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Post-COVID-19 invasive fungal infections in pulmonary ICU patients: Diagnosis, management, and clinical challenge

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ABSTRACT

Invasive fungal infections (IFIs) are among the most significant and challenging complications in critically ill patients, particularly those with underlying pulmonary diseases. Common causative organisms include *Aspergillus*, *Candida*, and *Mucorales*, which are associated with high morbidity and mortality due to delayed diagnosis, nonspecific clinical presentation, and host immune suppression. This narrative review provides a comprehensive overview of the epidemiology, pathophysiology, diagnostic methods, therapeutic options, and clinical challenges of pulmonary IFIs in intensive care unit (ICU) patients. Risk factors, advances and limitations in imaging, laboratory diagnostics including cultures, biomarkers, and molecular techniques, as well as antifungal treatment strategies are discussed. The review also addresses emerging issues such as antifungal resistance, adjunctive therapies, and the critical role of early recognition in improving clinical outcomes. The aim is to guide ICU clinicians in the effective management of critically ill pulmonary patients with invasive fungal infections while highlighting future research directions.

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1. Introduction

Invasive Fungal Infection (IFIs) are particularly significant and challenging complications in critically ill patients admitted to the intensive care unit (ICU), especially those with underlying pulmonary diseases. Recent studies indicate that the incidence of fungal infections in ICU patients has increased, particularly among those with sepsis, respiratory failure, or chronic lung conditions [1,2]. Common pathogens such as *Aspergillus fumigatus* and *Candida* species can exacerbate respiratory failure and are associated with high morbidity and mortality [3]. Early diagnosis remains difficult due to nonspecific clinical signs and limitations of conventional laboratory methods, particularly in patients with pre-existing pulmonary disease. These challenges can delay treatment and worsen outcomes [4]. Effective management requires precise identification of risk factors, the use of advanced diagnostic tools, and timely administration of appropriate antifungal therapy. Given the significant burden of disease, further research is essential to improve diagnostic and therapeutic strategies for invasive fungal infections in critically ill pulmonary patients [5].

IFIs in ICU patients with underlying pulmonary disorders such as chronic obstructive pulmonary disease (COPD), Coronavirus Disease 2019 (COVID-19), and immunosuppression represent a major clinical challenge. Recent studies indicate that the prevalence of fungal infections in these populations has increased. In a study of 168 ICU patients with COVID-19 disease, COVID-19 associated pulmonary aspergillosis (CAPA) occurred in a notable proportion of patients [6]. In patients with COPD, fungal infections can exacerbate respiratory failure and are associated with high mortality. In one study of COPD patients with invasive pulmonary aspergillosis (IPA), mortality was extremely high. Among immunocompromised ICU patients, the prevalence of IPA was also significant, with substantial associated mortality [7]. Given the increasing prevalence and mortality of IFIs in these high-risk groups, early diagnosis and timely management are essential for improving outcomes.

The aim of this article is to provide a comprehensive and up-to-date review of invasive fungal infections in pulmonary patients admitted to the ICU, focusing on three key aspects: diagnosis, treatment, and clinical challenges. The review explores novel and advanced diagnostic approaches, including laboratory assays and imaging techniques, while highlighting the limitations and difficulties in early detection. Additionally, it examines various therapeutic strategies, including antifungal medications and supportive care, as well as challenges related to drug resistance, dosing, and selection of appropriate therapy. The ultimate goal of this article is to offer practical guidance for ICU clinicians, support informed clinical decision-making, and identify future research directions to reduce mortality and improve outcomes in patients with invasive fungal infections.

2. Epidemiology and risk factors

In critically ill pulmonary patients, invasive fungal pathogens such as *Aspergillus* spp., *Candida* spp., and Mucorales play a significant yet varied epidemiological role. Among immunocompromised individuals, multicenter data have revealed that these fungi collectively account for approximately 14% of respiratory failure admissions, with *Aspergillus* and *Candida* being the most frequent culprits [8]. Meta-analytic evidence across ICU populations indicates a pooled prevalence of invasive fungal infections at around 5%, with *Aspergillus* responsible for 10% of cases and *Candida* about 3%, reflecting geographical and methodological heterogeneity [9]. Meanwhile, although less common, Mucorales are emerging as aggressive pathogens, particularly in immunosuppressed or post-COVID-19 patients, with pulmonary mucormycosis noted for its increasing incidence and high fatality rate [10,11].

