Comprehensive Review on Candidemia: Epidemiology, Diagnosis, Treatment, and Future Directions

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Abstract

Candidemia is a leading cause of nosocomial bloodstream infections, associated with high mortality and substantial healthcare costs. Management challenges primarily arise from diagnostic delays due to the limitations of conventional methods, along with the difficulty in optimizing antifungal regimens. This review provides a comprehensive analysis of these issues, beginning with an overview of the epidemiology, species distribution, and origins of candidemia. It then focuses on the need for improved diagnostic technologies and the importance of susceptibility-guided therapy in enhancing patient outcomes and combating resistance. The article assesses current diagnostic approaches, their limitations, and emerging technologies that may enhance detection performance. Therapeutic strategies are examined in detail, including empiric and targeted regimens, management of mixed infections, and host–drug interactions. Particular emphasis is placed on antifungal resistance and the potential of combination therapy. Advances in drug development are also highlighted, covering agents in clinical trials and compounds targeting novel fungal pathways. Finally, future directions are explored, such as the application of artificial intelligence in diagnostics, vaccine-based prophylaxis, and synergistic treatment strategies. By synthesizing recent progress, this review aims to support clinicians and researchers in addressing the evolving challenges of candidemia management.

Key word: Candidemia, Antifungal resistance, Diagnostic technologies, Drug development

Introduction

Candidemia, defined by the presence of *Candida* species in the blood accompanied by compatible clinical signs or risk factors after excluding contamination, is a critical clinical and public health concern. It represents the most common form of invasive candidiasis and is one of the most frequent hospital-acquired bloodstream infections in critically ill patients. Its clinical significance is underscored by high mortality rates, prolonged hospital stays, and increased healthcare costs, reflecting a substantial global burden. Rapid identification and treatment are paramount, as candidemia not only indicates severe underlying illness but also independently contributes to mortality; each hour of delayed treatment has been associated with worsening outcomes.

Given the high mortality and evolving epidemiology of candidemia, timely and accurate diagnosis remains a critical clinical priority. Although conventional blood cultures offer high specificity, their limited sensitivity and slow turnaround time impede early therapeutic intervention. To overcome these limitations, novel diagnostic modalities are increasingly being adopted to facilitate earlier detection and more targeted antifungal therapy. In parallel, treatment strategies are undergoing refinement in response to the rising threat of antifungal resistance. This growing challenge, driven by mechanisms like efflux pump overexpression and biofilm formation, complicates treatment and highlights the need for robust antifungal stewardship.

In this review, we provide a comprehensive overview of candidemia, with an emphasis on its epidemiology, diagnostic challenges, antifungal resistance, and contemporary therapeutic strategies. We focus on recent advances in diagnostic technologies, highlighting their clinical utility and limitations. We also examine current antifungal treatment paradigms, from empiric and targeted therapy to the management of mixed bacterial–fungal infections, with particular attention to resistance mechanisms, host–drug interactions, and the potential role of combination therapy. In addition, we discuss emerging antifungal agents and novel therapeutic targets that may reshape future clinical management. By delineating current knowledge and future research directions, this review aims to provide clinicians and researchers with an integrated framework to better understand and manage the evolving clinical challenges of candidemia.

1 Epidemiology

1.1 Common *Candida* species in bloodstream infections

Traditionally, *Candida albicans* has consistently dominated the spectrum of pathogens causing candidemia. However, recent epidemiological surveillance has revealed a significant increase in the proportion of cases caused by non-*albicans Candida* species (NAC), now accounting for over half of cases worldwide [1]. According to surveillance data from the United States, 92%–95% of candidemia cases are attributed to five major pathogenic species: *C. albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida krusei*. The current epidemiological landscape indicates that although *C. albicans* remains the single most predominant species, the overall disease burden caused by NAC has surpassed that of *C. albicans*, with distinct geographical variations [2]. The unique virulence traits and resistance profiles of each species directly influence individualized clinical treatment strategies.

From a pathogenic perspective, *C. albicans* exhibits superior tissue invasiveness due to its strong hyphal formation and biofilm production capabilities [3]. Although NAC lack typical hyphal structures, they employ distinct virulence factors to achieve clinical pathogenicity: (1) *C. glabrata* demonstrates intrinsic reduced susceptibility to azoles and is frequently isolated from immunocompromised hosts [4]; (2) *C. parapsilosis* has a propensity for medical device colonization, and its biofilm-forming ability on catheters increases the risk of outbreaks in neonatal intensive care units, along with relatively higher minimum inhibitory concentration (MIC) values for echinocandins [5]; (3) *C. tropicalis* shows a predominant distribution among hematologic malignancy patients in tropical regions, with some isolates (particularly in Asia) exhibiting high azole resistance rates [6,7]; (4) *C. krusei* displays intrinsic resistance to fluconazole and is often found in patients with prior azole exposure [8]. Notably, *Candida auris*, an emerging multidrug-resistant pathogen, not only exhibits cross-resistance to mainstream antifungal agents but also possesses a unique capacity for nosocomial transmission [9]. Table 1 summarizes the major *Candida* species involved in bloodstream infections, including their geographic distribution, resistance patterns, and relevant clinical characteristics.

Table 1. Major *Candida* species: global distribution, resistance rates

Strain	Main Distribution Area	Drug Resistance Rate	References
C. albicans	Common	*C. albicans* is almost uniformly sensitive to fluconazole, echinocandin, and amphotericin B. Fluconazole resistance occurs infrequently, generally reported at 0–3%, with the overall average remaining below 1%.	[10]
C. glabrata	Northern Europe, Australia and the USA	*C. glabrata* has echinocandin resistance between 2% and 8% while fluconazole resistance between 7% and 11%. The resistance rates to fluconazole and echinocandin drugs have increased.	[10]
C. parapsilosis	USA, Japan, Western Europe, and Latin America	The fluconazole resistance rate of *C. parapsilosis* ranges from 4% to 10% in the United States, while this proportion is much higher in other regions of the world. Resistance to echinocandins remains relatively low, at 0–3%.	[10]
C. tropicalis	Asia, the Caribbean, and Latin America	Baseline levels of fluconazole resistance are 3–5% in most regions, but resistance rates as high as 7–43% are reported in some Asia–Pacific countries. The resistance of *C. tropicalis* to fluconazole was 38.8% and to voriconazole was 27.8% in China. Echinocandin resistance remains low at 0–2%. Amphotericin B resistance remains rare.	[6,10]
C. krusei	Europe, North America, Latin America, Asia, and Africa	Intrinsic resistance to fluconazole. *C. krusei* resistance to voriconazole is emerging and is around 10% in some parts of the world. Echinocandin and amphoteric B resistance also appears to be emerging, with resistance rates ranging from 3% to 10% in large multicenter studies.	[8,10,11]
C. auris	India, South Africa	*C. auris* is resistant to fluconazole up to 70%–90%. Resistance to Echinocandin up to 7%. Resistance to amphotericin B up to 35%	[10]

1.2 Underlying diseases predisposing to candidemia

Immunosuppression and metabolic disorders are key predisposing factors for candidemia. Patients with hematologic malignancies, solid tumors, or those receiving immunosuppressive therapy following organ transplantation exhibit significantly elevated infection risks due to compromised immune systems [6]. Individuals with HIV/AIDS and critically low $CD4^+$ T-cell counts are prone to recurrent mucosal candidiasis, which may progress to invasive infections if untreated [12]. Metabolic diseases, particularly diabetes, also confer increased susceptibility, as chronic hyperglycemia and associated immune dysfunction promote *Candida* overgrowth. [13]; poorly controlled blood glucose further impairs neutrophil function and creates a sugar-enriched microenvironment that facilitates fungal proliferation [14].

Certain patient populations are particularly susceptible to hospital-acquired candidemia. Critically ill individuals requiring intensive care, including those with sepsis or acute kidney injury, exhibit markedly increased infection risks due to severe physiological stress and underlying organ dysfunction [15]. In this context, prolonged hospitalization and exposure to complex medical care often coexist with additional risk-enhancing factors, such as antimicrobial therapy and supportive interventions, which collectively predispose patients to invasive *Candida* infections [16-19].

In summary, high-risk populations for candidemia comprise three main groups: immunocompromised individuals (e.g., those with cancer, transplants, or HIV/AIDS), patients with metabolic dysfunction (e.g., diabetes), and those receiving intensive hospital therapies (e.g., ICU care, broad-spectrum antibiotics, or gastrointestinal surgery). These conditions predispose patients to infection by impairing immune defenses or disrupting mucosal barriers, thereby facilitating the transformation of commensal *Candida* into invasive pathogens. Moving forward, effective prevention requires a paradigm shift: from merely listing qualitative risk factors to developing quantitative predictive models. Such models must leverage specific clinical data on individual patients' metabolic and immunologic status to accurately translate risk profiles into targeted interventions.

1.3 Environmental and host factors triggering candidemia

The development of candidemia is typically mediated by a combination of hospital-related environmental factors and host susceptibility (Fig. 1). Within hospital settings, ICUs represent high-risk zones, where patients are predisposed to infection due to mechanical ventilation, central venous catheterization, and broad-spectrum antibiotic use [15]. Among these, central venous catheters constitute a primary risk factor: *Candida* can colonize catheter insertion sites or biofilms and directly enter the bloodstream, with studies indicating that catheter use increases infection risk nearly tenfold in non-ICU patients [15]. Total parenteral nutrition (TPN) serves as an independent risk factor, exhibiting an odds ratio of approximately 6.75 in ICU patients and 3.3 in non-ICU populations; its high-glucose content may further promote *Candida* proliferation [15]. Broad-spectrum antibiotics

elevate *Candida* colonization risk by disrupting commensal microbiota and may suppress bacterial growth in blood cultures, thereby "unmasking" underlying candidemia [15,20]. Notably, severe bacterial infections can obscure the clinical manifestations of candidemia, leading to delayed diagnosis [21]. Furthermore, environmental contamination in ICUs, such as on healthcare workers' hands or medical equipment, can facilitate pathogen transmission and contribute to outbreaks. This is exemplified by documented *C. parapsilosis* outbreaks in neonatal ICUs, which have been directly linked to contact transmission via contaminated surfaces or hands [22-24].

