A Comparative Overview of Various Fungal Menaces Amidst Corona Virus Disease

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Abstract

The disastrous Coronavirus Disease outbreak declared as a global pandemic, has become a potential hazard to public health. The second wave of COVID-19 in India has been strongly linked to the rising cases of various fungal infections including mucormycosis, aspergillosis, candidiasis, and mucor septicus. These fungal infections have been a cause for alarm for the general public. The colour-coding of the fungal infections is primarily based on the symptoms observed in the infected patients and not based on the color of the fungi itself. For busting the myths behind fungal infections, a comprehensive and deeper understanding of the facts is needed to overcome this challenge. Rapid diagnosis, reversal of underlying predispositions, surgical excision or debridement, and optimal antifungal therapy are some of the crucial factors in combating these fungal infections. This article provides a comparative review of literature on various fungal infections during COVID-19, that have been threatening worldwide, predominantly in India. Well-established databases literature search was conducted.

Keywords: COVID-19, Mucormycosis, Public health, Mycoses, Antifungal agents, Aspergillosis, Candidiasis

1. INTRODUCTION

The COVID-19 outbreak has been declared a pandemic and has caused a global health emergency. [1] The second COVID-19 wave has been strongly linked to the rising cases of various fungal infections including mucormycosis, aspergillosis, candidiasis, and mucor septicus, especially in India. [2] Mucormycosis is a life-threatening, relatively uncommon, and angioinvasive opportunistic fungal infection, primarily affecting immunocompromised hosts with either qualitative or quantitative defects in innate immunity. [3] Mucormycosis is the third most prevalent infection after candidiasis and aspergillosis in patients undergoing hematological and allogeneic stem cell transplantation. [4] Mucormycosis infection types are classified as Rhino-orbital/Rhino-cerebral, Pulmonary, Gastrointestinal, Cutaneous, Disseminated, and Miscellaneous. Amongst these, COVID-19 patients exhibit a high rate of pulmonary and rhino-cerebral/orbital mucormycosis. [5] Aspergillosis is a fungal infection caused by Aspergillus species and can cause a wide range of illnesses, the most common of which affect the sinuses, lungs, and brain. [6] Patients with pre-existing conditions such as asthma or cystic fibrosis are more likely to develop allergic forms of aspergillosis. [7] The chronic forms of aspergillosis are associated with long-term cough or other pulmonary and systemic symptoms. It is most commonly observed in patients with lung damage but with no significant immunocompromise. Invasive aspergillosis is most commonly observed in immunocompetent persons. [8] Recently, Aspergillus flavus and Candida species were identified in COVID-19 patients in India who were suspected of having invasive pulmonary aspergillosis caused by a ‘white fungus’. [9] Candidiasis is one of the most widely known opportunistic fungal infections. There are around 154 species of candida out of which six species are most frequently isolated causal agents from human infections. Candida albicans are the most common Candida species that cause oral candidiasis. [10] Different types of candidiasis infections include oral, oropharyngeal, vulvovaginal, cutaneous, systemic, mucosal, candidemia, and invasive candidiasis. [11] Recently in Ghaziabad, India, in the first known case of triple infection, a man was diagnosed with yellow fungus, also known as mucor septicus, along with black and white fungi. In Germany, an HIV-infected patient of Nigerian origin was also diagnosed with the same condition but the cause remains uncertain. [12] The yellow fungus that causes the yellow fungus disease is typically found in lizards, bearded...
For busting the myths around fungal infections, only a comprehensive and deep understanding of the facts can prove to be a cornerstone to overcoming the chaos created by various fungal infections amidst the COVID-19 pandemic. This review article provides an exhaustive and comparative review of the available literature on the various fungal infections that predominantly occurred in India during the COVID-19 pandemic. A well-established databases literature search was conducted. Only genuine, evidence-based articles including systematic reviews, and original research studies, specifically describing, guiding, or critically analyzing fungal infection along with COVID-specific data were considered for this review.