2.1 Epidemiological trends

Over the past decade, the epidemiology of invasive pulmonary fungal infections has undergone notable shifts. A recent narrative review emphasized growing trends in the incidence of candidiasis, aspergillosis, and mucormycosis, particularly with the emergence of drug-resistant and cryptic species, alongside an upswing in COVID-19 associated fungal infections [12]. Global data from 1990 to 2021 reveal a substantial burden of pulmonary fungal illness estimated at approximately 5.6 million cases in 2021 alone with mortality steadily rising, particularly in low and middle income regions [13]. One meta-analysis further confirmed that invasive aspergillosis and candidiasis remain dominant, accounting for around 10% and 3% of infections respectively, with prevalence notably higher in resource limited settings (pooled IFI prevalence of ~5%) [9].

2.2 High-risk groups

Critically ill pulmonary patients who are immunosuppressed (e.g., due to corticosteroids, organ transplantation, or hematologic malignancies), mechanically ventilated, or suffering from severe lung damage including COVID-19, constitute a particularly vulnerable cohort for invasive fungal infections. A recent French multicenter study reported a prevalence of CAPA of about 5.1% among all ICU COVID-19 patients, rising to 9.1% among those who are mechanically ventilated [14]. In non-neutropenic critically ill adults, invasive candidiasis continues to be the most common fungal complication in ICUs, with associated mortality rates often reported in the range of 35% to 50%, particularly in septic shock or when antifungal therapy is delayed or inadequate

(Candidemia surveillance studies; EMCCM *Candida* III analysis) [15,16]. These findings highlight the critical importance of early recognition, prompt treatment, and vigilant monitoring in these high-risk ICU populations.

3. Mechanisms and pathophysiology: Fungal invasion

The pathogenesis of invasive pulmonary fungal infections is driven by a combination of host susceptibility and fungal virulence factors. Inhalation of fungal spores (*conidia* from *Aspergillus* or sporangiospores from Mucorales) represents the primary portal of entry. In healthy individuals, alveolar macrophages and neutrophils act as the first line of defense, eliminating most inhaled spores. However, in immunocompromised hosts, defective phagocytic function allows fungal spores to germinate into hyphae, which can then penetrate the epithelial lining [17]. A critical mechanism in *A. fumigatus* is angioinvasion, where hyphae directly infiltrate endothelial cells, causing vascular injury, hemorrhage, and thrombosis, leading to tissue necrosis and systemic dissemination [18]. This process is potentiated by fungal toxins such as gliotoxin, which suppresses neutrophil oxidative burst and promotes immune evasion. Mucorales, in contrast, exploit host receptor-mediated endocytosis. Key receptors such as glucose-regulated protein 78 (GRP78) and integrin α3β1 on pulmonary epithelial cells facilitate adhesion and internalization of spores, with downstream activation of epidermal growth factor receptor (EGFR) signaling pathways, which are essential for fungal invasion [19]. *Candida* species follow a different invasive route by switching from yeast to filamentous forms, enabling tissue penetration and biofilm formation on endotracheal tubes or catheters, which are common in ICU patients [20]. Beyond *Aspergillus* and *Candida*, other significant fungal pathogens like Cryptococcus neoformans employ distinct pathogenic strategies. This organism typically initiates infection through the inhalation of desiccated yeast cells or basidiospores from the environment. A cornerstone of its virulence is a prominent polysaccharide capsule, which is instrumental in evading phagocytosis by alveolar macrophages. Furthermore, the capsule facilitates immune modulation by inhibiting complement deposition and skewing T-cell responses toward a non-protective T helper 2 (Th2) profile, thereby compromising host defenses. These mechanisms frequently culminate in disseminated disease, with a pronounced tropism for the central nervous system (CNS). Consequently, infection often manifests as life-threatening meningoencephalitis, a particular risk in immunocompromised individuals [21]. Collectively, these mechanisms illustrate how different fungal pathogens employ specialized strategies ranging from immune evasion and endothelial invasion to receptor-mediated adhesion to establish infection in pulmonary tissue and, in severe cases, disseminate systemically. In the Figure 1 the main pathways of invasive fungal entry into the lungs and their systemic dissemination are illustrated.