Regarding host factors, immunosuppressed states, including neutropenia, corticosteroid therapy or chemotherapy, impair anti-*Candida* defenses, while antibiotic-induced or disease-related gastrointestinal microbial dysbiosis facilitates *Candida* overgrowth and translocation into the bloodstream [25]. Pre-existing *Candida* colonization in sputum or urine serves as an early warning sign for invasive infection, indicating potential hematogenous dissemination. In summary, hospital-associated risks (ICU stays, invasive procedures, broad-spectrum antibiotics) and host vulnerabilities (immunosuppression, mucosal barrier disruption, microbial dysbiosis) synergistically drive the transformation of commensal *Candida* into invasive pathogens, culminating in candidemia.

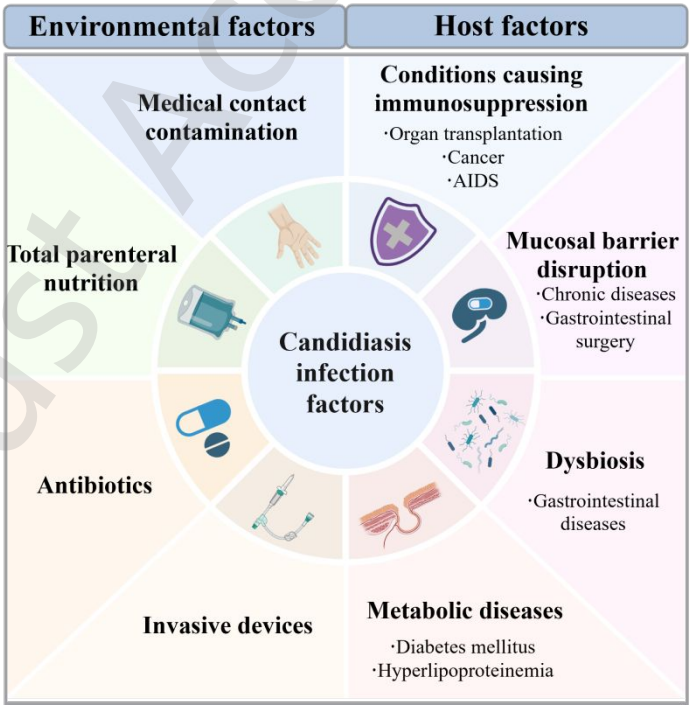

Fig. 1 Factors promoting candidemia, including environmental and host-related factors. Environmental factors for candidemia involve antibiotics (disrupting microbiota, raising *Candida* colonization and masking risks), invasive devices (central venous catheters letting *Candida* enter blood, total parenteral nutrition promoting proliferation), and medical contact

contamination (ICU - related, e.g., *C. parapsilosis* outbreaks). Host factors include metabolic diseases (e.g., diabetes), diseases disrupting mucosal barriers (enabling *Candida* overgrowth), and conditions like organ transplantation, cancer, AIDS (causing immunosuppression, impairing anti-*Candida* defenses). Created in https://BioRender.com.

1.4 Origin of candidemia: endogenous gut translocation vs exogenous sources

The origin of candidemia has long been debated, with accumulating evidence supporting predominantly endogenous sources. Current evidence indicates that most cases arise from the patient's own microbiota, particularly the gastrointestinal tract. *C. albicans* typically colonizes the gut and may invade the bloodstream during intestinal mucosal barrier disruption, serving as the primary source of systemic infection. Molecular typing studies demonstrate concordance between bloodstream isolates and strains colonizing the patient's gastrointestinal tract or catheter insertion sites, supporting this hypothesis. For instance, chemotherapy-induced mucositis or abdominal surgery can facilitate the translocation of commensal gut *Candida* into the bloodstream [25]. In critically ill patients receiving antibiotics, the natural bacterial suppression of *Candida* is compromised, leading to fungal overgrowth and intestinal barrier damage, thereby increasing bloodstream infection risk. Animal models corroborate that intestinal *Candida* overgrowth following antibiotic use precedes hematogenous and deep-organ infections [20].

Although exogenous sources are critical in specific scenarios, endogenous origins predominate in most candidemia cases. Catheter-related candidemia may originate from skin colonizing strains or contaminated infusates. Outbreaks of *C. parapsilosis* in neonatal intensive care units have been epidemiologically linked to healthcare worker hand contamination or medical device colonization [22-24]. *C. auris*, owing to its prolonged survival on environmental surfaces, can spread through healthcare settings, causing hospital outbreaks independent of patient microbiota [26]**.** Nevertheless, even in catheter-associated cases, the initial strains often derive from the patient's colonized skin or mucosa rather than the environment. DNA fingerprinting studies reveal that many candidemia cases exhibit matching bloodstream isolates with strains from the patient's gut, catheter tip, or skin, further affirming the predominance of endogenous origins [27].

In conclusion, intestinal *Candida* translocation constitutes the primary mechanism of candidemia, but exogenous routes, such as catheter contamination or healthcare-associated transmission, are significant for specific species (e.g., *C. parapsilosis* and *C. auris*). Thus, infection control cannot rely on a single strategy. Rigorous catheter management and environmental decontamination are essential to curb exogenous transmission. Moreover, a comprehensive prevention framework must incorporate the early identification and monitoring of intestinal colonization.

1.5 Mortality rate and survival outcomes in candidemia

Candidemia is associated with substantial mortality, with in-hospital mortality

ranging between 25% and 40% even among treated patients. Data from the U.S. Centers for Disease Control and Prevention indicate that approximately 25% of patients die during hospitalization, while Chinese studies report a 30-day mortality rate of 32.8% [6]. Since patients often present with critical underlying conditions, accurately distinguishing the contribution of *Candida* infection versus baseline diseases to mortality remains challenging [28]. Matching-controlled studies estimate an attributable mortality of approximately 19% to 24% [29], suggesting that candidemia increases absolute mortality risk by about 20%. Additionally, candidemia prolongs hospitalization by 3 to 13 days and substantially increases healthcare costs [29].

Mortality risks vary across populations. Neonatal mortality ranges from 11.4% to 44% [30], while rates among critically ill adult patients may exceed 50% [31]. Key risk factors include advanced age, persistent neutropenia, high Acute Physiology and Chronic Health Evaluation (APACHE II) scores, and delayed treatment [32]. Studies demonstrate that age ≥65 years, shock status, and elevated APACHE II scores independently correlate with 30-day mortality, showing odds ratios of 3 to 12 [6].

These findings collectively indicate that candidemia not only serves as a marker of disease severity but also acts as an independent mortality risk factor. With an overall mortality rate of 20% to 50%, survivors often face prolonged recovery periods and recurrence risks, underscoring the critical importance of early diagnosis and prompt therapeutic intervention.

2 Clinical diagnosis of candidemia

2.1 Diagnostic methods

Blood culture remains the gold standard for diagnosing candidemia [33]. By incubating blood samples in automated culture bottles, *Candida* growth can typically be detected within 24 to 72 hours [34]. Positive samples can be identified to species level using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI–TOF MS) and subsequently subjected to antifungal susceptibility testing [35,36]. Although blood culture remains the diagnostic gold standard, its sensitivity is particularly low in patients already exposed to antifungal therapy, often detecting only around half of true cases [37]. It should therefore be complemented by 1,3-β-D-glucan (BDG) assay or molecular assays to enhance early detection.

To address the limitations of culture-based methods, various molecular techniques have been developed. PCR-based methods enable direct detection of *Candida* DNA in blood, with some commercial assays or next-generation sequencing platforms achieving species identification within 24 hours without requiring culture [38]. The FDA-approved T2Candida panel utilizes magnetic resonance technology to identify five common *Candida* species within 4–5 hours, demonstrating sensitivities exceeding 90% for the targeted species, significantly outperforming conventional blood culture in this context. [39]. MALDI–TOF MS is widely used for rapid identification of yeasts following growth, enabling species-level diagnosis

approximately 1–2 days earlier than traditional subculture-based methods [40].

Serological assays assist diagnosis by detecting fungal cell wall components. The most widely used BDG test serves as a pan-fungal marker indicating invasive fungal infections including candidemia [41]. Some laboratories employ combined detection of mannan antigen and anti-mannan antibodies to enhance diagnostic specificity [41]. Notably, the galactomannan assay (GM test) is primarily applicable to *Aspergillus* infections and offers limited diagnostic value for *Candida* [42]. Mannan *Candida* antigen testing (Mn test) demonstrates clinical utility for candidemia diagnosis [43].

Emerging metagenomic next-generation sequencing (mNGS) technologies can detect all pathogen nucleic acids in blood [44], identifying *Candida* DNA even in culture-negative cases [45]. Although it currently remains cost-prohibitive and primarily utilized in research settings, this approach shows promising clinical potential. Additionally, specialized methods like peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) enable rapid species identification within hours after blood culture positivity through fluorescence probes targeting ribosomal RNA [46,47]. Taken together, current diagnostic tools for candidemia each offer distinct advantages but also carry substantial limitations. These shortcomings underscore that no single modality can reliably capture the full clinical spectrum of candidemia. A combined diagnostic strategy not only shortens diagnostic delay but also reduces mortality risk in high-risk ICU patients. Ultimately, optimizing diagnosis will depend not only on technological refinement but also on systematically incorporating multimodal strategies into routine clinical pathways, which remains an important but underimplemented need in current practice.

2.2 Characteristics and limitations of diagnostic methods

The diagnostic modalities for candidemia exhibit distinct characteristics, requiring clinicians to carefully balance their advantages and limitations (Fig. 2). While blood culture offers excellent specificity, its sensitivity is substantially affected in real-world clinical settings, particularly when fungal burden is low or when patients have already received antifungal therapy [33,37]. In addition, blood culture is inherently time-consuming, typically requiring approximately five days to yield positivity, followed by an additional one to two days for species identification. Such diagnostic delays may critically compromise timely initiation of appropriate antifungal therapy, especially in high-risk patients [48,49].

In contrast, molecular detection technologies significantly reduce diagnostic timelines. PCR-based methods can generate results within hours, though blood-borne inhibitors may lead to false negatives if amplification is suppressed, and the assays show limited sensitivity for low-burden specimens [47]. The T2Candida panel, while analytically sensitive within its defined scope, is restricted to a limited set of species and cannot detect uncommon or emerging Candida pathogens; moreover, its reliance on specialized instrumentation and associated costs constrains widespread clinical adoption [50]. While mNGS theoretically detects all pathogens, clinical implementation remains constrained by risks of detecting colonizing flora DNA,

coupled with current limitations in cost-effectiveness and processing time [51].