2. ETIOLOGY
The primary cause of any fungal infection is a sudden overgrowth of pathogenic fungal species in the human body. Depending on the characteristics of the infecting fungi and the specific infection sites, the fungal infections differ from each other. Superficial fungal infections are mainly caused by dermatophytes such as Tinea pedis, Tinea capitis, Tinea cruris, Tinea corporis, etc. Candida and Malassezia species primarily infect the skin, keratinous tissue, and a mucus layer. Candida species are predominantly associated with infections of the mucosal layers of the mouth and vagina. Amongst Candida species, Candida albicans may result in systemic fungal infections that may become life-threatening, associated with comparatively high morbidity and mortality rate. Zygomycetes, a ubiquitous filamentous fungus belonging to the order Mucorales, induce the fulminating fungal infection mucormycosis. Rhizopus and Mucor species are predominantly associated with the incidence of mucormycosis. Invasive fungal infections are mostly caused by Candida species such as Candida albicans, Aspergillus species such as Aspergillus fumigatus, and Aspergillus flavus.

In a previous study, three inland bearded dragons were infected with a keratinophilic ascomycetous fungus called Chrysosporium anamorph of Nannizziopsis vriesii (CANV) which caused deep fungal dermatitis named yellow fungus disease. In Taiwan, a bearded dragon was found infected with Nannizziopsis guarroi, whose characteristics and symptoms resemble CANV, a patient recently diagnosed with yellow fungus in India displayed symptoms similar to reptiles but were less severe. The taxonomy of some of the important human isolated fungal species is highlighted in Table 1.

Table 1 - The Taxonomy of Some Of The Important Human Isolated Fungal Species

<table>
<thead>
<tr>
<th>Genus &amp; Species</th>
<th>Sub Phylum</th>
<th>Family</th>
<th>Order</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucormycosis s etiological agents</td>
<td>Mucoromycotina</td>
<td>Mucoraceae</td>
<td>Mucorales</td>
<td>organic substrates, including bread, decaying fruits, vegetable matter, crop debris, the soil between growing seasons, compost piles, and animal excreta</td>
</tr>
<tr>
<td>Aspergillus s etiological agents</td>
<td>Pezizomycotina</td>
<td>Trichocomaceae</td>
<td>Eurotiales</td>
<td>Soil, water, decayed vegetation, seeds, and Grains as saprophytes</td>
</tr>
<tr>
<td>1. Aspergillus fumigatus</td>
<td>2. Aspergillus flavus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candidiasis etiological agents</td>
<td>Saccharomycotina/ Ascomycotina</td>
<td>Saccharomycetaceae</td>
<td>Saccharomycetales</td>
<td>Flowering plants, water, and dust. Natural flora of the skin, oral, GI, vagina, and urinary tract</td>
</tr>
<tr>
<td>1. Candida Albicans</td>
<td>2. Candida glabrata</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow fungus disease etiological agents</td>
<td>Pezizomycotina</td>
<td>1. Onygenaceae</td>
<td>2. Nannizziopsiaceae</td>
<td>Onygenales</td>
</tr>
<tr>
<td>1. Chrysosporium Anamorph of Nannizziopsi is Vriesii (CANV)</td>
<td>2. Nannizziopsis guarrro</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.1. MICROBIOLOGY OF PATHOGENIC FUNGI.
The classification of pathogenic fungi into respective genera is usually done based on differences in colony features, sporangiophore structure, and the presence of hyphae and rhizoids. Apart from these, microscopical features can also be accurately visualized using lactophenol cotton blue. However, it is impossible to differentiate fungal genera solely based on colony morphological features. A brief microbiological overview of various fungi is highlighted in Table 2.

Table 2 - A Brief/Microbiological Overview of Various Fungi

<table>
<thead>
<tr>
<th>PATHOGENIC FUNGI</th>
<th>BASIC MICROSCOPICAL FEATURES</th>
<th>CULTURE MEDIA &amp; IDEAL GROWTH CONDITION</th>
<th>COLONY COLOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucormycosis associated Mucorales</td>
<td>Mucorales possess irregular, thick-walled, ribbon-shaped, pauci-separate hyphae Stained with Grocott-Gomori methenamine silver. Rhizopus species display unbranched sporangiophores immediately above the rhizoids. Mucorspecies lack rhizoids. They possess branched or unbranched sporangiophores emerging erratically from mycelia.</td>
<td>Sabouraud’s Dextrose agar or brain-heart infusion agar at 25° to 37°C.</td>
<td>Greishy black to brown.</td>
</tr>
</tbody>
</table>
3. EPIDEMIOLOGY

