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REVIEW

Invasive candidiasis in intensive care medicine: shaping the future of diagnosis and therapy

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Abstract

Background: Invasive candidiasis (IC) remains one of the most challenging infections in critical care, contributing significantly to morbidity, prolonged organ support, and mortality among intensive care unit (ICU) patients. The clinical landscape of IC is evolving, with increasing recognition of Candida non-albicans species and other yeasts formerly classified as Candida spp., alongside emerging multidrug resistance and growing complexity in host immune profiles.

Objectives: This contemporary, multidisciplinary narrative review—authored by intensivists, infectious diseases specialists, clinical microbiologists, and pharmacologists—aims to provide ICU clinicians with practical, up-to-date insights into the diagnosis and management of IC. To maintain clinical focus, the review excludes non-IC fungal infections and non-ICU patient populations.

Methods: Relevant literature and expert consensus were critically reviewed to summarize current diagnostic and therapeutic approaches for IC in critically ill patients. Emphasis was placed on pragmatic clinical application, diagnostic limitations, antifungal stewardship, and personalized therapeutic decision-making.

Results: Despite the availability of novel antifungal agents with improved pharmacokinetic properties, treatment success in IC depends equally on timely and accurate diagnosis and individualized, context-aware therapy. Blood cultures continue to demonstrate limited sensitivity (~40%). Non-culture assays, including β-D-glucan and molecular diagnostics, provide faster detection and high negative predictive value but suffer from low positive predictive value and inconsistent adoption in clinical practice. The absence of validated host-derived biomarkers further limits risk stratification, antifungal discontinuation decisions, and personalized care.

Conclusions: Emerging antifungal agents, stewardship strategies, and multidisciplinary care models are essential to improve clinical outcomes and reduce antifungal resistance. This review underscores the need for integrated, team-based diagnostic and therapeutic approaches to close persistent gaps in IC management, ultimately promoting more effective, timely, and individualized care for critically ill patients with Candida spp. infections.

Keywords: Invasive candidiasis, Candida species, Critical care, Intensive care unit, Antifungal therapy, Diagnostic stewardship, β-D-glucan

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Introduction

Invasive candidiasis (IC) is a life-threatening fungal infection that disproportionately affects critically ill patients [1]. Approximately one-third of bloodborne *Candida* spp. infections occur in patients admitted to intensive care units(ICU) [2]. These individuals are particularly vulnerable due to a combination of factors, including

exposure to broad-spectrum antibiotics, invasive procedures and endovascular devices, immunoparalysis, organ support therapies, and total parenteral nutrition. In ICU, IC is a major complication associated with prolonged hospitalization and increased resource utilization despite antifungal therapy. Mortality from *Candida* spp. bloodstream infections (candidemia) in adults generally ranges from 30 to 60%, and may exceed 70% among critically ill ICU patients. [3–5]. *Candida albicans* remains the most commonly isolated species worldwide; however, the proportion of *Candida* non-*albicans* spp. (notably *C. glabrata*, *C. parapsilosis*, and the multidrug-resistant *C. auris*) has increased over the past two decades, with geographic variation and important therapeutic implications [6, 7]. The mortality rate has remained unchanged over the past two decades although it varies by location and case mix [8, 9].

This multidisciplinary narrative review, developed with contributions from experts in intensive care, infectious diseases, microbiology, and pharmacology, offers practical guidance on managing *Candida* spp. infections in critically ill patients. With an emphasis on bedside decision-making, it integrates recent advances with expert insights to support daily clinical practice, foster collaboration across specialties, and promote evidence-based, individualized care in the ICU.

Search strategy and selection criteria

This narrative review was conducted to consolidate current knowledge on IC and candidemia in critically ill patients, with a specific focus on *Candida* spp. *infections* occurring in ICU settings. A comprehensive literature search was performed across the PubMed, Embase, and Web of Science databases. The search employed a combination of Medical Subject Headings (MeSH) and free-text terms, including "invasive candidiasis," "candidemia," "*Candida*," "yeast infections," "critically ill patients," "intensive care unit," "antifungal therapy," "diagnostic biomarkers," and "antifungal resistance."

Filters were applied to restrict results to studies involving adult ICU populations, with a language limitation to English. The date range spanned from 2000 to 2025 to reflect both foundational and recent advances in epidemiology, diagnostics, treatment strategies, and antifungal stewardship relevant to ICU care.

Reference lists from key articles and relevant guidelines were also reviewed to ensure the inclusion of important studies not captured by the initial database search. Eligible publications included randomized controlled trials, observational cohort studies, systematic reviews, relevant clinical guidelines, and expert commentaries that provided data or expert perspectives on the diagnosis, treatment, or outcomes of *Candida* spp. infections in ICU settings. Studies focused solely on mold infections or non-ICU populations were excluded.

This review does not represent a systematic review, Delphi process, or formal consensus statement. Rather, it reflects a multidisciplinary synthesis of current knowledge by experts in intensive care, infectious diseases, microbiology, and pharmacology, to guide future practice and research in managing IC in the critically ill.

Take-home message

Invasive candidiasis in the ICU is a high-risk, life-threatening infection that demands speed, precision, and teamwork. This review delivers practical guidance on evolving species epidemiology, cutting-edge diagnostics, optimised antifungal therapy, and stewardship strategies. The focus is on rapid recognition, personalised treatment, and smart use of emerging tools to close care gaps and improve survival in critically ill patients.

