Unveiling the Silent Threat: An Exploration of Fungal Infections in Critical Care Environments

Mohammed Ahmed, MD[1]; Suhel.F.Batarseh[1]; Saja Al Zghoul, MD[1]; Adel Najed Algoussous, MD[2]; Ayoub Innabi, MD[3]

[1]Department of medicine, Jordan University of Science and Technology

[2]Intensive care department, Albashir Hospital, MOH, Amman, Jordan

[3]Pulmonary, critical care and sleep medicine, Trinity Health Oakland

Abstract:

Fungal infections are increasingly becoming a significant concern for patients in critical condition, particularly in intensive care units (ICUs), where mortality rates often surpass those associated with bacterial infections. Patients in ICUs, frequently immunocompromised and burdened with multiple comorbidities, face heightened susceptibility to fungal pathogens. This vulnerability is compounded by prolonged hospital stays, extensive use of antibiotics, and occurrences of multiorgan system failure.

This study aims to comprehensively explore fungal infections within the critical care setting, focusing on Aspergillus, Candida, and Mucormycosis. It investigates various risk factors contributing to the development of fungal infections, ranging from immunosuppression to exposures related to healthcare settings. Diagnostic methods, including traditional culture-based techniques and modern molecular assays, are evaluated alongside emerging prognostic indicators.

Given the ongoing advancements in antifungal treatments, timely and accurate diagnosis is critical for improving patient outcomes in ICU settings. This study endeavors to equip healthcare professionals with the necessary knowledge and tools to effectively manage fungal infections in critical care environments, ultimately enhancing patient care quality and survival rates.

Keywords: Antibiotic use, Aspergillus, Candida, Comorbidities, Critical care, Diagnostic methods, Fungal infections, Immunocompromised patients, Intensive care units (ICUs), Risk factors

1. Introduction:

Fungal infections have seen a rise within the critical care environment. While these infections are less common than bacterial ones, their associated mortality rate is higher. This trend could be attributed, in part, to an amplified presence of immunocompromised patients admitted to critical care units. (1) These infections are commonly labeled as either opportunistic or invasive fungal infections. Opportunistic infections usually do not result in illness among individuals with strong immune defenses (2). Patients in the intensive care unit (ICU) face the most significant susceptibility to risk, along with those having diabetes mellitus, hematologic malignancies, a history of undergoing transplantation, a record of extensive antibiotic usage, and multi-system organ failure(3).

Candida infections are the most prevalent, followed by Aspergillus infections and mucormycosis, in decreasing order of prevalence.(4) Aspergillosis has been shown to be more serious than candidiasis, with a significantly higher crude mortality rate (63% vs. 46%)(5). Each of these necessitates a distinct diagnostic and therapeutic strategy. The intent of this article is to furnish a practical guide covering the essential elements of fungal infections in the critical care environment.

2. Aspergillus infections

Aspergillus spp. is so common that exposure to Aspergillus is unavoidable due to its prevalence in the environment. Numerous proteolytic enzymes are secreted by Aspergillus to break down food sources, and they are frequently detected in soil and decaying vegetative matter. Aspergillus spp. are assumed to be more prevalent in some regions than others due to regional variations in temperature, humidity, and precipitation; a link between these variables and human infection has also been proposed. (6) Aspergillosis remains the most common fungal infection in people who had hematopoietic stem cell transplantation. (6)

The rise in infections may be related to an increase in immunosuppressed patients, the use of immunosuppressive agents and chemotherapeutic protocols, improvements in survival (such as extending the period during which patients are at risk), and wider adoption of noninvasive diagnostic tests.

Aspergillus can colonize the bloodstream, lungs, or surgical wounds, among other locations in the body. The signs of fungal infections in the ICU are sometimes nonspecific, making an early diagnosis difficult. Centers for Disease Control and Prevention (CDC) has mentioned some common symptoms such as cough, headache, and wheezing. Although these are nonspecific symptoms, they could raise suspicion of Aspergillosis in vulnerable patients.(7)

In addition to having greater mortality rates, patients in intensive care units (ICUs) colonized with Aspergillus also have a worse prognosis, as almost 50% of these patients may already have IA.(8) Invasive aspergillosis (IA) is thought to occur in 4% of nonhematological ICU patients. Chronic obstructive pulmonary disease is another risk factor for ICU patients. Liver cirrhosis, diabetes mellitus, malnourishment, and lung illness. Influenza infections have also been linked to IA. (9),(10) Furthermore, reports of IA have been made about individuals receiving peritoneal dialysis and those who have had abdominal surgeries. (11)

2.1 Prognosis and mortality rate:

Aspergillosis prognosis and fatality rates can change depending on several variables, such as the type and severity of the infection, underlying medical conditions, and the promptness and efficacy of therapy. According to recommendations from the Infectious Diseases Society of America (IDSA), invasive aspergillosis (IA) has a significant death rate that can range from 40% to 90% in specific patient populations (12). The IDSA guidelines stress the need for prompt identification and proper antifungal medication for improved outcomes in IA cases. (13) In general, the prognosis is better for non-invasive aspergillosis than it is for IA. Examples include chronic pulmonary aspergillosis (CPA) and allergic bronchopulmonary aspergillosis (ABPA). Patients with CPA and ABPA have a good long-term outlook with the appropriate management, which includes corticosteroids, antifungal medicine, and/or avoiding triggers.

