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Review

Fungal infections in immunocompromised critically ill patients

José Garnacho-Montero*, Irene Barrero-García, Cristina León-Moya

Unidad Clínica de Cuidados Intensivos, Hospital Universitario Virgen Macarena, Sevilla, Spain

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ABSTRACT

Diverse pathogenic fungi can produce severe infections in immunocompromised patients, thereby justifying intensive care unit (ICU) admissions. In some cases, the infections can develop in immunocompromised patients who were previously admitted to the ICU. *Aspergillus* spp., *Pneumocystis jirovecii, Candida* spp., and Mucorales are the fungi that are most frequently involved in these infections. Diagnosis continues to be challenging because symptoms and signs are unspecific. Herein, we provide an in-depth review about the diagnosis, with emphasis on recent advances, and treatment of these invasive fungal infections in the ICU setting.

Introduction

The proportion of critically ill immunocompromised patients has steeply increased in the last few decades.[1] These patients have an increased susceptibility to most pathogens, including invasive fungi. Recent data estimate approximately 250,000 cases of invasive aspergillosis (IA), 700,000 cases of invasive candidiasis, and 500,000 cases of *Pneumocystis jirovecii* pneumonia (PJP) among other fungal invasive diseases. Although the epidemiology of fungal diseases has greatly changed over the last decades, most of these infections afflict immunocompromised patients.[2]

Acute respiratory failure (ARF) is the leading cause of intensive care unit (ICU) admissions among immunocompromised patients, and the vast majority of them are due to respiratory infections.[3] In a multicenter study of 1611 immunocompromised patients requiring ICU admission for ARF, a fungal infection was responsible for 261 cases (14%).[4]

The two most important causes of pulmonary fungal infection are *Aspergillus* spp. and *Pneumocystis jirovecii* (*P. jirovecii*). Mucorales and *Fusarium* mostly affect patients with marked immunosuppression, such as in hematological malignancies with severe and long-lasting neutropenia, and usually involve the lungs or the sinuses. *Candida* spp. causes candidemia and invasive candidiasis.

In this narrative review based on a literature search (MEDLINE database) completed in October 2023, we focus on the diagnosis and management of invasive fungal infections in immunocompromised patients requiring ICU admission. The main search terms were “respiratory infection” OR “pneumonia” OR “opportunistic infection” OR “fungal infection” OR “parasitic infection”. The additional search terms were “immunocompromised” OR “cancer” OR “transplants” OR “steroids” OR “immunosuppressive drugs” (to identify publications about the epidemiology, outcomes, and diagnosis of ARF) and “ICU” OR “intensive care” OR “critical care” OR “critical illness”. Immunocompromised patients were defined as those receiving long-term (>3 months) or high-dose (>0.5 mg/(kg·day)) steroids or other immunosuppressant drugs, solid-organ transplant recipients, hematopoietic stem cell transplant (HSCT) recipients, patients with solid tumor requiring chemotherapy or with hematological malignancy, and human immunodeficiency virus (HIV)-positive patients who progressed to acquired immune deficiency syndrome.[5] Antifungal prophylaxis in these high-risk patients is beyond the scope of this review.

IA

Aspergillus spp. are responsible for a broad spectrum of illnesses, from saprophytic colonization of the bronchial tree to

* Corresponding author: José Garnacho-Montero, Intensive Care Unit, Hospital Universitario Virgen Macarena, Avd Dr Fedriani s/n. Sevilla 41008, Spain.
E-mail address: jgarnachom@gmail.com (J. Garnacho-Montero).

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invasive and disseminated diseases. IA remains a major cause of morbidity and mortality in immunosuppressed patients with severe neutropenia secondary to hematological malignancies or solid organ transplantation or HSCT recipients.[6]

Although almost every organ can be affected by *Aspergillus* spp., the lungs are the most common site of infection. *Aspergillus fumigatus* is the most frequently isolated species in IA (80%–90%), while in the last decade, there has been a trend for an increasing incidence of nonfumigatus species, especially *A. flavus, A. terreus, A. niger*, and cryptic species of *A. fumigatus* complex.[7–9] The introduction of molecular methods that allow the identification of cryptic species may explain these changes in the epidemiology of aspergillosis.