Changing epidemiology and risk factors

The epidemiology of IC in critically ill patients continues to evolve with changing case mix, device exposure, and antifungal selection pressure. Multicentre studies estimate ICU-acquired IC at about 7 per 1000 admissions with roughly 42% 30-day mortality (EUCANDICU), while other cohorts report ICU candidemia at about 4.8 per 1000 admissions with 47% 28-day and 60% 180-day mortality [10, 11]. Species distribution has shifted toward *Candida* non-*albicans* spp. with rising azole resistance. The ECMM *Candida* III study (2018–2022) reported fluconazole resistance at about 12% in *C. glabrata* (and even echinocandin-resistant *C. glabrata*) and about 17% in *C. parapsilosis* in parts of southern Europe, with uncommon but present echinocandin resistance, including FKS mutations. Important nosocomial threats include *C. auris* and fluconazole-resistant *C. parapsilosis*, which persist in healthcare environments, cause outbreaks, and show resistance across multiple antifungal classes, complicating prevention and control [6, 12, 13]. Marked regional variation is evident, with higher proportions of *C. tropicalis* in Asia, *C. parapsilosis* in southern Europe and Latin America, and increasing *C. auris* reports from South Asia and the Middle East. *C. tropicalis*, frequently linked to neutropenia, malignancy, and high mortality, is increasingly azole-resistant, particularly in low- and middle-income countries where fluconazole often remains the first-line agent [14–17] [18–20].

Molecular sequencing has reassigned several species historically grouped as *Candida* spp. to new genera, aligning nomenclature with phylogeny. Clinically, these changes alter nomenclature rather than patient management. Intrinsic resistance patterns, breakpoints, and guideline recommendations remain the same, so

Table 1 Updated nomenclature of common *Candida ssp.*

Former Name (Familiar)	New Genus/Updated Name
Candida glabrata	*Nakaseomyces glabratus*
Candida krusei	*Pichia kudriavzevii*
Candida kefyr	*Kluyveromyces marxianus*
Candida lusitaniae	*Clavispora lusitaniae*
Candida parapsilosis	*Pichia parapsilosis*
Candida guilliermondii	*Meyerozyma guilliermondii*
Candida rugosa	*Diutina rugosa*

therapeutic choices do not change on the basis of the new names alone. The practical impact is operational: microbiology laboratories, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) libraries, polymerase chain reaction (PCR) panels, laboratory information systems (LIS), electronic health records (EHRs), antibiograms, and stewardship alerts must map old and new names to maintain continuity of reporting and decision support. Most laboratories are expected to transition gradually and to dual-report for a period of time to avoid confusion while surveillance systems and guidelines are updated (See Table 1) [21].

Multiple ICU-related interventions are frequently cited as risk factors for IC, including prolonged admissions, central venous catheterisation, broad-spectrum antibiotics, parenteral nutrition, renal replacement therapy, and major surgeries, particularly of the gastrointestinal tract. However, while these associations are well known, their attributable risk is difficult to quantify. These factors often overlap and reflect underlying illness severity, limiting their standalone predictive value. As such, traditional tables listing risk factors, while common in the literature, provide limited clinical utility and may oversimplify the complex host–pathogen dynamics in critically ill patients [22]. Guidelines view Risk Prediction Scores for IC as simple, low-cost bedside tools to estimate pretest probability and curb overtreatment. Their main value is a high negative predictive value, which helps identify patients in whom empiric antifungals can be safely withheld. A high score should not be the sole basis for treatment. Scores should be used to prompt focused sampling, and only when the clinical picture supports invasive disease, a carefully planned empirical start should be used, with early reassessment and discontinuation as appropriate. Importantly, scores are intended to complement, not replace, clinical judgment [23].

The immune landscape of ICU patients has also grown more complex. IC often follows bacterial sepsis, and the recovery from sepsis includes a period of immunoparalysis. Therefore, the immune status of patients changes over time in the ICU. In addition, many critically ill patients are exposed to multiple lines of immunosuppressive therapy that affect distinct immune pathways. This includes patients with hematologic malignancies, allogeneic stem cell transplant recipients, CAR T therapy recipients, and those receiving other novel immunosuppressive agents in hematology, oncology, gastroenterology, rheumatology, and transplant medicine. The resulting immunosuppression is often multifactorial, impairing both innate and adaptive immune responses in heterogeneous and dynamic ways that increase vulnerability to fungal infections.

Advances in diagnostic approaches

Accurate and timely diagnosis of IC in the ICU remains difficult. Culture is still the reference for confirmation, yet sensitivity is often low, frequently below 40 percent, particularly in deep-seated disease or after antifungal exposure, and time to positivity may take days [24] [25]. MALDI-TOF expedites species identification once cultures are positive, but it still depends on viable growth and cannot substitute for antifungal susceptibility testing (AFST). Direct AFST from the supernatant of positive blood cultures can shorten the path to resistance profiling and help target therapy earlier [26–28]. Many molecular and serologic assays were developed and validated

Table 2 Overview of culture, BDG, PCR, T2, and MALDI-TOF with turnaround time and limitations