2.2 Diagnosis:

Diagnosis requires a low index of suspicion of invasive aspergillosis, especially in patients with risk factors who have a declining clinical course, i.e., an ICU patient with pneumonia not responding to antibiotic therapy. The physician could then order some imaging tests like an X-ray or CT scan according to the suspected site of infection. Respiratory tract fluid sample or tissue biopsy examined under the microscope could confirm the diagnosis of aspergillosis.(14)

The diagnosis of IA infection is based on the criteria of invasive Fungal Infections (IFIs) provided by the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) and the European Organization for Research and Treatment of Cancer (EORTC)/Invasive Fungal Infections Cooperative Group. Proven, probable, and possible (IA) can be characterized as follows:(15)

Proven IA: The diagnosis of Proven Invasive Aspergillosis (IA) requires the presence of well-defined risk factors, along with clinical or radiological abnormalities indicative of IA. Additionally, microbiological or histopathological evidence must be obtained from normally sterile sites (excluding bronchoalveolar lavage [BAL], the sinus cavity, and urine). This evidence could include the presence of fungal elements in tissue samples or a positive culture for Aspergillus species from a sterile site.

Probable IA: Probable IA is characterized by the combination of certain risk factors, clinical and radiological findings suggestive of IA, and positive results from indirect mycological tests, such as the detection of galactomannan (GM) or β-D-glucan in serum or BAL fluid. Additionally, positive cultures from non-sterile sites may support this diagnosis. However, the evidence is not as definitive as in Proven IA.

Possible IA: Possible IA is considered when there is clinical and radiological evidence suggestive of IA in the presence of known risk factors, but without confirmatory microbiological, histopathological, or indirect mycological evidence. This category is used when the diagnostic criteria for Proven or Probable IA are not fully met, but IA cannot be ruled out based on the available clinical data.

The EORTC/MSG criteria have been verified for ICU patients despite not being designed with immunocompetent ICU hosts in mind.(16)

Aspergillus species identification by microbiological cultures is insensitive and can take up to 10 days; however, it's usually identifiable in 1-3 days. (17) The same may be stated of histopathologic examination, which is pathologist-dependent (18) and similarly deficient in sensitivity and specificity. depends on a precise sampling of the impacted region.
To conclude, both microbiological cultures and histopathologic examination require precise sampling of the affected area to increase the chances of detecting Aspergillus species. If the sampling is not done accurately, it can further reduce the sensitivity and specificity of these diagnostic methods. Therefore, despite their utility, these diagnostic approaches have limitations and may not always provide timely and accurate identification of Aspergillus species.

2.3 Management

Aspergillosis should be managed promptly to decrease its mortality rate. Azoles, amphotericin B, and echinocandins are the available drugs that are used in the treatment of invasive aspergillosis. Voriconazole is currently the recommended first-line treatment.(19)

2.4 Therapeutic approaches:

It is crucial to promptly administer suitable antifungal medications for IA in order to reduce its death rate, which can range from 60% to 90%(20).Therefore, even those without the traditional risk factors (i.e., COPD, the use of steroids and other immunosuppressive drugs, liver failure, and Immune Suppression linked to intensive care unit) should begin appropriate antifungal medication as soon as they suspect infection before receiving conclusive evidence of infection. A retrospective cohort of 289 IA patients with distinct predictors of mortality has revealed better results with early treatment commencement in accordance with first-line medication at the point of probable infection. (21) Furthermore, the value of antifungal prophylaxis has not been proven when neutropenic and allogenic patients of hematopoietic stem cell transplantation are excluded. This preventative method is thus not advised for severely sick non-neutropenic patients admitted to the intensive care unit. (22)

Amphotericin B, echinocandins, and azoles (voriconazole, posaconazole, and itraconazole) are the three groups of antifungal drugs that can be used to treat IA. As a first-line therapy for IA, including extremely critically sick patients, current recommendations indicate voriconazole.

(23).Voriconazole has been continuously and widely utilized for the last ten years. The oral (PO form) of Voriconazole is just as effective as the IV form.

When voriconazole was used instead of amphotericin B in a randomized controlled study conducted in 2002 with 277 patients with IA mostly impacted by hematologic disorders, the results showed statistically significant increases in effective outcomes, survival rates, and less severe adverse events (24).The primary antifungal used to treat IA in a major prospective surveillance study carried out in North America between 2004 and 2008 was voriconazole (25). The authors of the retrospective study of 289 IA patients noted that the overall survival rate increased from 47.5% to 60.4% (P=0.01) following October 2002, when amphotericin formulations were replaced with voriconazole as the first-line anti-Aspergillus treatment, without corresponding changes to diagnosis or treatment plan.(21)

It is unknown how long IA therapy should last. Confirming the effectiveness of treatment requires early assessment of response. Physicians' judgments may be influenced by the site of infection, immunosuppressive state, initial clinical circumstances, and later therapeutic measures. Antifungals are often not stopped until all clinical symptoms have subsided and radiological abnormalities have resolved or stabilized. The main source of recommendations for the treatment of IA in non-neutropenic patients is data from hematological population studies. Large-scale observational cohort studies and interventional trials are required to determine the best treatment strategies for critically unwell, non-neutropenic ICU patients.

