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Candidiasis

Emerging Clinical Challenges and Novel Therapeutic Approaches

Edited by Mehdi Razzaghi-Abyaneh and Masoomeh Shams-Ghahfarokhi



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Infectious Diseases

Volume 43

Aims and Scope of the Series

This series will provide a comprehensive overview of recent research trends in various Infectious Diseases (as per the most recent Baltimore classification). Topics will include general overviews of infections, immunopathology, diagnosis, treatment, epidemiology, etiology, and current clinical recommendations for managing infectious diseases. Ongoing issues, recent advances, and future diagnostic approaches and therapeutic strategies will also be discussed. This book series will focus on various aspects and properties of infectious diseases whose deep understanding is essential for safeguarding the human race from losing resources and economies due to pathogens.

Meet the Series Editor



Dr. Alfonso J. Rodriguez-Morales received his MD from Universidad Central de Venezuela in Caracas and his MSc in Protozoology/Parasitology from Universidad de Los Andes in Trujillo, Venezuela. He received his Diploma in Tropical Medicine & Hygiene (DTM&H) from Universidad Peruana Cayetano Heredia, Lima, Peru, and the University of Alabama at Birmingham, Alabama, USA. He also holds a DipEd. Dr. Rodriguez-Morales is a fellow of the Royal Society for Tropical Medicine & Hygiene (FRSTMH), London, United Kingdom; of the Faculty of Travel Medicine (FFTM) of the Royal College of Physicians and Surgeons of Glasgow (RCPSG), Glasgow, Scotland, United Kingdom; of the American College of Epidemiology (FACE), USA; and the International Society for Antimicrobial Chemotherapy (FISAC). He has a HonDSc from Universidad Privada Franz Tamayo (UniFranz), Cochabamba, Bolivia. He is the President of the Latin American Society for Travel Medicine (SLAMVI) (2023-2025) and the Past President of the Colombian Infectious Diseases Association (2021–2023). He is a member of the Council (2020-2026) of the International Society for Infectious Diseases (ISID). He is a senior researcher at Colciencias (2015–2027) and a professor at the Fundación Universitaria Autónoma de las Américas in Pereira, Risaralda, Colombia, as well as at the Universidad Científica del Sur (UCSUR) in Lima, Peru. He is a visiting professor at multiple national and international universities.

Meet the Volume Editors



Professor Mehdi Razzaghi-Abyaneh was born in Tehran, Iran. He earned his Ph.D. in Medical Mycology from Tarbiat Modares University in Tehran, Iran. Dr. Razzaghi-Abyaneh pursued a 12-month sabbatical on the identification of antifungal compounds from bioactive plants at the Graduate School of Agriculture, Tokyo University, in the laboratory of Applied Biological Chemistry from 2006 to 2007. He is currently a full professor and eminent research scientist at the Pasteur Institute of Iran (Tehran, Iran), where he has been working on mycotoxins and mycotoxigenic fungi, as well as antifungal nanomaterials and biologically active antifungals of plant, fungal, and bacterial origin for more than 25 years. He has supervised and served as advisor for several Ph.D. and MSc theses. Dr. Razzaghi-Abyaneh has published over 200 papers in peer-reviewed international journals, 15 books, and numerous book chapters. His research is focused on the chemical basis of plant–fungal interactions and on determining the mode of action of antifungal bioactive compounds of natural origin, both small and macromolecular, at the cellular and molecular levels.



Professor Masoomeh Shams-Ghahfarokhi has been a faculty member at Tarbiat Modares University in Tehran, Iran, for approximately 25 years. After graduating in Medical Mycology in 2000, Dr. Shams-Ghahfarokhi passed a training course as a JSPS fellow in Japan during 2005-2007. Her investigation focuses on the identification and isolation of antifungal compounds from natural sources (including plants and organisms) and on their molecular mechanisms underlying the activity of pathogenic fungi. She is active in evaluating the inhibitory effects of bio-nanomaterials and anti-scaling membranes for the selective treatment of fungal infections, and in examining their mechanisms of action at the cellular and molecular levels. She is also investigating the identification of pathogenic fungi and their genetic diversity using molecular techniques such as Sequencing, real-time PCR, and multiplex PCR. Dr. Shams-Ghahfarokhi has over two decades of teaching and research experience, and she has supervised and advised numerous M. Sc. and Ph.D. theses.

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Preface

Candidiasis remains one of the most common and challenging fungal infections affecting humans, ranging from superficial mucocutaneous involvement to life-threatening invasive disease. Over recent decades, the global burden of candidiasis has increased significantly, driven by factors such as expanding immunocompromised populations, widespread use of broad-spectrum antibiotics, invasive medical procedures, and prolonged hospitalizations. Alongside this rise, the epidemiology of *Candida* infections has evolved, with the emergence of non-*albicans Candida* species and increasing antifungal resistance posing serious threats to effective clinical management.

The clinical landscape of candidiasis is further complicated by diagnostic limitations, delayed detection, host-pathogen interactions, and the complex biology of *Candida* species, including biofilm formation and phenotype switching. These challenges have exposed critical gaps in current therapeutic strategies and underscored the urgent need for innovative approaches in prevention, diagnosis, and treatment.

Candidiasis – Emerging Clinical Challenges and Novel Therapeutic Approaches brings together contributions from leading researchers and clinicians to provide a comprehensive and up-to-date overview of this evolving field. The book explores contemporary issues in the epidemiology, pathogenesis, and clinical manifestations of candidiasis, while critically examining current antifungal therapies and resistance mechanisms. Importantly, it highlights emerging diagnostic tools, novel antifungal agents, immunotherapeutic strategies, and alternative treatment modalities that hold promise for improving patient outcomes.

The book, comprising 10 chapters distributed in 4 sections, is intended for clinicians, microbiologists, infectious disease specialists, researchers, and graduate students seeking an in-depth understanding of the current challenges and future directions in the management of candidiasis. By integrating clinical perspectives with cutting-edge research, this book aims to support informed decision-making, stimulate further investigation, and ultimately contribute to more effective control of *Candida* infections worldwide.

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Section 1

Emerging Candidiasis and Antifungal Resistance

Chapter 1

Epidemiology and Management of Antifungal-Resistant *Candida* Bloodstream Infections in Healthcare Settings

Omar Sayyouh

Abstract

Antifungal-resistant *Candida* bloodstream infections are a growing global health concern, driven by shifts in species distribution, increasing resistance to azoles and echinocandins, and the emergence of multidrug-resistant pathogens such as *Candida auris*. These infections are associated with high morbidity, mortality, and healthcare costs, particularly in critically ill and immunocompromised patients. This review synthesizes recent literature on the epidemiology, resistance mechanisms, clinical management, and prevention of antifungal-resistant *Candida* bloodstream infections. We highlight global and regional epidemiological trends, the molecular basis of antifungal resistance, and current therapeutic strategies, including the role of novel agents such as rezafungin, ibrexafungerp, and fosmanogepix. The review underscores the importance of rapid diagnostics, antifungal stewardship, and rigorous infection prevention measures, especially in high-prevalence settings. We also outline future directions, including the integration of genomic surveillance, One Health approaches, and innovative therapeutic strategies to address the growing threat of resistant *Candida* infections in healthcare systems worldwide.

Keywords: *Candida* bloodstream infection, antifungal resistance, *Candida auris*, echinocandin resistance, infection prevention, antifungal stewardship

1. Introduction

Candidiasis is an infection caused by the excessive growth of pathogenic yeasts belonging to the genus *Candida*. It represents the most prevalent opportunistic fungal infection worldwide, affecting human health, with over one billion cases reported annually. Under normal conditions, *Candida* species reside harmlessly on mucosal surfaces such as the oral cavity, gastrointestinal tract, and vaginal mucosa; however, disruption of this balance can lead to infection. Individuals who are immunocompromised, elderly, or receiving palliative care are particularly vulnerable to *Candida* infections [1]. Oral candidiasis can manifest as localized pain and discomfort, increased oral dryness, altered taste perception, and food aversion, often

resulting in secondary complications [2, 3]. If left untreated, candidemia poses a serious threat, as delayed management is strongly associated with high mortality rates, particularly when it progresses to invasive fungal disease (IFD) [4].

Candida bloodstream infections (BSIs) continue to pose a serious threat to hospitalized patients, especially those who are immunocompromised or critically ill. Globally, the burden is substantial, with approximately 400,000 cases of *Candida* spp. BSIs occur annually, many resulting in mortality rates exceeding 40% [1]. Notably, recent estimates suggest up to 1.56 million cases of invasive candidiasis – including BSIs – and nearly 995,000 associated deaths per year [5].

Candida species rank among the most frequent agents of nosocomial infections, accounting for the fourth most common cause of BSIs in the United States and the seventh in Europe, with reported incidence rates ranging from 0.3 to 5 cases per 1,000 hospital admissions worldwide [6]. The shifting epidemiology – with non-*albicans* species such as *Candida glabrata*, *Candida tropicalis*, and *Candida parapsilosis* increasingly implicated – reflects growing concern over antifungal resistance driven by prolonged drug exposure and limited therapeutic options. In parallel, the global emergence of *Candida auris* has intensified alarm among public health and clinical communities. Since its initial identification in 2009, *Candida auris* has spread rapidly through healthcare settings worldwide and is now recognized for its multidrug resistance, difficulty of identification, environmental persistence, and propensity to cause outbreaks [7]. Systematic review and meta-analysis data report pooled crude mortality rates for *Candida auris* BSIs at around 45%, underscoring the high clinical impact of this pathogen [8].

Moreover, the active surveillance by the Centers for Disease Control and Prevention (CDC) during the period 2016–2021 indicates that approximately one in three patients with candidemia died during hospitalization, with the incidence averaging 7 cases per 100,000 persons per year across US surveillance sites [1].

Collectively, the convergence of a high case burden, evolving species epidemiology, rising antifungal resistance, and the emergence of *Candida auris* as a formidable nosocomial threat necessitate a comprehensive and updated review.

BSIs are defined as the presence of microorganisms such as viruses, parasites, bacteria, or fungi in the normally sterile bloodstream. These pathogens may occur in a wide range of combinations, leading to classifications such as monomicrobial infections (caused by a single pathogen) or polymicrobial infections (caused by multiple pathogens), among others. Collectively, BSIs represent a significant global health concern [6].

This article seeks to integrate the most recent global and regional surveillance data, deeper insights into resistance mechanisms, diagnostic and therapeutic challenges, infection control strategies, and future directions to guide clinicians and healthcare systems in managing antifungal-resistant *Candida* BSIs effectively.

2. Epidemiology

Invasive candidemia continues to be a major healthcare burden. *Candida*-caused BSIs account for more than 90% of fungal BSIs.

A comprehensive study estimates that approximately 1.56 million cases of *Candida* BSIs (including invasive candidiasis) occur globally each year, resulting in nearly 995,000 deaths – reflecting a remarkably high mortality rate of ~ 63.6% [2].

In the United States alone, candidemia is responsible for an estimated 22,000 cases annually, making it the second most common cause of healthcare-associated BSIs [3].

Surveillance over time has revealed shifting species dynamics and geographic variation in disease burden. A recent ten-year retrospective study from South Korea (2014–2023) highlights evolving trends: while *Candida albicans* remains the most common isolate (38%), non-albicans species collectively represent a growing share – with *Candida glabrata* (21.1%), *Candida parapsilosis* (20.5%), and *Candida tropicalis* (13.3%) prominent – and fluconazole non-susceptibility has increased post-2021 [9].

Similarly, longitudinal data from 2020 to 2024 show that *Candida albicans* declined from 28.3% of BSI cases in 2020 to 21.0% in 2024, while *Candida parapsilosis* rose dramatically – accounting for up to 61.3% of infections in 2022 [2].

Several studies, including recent ones, have documented a rising proportion of *Candida* BSIs caused by non-albicans species. For instance, Yang et al. conducted a five-year study on *Candida* BSI epidemiology and reported that non-albicans species collectively accounted for 62.8% of cases, compared with 37.2% for *Candida albicans*. The species distribution in that study was as follows: *Candida glabrata* (7.4%), *Candida parapsilosis* (19.8%), *Candida tropicalis* (14.9%), *Candida krusei* (4.1%), *Candida sake* (5%), *Candida guilliermondii* (5.8%), *Candida haemulonii* (0.8%), and *Candida theae*, *Candida intermedia*, and *Candida lusitaniae* (1.7% each). Similarly, hospital-based data covering 2010–2014 demonstrated a predominance of non-albicans species, with *Candida glabrata* (9%), *Candida parapsilosis* (23%), *Candida tropicalis* (10%), *Candida krusei* (0.8%), *Candida guilliermondii* (2%), and smaller contributions from *Candida utilis*, *Candida pelliculosa*, and *Candida lusitaniae* (0.4% each). During this period, the proportion of *Candida albicans* candidemia fell significantly from 68% to 48% ($p = 0.040$), while *Candida parapsilosis* increased from 8% to 30% ($p = 0.036$) [6].

Comparable findings were observed in a retrospective cohort study spanning 2006 to 2017, where non-albicans species were predominant, comprising *Candida glabrata* (30.1%), *Candida parapsilosis* (19.4%), *Candida tropicalis* (17.9%), *Candida krusei* (3.1%), *Candida famata* (2.3%), and rarer isolates such as *Trichosporon asahii*, *Candida dubliniensis*, *Candida kefyr*, and *Candida lusitaniae* (0.5% each), while only 23.5% of cases were attributed to *Candida albicans.* Furthermore, a four-year comparative analysis of species distribution before and after the introduction of echinocandins and fluconazole showed that the proportion of *Candida albicans* BSIs remained nearly unchanged (61% to 60%), whereas *Candida glabrata* increased from 0% to 16% in the post-antifungal era. These findings collectively highlight a global trend toward an increasing burden of non-albicans *Candida* species in BSIs [6].

A growing body of evidence identifies *Candida auris* as a globally emerging threat. One analysis outlines hundreds of *Candida auris* cases in six countries – including outbreaks in South Africa and Kenya – with widespread resistance to fluconazole reported [10]. Another recent review emphasizes the rapid international spread of *Candida auris* and its significant morbidity and mortality [11].

Genomic surveillance in the United Kingdom reveals multiple introductions of drug-resistant *Candida auris* clades and demonstrates both inter- and intra-hospital transmission dynamics, underscoring the pathogen's high transmissibility in healthcare settings. The spread of *Candida auris* in healthcare settings has been strongly linked to contact with contaminated environmental surfaces, fomites, and shared medical equipment, such as reusable temperature probes, portable

ventilators, and pulse oximeters. In addition, direct person-to-person transmission has also been documented. Patient transfers between hospitals for rehabilitation or further care are considered an important factor driving the regional dissemination of *Candida auris* and its propagation across interconnected healthcare networks [12].

Concerns are rising about less common *Candida* species. A systematic review covering 2001–2023 documented 45 cases of invasive infections caused by rare species – including *Candida haemulonii*, *Candida kefyr*, and *Candida duobushaemulonii* – highlighting their increasing detection in clinical contexts [13].

This epidemiological overview underscores the dynamic landscape of candidemia globally – marked by rising incidence, evolving species distribution, and emergent, hard-to-treat pathogens. It sets a compelling foundation for exploring resistance mechanisms and targeted management strategies ahead.

3. Risk factors

Candida BSIs represent a major complication in critically ill pediatric patients, particularly those undergoing congenital heart surgery. In this population, several patient-related and surgical factors significantly increase susceptibility to candidemia. Low birth weight (<2,500 g) and high surgical complexity, as reflected by RACHS-1 scores of 4 or greater, were independently associated with higher infection risk. These findings emphasize that underlying fragility and complex operative procedures predispose children to invasive fungal infections, often compounding their already vulnerable status in intensive care [9].

Prolonged exposure to invasive interventions emerged as another critical determinant. Extended central venous catheterization, mechanical ventilation exceeding 10 days, and the use of total parenteral nutrition were strongly linked to the onset of candidemia. Likewise, cumulative antibiotic exposure for seven days or more disrupted the host microbiota, while delayed sternal closure of ≥2 days created additional risk for invasive disease. Other associated factors included extracorporeal membrane oxygenation, peritoneal dialysis, and the presence of prior bacteremia or *Candida* colonization. Together, these reflect how necessary but invasive lifesaving measures can inadvertently create opportunities for *Candida* species to invade the bloodstream [14] (**Figure 1**).