Tool	Turnaround	Strengths	Limitations	Role in ICU
Blood culture	2–5 days	Gold standard, species ID	Slow, insensitive in pre-treated patients	Always send, but not reliable alone
BDG	Hours	High NPV, helps stop therapy	False positives (IVIG, hemodialysis), poor specificity	Support stopping empiric therapy
Mannan/anti-mannan	Hours	Useful with BDG	Variable sensitivity	Adjunctive use
T2*Candida*	< 5 h	Detects common species, rapid	Limited panel, cost	Rapid rule-in tool
PCR	< 1 day	High sensitivity	Detects DNA of dead yeast	Supports early initiation
MALDI-TOF	< 1 day	Fast species ID from colonies	Requires culture growth	Accelerates targeted therapy

BDG (1,3)-β-D-glucan; *IVIG* Intravenous immunoglobulin; *NPV* Negative predictive value; *PCR* Polymerase chain reaction; *MALDI-TOF* Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; *ID* Identification

primarily for candidemia, and their yield in the ICU, where non-candidemic disease is common, is further reduced in patients receiving antifungal prophylaxis or suboptimal therapy (for example, inadequate drug exposure or prior azole exposure leading to reduced susceptibility), contributing to under-recognition and therapeutic delay [29].

Among non-culture assays, (1→3)-β-D-glucan (BDG) is the most widely used pan-fungal biomarker. Its main limitation in critical illness is the risk of false positives, which may arise from gut translocation in severe sepsis, advanced liver disease, haemodialysis, or contact with surgical materials such as gauze[30–33]. Appropriately applied, BDG is most valuable as a rule-out tool, supporting stewardship-driven discontinuation of unnecessary empiric antifungal therapy (Table 2). Nonetheless, BDG has consistently shown a high negative predictive value (NPV) for invasive candidiasis (IC), making it most useful as a rule-out tool to support early discontinuation of empiric antifungals in ICU patients when suspicion decreases (Table 2). Reflecting this, recent ECMM/ISHAM/ASM guidelines advise against its use for treatment initiation[7]. Meta-analyses and ICU cohort studies further confirm BDG's strong rule-out performance, with an 80 pg/mL cutoff often applied to limit unnecessary echinocandin exposure [34].

Other serological markers, including mannan antigen, anti-mannan antibodies, and the *Candida* albicans germ-tube antibody, can provide species-leaning signals but have limited sensitivity, especially for *Candida* non-*albicans* spp., and should not be used in isolation to start therapy [33, 35]. Molecular approaches, including PCR and next-generation sequencing (NGS) performed on blood or tissue, offer higher analytical sensitivity and the ability to detect multiple species, including mixed infections, but broader clinical adoption is constrained by assay standardization, cost, and variable turnaround times [36, 37]. T2 *Candida* can detect candidemia rapidly and may help flag complicated cases, yet its routine use has been limited by financial and implementation barriers [38–40]. When IC is suspected in compartmental sites, such as intra-abdominal infection, targeted sampling improves diagnostic yield; BDG in peritoneal fluid has shown higher sensitivity and specificity than serum BDG for intra-abdominal candidiasis, but thresholds are not standardized, and results should be interpreted cautiously [41].

These test-level realities support a pragmatic, stewardship-aligned pathway rather than reliance on any single modality. At first clinical suspicion, clinicians should obtain paired blood cultures, sample likely foci such as peritoneal fluid, and consider BDG and, where available, molecular testing from blood and site-specific specimens. Empiric antifungal therapy is best reserved for patients with septic shock or very high-risk profiles, with a documented reassessment time point. Within 24–48 h, results and clinical trajectory should be integrated. When BDG is negative and no corroborating evidence of either *Candida* or *Aspergillus* spp. infection emerges, discontinuation of empiric echinocandin is appropriate. When BDG is positive, potential false-positive contexts and evidence of *Pneumocystis* or *Aspergillus* spp. infection should be reviewed before escalation. If cultures become positive, MALDI-TOF and direct AFST should guide species-directed therapy. Persisting concern despite negative blood tests, particularly in the presence of a plausible source, should prompt site-directed diagnostics and imaging. Source control, including endovascular devices removal or drainage, should proceed in parallel, and decisions should be made within a multidisciplinary ICU huddle that includes intensive care, infectious diseases, microbiology, and pharmacy. See Table 2 for comparative turnaround times, advantages, and limitations of each test.

Common pitfalls include initiating antifungals solely on the basis of BDG positivity without clinical correlation, relying on blood-only testing when compartmental infection is suspected, and treating species identification as a surrogate for susceptibility despite the need for AFST and the possibility that sanctuary-site pharmacokinetics may uncouple MIC from response. A simple approach can be seen in Fig. 1.

Taken together, an ICU-specific, multimodal diagnostic strategy that integrates culture-based methods, targeted biomarkers, molecular assays, and structured reassessment offers the best chance to balance early appropriate treatment with safe early de-escalation, aligning diagnostic practice with antifungal stewardship principles [42].

Antifungal resistance and susceptibility trends

Antifungal resistance is a growing challenge in ICUs, driven by prior antifungal exposure, clonal spread of resistant pathogens, delayed recognition, and the pharmacologic complexity of critical illness [43–45]. Access to broader-spectrum agents, such as echinocandins, is inconsistent; even where generics exist, their use may be constrained by cost and supply instability [46]. Amphotericin B lipid formulations are the preferred form of Amphotericin B; however, its conventional deoxycholate form remains a fallback in resource-limited settings, but nephrotoxicity and poor tolerability complicate its use.