Among serological assays, the BDG test demonstrates 69.9%–100% sensitivity. However, its specificity is compromised by cross-reactivity with other fungal infections or certain medical interventions. Notably, intravenous products (e.g., albumin, immunoglobulin) and therapeutic procedures (e.g., dialysis with cellulose filters, β-lactam antibiotics) may elevate BDG levels in the absence of true infection [50]. Mannan antigen detection demonstrates moderate sensitivity (approximately 60.7%) with relatively higher specificity, and combination with anti-mannan antibody testing improves overall diagnostic performance but complicates result interpretation [52]. Mass spectrometry techniques like MALDI-TOF MS enable rapid and accurate identification of cultured isolates, though remain dependent on microbial growth from cultures. Imaging studies, while non-diagnostic for candidemia, provide complementary value in detecting metastatic infectious foci [50].

In resource-limited settings, blood culture often remains the sole available method, though its low sensitivity poses clinical challenges. An optimal diagnostic strategy should integrate multiple approaches: blood cultures for definitive diagnosis, serological testing for early screening, and molecular methods for accelerated pathogen identification. Current guidelines recommend concurrent blood culture and BDG testing for high-risk patients, where positive serological results combined with clinical manifestations may guide early empirical therapy. Comprehensive understanding of each method's performance characteristics proves essential for appropriate result interpretation and optimized clinical decision-making [36,53]. Ultimately, the current evidence supports a tiered diagnostic framework in which each modality fulfills a distinct clinical role: culture remains essential for definitive confirmation, serological biomarkers provide valuable early screening support, and molecular assays offer rapid pathogen-specific guidance. These tools should be applied in a complementary rather than interchangeable manner, with their strengths and limitations clearly recognized to ensure timely and accurate diagnosis of candidemia.

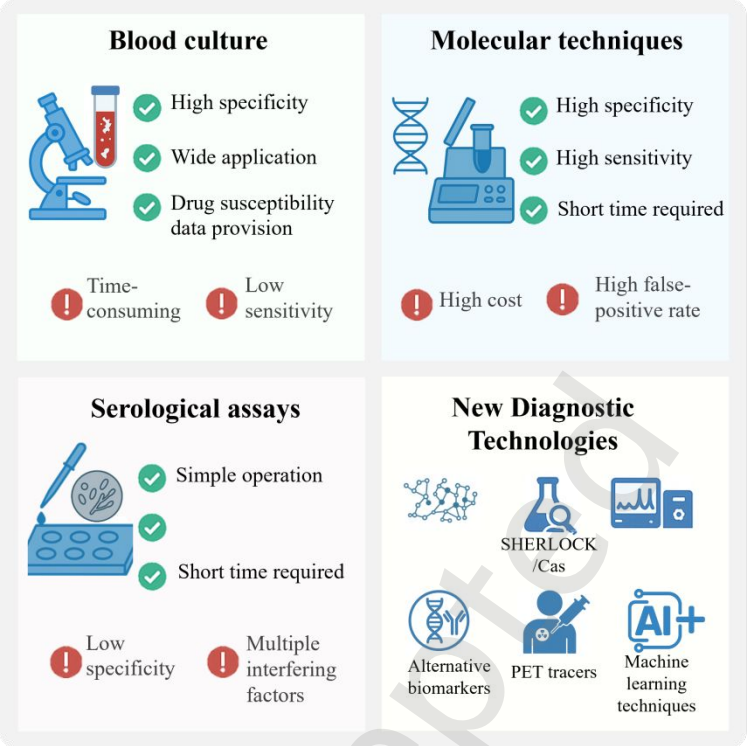

Fig. 2 The features and limitations of existing diagnostic methods and recent advances in novel diagnostic technologies. Blood culture, with high specificity, wide application, and drug susceptibility data provision, is time-consuming with low sensitivity. Molecular techniques, boasting high specificity, sensitivity, and short time-required, face issues of high cost and false-positive rate. Serological assays, simple to operate, acting as auxiliary methods with short time-required, suffer from low specificity and multiple interfering factors. Some new diagnostic technologies, like mNGS, SHERLOCK/Cas, PCR-ESI-MS, alternative biomarkers, PET tracers, and machine learning-based approaches, have implementation constraints in cost-effectiveness and processing time. An optimal diagnostic strategy should integrate multiple approaches: blood cultures for definitive diagnosis, serological testing for early screening, and molecular methods for accelerated pathogen identification. AI-assisted illustration tools were used to assist in generating the conceptual schematic figure.

2.3 Factors interfering with diagnostic accuracy

Laboratory testing for candidemia may be confounded by various factors, which can be categorized into three primary domains: therapeutic interventions, technical limitations, and microbial interactions. Regarding antifungal therapy, echinocandins and azoles can substantially suppress *Candida* growth even with short-term pre-culture administration, reducing colony-forming units (CFUs) in blood below detection thresholds [54]. Broad-spectrum antibiotics exert dual effects on candidemia diagnosis: while increasing the risk of candidemia through disruption of the normal flora, they may concurrently suppress concomitant bacterial growth, resulting in apparently "sterile" culture findings despite persistent, undetected fungal infection

[15,20,21]. Notably, certain antibiotics such as piperacillin-tazobactam and certain β-lactams can induce false-positive BDG results, potentially attributable to residual fungal polysaccharide contamination during manufacturing process [50]. Additionally, hemodialysis patients using cellulose membranes or those receiving wound care with dextran-containing dressings may similarly exhibit elevated BDG levels without true infection [55].

Technical limitations further involve issues related to specimen quality and processing protocols. Inadequate blood collection volume significantly diminishes culture sensitivity [56], while elevated triglyceride levels or hemolysis in samples may compromise PCR and BDG assay accuracy [57]. Although rare, laboratory contamination through PCR reagent carryover or specimen mislabeling can yield erroneous results [58]. Certain slow-growing *Candida* species might evade detection within standard 5-day incubation periods [59].

Microbial interactions introduce additional diagnostic challenges. In polymicrobial bloodstream infections involving both bacteria and *Candida*, rapidly proliferating bacterial species may obscure fungal detection through competitive growth advantages or alterations of the local microenvironment [60]. For instance, *Pseudomonas aeruginosa* produces antimicrobial substances capable of suppressing *Candida* proliferation, leading to preferential bacterial detection in blood cultures. Clinical confirmation bias may exacerbate this phenomenon, as detection of bacterial pathogens may lead clinicians to overlook coexisting fungal infections [61,62].

Comprehensive recognition of these confounders is crucial for appropriate test interpretation. A structured summary of the major factors interfering with diagnostic accuracy is provided in Table 2. In high-risk patients receiving antifungals, negative cultures cannot exclude infection, necessitating supplementation with non-culture-based methods or clinical assessment. Similarly, positive BDG results require cautious evaluation after excluding antibiotic-related confounding variables. Optimal diagnostic accuracy for candidemia demands multimodal diagnostic approaches integrating complementary methodologies while thoroughly considering clinical context.

Table 2. Factors interfering with diagnostic accuracy and practical measures

Factors interfering with diagnostic accuracy	Possible impact on results	Practical measures
Regarding antifungal therapy.	Reducing CFUs in blood below detection thresholds.	Detection by PCR or mNGS to improve sensitivity.
Broad-spectrum antibiotics.	Resulting in "sterile"	Detection by PCR or BDG

	culture findings.	to improve sensitivity.
Contamination of fungal polysaccharides residues during the manufacturing of certain antibiotics.	Inducing false-positive BDG results.	Optimizing antibiotic preparation process to minimize residual contamination of fungal polysaccharides.
Interference from dialysis membranes.	Exhibiting elevated BDG levels without true infection.	Improve dialysis membrane materials. Select non-glucan dressings.
Insufficient blood volume.	Significantly diminishing culture sensitivity.	Detection by PCR or mNGS to improve sensitivity.
Elevated triglyceride levels or hemolysis in samples.	Compromising PCR and BDG assay accuracy.	Optimize sample collection and processing processes.
Bacterial co-infection.	Overlooking coexisting fungal infections.	Comprehensive diagnostic strategy, multiple detection methods.

2.4 New diagnostic technologies and their potential

The emergence of novel diagnostic technologies has brought renewed hope for the early and accurate detection of candidemia (Fig. 2). In the molecular diagnostics domain, mNGS demonstrates unique advantages by enabling pathogen-agnostic detection of nucleic acids in blood samples, capable of identifying both common *Candida* species and rare strains, as well as polymicrobial infections [63-65]. Clinical studies have demonstrated that mNGS holds significant diagnostic value for culture-negative sepsis cases. Despite current limitations such as extended turnaround

times and challenges in distinguishing true pathogens from contamination, advances in sequencing technology and bioinformatic analysis are expected to enable pathogen identification within 24 hours in the near future [66,67].

Emerging molecular detection platforms, including CRISPR-based systems such as the Specific High-sensitivity Enzymatic Reporter UnLOCKing (SHERLOCK)/Cas technology, are under active development [68]. These methods leverage sequence-specific recognition of *Candida* DNA to generate visual readouts, potentially enabling rapid, equipment-free point-of-care testing. Nanopore sequencing technology, owing to its portability, shows promise for real-time *Candida* DNA detection in clinical settings [69]. Multiplex PCR panels continue to expand their pathogen coverage and are now capable of simultaneously screening dozens of bloodstream pathogens, including *Candida* species, thereby substantially reducing diagnostic delays [70,71]. Next-generation T2Candida system is anticipated to enhance detection capabilities for emerging species like *C. auris* while improving analytical sensitivity [50]. PCR-ESI-MS (polymerase chain reaction coupled with electrospray ionization mass spectrometry) has been investigated for fungal detection; one such platform identifies *Candida* DNA through mass spectrometric analysis of PCR amplicons, offering broad-spectrum pathogen coverage [72].