While *Candida albicans* remains a leading cause of BSIs, non-albicans species, particularly *Candida parapsilosis*, are increasingly identified in pediatric cardiac intensive care units. The predominance of *Candida parapsilosis* is especially concerning due to its strong association with catheter-related infections, reinforcing the importance of central venous catheters as a major reservoir and portal of entry. The burden of *Candida* BSIs in this setting is compounded by high mortality rates, often exceeding 50%, underscoring the urgent need for targeted prevention strategies, meticulous catheter care, and antimicrobial stewardship programs (ASPs) tailored to pediatric surgical patients [15].

The challenge is further amplified by the global emergence and spread of *Candida auris*, a multidrug-resistant species with a strong predilection for nosocomial transmission. Unlike other *Candida* species, *Candida auris* has demonstrated a remarkable ability to persist on contaminated environmental surfaces, medical equipment such as reusable probes and ventilators, and to spread directly between patients. Moreover, the transfer of patients between hospitals for rehabilitation or

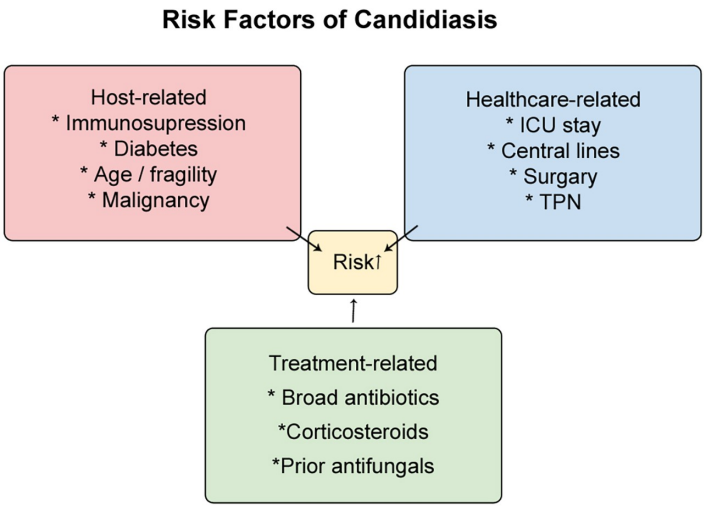


Figure 1.
Risk factors for Candida *infections.*

further treatment has been identified as a key driver of regional and inter-hospital dissemination. These unique epidemiological features highlight the necessity of combining patient-level risk reduction strategies with robust infection prevention and control practices, including environmental decontamination, screening, and coordinated surveillance across healthcare networks to contain the spread of this formidable pathogen [16, 17].

4. Antifungal resistance mechanisms

Antifungal resistance (**Figure 2**) is a growing global health challenge that complicates the treatment of invasive fungal infections. The limited number of antifungal drug classes – azoles, echinocandins, and polyenes – means that the development of resistance has severe clinical consequences, particularly in vulnerable populations such as critically ill patients. Unlike bacteria, fungi share many biological pathways with human hosts, making drug discovery difficult and amplifying the impact of resistance. The problem is exemplified by *Candida auris*, an emerging multidrug-resistant pathogen with a remarkable capacity for survival and spread in healthcare environments.

4.1 Azole resistance

Azoles are widely used because of their oral availability and broad activity. They inhibit the enzyme lanosterol 14 α -demethylase (Erg11p), disrupting ergosterol biosynthesis and compromising fungal cell membrane stability. Resistance arises through multiple mechanisms. Mutations in *ERG11*, such as Y132F and K143R, reduce drug-binding affinity, while overexpression of *ERG11* increases enzyme abundance, reducing the inhibitory effect. Equally important is the role of efflux pumps. Transporters from the ATP-binding cassette (ABC) family (*CDR1, CDR2*) and the major facilitator superfamily (MFS; *MDR1*) actively expel drugs from the

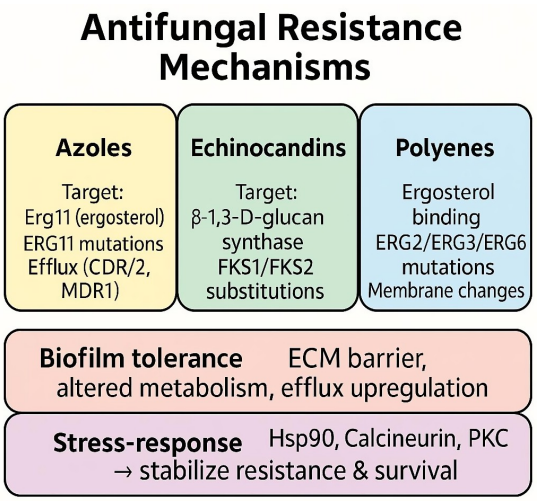


Figure 2.
Antifungal resistance mechanisms.

cell. These pumps are often upregulated by mutations in transcriptional regulators, such as *TAC1* and *UPC2*, amplifying azole tolerance[18].

In *Candida glabrata*, rapid microevolution involving simultaneous mutations in multiple resistance-associated genes has been reported, reflecting its adaptability under antifungal pressure. Whole-genome studies of *Candida auris* further link broad-spectrum resistance to mutations in *ERG11, FKS1,* and *UPC2*, along with enhanced efflux activity. These mechanisms often converge, producing strains resistant not only to fluconazole but also to newer triazoles, thereby limiting treatment options [19].

4.2 Echinocandin resistance

Echinocandins, including caspofungin, micafungin, and anidulafungin, are considered first-line therapy for invasive candidiasis. They inhibit β-1,3-D-glucan synthase, encoded by *FKS1* and *FKS2*, weakening the fungal cell wall. Resistance typically arises through amino acid substitutions in conserved "hotspot" regions of these genes. For instance, mutations such as S629P and truncating variants like W1497stop have been described, reducing drug binding and leading to clinical failure [19].

Resistance is especially problematic in *Candida glabrata*, where echinocandin resistance rates can reach 13%, compared with much lower frequencies in *Candida albicans*. Notably, some *FKS* mutations not only confer echinocandin resistance but may also contribute to cross-resistance with azoles, compounding treatment challenges. In *Candida auris*, hotspot mutations in *FKS1* have been increasingly reported, further limiting therapeutic options [20].

4.3 Polyene resistance

Polyenes, most notably amphotericin B, exert fungicidal activity by binding to ergosterol and creating pores in fungal membranes. Resistance is less common but

clinically important. Mechanisms include alterations in ergosterol biosynthesis through mutations in *ERG2, ERG3,* or *ERG6*, which reduce the available drug-binding sites. In some isolates, changes in membrane lipid composition or enhanced oxidative stress defenses provide additional survival advantages. Resistance to amphotericin B has been described in *Candida auris* and other non-*albicans Candida* species, raising concern because amphotericin often serves as a last-line therapy when resistance to other drug classes is present [21].

4.4 Biofilm-mediated resistance

Beyond genetic mutations, biofilm formation provides a major structural and phenotypic defense mechanism. *Candida* biofilms are commonly formed on intravascular catheters, prosthetic devices, and other medical implants. Encased in an extracellular matrix composed of β-glucans, proteins, and lipids, biofilm-embedded cells are shielded from antifungal penetration. Furthermore, cells within biofilms adopt altered metabolic states, display distinct gene expression profiles, and frequently upregulate efflux pumps. These adaptations render biofilm-associated *Candida* cells up to 1,000 times more tolerant to antifungal agents than planktonic cells. Biofilm-mediated resistance affects all major antifungal classes, including azoles, echinocandins, and polyenes, making eradication difficult without device removal [22, 23].

4.5 Stress response pathways

Adaptive resistance is also mediated by stress response pathways. Heat shock protein 90 (Hsp90), calcineurin, and protein kinase C pathways stabilize mutated proteins, maintain cell wall integrity, and promote survival in the face of antifungal stress. For example, Hsp90 stabilizes glucan synthase mutants, allowing echinocandin-resistant *Candida albicans* to persist despite therapy. Experimental inhibition of Hsp90 has been shown to restore antifungal susceptibility, highlighting stress response regulators as potential therapeutic targets [24].

4.6 *Candida auris*: A case study in multidrug resistance

The emergence of *Candida auris* exemplifies the convergence of multiple resistance mechanisms in a single species. Since its discovery, *Candida auris* has demonstrated resistance to fluconazole in the majority of isolates, variable susceptibility to echinocandins, and occasional resistance to amphotericin B. Mechanistically, resistance is driven by point mutations in *ERG11* and *FKS1*, overactive efflux pumps, and alterations in transcriptional regulators. Stress response pathways further enhance its survival under drug pressure. Recent work suggests that signaling pathway changes may augment both antifungal resistance and environmental persistence, explaining why *Candida auris* is so difficult to eradicate from healthcare environments. Its ability to withstand multiple drug classes simultaneously makes it a formidable healthcare-associated pathogen and a sentinel of the antifungal resistance crisis [25, 26].

5. Global distribution of multidrug-resistant *Candida* spp

The global rise in antifungal resistance among *Candida* species has become a major public health challenge, with clear geographic variability in distribution patterns. Over the past two decades, *Candida glabrata* has emerged as one of the most concerning pathogens due to its reduced susceptibility to both azoles and echinocandins [27]. Data from the ARTEMIS surveillance program revealed that the proportion of *Candida glabrata* causing invasive candidiasis increased from 18% in the 1990s to about 25% by the mid-2000s, with fluconazole resistance rates rising from 9% to 14% in the same period. More recent global studies, covering isolates from over 30 countries, show fluconazole resistance in approximately 12% of *Candida glabrata* and *Candida tropicalis*, highlighting their widespread resistance patterns across Europe, Asia, and the United States [28].

In Southern Europe, population-based studies (e.g., the CANDIPOP study) have documented a significant increase in *Candida glabrata* candidemia, rising from 8% in 2002–2003 to over 13% by 2010–2011. North America has reported parallel trends, with notable rises in echinocandin resistance among *Candida glabrata*, reaching 7%–10% in some institutions. By contrast, echinocandin resistance remains lower in Europe (<1%), underscoring differences in regional antifungal use and stewardship practices [29].

Other *Candida* species are also implicated in global resistance patterns. *Candida krusei* is intrinsically resistant to fluconazole and is increasingly detected in both Europe and Latin America. *Candida tropicalis*, particularly prevalent in Asia-Pacific countries, shows alarming fluconazole resistance exceeding 10% in multicenter surveys. Of special concern is the emergence of *Candida auris*, a multidrug-resistant yeast first identified in Asia but now reported on every continent except Antarctica. It has caused hospital outbreaks in India, South Africa, the Middle East, South America, and, more recently, North America and Europe, with mortality rates often exceeding 40%. The ability of *Candida auris* to resist multiple antifungal classes – including azoles, echinocandins, and amphotericin B – makes it a uniquely global threat[30–32].

These trends reflect both the selective pressure of antifungal overuse in medicine and agriculture, and the clonal spread of resistant strains across borders. Importantly, regional variations in drug availability, prescribing patterns, and infection control practices continue to shape the global epidemiology of resistant *Candida* species. Collectively, the data underscore that antifungal resistance is no longer localized but a truly global phenomenon requiring coordinated surveillance and stewardship efforts.

6. Clinical management

Effective management of antifungal-resistant *Candida* BSIs hinges on the rapid initiation of appropriate therapy, timely source control, and close monitoring, all guided by the latest clinical evidence and evolving antifungal options (**Figure 3**). Current consensus across recent surveillance and guideline data strongly supports echinocandins as the first-line therapy for candidemia, especially due to the rising resistance to fluconazole among non-albicans species and the notable mortality associated with delayed treatment [33, 34]. Global guidelines similarly recommend

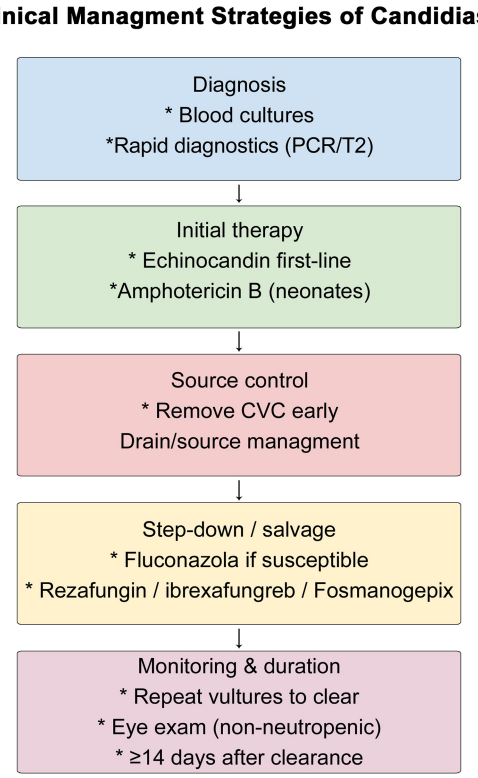


Figure 3.
Clinical management of candidiasis.

echinocandins – including newer agents like rezafungin – for most forms of invasive candidiasis, citing their efficacy, safety profile, and convenience [35].

In cases of suspected or confirmed *Candida auris* infection, initial treatment also relies on an echinocandin, as endorsed by the CDC's most recent clinical recommendations. Neonates and infants younger than two months are treated with amphotericin B deoxycholate when echinocandins are less appropriate [36]. Resistance to echinocandins, and even pan-resistance, has been reported; in these scenarios, treatment may require liposomal amphotericin B, off-label combinations, or investigational agents obtained through expanded access protocols [37].

Recent years have also seen the emergence of novel antifungal agents that offer promising options for resistant infections. Rezafungin, a long-acting echinocandin approved by the FDA in 2023, provides broad-spectrum activity, including activity against resistant *Candida* species, with simplified dosing regimens [38, 39]. Ibrexafungerp, an oral glucan synthase inhibitor, is advancing through phase II and III trials as a potential step-down or salvage therapy for resistant candidiasis – including infections caused by *Candida auris* – highlighting its clinical utility in cases where intravenous administration may be challenging [40].

Regardless of antifungal choice, source control remains a cornerstone of management. Early removal of central venous catheters, when safe and feasible, has been associated with improved outcomes and faster clearance of candidemia [41]. Regular monitoring – through repeat blood cultures every 24 to 48 hours until

clearance and dilated ophthalmologic exams to rule out endophthalmitis in non-neutropenic patients – is essential for guiding treatment duration and ensuring adequacy of response. Typically, therapy is continued for at least 14 days after documented clearance of candidemia and resolution of clinical signs, a timeframe that holds even for neutropenic patients following immune recovery [42].

7. Infection prevention and control

Preventing antifungal-resistant *Candida* BSIs requires a comprehensive strategy addressing both patient-level vulnerabilities and facility-wide infection control practices. *Candida* BSIs rank among the third to fourth most common healthcare-associated BSIs, with the highest incidence observed in intensive care units [43]. A significant proportion of these infections is linked to central venous catheters, underscoring the importance of strict adherence to insertion and maintenance bundles. Maximal sterile barrier precautions, chlorhexidine skin antisepsis, and daily evaluation of catheter necessity have consistently been shown to reduce candidemia rates. Standard of care includes prompt removal of intravascular catheters in patients with candidemia, particularly in non-neutropenic individuals, as catheter retention is strongly associated with persistent infection and treatment failure[44].

Beyond catheter management, appropriate antifungal use is central to prevention. Widespread fluconazole exposure has driven selective pressure favoring inherently less susceptible species, such as *Candida glabrata* and *Candida krusei*. Thus, antifungal stewardship (AFS) – minimizing unnecessary prophylaxis, tailoring therapy to species identification and susceptibility testing, and optimizing dosing regimens – remains essential. Risk stratification is also important; bone marrow transplant recipients, neutropenic patients, and those undergoing abdominal surgery or hyperalimentation are at particularly high risk and may require targeted prophylaxis depending on local epidemiology and resistance patterns [42, 45]. In under-resourced settings, active risk assessment, early prophylaxis in high-risk patients, and HEPA filtration in hematology and transplant units have been shown to reduce IFD.

Environmental persistence of *Candida auris* poses an added challenge to infection control. Unlike most *Candida* species, *Candida auris* can survive for weeks on hospital surfaces and shows resistance to commonly used disinfectants. The CDC and WHO recommend daily cleaning and terminal disinfection of patient rooms with products from EPA List P, including chlorine- or hydrogen peroxide-based agents. Additional measures include single-room isolation where feasible, contact precautions, and the use of dedicated medical equipment. Active surveillance cultures in high-risk units can aid in the early detection of colonized patients and facilitate timely containment [46, 47].