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) have proposed diagnostic criteria for invasive pulmonary aspergillosis with the last update published in 2022.[10] "Proven" cases require a positive lung histopathology result that is not possible in critically ill patients with severe respiratory failure and/or coagulation disorders. The diagnosis of "probable" IA is based on at least one host factor criterion and one microbiological criterion; and one major (or two minor) clinical criterion from abnormal sites consistent with infection. It is important to remember that these definitions are proposed in the context of clinical and/or epidemiological research but not for clinical decision-making. Nevertheless, these criteria focus primarily on immunocompromised populations. Diagnosis of IA in non-neutropenic critically ill patients presents special challenges. Thus, in 2021, the EORTC/MSG proposed specific IA criteria for critically ill patients.[11]

Symptoms are unspecific and indistinguishable from other pulmonary infections. The diagnosis of IA in critically ill patients is an unsolved challenge for clinicians, and this entity is still frequently underdiagnosed in the ICU setting.[12] A frequent clinical dilemma in the ICU is to differentiate colonization from true IA in patients with *Aspergillus*-positive respiratory tract cultures and to decide whether to initiate or withhold antifungal treatment.

Chest radiography commonly shows nonspecific details. One or more nodules are the most common finding on chest computed tomography (CT) in early invasive pulmonary aspergillosis that may go unnoticed on radiographic imaging. A characteristic finding in the chest CT scan suggestive of angioinvasive aspergillosis is the halo sign: a ground glass opacity surrounding a pulmonary nodule or mass. The air crescent sign within the nodules is seen in the recovery phase of the infection. These signs are almost exclusively seen in patients with severe neutropenia but are non-specific, as they can be seen in other infections (mucormycosis), neoplastic diseases, and inflammatory disorders.[13–15]

Diagnosis of IA remains challenging, particularly in patients receiving mold-active antifungals. Bronchoalveolar lavage (BAL) cultures have an approximate sensitivity of 50%.[16,17] Histopathologic examination of the infected tissue remains the gold standard for diagnosis of IA by demonstrating the presence of the characteristic invasively branching septate hyphae. Unfortunately, the biopsy procedure is an invasive method that can be performed only in a minority of patients, given the risk for critically ill immunocompromised patients.

Biomarkers

In the past few decades, several serological and molecular diagnostic tests have been developed to detect the surrogate markers for *Aspergillus* spp. 1,3-β-d-glucan (BDG) is a polysaccharide component of the cell wall of many pathogenic fungi (*Aspergillus* spp., *Candida* spp. *Fusarium* spp., or *P. jirovecii*) but not of Mucorales or *Cryptococcus*. BDG can be measured in the blood or BAL. The BDG technique has good sensitivity (80%–90% in serum and BAL) and a high negative predictive value, but poor specificity and a positive predictive value (<50%) for diagnosing IA owing to a high rate of false-positive results.[18,19] Most of these studies were carried out with the original Fungitell assay (Associates of Cape Cod, Inc., MA, USA), which is a colorimetric method (cut-off: ≥80 pg/mL). Nevertheless, a new Wako β-glucan assay (Wako Pure Chemical Industries, Osaka, Japan) that is a turbidimetric method (cut-off: ≥7–11 pg/mL) is now available.[20,21] Potential causes of false-positive results of serum BDG are presented in Table 1.

Aspergillus galactomannan (GM) is an enzyme-linked immunosorbent assay (ELISA) that detects the GM polysaccharide that primarily exists in the cell wall of *Aspergillus* species and is released when tissue invasion occurs. GM ELISA is used as mycological criteria for the diagnosis of IA.[22] The GM ELISA is used on serum or BAL specimens. Assay results are reported as optical density index (ODI). Positivity in the serum is considered when the index is > 0.7 in a single sample or > 0.5 in two consecutive determinations. In BAL, an ODI≥1 is required.[23 24] Diverse studies have demonstrated that the sensitivity of GM in BAL for the diagnosis of IA ranges from 81% to 86%, specificity from 88% to 91%, positive predictive value of 80%, and a negative predictive value of 95%.[25] This assay has not been validated to be performed on tracheal aspirates or mini-BAL. Potential causes of false-positive results of serum GM are summarized in Table 2.