3. Candida infections:

3.1 Risk factors.

Candida species are among the most common fungal microorganisms detected in patients with pneumonia and are part of the fungal microbiota of intubated or mechanically ventilated patients. The percentage of Candida species in the fungal microbiota increases rapidly after admission to the ICU. (26) Some patients were found to have abnormal Candida colonization in the oropharynx at the time of admission, and these findings were more pronounced in patients with chronic liver disease, a history of diabetes mellitus (DM), a lower body mass index (BMI), and the use of proton pump inhibitors (PPI). PPIs are medications used to decrease stomach acidity. The disruption of oral flora increases the chances of Candida colonization, which has been linked to prior PPI use (27). Other risk factors that can contribute to the progression of candidemia

include age (>50 years), prolonged ICU stays, indwelling devices, steroid use, and SARS-CoV-2 infection. (28)

The transfer of Candida spp. from their colonization sites (skin or gastrointestinal tract) to achieve hematogenous or contiguous spread is suggested to be connected to the pathogenesis of invasive candida (IC). It has been shown that Candida spp, colonizes up to 80% of ICU patients. Only 10% of them, it has been demonstrated, go on to develop IC.(29) Bronchial Candida isolates show colonization and are often regarded as non-pathogenic. Even in the few documented cases of pulmonary infection, hematogenous spread is the cause of the infection.(29) Measures have been taken to identify ICU patients who may develop IC.
In one study, invasive candida infection was predicted using the Candida score, which takes into account risk variables such as surgery during ICU admission, multifocal Candida colonization, severe sepsis or septic shock, and complete parenteral feeding. (30) It requires monitoring cultures from several body locations, which are not easily accessible in most centers and raises the expense of medical care.

In a multicenter trial, the administration of antibiotics in conjunction with the implantation of a central venous catheter during the previous three days, together with two of the following risk variables, might predict the development of an IC infection. Surgery, immunosuppression, pancreatitis, steroid usage, and complete parenteral feeding and/or dialysis during the previous three days are all included. Clinicians can confidently rule out patients who do not have a high risk of IC (negative predictive value of 97%) by applying this approach. (31)

3.2 Diagnosis

Common symptoms reported by most patients include headache, myalgia, arthralgia, fever, and dyspnea. Other patients also exhibited abnormal lab results, such as increased fasting blood sugar, elevated BUN, and elevated ESR and CRP. (32) Blood cultures are routinely used but are limited by their low sensitivity (around 50%).

Other tests have been established to diagnose Candida infections more accurately. (33) 1,3 beta glucan (BDG) is a component of the cell wall that can be detected by several assays. The

sensitivity and specificity of this test were 57%-97% and 56%-93%, respectively. (33) A BDG concentration of >80 pg/ml is considered positive for Candida infection. (34)

Another component of Candida that can be detected through serum assays is the mannan antigen, which is the polysaccharide part of the cell wall. The sensitivities and specificities of mannan antigen and anti-mannan antibody for invasive candidiasis were 58% and 93%, and 59% and 86%, respectively; when combining the mannan/antimannan assay, the sensitivity and specificity were 83% and 86%, respectively. (33,35)

Polymerase chain reaction (PCR) on blood samples is another test that can be used in the diagnosis of Candida. A meta-analysis involving almost 5000 patients has shown that the combined sensitivity and specificity for proven or presumed invasive candidiasis versus the control group were 95% and 92%, respectively (35). Detection of Candida nucleic acids, specifically Candida DNA, represents a powerful diagnostic tool. These techniques enable early detection of candidemia in extensively tested settings. Over the past five years, numerous studies on molecular tests for fungal identification have been published. In 2009, Khot and Fredricks (36) conducted a review of PCR-based studies for fungal diagnostics published over the past decade. These techniques enable early detection of candidemia, particularly in extensively tested settings. PCR has the capability to detect even small amounts of an organism, especially when targeting multicopy genes. Moreover, if nonviable organisms are present in the circulation, PCR may prove more useful than culture.

Various detection platforms, blood fractions, and gene targets have been employed in these studies. **A**ntimycelial antibodies (CAGTA, a germ tube-specific antibody against Candida albicans) For the detection of C. albicans germ-tube specific antibody (CAGTA), a commercially accessible immunofluorescence test is available (Candida albicans IFA IgG, Vircell, Granada, Spain). Limited clinical trials in a small number of patients with hematologic neoplasms and bone marrow transplantation or ICU patients have demonstrated a sensitivity of 77–89% and a specificity of 91–100% (37). Recent research has demonstrated the use of CAGTA in the detection of candidemia linked to deep-seated infection. (38)

3.3 Treatment

There is a controversy on whether starting empirical therapy is beneficial or not. Some guidelines recommend initiating empirical therapy in high risk patients, yet some clinical trials showed no benefit (39)(40). The development of resistant strains has been attributed to the overuse of empirical therapy before diagnostic test results become available (28). However, early and appropriate therapy for infected patients reduces mortality. The initial therapy options include either fluconazole or echinocandins. Both of these medications have similar efficacy, but current guidelines recommend using echinocandins as first-line therapy for invasive candidiasis and candidemia (40).

The effectiveness of echinocandin has been shown by several clinical studies. When compared to amphotericin B, caspofungin- which is a type of echinocandin- had a success rate of 73.4% as opposed to 61.7% with fewer side effects. (41) When caspofungin was administered at a high dose of 150 mg per day as opposed to a typical dose of 50 mg per day (after a loading dose of 70 mg), there was no discernible change in the frequency of adverse events or the outcome. (42) Another randomized, double-blind trial showed that micafungin was found to be as effective as liposomal amphotericin B in treating candidemia and invasive candidiasis, with a comparable safety profile and fewer adverse effects. (43)

It is advised that antifungal treatment be modified as soon as antifungal susceptibilities are known. Nevertheless, there is an increased chance of side effects and drug-drug interactions with other antifungal medication types.(44). For other therapy choices, please see Table 1. It's also advised to remove any central catheter and drain collections or remove contaminated items in order to manage the infection source. (45) It is advised that treatment for at least two weeks after the initial negative blood culture in patients with candidemia be maintained.(44) Once spread and end-organ infection has taken place, therapy is often continued for a further 4–6 weeks.