Species patterns illustrate distinct threats. *C. glabrata* (Table 3) is highly adaptive, with multiple resistance pathways and a propensity to develop pan-resistance under drug pressure, analogous to the adaptive behavior

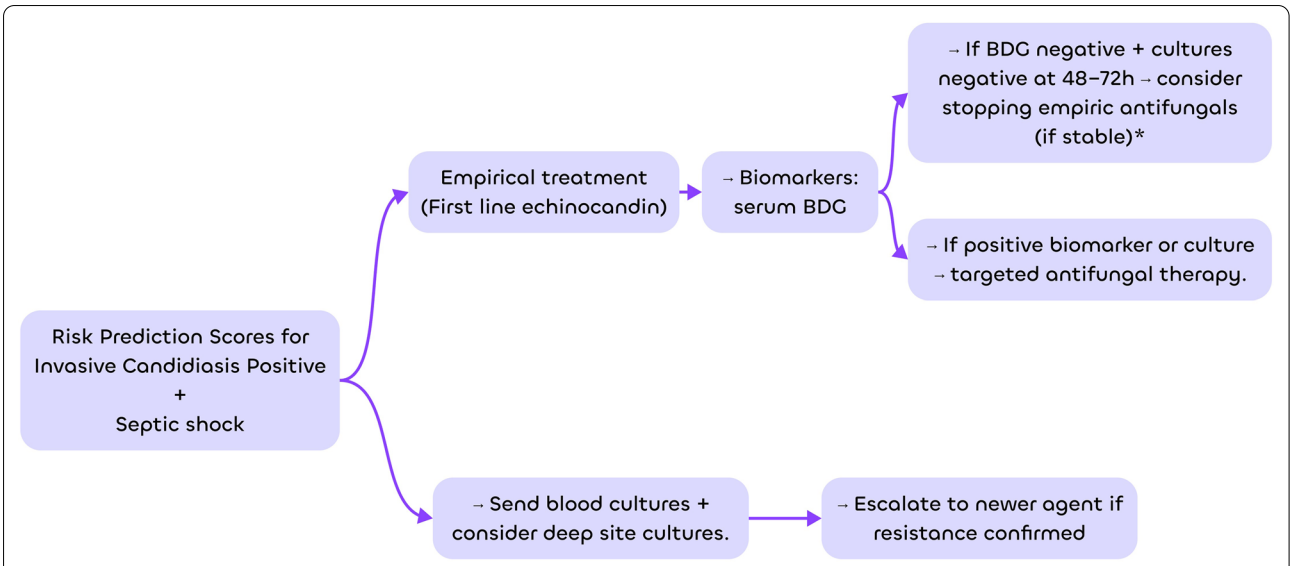

Fig. 1 Algorithm for the management of suspected IC with septic shock. *For patients with IC who do not present with septic shock, empiric antifungal therapy should be withheld. In these cases, investigations should focus on obtaining blood cultures and, where relevant, site-directed samples. Biomarkers such as serum BDG may support discontinuation when suspicion decreases but should not be used as a trigger to initiate antifungal therapy. *BDG* (1 → 3)-β-D-glucan; *IC* Invasive candidiasis; *R* Resistance

of *Pseudomonas aeruginosa* in bacterial [47–49]. *C. auris* behaves more like *Acinetobacter baumannii*, not because of intrinsic virulence but due to environmental persistence, disinfectant tolerance, and rapid spread in healthcare facilities (see Table 4) [50, 51].

In parallel, fluconazole-resistant *C. parapsilosis* strains, particularly those with the Erg11p Y132F substitution, are increasingly implicated in clonal ICU outbreaks and may also persist in the environment, especially where infection-control resources are limited [53].

AFST is unevenly performed, often delayed, and hampered by limited access to reference methods, imperfect validation of commercial procedures, and a weak correlation between MICs and outcomes in biofilm-related or deep-seated infections. Truly rapid, bedside AFST is rarely available [54]. Where feasible, direct testing from positive blood cultures using plastic gradient diffusion strips can shorten time to results and has shown good agreement with standard methods [26]. Molecular detection of resistance mutations provides an additional rapid route to flag resistant isolates [53].

Antifungal stewardship is central to improving outcomes. Programs that pair early diagnostics with predefined decision points facilitate faster rule-in and rule-out, earlier species-directed therapy, and reduced unnecessary exposure, resulting in consistent reductions in antifungal use, costs, mortality, and length of stay without harm [55]. Implementation is often limited by uneven access to rapid tests and therapeutic drug monitoring (TDM), workforce capacity, and inconsistent coordination between the ICU, infectious diseases, microbiology, and pharmacy. Priorities include expanding access to rapid diagnostics and TDM, embedding shared protocols, and adopting an economic stewardship lens that weighs the higher acquisition costs of newer agents against clinical value, resistance prevention, and system sustainability in time-sensitive ICU care [56, 57].