Mucormycosis is a deadly fungal disease with a mortality rate of >40% and is most prevalent among diabetic individuals in India and China. However, the disease is more prevalent across Europe than Asia, with 34% of the population being affected in Europe as compared to 31% in Asia, 28% in North or South America, 3% in Africa, and 3% in Australia and New Zealand. Overall in Europe, the mortality rates of invasive, disseminated, and localized cutaneous mucormycosis are >30-50%, 90%, and 10-30% respectively. A study was undertaken across four major tertiary care institutions in India (two in North India and two in South India) concluded that the majority of cases (82.7%) were observed in North India, with the mortality rate amongst North Indian patients being 50.5% in comparison to South Indian patients at 32.1%. A. flavus was considered responsible for 10% of all worldwide cases of bronchopulmonary aspergillosis. A multicenter study conducted among transplant recipients in the US during 2001-2006 reported that Invasive aspergillosis (IA) accounted for approximately 20% of all invasive fungal infections (IFI) next mostly to invasive candidiasis.

Candida species were identified in the community in 36.5% of cases between 2008 and 2009. Community cases of disseminated candidiasis were identified in the community in 36.5% of cases between 2008 and 2009. Community cases of Candida species were identified in the community in 36.5% of cases between 2008 and 2009.

4. RISK FACTORS

The prevalence of mucormycosis is higher in Immunocompromised hosts, and those individuals with reduced mononuclear and polymorphonuclear phagocyte numbers arising from underlying disease. Some reported cases also suggest that it can occur in individuals with no underlying immune impairment. The incidence rate is relatively high in patients with conditions like hematological malignancies (HM) and prolonged neutropenia. Diabetic ketoacidosis (DKA) is also a predominant risk factor. Cutaneous mucormycosis predominate in patients with soft tissue injuries caused by local trauma and burns, use of contaminated bandages or other medical apparatus. Injection drug therapy especially with iron chelators like deferoxamine and iridational or prolonged steroid treatment may enhance the threat of invasive mucormycosis. Natural disasters are also considered putative risk factors for mucormycosis as survivors of natural calamities such as tornadoes, tsunamis, hurricanes, and volcanic eruptions are often detected with cutaneous mucormycosis in the aftermath. Risk factors associated with aspergillosis and candidiasis are similar to that of mucormycosis. Immunocompromised patients with prolonged ICU stay, patients with HIV and COPD, postoperative patients, patients with hematological malignancy and solid organ transplants, patients undergoing new immunosuppression therapy with TNF alpha inhibitors, and patients undergoing aggressive chemotherapy are considered at-risk individuals for contracting invasive aspergillosis and candidiasis.

The most common risk factors associated with all fungal infections including yellow fungus disease caused by Nannizziopsis guarroii and CANV are high humidity, low temperature, poor nutrition, and underlying disease and other comorbid conditions.

5. CLINICAL MANIFESTATIONS

Mucormycosis is characterized by infarction of host tissue followed by necrosis resulting from invasion by the fungal hyphae. The progression of the infection is fairly rapid. IA infections are typically acquired through the inhalation of Aspergillus fungi, which results in pulmonary infection side effects like rales - Severe chest discomfort can also be observed during the early course of infection. Candida infections can cause a wide range of symptoms ranging from the least severe (also the most common kind) which mainly affects the mouth and vaginal area. Yellow fungus symptoms usually begin with individualized lesions that are yellow and gradually develop over a few months into brown hyperkeratotic necrotic crusty lesions, over the months these lesions develop into crusty. A brief overview of the clinical manifestation of fungal infections is illustrated in Figure 1.
6. MODE OF TRANSMISSION & SITE OF INFECTION