When outbreaks occur, molecular typing techniques, such as whole-genome sequencing, are essential to establish clonal relatedness, guide interventions, and assess the effectiveness of control strategies. Evidence shows that the transmission of *Candida*, particularly *Candida parapsilosis* and *Candida auris*, may occur via contaminated equipment or hands of healthcare personnel, making rigorous hand hygiene and staff education cornerstones of prevention. Outbreak management frequently requires coordination among infection prevention specialists, microbiology laboratories, and public health authorities to implement containment

measures and interrupt transmission chains. Ultimately, the prevention of antifungal-resistant *Candida* BSIs depends on the synergy between optimized clinical practices, antimicrobial stewardship, and robust infection prevention and control systems [12, 48].

8. Antifungal stewardship

AFS is critical to slowing the emergence of resistance and preserving the effectiveness of available drugs. Core components include optimizing the choice, dose, and duration of antifungal therapy, as well as avoiding unnecessary prophylaxis in low-risk patients. Early initiation of appropriate therapy improves outcomes, but equally important is de-escalation based on susceptibility testing and clinical response [49]. Multidisciplinary AFS programs – integrating infectious disease specialists, pharmacists, microbiologists, and infection preventionists – have been shown to reduce inappropriate antifungal use and healthcare costs without compromising patient outcomes [32]. Key strategies include implementing rapid diagnostic tools, such as PCR-based assays or T2Candida panels, to guide targeted therapy sooner, and developing local antifungal guidelines informed by hospital-specific epidemiology [50].

Evidence from ASPs further underscores the benefits of stewardship in preventing fungal infections. A retrospective interrupted time-series study from Japan demonstrated that the implementation of a multidisciplinary ASP significantly reduced the incidence of hospital-acquired candidemia. The program focused on reducing unnecessary broad-spectrum antibiotic use, particularly carbapenems, through weekly case conferences, post-prescription review, and specialist consultations. Following the intervention, carbapenem days-of-therapy (DOTs) declined from a median of 28.4 to 10.0 per 1,000 patient-days, paralleled by a significant reduction in candidemia incidence from 0.17 to 0.08 per 1,000 patient-days. These findings support the concept that stewardship activities targeting antibacterial use can indirectly reduce fungal disease by minimizing ecological pressure that favors *Candida* overgrowth [51].

The clinical benefits of AFS extend beyond infection control. Candidemia is associated with a 25%–40% mortality rate despite treatment, with delayed therapy further increasing fatality risks. By embedding stewardship protocols within daily clinical workflows, clinicians can ensure antifungal prescriptions are reviewed in real time alongside microbiology results and patient risk factors. Leveraging hospital information systems to generate alerts for inappropriate dosing, prolonged therapy, or unnecessary use of broad-spectrum antifungals enables timely interventions. Moreover, the integration of stewardship with infection prevention efforts is especially crucial in high-burden settings where multidrug-resistant *Candida auris* is prevalent. In such cases, stewardship and infection prevention teams should jointly develop action plans linking prescribing practices directly to surveillance data and outbreak response [52].

Finally, the economic implications of stewardship are noteworthy. Candidemia is associated with prolonged hospitalization and an average cost ranging between $48,000 and $150,000 per patient. By reducing inappropriate antifungal and antibiotic use, AFS programs can substantially lower healthcare costs while improving patient safety. Importantly, the sustainability of these benefits requires

continuous education of prescribers, integration of stewardship with electronic prescribing systems, and ongoing monitoring of outcomes. Together, these measures ensure that AFS remains a cornerstone of both clinical management and infection control strategies [53].

9. Future directions

The rising incidence of antifungal-resistant *Candida* BSIs, particularly those caused by *Candida auris* and other multidrug-resistant species, underscores the urgent need for innovative diagnostic, therapeutic, and prevention strategies. Rapid molecular diagnostics – including next-generation sequencing and real-time PCR assays – hold promise for enabling species identification and resistance profiling within hours rather than days, thereby guiding earlier, targeted therapy. Integration of whole-genome sequencing into routine surveillance could enhance outbreak detection and track resistance gene dissemination across healthcare networks.

On the therapeutic front, novel antifungal agents – including ibrexafungerp, rezafungin, and fosmanogepix – are expanding the treatment armamentarium against resistant *Candida* spp., with ongoing clinical trials assessing their role in both first-line and salvage therapy. Combination regimens and adjunctive therapies targeting biofilm disruption also warrant further investigation, particularly for device-associated infections.

From a public health perspective, One Health approaches that monitor antifungal resistance in environmental and agricultural reservoirs are critical, given the documented role of environmental azole use in driving resistance in human pathogens. Collaborative, multinational surveillance platforms will be essential for sharing data, harmonizing definitions, and guiding coordinated interventions across regions.

10. Conclusion

Antifungal-resistant *Candida* BSIs represent a critical global health threat, driven by shifting epidemiology, limited therapeutic options, and the unprecedented rise of multidrug-resistant species such as *Candida auris*. With mortality rates often exceeding 40%, these infections strain healthcare systems through prolonged hospitalizations, costly therapies, and complex infection control requirements. The convergence of host-related vulnerabilities, invasive medical interventions, and antifungal overuse has created an environment that fosters resistance and facilitates the rapid dissemination of resistant strains across hospitals and regions.

Addressing this crisis demands an integrated, multi-level response. At the patient level, timely diagnosis, rapid initiation of active therapy, and rigorous source control are indispensable to survival. At the healthcare facility level, AFS, strict infection prevention bundles, and environmental decontamination are necessary to prevent new cases and outbreaks. Globally, investment in genomic surveillance, novel antifungal development, and One Health strategies is essential to close knowledge gaps and anticipate emerging resistance threats. The path forward will require sustained collaboration between clinicians, researchers, policymakers, and public health systems to preserve antifungal efficacy and reduce the burden of resistant *Candida* BSIs worldwide.

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Chapter 2

Candida lusitaniae from Commensal to Opportunistic: A Growing Clinical Concern

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Abstract

Candida lusitaniae is a rare non-*albicans* species and an emerging opportunistic pathogen in humans. *C. lusitaniae,* the anamorph of *Clavispora lusitaniae*, is not a strictly dimorphic yeast and exhibits a range of morphological forms. This yeast has been isolated from fermentable fruit and vegetables, the environment, soil, and river water, and is also part of the normal gastrointestinal microbiota in humans. *C. lusitaniae* can cause invasive infections, particularly in immunocompromised patients and pediatric patients with hematologic malignancies. Although it is a low-frequency pathogen, mortality rates remain under 5%. Recent studies have revealed several virulence factors, including the ability to colonize epithelial cells, high cell wall hydrophobicity facilitating adherence to plastic surfaces such as catheters and drains, and biofilm formation, which provides protection to fungal cells. Additionally, this species produces hydrolytic enzymes, exhibits thermotolerance, and displays multiple mechanisms of immune evasion. *C. lusitaniae* is intrinsically resistant to amphotericin B and can develop resistance to flucytosine and azoles, making it a therapeutically challenging pathogen. Resistance to more than one of the three major classes of antifungals (azoles, echinocandins, and polyenes), referred to as multidrug resistance, can occur and is more frequent in haploid species such as *C. lusitaniae.* Antifungal susceptibility testing is used in clinical laboratories to guide the selection of the optimal antifungal agent. Multidrug resistance arises from the accumulation of multiple distinct resistance mutations. Antifungal susceptibility testing is therefore crucial in clinical settings to guide appropriate and effective therapy. Rapid and accurate identification of yeasts at the species level is critical for timely diagnosis and effective antifungal treatment. Several molecular diagnostics have been developed for this purpose, including various formats of polymerase chain reaction (PCR) such as simplex, multiplex, nested, semi-nested, real-time PCR, as well as PCR linked to enzyme immunoassay or enzymatic restriction. Other advanced tools include peptide nucleic acid fluorescent in situ hybridization and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. In the absence of robust clinical data, empirical treatment should initially include an echinocandin, with subsequent adjustment based on *in vitro* susceptibility results and clinical response.

Keywords: *Candida lusitaniae*, *Clavispora lusitaniae*, opportunistic yeast, commensal, emergent pathogen, antifungal resistance

1. Introduction

Candidiasis is a disease caused by *Candida* species and is recognized as a significant clinical concern. It can be classified as either superficial (localized) or systemic (deep and disseminated). Superficial candidiasis, also known as mucocutaneous candidiasis, contrasts with invasive candidiasis and severe forms, which are frequently associated with immunodeficiency or profound physiological exhaustion.

Candida albicans remains the most prevalent and virulent species; however, non-*albicans Candida* (NAC) species are increasingly being reported, particularly among immunocompromised and hospitalized patients. While common species such *as C. albicans* and *Candida glabrata* (*Nakaseomyces glabratus*) are well characterized, rare and emerging species such as *Candida lusitaniae* (*Clavispora lusitaniae*) and *Candida auris* (*Candidozyma auris*) pose distinct diagnostic and therapeutic challenges [1, 2].

C. lusitaniae is an emerging opportunistic pathogen in humans. It primarily causes life-threatening invasive infections, often occurring in healthcare settings, and is capable of rapidly acquiring antifungal resistance, including multidrug resistance [3]. This yeast was first isolated in 1959 by van Uden and do Carmo-Sousa. It was later proposed as *Clavispora lusitaniae,* a new species, by Rodriguez Miranda in 1979, based on its production of distinctive clavate ascospores. The first clinical recognition of *C. lusitaniae* as an opportunistic pathogen came from Papagianis, who reported an infection in an immunosuppressed patient with acute myelogenous leukemia. *C. lusitaniae,* associated with infection in this patient, developed resistance to amphotericin B (AMB) during systemic treatment.

The species is characterized by variable morphology, multipolar budding, and potential pseudomycelium formation. Sexual reproduction involves mating-type conjugation followed by ascus formation containing one to four smooth, clavate, hyaline spores, often with a small oil droplet. Spores are easily released from the ascus, and the organism exhibits both oxidative and fermentative metabolism [4, 5].

Since its initial identification, *C. lusitaniae* has been implicated in an increasing number of breakthrough fungal infections, especially in immunocompromised individuals. This rise appears to be multifactorial, involving both a growing population of at-risk patients and increasing antifungal resistance. Infections are most frequently reported in patients undergoing prolonged broad-spectrum antibiotic therapy, immunosuppressive treatment, hematologic malignancies, solid organ or bone marrow transplantation, or with comorbidities such as cancer, diabetes mellitus, or AIDS [6, 7].

Although still considered a rare pathogen, *C. lusitaniae* has drawn significant scientific attention over the last decade due to its association with resistance to AMB, often leading to therapeutic failure, a trait it shares with the closely related species *C. auris* (*Candida auris*). This yeast has been isolated from diverse environmental sources and is also a component of the normal gastrointestinal microbiota [8–11].

Understanding the biology, pathogenicity, and therapeutic challenges of *C. lusitaniae* is critical for improving diagnostic and management strategies,

especially in an era of rising fungal resistance. For these reasons, it is increasingly recognized as a clinically significant and potentially worrisome pathogen.

2. Phenotypic and genomic features of *C. lusitaniae*

C. lusitaniae, the anamorph of *Clavispora lusitaniae*, is not a strictly dimorphic yeast and exhibits a range of morphological forms. It produces ovoid to elongated yeast cells measuring 2–6 × 2–10 μm, as well as pseudohyphae with chains of blastoconidia. These elongated structures resemble true hyphae but lack complete septation, distinguishing them from filamentous fungi. This ability to switch between yeast and pseudohyphal forms is a hallmark of its morphological plasticity, contributing to tissue invasion and evasion of host immune responses.

The colony morphology on solid media, such as Sabouraud Dextrose Agar, is another distinctive feature. Colonies are typically smooth, creamy, and exhibit a slight sheen, which can help differentiate them from other *Candida* species. Their color ranges from white to cream, often displaying a soft, buttery texture. This characteristic appearance not only serves as a diagnostic tool but also reflects the organism's metabolic versatility. On CHROMagar, colonies acquire a pink to purple coloration, which facilitates their distinction from *C. tropicalis*, a species with comparable morphological characteristics.

The *Candida* genus, once thought to comprise only asexual species, has revealed that some members possess alternative reproductive cycles. While *C. albicans* can undergo both parasexual and asexual cycles, *C. lusitaniae* displays both asexual and sexual reproduction. Its teleomorph, *Clavispora lusitaniae,* undergoes meiosis during spore formation, confirming its sexual cycle [12–14].

The complete genome of *C. lusitaniae* has been elucidated, revealing a wealth of information about its genetic architecture. The genome is relatively small compared to other *Candida* species, comprising approximately 12.3 million base pairs (see **Table 1**), which encode around 5,300 genes. Such a compact genome is intriguing, as it suggests a streamlined, yet-efficient genetic toolkit that supports the organism's survival in diverse environments.

C. lusitaniae is a heterothallic ascomycetous yeast whose sexual cycle is regulated by the MATa and MATα loci. Mating between opposite haploid types is induced under stress conditions, leading to cell fusion and ascospore formation [13, 14].

3. Epidemiology and risk factors

Invasive fungal infections are responsible for nearly 1.5 million deaths annually worldwide. About 80% of fatalities from fungal sepsis are attributed to hospital-acquired opportunistic infections, predominantly by *C. albicans* [15, 16]. Invasive infections caused by *Candida* species are closely associated with medical advances. In the United States, candidemia is the fourth most common healthcare-associated infection and the second leading cause of hospital-acquired bloodstream infections. Although *C. albicans* is still the most common species, other *Candida* species now cause over 50% of cases. The epidemiology of fungemia is changing, with an increasing proportion of cases caused by emerging opportunistic pathogenic yeasts [17].

Species	New name	Genome size (Mb)	Ploidy
Candida albicans	–	~14.3 Mb haploid ~28Mb diploid	Diploid
Candida tropicalis	–	~14.5 Mb	Diploid
Candida parapsilosis		~13.1 Mb	Diploid
Candida glabrata	*Nakaseomyces glabratus*	~12.3 Mb	Haploid
Candida guilliermondii	*Meyerozyma guilliermondii*	~10.6 Mb	Haploid
C. lusitaniae	*Clavispora lusitaniae*	~12.3 Mb	Haploid
Candida auris	*Candidozyma auris*	~12.3–12.5 Mb	Haploid or variable
Candida krusei	*Pichia kudriavzevii*	~10.8–10.8 Mb	Diploid
Candida haemulonii	–	~13.3 Mb	Haploid
Candida kefyr	*Kluyveromyces marxianus*	~10.8–11.1 Mb	Haploid or variable
Candida dubliniensis	–	~14.6–14.85 Mb	Haploid
Candida lipolytica	*Yarrowia lipolytica*	~20.1–21 Mb	Haploid
Candida famata	*Debaryomyces hansenii*	~11.4–12.4 Mb	Haploid
Candida pelliculosa	*Wickerhamomyces anomalus*	~12–14 Mb	Haploid

Megabase, Mb.

Table 1.
Comparative Candida *species and genome features.*

In recent years, there has been a growing incidence of rare *Candida* species, such as *Candida lusitaniae*, *Candida lipolytica* (*Yarrowia lipolytica*), *Candida famata* (*Debaryomyces hansenii*), *Candida guilliermondii* (*Meyerozyma guilliermondii)*, and *Candida pelliculosa (Wickerhamomyces anomalus)*, which present significant challenges in terms of identification and interpretation of antifungal susceptibility tests (see **Table 2**) [18]. The pathogenic yeast *C. lusitaniae* accounts for about 1% of invasive candidiasis cases and has emerged as a cause of candidemia. Disseminated infections can be severe, partly due to strains resistant to antifungal therapy, often appearing as breakthrough fungemia in cancer or bone marrow transplant patients [19].

C. lusitaniae has been reported to account for 19.3% of fungemia in immunosuppressed patients and 1.7% of candidiasis in the general population. In addition to fungemia and urinary tract infection, *C. lusitaniae* can cause meningitis, empyema, and peritonitis. This species displays an atypical antifungal susceptibility pattern, with a marked tendency for rapid resistance development. Some strains are intrinsically or secondarily resistant to AMB [20].

C. lusitaniae has been reported as a vaginal commensal, although cases of vulvovaginitis and recurrent vulvovaginitis are very rare. In the oral cavity, it may cause stomatitis in immunocompromised individuals. In children and adolescents with neoplasms, it has been associated with tongue candidiasis; in HIV patients, it can cause angular cheilitis and is also implicated in esophageal candidiasis [21].