Table 1
Potential causes of false-positive beta-D-glucan in critically adult patients.

Causes of false-positive beta-D-glucan
Cardiopulmonary bypass
Surgical gauze containing glucan
Bacteriemia by diverse pathogens; especially Streptococcus spp. or *Pseudomona* spp.
Mucositis or other disruptions of GI integrity
Diverse antibiotics, especially intravenous injection amoxicillin-clavulanate
Cellulose containing filters for hemodialysis
Immunoglobulin administration
Excessive sample manipulation

Table 2
Potential causes of false-positive Galactomannan in critically adult patients.

Causes of false-positive Galactomannan
Use of PlasmaLyte
Enteral nutrition
Mucositis or other disruptions of GI integrity
Diverse antibiotics, especially intravenous injection piperacillin/tazobactam or amoxicillin-clavulanate
Immunoglobulin administration
Multiple myeloma, not related to any particular type

Lateral flow is an immunochromatography technique used as a Point-of-Care diagnostic platform that can be performed in serum or BAL. Two lateral flow tests have been developed that could facilitate a rapid diagnosis of IA on single samples. These are the AspLFD lateral flow device (LFD) by OLM Diagnostics (Newcastle upon Tyne, UK) that detects an extracellular 40 kD-glycoprotein secreted by *Aspergillus* spp. during active growth and the *Aspergillus* GM lateral flow assay by IMMY (Norman, OK, USA). Cross-reactivity with other fungi such as *Paracoccidiodes brasiliensis, Coccidioides* spp., *Saccharomyces cerevisiae, Histoplasma* spp., and *Candida* spp. can occur.[26–28] The results from both lateral flow tests are available within 15 min to 1 h after sampling.

A meta-analysis of 13 studies that included 1513 patients evaluated the combined performance of GM with BDG or A-LFD for the diagnosis of IA.[29] Pooled GM and BDG combination data showed a sensitivity of 49% (95% confidence interval [CI]: 0.27 to 0.72) and a specificity of 98% (95% CI: 0.94 to 1.00).

Because the mortality rate with IA remains high, the workup in immunocompromised critically ill patients must be early and aggressive. Uncertainty in disease definition is a key contributor to the controversy regarding the onset of antifungal therapy. However, it must be kept in mind that prompt initiation of antifungal therapy has demonstrated benefits in terms of mortality in patients with IA. A retrospective study that evaluated 412 ICU patients with invasive pulmonary aspergillosis showed that a delay in the initiation of antifungal therapy is associated with increased length of hospital stay and correspondingly increased hospital costs.[30]

Currently, voriconazole and isavuconazole are considered as first-line agents, while liposomal amphotericin B (3 mg/(kg·day)) is recommended for species with azole resistance or azole intolerance.[24,31–34] Table 3 resumes the recommendations of different scientific societies for IA treatment. The efficacy of voriconazole was assessed in a randomized trial demonstrating superior efficacy and better survival than amphotericin B deoxycholate for primary therapy of this infection. Voriconazole improved survival at 12 weeks (71% *vs.* 58%) and had a significantly higher rate of favorable response (55% *vs.* 38%) with fewer side effects than amphotericin B deoxycholate.[35] Different observational studies confirmed the clinical utility of voriconazole for the management of IA in critically ill patients.[36,37] Serum concentrations of voriconazole present great variability, and drug monitoring is strongly recommended by recent guidelines.[24,33,34] Voriconazole levels < 1 mg/L are associated with therapeutic failure, but levels >5 mg/L are associated with hepatic and neurological toxicity. For severe infections, a trough between 2 mg/L and 6 mg/L is recommended.[34]

