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NARRATIVE REVIEW

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Antifungal treatment strategies in intensive care unit patients

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Abstract

Background: Invasive fungal infections (IFIs) are a major cause of morbidity and mortality among critically ill patients. In the intensive care unit (ICU), invasive candidiasis (IC), invasive pulmonary aspergillosis (IPA), and Pneumocystis jirovecii pneumonia (PjP) represent the most prevalent and clinically relevant fungal diseases. Their diagnosis is often hampered by nonspecific clinical and radiological findings, delayed or negative cultures, and suboptimal performance of fungal biomarkers in this population. As a result, antifungal treatment strategies in the ICU must balance the need for early initiation with the risk of overtreatment and resistance.

Methods: This review summarizes current therapeutic approaches, evidence-based recommendations, and recent advances for the treatment of IC, IPA, and PjP in critically ill patients. Pharmacokinetic/pharmacodynamic (PK/PD) considerations, therapeutic drug monitoring, and emerging antifungal agents are also discussed.

Results: For IC, echinocandins remain the cornerstone of therapy, while biomarker-guided strategies appear more useful for treatment discontinuation than initiation. In IPA, voriconazole and isavuconazole are first-line agents, with liposomal amphotericin B as an alternative in case of azole resistance or intolerance; the role of combination therapy remains uncertain. For PjP, trimethoprim–sulfamethoxazole is the treatment of choice, while adjunctive corticosteroids are recommended mainly for people with HIV and severe disease. Emerging antifungal agents, including rezafungin, fosmanogepix, and olorofim, may enhance future treatment options.

Conclusions: Optimizing antifungal stewardship through individualized therapy and early diagnosis remains essential to improve outcomes in this high-risk population.

KEYWORDS

antifungal stewardship, critically ill patients, intensive care unit, invasive fungal infections

1 | BACKGROUND

Invasive fungal diseases (IFDs) are a major cause of morbidity and mortality, with a global burden exceeding over 6.55 million people affected each year, leading to over 3.75 million deaths.[1] Within intensive care units (ICUs), *Candida* spp., *Aspergillus* spp. and *Pneumocystis jirovecii* are responsible for the vast majority of severe fungal infections.[2] Their diagnosis is particularly complex due to nonspecific clinical manifestations, overlapping radiological findings and the suboptimal performance of fungal biomarkers in non-neutropenic hosts.[2] Recent attempts to standardize the definition of IFDs in critically ill patients—such as the Invasive Fungal Diseases in Adult Patients in ICU (FUNDICU) criteria—were designed to harmonize inclusion criteria across studies and improve comparability between clinical trials (Table 1).[3] While these standardized definitions have proved valuable for research purposes, they may be, although useful, too restrictive in some cases for daily clinical decision-making, where diagnostic uncertainty, complex trajectories and the urgency of initiating therapy demand a more pragmatic and individualized approach. At the same time, the global rise of antifungal resistance—especially among non-albicans *Candida* species and azole-resistant *Aspergillus fumigatus*—has underscored the need for optimized therapeutic strategies and enhanced antifungal stewardship.[4] In the ICU, stewardship principles are crucial to balance early, life-saving treatment with avoidance of unnecessary antifungal exposure, toxicity and resistance selection. Integrating rapid diagnostics, individualized pharmacokinetic/pharmacodynamic optimization and targeted de-escalation strategies represents the cornerstone of modern antifungal management.[5] This review provides a pathogen-oriented overview of current treatment approaches and emerging perspectives for antifungal therapy in critically ill patients.

2 | LITERATURE SEARCH

A literature search was performed in PubMed for articles published in English before September 1st, 2025, using various combinations of the keywords 'Candida/Candidiasis', 'Aspergillus/Aspergillosis', 'Pneumocystis/Pneumocystosis', 'Invasive fungal infections', 'Intensive Care Unit' and 'critically ill patients', with a particular focus on studies published within the last 5 years. Titles and abstracts were screened to identify relevant publications, which were then retrieved for full-text review. Given the broad spectrum of IFDs and the aim of providing a focused overview, we decided to concentrate on the main therapeutic strategies and treatment options for the three most prevalent IFDs in the ICUs, namely invasive candidiasis (IC), invasive pulmonary aspergillosis (IPA) and *Pneumocystis jirovecii* pneumonia (PjP), focusing on the available evidence and prioritizing multicenter studies and randomized clinical trials involving critically ill patients. The present review is therefore structured into three sections regarding therapeutic strategies on: (i) *Candida* spp., (ii) *Aspergillus* spp. and (iii) *Pneumocystis jirovecii* infections.

2.1 | Invasive candidiasis in critically ill patients

Invasive candidiasis (IC) remains a major challenge in the intensive care unit (ICU), where it is associated with high morbidity and mortality.[1] The large multicentre EUCANDICU study reported a cumulative incidence of around 7.07 episodes per 1000 ICU admissions, with candidemia accounting for about three quarters of cases and intra-abdominal candidiasis for nearly one quarter. Mortality exceeds 40%, reflecting the severity of diseases in this population.[6] Regarding species distribution, over the past decade, a progressive shift from *Candida albicans* to non-*albicans* species has been observed, which now account for more than half of ICU cases.[7] Yet, this pattern may not be uniformly observed in ICU populations, as documented in a meta-analysis and meta-regression.[8] This variability, along with rising antifungal resistance and outbreak reports, highlights the need for more individualized therapeutic approaches. Among non-*albicans* species, *Candida auris* has emerged as a significant healthcare-associated pathogen, with rising infection rates and numerous ICU outbreaks, particularly during and after the COVID-19 pandemic.[9] Its efficient transmission and undefined prolonged colonization make containment challenging, especially in the ICU setting.[10] From a clinical standpoint, although most studies have not shown increased 30- or 90-day mortality compared with other *Candida* species, *C. auris* has been associated with a higher risk of microbiological recurrence, warranting close follow-up.[11,12] Likewise, azole-resistant *Candida parapsilosis* has become increasingly frequent, with a rise in incidence and outbreak reports, often involving ICUs, especially after the COVID-19 pandemic.[13] While data on its clinical impact are conflicting, some reports available in the literature describe an increased mortality among patients with fluconazole-resistant *Candida parapsilosis* infections, whereas others do not.[14] However, these studies are affected by several methodological limitations, including heterogeneity of the included populations and

TABLE 1 Invasive Fungal Diseases in Adult Patients in ICU (FUNDICU) criteria for the diagnosis of invasive fungal infections in critically ill patients.