Antifungal Class	Antifungal Drug	Dose	Spectrum	Comments

Triazoles	Fluconazole	400–800 mg/day	Candida spp. (except C. krusei)	Cytochrome P450 inducers can increase liver enzymes
	Voriconazole	200 mg (3–4 mg/kg)	Candida spp., Aspergillus spp.	Cytochrome P450 inducers can increase liver enzymes CNS toxicity Visual changes Bone toxicity
	Posaconazole	300 mg/day	Candida spp., Aspergillus spp.	
	Isavuconazonium sulfate	372 mg/day	Candida spp., Aspergillus spp.	
Echinocandins	Micafungin	100 mg/day	Candida spp., Aspergillus spp.	
	Caspofungin	50 mg/day (70 mg loading dose)	Candida spp., Aspergillus spp.	May need dose adjustment in severe hepatic dysfunction
	Anidulafungin	100 mg/day (200 mg loading dose)	Candida spp., Aspergillus spp.	
Amphotericin	Deoxycholate formulation	0.1–1.5 mg/kg/day	Candida spp., Aspergillus spp. (except A. terreus)	Nephrotoxic Electrolyte Imbalance Infusion reactions
	Liposomal formulation (AmBisome)	3–5 mg/kg/day	Candida spp., Aspergillus spp.	Less nephrotoxic
Other	Flucytosine	25 mg/kg/day	Candida spp.	High concentration can lead to hepatitis and bone marrow suppression. Should be used

	in combination with another antifungal therapy.

Table 1: Common antifungal medications used for either Candida spp. and/or Aspergillus spp. and their doses, spectrum, and relevant comments. (46)

4. Mucormycosis:

Given that mucormycosis frequently progresses quickly and can cause significant morbidity and mortality, prompt management is necessary if the infection is suspected.(47) A delayed start to treatment is linked to a higher death rate.(47)
To optimize survival rates, prompt diagnostic and treatment measures must be taken, along with the urgent engagement of a multidisciplinary team comprising medical, surgical, radiological, and laboratory professionals.(48)

To maximize patient prognosis and guarantee effective diagnosis and treatment, readily available guidance is essential. Understanding disease patterns and the range of diagnostic and treatment options that are available—which vary depending on the location of the patient—are essential to optimal care.
The recommendations that are now accessible are either outdated or restricted to particular patient groups in hematology or a particular geographic area.(49) The management of this illness has undergone a major transformation recently due to a number of significant developments. These include the creation of fresh and more popular molecular methods for the detection of mucormycosis, the approval of isavuconazole for the treatment of the disease, and the accessibility of novel posaconazole formulations. Furthermore, prior guidelines lacked information on surgery as a crucial component of managing mucormycosis, as well as thorough clinical and radiological imaging, pathological, and histological results.

Rhizopus, Mucor, and Rhizomucor are the most commonly observed genera in human infections.(50)The hyphae of Mucorales possess distinctive characteristics that aid in their preliminary identification in clinical samples. These hyphae are wide (with a diameter of 5 to 15

microns), irregularly branched, and infrequently segmented, in contrast to the narrower and regularly branched hyphae of ascomycetous molds like Aspergillus. (51)

Rhizopus organisms possess ketone reductase, an enzyme that enables their survival in acidic, high-glucose environments, making diabetic ketoacidosis patients highly susceptible to such infections. Rhizopus spores usually enter through inhalation, causing rhino-orbital-cerebral and pulmonary mucormycosis. These spores are usually eliminated by healthy cilia in the respiratory tract, but in susceptible individuals, they stay there, and infection starts in the alveoli or nasal turbinates. (52) Tissue infarction can also occur from the angioinvasive nature of the mucormycosis agents. (53)

4.1 Risk factors.

Invasive mucormycosis often occurs in conjunction with an existing medical condition that makes individuals more susceptible to infection and can influence how the infection manifests clinically. The most frequently observed underlying conditions encompass diabetes mellitus accompanied by ketoacidosis, the use of glucocorticoid medications, organ transplant surgery, hematological cancers, Bone marrow transplantation, deferoxamine therapy, recent infection with COVID-19, AIDS, iron overload, intravenous drug use, traumatic injuries/burns, and malnutrition. (54)

Clinical presentation and symptoms

Pulmonary mucormycosis is an infection that progresses rapidly Upon the inhalation of spores into the bronchioles and alveoli. This leads to pneumonia accompanied by infarction and necrosis, with the possibility of the infection spreading to nearby structures like the mediastinum and heart. Moreover, it can disseminate through the bloodstream to affect other organs. (55,56)

Typically, patients experience fever along with hemoptysis, which can occasionally be severe. The most common underlying conditions associated with this infection include hematologic malignancies, the use of deferoxamine or Glucocorticoids, and solid organ transplantation. Notably, infection is less frequent in diabetics compared to rhino-orbital-cerebral infection. Among a group of 24 patients with mucormycosis and hematologic malignancies, around 71 percent displayed pulmonary involvement, while only one had rhino-orbital-cerebral involvement.

Sporangiospore inhalation appears to be the primary route of infection in immunocompromised patients, leading to pulmonary illness. Individuals with graft-versus-host disease and significant neutropenia(57) are more likely to develop pulmonary mucormycosis, whereas individuals with diabetes usually present with rhino-orbital illness. Most patients have a persistent fever; however, some may be asymptomatic. The arrangement, size, quantity, and dispersion of lesions in radiological results might vary; common examples are shown below. (58) It is possible for pulmonary mucormycosis to extend adjacently to other organs, such as the belly, through the diaphragm.