Beyond pathogen DNA detection, multiple innovative approaches target alternative biomarkers. Host gene expression profiling analyzes patient immune responses to predict fungal infections. Previous studies have identified specific immune signatures, such as elevated interleukin-17 (IL-17) levels, that may indicate invasive *Candida* infections prior to direct pathogen detection [45,73]. In imaging diagnostics, novel radiolabeled tracers like fluconazole-conjugated positron emission tomography (PET) tracers are under evaluation. These techniques provide indirect evidence of candidemia by visualizing deep-seated *Candida* lesions in organs [74]. Antigen detection research focuses on *Candida*-specific markers, including assays targeting enolase antigen and heat shock protein 90 (Hsp90) fragments [75,76]. Artificial intelligence (AI) applications are advancing early candidemia prediction, as machine learning algorithms integrate electronic health records and laboratory data to identify high-risk patients and prompt preemptive testing [77].

Key challenges for these innovations include clinical validation, specificity assurance, and cost-effectiveness evaluation. Nevertheless, rapid progress in diagnostic technologies has driven substantial improvements in early candidemia detection. By advancing diagnosis by several days, these developments hold potential to facilitate preemptive therapeutic interventions and improve patient outcomes.

3 Clinical antifungal therapy for candidemia

3.1 Empiric treatment in acute phase of candidemia

For critically ill patients with suspected candidemia, delayed antifungal therapy is strongly associated with increased mortality, necessitating empirical treatment initiation prior to culture confirmation [78]. Current guidelines recommend echinocandins as first-line agents due to their fungicidal activity against most

Candida species and favorable safety profile [33,79]. For patients who cannot receive echinocandins, fluconazole serves as an alternative; however, its limited activity against *C. glabrata* and *C. krusei* restricts its clinical use [33].

Voriconazole is generally not recommended as primary therapy for uncomplicated candidemia but may be empirically considered in specific scenarios, such as when concurrent *Aspergillus* coverage is required. Amphotericin B, historically a standard broad-spectrum agent, is now generally reserved for suspected resistant candidemia or severe invasive fungal infections. However, its nephrotoxicity and infusion-related reactions restrict it to salvage therapy for refractory cases or when alternatives are unavailable [80,81].

Empirical therapy decisions should integrate risk stratification and clinical manifestations. In intensive care units, patients receiving total parenteral nutrition or broad-spectrum antibiotics who develop unexplained fever with sepsis manifestations or positive BDG assays warrant prompt consideration of antifungal therapy [82]. Clinical prediction tools like the *Candida* Score may aid decision-making [83]. Given that each hour of treatment delay correlates with worse outcomes, high-risk patients (e.g., septic shock with multiple risk factors) should receive first-line agents without awaiting blood culture results [82]. For critically ill adults, intravenous echinocandins remain the preferred initial choice. In hemodynamically stable patients without recent azole exposure, high-dose fluconazole represents a viable alternative [33].

Therapeutic adjustments should follow culture and antifungal susceptibility results. Regardless of regimen selection, repeat blood cultures are essential to assess clearance efficacy, coupled with prompt central venous catheter removal to control infection sources [33].

3.2 Targeted treatment after species identification

Following confirmation of candidemia, therapeutic strategies require individualized adjustment based on species identification and AST results. For *C. albicans* infections with fluconazole-susceptible strains in hemodynamically stable patients, de-escalation from echinocandins to fluconazole is appropriate, with a standard treatment duration of 14 days after blood culture clearance [33,84]. *C. glabrata* infections typically necessitate continued echinocandin therapy due to frequent fluconazole resistance [85]; however, alternative azole therapy may be considered in selected cases if susceptibility is confirmed and guided by expert consultation [86]. For *C. parapsilosis*, which exhibits reduced echinocandin susceptibility due to intrinsic *FKS* polymorphisms (though remaining within susceptible ranges), fluconazole remains preferred for susceptible strains in clinical practice [87]. *C. tropicalis* generally demonstrates fluconazole susceptibility, but echinocandins or voriconazole should be used when resistance is identified [7,88]. *C. krusei*, inherently resistant to fluconazole, requires echinocandins, with amphotericin B as a secondary option [89,90].

The emerging multidrug-resistant *C. auris* poses therapeutic challenges. High-dose echinocandins are first-line for susceptible strains [91], while amphotericin

B, isavuconazole, or voriconazole may be considered for resistant isolates. Severe infections may warrant combination therapy (e.g., echinocandin plus liposomal amphotericin B), with infectious disease consultation strongly recommended [92].

The standard treatment duration for uncomplicated candidemia is 14 days post-blood culture clearance. Metastatic infections (e.g., endocarditis) require extended courses of ≥6 weeks, typically involving amphotericin B plus flucytosine or echinocandins. For stable patients with susceptible pathogens, transitioning from intravenous to oral fluconazole or voriconazole is feasible [33].

This pathogen-guided therapeutic approach optimizes efficacy while minimizing unnecessary overtreatment. Clinicians must integrate patient-specific factors, drug availability, and regional epidemiology into final decision-making. Given regional resistance heterogeneity, treatment algorithms should not rigidly follow global guidelines but integrate local epidemiologic data to balance efficacy and stewardship.

3.3 Treatment of mixed bacterial and fungal bloodstream infections

ICUs frequently encounter complex scenarios of polymicrobial bloodstream infections involving both bacterial and *Candida* pathogens [93]. Therapeutic management necessitates balancing antimicrobial spectrum coverage with safety considerations. Clinical protocols should adhere to the following principles: appropriate antibacterial and antifungal therapies should be initiated simultaneously to prevent adverse outcomes from delays in either component of treatment [94]; drug combinations with minimal clinically significant interactions or overlapping toxicities should be prioritized; and rigorous infection source control, such as prompt removal of suspected contaminated catheters, is imperative.

Antimicrobial selection requires comprehensive evaluation of spectrum coverage, interaction profiles, and toxicity characteristics. Echinocandins, owing to their broad-spectrum antifungal activity and minimal drug interactions, serve as the first-line antifungal agents in mixed infection [95]. Azoles require cautious use, particularly voriconazole, which exhibits clinically significant bidirectional interactions with rifampin: rifampin strongly induces CYP450 enzymes, markedly reducing voriconazole exposure, while voriconazole-mediated CYP inhibition does not reliably offset rifampin induction, rendering coadministration contraindicated [96,97]. Fluconazole may also interfere with the metabolism of immunosuppressants, necessitating therapeutic drug monitoring [98].

Toxicity management is critical. In patients with renal impairment, combinations of nephrotoxic agents, such as conventional amphotericin B paired with aminoglycosides or vancomycin, should be avoided due to the risk of exacerbated kidney injury [99,100]. Alternatives include liposomal amphotericin B or echinocandins, or antibiotics with lower nephrotoxic potential [101]. Close monitoring of renal function and inflammatory responses is essential during treatment, as pathogen lysis may transiently exacerbate septic shock [102].

Therapeutic regimens should be dynamically adjusted based on culture results. For instance, initial broad-spectrum antibiotics may be de-escalated to

narrow-spectrum agents once pathogens are identified, while antifungal therapy should be continued for the recommended duration based on clinical response and microbiological clearance. For complex cases, multidisciplinary consultation involving infectious disease specialists is recommended to develop individualized regimens, ensuring optimal management of each pathogen and determination of appropriate treatment durations.

3.4 Effect of mixed therapy on bacterial and *Candida* clearance

The management of bacterial-fungal co-infections necessitates careful consideration of interactions between antibacterial and antifungal agents. While these drug classes typically target distinct pathways without direct antagonism, certain combinations may exhibit synergistic effects. Studies have demonstrated that minocycline significantly reduces the MIC of fluconazole against drug-resistant *C. albicans* by enhancing fluconazole's biofilm penetration capacity and disrupting cellular calcium homeostasis [103,104]. Similarly, the combination of caspofungin and minocycline demonstrates synergistic antifungal activity against over 90% of tested *C. auris* isolates [105]. Amphotericin B combined with rifampin also displays synergy, as amphotericin B increases cell membrane permeability, enabling rifampin to penetrate and inhibit mRNA synthesis [106]. Polymyxin antibiotics enhance fluconazole's antifungal efficacy by modifying fungal membrane properties to facilitate drug uptake [107].

Antagonistic interactions, though uncommon, may theoretically occur when azoles diminish amphotericin B efficacy by reducing ergosterol content in cell membranes, thereby compromising amphotericin B's target binding. Laboratory studies confirm that fluconazole pretreatment reduces amphotericin B's fungicidal activity, justifying clinical avoidance of concurrent administration [108]. Additionally, β-lactam antibiotics may antagonize fluconazole activity through undefined mechanisms [109].

Clinical practice requires comprehensive evaluation of multiple factors, including immunological effects and toxicity profiles. Clearing bacteria effectively can improve immune function and indirectly aid in *Candida* clearance. Likewise, controlling *Candida* infection may relieve immunosuppression and support bacterial elimination. For instance, bacterial cell fragments may induce host responses that either promote or hinder fungal elimination [110]. Concurrently, it is important to monitor for additive or synergistic toxicities arising from combined pharmacologic interactions. For example, combining vancomycin with amphotericin B increases nephrotoxicity risks, necessitating intensified monitoring and supportive measures [111].

In summary, antibiotic-antifungal combinations in co-infections predominantly exhibit independent or additive effects, with select pairs demonstrating synergy. Clinical decisions should prioritize pathogen-directed therapy guided by microbiological evidence, reserving synergistic combinations for refractory infections while maintaining rigorous toxicity and therapeutic response monitoring.

3.5 Effects of antifungal drugs on the host

Antifungal agents exert multifaceted physiological effects on the host during candidemia treatment, primarily manifesting as organ toxicity and immunomodulation. Echinocandins are generally well-tolerated but may induce infusion-related histamine reactions (e.g., rash and flushing) [112] and liver injury [113], necessitating caution in patients with pre-existing liver disease. Through fungal cell lysis, these agents release cell wall fragments that may transiently exacerbate inflammatory responses. While this process aids immunological clearance, vigilance against initial inflammatory storms is crucial in cases of high fungal burden [114].

Azoles exhibit broader systemic effects due to sterol metabolism interference. Voriconazole may induce hepatotoxicity, photosensitivity, and neurological symptoms (e.g., visual disturbances), requiring close monitoring during prolonged use [115,116]. Most azoles significantly modulate the CYP450 enzyme system, potentially elevating serum concentrations of immunosuppressants such as sirolimus, thereby increasing toxicity risks [117]. Additionally, itraconazole and ketoconazole may disrupt adrenal and sex hormone synthesis [118].