Wawrysiuk et al. reported a case of *C. lusitaniae* infection in an immunocompetent female patient who developed an intraperitoneal infection following laparoscopic surgery for hydrosalpinx. The patient was treated with FLC

Species	Frequency	Associate infection	Notable features
Candida albicans	Very common	Bloodstream, oropharyngeal, vulvovaginal	Most virulent form: true hyphae, sensitive to azoles.
C. glabrata (Nakaseomyces glabratus)	Common	Bloodstream, urinary tract	Often azole-resistant; lacks true hyphae.
C. parapsilosis	Common (neonates)	Catheter-related fungemia	Biofilm formation, prevalent in NICU
C. tropicalis	Common (neutropenic patients)	Bloodstream, deep tissue	High mortality is associated with hematologic malignancies.
C. krusei (Pichia kudriavzevii)	Less common	Bloodstream, especially in immunosuppressed	Intrinsic fluconazole (FLC) resistance.
C. auris (Candidozyma auris)	Emerging	Invasive candidiasis, outbreaks	Multidrug resistance, high environment persistence.
C. haemulonii	Rare/ emerging	Bloodstream, skin, catheter-related infections	Closely related to *C. auris*; highly resistant to amphotericin and azoles.
C. lusitaniae (Clavispora lusitaniae)	Rare	Fungemia, solid organ transplants, cancer, and peritonitis	Can develop resistance to AMB.
C. guilliermondii (*Meyerozyma guilliermondii*)	Rare	Fungemia onychomycosis	Occasionally azole-resistance.
C. kefyr Kluyveromyces marxianus	Rare	Bloodstream, gastrointestinal tract	Emerging in neutropenic patient
C. dubliniensis	Rare (HIV)	Oropharyngeal candidiasis (HIV)	Similar to *Candida albicans,* but less virulent.
C. lipolytica (*Yarrowia lipolytica)*	Rare	Fungemia, catheter-related infections	Environmental yeast; occasional human infections; forms biofilms.
C. famata (*Debaryomyces hansenii*)	Rare	Fungemia, endocarditis, peritonitis	Often misidentified, low pathogenicity, but with increasing reports.
C. pelliculosa (*Wickerhamomyces anomalus)*	Rare	Fungemia in neonates and immunocompromised patients	Outbreaks reported in neonatal ICU.

Intensive care unit, ICU; neonatal intensive care unit, NICU; human immunodeficiency virus, HIV.

Table 2.
Comparison of common and rare Candida *species in human infections.*

according to susceptibility testing, which led to temporary clinical improvement and reduction in the pseudocyst [22].

These clinical reports highlight the evolving epidemiological landscape of *C. lusitaniae,* traditionally regarded as an opportunistic pathogen affecting

immunocompromised hosts. However, the documented case in an immunocompetent patient underscores the need to broaden our understanding of its pathogenic potential. As this species continues to emerge in both typical and atypical clinical settings, heightened awareness, accurate identification, and a better understanding of its variable pathogenicity are essential for timely and effective management.

4. Pathogenicity and virulence factors

C. lusitaniae exhibits both sexual and asexual reproductive cycles, with its teleomorph *Clavispora lusitaniae* mediating meiotic spore formation [23]. Several factors likely drive the rising emergence of new fungal pathogens in clinical settings, including the widespread use of antifungal drugs in hospitals (e.g., azoles and/or echinocandins), the use of triazoles in agriculture, global warming, and a significant number of ecological disturbances.

The yeasts *Candida haemulonii* and *C. lusitaniae* are closely related to *C. auris.* A shared trait among these species is intrinsic resistance to multiple antifungals, particularly azoles. The recently described *Clavispora sputum*, which is closely related to *C. lusitaniae*, possesses a reduced number of proteins across several gene families, such as ferric reductases, secreted lipases, cytochrome P450s, and OPT transporters, relative to other *Candida* and *Clavispora* species. Both *Clavispora sputum* and *C. lusitaniae* carry four Flo11-domain proteins, which are critical for surface adhesion, invasion, and pseudohyphal development [24]. Adhesins play a critical role in fungal cell–cell interaction and in mediating host–fungus interplay [25]. *C. lusitaniae* is capable of colonizing a host's epithelial cells during the early stages of infection, although it does not cause tissue damage as efficiently as other *Candida* species. For example, *C. albicans* exhibits significantly higher adherence to buccal epithelial cells (61.6%) compared to *C. lusitaniae* (2%) [26]. *C. lusitaniae* can also adhere to abiotic surfaces. Isolates have demonstrated high cell surface hydrophobicity (37.52%) compared to *C. albicans* (8.48%). Despite its greater hydrophobicity, *C. lusitaniae* generally exhibits lower adherence capacity [27]. In a recent study by Angiolella et al., four *C. lusitaniae* isolates – two from blood and two from urine – were found to be adherent but exhibited considerable interstrain variability in biofilm formation. These properties are consistent with the overall lower virulence attributed to *C. lusitaniae* compared to other *Candida* species [28].

When comparing the proteolytic activity of four different Candida species – *C. albicans, C. tropicalis, C. parapsilosis, and C. lusitaniae* – all demonstrated hydrolytic potential (e.g., aspartyl proteinases [SAPs], phospholipases, and lipases). Notably, *C. lusitaniae* exhibited the highest specific proteolytic activity of SAPs despite lower enzyme secretion levels, suggesting that its elevated enzymatic efficiency may compensate for the reduced production, enabling effective substrate hydrolysis [29].

Calcineurin has been investigated in *C. lusitaniae* for its role in maintaining cell wall integrity, managing endoplasmic reticulum (ER) stress response, optimal growth in serum, and calcium homeostasis. Studies have demonstrated that both calcineurin and its downstream target Crz1 are required for pseudohyphal development, optimal growth, and virulence in murine models of systemic infection.

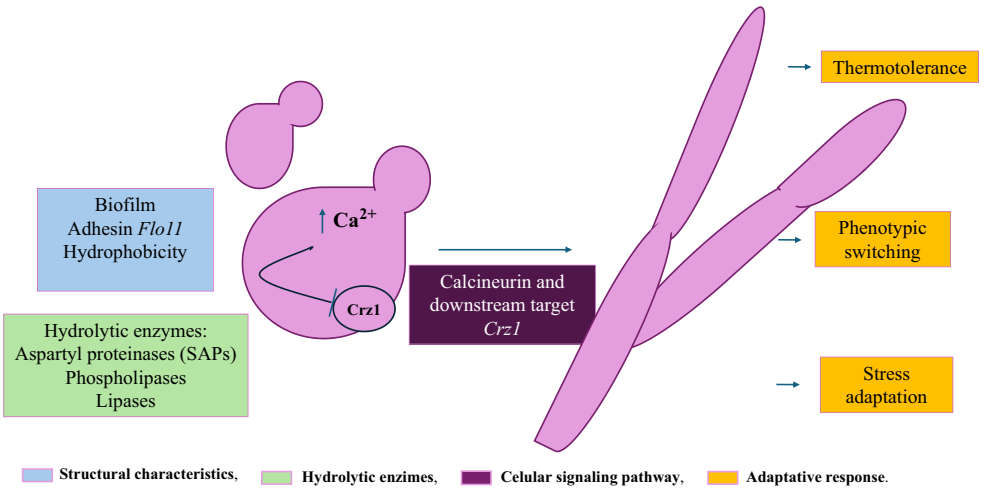


Figure 1.
Pathogenicity and virulence factors of C. lusitaniae: *structural characteristics; hydrolytic enzymes; cellular signaling pathway; adaptive response.*

Furthermore, inhibition of calcineurin has shown synergistic antifungal activity [30].

In summary, the pathogenicity of *C. lusitaniae* appears to be multifactorial, involving a combination of traits such as moderate adhesion, variable biofilm formation, hydrophobicity, limited enzyme secretion, and signaling pathways associated with stress adaptation and morphogenesis (**Figure 1**). These virulence factors indicate that *C. lusitaniae* possesses a significant, albeit generally lower, pathogenic potential, especially in immunocompromised hosts.

5. Antifungal susceptibility testing

Antifungal susceptibility testing is employed for various reasons, one of the most important being its use in clinical laboratories to guide the selection of the optimal antifungal agent for treating a patient with a specific mycosis. These tests provide an in vitro measurement of susceptibility or resistance through a parameter known as the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of a drug required to inhibit fungal growth to a predetermined or specified degree.

With the increasing number of antifungal agents available on the market, as well as the growing population of high-risk patients susceptible to life-threatening fungal infections, the need to implement these tests in clinical laboratories has become imperative. The standardization of the technical aspects and interpretation of antifungal susceptibility testing has been developed by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). These methodologies were initially standardized for yeasts and later extended to filamentous fungi [31–34].

A large number of studies on invasive candidiasis or candidemia, both monocentric and multicentric in nature, have been published in global scientific

literature. In many of these studies, species-level identification and in vitro susceptibility testing have been performed using appropriate methodologies. However, the number of reported cases involving *C. lusitaniae* remains low, which limits the ability to define a reliable antifungal susceptibility profile for this species. Therefore, we will focus on in vitro antifungal susceptibility studies that include a significant number of *C. lusitaniae* isolates.

In vitro susceptibility study involving three azoles (FLC, posaconazole (PSC), and voriconazole (VRC)) was conducted in France using the EUCAST methodology on more than 9,000 yeast isolates recovered from invasive infections between 2003 and 2019. This study included 221 *C. lusitaniae* strains identified by sequencing of the ITS1–5.8S–ITS2 region and the D1/D2 domains. The results showed that all isolates were susceptible to FLC and PSC, and only 4.5% were classified as nonwild type to VRC. This represents the largest number of *C. lusitaniae* isolates included to date in a single study, highlighting its value in characterizing the antifungal susceptibility profile of this rarely encountered agent of invasive fungal disease [35].

An in vitro susceptibility study was conducted on 48 *C. lusitaniae* strains from various clinical sources. The isolates were identified using Vitek 2 and MALDI-TOF and confirmed by ITS sequencing. Susceptibility testing was performed using the CLSI protocol, evaluating nine antifungal agents: AMB, anidulafungin (ANF), caspofungin (CSF), fluconazole (FLC), isavuconazole, itraconazole (ITC), PSC, VRC, and 5-flucytosine (5-FC). AMB and the echinocandins ANF and CSF showed narrow MIC ranges, with no non-wild-type strains detected. In contrast, azoles demonstrated broad MIC ranges, with non-wild-type rates of 4.16% for ITC, 60.41% for PSC, and 33.33% for FLC.

Due to the narrow MIC distribution observed with AMB, additional susceptibility testing was performed using antifungal gradient strips (E-test). A good correlation was observed between CLSI MIC results and those obtained with E-test strips in 43 of the 48 strains. In these 43 strains, no colonies were observed within the ellipse of inhibition, indicating a clear zone of inhibition. However, in the remaining five strains, colonies were found within the ellipse, leading to increased MIC values. These colonies were subcultured for re-identification and susceptibility testing. All were confirmed as *C. lusitaniae* and exhibited MICs at least fourfold higher than the original isolates. This study highlighted a limitation of the CLSI protocol in distinguishing between AMB-susceptible and AMB-resistant *C. lusitaniae* strains [36].

6. Antifungal resistance and molecular mechanisms

C. lusitaniae can develop resistance to AMB, although it is generally considered susceptible to most systemic antifungal agents [37, 38]. Young et al. suggest that diminished expression or mutation in the *ERG6* gene is associated with the acquisition of AMB resistance in clinical isolates of *C. lusitaniae* [39].

Echinocandins have been used for decades as the first-line therapy for candidemia caused by *C. lusitaniae*; however, resistance to these drugs has also been observed. These agents act by inhibiting 1,3-β-D-glucan synthase, and several missense mutations in the *FKS1* gene, particularly within hot spot 1 (HS1), have been identified. In the United States, a considerable proportion (30–40%) of echinocandin-resistant isolates also exhibit resistance to azoles, highlighting the

emergence of multidrug resistance and the consequent restriction of therapeutic options [40–42].

Asner et al. documented the swift development of antifungal resistance in a *Candida lusitaniae* isolate obtained from a 3-year-old girl presenting with hematologic and central nervous system relapse of acute myeloid leukemia. The patient underwent second-line induction treatment with high-dose cytarabine and clofarabine. During AMB treatment, she developed severe enterocolitis, with *C. lusitaniae* isolated from stool and subsequently from blood cultures. Despite treatment with CSF and azoles, the isolate acquired resistance to all commonly used antifungal agents. The patient died two months after therapy initiation [42].

In *C. lusitaniae*, resistance to 5-fluorocytosine (5-FC) has been associated with defects in cytosine permease and with mutations in the genes *FCY1* and *FCY2*, which are involved in drug transport and metabolism. While resistance to echinocandins or azoles commonly develops after monotherapy, multidrug resistance has also been reported following combination antifungal therapy [41].

Azole resistance in *C. lusitaniae* can occur through gain-of-function (GOF) mutations in the transcriptional regulator MRR1, which controls the expression of the major facilitator superfamily transporter MFS7, a key player in FLC resistance. In addition, CDR1, an ATP-binding cassette transporter, has been implicated as another mediator of azole resistance. Bogaert et al. provided evidence that CDR1 expression is regulated by MRR1 and is associated with GOF mutations in this transcription factor [43]. Azoles inhibit ERG11, leading to the accumulation of 14β-methyl -3,6-diol, a toxic sterol intermediate generated by Erg3. Mutations in ERG11 and other genes involved in ergosterol synthesis are frequent mechanisms of azole resistance in *Candida* spp. Studies in *C. lusitaniae* have used both heterologous and homologous expression systems to demonstrate that the impact of specific ERG11 mutations on resistance varies among species, underscoring the role of species-specific genetic context [44].

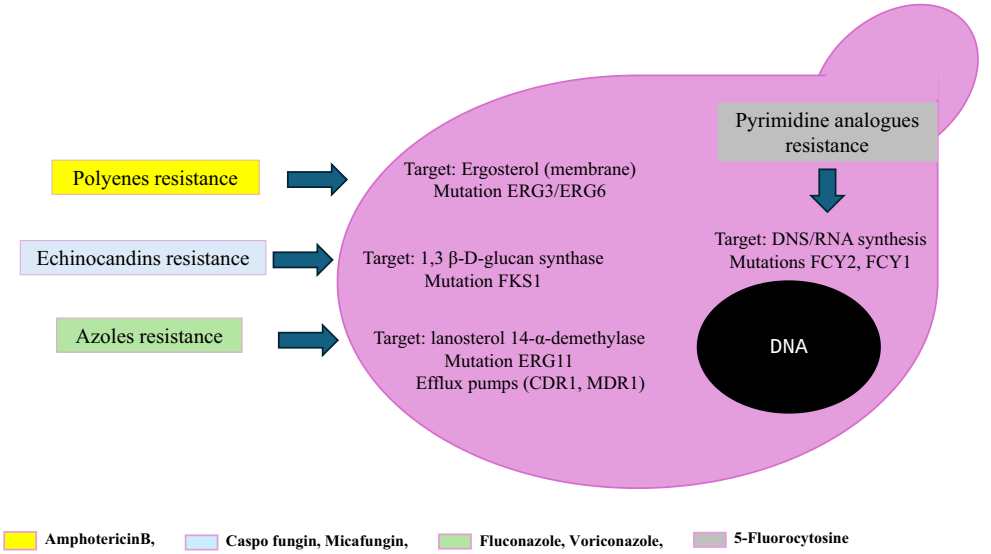


Figure 2.
Major antifungals and their molecular resistance mechanisms in C. lusitaniae*: AMB; CSF, micafungin; FLC, VRC; 5-fluorocytosine.*

Resistance to more than one of the three major classes of antifungals (azoles, echinocandins, and polyenes) (**Figure 2**), referred to as multidrug resistance, can occur and is more frequent in haploid species such as *C. lusitaniae, C. auris, and C. glabrata* than in diploid species such as *C. albicans* [45]. Typically, multidrug resistance arises from the accumulation of multiple distinct resistance mutations [3].

7. Current emerging therapeutic approaches

C. lusitaniae is responsible for fungemia in cancer patients and for genitourinary candidiasis in ambulatory individuals. It has also been associated with peritonitis and meningitis. In rare cases, it may cause cheilitis, oral candidiasis (including tongue involvement), and esophageal candidiasis. This species is intrinsically susceptible to echinocandins [21, 28, 40]. CSF can be used as a first-line agent in candidemia and is even recommended for patients with prior exposure to azoles [45].