The most common forms of mucormycosis in immunocompetent patients include cutaneous and soft tissue mucormycosis, which usually arises from skin disruption brought on by traumatic injury (such as that sustained in natural disasters, car crashes, improvised explosive devices in war zones, or iatrogenic sources), surgery, or burns.(59) Characteristic presentations include abscesses, skin swelling, necrosis, dry ulcers, and eschars. Out of the 12 patients who underwent autopsy, seven showed disseminated disease alongside pulmonary infection. (56)

4.2 Diagnosis

Mucormycosis is diagnosed by detecting fungi in tissue samples using histopathological analysis and culture confirmation. However, culture often fails to yield results, and histopathology may be the only evidence of infection. Clinicians should consider mucormycosis in relevant clinical cases and pursue invasive testing for an early diagnosis. It is crucial to recognize that the presence of fungi in a culture does not necessarily signify an active infection, as they might be contaminants or commensal organisms.

Tests like the 1,3-beta-D-glucan assay and the Aspergillus galactomannan assay are increasingly utilized in diagnosing suspected invasive fungal infections. However, these tests are not effective for detecting mucormycosis because the causative agents lack the specific cell wall components targeted by these tests. PCR-based methods performed on histological samples revealing fungal elements can confirm the diagnosis of mucormycosis. (60)

However, the usefulness of these tests on samples without visible fungal elements is uncertain. PCR tests on serum or plasma samples would be preferable as they eliminate the need for invasive sampling. While some studies have demonstrated the value of serum or plasma PCR tests, their practicality in clinical settings is unclear, and they are not widely available commercially. A positive test may influence the choice of antifungal treatment, but a negative test doesn't rule out mucormycosis. (61)

The diagnosis of pulmonary mucormycosis can be challenging as its presentation resembles pneumonia caused by other anti-invasive molds. Isolating the mucormycosis agent from respiratory cultures in a high-risk patient with compatible clinical symptoms indicates the need for empiric treatment. However, establishing a definitive diagnosis can be difficult as it requires demonstrating the organism in tissue.

In situations where obtaining tissue samples is difficult, healthcare providers frequently rely on radiographic evidence to support the diagnosis. Chest radiographs can unveil various findings, such as common abnormalities like localized consolidation, masses, pleural effusions, or multiple nodules. The existence of a pleural effusion or over ten nodules may independently indicate mucormycosis and distinguish it from aspergillosis in immunocompromised individuals. The presence of a halo sign (ground-glass attenuation surrounding a nodule) strongly suggests invasive fungi, including mucormycosis. Reversed halo signs (focal areas of ground-glass attenuation surrounded by a ring of consolidation) are more commonly seen in mucormycosis than in other invasive mold infections. Sputum or samples obtained through bronchoalveolar lavage (BAL) may exhibit the presence of wide, non-septate hyphae, which is a distinctive hallmark of mucormycosis. However, positive results from these specimens are not always obtained before death. A lung biopsy can also demonstrate the presence of hyphae(62).

If sinusitis is identified, endoscopy is highly advised in order to identify mucormycosis. Due to its far higher sensitivity than a CT scan, an MRI should be performed instead if illness of the eye or brain is suspected. It is highly advised to have a biopsy if mucormycosis is suspected. (63)

A pulmonary CT scan is advised for patients with suspected pulmonary mucormycosis and a hematological malignancy to detect the inverted halo sign, vascular occlusion on CT pulmonary angiography, or a region of ground glass opacity surrounded by a ring of consolidation on

thoracic CT. (63) In diabetic patients with facial pain, sinusitis, proptosis, ophthalmoplegia, newly diagnosed amaurosis, or both, cranial CT or MRI is strongly recommended to determine if sinusitis is present.(63)

4.3 Management, prognosis, and treatment

Managing mucormycosis typically necessitates a dual strategy comprising surgical removal of affected tissues and the administration of antifungal treatment. It is crucial to eliminate predisposing factors such as hyperglycemia, metabolic acidosis, administration of deferoxamine, use of immunosuppressive drugs, and neutropenia. Consequently, many patients are empirically treated based on risk factors, positive cultures, and compatible clinical symptoms(64).

Initial treatment involves intravenous (IV) amphotericin B. If a positive response is observed with amphotericin B, a transition to step-down therapy is made using either posaconazole or isavuconazole. In cases where patients do not respond to or are contraindicated to amphotericin B, posaconazole or isavuconazole can be used as salvage therapy. The decision to use oral or IV posaconazole or isavuconazole depends on the patient's condition, whether they have received initial amphotericin B treatment, and the functionality of their gastrointestinal tract. (65,63)

Surgical intervention plays a crucial role in the treatment plan and should be contemplated promptly upon suspicion of mucormycosis. The practice of aggressive surgical debridement, which entails the removal of necrotic tissue and reducing the extent of the infection, has shown a correlation with enhanced survival rates in clinical evaluations involving rhinocerebral and pulmonary infections. In cases of rhinocerebral infection, extensive debridement may be required, which could involve the removal of the palate, nasal cartilage, and orbit. However, recent experiences have shown that endoscopic debridement with limited tissue removal can be effective. Lobectomy has been successful in curing some patients with early pulmonary infection. However, in cases where complete resection is not feasible or profound thrombocytopenia is present, surgery may not be an option. In such situations, efforts should be made to reverse immunosuppression, optimize underlying medical conditions, and promptly administer antifungal medication. (63)