Definition of proven invasive aspergillosis: proven invasive aspergillosis is defined by at least one of the following
Tissue invasion shown by histological or cytopathological evidence on a specimen obtained from a normally sterile site or the lung with biopsy or needle aspiration, combined with detection of hyphae compatible with Aspergillus spp. (confirmed by culture or PCR)
Recovery of Aspergillus spp. by culture on a specimen obtained from a normally sterile site by means of biopsy or needle aspiration, from a lesion consistent with an infectious process
Definitions of probable IPA and probable TBA
Evaluation for defining probable IPA and probable TBA in research studies should be performed only in patients with at least one of the following compatible signs and symptoms (precondition for evaluation)
Fever (38.3°C or higher) persisting after at least 3 days of appropriate antibiotic therapy (and source control for bacterial infection, if necessary)
Relapse of fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
Pleuritic chest pain
Pleuritic rub
Dyspnea[a]
Hemoptysis
Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
Patients with at least one compatible sign or symptom should be evaluated for the presence of at least one of the following ICU host factors for probable IPA and probable TBA
Influenza
COVID-19
Moderate/severe COPD
Decompensated cirrhosis
Uncontrolled HIV infection with CD4 cell count <200/mm^3
Solid tumours
In patients with at least one compatible sign or symptom and at least one entry criterion, probable IPA or probable TBA are defined by the presence of at least one clinical criterion and at least one mycological criterion
Clinical criteria
Presence of tracheobronchial ulceration and/or nodule and/or pseudomembrane and/or plaque, and/or eschar on bronchoscopy (for defining probable TBA[b])
Presence of pulmonary infiltrate/s documented by chest CT or presence of cavitation not attributable to other causes (for defining probable IPA)
Mycological criteria
Positive Aspergillus BALF culture
Serum galactomannan >.5 ODI[c]
BALF galactomannan ≥1.0 ODI[c,d]

Abbreviations: BALF: bronchoalveolar lavage fluid; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CT: computerized tomography; HIV: human immunodeficiency virus; ICU: intensive care unit; IPA: invasive pulmonary aspergillosis; ODI: optical density index; PCR: polymerase chain reaction; TBA: tracheobronchial aspergillosis.

[a]Not applicable for patients ventilated for more than 48 h at the time of assessment for probable IPA/TBA. Applicable in the first 48 h if dyspneic at the time of initiation of ventilation.

[b]In patients with COVID-19 or with influenza, probable TBA may be defined also in the absence of compatible signs and symptoms, provided both the following are present: (i) presence of tracheobronchial ulceration and/or nodule and/or pseudomembrane and/or plaque, and/or eschar on bronchoscopy; (ii) any positive mycological criterion.

[c]Platelia Aspergillus Ag Kit.

[d]When the Platelia test is unavailable, another galactomannan test can be used when this test was compared with the Platelia test in a well-designed study and shown to have comparable specificity to the 1.0 Platelia cut-off.

small cohort sample sizes.[14] The largest available multicenter study, however, found no significant difference in 30-day mortality between resistant and susceptible isolates, although resistance was linked to a higher risk of one-year recurrence.[15] Overall, antifungal resistance may not affect short-term outcomes but can complicate

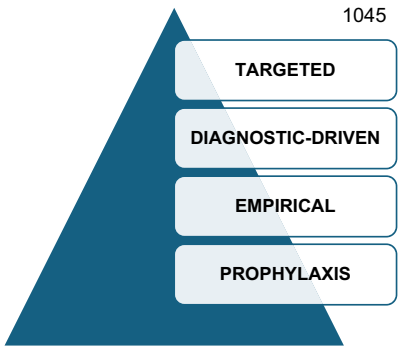
long-term disease control and therapeutic decision-making. The evolving epidemiology and emergence of resistant *Candida* species highlight the urgent need for vigilant surveillance and optimized, species-specific management strategies, as treatment in critically ill patients remains particularly challenging due to the high mortality rates, severe clinical presentation, and, in some cases, limited therapeutic options.

2.1.1 | Therapeutic approaches for invasive candidiasis in critically ill patients

Several therapeutic strategies are used in clinical practice, each with its own rationale and evidence base (Figure 1).[16] Prophylaxis (i), while conceptually attractive, has not demonstrated a clear mortality benefit in non-neutropenic and non-transplanted ICU populations and is therefore not recommended routinely.[17] Its use could possibly be considered for very specific high-risk scenarios, such as patients who have undergone recent abdominal surgery complicated by recurrent perforations or anastomotic dehiscence.[18] Empirical antifungal therapy (ii)—that is, initiating antifungal treatment in the presence of clinical suspicion of infection (based on risk factors and compatible signs or symptoms) but in the absence of microbiological confirmation or biomarker support—has similarly failed to show a clear survival benefit in randomized controlled trials compared with placebo, although the denominator of patients who ultimately are found to have candidemia in similar studies usually remains small, thus a true advantage in this subgroup may be missed owing to reduced power.[19,20] Given this consideration, empirical therapy could remain, in our opinion, a reasonable option in selected cases, particularly in patients with septic shock or rapidly deteriorating clinical status in the context of well-established risk factors, such as multifocal *Candida* colonization or prolonged ICU stay.[18,21] A diagnostic-driven approach in patients with consistent signs and symptoms (iii), often based on fungal biomarkers, is increasingly being explored as a means of optimizing the initiation and discontinuation of therapy. Among the available tools, serum β-D-glucan (BDG) is the most extensively studied. However, its clinical utility in the ICU is limited by frequent false positives (for example, following abdominal surgery or intravenous immunoglobulin administration) and by reduced sensitivity for certain species such as *C. auris* and *C. parapsilosis*.[22] As a result, the positive predictive value of BDG is low, and even its sensitivity may be compromised for some *Candida* spp., despite a high overall negative predictive value. When the impact of a biomarker-guided approach to antifungal therapy initiation was evaluated, the CANDISEP trial demonstrated that BDG-based initiation did not improve 28-day mortality compared with culture-based strategies but did significantly increase antifungal exposure.[23] By contrast, BDG-guided discontinuation strategies may offer some advantages, although the available evidence has yielded mixed results. A recent randomized control trial (RCT) has showed that the strategy of combining two negative BDG and mannan determination to stop antifungal therapy failed to reduce antifungal consumption with even increased healthcare costs,[24] whereas another RCT has shown shorter treatment durations using a BDG-guided antifungal therapy algorithm without adverse effects on outcomes.[25] The role of BDG in treatment monitoring is also uncertain, as clearance kinetics are highly variable and often delayed, particularly in deep-seated infections.[26] Overall, biomarker-based approaches appear to be most useful for guiding decisions about discontinuing antifungal therapy rather than initiating it.[18]

2.1.2 | Targeted antifungal therapy for invasive candidiasis

Once infection is confirmed, targeted antifungal therapy remains the cornerstone of management (Table 2).