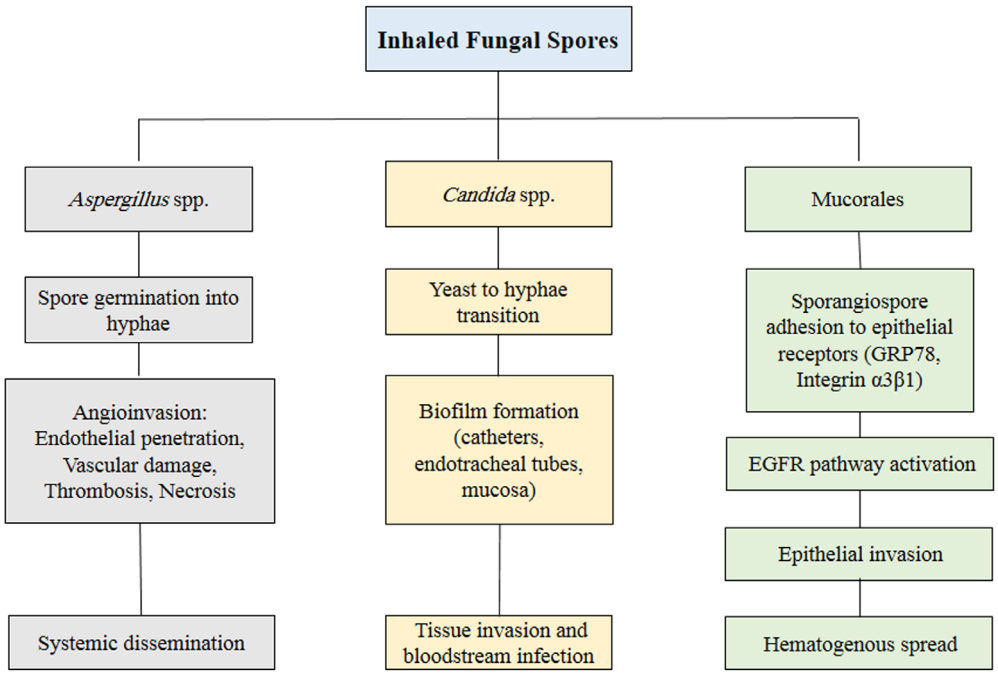

Figure 1. Mechanistic pathways of pulmonary invasion by major fungal pathogens. Inhaled spores of *Aspergillus spp.* germinate into hyphae, leading to angioinvasion, vascular damage, and systemic dissemination. *Candida spp.* invade via yeast-to-hyphae transition and biofilm formation on medical devices, resulting in tissue invasion and candidemia. *Mucorales* utilize host receptors (glucose-regulated protein 78 (GRP78) and integrin α3β1) and epidermal growth factor receptor (EGFR) signaling for epithelial invasion, causing rapid pulmonary necrosis and hematogenous spread.