Patients with pulmonary mucormycosis have a poorer prognosis compared to those with rhino-orbital-cerebral involvement. Mortality rates for pulmonary mucormycosis can be as high as 87

percent, possibly due to underlying conditions and the challenges in completely removing the affected tissues; in cases of widely disseminated mucormycosis, the mortality rate is even higher, ranging from 90 to 100 percent. (64)

5. Conclusion:

Fungal infections hold significant importance among patients in the ICU. The indiscriminate use of broad-spectrum antibiotics in the management of life-threatening infections within intensive care units has notably decreased mortality rates. However, this advancement has also increased in the occurrence of invasive fungal infections. Compounded by intricate underlying conditions in these patients and the vague nature of symptoms, the accurate identification of such infections can be challenging, resulting in potential underdiagnosis. Timely and precise diagnosis holds paramount importance, considering that the decision to address these uncommon infections is frequently made with limited clinical and microbiological data. Finally, the advances in antifungal therapy and diagnostics have improved the outcomes of infections in intensive care settings (66).

We recommend implementing several strategies to address the challenges posed by fungal infections in ICU patients. These include increasing awareness and surveillance efforts, improving diagnostic techniques, optimizing antifungal treatment strategies, adopting a multidisciplinary approach to patient management, and promoting continued research and education in the field. By implementing these recommendations, healthcare providers can work towards improving outcomes and reducing the burden of fungal infections in intensive care settings.

References:

1. Beed M, Sherman R, Holden S. Fungal infections and critically ill adults. Continuing Education in Anaesthesia Critical Care & Pain. 2014 Dec;14(6):262–7.

2. Luis Ostrosky-Zeichner 1, Mohanad Al-Obaidi 2. Invasive Fungal Infections in the Intensive Care Unit.

3. Parisa Badiee 1, Abdolvahab Alborzi, Mehrvash Joukar. Molecular assay to detect nosocomial fungal infections in intensive care units.

4. Bassetti M, Bouza E. Invasive mould infections in the ICU setting: complexities and solutions. Journal of Antimicrobial Chemotherapy. 2017 Mar;72(suppl_1):i39–47.

5. Viscoli C, Bassetti M, Castagnola E, Cesaro S, Menichetti F, Ratto S, et al. Micafungin for the treatment of proven and suspected invasive candidiasis in children and adults: findings from a multicenter prospective observational study. BMC Infect Dis. 2014 Dec;14(1):725.

6. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. The Lancet Respiratory Medicine. 2018 Oct;6(10):782–92.

7. CDC [Internet]. Available from: [Internet]. Available from: https://www.cdc.gov/fungal/diseases/aspergillosis/symptoms.html

8. Faisal Khasawneh 1, Tamam Mohamad, Mahmoud K Moughrabieh, Zongshan Lai, Joel Ager, Ayman O Soubani. Isolation of Aspergillus in critically ill patients: a potential marker of poor outcome.

9. Taccone FS, Van Den Abeele AM, Bulpa P, Misset B, Meersseman W, Cardoso T, et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care. 2015 Dec;19(1):7.

10. Vandewoude K, Blot S, Depuydt P, Benoit D, Temmerman W, Colardyn F, et al. Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. Crit Care. 2006;10(1):R31.

11. Karl Dichtl 1, Johannes Wagener 2, Johannes Tschöp 3, Ludwig Ney 3. Analysis of peritoneal galactomannan for the diagnosis of Aspergillus peritonitis.

12. Tong X, Liu T, Jiang K, Wang D, Liu S, Wang Y, et al. Clinical Characteristics and Prognostic Risk Factors of Patients With Proven Invasive Pulmonary Aspergillosis: A Single-Institution Retrospective Study. Front Med. 2021 Dec 23;8:756237.

13. Patterson TF, Thompson GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2016 Aug 15;63(4):e1–60.

14. Diagnosis and Testing for Aspergillosis [Internet]. Available from: https://www.cdc.gov/fungal/diseases/aspergillosis/diagnosis.html

15. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. CLIN INFECT DIS. 2008 Jun 15;46(12):1813–21.

16. Stijn I Blot 1, Fabio Silvio Taccone, Anne-Marie Van den Abeele, Pierre Bulpa, Wouter Meersseman, Nele Brusselaers, George Dimopoulos, José A Paiva, Benoit Misset, Jordi Rello, Koenraad Vandewoude, Dirk Vogelaers; AspICU Study Investigators. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients.

17. K L Mortensen 1, H K Johansen, K Fuursted, J D Knudsen, B Gahrn-Hansen, R H Jensen, S J Howard, M C Arendrup. A prospective survey of Aspergillus spp. in respiratory tract samples: prevalence, clinical impact and antifungal susceptibility.

18. Akeesha A Shah 1, Kevin C Hazen. Diagnostic accuracy of histopathologic and cytopathologic examination of Aspergillus species.

19. Bassetti M, Righi E, De Pascale G, De Gaudio R, Giarratano A, Mazzei T, et al. How to manage aspergillosis in non-neutropenic intensive care unit patients. Crit Care. 2014 Aug;18(4):458.

20. Meersseman W, Lagrou K, Maertens J, Wijngaerden EV. Invasive Aspergillosis in the Intensive Care Unit. Clinical Infectious Diseases. 2007 Jul 15;45(2):205–16.

21. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, et al. Factors Associated with Overall and Attributable Mortality in Invasive Aspergillosis. CLIN INFECT DIS. 2008 Nov;47(9):1176–84.

22. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clinical Microbiology and Infection. 2012 Dec;18:19–37.

23. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clinical Infectious Diseases. 2008 Feb 1;46(3):327–60.