Strategy	Risk factors	Clinical Signs	Biomarker/ Radiology	Culture
Targeted	-/+	+	+/-	+
Diagnostic driven	+	+	+	-
Empirical	+	+	-	-
Prophylaxis	+	-	-	-

FIGURE 1 Therapeutic approaches for invasive candidiasis in critically ill patients.

TABLE 2 Therapeutic options for candidemia in critically ill patients (based on Cornely et al. Global guideline for the diagnosis and management of candidiasis: An initiative of the ECMM in cooperation with ISHAM and ASM[17]).

Clinical setting	Recommended first-line therapy	Alternative therapy	Comments
Initial targeted therapy	Echinocandin (caspofungin, micafungin, anidulafungin or rezafungin)[a]	Liposomal amphotericin B or fluconazole (if susceptible strain and low risk for resistance)	Echinocandins remain preferred for broad spectrum, fungicidal activity and safety profile. Rezafungin is now included as a first-line option due to once-weekly dosing and potent *Candida* activity.
Step-down therapy	Fluconazole (if susceptible isolate, stable patient, negative blood cultures, adequate source control)	Voriconazole or posaconazole (if resistant to fluconazole)	Early transition to oral azole (after ≥5 days) reduces catheter-related and cost burden. Step-down only after clinical improvement and microbiological clearance.
Central nervous system/ocular involvement	Liposomal amphotericin B ± flucytosine	High-dose fluconazole or voriconazole (if susceptible)	Echinocandins have poor penetration; thus not recommended for CNS/ocular infections.
Echinocandin- or azole-resistant species	Liposomal amphotericin B	Fosmanogepix or ibrexafungerp (where available)	Consider combination therapy in refractory cases. Implement infection control and antifungal stewardship measures.
Duration of therapy	Minimum 14 days after first negative blood culture and resolution of symptoms	–	Shorter courses not routinely recommended; observational studies suggested potential safety of short courses in selected 'uncomplicated candidemia' cases (need to be validated by RCTs)
Source control	–	–	Essential component of management: remove intravascular catheters, drain abscesses and treat intra-abdominal foci.

Abbreviations: CNS, central nervous system; LD, loading dose; RCT, randomized controlled trial.

[a]Echinocandins: caspofungin 70 mg LD → 50 mg once daily; micafungin 100 mg once daily; anidulafungin 200 mg LD → 100 mg once daily; rezafungin 400 mg once weekly; Fluconazole: 400–800 mg daily; Liposomal amphotericin B: 3–5 mg/kg daily.

Current guidelines recommend echinocandins as the first-line treatment for candidemia and other forms of IC, given their broad spectrum, fungicidal activity and excellent safety profile.[18] Step-down to an azole, typically fluconazole, is advised in uncomplicated cases once certain conditions are met, including hemodynamic stability, documented clearance of blood cultures, species susceptibility and, critically, adequate source control. Timely removal of infected intravascular catheters, drainage of abscesses and surgical management of infected foci are all essential components of therapy and should not be considered ancillary to antifungal treatment.[18] Without effective source control, microbiological eradication is less likely to occur, the risk of relapses increases and treatment failure becomes significantly more probable. Achieving all these criteria, however, is often challenging in critically ill patients, in whom hemodynamic instability, multifocal disease and difficult-to-control sources are common.

In this context, the recent introduction of rezafungin, a long-acting echinocandin with once-weekly dosing and potent in vitro activity against most *Candida* species including *C. auris*, may offer greater flexibility, especially for patients requiring prolonged treatment or with limited vascular access. Rezafungin has also been included as a first-line option, alongside other echinocandins, in the latest global guidelines.[18] Beyond echinocandins, several novel antifungal agents have entered advanced stages of clinical development, potentially expanding future therapeutic options for invasive candidiasis. These include as follows: (i) fosmanogepix, the prodrug of manogepix, a first-in-class *Gwt1* inhibitor that disrupts fungal cell wall protein anchoring. It exhibits broad-spectrum activity, including against azole- and echinocandin-resistant *Candida* isolates, except for *C. krusei*, against which it lacks in vitro activity. Phase II studies have shown promising efficacy and a favourable safety profile, with ongoing trials evaluating its role as a first-line therapy for invasive fungal infections; and (ii) ibrexafungerp, an orally bioavailable glucan synthase inhibitor (triterpenoid class) that acts through a mechanism similar to echinocandins but binds to a distinct site, potentially leading to partial cross-resistance between the two classes. It demonstrates potent fungicidal activity against *Candida* spp., including *C. auris*, although its activity against *C. lusitaniae* and *C. krusei* is slightly

reduced compared with other species. Ibrexafungerp is currently approved for the treatment of vulvovaginal candidiasis, with phase III studies ongoing for invasive infections.[27]

2.1.3 | PK/PD issues for invasive candidiasis in critically ill patients

Pharmacokinetic and pharmacodynamic (PK/PD) variability represents another layer of complexity in ICU antifungal management. Altered fluid distribution, hypoalbuminemia, organ dysfunction, extracorporeal therapies such as renal replacement therapy or extracorporeal membrane oxygenation (ECMO) and multiple drug interactions all affect drug exposure and efficacy. Moreover, many patients in intensive care develop acute kidney injury, either due to pre-existing conditions or as a consequence of sepsis itself.[28] Dose optimization and therapeutic drug monitoring (TDM), especially for triazoles, are therefore reasonable approaches to ensure therapeutic efficacy and avoid toxicity.[18] Regarding echinocandins, which remain the first-line treatment for IC, dose optimization in specific settings, such as during continuous renal replacement therapy (CRRT), is an area of ongoing debate. The extent of echinocandin adsorption by dialysis membranes remains controversial: preclinical studies have suggested a significant reduction in caspofungin concentrations with certain CRRT systems,[29] whereas preliminary retrospective clinical data did not confirm this effect in vivo.[30] Further prospective studies are therefore needed to clarify the clinical relevance of these findings and to guide dosing recommendations in this population. Another important and still debated aspect concerns the role of TDM for echinocandins, which may be potentially useful in selected cases—not primarily to detect toxicity, which is generally low, but rather to assess the need for dose escalation in patients at risk of suboptimal drug exposure.[31]