Isavuconazole has shown non-inferiority when compared with voriconazole for the primary treatment of suspected IA in a multicenter, double-blind, randomized clinical trial enrolling 532 patients.[38] A double-blind randomized clinical trial confirmed the non-inferiority of posaconazole compared to voriconazole, mainly in onco-hematological patients.[39] Although isavuconazole serum levels show less variability than voriconazole levels,[40] diverse observational studies confirm that isavuconazole plasma concentrations vary in critically ill patients being below the plasma target concentrations (1 μg/mL) in up to one-third of the patients.[41–42]

The benefits of combination antifungal therapy lack sufficient scientific evidence, but this strategy may be considered in patients with breakthrough infections or refractory disease. Although the optimal duration of therapy is unknown, the international guidelines suggest 6–12 weeks.[24,34]

It should be highlighted that clinical trials carried out to obtain the indication for IA treatment did not include critically ill patients. In fact, these studies excluded patients on mechanical ventilation.[38,39] Therefore, current recommendations are extrapolated from these trials that enrolled mostly onco-hematologic patients in non-critical conditions.

Table 3
Current recommendations of the scientific societies for antifungal therapy against invasive pulmonary *Aspergillosis* in adults.

Agent	IDSA Guidelines 2016[31]	*ECIL-6 Guidelines 2017[32]	*ESCMID Guidelines 2018[24]	*SEIMC Guidelines 2019[34]	Australasian Antifungal Guidelines 2021[33]
Voriconazole	First line (strong recommendation; high-quality evidence).	First line (AI)	First line (AI)	First line (AI)	First line (Strong recommendation, Level I evidence).
Isavuconazole	Alternative therapy (strong recommendation; moderate-quality evidence),	First line (AI)	First line (AI)	First line (AI)	Alternative therapy (Strong recommendation, Level I evidence).
Posaconazole	Not mentioned	Not mentioned	Not mentioned	Alternative as salvage therapy when other azoles and liposomal amphotericin B cannot be used (BIII)	Alternative therapy (Strong recommendation, Level I evidence).
Liposomal Ampho B	Alternative therapy (strong recommendation; moderate-quality evidence),	First line (BI)	First line (BII)	Alternative or salvage treatment (AII)	Alternative therapy (Moderate recommendation, Level II evidence)
AmB lipid complex	Not mentioned	First line (BII)	First line (CIII)	Not mentioned	Not mentioned
Echinocandin	Alternative therapy: Caspofungin or Micafungin (weak recommendation; moderate-quality evidence).	First line Caspofungin (CII)	First line Caspofungin (CII) Micafungin (CIII)	Alternative as salvage therapy when other azoles and liposomal amphotericin B cannot be used (BIII)	Second-line or salvage therapy (Marginal recommendation, Level II evidence).

ECIL: European Conference on Infections in Leukemia; ESCMID: European Society for Clinical Microbiology and Infectious Diseases; IDSA: Infectious Diseases Society of America; SEIMC: Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica.

* Recommendations were graded based on the strength of recommendations (3-level scale: A, B, or C) and quality of evidence (3-level scale: I, II, or III).

PJP

Although debatable in the past, all recent phylogenetic analyses place *Pneumocystis* within the fungal kingdom. However, *Pneumocystis* are fungal microorganisms with atypical characteristics: (1) they are unable to grow *in vitro* in fungal culture media; (2) they respond to antibiotics like cotrimoxazole; (3) their cell wall does not contain ergosterol, which explains why amphotericin B or azoles are inactive against *Pneumocystis* spp. However, BDG is an antigenic component of the cell wall of *Pneumocystis,* which explains the utility of BDG test for the diagnosis of infections caused by *Pneumocystis* and why echinocandins might be a therapeutic alternative.[43]

PJP, classically considered to be typical of HIV patients, is increasingly occurring in transplanted patients or patients treated with oncological chemotherapy. In this situation that is uncommon in developed countries, PJP is still the most frequent opportunistic infection in developed areas. Nowadays, most of the HIV-infected patients who develop PJP are unaware of their HIV infection or do not follow medical advice. The mortality rate associated with PJP in non-HIV high-risk patients is 30%–60%.[44,45]