Persistent candidemia is defined as the continued recovery of *Candida* spp. in blood cultures for ≥ 5 days despite appropriate antifungal therapy and adequate source control. It most often reflects delayed recognition, subtherapeutic drug exposure (e.g., during extracorporeal support, obesity, or hypoalbuminemia), or inadequate source control, rather than true resistance. In contrast, breakthrough candidemia refers to *Candida* bloodstream infection occurring while the patient is already on systemic antifungal therapy to which the isolate would normally be considered susceptible. This may signal acquired resistance (e.g., FKS mutations), infection with an intrinsically resistant species, or insufficient drug exposure, and should be distinguished from persistence to ensure appropriate management [58, 59]. Table 5 outlines a structured approach to these entities. In critically ill patients, however, failure frequently reflects delayed recognition, altered pharmacokinetics with ECMO or continuous renal replacement therapy (CRRT), or especially inadequate source control. So-called breakthrough infections often arise from such system-related factors rather

Table 3 *C. glabrata* mechanism of resistance

Mechanism	Functional impact	Antifungals most affected	Reported incidence (illustrative ranges*)
PDR1 gain-of-function (esp. *C. glabrata*)	Overexpression of efflux pumps CDR1, CDR2, SNQ2 → reduced intracellular drug levels	Azoles (fluconazole, voriconazole, posaconazole, isavuconazole)	Azole resistance among *C. glabrata* bloodstream isolates often 10–30%; PDR1 mutations present in a majority of azole-resistant isolates
FKS1/FKS2 hotspot mutations	Altered β-1,3-glucan synthase → decreased drug binding	Echinocandins (caspofungin, micafungin, anidulafungin, rezafungin)	Echinocandin resistance: *C. glabrata* 3–10% overall, higher in some centers; other species < 1–2% but reported
Biofilm formation	Matrix limits penetration and promotes tolerance and persistence on devices	Greatest impact on azoles and polyenes; echinocandins retain activity but may be less effective within mature biofilms	Device-associated candidemia is common; biofilm phenotype is frequent among clinical isolates involved in endovascular devices or prosthesis infection
Altered sterol synthesis (e.g., ERG11 overexpression/mutation; ERG3 defects)	Reduced azole target binding or bypass of toxic sterol intermediates	Primarily azoles; ERG3 loss can reduce amphotericin B susceptibility	Azole resistance due to ERG pathway changes: uncommon in *C. albicans*, variable in *C. parapsilosis* and *C. tropicalis*; hot spots report 10–30% fluconazole resistance in *C. parapsilosis*
Mitochondrial dysfunction ("petite" mutants, GOA1 pathways)	Global stress response with efflux upregulation and membrane changes → multidrug phenotype	Mainly azoles and sometimes polyenes; echinocandin effect variable	Rare in routine clinical isolates, described sporadically in outbreaks or salvage settings

PDR1 Pleiotropic drug resistance 1 (transcription factor regulating efflux pumps); *CDR1, CDR2 Candida* drug resistance transporters 1 and 2 (ATP-binding cassette efflux pumps); *SNQ2* Multidrug efflux transporter (ABC family); *FKS1/FKS2* Genes encoding β-1,3-glucan synthase (echinocandin target); *ERG11* Gene encoding lanosterol 14-α-demethylase (azole target enzyme); *ERG3* Gene encoding sterol C-5 desaturase (involved in sterol biosynthesis)

than true microbiological resistance [60]. Addressing both persistence and resistance requires improved diagnostic precision, reliable surveillance, rigorous source control, and coordinated multidisciplinary management that integrates pharmacologic, microbiological, and clinical expertise [52].

Clinical management and next-generation antifungals

In this manuscript, we use precise terminology to avoid ambiguity. Prophylaxis refers to antifungal use in high-risk patients without suspected infection. Pre-emptive therapy is initiated on the basis of colonization, biomarker detection, or imaging findings in the absence of culture isolation. Empirical therapy is a short, risk-based course started for suspected invasive candidiasis (IC) while definitive diagnostics are pending. Targeted therapy is guided by pathogen identification + / − AFST. Although earlier practice in many centers favored starting definitive antifungal therapy only after culture confirmation, with empiric or pre-emptive treatment reserved for selected high-risk patients, current evidence shows that delays in initiating appropriate therapy are associated with worse . Accordingly, expert guidelines support early, appropriate empirical therapy for suspected IC in patients with severe illness or septic shock, undertaken while urgently pursuing microbiological confirmation. In practice, this represents a risk-based approach guided by ICU-specific stratification tools and paired with a pre-specified stewardship plan for reassessment and de-escalation, mirroring antimicrobial stewardship in sepsis, including prompt discontinuation when diagnostic results do not support IC [63–65].

Fluconazole has historically been widely used for empirical therapy, particularly in regions with low prevalence of azole resistance. However, current guidelines increasingly recommend echinocandins as first-line therapy in critically ill patients. Antifungal options remain limited, and in the ICU, echinocandins are the mainstay for initial and empirical therapy [7]. Their performance, however, can be constrained by suboptimal penetration into sanctuary sites (central nervous system, peritoneum, urinary tract, ocular tissues), pharmacokinetic variability in critical illness, and emerging resistance, notably in *C. glabrata*. These challenges are amplified in compartmental infections (e.g., peritoneal candidiasis, *Candida* endocarditis, endophthalmitis) and during extracorporeal support such as ECMO or continuous renal replacement therapy (CRRT), where altered volume of distribution, adsorption to circuits, and other circuit-related losses may reduce exposure and effectiveness [66, 67]. Given the risk of underdosing, particularly in patients receiving extracorporeal support, with severe hypoalbuminemia,

Table 4 Infection control strategies for *C. auris*

Strategy	Purpose
Active surveillance cultures*	Identify colonized patients
Contact precautions	Prevent transmission in multi-bed ICUs
Dedicated equipment and staff	Avoid cross-contamination between patients
Sink and drain decontamination	Interrupt environmental reservoirs
Sporicidal cleaning agents	Reduce surface contamination
Patient cohorting	Limit exposure to other patients and cross-contamination
Outbreak tracing	Identify and isolate transmission networks