Amphotericin B predominantly demonstrates nephrotoxicity, causing renal tubular damage with electrolyte imbalances and potentially triggering acute kidney injury in patients with borderline renal function [119]. Its infusion-related reactions reflect cytokine-mediated immune activation [120]. Flucytosine may induce myelosuppression with leukopenia and thrombocytopenia, mandating regular hematological monitoring [121]. Special populations require tailored approaches: heart failure patients should avoid itraconazole's negative inotropic effects [122], neurological patients require cautious voriconazole use [123].

Regarding immunomodulation, echinocandin exposure elicits multiple immune alterations, including enhanced dectin-1-mediated and opsonic recognition of fungal cells, amplified inflammatory signaling, and improved antifungal activity of innate immune cells. Some of these effects may be related to overall perturbation of cell wall structure and more efficient dectin-1-mediated β-glucan recognition [124]. High-dose azoles may suppress immune cell CYP450 enzymes, potentially altering inflammatory mediator synthesis, though clinical relevance remains unconfirmed [125]. Antifungal therapy also perturbs gut microbiota balance, potentially facilitating resistant pathogen colonization [126].

In summary, antifungal agents directly impact host organs (liver, kidneys, central nervous system, skin) through adverse effects and indirectly via drug interactions and immunomodulation. Clinical practice demands dose adjustments based on organ function. Despite these considerations, the benefits of antifungal therapy for life-threatening candidemia consistently outweigh risks, provided complications are proactively recognized and managed.

3.6 Baseline antifungal resistance rates and resistance development

Candida species exhibit marked variations in antifungal susceptibility profiles. As summarized in Table 1, these differences are clinically meaningful and necessitate

species-level identification. *C. albicans* generally remains susceptible to major antifungal classes, whereas *C. glabrata* and *C. krusei* demonstrate substantially reduced azole susceptibility, with *C. krusei* exhibiting intrinsic fluconazole resistance [127]. *C. parapsilosis* has raised increasing concern because of rising fluconazole resistance and its inherently reduced susceptibility to echinocandins. Regional variability is particularly notable in *C. tropicalis*, where azole susceptibility differs widely across geographic areas. Collectively, these patterns highlight the importance of integrating species identification with local epidemiological data to guide optimal antifungal selection. Multidrug-resistant *C. auris* further underscores the evolving resistance landscape, with frequent azole resistance and variable susceptibility to echinocandins and amphotericin B [128]. Additionally, the inherent resistance characteristics vary among species: *C. krusei*'s natural fluconazole resistance stems from structural differences in the Erg11 enzyme [129], whereas *Candida lusitaniae* generally demonstrates reduced susceptibility to amphotericin B [130].

Antimicrobial resistance mechanisms primarily involve target enzyme modification, drug efflux pump activation, and biofilm formation (Fig. 3). Azole antifungals inhibit the enzyme CYP51 (Erg11), blocking ergosterol synthesis and disrupting fungal cell membranes. Resistance arises through multiple mechanisms, including *ERG11* mutations or overexpression and upregulation of efflux pumps (Cdr1, Cdr2, Mdr1), all of which reduce drug efficacy. Additionally, mutations in *ERG3, ERG4,* and *ERG5* can activate bypass pathways that produce alternative sterols, avoiding toxic intermediates and maintaining membrane function. Resistance to flucytosine is primarily caused by mutations in the *FCY2*, *FCY1*, or *FUR1* genes, which impair drug uptake or its intracellular activation, thereby abolishing antifungal activity [131]. Echinocandin resistance predominantly stems from *FKS* gene hotspot mutations that impair drug binding to 1,3-β-D-glucan synthase, with *C. glabrata* showing a particular propensity to acquire such mutations. In addition, the adaptive stress response mechanism, which involves a compensatory increase in the synthesis of chitin, an essential component of the cell wall, enhances the resistance of *Candida* species to echinocandins [5]. Although baseline echinocandin resistance remains low, prolonged therapeutic use may select resistant subpopulations. Polyene (amphotericin B) resistance, though rare, may occur through ergosterol depletion or structural alterations in the cell membrane [132]. In addition, aneuploidy has emerged as an important resistance mechanism. For example, aneuploidy and isochromosome formation in pathogenic *C. albicans* can increase the copy number and transcriptional expression of key genes for fluconazole resistance [133,134]. Biofilm formation substantially reduces *Candida* susceptibility to antifungal drugs, complicating the eradication of catheter-associated infections [131].

Inappropriate antifungal utilization serves as the principal driver of resistance development. Extended azole prophylaxis enables replacement of susceptible strains by resistant variants, as evidenced by azole-resistant oral candidiasis frequently observed in HIV patients following prolonged fluconazole exposure [135]. Cross-resistance patterns are prevalent among azole agents [136], while multidrug

resistance, though uncommon in *C. albicans*, poses significant therapeutic challenges in *C. glabrata* and *C. auris* [137]. For species such as *C. glabrata* and *C. auris*, the trend of resistance indicates that empirical therapy should be adjusted promptly once susceptibility results are available.

In summary, baseline resistance rates exhibit species-specific variations, with resistance emerging through genetic mechanisms (efflux pumps, target mutations, biofilm formation) and selective pressure induction. Consequently, rational antifungal stewardship combined with susceptibility-guided therapy proves crucial for preventing and managing *Candida* resistance.

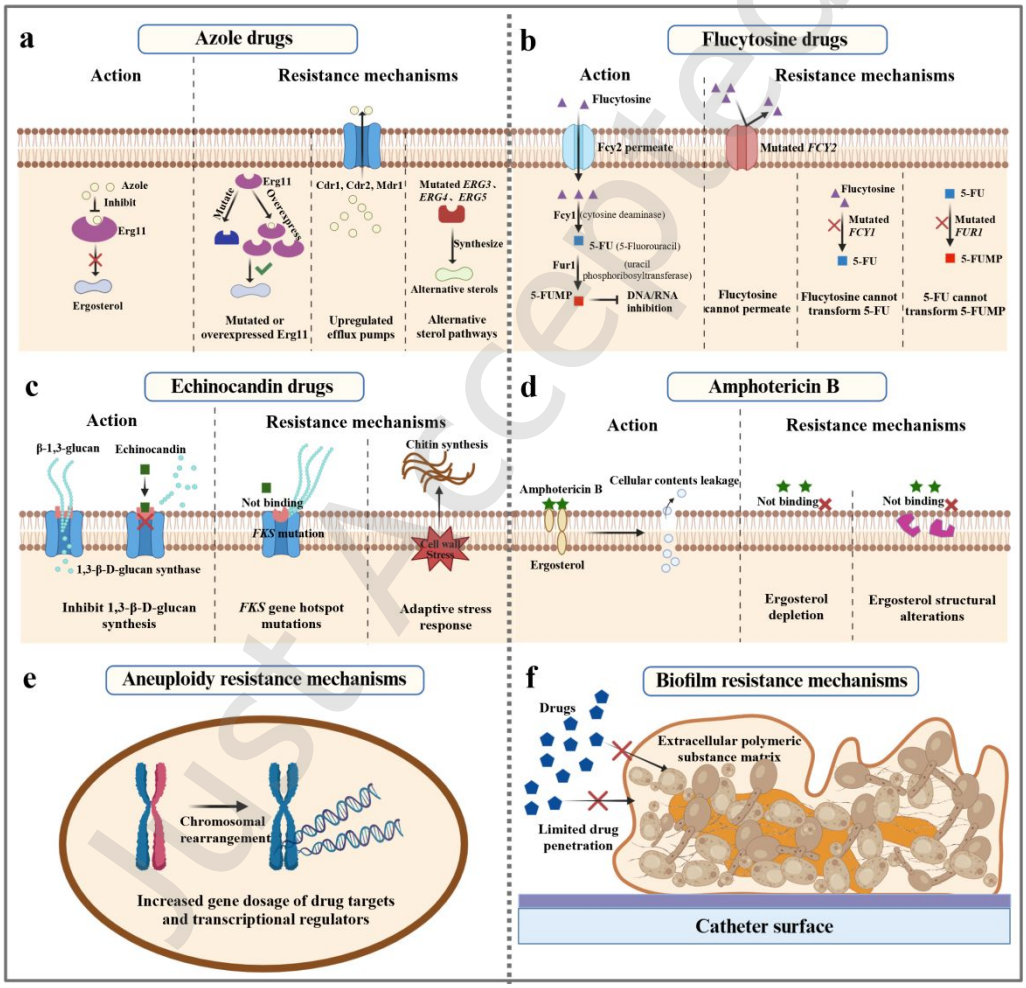

Fig. 3 Mechanisms of resistance to commonly used antifungal drugs. a. Azole resistance arises from *ERG11* mutations/overexpression, efflux pump (*CDR1/CDR2/MDR1*) upregulation and mutations in *ERG3/4/5* activating bypass sterol-synthesis pathways. b. Flucytosine resistance is due to *FCY2/FCY1/FUR1* gene mutations blocking drug uptake and activation. c. Echinocandin resistance mainly stems from *FKS* gene hotspot mutations impairing drug binding to 1,3-β-D-glucan synthase and adaptive stress response causing compensatory increase in the synthesis of chitin which enhance cell wall. d. Amphotericin B resistance occurs via ergosterol depletion or membrane structural changes. e.

Aneuploidy enhance drug resistance by increasing resistance-related gene copy and expression. f. Biofilms enhance drug resistance by altering the metabolic state of fungal cells and forming barriers. Created in https://BioRender.com.

3.7 Antifungal resistance across *Candida* species: from molecular basis to clinical strategies

Antifungal resistance in *Candida* species has emerged as a critical challenge in clinical management, with mechanisms varying by drug class. Azole resistance primarily involves target enzyme mutations and efflux pump activation. *C. albicans* develops cross-resistance through *ERG11* mutations and *CDR1/CDR2/MDR1* efflux pump overexpression [131,138], whereas *C. glabrata* tends to form multidrug-resistant phenotypes via *CgCDR1/CgCDR2* upregulation [139]. The high azole resistance rates observed in *C. tropicalis* in certain regions may correlate with extensive agricultural and medical azole usage [140].