3.1 *Immune response and disease severity*

The severity of invasive pulmonary fungal infections reflects a dynamic balance between pathogen burden and the quality of host immunity. Innate recognition of fungal cell wall β-glucans and mannans via pattern-recognition receptors (PRRs) notably Dectin-1 and Toll-like receptors activates Spleen Tyrosine Kinase/Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (Syk/NF-κB) signaling, inducing protective cytokines (e.g., IL-1β, TNF, IL-6) and recruiting neutrophils and monocytes to contain germinating hyphae (Dectin-1 also contributes to trained innate immunity) [22-24]. Alveolar epithelium and airway fluids add soluble PRRs such as Pentraxin 3 (PTX3), mannose-binding lectin (MBL), and surfactant proteins A/D that opsonize conidia and amplify complement-mediated clearance; PTX3 in particular correlates with antifungal protection and may aid diagnosis [25]. Genetic or acquired defects in signaling adaptors [e.g., Caspase Recruitment Domain-containing protein 9 (CARD9)] blunt cytokine production and phagocyte trafficking, predisposing to severe, disseminated disease [26]. Neutrophils are pivotal effectors through oxidative burst, degranulation, and neutrophil extracellular traps (NETs), but their quantitative or functional impairment (neutropenia, steroid exposure) allows unchecked hyphal growth and angioinvasion, a hallmark of *Aspergillus* that drives vascular thrombosis, tissue necrosis, and hematogenous spread; fungal metabolites such as gliotoxin further suppress macrophage activation and skew lipid-mediator responses, intensifying tissue injury [23,27]. In *Candida*, yeast-to-hyphae transition and robust biofilms on endotracheal tubes/catheters create immunoprivileged niches that resist phagocytosis and dampen leukocyte responses, increasing the risk of persistent candidemia and deep organ seeding [28,29]. Mucorales exploit host receptors GRP78 and integrin β1/α3β1 on alveolar epithelium to trigger EGFR-dependent endocytosis and invasion; antibody blockade of integrin β1 mitigates disease in neutropenic models, underscoring the causal role of host–pathogen receptor crosstalk in severity [19]. On the adaptive side, T helper 1/T helper 17 skewed responses generally aid fungal killing (Interferon-gamma (IFN-γ), Interleukin-17 (IL-17)), whereas Th2-biased inflammation and excessive cytokine production can exacerbate lung damage, gas-exchange failure, and ultimately ICU mortality illustrating that both immune deficiency and immune dysregulation amplify clinical severity [23,24].

3.2 *Clinical differences among fungal species*

The clinical presentation and progression of invasive pulmonary fungal infections differ considerably among fungal species, reflecting variations in virulence mechanisms and host–pathogen interactions [30]. *A. fumigatus* typically causes angioinvasive pulmonary aspergillosis in immunocompromised or critically ill patients, manifesting with vascular thrombosis, tissue necrosis, and systemic dissemination, which account for its high mortality [31,32]. In contrast, *Candida* species rarely cause primary pneumonia; instead, they are more often associated with biofilm-related infections on endotracheal tubes or intravascular catheters, leading to persistent candidemia and secondary pulmonary involvement [28]. *Mucorales* species, such as *Rhizopus*, exhibit rapid tissue invasion via GRP78- and integrin-mediated mechanisms, resulting in fulminant pulmonary mucormycosis, especially in diabetic or COVID-19 patients, with hallmark findings of massive necrosis and angioinvasion [19]. *C. neoformans* presents differently, with pulmonary nodules or diffuse infiltrates that may progress to meningoencephalitis due to its polysaccharide capsule and immune evasion strategies, even in patients with relatively preserved immunity [33]. These interspecies clinical differences underscore the importance of early species-level identification to optimize antifungal therapy and predict patient outcomes.

4. Clinical methods: Nonspecific signs and symptoms

The clinical diagnosis of invasive pulmonary fungal infections (IPFIs) is often complicated by their nonspecific presentation, which overlaps with bacterial or viral pneumonias in critically ill patients. Common symptoms include fever unresponsive to broad-spectrum antibiotics, persistent cough, dyspnea, chest pain, and hemoptysis, yet none of these are pathognomonic [34]. Radiologic findings such as pulmonary nodules, cavitary lesions, or ground-glass opacities may suggest fungal disease, but they lack specificity, particularly in mechanically ventilated or immunosuppressed individuals [35]. Moreover, patients with underlying chronic lung disease, including COPD or post-COVID-19 lung injury, often exhibit baseline respiratory symptoms that mask early signs of fungal infection [36]. This clinical ambiguity contributes to delayed diagnosis and worsened outcomes, underscoring the necessity of integrating clinical suspicion with laboratory and imaging modalities for timely recognition. The clinical manifestations of invasive pulmonary fungal infections vary considerably by pathogen, further complicating diagnosis. *Aspergillus spp.* typically cause persistent fever, pleuritic chest pain, hemoptysis, and nodular or cavitary infiltrates, often linked to angioinvasion [32]. *Candida spp.*, in contrast, rarely cause primary pneumonia but may lead to diffuse pulmonary infiltrates in ventilated or immunocompromised patients as part of hematogenous dissemination [37]. Infections due to *Mucorales* progress rapidly, with necrotizing pneumonia, hemoptysis, and frequent vascular invasion leading to massive tissue destruction [38]. *C. neoformans* and *Cryptococcus gattii* often present with