In a recent case involving an immunosuppressed adult with a central venous catheter who developed thrombophlebitis in the intensive care unit, symptoms eventually improved with combination therapy using micafungin and flucytosine; however, candidemia was not rapidly resolved [46].

Another case involved a 50-year-old immunosuppressed patient with a complex medical history who was admitted to a clinical care unit with sepsis caused by *C. lusitaniae.* The patient was started on intravenous micafungin at 150 mg every 24 hours for one week. On Day 8, the dose was increased to 150 mg every 12 hours. During micafungin monotherapy, rapid development of cross-resistance to antifungal drugs was observed. Analysis of 20 *C. lusitaniae* isolates from that patient revealed three unique mutations in *FKS1,* highlighting the importance of *FKS* in echinocandin resistance [3].

Demers et al. reported FLC resistance in 20 clinical *C. lusitaniae* isolates obtained from a single cystic fibrosis patient with no prior history of antifungal treatment. They identified multiple MRR1 alleles with GOF mutations correlating with elevated FLC resistance. The transcription factor MRR1 is known to regulate *C. lusitaniae* azole resistance genes, including MDR1 [47].

Significant physiological and antifungal resistance differences were observed between two *C. lusitaniae* strains, revealing notable genetic variability. One strain exhibited higher resistance to AMB and slower growth compared to the second strain, despite both showing minimal β-D-glucan production, suggesting alternative pathogenic mechanisms. The isolation of a genetically related environmental strain raises important questions about the factors driving its selection and potential increased aggressiveness in hospital environments. These findings highlight the relevance of understanding microbial adaptation, environmental influences, and selective pressures in clinical settings to better address the emergence of multidrug resistance [48].

A report on neonatal fungemia highlighted the swift onset of multidrug resistance in *C. lusitaniae* against AMB, CSF, flucytosine, and azoles during therapy for persistent candidemia in an immunocompromised infant. The authors suggested that the selective pressure exerted by the sequential use of different antifungal agents

could have promoted the stepwise emergence of resistant strains throughout treatment [20].

Antifungal susceptibility testing is, therefore, crucial in clinical settings to guide appropriate and effective therapy [49].

8. Diagnostic approaches and advance in *C. lusitaniae* identification

Unfortunately, routine identification of *C. lusitaniae* using conventional methods, such as colony morphology and metabolic characteristics, can be time-consuming (up to 72 hours) and challenging. Several misidentifications have been reported in the past, often confusing *C. lusitaniae* with *C. parapsilosis*, *C. tropicalis,* or even *Saccharomyces cerevisiae.* Identification based on carbon assimilation (e.g., rhamnose) and fermentation (e.g., cellobiose) may be insufficient to clearly distinguish it from atypical strains of *C. tropicalis* [50].

In recent years, enzyme-based yeast identification systems have been developed for routine use in clinical microbiology. Although the API *Candida* system is commonly used for rapid identification of the most prevalent yeast species, it is not well suited for identifying C. *lusitaniae*. This species has been systematically misidentified by phenotypic methods in many clinical microbiology laboratories.

The colorimetric VITEK® 2 system (bioMérieux, France) is an automated tool for yeast identification that compares the metabolic profile of the isolate against reference strains (currently covering 136 yeast species). While *C. lusitaniae* is included in the database and is generally identified accurately, occasional misidentification with closely related species such as *C. guilliermondii* or *C. famata* may still occur, particularly in atypical isolates [51].

Rapid and accurate identification of yeasts at the species level is critical for timely diagnosis and effective antifungal treatment. Several molecular diagnostics have been developed for this purpose, including various formats of polymerase chain reaction (PCR) such as simplex, multiplex, nested, semi-nested, real-time PCR, as well as PCR linked to enzyme immunoassay or enzymatic restriction. Other advanced tools include peptide nucleic acid fluorescent in situ hybridization and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) [52–55]. MALDI-TOF MS has shown excellent accuracy in species-level identification of *Candida* spp., with reported sensitivities and specificities exceeding 95%, and the capability to provide results within minutes once the culture is obtained. Moreover, recent developments have enabled its application directly from positive blood cultures, significantly reducing the time to identification and facilitating earlier initiation of targeted antifungal therapy. This technology allows the discrimination of closely related species, which is particularly valuable for NAC with variable antifungal susceptibility profiles. These assays offer high sensitivity, specificity, and rapid turnaround time in detecting and identifying *Candida* spp.; however, their implementation in many hospital laboratories remains limited, partly due to the lack of specialized infrastructure and the methodological complexity of some techniques [56].

Accurate species-level identification, comprehensive in vitro susceptibility testing, and strict adherence to the principles of source control are all critical components for the optimal management of *C. lusitaniae* infections.

9. Perspectives and clinical challenges

C. lusitaniae is an emerging opportunistic pathogen with the capacity to cause nosocomial infections, particularly in immunocompromised adults, neonates, and pediatric patients with hematologic malignancies. Although relatively uncommon, it has drawn increasing scientific attention due to its intrinsic or acquired resistance to multiple antifungals, including AMB, 5-FC, and FLC. Its ability to adapt to the human host may further enhance its pathogenic potential, posing significant therapeutic challenges in high-risk populations [11]. Recent multi-locus phylogenetic analyses have revealed that several species within the *Clavispora* clade are conspecific with anamorph-based *Candida* species, prompting taxonomic reclassifications [57].

Rapid and accurate identification of *Candida* species remains critical for guiding appropriate antifungal therapy. However, atypical strains may be difficult to identify using standard diagnostic methods, and the species is notable for its capacity to rapidly develop resistance to AMB during treatment. In the absence of robust clinical trial data, current recommendations suggest initiating empirical therapy with an echinocandin, followed by targeted treatment adjustment based on *in vitro* susceptibility testing and clinical response [6].

Rapid and accurate identification remains essential to guide targeted antifungal therapy, yet atypical strains can be missed by conventional diagnostics. Integration of advanced platforms, such as MALDI-TOF MS and molecular assays, into routine workflows, together with genomic surveillance, will be crucial to shorten the time to identification and detect emerging resistance mechanisms [54].

Beyond diagnostics, preventive strategies have begun to gain attention. In this context, Naz et al. [58] proposed a vaccine design against *C. lusitaniae*, utilizing immunoinformatic approaches to identify immunogenic epitopes with the potential to elicit a protective immune response. Although still in the early stages, such initiatives reflect a growing recognition of the need for proactive measures to combat emerging fungal pathogens such as *C. lusitaniae*.

Overall, improving early identification, expanding genomic surveillance, and fostering translational research – including vaccine development – are key priorities to address the clinical challenges posed by *C. lusitaniae* and to mitigate the emergence of antifungal resistance.

10. Conclusions

C. lusitaniae is a rare opportunistic fungal pathogen with distinctive biological and clinical features that set it apart from other members of the *Candida* genus. Initially emerging as a rare species with multidrug resistance, it has expanded worldwide. It has increasingly been recognized in clinical settings, particularly in immunocompromised patients. Morphologically, it exhibits characteristics consistent with yeast-form growth. Its pathogenic potential is supported by several virulence traits, including adhesion to host tissue, production of proteolytic enzymes, hydrophobic cell surfaces, and the ability to form biofilms, all of which enhance its survival and persistence. *C. lusitaniae* demonstrates an unpredictable susceptibility profile, with intrinsic or acquired resistance to AMB and azoles posing significant therapeutic challenges. Genomic analyses reveal elements involved in

antifungal resistance, notably within genes such as ERG, which contribute to resistance to multiple drug classes. From an epidemiological standpoint, its incidence may be underreported due to diagnostic limitations. Ongoing research into its molecular biology, resistance mechanisms, and immunogenic properties is essential for the development of novel therapeutic strategies, including potential vaccines. *C. lusitaniae* must be considered not only as a rare opportunistic yeast but as a clinically relevant pathogen with the capacity for adaptation and persistence in diverse host environments.

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Chapter 3

The Rise of *Candida auris*: A Global Health Threat

Anup R. Warrier and Serra Saji Moses

Abstract

Candida auris is an emerging multidrug-resistant yeast that has rapidly become a significant global health concern, particularly in healthcare settings. Since its initial identification in 2009, *C. auris* has been reported in over 50 countries and is associated with high morbidity and mortality, especially among critically ill and immunocompromised patients. Its ability to persist on surfaces, form biofilms, and resist common antifungal agents has contributed to frequent outbreaks and challenges in infection control. Diagnostic difficulties arise due to frequent misidentification by conventional laboratory methods, necessitating the use of advanced techniques such as matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry and molecular assays for accurate detection. Genomic analyses have revealed multiple phylogenetic clades with distinct geographic distributions, suggesting independent emergence events rather than a single-source spread. The COVID-19 pandemic has further exacerbated the incidence and transmission of *C. auris*, highlighting vulnerabilities in infection prevention infrastructure. Antifungal-resistance mechanisms in *C. auris* include mutations in ERG11 and FKS1 genes, efflux pump overexpression, and biofilm-mediated protection, resulting in limited therapeutic options and the emergence of pan-resistant strains. Effective management requires enhanced surveillance, rapid diagnostics, robust infection control measures, and ongoing research into novel antifungal strategies. The continued evolution and adaptability of *C. auris* underscore the urgent need for coordinated global efforts to mitigate its impact on public health.

Keywords: *Candida auris*, multidrug resistance, nosocomial infection, antifungal resistance, diagnostics, outbreak, biofilm, infection control, phylogenetics, COVID-19

1. Introduction

Candida auris is an emerging multidrug-resistant fungus, belonging to the order Saccharomycetales, family *Metschnikowiaceae*, and clade ascomycetous *Clavispora* [1, 2]. The term "*auris*" is derived from the Latin word meaning "ear" [2]. It is a colonizer found in the ears, wounds, respiratory tracts, urinary tracts, and skin of immunocompetent individuals, while it can also cause serious invasive infections, mainly in immunocompromised patients [3, 4]. It is characterized by high overall

mortality and has been identified as a global health threat worldwide [5–7]. In 2019, the Centers for Disease Control and Prevention (CDC), in its antibiotic resistance threats report, listed *C. auris* as the only fungal pathogen among the five most urgent threats [8]. *C. auris* has also been ranked second by the WHO as a critical group in the fungal pathogens priority list [9]. Given its recent emergence and rapid spread worldwide, it is of utmost importance to understand how *C. auris* rapidly evolved from an environmental colonizer to a critical pathogen, in order to manage and prevent outbreaks of *C. auris* as well as other emerging fungal pathogens in the future.

1.1 Epidemiology and review of literature

C. auris is generally believed to be acquired nosocomially; however, its source in hospitals remains unknown [10]. Independent introductions of multiple *C. auris* clonal lineages into the same hospital have been demonstrated, suggesting the possibility of community reservoirs as well [11]. While *Candida albicans* continues to be the leading cause of candidiasis, there has been a drastic shift toward *C. auris* in the proportion of infections caused by non-albicans *Candida spp.* [12]. The burden of *C. auris* infection remains unknown as the majority of the studies are from single centers without known denominators [10]. Although the first retrospective isolation of *C. auris* dates back to 1996, it was first described in 2009 in Japan from a 70-year-old Japanese patient's ear canal [2, 10, 13–15]. By 2013, *C. auris* was identified in India, South Korea, South Africa, and Venezuela, and since then, it has spread globally [16]. Many isolates have been identified across six continents as agents of nosocomial infections, with the majority of the reported infections involving critically ill patients [6, 14, 17, 18].

In a study from the USA, whole genome sequence analysis of 54 isolates collected from multiple geographical locations differentiated isolates into four clades: the South Asian clade (clade I), the East Asian clade (clade II), the South African clade (clade III), and the South American clade (clade IV). Recently, in 2018, a potential clade IV was found, which was exclusively seen in Iran – the Iranian clade [3, 19]. This indicates that there were minor differences among isolates in the same geographical area, suggesting simultaneous emergence of *C. auris* at multiple geographical regions rather than spreading from one place to another [20]. The number of reported cases in the US increased from 476 in 2019 to 1,471 in 2021 [21].

The first recorded case of *C. auris* in Europe, dating back to 2007, belongs to the South Indian Clade (clade I). Out of 15,271 *Candida* isolates collected between 2004 and 2015, only four were identified as *C. auris* [22]. In an outbreak investigation at a cardiac hospital in the UK, 2,246 patients were screened, from which only one patient (0.04%) had *C. auris* isolated from colonizing sites at the time of admission, indicating that the hospital is the likely source of the organism [23]. The reported cases in Europe rose from 335 in 2020 to 655 in 2021 [21].

A study covering 27 ICUs in India from 2011 to 2012 reported *C. auris* as the 5th most frequent cause of candidemia, accounting for 74 out of 1,400 (5.3%) cases [24]. Longer duration of ICU stay, multiple invasive procedures, and previous antifungal therapies were identified as the major risk factors for *C. auris* infection [6]. In a recent study in a tertiary care multispecialty center in Western India, *C. auris* was reported to be the most predominant causative agent of candidemia, constituting approximately 43% of all *Candida* isolates [25].

2. Pathogenesis and virulence

C. auris is hypothesized to have existed as a colonizer in the environment before emerging as a human pathogen [26]. It has been isolated from marine environments, including a salt marsh wetland devoid of human activity [27]. *C. auris* can grow well at 42°C due to its thermal tolerance and is also resistant to commonly used antiseptics such as chlorhexidine gluconate [3, 10, 28].

C. auris exhibits both yeast and filamentous forms. Filamentous form cells are promoted at lower temperatures (25°C), and so clinical isolates rarely undergo filamentation due to the higher human body temperature [3]. This explains the ability of *C. auris* to form robust biofilms on human skin as well as in hospital environments, as they are generally cooler than the core body temperature [29]. It sheds from the skin and persists on medical equipment or surfaces, creating a reservoir in the environment of hospitals or other long-term care facilities, and thus becomes a source of continuous transmission [23, 27, 30]. *C. auris* also has the ability to form multicellular aggregates, known as pseudohyphae-like cells. These are of two types that differ in their biofilm-forming abilities and virulence: one formed due to defective cell division, while the other is a result of the overexpression of adhesion-associated genes [13, 29, 31]. Compared to their non-aggregated counterparts, these cells seem to be less virulent but can evade the immune system and show reduced susceptibility to antifungal treatment [3].

Biofilm formation by *C. auris* is an important virulence factor that confers protection against various extrinsic insults. On the skin surface, high-burden, dense multilayer biofilms are formed, which is why *C. auris* can successfully colonize and persist on human skin and spread easily among patients [32, 33]. This property also makes central venous catheters a common finding in patients diagnosed with invasive *C. auris* infection [34]. There are studies that report the presence of catheters in up to 100% of patients [35], while a study in Kenya reported that 84% of patients with *C. auris* candidemia had an indwelling central line [36]. *C. auris*, being an opportunistic pathogen, requires an immunocompromised host, and thus advanced age, recent surgery, presence of comorbidities like diabetes, or the use of broad-spectrum antibiotics or antifungals are major drivers of infection [3]. A Pakistani study reported a history of antifungal therapy in 37% of *C. auris* candidemia patients, compared to only 1% of those with non-*C. auris* candidemia [37].