Echinocandin resistance predominantly occurs in *C. glabrata* and *C. auris*, driven by hotspot mutations in *FKS1/FKS2* genes. For instance, resistance in *C. glabrata* is primarily driven by *FKS1* and *FKS2* mutations that alter drug targets and reduce sensitivity [141]. Amphotericin B resistance remains relatively rare, often associated with altered ergosterol content [142], though *C. lusitaniae* exhibits intrinsic resistance [143,144]. Flucytosine monotherapy readily induces rapid resistance via single-step mutations, necessitating combination regimens in clinical practice [145,146]. Biofilm formation induces phenotypic resistance, complicating catheter-related infections until source removal [147,148].

Species-specific intrinsic resistance profiles vary markedly: *C. krusei* and *C. auris* demonstrate primary resistance to fluconazole, while *C. albicans* resistance is predominantly acquired [149-151]. Clinically, prompt regimen adjustment based on AST results is essential. For example, echinocandins should replace fluconazole upon treatment failure, whereas high-dose micafungin combined with voriconazole or amphotericin B may address echinocandin-resistant strains [152]. Antifungal stewardship programs must align empirical therapy with regional resistance epidemiology, prioritizing echinocandins in areas with high *C. tropicalis* resistance [153]. Hospitals should establish resistance surveillance systems to monitor emerging pan-resistant strains, particularly in *C. glabrata* [154].

The escalating resistance crisis underscores the importance of AST implementation and the urgent need for novel antifungal development. Clinical practice demands balanced therapeutic efficacy and resistance mitigation, emphasizing rational drug utilization to delay resistance progression.

3.8 Azole-induced tolerance and treatment failure

The long-term or inappropriate use of azole antifungals may induce *Candida*

tolerance, a critical contributor to therapeutic failure. Tolerance refers to the ability of susceptible strains to exhibit slow growth under drug concentrations exceeding the MIC. Clinically, this manifests as persistent low-grade infections despite azole therapy. Variations in tolerance phenotypes among clinical isolates are primarily reflected in divergent growth proportions at supra-MIC concentrations and differences in colony formation rates. Tolerant strains typically exhibit sluggish growth, with survival predominantly dependent on exposure duration rather than drug concentration. In *C. albicans*, isolates recovered from fluconazole treatment demonstrate the highest propensity for tolerance development. This sustained replicative capacity under azole pressure likely facilitates recurrent infections and may ultimately drive full resistance acquisition [155]. Tolerance contributes to incomplete fungal eradication and increases relapse risk, particularly in patients receiving prolonged azole therapy.

In acute candidemia patients receiving fluconazole, strains with moderate tolerance mechanisms may exhibit suboptimal initial responses or infection rebound. Breakthrough candidemia caused by tolerant strains may still occur in patients undergoing prolonged fluconazole prophylaxis. Persistent blood culture positivity after 3–5 days of adequate fluconazole therapy necessitates tolerance evaluation [156]. Metabolic tolerance represents another critical mechanism, where *C. albicans* enters a dormant state (persister cells), evading fungistatic azoles until drug withdrawal permits regrowth [157].

Biofilm-associated *Candida* can persist despite planktonic susceptibility, often necessitating removal of infected devices to achieve clearance. Treatment failure due to biofilm-mediated tolerance is prevalent in catheter-associated candidemia. While fluconazole may suppress circulating planktonic cells, tolerant biofilm-embedded strains persist, driving infection recrudescence [147,157]. This growing evidence of tolerance underscores the need to redefine "susceptibility" beyond static MIC thresholds, urging clinicians to consider pharmacodynamic behavior and biofilm context. Based on the mechanisms of azole-induced tolerance and its clinical implications described above, current clinical guidelines recommend: initiating echinocandins for unstable patients, considering step-down therapy only after confirming azole susceptibility and infection stabilization; mandating serial blood culture monitoring with regimen adjustment if fungal clearance fails; compulsory removal of infected devices in catheter-related infections; and implementing rotating or combination strategies for chronic cases. These protocols underscore antimicrobial stewardship's critical role in mitigating tolerance development through judicious azole utilization [33].

3.9 Potential of combination therapy

Combination antifungal therapy demonstrates significant potential in managing invasive *Candida* infections, particularly for addressing drug resistance and severe infections. While monotherapy remains the standard for candidemia, combination regimens warrant consideration in specific clinical scenarios, including refractory

infections (e.g., endocarditis or central nervous system candidiasis), multidrug-resistant *Candida* infections, and cases unresponsive to single-agent therapy [158,159].

The most studied combinations involve echinocandins paired with azoles. This approach leverages echinocandins' rapid fungicidal activity and cell wall disruption, which may enhance azole penetration to inhibit ergosterol synthesis [160,161]. Another clinically validated combination, amphotericin B plus flucytosine, has established efficacy in cryptococcal meningitis [162]. For *Candida* endocarditis, amphotericin B combined with 5-FC is recommended for fungal eradication [33]. Their synergy stems from amphotericin B's membrane permeability enhancement, facilitating intracellular 5-FC activity [163]. Although toxicity concerns limit routine use in uncomplicated candidemia, this combination retains value in specialized contexts like endocarditis or endophthalmitis. Against emerging *C. auris* infections, echinocandin-amphotericin B combinations are under investigation [164]. Preclinical studies also highlight promising novel pairings, such as amphotericin B with minocycline, which exhibits synergistic effects against *C. auris* [105]. Such antibiotic-antifungal combinations hold developmental promise, as minocycline not only demonstrates antibiofilm properties but also modulates immune responses to enhance fungal clearance [103,104,165].

Immunomodulatory therapies combined with antifungals are gaining traction. In neutropenic patients, adjunctive granulocyte-macrophage colony-stimulating factor (GM-CSF) or interferon-γ may amplify immune-mediated fungal killing. Small-scale studies suggest that adding GM-CSF or granulocyte transfusions to antifungal regimens improves outcomes in refractory candidemia [166].

Antibody-based therapies represent another investigational frontier. Though no anti-*Candida* monoclonal antibodies are currently approved, antibodies targeting fungal cell wall components are under development and may emerge as critical adjunctive treatments [167].

Future directions include optimizing dosing protocols for existing combinations and exploring novel adjuvant therapies such as statins [168], calcineurin inhibitors [104], and probiotics [169]. With advances in antifungal agents and adjunctive strategies, combination therapies may play expanded roles in challenging scenarios, particularly against *C. auris* and biofilm-associated infections. Success hinges on balancing therapeutic efficacy with toxicity to deliver personalized, optimized treatment regimens.

4 Development of new antifungal drugs

4.1 New antifungals in clinical trials: targets, spectrum & developers

In response to the challenges of antifungal drug resistance and toxicity, several novel antifungal agents are currently under clinical development (Fig. 4). Table 3 provides an integrated summary of key antifungal agents currently in development, including their molecular targets, clinical development stage, route of administration, and reported activity against resistant *Candida* species.

Ibrexafungerp, developed by Scynexis, represents the first triterpenoid glucan synthase inhibitor. While sharing a mechanism of action similar to echinocandins, it binds to distinct target sites. The FDA has approved it for vulvovaginal candidiasis (VVC) and recurrent vulvovaginal candidiasis (RVVC) in adult and post-menarchal pediatric females. Its oral administration advantage and efficacy against azole-resistant *C. albicans* and *C. auris* are notable, though cross-resistance may occur in strains with common *FKS* mutations [170-173].

Rezafungin, a next-generation echinocandin from Cidara Therapeutics, features an extended half-life of 130 hours, enabling once-weekly intravenous dosing. Laboratory studies demonstrate comparable or lower MICs against *Candida* species relative to existing echinocandins, with partial efficacy against *FKS* mutants at elevated concentrations. Having completed Phase III trials for candidemia, it received FDA approval in 2023 [174-176].

Fosmanogepix, originally developed by Amplyx Pharmaceuticals and now under Pfizer, metabolically transforms to form the active compound manogepix, which inhibits Gwt1, an inositol acyltransferase essential for glycosylphosphatidylinositol (GPI) anchor biosynthesis, thereby disrupting the maturation of GPI anchor proteins and anchoring to fungal cell walls. This agent exhibits fungicidal activity against various *Candida* species, including *C. auris* and echinocandin-resistant strains and phase II trials have been completed. Its dual oral/intravenous formulations and novel mechanism avoid cross-resistance with existing antifungals [177].

Oteseconazole, a Mycovia Pharmaceuticals product, is a next-generation azole with enhanced CYP51 specificity to reduce toxicity. Approved by the FDA in 2022 for recurrent vulvovaginal candidiasis, it demonstrates efficacy against drug-resistant *C. glabrata* and *C. krusei* strains. Although invasive candidiasis trials remain pending, its optimized pharmacokinetic profile holds promise for resistant infections [178-180].

Opelconazole, developed by Pulmocide Ltd., is an inhaled triazole with broad-spectrum activity against *Candida* (including *C. auris*), *Aspergillus*, *Rhizopus* and *Cryptococcus spp*. Opelconazole inhibits the conversion of lanosterol to ergosterol by inhibiting lanosterol 14α-demethylase (CYP51A1) [181]. It is currently in Phase III clinical trials [182].

Encochleated Amphotericin B, developed by Matinas BioPharma, is an oral lipid-based formulation of conventional amphotericin B. While retaining the broad-spectrum activity of its parent compound, this formulation significantly reduces nephrotoxicity. Currently in Phase II trials for cryptococcal meningitis, it may extend to invasive candidiasis treatment [183,184].

Olorofim (F901318) developed by F2G Ltd., is a first-in-class antifungal agent selectively targets dihydroorotate dehydrogenase (DHODH), a pivotal enzyme in pyrimidine biosynthesis. While exhibiting broad-spectrum activity against *Aspergillus* spp. and rare molds (e.g., *Scedosporium*), its efficacy against *Candida* is limited due to structural divergence in the fungal DHODH isoenzyme. This mechanistic specificity positions olorofim as a breakthrough therapy for invasive mold infections, though it holds minimal therapeutic value for candidiasis [185].

VT-1598 is Mycovia Pharmaceuticals' next-generation azole derivative, which demonstrates dual targeting of CYP51 isoforms. Notably, its optimized molecular architecture reduces off-target interactions, enabling ancillary activity against select *Candida* species while potentially mitigating resistance development. Current Phase I trials focus on pharmacokinetic optimization and spectrum refinement [186,187].