subacute respiratory symptoms such as cough and dyspnea, but in many cases, pulmonary signs are overshadowed by central nervous system involvement due to hematogenous spread [39]. Recognizing these species-specific clinical differences is critical for raising suspicion and guiding timely diagnostic evaluation in high-risk ICU patients.

4.1 *Imaging: CT, X-ray, and classic signs*

Imaging plays a central role in the early diagnosis of IPFIs, particularly in ICU patients where invasive procedures such as bronchoscopy or biopsy are often limited by clinical instability. Chest X-ray (CXR) is widely available as a bedside tool but has low sensitivity and specificity, frequently showing only nonspecific findings such as consolidation or diffuse infiltrates [40]. High-resolution computed tomography (HRCT) is therefore considered the gold standard and provides earlier and more characteristic findings. The halo sign, seen in up to 60–70% of cases of invasive pulmonary aspergillosis during the first week of infection, represents a nodule surrounded by ground-glass opacity caused by hemorrhagic infarction secondary to angioinvasion [41]. The air-crescent sign, which appears later typically in the second to third week coincides with neutrophil recovery and indicates retraction of necrotic lung tissue, often correlating with improved prognosis but also with risk of hemoptysis. These signs are highly suggestive of invasive mold infections but are not entirely specific, as similar patterns can be observed in mucormycosis, granulomatosis with polyangiitis, or necrotizing bacterial pneumonias. Therefore, radiologic findings must always be interpreted in conjunction with host immune status, clinical suspicion, and microbiological or biomarker confirmation [40,41].

4.2 *Laboratory diagnosis*

Laboratory-based diagnosis of IPFIs relies on a combination of culture, non-culture biomarker assays, and molecular techniques, yet each approach has limitations that may delay timely treatment. Fungal culture from bronchoalveolar lavage (BAL) or tissue biopsy remains the gold standard for definitive diagnosis and allows antifungal susceptibility testing, but sensitivity is limited especially in patients already on antifungal prophylaxis and results often take several days [10]. Non-culture-based assays have significantly improved early detection: galactomannan (GM) enzyme immunoassay is widely used for the diagnosis of invasive aspergillosis and has a high sensitivity in neutropenic patients, though false positives may occur with certain antibiotics (e.g., piperacillin-tazobactam) and dietary factors [42]. (1→3)-β-D-glucan (BDG) testing offers broad-spectrum detection of most invasive fungal infections but lacks specificity for *Aspergillus* versus *Candida* and is negative in mucormycosis [43]. PCR-based assays and next-generation sequencing (NGS) have shown promise in detecting fungal DNA directly from blood or BAL fluid, with higher sensitivity and faster turnaround times, but remain limited by lack of universal standardization and availability [44]. A major diagnostic challenge remains the differentiation between colonization and true infection, particularly in ICU patients with pre-existing lung disease or those on mechanical ventilation, where over-diagnosis can lead to unnecessary antifungal therapy and resistance development [1]. Integrating multiple diagnostic modalities and clinical risk stratification remains the current best practice for improving early and accurate diagnosis. Figure 2 presents a comprehensive diagnostic algorithm for the management of suspected invasive fungal pulmonary infections in critically ill ICU patients, outlining a stepwise approach from initial clinical suspicion to definitive diagnosis and targeted therapy [32,45].