2.1.4 | Treatment duration for candidemia in critically ill patients

The duration of antifungal therapy for invasive candidiasis varies according to the site of infection, with longer courses required for deep-seated or intra-abdominal localizations, where treatment length is strongly influenced by the timing and adequacy of source control.[18] For candidemia, the long-standing recommendation to continue treatment for at least 14 days after the first negative blood culture, still endorsed by the most recent international guidelines,[18] originates from a single comparative trial published in 1994, in which both treatment arms used this fixed duration.[32] This approach was subsequently incorporated into routine practice and has since persisted as a therapeutic dogma, despite the lack of further validation. However, in line with a broader movement in infectious diseases toward antimicrobial stewardship and treatment shortening, there is now growing interest in applying shorter antifungal courses also for candidemia.[33] The first step toward achieving this goal is to identify the subset of patients who may benefit from a reduced treatment duration without compromising therapeutic efficacy. A recent proposed operational definition of 'uncomplicated candidemia' incorporates host-related factors, clinical criteria and microbiological parameters including the absence of major immunosuppressive conditions, timely and effective source control, early clinical response, rapid clearance of candidemia and favourable antifungal susceptibility profiles.[34] However, this definition has not yet been validated in prospective clinical studies, and its applicability to routine clinical decision-making remains uncertain, especially for critically-ill patients. Previous evidence from few observational studies suggests that, in selected cases of 'uncomplicated candidemia', shorter treatment courses may be both safe and effective, with no significant differences in mortality or recurrence compared with standard durations.[35] Although these findings are encouraging, they are largely retrospective, and prospective randomized trials are required to confirm the safety and efficacy of a shortened therapeutic approach; therefore, at present, the classical recommendation of continuing antifungal therapy for at least 14 days after documented microbiological clearance remains in place.

2.2 | Invasive pulmonary aspergillosis in critically ill patients

IPA, traditionally associated with neutropenia and profound immunosuppression, is increasingly recognized among critically ill non-neutropenic patients in ICUs.[36,37] The global burden is estimated at 200,000–1000,000 cases annually, accounting for 1%–5% of medical ICU admissions, with incidence further rising during influenza and COVID-19 outbreaks.[1,36,38,39] Mortality remains substantial, with nearly 400,000 deaths annually, approximately half directly attributable to IPA.[1] Several host-related factors predispose critically ill patients to IA, including severe viral pneumonia, prolonged corticosteroid exposure, liver failure, chronic respiratory diseases (e.g. COPD), uncontrolled HIV infection, solid tumours and trauma, including severe burns.[40–42]

Diagnosis is particularly challenging, as clinical presentation is nonspecific and classic radiological findings are uncommon in ICU patients.[38] The EORTC/

MSGERC criteria, although standard in immunocompromised populations, are overly restrictive in this setting.[43] Alternative definitions, such as the Asp-ICU algorithm, its biomarker-enhanced variant (Asp-ICU-BM) and most recent FUNDICU criteria, have been developed to improve diagnostic accuracy.[40,44,45] When these definitions were applied in a multicentre observational study including 202 critically ill patients, the FUNDICU criteria proved to be the most accurate, although they showed only 53% agreement with the clinical diagnosis of IPA, limiting their direct applicability as a routine diagnostic tool in daily practice (although it is worth noting that this result is in line with the fact that FUNDICU criteria were developed for research purposes, that is, to increase standardization and comparability of research studies, thereby prioritizing specificity without a strict maximization of sensitivity, and not for use as diagnostic tools in clinical practice). However, as proposed by the authors of the multicentre observational study detailed above, incorporating additional host factors—such as the presence of moderate or severe acute respiratory distress syndrome (ARDS) and post-cardiac surgery—could significantly improve diagnostic performance, with the updated FUNDICU-clinical algorithm achieving a sensitivity of 97% and a specificity of 63%.[46]

2.2.1 | First-line and alternative antifungal treatment for IPA in critically ill patients

Current first-line therapy for IPA in critically ill patients relies on mould-active triazoles, primarily voriconazole and isavuconazole. Voriconazole remains the agent with the strongest evidence of efficacy. In the comparative randomized trial by Herbrecht and colleagues, voriconazole demonstrated significantly improved survival compared with amphotericin B, which had previously represented the standard of care.[47] Its high oral bioavailability enables early transition from intravenous (IV) to oral formulations, potentially facilitating shorter hospitalization and reducing intravenous catheter-related complications.[48] Despite its efficacy, voriconazole requires TDM due to nonlinear pharmacokinetics, pronounced interindividual variability and the risk of adverse events, particularly hepatotoxicity and neurotoxicity.[49,50] Isavuconazole, a newer broad-spectrum azole, has emerged as a valid alternative. The SECURE trial demonstrated non-inferiority to voriconazole, with a more favourable safety profile characterized by fewer hepatotoxic, cutaneous and visual adverse events and fewer drug–drug interactions.[51] More recently, the multicentre ISA-SITA study provided real-world evidence describing the use of isavuconazole in 177 critically ill ICU patients, noticing generally favourable survival estimates in comparison with most previous literature on IPA in ICU and good tolerability despite some possible variability in plasmatic levels.[52] Of note, routine TDM is not currently required for isavuconazole; however, in critically ill patients, pronounced pharmacokinetic variability has been observed, with subtherapeutic levels reported, supporting the consideration of TDM in this setting.[53,54] Posaconazole has also been investigated as a therapeutic option, demonstrating non-inferiority to voriconazole[55]; nonetheless, its clinical use in IPA remains largely confined to prophylaxis in high-risk populations and to salvage therapy.[56] Liposomal amphotericin B (L-AmB) remains an important alternative, particularly in cases of azole resistance, contraindication, or intolerance.[48] Echinocandins, such as caspofungin, anidulafungin and micafungin, are generally reserved for salvage therapy or as adjunctive agents in refractory disease.[48] A summary of antifungal agents currently used for the treatment of IPA in ICU patients is provided in Table 3. It is important to note that the pivotal trials establishing voriconazole, isavuconazole and posaconazole as first-line or alternative therapies were conducted predominantly in patients with haematological malignancies (HM) or haematopoietic stem cell transplant (HCT) recipients, with very limited inclusion of non-neutropenic ICU patients.[47,51,55]