T-2307, developed by Toyama Chemical Company, exerts its antifungal effect by disrupting the mitochondrial membrane potential of fungal cells. This investigational agent demonstrates potent activity against *Candida* species, including azole-resistant strains. Currently, T-2307 is undergoing evaluation in early-stage clinical trials [188,189].

Icofungipen, an oral antifungal agent targeting fungal aminoacyl-tRNA synthetase, represents a novel mechanistic approach. However, its development was discontinued during experimental-stage evaluation due to undisclosed pharmacokinetic challenges [190].

Nikkomycin Z, a chitin synthase inhibitor initially investigated primarily for coccidioidomycosis, demonstrated species-selective efficacy in preclinical models but has not progressed beyond exploratory trials [191].

MGCD290 is an in vitro inhibitor targeting fungal Hsp90, which has shown synergistic effects in reversing azole resistance in laboratory studies, but has not yet entered clinical development [192]. These drug candidates remain in exploratory research phases with limited clinical data available.

These innovations mark substantial progress in antifungal therapeutics: Ibrexafungerp, Fosmanogepix, and T-2307 pioneer novel targets; Rezafungin optimizes dosing regimens; and oral formulations enhance treatment accessibility. As these agents advance toward approval, they promise expanded therapeutic options for drug-resistant candidiasis, particularly in refractory infections [170-172,174,175,177-179,183-186,188,189,191,193,194].

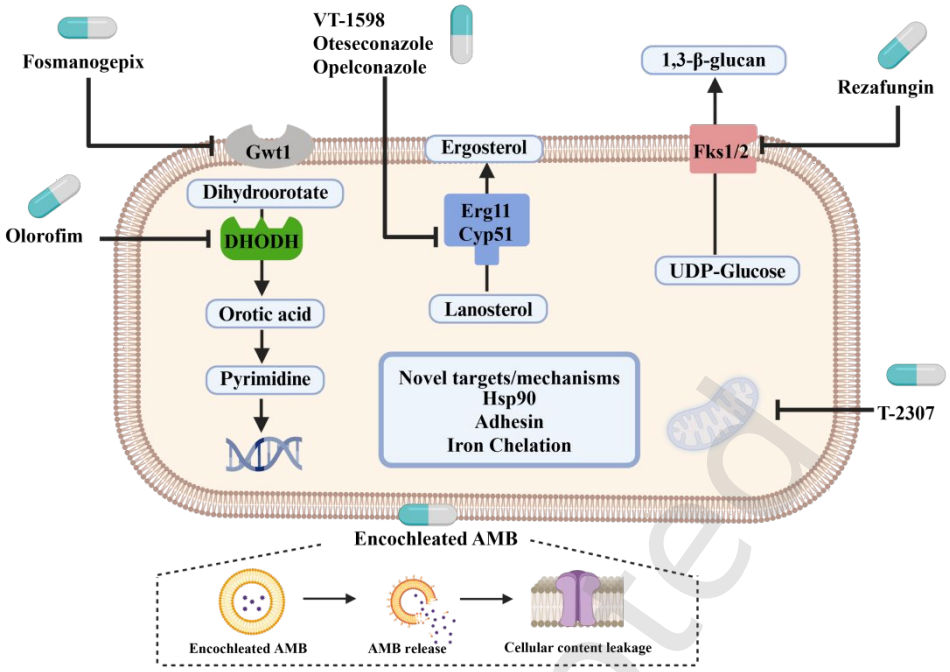

Fig. 4 Antifungal candidate molecules and their associated targets and mechanisms. Antifungal candidate molecules mainly include, rezafungin (the next-generation echinocandin with an extended half-life), fosmanogepix (inhibiting the Gwt1 enzyme to disrupt fungal cell membrane), VT-1598 (the next-generation azole derivative, targeting Cyp51 isoforms), oteseconazole (the next-generation azole with enhanced Cyp51 specificity to reduce toxicity), opelconazole (inhaled triazole with broad-spectrum activity), encochleated Amphotericin B (an oral lipid-based formulation of conventional amphotericin B), olorofim (targeting DHODH and exhibiting broad-spectrum activity against *Aspergillus* spp.) and T-2307 (disrupting mitochondrial membrane potential). Created in https://BioRender.com.

Table 3. Antifungal candidates in development.

Drug	Target	Stage of development	Route of administration	Activity against resistant strains	References
Ibrexafungerp	Non-competitive inhibition of the 1,3-β-D-glucan synthase enzyme.	The drug was approved for VVC and RVVC.	Oral.	Efficacy against azole-resistant *C. albicans* and *C. auris* are notable.	[170-172]
Rezafungin	1,3-β-D-glucan synthase.	Having completed Phase III trials for candidemia.	Intravenous.	Partial efficacy against *FKS* mutants at elevated concentrations.	[174-176]

		It received FDA approval in 2023.			
Fosmanogepix	Gwt1 enzyme.	Phase II trial has completed.	Oral. intravenous.	This agent exhibits bactericidal activity against various *Candida* species, including *C. auris* and echinocandin-resistant strains.	[177]
Oteseconazole	CYP51.	Invasive candidiasis trials remain pending.	Oral.	It demonstrates efficacy against drug-resistant *C. glabrata* and *C. krusei* strains.	[178,179]
Opelconazole	CYP51A1.	In Phase III clinical trials.	Inhalation.	Broad-spectrum activity against *Candida* (including *C. auris*), *Aspergillus*, *Rhizopus* and *Cryptococcus spp.*	[181,182]
Encochleated Amphotericin B	Ergosterol.	In Phase II trials for cryptococcal men-ingitis.	Oral.	/	[183,184]
Olorofim (F901318)	DHODH.	Phase III trials are currently underway.	Oral. intravenous.	It is effective against *Aspergillus* species but not against *Candida* species.	

VT-1598	CYP51.	In Phase I clinical trial refinement.	Oral.	Against select *Candida* species while potentially mitigating resistance development.	[186,187]
T-2307	Disrupting the mitochondrial membrane potential of fungal cells.	In early-stage clinical trials.	Subcutaneous injection.	Demonstrates potent activity against *Candida* species, including azole-resistant strains.	[188,189]
Icofungipen	Aminoacyl-tRNA synthase.	Its development was discontinued during experimental-stage evaluation.	Oral.	Is toxic against *Candida* species.	[190]
Nikkomycin Z	Chitin synthase inhibitor.	Has not progressed beyond exploratory trials.	Oral.	Coccidioidomycosis.	[191]
MGCD290	Hsp90.	Has not yet entered clinical development.	No.	Has shown synergistic effects in reversing azole resistance in laboratory studies.	[192]

4.2 New-target antifungal agents in development

Beyond drugs in clinical trials, multiple novel targets are being explored for antifungal therapy, aiming to develop mechanisms with reduced resistance potential and improved host safety. The calcineurin pathway represents a crucial target, where

inhibitors combined with Hsp90 inhibitors can attenuate fungal stress responses to drug resistance, though achieving fungal-specific targeting remains challenging [195]. Hsp90 inhibitors sensitize *Candida* to clearance by compromising stress responses, with fungal-selective compounds in early development [196].

Fungal virulence factors constitute another critical target class. *Candida*-secreted aspartyl proteases are essential for tissue invasion, and inhibiting these enzymes reduces virulence while aiding immune clearance. Researchers are developing small molecules targeting adhesins like Als3 to disrupt *Candida*-host cell adhesion and diminish pathogenicity [197,198]. Biofilm disruptors, including modified denture disinfectant molecules and HIV protease inhibitors like lopinavir, can damage *Candida* biofilm matrices. Their combination with conventional antifungals shows promise for clearing device-associated infections [199,200].

Host-directed therapies embody an innovative strategy by indirectly combating *Candida* through host pathway modulation. Iron chelators such as deferasirox restrict fungal iron acquisition and are being tested as adjuncts for refractory infections. Immunomodulators like granulocyte-macrophage colony-stimulating factor (GM-CSF) enhance antifungal efficacy by boosting host immune cell function [166,201,202].

Monoclonal antibodies targeting *Candida* cell wall components (e.g., adhesins) promote fungal opsonization and clearance. While efungumab faced clinical setbacks, next-generation antibody therapies remain under development [203,204]. Vaccine strategies like the Als3-targeting NDV-3 vaccine aim to prevent *Candida* infections in high-risk populations [205].

Antifungal peptides (AFPs) have become promising drug candidates for *Candida* infections due to their broad-spectrum antimicrobial activity, especially their specific efficacy against *C. albicans* [206]. For example, a specific form of Paneth cell–derived PYY was recently discovered, which acts as an antimicrobial peptide and inhibits the transformation of *C. albicans* to pathogenic forms, thereby maintaining a homeostatic balance of the intestinal fungal community [207]. In recent years, the focus of research has shifted toward the discovery and development of new AFPs, aiming to obtain peptides with better efficacy, stronger targeting, and higher selectivity to *Candida* strains. However, significant challenges remain to be solved in order to promote the real clinical application of antifungal peptides, including the optimization of peptide molecular stability, the improvement of drug delivery systems, the avoidance of potential toxicity risks, and the conduct of systematic and comprehensive pre-clinical studies and clinical trials [206].

Hybrid drugs represent another emerging research direction. Developing hybrid molecules containing natural product moieties is a promising synthetic approach. The structural combination of two or more natural product fragments yields novel structures with stronger activity than their parent molecules. This constitutes an effective strategy to enhance the antifungal activity of natural products, improve their pharmacodynamic and pharmacokinetic profiles, and minimize toxicity. Hybrid modification of coumarins, essential oils, cinnamaldehyde, and curcumin has been

proven to boost antifungal activity [208] .

In recent years, research on innovative targets for invasive fungal infections has significantly expanded, encompassing multiple novel therapeutic approaches. Studies have shown that fungal DNA topoisomerases (Topo I and II) are potential antifungal targets, and their inhibitors have demonstrated antifungal activity against various pathogenic fungi, such as *C. albicans* and *Aspergillus niger* [209]. Quorum-sensing blockers (e.g., farnesol) inhibit the yeast-to-hypha transition in *Candida*, and research is underway to develop them as anti-morphogenesis agents [210]. The cAMP–PKA signaling pathway plays a critical role in regulating morphogenesis and virulence in fungi; experimental inhibition of this pathway has been shown to reduce fungal pathogenicity [211]. While these mechanisms have demonstrated potential antifungal effects, they remain at an early stage of investigation, with most findings limited to in vitro studies or animal models, and have yet to progress to widespread clinical evaluation.