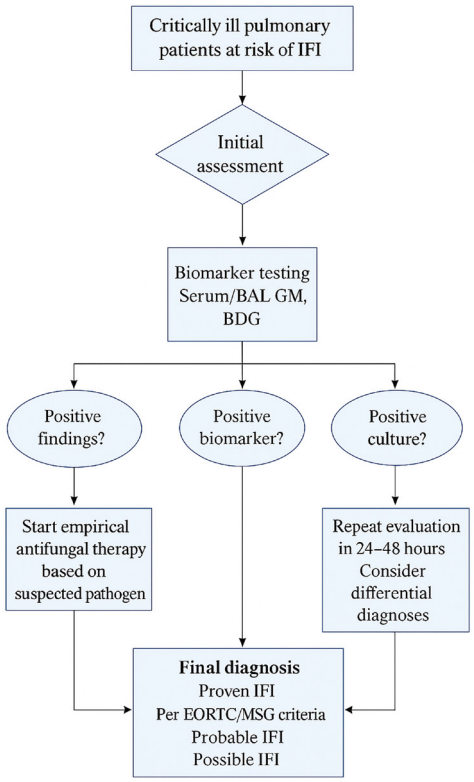

Figure 2. Diagnostic algorithm for suspected invasive fungal infections (IFIs) in critically ill pulmonary patients. The flowchart outlines stepwise evaluation, including initial clinical assessment, imaging (HRCT), biomarker testing (serum/BAL GM, BDG), and microbiological cultures, leading to empiric or targeted antifungal therapy and classification into proven, probable, or possible IFI according to EORTC/MSG criteria. BAL: Bronchoalveolar lavage; GM: Galactomannan; BDG: (1→3)-β-D-Glucan; EORTC/MSG: European Organization for Research and Treatment of Cancer/Mycoses Study Group.

4.3 *Integrated fungal diagnostics*

Traditional microbiological methods, including

culture of BAL, blood, or tissue samples, remain the cornerstone of diagnosis, as they allow for species-level identification and antifungal susceptibility testing (AST), which is critical for guiding targeted therapy [32]. However, their clinical utility is limited by the low sensitivity of blood culture for filamentous fungi such as *Aspergillus*, potential false positives from airway colonization, and the slow turnaround time, often requiring several days for definitive results. AST, performed according to Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility

Testing (EUCAST) guidelines, has become increasingly important in the era of emerging antifungal resistance, particularly azole-resistant *A. fumigatus* strains [46] Complementing these classical methods, serological and molecular biomarkers have revolutionized early and non-invasive diagnosis. GM, a polysaccharide antigen released during fungal growth, can be detected by enzyme immunoassay (EIA) in serum or BAL samples and serves as a valuable tool for diagnosing invasive aspergillosis, though false positives may occur with certain antibiotics (e.g., piperacillin-tazobactam) or other fungal infections, and false negatives are common in patients on antifungal therapy or infected by Mucorales [47]. Similarly, BDG, a pan-fungal cell wall component, is an excellent screening marker but lacks pathogen specificity and may yield false positives due to sample contamination, hemodialysis membranes, or intravenous immunoglobulin therapy [48]. Molecular techniques such as PCR, including species-specific and pan-fungal assays, offer increased sensitivity and faster detection, especially when combined with GM testing, but remain hindered by the lack of global standardization, contamination risk, and the inability to reliably differentiate colonization from invasive disease [43]. Ultimately, early diagnosis faces several key challenges, including low fungal burden in the initial disease stages, difficulty distinguishing colonization from infection especially in BAL samples and reduced test sensitivity in patients receiving empirical antifungal therapy. Consequently, a multimodal diagnostic strategy integrating clinical, radiological, microbiological, and biomarker data is considered essential for timely and accurate diagnosis of invasive fungal infections [10]