24. Herbrecht R, Greene RE, Ribaud P, Wingard JR, Chandrasekar PH, Pauw BD. Voriconazole versus Amphotericin B for Primary Therapy of Invasive Aspergillosis. The New England Journal of Medicine. 2002;

25. Azie N, Neofytos D, Pfaller M, Meier-Kriesche HU, Quan SP, Horn D. The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. Diagnostic Microbiology and Infectious Disease. 2012 Aug;73(4):293–300.

26. Britton N, Yang H, Fitch A, Li K, Seyed K, Guo R, et al. Respiratory Fungal Communities are Associated with Systemic Inflammation and Predict Survival in Patients with Acute Respiratory Failure [Internet]. Intensive Care and Critical Care Medicine; 2023 May [cited 2024 Mar 6]. Available from: http://medrxiv.org/lookup/doi/10.1101/2023.05.11.23289861

27. Mojazi Amiri H, Frandah W, Colmer-Hamood J, Raj R, Nugent K. Risk factors of Candida colonization in the oropharynx of patients admitted to an intensive care unit. Journal de Mycologie Médicale. 2012 Dec;22(4):301–7.

28. Rajni E, Jain A, Gupta S, Jangid Y, Vohra R. Risk Factors for Candidemia in Intensive Care Unit: A Matched Case Control Study from North-Western India. Acta Med (Hradec Kralove, Czech Repub). 2022;65(3):83–8.

29. Eggimann P, Pittet D. Candida colonization index and subsequent infection in critically ill surgical patients: 20 years later. Intensive Care Med. 2014 Oct;40(10):1429–48.

30. Cristóbal León 1, Sergio Ruiz-Santana, Pedro Saavedra, Benito Almirante, Juan Nolla-Salas, Francisco Alvarez-Lerma, José Garnacho-Montero, María Angeles León; EPCAN Study Group. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization.

31. L Ostrosky-Zeichner 1, C Sable, J Sobel, B D Alexander, G Donowitz, V Kan, C A Kauffman, D Kett, R A Larsen, V Morrison, M Nucci, P G Pappas, M E Bradley, S Major, L Zimmer, D Wallace, W E Dismukes, J H Rex. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting.

32. Erami M, Raiesi O, Momen-Heravi M, Getso MI, Fakhrehi M, Mehri N, et al. Clinical impact of Candida respiratory tract colonization and acute lung infections in critically ill patients with COVID-19 pneumonia. Microbial Pathogenesis. 2022 May;166:105520.

33. León C, Ostrosky-Zeichner L, Schuster M. What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients. Intensive Care Med. 2014 Jun;40(6):808–19.

34. Pruller F, Wagner J, Raggam RB, Hoenigl M, Kessler HH, Truschnig-Wilders M, et al. Automation of serum (1->3)-beta-D-glucan testing allows reliable and rapid discrimination of patients with and without candidemia. Medical Mycology. 2014 Jul 1;52(5):455–61.

35. Clancy CJ, Nguyen MH. Diagnosing Invasive Candidiasis. Kraft CS, editor. J Clin Microbiol. 2018 May;56(5):e01909-17.

36. Khot PD, Fredricks DN. PCR-based diagnosis of human fungal infections. Expert Review of Anti-infective Therapy. 2009 Dec;7(10):1201–21.

37. the study group Candida albicans Germ Tube Antibody Detection in Critically Ill Patients (CAGTAUCI), Pemán J, Zaragoza R, Quindós G, Alkorta M, Cuétara MS, et al. Clinical factors associated with a Candida albicansGerm Tube Antibody positive test in Intensive Care Unit patients. BMC Infect Dis. 2011 Dec;11(1):60.

38. Martínez-Jiménez MC, Muñoz P, Guinea J, Valerio M, Alonso R, Escribano P, et al. Potential role of Candida albicans germ tube antibody in the diagnosis of deep-seated candidemia. Medical Mycology. 2014 Apr 1;52(3):270–5.

39. Terraneo S, Ferrer M, Martín-Loeches I, Esperatti M, Di Pasquale M, Giunta V, et al. Impact of Candida spp. isolation in the respiratory tract in patients with intensive care unit-acquired pneumonia. Clinical Microbiology and Infection. 2016 Jan;22(1):94.e1-94.e8.

40. Cuenca-Estrella M, Kett DH, Wauters J. Defining standards of CARE for invasive fungal diseases in the ICU. Journal of Antimicrobial Chemotherapy. 2019 Mar 1;74(Supplement_2):ii9–15.

41. Jorge Mora-Duarte 1, Robert Betts, Coleman Rotstein, Arnaldo Lopes Colombo, Luis Thompson-Moya, Juanita Smietana, Robert Lupinacci, Carole Sable, Nicholas Kartsonis, John Perfect; Caspofungin Invasive Candidiasis Study Group. Comparison of caspofungin and amphotericin B for invasive candidiasis.

42. Betts RF, Nucci M, Talwar D, Gareca M, Queiroz-Telles F, Bedimo RJ, et al. A Multicenter, Double-Blind Trial of a High-Dose Caspofungin Treatment Regimen versus a Standard Caspofungin Treatment Regimen for Adult Patients with Invasive Candidiasis. CLIN INFECT DIS. 2009 Jun 15;48(12):1676–84.

43. Ernst-Rüdiger Kuse 1, Ploenchan Chetchotisakd 2, Clovis Arns da Cunha 3, Markus Ruhnke 4, Carlos Barrios 5, Digumarti Raghunadharao 6, Jagdev Singh Sekhon 7, Antonio Freire 8, Venkatasubramanian Ramasubramanian 9, Ignace Demeyer 10, Marcio Nucci 11, Amorn Leelarasamee 12, Frédérique Jacobs 13, Johan Decruyenaere 14, Didier Pittet 15, Andrew J Ullmann 16, Luis Ostrosky-Zeichner 17, Olivier Lortholary 18, Sonja Koblinger 19, Heike Diekmann-Berndt 19, Oliver A Cornely 20; Micafungin Invasive Candidiasis Working Group. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial.