Also, candidemia incidences are reported to be comparably higher in COVID-19 patients than in non-COVID-19 patients [29]. This could be attributed to a weakened immune system due to the underlying viral infection as well as the antiviral therapies, which may thereby result in higher vulnerability of COVID-19 patients [26]. Several case studies all over the globe have documented coinfection of COVID-19 and *C. auris* in ICUs, resulting in devastating outcomes with mortality rates of up to 80%, despite adequate antifungal therapy [19, 38]. These patients had significant underlying comorbidities, were treated with broad-spectrum antibiotics and immunosuppressive therapies, and also had indwelling urinary catheters and intravenous catheters [39]. Moreover, there was a breakdown of routine infection prevention protocols, limited availability as well as prolonged use/reuse of protective equipment such as gloves or gowns, and alterations in cleaning and disinfection practices during the pandemic that would have provided a perfect breeding ground for *C. auris* outbreaks [19, 29]. However,

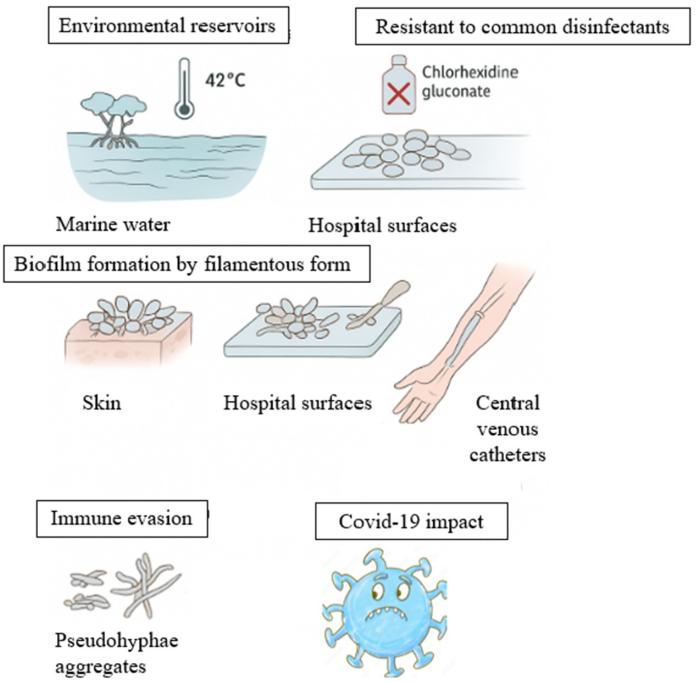


Figure 1.
Pathogenesis and virulence of C. auris.

this correlation between *C. auris* outbreaks and severely ill COVID-19 patients was only observed in certain countries, such as Italy and the USA [40]. An epidemiological analysis conducted during the pandemic in the UAE found an increased COVID-19 and *C. auris* coinfection in hospitals with overwhelmed ICUs [41]. A *C. auris* outbreak was identified in an ICU with COVID-19 patients in India, with the time of infection onset ranging from 3 to 8 weeks after admission. Most patients had central venous and urinary catheters, required mechanical ventilation, and had underlying chronic diseases such as diabetes mellitus and hypertension (**Figure 1**) [42].

3. Spectrum of infections caused by *C. auris*

C. auris has been implicated in a variety of superficial and invasive infections from multiple body sites, among which, the bloodstream is by far the most common site [43]. In a meta-analysis of reports from 2012 to 2017 describing 742 confirmed *C. auris* isolates from 16 countries, 67% were isolated from blood [7]. Similarly, blood was the culture source for 5 out of 7 patients infected with *C. auris* in the USA (from 2013 to 2017) [44]. Interestingly, some *C. auris* clades appear to be more commonly associated with bloodstream infections than others [34]. A wide-scale analysis of multiple *C. auris* outbreaks showed that clade I and IV isolates have a higher rate of candidemia than clade II or III [45].

C. auris has also been linked to skin and soft tissue infections, intra-abdominal infections, ear infections, respiratory infections, urinary tract infections, cholangitis,

and small bowel infections [2]. Among US patients, approximately 46% of *C. auris* infections have been identified from sites other than blood [46]. *C. auris* was isolated from bone, urine, peritoneal fluid, and cerebrospinal fluid in a survey, where misidentification, along with antifungal resistance, contributed to a 30-day mortality rate of 35.2% [47]. A case of fatal *C. auris* pericarditis was reported in a patient with chronic liver disease on empiric fluconazole therapy, with concurrent recovery of *C. auris* from urine, bronchoalveolar lavage, and blood [48]. A study recently reported a donor-derived, transplant-transmitted *C. auris* in a bilateral lung transplant recipient, which suggested reconsideration of the clinical significance of yeast in donor lung surveillance cultures [49].

4. Identification

Macroscopic characteristics of *C. auris* on standard fungal media like Sabouraud dextrose agar (white to cream-colored, smooth, butyrous colonies) do not provide sufficient information for definitive differentiation from other species [43]. Microscopically, aggregated or single-budding yeast cells without pseudohyphae are seen, typically formed on cornmeal agar or Tween 80 agar [7, 14]. On chromogenic agar, *C. auris* colonies appear beige or pink to red [50]. Supplementation of chromogenic agar media with sunflower seed extract (Pal agar) has been reported to be useful, and when combined with temperature tolerance, helps to differentiate *C. auris* from the *C. haemulonii* complex [51].

C. auris ferments glucose, sucrose, and trehalose, and assimilates carbon sources such as glucose, sucrose, maltose, D-trehalose, D-raffinose, D-melezitose, D-mannitol, sorbitol, citrate, inulin, starch, ribitol, and galactitol [7]. However, these biochemical identification methods can be difficult and unreliable if the test has not been updated to include *C. auris*, due to phenotypic similarities with other species such as *C. haemulonii, C. duobushaemulonii, C. lusitaniae,* and *C. famata* [52]. Also, commonly used automated systems like VITEK 2 XL can detect *C. auris* isolates from the South American clade but have limited ability to correctly identify *C. auris* from the African or East Asian clades [53]. Thus, both non-automated and automated biochemical methods commonly used in clinical microbiology laboratories have well-described performance issues that lead to inaccurate identification [43].

Reliable options for species identification include matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry and sequencing of different DNA loci in specific regions of ribosomal genes (18S rDNA, 28S rDNA, or internal transcribed spacers ITS1 and ITS2) using molecular methods like PCR and LAMP [52].

5. Treatment challenges

The appropriate treatment of *C. auris* infections remains very challenging, with a crude mortality rate of 30–60% [3]. A crude mortality rate of 34% was cited in a study by the Centers for Disease Control and Prevention (CDC) that analyzed 192 *C. auris* cases in a U.S. hospital database [54]. Treatment should be reserved for patients with a documented invasive infection and avoided for cases of colonization at non-sterile sites [34]. Three antifungal drug classes have been approved for the

treatment of invasive candidiasis: echinocandins (caspofungin, micafungin, anidulafungin), triazoles (fluconazole, voriconazole), and amphotericin B formulations [55].

5.1 Antifungal resistance

A crucial characteristic of *C. auris* is antifungal resistance, with 90% of isolates reported to be resistant to at least one class of antifungal agents and 30% to at least two different classes [29]. It is estimated that approximately 50% of isolates from five continents are resistant to one or more classes of antifungal agents [56]. Even pan-resistant isolates have been described, although the overall number of cases reported so far is low [57, 58]. A recent analysis of 67 studies containing data from 33 countries with more than 4,000 *C. auris* cases revealed extraordinarily high rates of fluconazole resistance (91%), with lower resistances to amphotericin B (12%), caspofungin (12%), micafungin (0.8%), and anidulafungin (1.1%) [45]. Fluconazole resistance is uniformly found among isolates across geographic regions; however, MICs to echinocandins and amphotericin B vary [34]. Within the US, amphotericin B resistance varies from 5% in the Midwest and West to 85% in the Mid-Atlantic. Echinocandin resistance, although reported to be low, has occasionally emerged in patients undergoing therapy [59]. Similarly, a study from Qatar reported 85% resistance to amphotericin B [60]. However, a multicountry analysis found that isolates from India have a higher rate of caspofungin resistance (23.6%) than isolates from other countries (0.2%) [45].

Antifungal drug resistance in *C. auris* is acquired through various mechanisms, including the alteration of drug targets, increased efflux pump activity, or the activation of cellular stress response pathways (**Figure 2**) [61]. Triazole derivatives like fluconazole interfere with ergosterol biosynthesis by inhibiting the enzyme lanosterol α 1-4 demethylase, coded by ERG11 gene. These ERG11 gene mutations (target alteration) are responsible for azole resistance [2]. Overexpression of genes encoding major efflux pumps, as well as mutations in the Upc2 gene that lead to overexpression of the ERG11 gene, can also lead to azole resistance [62].

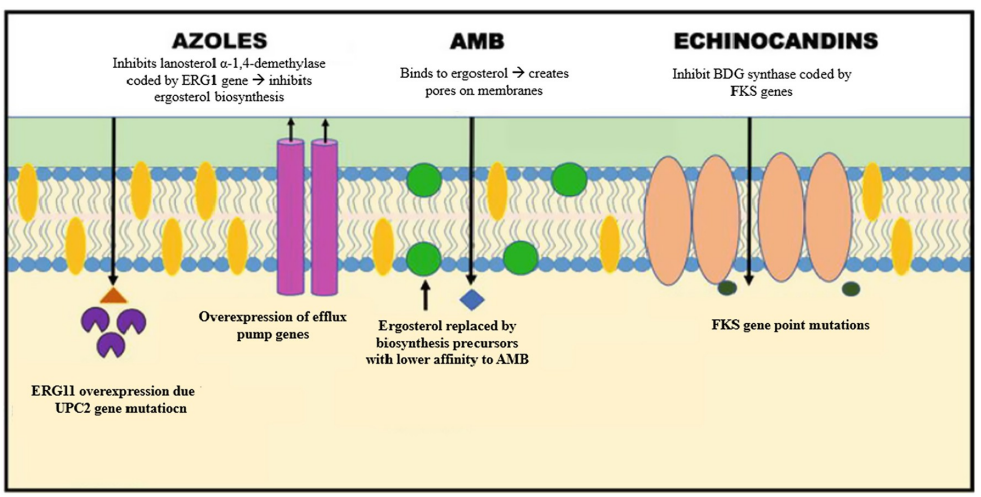


Figure 2.
Antifungal resistance mechanisms in C. auris.

Amphotericin B, a polyene that binds to ergosterol, creates pores at the membrane level. Resistance to this drug is primarily caused by replacing the membrane ergosterol with biosynthetic precursors such as lichesterol, lanosterol, and fecosterol, which have reduced affinity for amphotericin B [2]. Echinocandins are lipopeptidic antifungal drugs that inhibit β-(1-3)-D-glucan synthase, coded by the FKS genes, point mutations of which lead to resistance to echinocandins in *C. auris* [63].

5.2 Treatment choices

Given the high resistance rates, MIC testing (CLSI or EUCAST) is routinely recommended for isolates from patients requiring treatment [34]. However, due to the absence of established susceptibility breakpoints, determining the most effective treatment for *C. auris* is difficult [2] (**Table 1**). In light of their more favorable susceptibility profiles, echinocandins are recommended as first-line therapies for most patients and should be initiated empirically [64]. Some limitations of echinocandin therapy include parenteral-only daily dosing formulations, lack of accessibility in resource-limited areas, and reduced penetration to the CNS, urine, and eyes [38]. Late complications, as well as the emergence of echinocandin-resistant strains, are the other challenges faced, which highlights the significance of monitoring the patient's clinical progress during therapy by repeating susceptibility testing, in order to assess possible acquisition of resistance [2, 65]. Transition to liposomal amphotericin B can be considered for patients who are not clinically responding to echinocandins or have persistent candidemia for more than 5 days [64]. Amphotericin B deoxycholate is recommended in neonates and infants below two months of age [2]. The use of second-generation triazoles like voriconazole can be considered on a case-by-case basis [66]. The role of flucytosine for the treatment of *C. auris* is not clearly defined, though it has been reported to be administered as

Antifungal agent	Indication	Limitation
Echinocandins	First-line agent	Parenteral only, daily formulation
		Not accessible in resource-limited settings.
		Low penetration in CNS, urine, or eyes.
Amphotericin B	No clinical response to Echinocandins	Renal impairment
	Persistent candidemia for >5 days	
	Infants <2 months age	
Flucytosine	Combination therapy in refractory infections	Pancytopenia on long term use
Combination therapy	CNS/urine infections	-
	Critically ill patients	
	Patients with relapse/ persistent candidemia	
	Pan-resistant isolates	

Table 1.
Treatment choices for C. auris *infections.*

part of a combination therapy and reserved for refractory infections, such as endocarditis, meningitis, and endophthalmitis [34, 55].

Thus, it is crucial to develop new antifungal drugs that target *C. auris*. Rezafungin, ibrexafungerp, and fosmanogepix are three compounds currently in the pipeline [2]. Rezafungin is a new echinocandin with a prolonged half-life that allows once-weekly dosing, whereas ibrexafungerp is a first-in-class triterpenoid, and fosmanogepix is a novel Gwt1 enzyme inhibitor. These are promising candidates for the treatment of invasive candidiasis, including multidrug-resistant isolates of *C. auris* [67]. Fosmanogepix specifically shows excellent concentrations in the eye and CNS, contrary to ibrexafungerp, which doesn't seem to penetrate the blood–brain barrier [68].

Also, there has been interest in assessing the efficacy of dual antifungal therapy. Additive or synergistic activity has been demonstrated in various in vitro and modeling studies, with some combinations of amphotericin B, triazoles, echinocandins, and flucytosine [69, 70]. Rather than routine use, combination therapy can be considered on a case-by-case basis for seriously ill patients, those with relapsed or persistent candidemia, pan-resistant isolates, and infections involving the CNS and urine (given the limited penetration of echinocandins to these sites) [64]. The combinations studied include azoles with echinocandins, polyenes with flucytosine, and caspofungin with posaconazole [5]. In a *C. auris* outbreak of more than 70 patients, 45% required a second agent due to non-response or persistent fungemia while on echinocandin monotherapy, the most common agent being liposomal amphotericin B [71].

The treatment strategy that can be used for *C. auris* infections is illustrated in **Figure 3**.

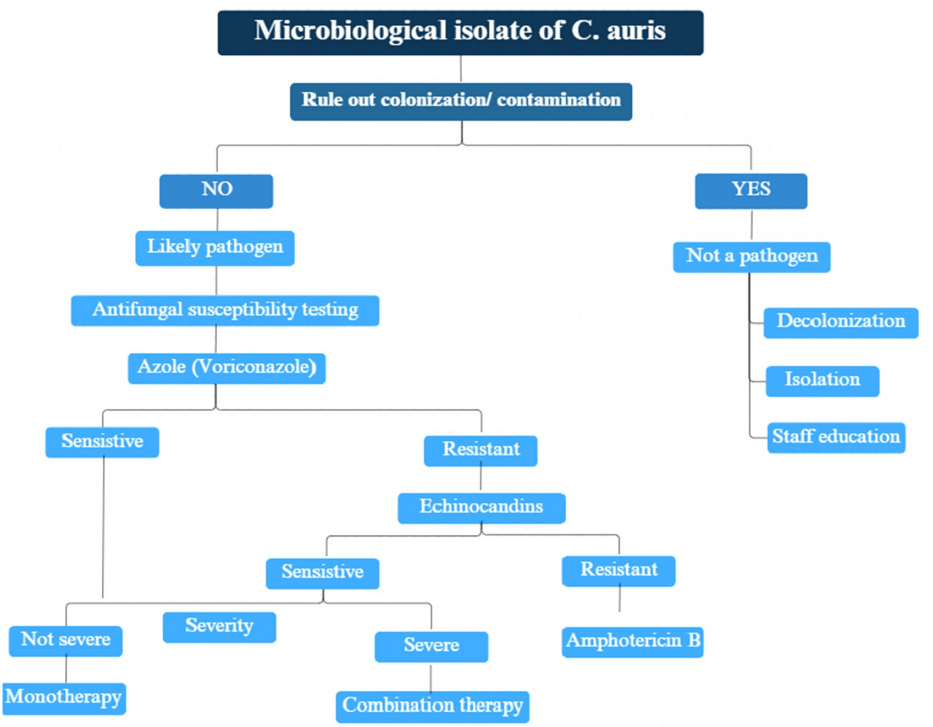


Figure 3.
C. auris *treatment strategy.*

The association between *C. auris* candidemia and the presence of a central venous catheter warrants prompt removal of the catheter in such patients [34]. In a case series, a mortality rate above 80% was reported in patients without prompt catheter removal [60]. Another report described similarly high mortality (84%) for patients without source control [37]. Literature also suggests the removal of other devices, like infected urinary catheters or other prosthetic material, as well as the timely drainage of abscesses, for source control [55]. Moreover, dilated eye examinations are recommended for patients with *C. auris* candidemia, given the high usage of echinocandins and the poor penetration of these compounds into eye compartments [34].

6. Treatment duration

The presence or absence of complications determines the treatment duration. Guidelines recommend an antifungal duration of at least two weeks from bloodstream clearance for patients with uncomplicated invasive infection or candidemia [34]. Longer therapeutic durations are required for patients with more complicated infections, such as osteomyelitis, meningitis, endocarditis, or endophthalmitis [55]. Repeat blood cultures are recommended to guide antifungal duration and to assess persistent candidemia, as reports of breakthrough fungemia (persistent fungemia after three days of antifungal treatment) are common [72]. Repeat MIC testing is also recommended in order to evaluate the need for an alternative agent, as resistance can develop while patients are receiving therapy [64].

7. Outbreak management

7.1 Skin disinfection and surface decontamination

Reduction of transmission of *C. auris* infection involves screening methods as well as infection prevention and control protocols, mainly skin disinfection and surface decontamination [66]. Currently, there are no recommended methods for decolonization or for removing *C. auris* from the skin of an infected person [73].