A recent multinational, multicenter, retrospective study (from January 1, 2016 to December 31, 2020), which included 118 presumptive or proven PJP patients who required ICU admission, revealed that only a minority (19.9%) were HIV patients; with hematological malignancy, solid tumor, inflammatory diseases, and solid organ transplants, in this order, were the most frequent underlying conditions.[45]

The signs and symptoms of PJP are non-specific. Low-grade fever, cough, and dyspnea are the typical triad. Severe respiratory insufficiency predominates in patients requiring ICU admission. This pathogen should be suspected in patients with bilateral pneumonia showing diffuse pulmonary infiltrates and a previous history of HIV disease, malignancy, high-dose steroid use, and/or immunosuppressive drugs. The presentation is typically sub-acute although rapidly progressive courses may occur especially in non-HIV patients.

High serum lactate dehydrogenase (LDH) is a typical biochemical finding in patients with PJP. Serum LDH has a very high sensitivity for PJP (nearly 100%) but lacks specificity.[46]

Chest radiography shows bilateral, diffuse, often perihilar, fine, and reticular interstitial opacification, which may appear granular although no pathognomonic radiological presentation of PJP exists. Spontaneous pneumothorax is a typical albeit infrequent presentation of PJP and seems more common in HIV patients. PJP typically presents with a diffuse ground-glass pattern in both lungs on high-resolution CT although other radiological features, including cysts and air-space consolidation, may be found.

Cultures are not used in the diagnosis of PJP in clinical practice. Diagnosis requires direct visualization or application of molecular techniques (polymerase chain reaction [PCR] for the detection of *P. jirovecii* DNA) on induced sputum or BAL. These samples can be subjected to staining techniques (Grocott–Gömöri's stain) or to direct immunofluorescence for detecting this fungus. PCR has a very high sensitivity and specificity close to 100% in HIV/acquired immune deficiency syndrome patients, whereas in non-HIV immunocompromised patients, these figures drop to 85%–90%.[47]

Serum BDG is a good alternative for diagnosing PJP and can be a good diagnostic test for non-ventilated patients who cannot tolerate bronchoscopy usually because of the severity of respiratory failure. Moreover, BDG assay represents a valuable adjunctive tool to distinguish between colonization and infection.[43,48]

P. jirovecii can colonize the respiratory tract without causing pneumonia. A positive PCR in respiratory specimens without signs and symptoms of infection should be considered as a colonization. In these patients, low amounts of DNA are expected. Thus, a cycle threshold (Ct) value >30 is suggestive of colonization.[49]

Trimethoprim-sulfamethoxazole (TMP 15–20 mg/(kg·day) + SMX 75–100 mg/(kg·day) given every 6 h) remains the first-choice agent for treatment independently of the underlying condition. Pentamidine 4 mg/kg intravenous injection given once a day constitutes second-line therapy. Other alternative therapies like primaquine 30 mg/day by oral route plus intravenous clindamycin 600 mg every 6 h or atovaquone (750 mg every 8–12 h daily) are less favorable in critically intubated patients.[50]

In rodent models of PJP, caspofungin has shown beneficial effects in terms of survival and reduction of fungus burden when administered in combination with TMP/SMX.[51,52] Diverse observational studies have reported that caspofungin alone or in combination with TMP/SMX could be a possible alternative for this infection.[53,54] However, no clinical trials have investigated this combination treatment.[55]

In HIV-positive patients with moderate-to-severe hypoxemia due to PJP, current guidelines recommend the use of glucocorticoids based on the positive effect on survival, as reported by a meta-analysis that included six randomized controlled trials.[56] However, the adjunctive use of glucocorticoids in non-HIV patients with PJP and respiratory failure is not routinely recommended and should be individualized in each patient.[50]

Treatment should be maintained for 3 weeks although longer courses may be required depending on the severity and clinical response. Secondary prophylaxis with TMP/SMX is indicated in all patients thereafter.