2.2.2 | Therapeutic approaches for IPA in critically ill patients

Pre-emptive treatment for IPA relies on antifungal treatment initiation mainly guided by positive galactomannan testing or chest CT showing pulmonary infiltrates, in the absence of clinical signs and symptoms. Although the incidence of IPA is increasing among non-neutropenic patients, including those admitted to the ICU, this approach has been primarily evaluated in patients with HM and HCT recipients.[48,57] In critically ill ICU patients, pre-emptive therapy is not recommended due to insufficient evidence supporting its routine use.

Evidence supporting prophylactic strategies in ICU patients remains limited, and, apart from solid organ transplant recipients, mould-active prophylaxis is not recommended.[48,57,58] The most recent data derive from a prospective multicentre case–control study (POSACOVID) which evaluated posaconazole prophylaxis in mechanically ventilated COVID-19 patients receiving corticosteroids. In this cohort of 83 patients given prophylaxis and 166 matched controls, COVID-19-associated pulmonary aspergillosis (CAPA) incidence rates varied across centres: 1.69 and .84 events per 1000 ICU-days in centres 1 and 2, respectively, and 7.18 events per 1000 ICU-days in

TABLE 3 Antifungal agents for the treatment of invasive aspergillosis in ICU patients.

Drug	Indication	Dosage (standard regimen)	Advantages	Limitations	TDM
Voriconazole	First-line	6 mg/kg IV q12h × 2 doses, then 4 mg/kg IV/Oral q12h	Strongest efficacy data, oral/IV switch	Nonlinear PK, high interindividual variability, hepatotoxicity, neurotoxicity	Yes
Isavuconazole	First-line alternative	372 mg (isavuconazonium sulfate; 200 mg isavuconazole) q8h × 6 doses, then 372 mg q24h IV/Oral	Non-inferior to voriconazole, fewer adverse events and interactions, no routine TDM	PK variability in ICU, subtherapeutic levels in obese/severe illness	Consider
Posaconazole	Salvage / alternative	300 mg IV/Oral q12h on day 1, then 300 mg q24h	Non-inferior to voriconazole in one trial, prophylactic efficacy in high-risk patients	Limited use in IA (mainly prophylaxis/salvage)	Yes
Liposomal amphotericin B (L-AmB)	Alternative (azole resistance/intolerance)	3–5 mg/kg IV daily	Active against resistant strains, established use	Nephrotoxicity, electrolyte disturbances	No
Echinocandins (caspofungin, micafungin, anidulafungin)	Salvage/combination	Caspofungin: 70 mg IV LD, then 50 mg daily; Micafungin: 100 mg IV daily; Anidulafungin: 200 mg IV LD, then 100 mg daily	Good safety, useful in refractory disease, adjunct role	Suboptimal efficacy in monotherapy, limited data in ICU	No

Abbreviations: IA, invasive aspergillosis; ICU, intensive care unit; IV, intravenous; LD, loading dose; TDM, therapeutic drug monitoring.

centre 3. Although the lower incidence observed in centre 1 (where prophylaxis was systematically used) compared with centre 3 may suggest a potential reduction in CAPA risk, this effect was not consistent across all centres, as demonstrated by the similarly low incidence in centre 2, where no prophylaxis was administered.[59] Importantly, while earlier work by Hatzl et al. did not demonstrate any mortality benefit, the POSACOVID study did not assess survival outcomes; therefore, no conclusions regarding the impact of posaconazole prophylaxis on mortality can be drawn from this cohort.[59,60] The observation that CAPA incidence may decrease without corresponding evidence on survival outcomes highlights the uncertainty that still surrounds the interpretation of these findings. Overall, these data support a cautious, centre-specific approach and underscore the need for further high-quality studies before routine prophylaxis can be recommended in ICU settings.

For this reason, early recognition relies on close clinical surveillance, with clinical suspicion arising in patients with persistent fever and/or new or worsening respiratory or systemic deterioration that cannot be explained by other causes despite broad-spectrum antibacterial therapy.[40] Given the high mortality associated with IPA, empirical antifungal therapy should be initiated as rapidly as possible once such suspicion arises.[61] Current empiric approaches rely primarily on mould-active triazoles, particularly voriconazole and isavuconazole.[48,57,58]

2.2.3 | Combination therapy and salvage treatment for IPA

Combination antifungal therapy has been investigated both as first-line and, more consistently, as salvage treatment, given the paucity of available randomized trials.[48,57,58] Regarding first-line therapy, the 2025 American Thoracic Society (ATS) guidelines include a conditional recommendation for the use of a triazole plus an echinocandin.[58] However, this recommendation is based on low-quality evidence, predominantly derived from HM and HCT populations, and its applicability to ICU patients without underlying malignancy remains uncertain.[62–64] Combination therapy is also proposed to be considered by international guidelines as a possible rescue or salvage option.[48,57,58] Observational studies and one pilot RCT exploring different antifungal combinations have yielded conflicting results: some have suggested improved outcomes,[65–67] whereas others reported no significant differences compared to standard first-line monotherapy[62]

or better response to monotherapy.[68] Importantly, the majority of these studies enrolled patients with HM, with limited relevance to 'non-classical' settings such as critically ill patients. Indeed, the pharmacokinetic and pharmacodynamic profiles in ICU populations differ substantially from those observed in non-ICU settings, limiting the generalizability of the available evidence.[69] Two studies specifically evaluated combination therapy in ICU patients. Yang and colleagues compared caspofungin, voriconazole and their combination, reporting no significant differences in response rates across treatment arms.[70] Similarly, Zhuo Li and colleagues found that voriconazole plus caspofungin did not improve all-cause mortality and was even associated with pancytopenia, suggesting a potential safety concern.[71] Overall, evidence regarding combination therapy in non-neutropenic ICU patients remains scarce and largely observational.[70,71] Available data do not support a clear advantage over monotherapy, although potential benefit may exist in selected high-risk or salvage settings.[48,57,58] Prospective studies specifically designed for critically ill, non-haematological populations are needed to clarify the role of this therapeutic approach.