Most fungal infections including mucormycosis, aspergillosis, and candidiasis are not considered contagious since the causative agents are part of the normal human microbial flora. A healthy person's immunity can overcome most of the pathogenic fungi contacted from decayed vegetation, soil, or contaminated food products either inhaled or dermatologically contracted. But the immune system of immune-compromised patients and those individuals with underlying comorbidities and other risk factors are vulnerable to these opportunistic pathogenic species. Human to human (anthrophilic) and animal to human (zoophilic) transmission is extremely rare. Very few studies report that some of the dermatophytes fungal infections such as *Tinea capitis* may have the capacity for anthrophilic spread. A brief detail of the modes of transmission and infection sites of various types of mycoses is highlighted in Table 3. [64-75]

7. PATHOPHYSIOLOGY

All fungal infections have 4 major phases of pathophysiology viz. Exposure or contact phase, Adhesion or attachment phase, Invasion phase, and Dissemination phase as well as the differences in the pathology of mucormycosis, aspergillosis, candidiasis, and yellow fungus disease can be noticed at DNA and molecular levels. A brief illustration is provided in Figure 2.

- Inhalation/Ingestion/Inoculation/Implantation of sporangiophores or conidia of the pathogenic fungi from various outdoor and indoor environmental sources (soil, water, decayed vegetation, fermented food, etc). [77]
- Rhizopus species attach their spores to the extracellular matrix and laminin of cells forms colonies leading to neutropenia. Aspergillus species bind to basal lamina and fibronectin of damaged lungs and form colonies, especially in individuals suffering from asthma and COPD. Candida species bind to agglutinins like sequence protein, laminin,
collagen, and fibronectin. In Yellow fungus disease, the conidia initially adhere to abraded skin superficially in the tail and limb region of reptiles like bearded dragons. [78-79]

- A lack of defense mechanism in immune-compromised individuals with underlying conditions such as neutrophil circulation, macrophages, endothelial cells, and iron-binding protein and an acidic pH of the serum leads to the dissociation and release of free iron which in turn help rapid rhizopus growth and proliferation. This further promotes angioinvasion. Aspergillus species grow abundantly in the pulmonary environment by damaging the surrounding parenchyma. Candida hyphae transform from yeast through the thigmotropism process and then form colonies. In yellow fungus disease, hyphae proliferate in the outer epidermal stratum corneum which causes dry and yellow lesions. This deepens into the dermis and forms hyperkeratotic plaques via exudative and necrotic ulcers along with granulomatous inflammation. [80-82]

- The above scenario leads to cell deficiency and favors conditions like acidosis and hyperglycemia. The Proliferated fungal hyphae in turn destroy endothelial cells angio invasion, successive thrombosis, tissue necrosis, and dissemination of infection throughout the body. This is especially observed in patients with hematomal malignancies. The invasion pattern of Aspergillus species is similar. The ineptitude of neutrophils to recover facilitates an attack of the Aspergillus species. Candida species form a biofilm, invade a host cell, and disseminate to other organs through phagocytosis and active penetration mechanisms. N. guarroi and CANV infection disseminate to muscle, bone, and tissues of internal organs including the liver, heart, kidney, and the intestines. [80-82]