5. Supportive care

Supportive care in invasive pulmonary fungal infections focuses on strengthening host defenses and optimizing respiratory mechanics. Recent evidence suggests that in solid organ transplant recipients admitted to the ICU, a “suspensive” strategy temporarily withholding immunosuppressive agents during critical illness can reduce the incidence of ICU-acquired infections without increasing short-term mortality, particularly in patients presenting with sepsis [49]. In parallel, lung-protective ventilation remains a cornerstone of supportive therapy in patients with severe pulmonary involvement or acute respiratory distress syndrome (ARDS), including those with fungal pneumonia. Adherence to strategies such as low tidal volume ventilation (≤ 6 mL/kg predicted body weight), limiting plateau pressures (≤ 30 cm H_2O), and applying adequate positive end-expiratory pressure (PEEP) has been associated with improved survival and reduced ventilator-induced lung injury [50]. Additional measures, such as prone positioning and conservative fluid balance, may enhance oxygenation and reduce alveolar edema, thereby improving host capacity to clear infection. Together, immune modulation and lung-protective ventilation are integral adjuncts to antifungal pharmacotherapy for optimizing outcomes in critically ill patients.

6. Role of surgical intervention

Surgical intervention serves as a critical adjunct to antifungal therapy in select cases of invasive fungal pulmonary infections. This approach is particularly vital in pulmonary mucormycosis, which is characterized by angioinvasion, thrombosis, and progressive tissue necrosis [51,52]. Surgical debridement of infected and necrotic tissue significantly reduces the fungal burden and enhances antifungal drug penetration into otherwise poorly accessible ischemic areas [38]. The decision to pursue surgery should be made by a multidisciplinary team including infectious disease specialists, thoracic surgeons, and intensivists, considering factors such as disease extent, immunological status, and hemodynamic stability. Optimal timing is crucial, typically performed after initial stabilization with antifungal therapy and as early as feasible to prevent further dissemination and maximize the likelihood of complete resection [45]. In the post-COVID-19 setting, surgical management becomes even more challenging due to extensive pulmonary involvement from prior viral pneumonia, pre-existing fibrosis, and frequent comorbidities such as diabetes mellitus and corticosteroid-induced immunosuppression [53,54]. These factors may increase surgical risks and limit resection margins, underscoring the importance of careful patient selection and individualized surgical planning. Nonetheless, when feasible, timely surgical intervention in post-COVID-19 invasive fungal infections has been associated with improved outcomes compared with antifungal therapy alone, highlighting its indispensable role in comprehensive management [55,56].

7. Clinical challenges

The management of invasive fungal infections in the ICU is fraught with significant clinical challenges that directly impact patient mortality. A primary obstacle is delayed diagnosis; the non-specific clinical presentation and radiological similarities to other pneumonias often lead to postponement of initiating effective antifungal therapy. This delay is strongly associated with poor

prognosis and high mortality, particularly in patients with severe immunodeficiency [34]. A second major challenge is the emergence of antifungal resistance. Increasing azole resistance in *A. fumigatus* species and echinocandin resistance in certain *Candida* species (e.g., *Candida glabrata* and *Candida auris*) have limited treatment options, necessitating careful antifungal susceptibility testing and regimen adjustments based on AST results [57]. Third, the complexity of managing patients with multiple comorbidities presents substantial difficulties. Conditions such as persistent neutropenia, organ transplantation, or chronic obstructive pulmonary disease diminish treatment response and increase the risk of infection recurrence. In these patients, concurrent organ failures complicate drug dosing and toxicity management [58]. Finally, limitations in clinical trial data and the absence of unified guidelines for specific ICU populations represent a fundamental challenge. Many existing guidelines are derived from studies that underrepresent critically ill patients, resulting in a lack of robust evidence to support standardized protocols [59]. This knowledge gap underscores the urgent need for prospective studies focused on this vulnerable patient population. Similar to the paradigm shift prompted by the recognition of concurrent EGFR and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations in non-small cell lung cancer (NSCLC), which highlights the complexity of host-pathogen and therapeutic interactions [60]. invasive fungal infections in ICU patients also demand multifaceted approaches. This parallel underscores that linear, single-target strategies may be insufficient in critically ill patients, where immune dysfunction, drug interactions, and pathogen virulence collectively shape outcomes