Core measures (hand hygiene, contact precautions, equipment and environment decontamination, and targeted screening) are also applicable to other Candida spp., *including azole-resistant C. tropicalis; however, the environmental persistence and disinfectant-tolerance profile prompting enhanced protocols are most characteristic of C. auris*[51].* for high-risk patients (e.g., prolonged ICU stay, abdominal surgery, Extra-corporeal membrane oxygenation [ECMO])[52]

Table 5 Key Actions in the management of persistent candidemia

Domain	Key actions
1. Source control	Remove/change endovascular devices Manage deep-seated infection (e.g., endocarditis): surgical procedure ± antifungal therapy Biofilm suspected → Liposomal Amphotericin B If still positive after source control → consider combination therapy in refractory cases
2. Antifungal therapy	Check adequate dosing Review drug–drug interactions Account for ECMO/CRRT effects Perform TDM If persistent candidemia develops while on liposomal Amphotericin B: Confirm source control Perform susceptibility testing Consider switching to echinocandin (if susceptible), or Initiate combination therapy with an alternative as per AFST
3. Microbiological monitoring	Repeat blood cultures Monitor clearance
4. Resistance testing	Perform AFST (look for azole-, echinocandin-, or multidrug-resistant strains) If resistance confirmed * → switch to alternative/emerging antifungal If adequate therapy + source control but still positive → consider combination antifungal therapy in refractory cases

AFST Antifungal susceptibility testing; *CRRT* Continuous renal replacement therapy; *ECMO* Extracorporeal membrane oxygenation; *R* Resistance; *TDM* Therapeutic drug monitoring. *Resistance testing should include screening for FKS1/FKS2 mutations (β-1,3-D-glucan synthase, echinocandin resistance) and ERG11 mutations (lanosterol 14-α-demethylase, azole resistance)

or with morbid obesity, the use of therapeutic drug monitoring (TDM) is recommended, where available, to optimize antifungal dosing. This should not be considered a universal standard as agents such as rezafungin have a distinct pharmacokinetic profile that may not require such monitoring [68].

An additional and important consideration is the role of liposomal amphotericin B in patients who fail to improve on echinocandin therapy. Current ECMM/ISHAM/ASM guidelines strongly recommend this agent in such scenarios, given its broad-spectrum and reliable fungicidal activity. Liposomal amphotericin B is particularly relevant in difficult-to-treat sites, such as peritoneal candidiasis, where echinocandin penetration may be suboptimal and clinical outcomes are poor if therapy is delayed or inadequate. Highlighting this established role is crucial before shifting focus to newer antifungal agents as amphotericin B remains a cornerstone salvage option in the ICU setting [7].

Despite promising preclinical data, real-world pharmacologic challenges in critically ill patients—such as altered drug distribution and immune dysregulation—often limit antifungal efficacy. This underscores the need for strategies such as therapeutic drug monitoring (TDM), which remain underutilized in ICU practice [69–71].

Recognizing these limitations, several investigational antifungal agents are being developed to overcome these ICU-specific barriers. Rezafungin, a next-generation echinocandin with once-weekly intravenous dosing,

achieves sustained plasma concentrations and a front-loaded pharmacokinetic profile that may improve early fungal clearance and maintain drug levels in critically ill patients with altered pharmacokinetics [72]. Its long half-life reduces the need for frequent line access, lowering the risk of catheter-related complications and easing ICU workflow. By increasing the likelihood of early culture negativity and supporting simplified transitions to step-down or outpatient care, rezafungin offers both therapeutic and operational advantages in the management of IC. However, more data are needed in critically ill patients.

Fosmanogepix (APX001) is a first-in-class antifungal targeting Gwt1, with broad-spectrum activity against *Candida* spp., including echinocandin-resistant strains. Its availability in both intravenous (IV) and oral formulations makes it particularly attractive for ICU patients, offering flexibility for those with limited IV access or during step-down therapy. Although initially studied in invasive mold diseases, recent phase 2 data in non-neutropenic patients with candidemia reported an 80% treatment success rate and 85% 30-day survival, with good tolerability. A Phase 3 trial focusing specifically on IC is currently ongoing, reinforcing fosmanogepix's potential role in critical care antifungal strategies [73, 74].

Ibrexafungerp, the first oral glucan synthase inhibitor, shows activity against both azole- and echinocandin-resistant *Candida* spp. Although currently limited in ICU use due to the absence of an IV formulation, it has demonstrated promise as salvage therapy in candidemia. It is being evaluated for step-down treatment in a phase 3 trial. Notably for ICU relevance, recent in vitro data show that ibrexafungerp retains activity against some echinocandin-resistant *Candida* isolates, particularly *C. glabrata*, including those with resistance-associated FKS mutations [75, 76] and *C. auris* [77].

Rezafungin, fosmanogepix, and ibrexafungerp currently represent the most promising agents for ICU patients with IC, given their activity against resistant strains and potential integration into hospital protocols and recent clinical guideline recommendations.

Combination therapy in ICU for IC

Combination antifungal therapy is not a routine strategy for IC in the ICU [78]. The evidence base consists largely of observational studies, so any potential advantage must be balanced against real risks, including additive toxicity, clinically relevant drug–drug interactions, and unnecessary exposure to broad-spectrum agents [79, 80]. In this context, combination therapy should be viewed as a targeted intervention rather than a default approach.