Alcohol-based products like 70% isopropyl alcohol and 70% ethanol have been tried to disinfect hands or skin. Using a pig skin model, Fu et al. reported good efficacy for various alcohol-based products against Candida species, including *C. auris* and *C. albicans* [74]. Chlorhexidine is found to be minimally efficacious against *C. auris* when used as the sole active ingredient, but the yeasticidal performance might substantially improve when combined with alcohol [73]. This was demonstrated by Moore et al., on comparing the efficacy of 2% chlorhexidine + 70% isopropyl alcohol with 4% chlorhexidine alone [75]. A contradictory yeasticidal performance against *C. auris* is reported for 10% povidone iodine. Moore et al. observed poor performance, while Abdolrasouli et al. reported sufficient efficacy [75, 76]. An antiseptic containing 3% hydrogen peroxide has been shown to have poor performance against *C. auris* when compared to 1% chloroxylenol [66, 77].

C. auris is said to be present on hospital environmental surfaces as biofilms, including ventilators, floors, patient bed trolleys, chairs, and window sills [63]. This warrants proper decontamination of non-disposable biomedical equipment prior to reuse on another patient, in order to control the transmission of *C. auris* infection

[2]. The disinfectants should be able to penetrate the protective layers of biofilms formed on equipment and kill the viable fungi [66]. For hard surface disinfection, the CDC suggests the use of EPA-registered products approved for healthcare [73]. A study conducted during an outbreak at a UK hospital reported that routine disinfection of patient-care areas and equipment with chlorine-based disinfectants at 1,000 ppm was sufficient to prevent *C. auris*, as recommended by the WHO, PHI, and COTHI [23, 73]. Though dependent on the composition of the final formulation, the best-performing biocidal actives against *C. auris* have been shown by chlorine-based products containing sodium dichloroisocyanurate or sodium hypochlorite at 1,000 ppm [78]. Many healthcare facilities favor the use of quat-based disinfectants due to their fungicidal, bactericidal, and virucidal activity; however, laboratory studies show that they have poor performance against *C. auris*, and it has been implied to be the cause of an outbreak in an ICU at the Oxford University Hospital in 2018 [73, 79]. Non-quat–based disinfectants used in healthcare contain hydrogen peroxide or peracetic acid with acetic acid, which, when used at the reported concentration, could eliminate dry biofilms formed by *C. auris* and prevent regrowth shortly after cleaning [66]. Other biocidal products commercially available as hard-surface disinfectants with limited information on anti-*C. auris* action include an alcohol-based product with 12% ethanol, 17.5% propan-1-ol, glutaraldehyde, and ortho-phthalaldehyde [74]. No-touch disinfection methods, such as UV–C, can be used for treating hospital surfaces after manual cleaning or disinfection, in order to cover the areas that might have been missed or cleaned improperly [66].

7.2 Patient screening

Even though there is no routine screening for *C. auris* on admission to the hospital due to its indefinite prevalence in the community, there is considerable evidence to support the importance of screening all critically ill patients [2]. Studies have demonstrated that patients discharged to the community typically take around eight months to become colonization-negative; however, persistent colonization is seen in patients who remain in healthcare facilities [80, 81]. The CDC recommends that patients undergo screening for *C. auris* colonization if they have a history of admission to any healthcare facility within the last year, to a healthcare facility abroad, or are infected with carbapenem-resistant gram-negative bacteria [82]. This is because of reported co-colonization of *C. auris* with these microorganisms, especially in countries with documented *C. auris* cases [2].

7.3 Outbreak investigation

Investigations into potential outbreaks should be initiated as soon as a single case is detected in a hospital setting. During *C. auris* outbreaks, the most commonly sampled sites include the nares, axilla, and groin, similar to screening protocols for MRSA [81]. These remain recommended sampling locations as these skin sites typically have high burdens of *C. auris*; however, other body sites may also be colonized with *C. auris* and contribute to its spread, including hands, toe webs, and perianal skin [34]. To provide information on the likely source during an outbreak, higher-resolution methods such as whole genome sequencing analysis and typing by amplified fragment length polymorphism can be used to identify the route of disease

transmission within a population [2]. Identifying the clade level will provide information on the strain's antimicrobial resistance, virulence, biofilm production, and mortality rate [82].

8. Conclusion

Candida auris has rapidly emerged as a formidable global health threat due to its multidrug resistance, persistence in healthcare environments, and diagnostic challenges. Its widespread distribution, frequent outbreaks, and potential for pan-resistance underscore the urgent need for coordinated international strategies. Strengthening global surveillance, improving rapid diagnostic capabilities, enforcing stringent infection control practices, and advancing research into novel antifungal agents are critical to curbing its spread and reducing associated morbidity and mortality. Without prompt and collaborative action, *C. auris* could become an increasingly unmanageable burden on healthcare systems worldwide.

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Section 2

Immunological Aspects of Candida-associated Infections

Chapter 4

Chimeric Antigen Receptor (CAR)-based and Other Novel Immunotherapies for Invasive Candidiasis

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Abstract

Invasive candidiasis remains a critical clinical challenge, marked by high mortality, limited treatment options, and increasing antifungal resistance. The World Health Organization has classified *Candida* spp. as critical priority fungal pathogens, highlighting the urgent need for innovative strategies to enhance prevention and treatment. This chapter explores the *Candida* cell wall as a key target for immunotherapy, given its essential role in fungal virulence, host–pathogen interactions, and immune evasion. Specific components of the cell wall, including β-glucans, mannans, Als3, and Hsp90, are recognized both as virulence factors and as promising immunotherapeutic targets. The chapter provides an overview of innovative immunotherapeutic approaches directed against these targets, including monoclonal antibodies, adoptive cell therapy, and a special emphasis on chimeric antigen receptor-engineered immune cells. Together, these strategies pave the way for novel antifungal therapies, offering targeted and immune-based solutions for the treatment of invasive candidiasis.

Keywords: invasive candidiasis, immunotherapy, chimeric antigen receptor, cell wall, monoclonal antibodies, adoptive cell therapy

1. Introduction

Invasive candidiasis refers to infections caused by *Candida* spp. that disseminate from superficial colonization sites, such as the skin or mucous membranes, into the bloodstream (candidemia) and organs, including the liver, spleen, kidneys, eyes, heart, and brain. The most common species causing invasive candidiasis include *Candida albicans*, *Candida auris*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata* (*Nakaseomyces glabrata*) [1]. *C. albicans* remains the predominant

pathogen, and *C. auris* has emerged as a concern due to its multidrug resistance, contributing to increased infection-related mortality [2]. Globally, invasive candidiasis affects more than 1,560,000 individuals per year and accounts for 995,000 annual deaths [3]. It predominantly occurs in hospitalized and immunocompromised patients, with the highest-risk groups including premature neonates, patients with central venous catheters, those using broad-spectrum antibiotics, and individuals who have undergone abdominal surgery [4]. Despite medical advances, drug-resistant *Candida* spp. still cause high mortality rates.

An effective immune response against candidiasis relies on the activity of innate immune cells, followed by the development of adaptive immunity to eliminate *Candida* spp. A balanced immune response is required to minimize immune-mediated tissue damage. Upon first contact, innate immune cells recognize *Candida* spp. through pattern recognition receptors (PRRs) such as Dectin-1, which detects β-glucans in the fungal cell wall; Toll-like receptors (TLRs), which recognize mannans and other fungal compounds; and mannose receptor (MR), Dectin-2, and Mincle, which recognize surface mannose residues [5, 6]. PRRs activate intracellular signaling pathways (e.g., NF-κB pathway), triggering the production of pro-inflammatory cytokines and chemokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α. Epithelial cells contribute by acting as a physical and immunological barrier, producing cytokines such as IL-8 to recruit neutrophils and antimicrobial peptides (AMPs) such as defensins [7, 8]. Neutrophils play an essential role by phagocytosing fungi, generating reactive oxygen species, and releasing neutrophil extracellular traps to capture and kill pathogens [9]. Natural killer (NK) cells control *C. albicans* filament growth by releasing cytotoxic granules, including perforins and granzymes [10]. Dendritic cells (DC) and macrophages are involved in phagocytosis and pathogen clearance while also shaping the adaptive immune response. The efficiency of the innate immune response plays a role in the development of adaptive immunity against invasive candidiasis. Antigen-presenting cells phagocytose *C. albicans*, process fungal antigens, and display them on MHC class II molecules before migrating to lymph nodes to interact with $CD4^+$ T helper cells [11]. The maturation of DCs, the polarization of macrophages, and the cytokine milieu within the microenvironment play pivotal roles in shaping T-cell differentiation. Depending on these signals, T cells may develop into Th1 cells, which produce IFN-γ to potentiate macrophage and neutrophil activity, or into Th17 cells, which secrete IL-17 and IL-22, cytokines essential for mucosal defense and neutrophil recruitment [12]. Additionally, adaptive immunity involves cytotoxic T ($CD8^+$ T) cells, including Tc1 and Tc17 subsets, which release cytotoxic granules and pro-inflammatory mediators at the site of infection. Both Th1/Th17 and Tc1/Tc17 responses are crucial for mounting an effective immune response against invasive fungal infections, ensuring both pathogen clearance and the coordination of local immune effector mechanisms [13].

Given the central role of these immune pathways in controlling *Candida* infections, enhancing host immunity has emerged as a promising therapeutic strategy. As antifungal resistance continues to rise, the antifungal drugs available are often inefficient, underscoring the need for the discovery of new antifungal drugs and the generation of innovative approaches. Unlike the antifungal drugs available that act directly on fungal cells, immunotherapies aim to modulate and strengthen the host response, thereby improving pathogen recognition, immune activation, and fungal clearance. In this context, the *Candida* cell wall plays a pivotal role, not only as a structural component essential for fungal survival and virulence but also as a significant source of antigens that can be exploited as therapeutic targets.

This chapter will explore the main immunotherapeutic strategies currently under investigation for the treatment of *Candida* infections. These include monoclonal antibodies (mAbs) targeting specific fungal cell wall antigens, such as mannans and adhesins, as well as more advanced approaches, including the adoptive transfer of immune cells and the development of chimeric antigen receptor (CAR)-engineered Tor NK cells.

2. Composition of the *Candida* cell wall that became a therapeutic target

The cell wall of *Candida* spp. plays a key role in fungal pathogenicity, acting as both a protective barrier and a mediator of host–pathogen interactions [14]. Its composition ensures fungal survival under hostile conditions and provides multiple virulence mechanisms that enable colonization, invasion, and persistence in the host. For these reasons, the *Candida* cell wall represents an attractive target for both antifungal drugs and immunotherapeutic interventions.

Structurally, the *Candida* spp. cell wall is a multilayered, carbohydrate-rich structure that accounts for approximately 80–90% of the total wall mass [15]. The inner layer contains mainly β-glucans and chitin [15]. β-1,3-glucan serves as the major polysaccharide backbone, while β-1,6-glucan acts as a branching polymer that links β-1,3-glucan chains to other cell wall components [14]. Chitin, a polymer of N-acetylglucosamine, is less abundant but plays a critical role in maintaining structural integrity during stress conditions or morphogenetic transitions. Together, these inner-layer components provide support that sustains fungal growth and morphogenesis, particularly during adaptation to host environments [16].

The outer wall layer is enriched in mannoproteins, which are glycosylated and often anchored by glycosylphosphatidylinositol residues linked to β-1,6 glucans [14]. These mannoproteins interact directly with host immune cells and tissues, mediating adhesion, colonization, and immune recognition [16]. The mannan portion of these molecules is highly variable and dynamic, adapting to environmental factors such as pH, nutrient availability, and host defenses. N-linked mannans typically consist of an α-1,6-mannose backbone with α-1,2-oligomannose sidechains, whereas O-linked mannans form shorter chains attached to glycoproteins [14]. These glycans confer hydrophobic properties that enhance tissue adhesion, facilitate biofilm formation, and ultimately act as critical virulence factors in invasive infections. Experimental evidence has shown that *C. albicans* mutants lacking mannosyltransferases, such as MNT1 and MNT2, which encode enzymes responsible for O-mannan synthesis, display impaired adhesion and virulence, emphasizing the central role of mannan structures in host–pathogen interactions [17].

One remarkable property of the *Candida* cell wall is its structural plasticity. Remodeling of wall components occurs dynamically during morphogenetic transitions, such as the switch from yeast to hyphal or pseudohyphal forms. Hyphal growth is associated with the expression of specific cell wall proteins, including Hwp1, Hyr1, and Als3, which function as adhesins and invasins [18, 19]. At the same time, the mannan content is reduced, exposing immunostimulatory epitopes, such as β-glucans, to the host immune system. Hypha-specific proteins enhance biofilm formation and immune modulation, increasing resistance to antifungal treatment and contributing to the chronicity of infection [20]. The *Candida* spp. cell wall

remodeling allows the formation of persister cells that are resistant to very high concentrations of antifungal drugs, and biofilm formation is required to produce persister cells [21]. Furthermore, morphological flexibility enables *Candida* spp. to exploit diverse host niches and contributes directly to its ability to establish invasive infections.

The role of the cell wall in immune evasion is another fundamental aspect of its pathogenic potential. As mentioned before, the cell wall components act as PAMPs recognized by PRRs, including Dectin-1, MR, and TLRs. However, *Candida* employs strategies to mask these epitopes, particularly β-glucans, beneath the mannan-rich outer layer, thereby delaying recognition by innate immune cells and reducing the activation of antifungal immune responses [16]. This capacity to hide immunogenic ligands represents an efficient immune evasion mechanism that impairs fungal clearance and contributes to pathogenicity.

From a therapeutic context, the current antifungal drugs in the echinocandin class, which inhibit β-1,3-glucan synthase, represent the most successful class of agents targeting the fungal cell wall. Echinocandins are fungicidal against most *Candida* species and are used as first-line therapy for invasive candidiasis due to their high efficacy and low toxicity in humans. However, resistance is increasingly reported, especially *in C. glabrata* and *C. auris* infections, mediated by mutations in the FKS genes encoding glucan synthase subunits [22, 23].

Beyond the antifungal drugs available, the *Candida* cell wall has emerged as a promising target for innovative immunotherapies, such as mAbs directed against cell wall epitopes [24], single-chain variable fragments (scFvs) used as antigen-binding domains to redirect engineered immune cells [25, 26], and nanoparticles coated with fungal-targeting ligands [27]. These novel approaches to immunotherapy highlight that the *Candida* spp. cell wall is recognized as the main target to overcome antifungal multidrug resistance. The antifungal drugs available can be paired with immunotherapies to achieve synergistic effects. The mechanism of action, based on the disruption of the cell wall and regulators of the morphological transition of *Candida* spp., should inspire novel designs to combat invasive candidiasis.

3. Immunotherapies for invasive candidiasis

3.1 Monoclonal antibodies

Monoclonal antibodies are highly specific molecules derived from a single clone of B cells, allowing them to interact with a specific antigen in an epitope-dependent manner. The specificity of mAbs is determined by two variable regions of the light (VL) and heavy (VH) chains, which compose the antigen-binding site characterized by variability due to complementarity-determining regions encoding a site to recognize a specific antigen. The antigen-recognition portion of the mAbs, composed of VL and VH chains, can be engineered as a scFv using a linker between the variable domains of the VH and VL chains [28]. Several approaches are employed to obtain mAbs, including hybridoma technology, phage display, and the selection of B cells sourced from convalescent patients to screen for new antibodies [29]. mAbs have a repertoire of mechanisms of action with minimal off-target toxicity, as follows: blocking signaling pathways via antigen binding, activating the complement cascade, promoting phagocytosis, and eliciting durable immune responses [29].

Several mAbs have shown significant protective effects by specifically targeting fungal antigens, including polysaccharides and cell wall proteins. One example is mAb C7, which targets Als3, a hypha-associated adhesin expressed on the cell wall of *C. albicans* during both the blastoconidium and germ tube phases [30]. This antibody exhibited broad cross-reactivity with multiple *Candida* species, including *C. krusei*, *C. tropicalis*, *C. glabrata*, *C. dubliniensis*, and *C. lusitaniae*, and demonstrated direct candidacidal activity [31]. Another set of mAbs was generated using phage display to target cell wall glycoproteins Pga31 and Utr2, which are highly expressed during infection and accessible on the fungal surface [32]. These antibodies preferentially recognized hyphal forms of *C. albicans*, and their binding was further enhanced in the presence of caspofungin. Functional assays revealed that these mAbs acted as potent opsonins, accelerating macrophage-mediated phagocytosis and significantly reducing fungal burden in murine models of systemic candidiasis, with survival rates reaching 83%, comparable to treatment with caspofungin [32].