8. Future Perspectives

The future management of invasive fungal infections in ICU patients hinges on advancements across three critical domains: diagnostic innovation, optimized prevention, and novel therapeutic strategies. Significant research efforts are directed toward developing rapid and highly sensitive diagnostic tools. Next-generation molecular techniques, including multiplex PCR panels and next-generation sequencing (NGS), promise to detect fungal pathogens and resistance markers directly from clinical samples within hours, potentially revolutionizing early targeted therapy [43]. Furthermore, the refinement of existing biomarkers and the discovery of new ones aim to improve the non-invasive differentiation between colonization and invasive disease, thereby enhancing diagnostic accuracy In terms of prevention and prophylaxis, future strategies are evolving toward a risk-adapted, personalized approach. This involves better identification of high-risk subpopulations within the ICU using predictive scores that incorporate clinical and immunological parameters. The role of universal antifungal prophylaxis remains controversial; however, targeted prophylaxis in specific high-risk cohorts (e.g., patients with prolonged neutropenia, post-lung transplantation, or those on extracorporeal membrane oxygenation is an area of active investigation to define optimal agents and durations. For example, a recent expert review recommended targeted prophylaxis with liposomal amphotericin B in solid organ transplant recipients at high risk, showing a lower incidence of IFIs (2.6% vs. 11.8%) in treated vs. historical controls [61]. Additionally, research into environmental control measures, such as advanced air filtration systems and strict infection control bundles, continues to be a priority to reduce exposure to fungal spores. Finally, addressing the growing challenge of antifungal resistance necessitates a dual approach: vigilant surveillance and the development of new therapeutic agents. Global surveillance programs are crucial for monitoring the emergence and spread of resistant isolates of *Candida auris* and azole-resistant *A. fumigatus*. Pharmacokinetic/pharmacodynamic (PK/PD) studies in critically ill patients are essential to optimize dosing regimens for existing drugs and prevent the development of resistance [62]. The pipeline for novel antifungals is promising, with several agents in advanced clinical development. These include new drug classes with novel mechanisms of action, such as fosmanogepix (a Gwt1 inhibitor), ibrexafungerp (a triterpenoid), and olorofim (a dihydroorotate dehydrogenase inhibitor), which offer hope for treating infections resistant to current therapies [46]. The integration of these diagnostic, preventive, and therapeutic advancements holds the potential to significantly improve outcomes for critically ill patients with invasive fungal infections.

9. Conclusion

IFIs in ICU patients with pulmonary involvement represent a formidable and increasingly prevalent clinical challenge, characterized by unacceptably high attributable mortality, significant healthcare costs, and prolonged ICU stays. Effectively managing these infections demands a multifaceted and agile approach that integrates early and accurate diagnosis using advanced biomarkers and imaging, timely initiation of appropriate antifungal therapy, and comprehensive supportive care. This review has provided a synthesis of evidence specifically tailored to the complex ICU environment, focusing on unique challenges such as differentiating colonization from infection in ventilated patients, managing drug interactions and organ dysfunction, and addressing the looming threat of antifungal resistance. Looking ahead, conquering this challenge necessitates concerted efforts in several critical directions, including the development and validation of sophisticated risk-stratification tools to guide targeted prophylactic and pre-emptive strategies. Furthermore, optimizing antifungal dosing through advanced PK/PD studies in special ICU populations is

essential, particularly for those receiving organ support therapies. Robust health-economic analyses of novel diagnostics and therapeutics are needed to ensure sustainable implementation, while the establishment of international, standardized protocols for surveillance and management through global collaborative networks remains imperative. The future of IFIs management in the ICU lies in precision medicine leveraging continuous innovation in rapid diagnostics, novel therapeutic agents, and patient-specific treatment algorithms based on individual risk profiles and pathogen characteristics. Through dedicated collaboration between clinicians, researchers, and policymakers, we can aspire to significantly reduce the devastating mortality associated with these infections.

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Authors' contributions

NK, HA: conceived the concept and scope of the review. NK, HA, KK, MF: performed the literature search and data curation. NK, KK: drafted the initial manuscript. HA, MF: critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

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