2.2.4 | PK/PD issues and therapeutic drug monitoring for IPA

As mentioned in a previous section, certain antifungal agents require TDM due to their pharmacokinetic characteristics, notably voriconazole and posaconazole.[49,72] In critically ill patients, however, PK/PD differ substantially from those observed in the populations included in registration trials, with pronounced interindividual variability.[73] For this reason, TDM should be considered for all antifungal agents in critically ill patients. The SAFE-ICU study highlighted this issue, showing that, similar to antibiotics, antifungal plasma concentrations frequently fail to reach recommended targets, a finding associated with worse outcomes. Voriconazole, posaconazole, micafungin and amphotericin B were among the agents with the lowest target attainment rates (≤35%).[73]

Some studies have also explored isavuconazole exposure in ICU patients, consistently revealing high pharmacokinetic variability and frequent subtherapeutic concentrations. In a retrospective monocentric analysis, Höhl and colleagues reported that more than 30% of ICU patients failed to achieve target trough concentrations, with subtherapeutic levels more frequently observed in those with a Body Mass Index (BMI) ≥25 kg/m^2 or elevated SOFA scores.[53] Mikulska and colleagues later confirmed significantly lower isavuconazole levels in ICU compared with non-ICU patients (mean 2.0 mg/L vs. 4.1 mg/L), identifying ICU admission, BMI >25 kg/m^2, elevated bilirubin and the absence of hematologic malignancy as predictors of low exposure.[74] More recently, the multicentre ISA-SITA study found trough concentrations <2 mg/L in 44.9%, <1 mg/L in 10.2% and >5 mg/L in 22.4% of 177 critically ill patients, with minimal dose adjustments despite standard dosing.[52] Given the high pharmacokinetic variability and the high-risk context of ICU patients, further studies are needed to assess the clinical utility of antifungal TDM, including the impact of dose adjustment strategies on outcomes in IPA. Such strategies should take into account patient-specific factors including BMI, severity of illness (e.g. SOFA score), use of CRRT and other extracorporeal support devices, all of which may significantly influence drug exposure. At the same time, TDM may help mitigate drug-related toxicity.[73] Until such evidence is available, individualized TDM-guided dosing remains, in our opinion, a critical component of antifungal stewardship in the ICU setting.

2.2.5 | New antifungal agents and future directions

The emergence of antifungal resistance and difficult-to-treat infections has spurred the development of novel antifungal agents, several of which are in Phase II or III clinical trials. Olorofim, a first-in-class orotomide in Phase III development, exhibits potent in vitro activity against *Aspergillus* spp., including cryptic and azole- or amphotericin B-resistant strains.[75,76] Available in oral and intravenous forms, olorofim shows favourable tissue distribution including central nervous system (CNS) penetration. It undergoes hepatic metabolism via CYP450 enzymes and is a weak CYP3A4 inhibitor, raising potential drug–drug interaction concerns.[77–79] Given frequent oral intolerance in ICU patients, further data on intravenous use are needed. Fosmanogepix (prodrug of manogepix), a first-in-class Gwt1 inhibitor in Phase III trials, has broad-spectrum activity against yeasts and moulds, including azole-resistant *A. fumigatus*.[80] This dual coverage may benefit critically ill patients with candidemia and concurrent mould infections, and the availability of both oral and intravenous formulations enhances its ICU applicability. Inhaled antifungals, such as opelconazole (NCT05238116), thin-film freezing (TFF) voriconazole and itraconazole (PUR1900), are under investigation as adjuncts in severe or refractory invasive pulmonary aspergillosis, potentially optimizing local delivery and reducing systemic toxicity.[81,82] Additional agents, such as ibrexafungerp and rezafungin, are advancing clinical development, broadening options against invasive fungal infections.[83,84] Novel antifungal

TABLE 4 Novel antifungal agents in development for treatment of invasive aspergillosis.

Agent	Mechanism of action	Dosage (investigational)	Development stage	Potential advantages	Current limitations
Olorofim	Inhibitor of dihydroorotate dehydrogenase (DHODH)	Oral 90 mg q12h (Phase II/III studies); IV formulation under evaluation	Phase III	Potent activity against azole- and AmB-resistant *Aspergillus* spp., good tissue and CNS penetration	Limited IV data, CYP3A4-mediated interactions
Fosmanogepix (prodrug of manogepix)	Inhibitor of Gwt1 (glycosylphosphatidylinositol anchor biosynthesis)	Oral/IV: 1000 mg LD, then 600 mg daily (trial regimen)	Phase III	Broad-spectrum activity (moulds + yeasts), including azole-resistant *A. fumigatus*	Clinical experience still limited
Opelconazole (PC945, inhaled triazole)	Inhibition of ergosterol biosynthesis (local delivery)	Inhaled; investigational dosing (ongoing trials)	Phase II (NCT05238116)	High pulmonary concentrations, reduced systemic toxicity	Experimental, no systemic coverage
Ibrexafungerp	Glucan synthase inhibitor (triterpenoid)	Oral: 750–1500 mg daily in studies	Phase II/III	Activity against azole-resistant *Aspergillus*, oral bioavailability	Limited data in aspergillosis (mainly candidiasis)

Abbreviations: CNS, central nervous system; IA, invasive aspergillosis; IV, intravenous.

agents in clinical development for invasive aspergillosis are summarized in Table 4. Immunotherapeutic approaches, including adoptive transfer of fungal-specific T cells, are experimental but highlight the increasing interest in host-directed therapies complementing antifungal drugs.[85]