Candida spp. Infections

Candida infections are one of the most common hospital-acquired infections. Immunocompromised critically ill patients constitute one of the populations with the highest risk of candidemia and invasive candidiasis, and these fungal infections have an unacceptably high mortality rate. In a recent observational study, hospital mortality of candidemia affecting immunocompromised patients in the ICU was 60%.[57]

Most infections are caused by *C. albicans* although *Nakaseomyces glabratus* (*C. glabrata*) and other non-albicans species are increasingly involved in fungemia in this patient population.[58] *Candida auris* has become a major concern worldwide owing to its invasiveness, capacity to cause outbreaks, and pattern of resistance. In fact, *C. auris* isolates can be resistant to all three major classes of antifungals. Moreover, *C. auris* can be misidentified as other types of yeasts (especially *C. haemulonii*) unless specialized microbiological methods are used.[59]

The clinical presentation of candidemia in immunocompromised patients is non-specific and similar to other critically ill patients. A previous history of surgery is more common in immunocompromised patients in the ICU than inpatients not in the ICU at the time of fungemia.[58]

Positive cultures from normally sterile specimens such as blood, pleural fluid, cerebrospinal fluid, pericardium, pericardial fluid, or biopsied tissue provide definitive evidence of invasive candidiasis. However, isolation of *Candida* spp. from any drainage (e.g., pleural drainage and abdominal drainage) does not signify invasive candidiasis. Because *Candida* spp. are commensals, their culture from the respiratory tract (including samples obtained by BAL) does not indicate an invasive infection. A characteristic clinical lesion must also be present, and histopathologic evidence of tissue invasion (e.g., yeasts, pseudohyphae, or hyphae in tissue specimens) must be documented. However, histologically proven *Candida* pneumonia has been documented in severely immunocompromised cancer patients.[60]

Diagnosis of candidemia and invasive candidiasis remains challenging because of the suboptimal sensitivity of blood cultures. Biomarkers such as BDG or *C. albicans* germ tube antibodies (CAGTA) can be used as an alternative.[61] Many studies that evaluated these biomarkers for the diagnosis of invasive candidiasis specifically excluded patients with hematological malignancies or neutropenia.[62,63] One study included 737 consecutive patients with hematological malignancies admitted to the ICU (60% on mechanical ventilation) who routinely underwent a BDG assay upon ICU admission. BDG showed an acceptable performance for diagnosis of candidemia that was not affected by the presence of neutropenia.[19]

The T2Candida Panel is a magnetic resonance assay that directly detects five *Candida* spp., namely *C. albicans, C. tropicalis, C. parapsilosis, Pichia kudriavzevii* (formerly known as *Candida krusei*), and *N. glabratus*, in whole blood samples in 3–5 h. It is highly sensitive and has an excellent negative predictive value.[64]

There is compelling clinical evidence that delayed initiation of appropriate antifungal therapy is associated with increased mortality in patients with candidemia or invasive candidiasis. This association is particularly evident in patients with septic shock. One observational study also confirmed, after adjustment for confounders, the strong association between delayed antifungal therapy and mortality in 106 cancer patients with candidemia.[65]

For most forms of invasive candidiasis, echinocandins (caspofungin, anidulafungin, or micafungin) are recommended as first-line agents, regardless of the underlying disease.[66,67] This recommendation is also applicable to patients with severe immunodepression including patients with prolonged neutropenia. A recent meta-analysis confirmed that monotherapy with an echinocandin is a valid therapeutic option for the management of immunocompromised patients with invasive candidiasis.[68]

Rezafungin is a new long-acting, weekly once-administered echinocandin that is non-inferior to caspofungin in the treatment of candidemia or invasive candidiasis based on the primary endpoints of day-14 global cure (European Medicine Agency [EMA]) and 30-day all-cause mortality (Food and Drugs Administration [FDA]). Rezafungin exhibits potent activity against *Candida* spp., including *C. auris* or species resistant to azoles. Rezafungin does not interact with the cytochrome P450 isoenzymes; therefore, drug–drug pharmacokinetic interactions are not expected, similar to what occurs with the other echinocandins.[69] This new echinocandin has been recently licensed by the FDA and the EMA for the treatment of candidemia or invasive candidiasis including immunocompromised patients.