44. Peter G. Pappas, Carol A. Kauffman, David R. Andes, Cornelius J. Clancy, Kieren A. Marr, Luis Ostrosky-Zeichner, Annette C. Reboli, Mindy G. Schuster, Jose A. Vazquez, Thomas J. Walsh, Theoklis E. Zaoutis, Jack D. Sobel. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America.

45. Barchiesi F, Orsetti E, Osimani P, Catassi C, Santelli F, Manso E. Factors related to outcome of bloodstream infections due to Candida parapsilosis complex. BMC Infect Dis. 2016 Dec;16(1):387.

46. Ostrosky-Zeichner L, Al-Obaidi M. Invasive Fungal Infections in the Intensive Care Unit. Infectious Disease Clinics of North America. 2017 Sep;31(3):475–87.

47. Georgios Chamilos 1, Russell E Lewis, Dimitrios P Kontoyiannis. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis.

48. Hsin-Yun Sun 1, Nina Singh. Mucormycosis: its contemporary face and management strategies.

49. O A Cornely 1, S Arikan-Akdagli, E Dannaoui, A H Groll, K Lagrou, A Chakrabarti, F Lanternier, L Pagano, A Skiada, M Akova, M C Arendrup, T Boekhout, A Chowdhary, M Cuenca-Estrella, T Freiberger, J Guinea, J Guarro, S de Hoog, W Hope, E Johnson, S Kathuria, M Lackner, C Lass-Flörl, O Lortholary, J F Meis, J Meletiadis, P Muñoz, M Richardson, E Roilides, A M Tortorano, A J Ullmann, A van Diepeningen, P Verweij, G Petrikkos; European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013.

50. Kwon-Chung KJ. Taxonomy of Fungi Causing Mucormycosis and Entomophthoramycosis (Zygomycosis) and Nomenclature of the Disease: Molecular Mycologic Perspectives. Clinical Infectious Diseases. 2012 Feb 1;54(suppl_1):S8–15.

51. G R GALE, A M WELCH. Studies of opportunistic fungi. I. Inhibition of Rhizopus oryzae by human serum.

52. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses.

53. Greenberg RN, Scott LJ, Vaughn HH, Ribes JA. Zygomycosis (mucormycosis): emerging clinical importance and new treatments: Current Opinion in Infectious Diseases. 2004 Dec;17(6):517–25.

54. Levy E. Isolated Renal Mucormycosis: Journal of the American Society of Nephrology.

55. Marin-Garcia J. Echocardiographic Midsystolic Notching of Pulmonic Valve and Hypertension. Chest. 1979 Apr;75(4):530.

56. Mayberry J, Rhodes J, Matthews N, Wensinck F. Serum antibodies to anaerobic coccoid rods in patients with Crohn's disease or ulcerative colitis, and in medical and nursing staff. BMJ. 1981 Jan 10;282(6258):108–108.

57. Maureen M Roden 1, Theoklis E Zaoutis, Wendy L Buchanan, Tena A Knudsen, Tatyana A Sarkisova, Robert L Schaufele, Michael Sein, Tin Sein, Christine C Chiou, Jaclyn H Chu, Dimitrios P Kontoyiannis, Thomas J Walsh. Epidemiology and outcome of zygomycosis: a review of 929 reported cases.

58. Mark M Hammer 1, Rachna Madan 1, Hiroto Hatabu 1. Pulmonary Mucormycosis: Radiologic Features at Presentation and Over Time.

59. Bhatia N, Singla K, Samra T. Indian Journal of Critical Care Medicine. 2018 May;22(5):375–7.

60. Machouart M, Larché J, Burton K, Collomb J, Maurer P, Cintrat A, et al. Genetic Identification of the Main Opportunistic Mucorales by PCR-Restriction Fragment Length Polymorphism. J Clin Microbiol. 2006 Mar;44(3):805–10.

61. Fiona Senchyna1, Catherine A. Hogan1,2, Kanagavel Murugesan1, Angel Moreno1, Dora Y. Ho3, Aruna Subramanian3, Hayden T. Schwenk4, Indre Budvytiene2, Helio A. Costa1,5, Saurabh Gombar1, and Niaz Banaei1,2,. Clinical Accuracy and Impact of Plasma Cell-Free DNA Fungal PCR Panel for Non-Invasive Diagnosis of Fungal Infection.

62. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of Pulmonary Zygomycosis versus Invasive Pulmonary Aspergillosis in Patients with Cancer. Clinical Infectious Diseases. 2005 Jul 1;41(1):60–6.

63. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. The Lancet Infectious Diseases. 2019 Dec;19(12):e405–21.

64. Ling H, Yuan Z, Shen J, Wang Z, Xu Y. Accuracy of Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry for Identification of Clinical Pathogenic Fungi: a Meta-Analysis. Warnock DW, editor. J Clin Microbiol. 2014 Jul;52(7):2573–82.

65. McCarthy M, Rosengart A, Schuetz AN, Kontoyiannis DP, Walsh TJ. Mold Infections of the Central Nervous System. N Engl J Med. 2014 Jul 10;371(2):150–60.

66. Miceli MH, Díaz JA, Lee SA. Emerging opportunistic yeast infections. The Lancet Infectious Diseases. 2011 Feb;11(2):142–51.