There are, however, selected scenarios where a short, carefully supervised course can be justified. These include proven or strongly suspected endocarditis, obstructed renal candidiasis, ocular or central nervous system involvement, and cases with persistently high fungal burden or ongoing candidemia despite source control. Combination therapy may also be reasonable when resistance is suspected or confirmed, or when pharmacokinetics are highly uncertain or TDM is delayed, for example, in patients receiving ECMO or CRRT or in those with marked obesity and complex drug interactions [79, 80].

When a combination is used, the most common pairs are an echinocandin with an azole or an echinocandin with liposomal Amphotericin B. Flucytosine can be added for endocarditis or central nervous system disease due to its favorable penetration. However, access, cytopenias, and the need for monitoring often limit its use [81]. In situations where echinocandin resistance is a concern, such as infections caused by *C. glabrata* or *C. auris*, an initial combination therapy may provide coverage. At the same time, urgent AFST and definitive source control are pursued [79, 80].

Operationally, any combination should begin with a pre-defined 48–72-h reassessment that incorporates rapid AFST, evaluation of drug exposure, and early TDM for azoles, with consideration of monitoring for echinocandins when absorption, extracorporeal support, obesity, or unexplained failure raise concern. De-escalation to the narrowest effective monotherapy should occur as soon as source control is secured and diagnostics clarify pathogen identity and susceptibility. In summary, combination therapy should not be used routinely; it should be reserved for the specific indications (Table 6), chosen from the regimen pairs outlined, and coupled with early reassessment, TDM, and timely de-escalation [79–81]. Better-designed trials and improved predictive tools are needed before wider adoption.

Future directions in ICU candidiasis: innovation, stewardship, and value

Near-term innovation in ICU candidiasis is expected to drive three pragmatic shifts. First, diagnostics will consolidate into faster rule-in and rule-out bundles that combine serum and compartmental biomarkers, such as peritoneal BDG, rapid species identification, on-plate or rapid AFST, and NGS, for resistance markers and outbreak tracking, with electronic health record risk scores that trigger pre-defined start, stop, and switch decisions. Second, exposure optimisation will be enabled by bedside micro-sampling, point-of-care TDM for azoles, model-informed precision dosing that accounts for extracorporeal support and obesity, and dosing calculators that account for circuit losses. Third, therapeutics will expand with long-acting echinocandins and new oral agents that retain activity against resistant *Candida* spp., including

Table 6 Combination strategies for difficult deep-seated refractory infections

Clinical scenario	Preferred initial combination	Primary goal of combination	Key adjuncts	Reassessment and de-escalation	TDM and PK priorities	Evidence signal
Endocarditis (native or prosthetic)	Liposomal amphotericin B + flucytosine, or echinocandin + azole when amphotericin B or flucytosine are unsuitable	Rapid fungicidal exposure and CNS/vegetation penetration	Early surgical consult for valve surgery where indicated; source control of intravascular devices	Reassess at 48–72 h, de-escalate to targeted monotherapy once species and susceptibility are known and surgery/source control achieved	TDM for azoles; consider PK variability with renal dysfunction and CRRT	Low, observational and guideline-based
CNS involvement (meningitis, ventriculitis)	Liposomal amphotericin B + flucytosine; step-down to high-dose fluconazole if susceptible	CSF penetration and early sterilization	Remove or exchange neurosurgical hardware if feasible	Reassess at 48–72 h, de-escalate when pathogen and susceptibilities defined and CSF clears	Flucytosine level monitoring where available; azole TDM for step-down	Low, case series and guidelines
Ocular disease (endophthalmitis)	Systemic azole (voriconazole or fluconazole per species) + liposomal amphotericin B; consider short course with echinocandin only as a bridge	Achieve therapeutic intraocular levels and rapid organism kill	Intravitreal therapy and early vitrectomy per ophthalmology	Reassess at 48–72 h, tailor to species and ocular response; step to monotherapy when stable	Azole TDM; note poor ocular penetration of echinocandins	Low, case series and guidelines
Renal candidiasis with obstruction	Echinocandin + azole, or liposomal amphotericin B + flucytosine if concern for azole resistance	Coverage during relief of obstruction and high fungal burden	Urgent source control: stent or nephrostomy; remove colonized devices	Reassess at 48–72 h after drainage, de-escalate once clinical improvement and culture data support	Azole TDM; consider PK changes with renal support modalities	Low, observational
Persistent candidemia or very high fungal burden despite source control	Echinocandin + azole, or echinocandin + liposomal amphotericin B	Broaden exposure while awaiting rapid susceptibility testing	Intensify search for hidden foci; remove intravascular devices	Reassess at 48–72 h, narrow to single active agent once AFST returns and source control verified	Azole TDM; consider echinocandin exposure issues on ECMO	Low, observational
Suspected or proven resistance (for example *C. glabrata*, *C. auris*)	Echinocandin + liposomal amphotericin B pending AFST	Ensure activity against potential echinocandin or azole resistance	Early AFST including molecular markers where available	Reassess at 48–72 h, de-escalate to active monotherapy as soon as susceptibilities are clear	Azole TDM; adjust for organ dysfunction and extracorporeal support	Low, observational and expert opinion
Major PK uncertainty or delayed TDM (ECMO, CRRT, morbid obesity, complex interactions)	Temporary echinocandin + azole while confirming exposure	Mitigate under-exposure risk during the first 48–72 h	Prompt TDM setup and drug interaction review	Reassess at 48–72 h when TDM available, de-escalate once target exposures confirmed	TDM for azoles; consider echinocandin monitoring where available	Very low, pragmatic practice
Routine candidemia with rapid clearance, susceptible isolate, and source control	Combination not indicated; use single active agent per guidelines	Avoid unnecessary exposure, toxicity, and cost	Remove endovascular devices, pursue source control	N/A	TDM if on azoles and risk of interactions or malabsorption	Guideline consensus