Liposomal amphotericin B (3 mg/(kg·day)), a lipid-based formulation of amphotericin B with lower toxicity than amphotericin B deoxycholate, is the alternative to echinocandins in cases of intolerance or resistance.[67]

The use of a biomarker-based strategy increases the percentage of early discontinuation of empirical antifungal treatment among critically ill patients with suspected invasive *Candida* infection without affecting survival rates.[70,71] However, as these studies excluded immunocompromised patients, its applicability in this high-risk population needs to be further confirmed in the future.

Current guidelines for the management of candidemia recommend 14 days of antifungal therapy after the first negative blood culture. In the case of neutropenia, the guidelines also require the recovery of the white cell count.

Mucormycosis

In immunocompromised critically ill patients, mucormycosis is a rare fungal infection but with a high morbidity and mortality. The most common agents of mucormycosis are *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp. The etiology of mucormycosis differs considerably across the different continents.[72]

In an ICU setting, the most common clinical presentation of mucormycosis is pulmonary followed by disseminated disease and the rhino-orbito-cerebral form. In pulmonary mucormycosis, typical chest radiography shows multiple small nodules frequently with pleural effusion. The CT scan may show the reverse halo sign.[15] Nevertheless, this sign is not exclusive to mucormycosis and has been described in other fungal and non-fungal infections.[13]

Microscopy and culture of clinical specimens are the cornerstones of diagnosing mucormycosis. In patients with pulmonary mucormycosis, samples are usually obtained by bronchoscopy. Direct microscopy, using Calcofluor staining, reveals the width and non-septate or pauci-septate hyphae. Mucorales grow rapidly (3–7 days) on most fungal culture media.[72]

BDG is not considered useful for the diagnosis of mucormycosis because of the lack of this polysaccharide in the cell wall of these fungi. However, low amounts of BDG are present in the cell wall of *Rhizopus,* which likely explains why different reports have reported positive results of serum BDG in patients with infections caused by this genus without apparent causes of false-positive results or the possibility of a mixed infection with another glucan-producing fungus.[73]

Amphotericin B is active against Mucorales. Among azoles, posaconazole and isavuconazole are also active. Liposomal amphotericin B is the first-line therapy for mucormycosis. The recommended doses are 5–10 mg/(kg·day), although 10 mg/(kg·day) must be administered in case of central nervous system involvement.[74] The efficacy of isavuconazole has been confirmed in a matched control study that compared 37 patients with isavuconazole as first-line treatment compared with

patients treated with amphotericin B-based formulations.[75] Isavuconazole is also considered a first-line drug for mucormycosis. Limited data support antifungal combination therapy for mucormycosis.[74] In rhino-orbito-cerebral mucormycosis, management includes antifungal agents in combination with surgical intervention.

Take-home Messages

Fungal infections are becoming increasingly common in critically ill immunocompromised patients. Diagnosis can be challenging given the lack of consensus definition, nonspecific clinical presentation, and poor sensitivity of diagnostic assays. However, the use of biomarkers may facilitate early diagnosis at least of IA or PJP. Similarly, the treatment can be challenging because of the limited number of available antifungal drug classes and the emergence of resistance. Several new drug classes are now in late-phase clinical studies, including olorofim (a dihydroorotate dehydrogenase inhibitor) or fosmanogepix (disrupts glycosylphosphatidylinositol-anchor biosynthesis by inhibiting the enzyme Gwt1).[76] Therefore, the emergence of these novel drugs is promising for future disease management.

Author Contribution

José Garnacho-Montero: Writing – original draft, Writing – review & editing, Conceptualization. **Irene Barrero-García:** Writing – review & editing. **Cristina León-Moya:** Writing – review & editing, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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