8. DIAGNOSIS

Individuals infected with fungal pathogens display diverse signs and symptoms depending on their age, gender, host susceptibility, and environmental exposure variables. Moreover, since the symptoms of fungal infections are often very similar to those of different illnesses, it is very difficult to detect them. Diagnosis of mucormycosis is reliant on imaging technology, and mycological and histological examinations. [83] The presence of a reverted halo sign on a thorax CT is indicative of an area of dead tissue which typically has a ground-glass-like opaqueness. Direct microscopy is performed by staining clinical samples, using fluorescent agents such as calcfluor white or blankophor. These are frequently used to suggest mucormycosis. For the identification of infections, tissue segments are stained with hematoxylin-eosin, periodic acid-Schiff stain, Grocott-methenamine-silver Gomori's stain, or in certain cases both are used. Specimens must exhibit non-pigmented hyphae. [84] Polymerase chain reaction (PCR) may also be performed to identify the infection’s underlying species if histopathological examination show infection and a fungal culture test are negative. [83] Diagnosis for aspergillosis is similar to that of mucormycosis. Radiographically, bronchial aspergillosis often appears as obstructed pneumonia. As a result, severe Aspergillus spp infection should be prioritized as a cause in immunocompromised individuals regardless of the radiographic appearance. With increased immunosuppressive underlying factors, the predictive accuracy for detecting Aspergillus spp in respiratory samples as a cause for IA rises. Since biopsy is invasive, histology is used less frequently. [85] The galactomannan assay (GM) is becoming more often utilized to identify IA. Growing hyphae emit GM, which is a polycarboxylate component of the cell of Aspergillus spp. The b-glucan test identifies beta-glucans inside the cell walls of Candida, Aspergillus spp., and Pneumoniae, among other fungi. PCR is increasingly being used to detect Aspergillus spp nucleic acid, and it is also being investigated for usage as a proactive screening tool. [86] As individuals display diverse signs and symptoms depending on age, gender, host susceptibility, and environmental exposure variables, the diagnosis of candidiasis can become highly intricate and difficult to evaluate in some situations. [87] Early laboratory detection potential of candidemia and CNS candidiasis are provided by the development of non-cultural technologies such as the T2Candida system and 1→3)-β-d-glucan detection test, respectively. The presence of (1→3)-β-d-glucan in the cerebrospinal fluid is a useful early diagnostic sign as well as a biomarker of therapy response. [88] A combination of histology, biochemical, and PCR testing gives a certain diagnosis. Further research is suggested by histopathological findings from intricate fungal hyphae and granulomas. If Nannizzioiosis infection is diagnosed, cultures can be conducted and the lab and pathologist must be told that higher temps may prevent growth and lead to fake negative effects since lower incubation temperatures are necessary (25-35°C). Slower development of these lower temperatures suggests increased incubation periods of 2-3 weeks. This approach has made a conclusive diagnosis feasible recent advent of very sensitive and special PCR tests. [89]

9. PREVENTIVE MEASURES

1. Immuno-compromised patients should not be in dusty regions since the fungus grows in the presence of dust and building materials.
2. Ascertain that the patient is wearing a suitable mask to filter fungal particles.
3. Maintain proper hand hygiene.
4. Maintain blood sugar levels because the fungus thrives on high sugar levels.
5. Steroids should not be prescribed to patients who are alone at home, especially if their blood sugar levels are uncontrollable.
6. Sanitize the patients’ equipment before each usage and daily
7. Beddings and linen should be washed every day to prevent dust collection. [5,87]

10. PHARMACOTHERAPY

Systematic management of fungal infection involves 4 basic principles of Rapid Diagnosis, Reversal of underlying risk factors, appropriate surgical excision/debridement, and Optimal antifungal therapy. Though the basic management is
similar, following accurate individual steps for various types of fungal infections is recommended for maximum benefit.

**Figure 3:** Alignment briefly illustrates the steps to be followed.

Identification of condition-specific clinical manifestations and other diagnostic parameters is important for successful management and an early reversal of underlying risk factors. Suitable surgical procedures in combination with appropriate antifungal therapy also play an equal role in successfully combating fungal infections. [89]

Antifungal therapy primarily includes drugs like Polyenes (Liposomal Amphotericin B, Amphotericin B deoxycholate), Azoles (Fluconazole, Itraconazole, Voriconazole, Miconazole, Posaconazole, Isavuconazole), Echinocandins (Caspofungin, Micafungin, Anidulafungin) and Allylamines (Naftifine, Terbinafine). A highly individualized dose and treatment duration is advised based on patient-related factors such as the severity, or nature of the infection. [90]