CNS Central nervous system; *CSF* Cerebrospinal fluid; *ECMO* Extracorporeal membrane oxygenation; *CRRT* Continuous renal replacement therapy; *PK* Pharmacokinetics; *TDM* Therapeutic drug monitoring; *AFST* Antifungal susceptibility testing. Combination therapy is not routine. Reserve it for the specific scenarios above, begin with a pre-defined 48–72 h reassessment, obtain early susceptibility testing, perform TDM for azoles and consider it for echinocandins in complex PK settings, and de-escalate to the narrowest effective monotherapy as soon as feasible. In summary, avoid routine concurrent Amphotericin B–azole combinations for *Candida* spp. unless there is a compelling salvage reason; prefer alternative pairs (e.g., echinocandin + azole) if combination therapy is needed. If stepping from an azole to Amphotericin B, be aware of potential carry-over effects; if stepping from Amphotericin B to an azole, keep the overlap brief

echinocandin-resistant *C. glabrata*, azole-resistant *C. parapsilosis*, and *C. auris*, which should permit earlier step-down and safer discharge pathways. Rezafungin, a once-weekly echinocandin, exemplifies this shift by offering the potential to reduce line manipulations, nursing workload, and length of stay, while enabling outpatient management in selected patients [82]. Together, these advances are positioned to reinforce guideline-concordant care by prioritizing an echinocandin as first-line therapy with early source control. They also support the use of biomarkers to discontinue empiric therapy when the pretest probability falls, enable rapid targeting once susceptibility and resistance data are available, allow shorter treatment courses after source control, and embed stewardship checkpoints into routine ICU workflow [83].

As the antifungal armamentarium expands, so does its clinical and economic complexity. Agents with broad-spectrum activity, including those that target both yeasts and molds, may help streamline early treatment decisions and improve outcomes in high-risk patients [84]. However, the indiscriminate use of such broad-spectrum agents may accelerate the development of resistance, paralleling the antimicrobial resistance crisis seen with carbapenems in bacterial infections. The emergence of multidrug- and pan-resistant *C. auris* already signals this risk, underscoring the need for judicious use grounded in diagnostic clarity and stewardship principles [85].

The economic burden of delayed or inappropriate treatment of IC extends far beyond the acquisition cost of antifungal agents. In critically ill patients, ineffective therapy often results in prolonged ICU stays, secondary infections, increased organ support requirements, and higher mortality, all of which exert substantial strain on already resource-intensive healthcare systems. In this context, the downstream costs of mismanagement can dwarf the price of the antifungal drug itself. Yet, current clinical trials are rarely designed to capture these broader . Most pivotal studies employ non-inferiority designs, comparing new drugs to established therapies in narrowly defined populations, without assessing real-world endpoints such as earlier ICU discharge, reduced hospital costs, prevention of secondary infections, or mitigation of resistance [88]. Thus, true value must be defined through phase IV studies, real-world data, and post-marketing surveillance, particularly in underrepresented populations such as the critically ill, those on extracorporeal support, or patients in resource-limited settings.

Conclusion

IC in the ICU demands fast, structured action: recognize risk early, bundle rapid diagnostics, and apply stewardship at every step. Use BDG for its high negative predictive value to withhold or stop empiric antifungals within a pre-defined stop plan, and avoid indiscriminate BDG screening. Shift from blanket empirical therapy to risk-stratified, biomarker-supported initiation; shorten courses once source control is achieved; and reserve long-acting agents with broader spectrum for resistance, better penetration, or adherence needs. Optimize exposure with PK/PD-guided dosing and routine azole TDM. These steps deliver practical, precision medicine in the form of IC while creating space to evaluate and adopt new agents as evidence matures.

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Declarations

Conflicts of interest

Ignacio Martin-Loeches reports speaker fees and/or research funding from Mundipharma, Gilead, Pfizer, MSD, and Menarini. Oliver A. Cornely reports grants or contracts from iMi, iHi, DFG, BMBF, Cidara, DZIF, EU-DG RTD, F2G, Gilead, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; consulting fees from numerous companies, including AbbVie, GSK, IQVIA, Janssen, MedPace, Menarini, and Shionogi; speaker and lecture honoraria from various institutions and industry partners; expert testimony for Cidara; and participation on advisory boards. David W. Denning holds founder shares in F2G Ltd., a University of Manchester spin-out antifungal discovery company; is or has recently been a consultant to Pulmatrix, Pulmocide, Biosergen, TFF Pharmaceuticals, Pfizer, Omega, Novacyt, Rostra Pharmaceuticals, MucPharm, Mundipharma, Lifemine, and Cipla; chairs a Data Review Committee for Pulmocide and acts as a Phase 1 Medical Monitor for Biosergen; has been paid for talks on behalf of BioRad, Basilea, and Pfizer; and is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group and the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group, and recently joined the One World Guideline for Aspergillosis. Jesús Guinea has received funds for educational activities and

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