus infections, especially in cases where itraconazole resistance is present. However, there have been reports of voriconazole resistance in some fungal species, including Aspergillus.[21]

Fluconazole is a widely used antifungal medication against Candidiasis, but like all antifungal agents, it can face resistance from certain strains of fungi. Fungal resistance to Fluconazole occurs when the fungal cells develop mechanisms to pump out the drug before it has a chance to act. This can result in reduced efficacy of fluconazole and a greater risk of fungal infections becoming more difficult to treat.[21]

Conclusion

The majority of the research referenced in the reference, along with additional epidemiological observations and case reports following the Covid-19 pandemic, demonstrate the significance

and burden of fungal infection that resulted from Covid-19 infection. Additionally, the likelihood of developing an opportunistic fungal infection was increased by a number of comorbidities, including diabetes, renal failure, increased use of corticosteroids and other medications, such as IL 6 inhibitors, cocktail therapy, and living in unhygienic conditions. Catheterization, mechanical ventilation, and other procedures can affect how various fungal infections present in COVID-19. Additionally, we have observed fungal invasion of the lung as well as fungal infection of the maxillofacial region as a result of mucormycosis, which presents with pain and a blackish discoloration, among other symptoms. It becomes crucial that patients see a health professional. Health care provider if he feels any pain in the maxillofacial area or any other symptoms listed in the study. It's also critical that health care providers recognize these symptoms and check for fungal infections in order to provide early intervention. For Post-Covid 19 patients, judicial use of different medications (drug stewardship) combined with rigorous adherence to personal and environmental hygiene can prevent fungal infection.

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