2.3 | *Pneumocystis jirovecii* pneumonia in critically ill patients

Pneumocystis jirovecii pneumonia (PjP) has historically been recognized as a severe opportunistic infection predominantly affecting individuals with human immunodeficiency virus (HIV).[86] In recent decades, however, the widespread use of immunosuppressive therapies, including biologic agents and corticosteroids, for conditions such as autoimmune disorders, HM and solid tumours, has broadened the spectrum of at-risk patients.[87] In a retrospective institutional cohort of 240 patients, the mean annual incidence was 13 ± 5 cases, with a peak between 2005 and 2010. Notably, 41.7% of these patients required ICU admission, 36.6% underwent mechanical ventilation, 16.3% received renal replacement therapy, and 4.5% were supported with ECMO. Overall, in-hospital mortality stood at 25.4%, rising to 58% among ICU-treated patients, while only 1.6% of non-ICU patients died. Mortality was lowest among HIV-infected patients (12.8%), and substantially higher in solid organ transplant recipients (38.4%), patients with rheumatic diseases (30.0%) and those with hematologic-oncologic conditions (44.7%).[88] Complementing these findings, a post-hoc analysis of an international multicenter ICU cohort (107 patients) reported a 30-day mortality of 52.7%, with independent predictors of poor outcome including metastatic solid tumours and chronic liver disease. Together, these data underscore the persistent high mortality of PjP in critically ill, non-HIV immunocompromised patients and highlight the need for improved management strategies.[89]

2.3.1 | Treatment options for PjP in critically ill patients

The treatment of choice for PjP is trimethoprim-sulfamethoxazole (TMP/SMX) both for HIV-infected individuals and non-HIV immunocompromised patients.[90–92] For patients who are intolerant to TMP/SMX or have contraindications, several second-line therapeutic options are available. Intravenous pentamidine could be an alternative, but due to its risk of toxicities (including pancreatitis, hypo- and hyperglycemia, bone marrow suppression, renal failure and electrolyte disturbances), it should be avoided in pancreas transplant recipients because of the potential for islet cell necrosis. Clindamycin in combination with primaquine represents another alternative, but is typically reserved for patients unable to tolerate TMP/SMX. Gastrointestinal adverse effects are common, and hematologic monitoring is recommended.

Atovaquone is generally well tolerated and suitable for mild to moderate infections, although its bioavailability may be variable. Finally, dapsone combined with trimethoprim offers an oral alternative for patients without severe disease; caution is advised in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of hemolysis.[90,92]

2.3.2 | Combination therapy for PjP

To date, no randomized controlled trials have evaluated the efficacy and safety of antimicrobial combination strategies for the treatment of PjP, and evidence is even more limited in the intensive care setting. However, the high mortality associated with this infection (particularly outside the context of HIV) has raised an important clinical question regarding the potential role of rescue strategies, such as combination therapy, for the management of severe disease. The treatment of PjP in non-HIV patients is often particularly challenging due to the risk of rapid clinical deterioration and the frequent need for non-invasive or even invasive ventilation and intensive care support. Although data remain scarce, some evidence from case series and observational studies has explored the potential role of combination regimens, particularly those including echinocandins, in this context. The rationale for this combination is supported by animal-model studies suggesting a synergistic effect between TMP/SMX and echinocandins in promoting infection clearance. Echinocandins have demonstrated anti-*Pneumocystis* activity, although they are not capable of achieving eradication when used alone. This indicates that echinocandin monotherapy is not appropriate, but these agents have been suggested to have a possible role as part of a combination regimen.[93] Although clinical evidence remains limited to retrospective cohorts and observational studies, a meta-analysis including four studies ($n = 536$ patients with available outcome data) suggested that the combination of TMP/SMX with an echinocandin was associated with significantly lower mortality compared with TMP/SMX monotherapy (20.9% vs. 35.2%). However, this mortality benefit was primarily observed among people with HIV rather than in non-HIV patients. Nevertheless, an overall positive effect of combination therapy was also reported in non-HIV patients with severe disease, with significantly improved survival outcomes (OR = 5.07, 95% CI = 1.40–18.37). Regarding clinical response, two studies demonstrated that combination therapy was associated with significantly higher rates of positive treatment response compared with monotherapy (OR = 2.13, 95% CI = 1.41–3.23, $I^2 = 0\%$).[94]

Regarding the evidence specifically in the subset of critically ill patients, in a retrospective study by Qi and colleagues, conducted in a cohort of 93 non-HIV ICU patients, initial combination therapy with caspofungin and TMP/SMX was associated with a significantly higher clinical response rate compared with either monotherapy or salvage therapy with the subsequent addition of caspofungin (76.7% vs. 58.1%, $p = .001$). However, although 90-day mortality was lower in the initial combination group, the difference did not reach statistical significance compared with monotherapy (39.5% vs. 48.6%, $p = .322$), while it was significantly lower compared with the group receiving caspofungin as salvage therapy (65.5%, $p = .024$).[95] Another retrospective study conducted at a tertiary hospital evaluated 38 non-HIV-infected patients with severe PjP, divided into two groups: one receiving combination therapy with TMP/SMX and caspofungin (ST), in association with corticosteroids, and the other receiving TMP/SMX monotherapy (MT). The combination therapy group demonstrated a higher clinical response rate compared to monotherapy (100.00% vs. 66.70%, $p = .005$). However, there were no statistically significant differences in all-cause mortality between (ST 25.00% vs. MT 16.67%, $p = .277$) or length of hospital stay between the two groups (ST median 30 days vs. MT median 15 days, $p = .059$).[96] In conclusion, to support the use of combination strategies—particularly in critically ill patients—more robust evidence is needed, and a randomized controlled trial is required to guide an evidence-based and effective clinical approach.[97]

2.3.3 | Adjunctive corticosteroid therapy for PjP

Adjunctive corticosteroids are recommended for adults and adolescents with HIV infection and moderate to severe PjP, defined as a room air arterial oxygen partial pressure (PaO_2) less than 70 mm Hg or an alveolar-arterial oxygen gradient greater than 35 mm Hg.[98,99] Corticosteroids should be initiated as early as possible, ideally within 72 h of starting antimicrobial therapy, as this approach reduces mortality and the need for mechanical ventilation; the recommended regimen is prednisone 40 mg orally twice daily for 5 days, then 40 mg once daily for 5 days, followed by 20 mg once daily for the remaining 11 days, for a total of 21 days.[99] A large meta-analysis assessing the impact of adjunctive corticosteroids in HIV-infected patients with PjP with hypoxemia including six RCTs (242 individuals in the intervention groups and 247 individuals in the control groups) demonstrated a significant reduced risk for overall mortality by adding adjunctive corticosteroids (pooled risk ratio .56; 95% CI .32 to .98).[100] In a recent multicenter, double-blind, randomized controlled trial, the effect of adjunctive corticosteroid therapy was evaluated in

TABLE 5 Therapeutic regimens for *Pneumocystis jirovecii* pneumonia in critically ill patients.