Most novel targets show no cross-resistance with existing drugs, and some (e.g., Gwt1 inhibitors and mitochondrial-targeted agents) have entered clinical testing. They represent a transformative direction in antifungal therapy, potentially addressing the growing threat of drug-resistant *Candida* infections with safer, more effective solutions [177,188].

5 Future perspectives

5.1 Artificial intelligence and predictive diagnostics

AI technologies are being applied to the early prediction of candidemia. By analyzing critical indicators in electronic health records, including antibiotic usage history, duration of central venous catheter placement, vital sign fluctuations, and laboratory parameters, machine learning algorithms can identify high-risk patients [212]. Such systems may combine with continuous BDG monitoring data to provide clinicians with early warnings, guiding preemptive testing and empirical treatment. Natural language processing of medical records further enables the identification of subtle candidemia risk clues (e.g., "white plaques in catheter" or "recent severe mucositis"), which are synthesized into comprehensive risk scores [213].

Proactive diagnostics also involve next-generation technologies for routine screening of high-risk populations. For instance, weekly blood BDG or PCR testing is recommended for all critically ill patients receiving total parenteral nutrition in intensive care units. The development of microfluidic point-of-care testing devices has significantly improved bedside rapid screening capabilities, while wearable biosensors demonstrate potential for real-time monitoring of fungal biomarkers [214,215].

5.2 Vaccines and targeted prophylaxis

Advancements in preventive strategies emphasize precision interventions. The NDV-3A vaccine has shown safety in Phase II clinical trials and induces cross-reactive immune responses against both *C. albicans* and *C. auris*. Other vaccine candidates, including PEV7 and β-glucan-binding protein vaccines, have

demonstrated efficacy in animal models [205,216,217]. Microbiome modulation through probiotics or selective bacterial strain transplantation helps maintain gut microbiota equilibrium, reducing *Candida* colonization [169]. Novel preventive options for catheter-related infections include antifungal lock therapies and passive immunization with monoclonal antibodies [218]. When integrated with AI-driven risk stratification, these measures enable precision prophylaxis.

Risk factor mitigation remains integral to prevention: priority is given to enhancing infection control protocols to prevent cross-transmission of *C. auris*. In intensive care settings, minimizing broad-spectrum antibiotic use indirectly prevents candidemia by preserving microbial homeostasis. Genetic screening identifies patients who may benefit from targeted prophylaxis. For example, individuals with Dectin-1 mutations (associated with impaired *Candida* recognition) could be candidates for primary prophylaxis during ICU hospitalization [219].

5.3 Nutritional immunomodulation

Nutritional interventions influence *Candida* infection progression through multifactorial mechanisms. Precision regulation of key micronutrients is particularly critical: controlled supplementation of zinc [220], selenium [221,222], and vitamin D [223,224] enhances immune function, whereas iron overload may promote fungal proliferation [202,225]. Host defense mechanisms, such as calprotectin-mediated sequestration, restrict pathogens' access to essential trace elements, forming a "nutritional immunity" barrier [226]. Glycemic control is equally pivotal, as hyperglycemia not only impairs neutrophil activity but also directly stimulates *Candida* biofilm formation [13].

Specialized nutritional formulations enriched with arginine, glutamine, and omega-3 fatty acids exert protective effects by preserving intestinal barrier integrity and modulating immune responses [227-229]. Additionally, microbial metabolites like short-chain fatty acids (SCFAs) inhibit *Candida* overgrowth through gut microbiome equilibrium maintenance [230].

Future nutritional strategies will prioritize personalization, tailoring macronutrient/micronutrient ratios to individual patient profiles while integrating functional foods and probiotics. These low-risk, high-synergy adjuvant therapies are poised to become integral components of comprehensive candidemia treatment.

5.4 Synergistic therapeutic strategies

Natural compound-antifungal drug synergies are gaining scientific traction. Curcumin reverses azole resistance, restoring susceptibility in fluconazole-resistant strains when co-administered [231]. Phytochemicals like garlic extracts and cinnamaldehyde enhance drug efficacy by disrupting biofilms [232,233]. Berberine, an active compound from *Coptis chinensis*, potentiates fluconazole by inhibiting fungal efflux pumps [234]. Such combinations improve therapeutic outcomes while minimizing dosage and toxicity. Despite their favorable safety profiles, challenges like low bioavailability necessitate advanced delivery systems (e.g., nanoformulations) to enhance plasma concentrations. Emerging approaches under investigation include intravenous curcumin nanoemulsions paired with echinocandins

and nebulized essential oil adjuncts. Caution remains warranted regarding potential drug interactions (e.g., hepatic enzyme induction), mandating further research to optimize safety-efficacy profiles.

5.5 Key challenges

Despite substantial progress across diagnostic, preventive, and therapeutic domains, several critical barriers continue to hinder the full clinical translation of these innovations.

AI-assisted diagnostic systems for candidemia still face limited clinical validation and lack harmonized standardization, which constrains their implementation. At the same time, the emergence of multidrug-resistant *Candida* species, particularly *C. auris*, continues to outpace the development of antifungal agents with novel mechanisms of action, leaving clinicians with a narrow therapeutic arsenal. Compounding these issues, the high cost and restricted availability of next-generation antifungals and vaccines significantly limit access in resource-limited environments. Moreover, although host-directed and nutritional immunotherapies show promising potential, current clinical evidence remains preliminary, underscoring the need for comprehensive mechanistic and translational studies to confirm their safety and efficacy.

Overcoming these challenges will require close interdisciplinary collaboration. Through integrative innovation and rigorous clinical validation, the field can progress toward a future defined by precision prevention, early diagnosis, and personalized therapy for candidemia.

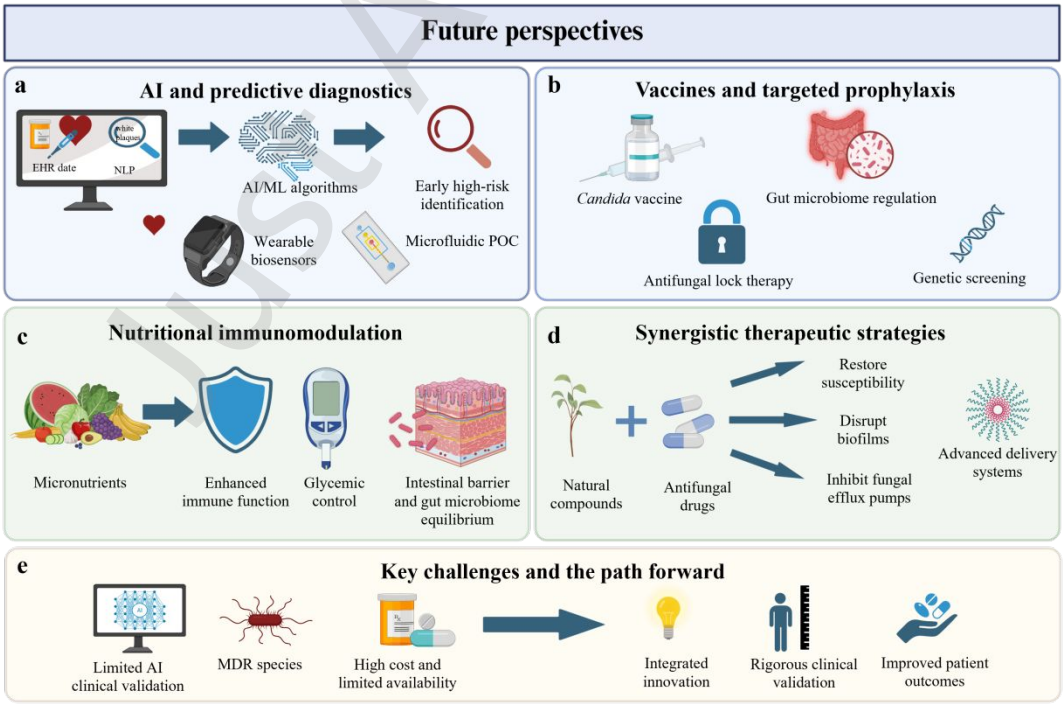

Fig. 5 Future perspectives in candidiasis management. a. AI and next-generation detection

technologies facilitate early warning of invasive candidiasis, enabling proactive screening and risk stratification of high-risk patients through machine learning analysis of clinical indicators and continuous biomarker monitoring. b. Vaccines, targeted prophylaxis, and AI-driven risk stratification together form a precision intervention strategy aimed at reducing the incidence of invasive candidiasis, including immunization for high-risk patients, microbiome modulation, and comprehensive risk factor management. c. Nutritional immunomodulation regulates host immunity and suppresses *Candida* overgrowth through precise supplementation of key micronutrients, enhanced blood glucose control, and the addition of intestinal barrier-protecting components, offering personalized adjuvant therapy for the management of candidemia. d. Based on the synergistic effects of natural compounds and antifungal drugs, novel combination therapies provide enhanced efficacy and reduced toxicity for the treatment of candidemia through mechanisms such as reversing drug resistance, disrupting biofilms, and inhibiting efflux pumps. e. The clinical translation of diagnostics and therapeutics for candidemia faces numerous challenges, including insufficient validation of AI diagnostic systems, rapid evolution of drug-resistant strains, limited accessibility to innovative drugs, and inadequate clinical evidence for novel therapies. Addressing these issues requires interdisciplinary collaboration and integrative innovation. Created in https://BioRender.com

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Conflicts of Interest

The authors declare no competing interests.

Author contributions

Haojie Dong: literature retrieval and selection, manuscript writing and formatting.
Minghui Song: Figure preparation, manuscript integration and revision.
Jingfang Sun, Xiaoyi Luan: Manuscript writing and revision.
Ming Zhang, Yeji Wang, Yuemei Dong, Dongmei Shi, Lintao Sai: Manuscript revision.
Wenqiang Chang, Ying Li: Supervision and conceptualization of the review framework, manuscript revision.

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