Details of the most commonly used antifungal agents are highlighted in Table 4.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>ROUTES OF ADMINISTRATION</th>
<th>ADVERSE EFFECTS</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal Amphotericin B</td>
<td>3-4 mg/kg IV every day for 2 to 6 hours</td>
<td>Intravenous</td>
<td>Hypotension, Tachycardia, Anemia, Arthralgia</td>
<td>Macromycosis, Candidiasis</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>200mg orally twice daily</td>
<td>Intravenous, Oral</td>
<td>Hypertension, Peripheral Oedema, Abdominal pain</td>
<td>Aspergillosis, Candidiasis</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>200mg orally twice daily, 400mg orally thrice daily</td>
<td>Intravenous, Oral, Injection, Oral</td>
<td>Hypokalemia, Diarrhea, Vomiting, Hypertension</td>
<td>Aspergillosis, Candidiasis</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>372 mg oral or IV every 8 hours over 6 divided doses</td>
<td>Intravenous, Oral</td>
<td>Periaphlegms edema, Hypokalemia, Diarrhea</td>
<td>Macromycosis, Aspergillosis</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200mg orally once daily</td>
<td>Oral</td>
<td>Edema, Hypertension, Pruritis, Rash</td>
<td>Aspergillosis, Candidiasis</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Day 1 infusion 70 mg in IV, and then 50 mg in IV daily</td>
<td>Intravenous, Topical</td>
<td>Periaphlegms edema, tachycardia, Phlebitis</td>
<td>Aspergillosis, Candidiasis</td>
</tr>
</tbody>
</table>

11. Fungal Infections During COVID-19

Initially, Aspergillosis and Candidiasis were reported as the primary opportunistic fungal infections associated with COVID-19. However, a thorough review of current studies and cases suggests that mucormycosis of COVID-19 is increasing globally, notably in India. Diabetes mellitus, Diabetic Ketoacidosis, presence of hypoxia in COVID-19 patients, increased blood glucose levels due to long-term use of high dose steroids, elevated levels of ferritin, prolonged hospitalization or ICU stay with or without mechanical ventilators are considered critical multiple risk factors predisposing COVID 19 associated mucormycosis. A pre-month administration of Prednisone and Methylprednisolone with a cumulative dose of more than 600mg and 2-7g respectively, makes immunocompromised patients highly susceptible to COVID-19-associated mucormycosis. Pulmonary mucormycosis, Rhino-Cerebro orbital mucormycosis, and invasive pulmonary aspergillosis were the most commonly observed opportunistic fungal infections in COVID-19 patients in India. [91]

A study conducted to analyze pre- and post-COVID mucormycosis characteristics concluded that the severity of post-COVID mucormycosis was higher than that of pre-COVID mucormycosis and male patients (80%) aged 45 and above.
were more likely to contract mucormycosis.\cite{92} Different pathophysiological mechanisms of COVID-19 leading to events such as Endothelialitis, endothelial damage, thrombosis, lymphopenia, and reduction in CD4+ and CD8+ level might aggravate the risks of opportunistic fungal infection development.\cite{93} There is no supporting literature regarding the causes of yellow fungus disease in humans during the COVID-19 pandemic. The only case detected was in Ghaziabad, India, and the patient recovered with the help of optimal antifungal therapy. This gives partial evidence that the incidence rate of yellow fungus disease during the COVID-19 pandemic might be exceedingly limited.\cite{94}

12. CONCLUSION
The occurrence of fungal infections is not a new phenomenon restricted to the COVID-19 pandemic. Most of the fungal species are part of the normal human microbial flora. Its overgrowth and deformities in the defense system of humans or animals lead to fungal infections. Color coding of these fungal infections as black fungus (mucormycosis), white fungus (candidiasis), and yellow fungus (mucorosepticus) is primarily based on the symptoms observed in fungus-infected patients and is not based on fungus color. The Color of the fungus varies widely as the colonies formed in various culture media exhibit a varied color differences. Mucormycosis, Aspergillosis, Candidiasis, and Yellow fungus disease worsen in immune-compromised individuals with multiple risk factors. Long-term use of steroids and high blood glucose levels collectively render diabetic COVID-19 patients as victims of these fungal infections, especially mucormycosis. Chances of healthy individuals getting infected with these fungi are extremely rare. Undertaking steps such as adhering to appropriate preventive measures, early detection, and optimal antifungal therapy are crucial factors to combat these fungal infections.

**List Of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANV</td>
<td>Chrysosporium anamorph of Nannizzioopsis vriesii</td>
</tr>
<tr>
<td>IA</td>
<td>Invasive Aspergillosis</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>GM</td>
<td>Galactomannan assay</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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</tbody>
</table>

**REFERENCES:**