Drugs	Line of therapy/Indication	Dosage and administration	Duration	Combination/Notes	References
TMP/SMX	First-line therapy for all patients (HIV and non-HIV)	TMP 15–20 mg/kg/day + SMX 75–100 mg/kg/day IV or PO, divided q6–8h	21 days	Monitor renal function, potassium and hematologic toxicity. Adjust dose in renal impairment.	87,88
Pentamidine (IV)	Second-line option when TMP–SMX not tolerated or contraindicated	4 mg/kg IV once daily (infuse over ≥60 min)	21 days	Monitor for nephrotoxicity, electrolyte imbalance, pancreatitis, hypoglycemia/hyperglycemia. Avoid in pancreas transplant recipients.	87,89
Clindamycin + primaquine (PO)	Alternative regimen for TMP–SMX intolerance	Clindamycin 600 mg PO/IV q6h or 900 mg IV q8h + primaquine 15–30 mg PO once daily	21 days	Check G6PD status before use (risk of hemolysis). Monitor hematologic profile.	87,89
Atovaquone (PO)	Alternative for mild to moderate PjP (TMP/SMX intolerance)	750 mg PO twice daily with high-fat meal to enhance absorption	21 days	Well tolerated; variable bioavailability; not recommended for severe disease.	87,89
Dapsone + trimethoprim (PO)	Alternative oral regimen for mild disease	Dapsone 100 mg PO once daily + TMP 20 mg/kg/day divided q6–8h	21 days	Avoid in G6PD deficiency; monitor for hemolytic anaemia.	87,89
TMP/SMX + echinocandin (e.g. caspofungin)	Combination / rescue therapy for severe or refractory PjP, especially in ICU patients	TMP–SMX as above + caspofungin 50 mg IV daily (after 70 mg loading dose)	21 days (case-dependent)	Potential synergistic effect; may improve clinical response in severe non-HIV cases. Evidence from retrospective studies; no RCTs available.	90–93
Adjunctive corticosteroids (HIV-positive)	For moderate-to-severe disease (PaO_2 <70 mmHg or A–a gradient >35 mmHg)	Prednisone PO: 40 mg BID ×5d → 40 mg QD × 5d → 20 mg QD × 11d (total 21d) or methylprednisolone IV (80% of oral dose)	21 days	Initiate within 72 h of antimicrobial therapy; reduces mortality and ventilation need.	96
Adjunctive corticosteroids (HIV-negative)	Currently no definitive conclusion regarding the related benefit	Methylprednisolone 30 mg IV BID ×5d → 30 mg QD × 5d → 20 mg QD until day 21 (used in RCT)	21 days	A recent RCT shows no mortality benefit in non-HIV critically ill patients, although the magnitude of the difference in absolute mortality rates between study arms may still require further investigations.	98–100

Abbreviations: A–a gradient, alveolar–arterial oxygen gradient; BID, twice daily; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous; PaO_2, arterial oxygen partial pressure; PO, per os (oral); PjP, *Pneumocystis jirovecii* pneumonia; q6–8h, every 6–8 hours; QD, once daily; RCT, randomized controlled trial; TMP–SMX, trimethoprim–sulfamethoxazole.

immunocompromised, HIV-negative adults with severe PjP and acute hypoxemic respiratory failure. A total of 226 patients were randomized to receive intravenous methylprednisolone (30 mg twice daily for 5 days, then 30 mg once daily for 5 days, then 20 mg once daily until day 21) or placebo, initiated within 7 days of starting anti-*Pneumocystis* therapy. Adjunctive corticosteroid therapy did not reduce 28-day mortality compared to placebo (21.5% in the corticosteroid group vs. 32.4% in the placebo group; mean difference 10.9%, 95% CI −.9 to 22.5; $p = .069$) in a statistically significant way (although it cannot be excluded that the registered >10% mean difference may be clinically significant and support the protective role of steroids if confirmed in slightly larger studies with increased power), whereas 90-day mortality was 28.0% in the corticosteroid group compared with 43.2% in the placebo group (hazard ratio, .59; 95% confidence interval, .37–.93; $p = .022$), and no significant differences in adverse events were reported between the groups, including the incidence of secondary infections.[101] On the other hand, additional evidence from retrospective studies in non-HIV populations also indicates the absence of clear benefit from the use of corticosteroid therapy in patients with PjP.[102,103] Therefore, based on the currently available evidence, no definitive recommendation can be made regarding the routine use of adjunctive corticosteroid therapy in non-HIV critically ill patients with PjP. However, given the signal toward improved longer-term mortality observed in randomized studies, its use may be considered in selected cases, while awaiting further confirmatory evidence. Current recommendations for the treatment of PjP are summarized in Table 5.

3 | CONCLUSIONS

Invasive fungal infections remain a major challenge in ICU patients, requiring timely recognition, targeted therapy and optimized antifungal stewardship. Advances in diagnostics, new antifungal agents and refined pharmacokinetic/pharmacodynamic strategies are progressively improving outcomes. However, individualized management remains essential, considering pathogen, host factors and drug characteristics. Future research should focus on integrating rapid diagnostics and real-time therapeutic monitoring to guide early, personalized treatment and reduce unnecessary antifungal exposure in the ICU setting.

AUTHOR CONTRIBUTIONS

Matteo Bassetti, Antonio Vena and Daniele Roberto Giacobbe conceived the article. Claudia Bartalucci, Laura Mezzogori and Riccardo Schiavoni equally contributed to writing different sections of the manuscript. Claudia Bartalucci harmonized the text, while Daniele Roberto Giacobbe, Antonio Vena and Matteo Bassetti supervised and critically revised the entire manuscript.

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The manuscript was written independently by the authors without the use of generative AI. Thereafter, a large language model-based tool (ChatGPT 4) was used to improve the clarity and readability of the text. The final version was carefully reviewed by all authors to confirm that the content and meaning were fully preserved.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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