Beyond conventional mAbs, innovative approaches include the development of bispecific antibodies, such as one combining specificity for β-1,3-glucan, a pan-fungal biomarker, and MP65, a hypha-secreted protein [33]. This bispecific construct, generated through a redox-based method, offers the potential to enhance both diagnostic sensitivity and therapeutic efficacy against systemic invasive candidiasis [33]. Other notable examples include Ca37, an antibody targeting alcohol dehydrogenase present in both yeast and hyphal forms of *Candida albicans*, which demonstrated synergistic antifungal activity when combined with amphotericin B or fluconazole [34]. Similarly, Mycograb, a recombinant human antibody fragment against fungal Hsp90, improved survival in invasive candidiasis patients in combination with amphotericin B, although its clinical use was limited by cytokine release syndrome (CRS) due to cross-reactivity with human Hsp90, underscoring the need for fungal-specific targets [35, 36]. Additional mAbs, such as C12 and C346 targeting mannosyltransferase 4, have shown strong binding affinity to *C. albicans* and effectively activated macrophage and neutrophil antifungal mechanisms, reducing fungal load *in vivo* [37]. However, these antibodies were unable to inhibit hyphal growth or biofilm formation, highlighting limitations that still need to be addressed [37].

The scFv is a mAb fragment that lacks the Fc (constant) region and has been widely explored in studies due to its various advantages. Among these, the low production cost – enabled by expression in bacterial systems – and its multispecific nature stand out, providing higher functional affinity, improved tissue retention, and enhanced effector functions. Additionally, scFvs exhibit excellent tissue penetration, facilitated access to the antigen, a superior pharmacokinetic profile, and reduced immunogenicity due to the absence of the Fc region [28]. However, scFvs present some limitations, such as low thermostability and a tendency to aggregate, which may promote undesirable immune responses. Additionally, they have a shorter half-life compared to full-length antibodies, and due to the absence of the Fc region, the scFv is unable to mediate the classical effector mechanisms of mAbs [38]. Phage display technology has proven to be a valuable tool for the characterization and development of new scFv antibody fragments, which can be conjugated to various molecules for diverse therapeutic applications. Studies have shown that scFv, when combined with the antifungal drug caspofungin, exerts a synergistic effect by inducing alterations in the fungal cell wall and increasing its sensitivity to treatment [39].

The study conducted by Haidaris et al. [40] used a combinatorial phage display library to isolate human scFvs capable of recognizing surface antigens of *Candida* spp. Three distinct scFvs were identified and characterized: l2-9 and l2-18, derived from the lambda 2 (λ2) light chain library, and k3-1, from the kappa 3 (κ3) light chain library [40]. The targets recognized by these scFvs were epitopes located in the *C. albicans* cell wall, predominantly composed of carbohydrates. Reactivity analysis showed that scFvs l2-9 and l2-18 had strong binding to blastoconidial forms but exhibited low or no interaction with filamentous forms [40]. In contrast, scFv k3-1 displayed a broader recognition profile, detecting antigens in both blastoconidial and filamentous forms [40]. Furthermore, all three scFvs were able to recognize antigens present in other *Candida* species, such as *C. tropicalis*, *C. glabrata*, and *C. dubliniensis*. The expression of the recognized antigens was also confirmed *in vivo*, reinforcing their potential for application [40]. Recent data from our group indicate that scFv k3-1 specifically recognizes β-1,2-linked mannose residues, which are important components of the fungal cell wall structure [25]. In this context, the use of antibody fragments such as scFvs represents a promising immunotherapeutic strategy, for example, with the potential to direct effector cells. Thus, cell-based therapies involving scFvs offer an innovative and targeted approach to combating fungal infections.

3.2 Adoptive cell therapy

In general, a strategy with high potential to subvert existing immune evasion mechanisms in invasive candidiasis is the use of adoptive cell therapy. This approach involves isolating immune cells of interest, activating and expanding them *ex vivo* through stimulation with defined antigens or activating factors, and subsequently reinfusing these activated or primed cells into the patient [41]. The ability of DCs to induce specific T cell responses has been explored as a therapeutic tool in adoptive cell therapy protocols, with the DCs cultured and primed *in vitro* with *Candida* spp. antigens, aiming to promote a specific immune response against infection in immunocompromised patients. Previous studies demonstrated that, in experimental models, DCs pulsed with *Candida* yeast RNA or loaded with fungal peptides (Fba, Met6) were capable of inducing a protective Th1 response, significantly reducing fungal burden and improving survival in mice with candidiasis [42, 43]. In the case of invasive candidiasis, we can also highlight the use of NK cells or T lymphocytes, native or genetically modified, as therapeutic tools. A previous study showed that T cells stimulated with a soluble extract of *C. albicans* were expanded *ex vivo,* and their ability to induce damage to *Candida* hyphae was enhanced, suggesting that the generation of functionally active anti-*Candida* T cells is feasible [44]. Although preclinical studies have yielded encouraging results, translating fungal-specific adoptive cell therapies into the clinic remains challenging, requiring rigorous evaluation of safety, efficacy, persistence, and scalability. Continued investigation in this field may pave the way for immune-based interventions to complement or even overcome the limitations of current antifungal treatments.

3.3 CAR-based cell therapy

Modifying immune cells to specifically recognize antigens preferentially present on the cell surface of pathogens is a state-of-the-art therapeutic strategy. In this

context, CAR technology has emerged as a promising approach for redirecting immune cells to attack a specific target. CAR combines distinct domains to provide specificity in the recognition of cell targets mediated by scFv, followed by a domain responsible for cell activation to deliver an effector function against the pathogen. The expression of CAR in T cells enables the recognition of specific targets by eliminating the antigen processing and presentation step by MHC. Therefore, the activation of CAR-expressing T cells occurs through mechanisms that replicate the signal transduction typically triggered by the immunological synapse, with signaling pathways derived from the T-cell receptor (TCR) and costimulatory molecules representing a fundamental principle underlying CAR-T cell function [45]. Considering CAR-T therapy using autologous methods approved for clinical application, the beginning of the process is leukapheresis, involving the harvest of patients' T cells from their blood. Then, lentivirus or retrovirus vectors are used to modify T cells and express the CAR. Once modified, CAR-T cells are expanded *ex vivo* and reinfused into the patient [46]. The clinical success of cell therapy coupled with CAR technology in the treatment of hematologic neoplasia is recent, although the concept of CAR-T cells emerged in the late 1980s [47, 48]. This technology gained greater notoriety in its application against neoplasms of hematologic origin, with CD19 being the best-known target, which refers to the antigen present in B cells. The clinical impact of CAR-T cell therapy is increasingly recognized, with multiple products approved by the US FDA for the treatment of hematologic malignancies. These include idecabtagene vicleucel (ABECMA, Bristol Myers Squibb) and ciltacabtagene autoleucel (CARVYKTI, Janssen Biotech) for multiple myeloma, as well as autologous CAR-T products for B-cell malignancies, such as tisagenlecleucel (KYMRIAH, Novartis), axicabtagene ciloleucel (YESCARTA, Kite Pharma), brexucabtagene autoleucel (TECARTUS, Kite Pharma), lisocabtagene maraleucel (BREYANZI, Bristol Myers Squibb), and obecabtagene autoleucel (AUCATZYL, Autolus) [49]. These therapies are designed to target CD19 or BCMA antigens on malignant cells, demonstrating remarkable efficacy in relapsed or refractory hematologic cancers and establishing CAR-T therapy as a transformative approach in oncology.

3.3.1 Basic principles of CAR structure and generations

CAR is generally composed of four domains: an extracellular region responsible for recognizing the target antigen; the hinge or spacer domain that connects the antigen recognition domain with the transmembrane portion, which anchors the receptor to the cell membrane; and an intracellular domain consisting of activation motifs originating from costimulatory molecules and the CD3z chain that induce T-cell activation. Different molecules can compose the domains for the formation of different CARs, and minimal differences in the design of these receptors influence the effectiveness of cell therapy [50]. The application of CAR technology to modify distinct immune cells has enabled the replacement of costimulatory molecules and the CD3ζ chain, which mediates T-cell activation, with intracellular domains derived from PRRs and other receptors that are essential for NK cell and macrophage activation.

The extracellular recognition domain confers target-binding specificity to CAR, and the use of a recognition portion with optimal antigen interaction is a key advantage for achieving successful CAR efficiency. scFvs are the most commonly

used molecules to compose the antigen recognition region, although other recognition domains can be used, such as portions of receptors or their ligands, nanobodies, lectins, and small peptides [51]. Ideally, the recognition domain should have a sufficiently high affinity for the target of interest. Low affinity can hinder antigen recognition and cell activation, but high affinity can trigger excessive cellular activation, leading to cell exhaustion. Furthermore, the CAR antigen recognition domain must be incapable of interacting with molecules present in healthy tissues; in other words, off-targeting is unacceptable [52–54].

CAR stability can be achieved through the insertion of a nonsignaling extracellular domain, called a spacer or hinge, linking the transmembrane region to the target recognition region. The hinge portion also provides flexibility to the extracellular portion, facilitating the interaction of the recognition region with the antigen [45, 55]. While the main function of the transmembrane domain is to anchor the CAR to the cell plasma membrane, there is a predilection for a hydrophobic amino acid sequence because of this. There is some evidence to suggest that the transmembrane domain also plays a role in the effector functions of CAR cells, such as influencing receptor expression levels and stability, being active in signaling and synapse formation, and favoring dimerization with other signaling molecules [56, 57].

The signal transduction domain is the region of the CAR molecule that receives the most emphasis in CAR optimization studies, being the key element in receptor functionality after CAR interacts with the ligand for cellular activation. Based on the signal transduction domain, CARs are categorized into generations. The first-generation CAR was designed in the late 1980s and contained only one signaling molecule in the intracellular domain, and the possible signal-transmitting subunits came from the CD3ε or CD3ζ chains of the TCR [58, 59]. Cells expressing first-generation CAR receptors showed insufficient expansion, low cytokine production capabilities, and were highly prone to anergy. Clinical results from the application of this generation of receptors in the context of ovarian cancer, non-Hodgkin's lymphoma, and neuroblastoma have also been limited [58–60]. To overcome the limitations observed with the first-generation CAR, a costimulatory molecule was added to the signal transduction domain, giving rise to the second-generation CAR. These second-generation receptors consist of an activating molecule for the first signal, such as CD3ζ, and a costimulatory molecule for the second activation signal. The most commonly used costimulatory molecules are CD28, iCOS, CD137 (4–1BB), or CD134 (OX40), as they differ in their functional profiles, and the ideal molecule for each receptor is determined empirically. Clinically, second-generation CARs produce a more effective therapeutic response in several hematologic malignancies, with FDA-approved therapies utilizing second-generation receptors [52, 61, 62]. Hypotheses emerged that costimulation through only one molecule produced incomplete activation, and this led to the production of third-generation CARs that present two costimulatory molecules acting synergistically with CD3ζ signaling. Preclinical results with third-generation CARs have yielded heterogeneous results; in some cases, third-generation CARs demonstrated a better antitumor response compared to second-generation CARs, with enhanced expansion and persistence [63]. In other cases, the third-generation CAR showed no benefit in *in vivo* treatment, being outweighed by the effects of the second-generation CAR [64, 65]. Technological advancements in molecular

and synthetic biology have enabled significant progress in CAR bioengineering, with several strategies being tested to overcome limitations and enhance therapeutic outcomes. In this regard, fourth-generation CARs, also called "TRUCKs," are being developed. These are second-generation CARs containing genes inducible by receptor activation that lead to the production of molecules such as enzymes, cytokines (e.g., IL-12), and costimulatory ligands, which aid in the cytotoxic activity of cells, improving the therapeutic efficacy of CAR cell therapy. Fifth-generation, or "next-generation," CARs were built on second-generation designs by incorporating features such as a cytokine receptor fragment (e.g., IL-2Rβ) that activates the JAK/STAT pathway or switch receptors, enabling controlled CAR activation via drugs [66, 67].

CAR-T cell therapy has had remarkable success in the treatment of hematologic malignancies, but it faces some limitations, such as systemic toxicity with CRS and manufacturing difficulties, including high costs. However, research continues to advance in addressing the challenges faced by CAR technology, focusing on enhancing cell expansion and persistence, reducing toxicity and costs, and broadening its application to other immune cells and diseases, such as solid tumors, autoimmune disorders, and infectious diseases. In this context, several modifications in the signaling domains of CARs have been studied to improve their expression and effector activity in different immune cells, such as the addition of various domains of innate immunity to the CAR receptor, including but not limited to TLR2, MyD88, and NKG2D [68–70].

3.3.2 CAR therapy beyond cancer

Although CAR-T cell therapy has gained notoriety for its effectiveness in treating hematological malignancies, advances in this technology provide further opportunities for the application of CAR therapy beyond oncology, including autoimmune diseases and infectious diseases [71, 72]. In 2014, Kumaresan et al. developed a pioneering study using CAR-T cell therapy focused on the treatment of IFIs, aiming to control the growth of *Aspergillus fumigatus* hyphae. The authors fashioned a glycan-specific receptor containing an extracellular recognition portion derived from the carbohydrate recognition domain of Dectin-1, specific for β-glucan, and the costimulatory signaling domains composed of CD28 followed by CD3ζ. Dectin-CAR recognized the germline form of *A. fumigatus* and also redirected the cytotoxic $CD8^+$ T cells to inhibit *in vitro* conidial germination, causing a significant reduction in pulmonary fungal burden in an immunocompromised mouse model (NSG mice) infected with *A. fumigatus* [73]. These findings paved the way for the application of CAR technology in the treatment of IFIs, and new studies seek to redirect immune cells to combat diverse fungal species. More recently, Kumaresan et al. developed a novel CAR specific to *A. fumigatus*, called AF-CAR, that suppressed fungal growth after recognition of distinct morphological forms of *A. fumigatus*. AF-CAR-T cells combined with the antifungal drug caspofungin showed a synergistic effect against *A. fumigatus* infection [74]. Furthermore, another research group developed a CAR, also named AF-CAR, specifically targeting *A. fumigatus* hyphae [75]. AF-CAR-T cells, particularly the $CD8^+$ subset, recognized hyphae, secreted perforin and granzyme B, activated macrophages, and markedly reduced fungal burden in a murine model of invasive pulmonary aspergillosis, thereby improving

survival [75]. More recently, the same construct was introduced into NK-92 cells using a nonviral approach, although their antifungal activity has not yet been evaluated [76].

CAR technology applied in IFI therapy was expanded to other fungal species by da Silva and collaborators through the creation of a CAR-targeting *Cryptococcus* spp. yeast and glucuronoxylomannan (GXM), the major capsular polysaccharide. GXMR-CAR mediated the recognition of soluble GXM and induced the secretion of granzymes and IFN-γ by $CD8^+$ T cells, besides helping to decrease the pulmonary fungal burden with a lower proportion of titan cells that contribute to the greater virulence of cryptococcosis [77]. GXMR-CAR structure and costimulatory domains were subsequently evaluated, and GXMR-CAR modifications were performed to improve cell activation in the presence of the target, as follows: distinct scFv specific to GXM to determine the effect on tonic signaling [78]; transmembrane/hinge domains to evaluate the stability of GXMR-CAR on the cell surface [79]; and costimulatory signaling domains to investigate the molecules able to induce strong T cell activation [79]. These studies demonstrated that the modification of GXMR-CAR allows an improvement in cell activation against *Cryptococcus* spp.; therefore, these findings reinforce the possibility of generating novel CARs specific to other fungal species with the perspective of optimizing CAR-fungi-specific expression in distinct immune cells.

Recent studies have shown promising effects in the application of CAR technology against invasive candidiasis caused by different clinically relevant *Candida* species [25, 26]. A novel CAR specific to *Candida* spp., termed M-CAR, showed the ability to induce strong activation against distinct species and morphological forms of *Candida* [26]. M-CAR is a second-generation CAR composed of an scFv specific to the α-1,6 mannose backbone of fungal mannan as a recognition domain, linked to a hinge/transmembrane domain from CD8, the CD137 costimulatory domain, and CD3ζ as a signaling domain. The functional and structural characterization of the M-CAR construct was performed in Jurkat cells, a human T cell line commonly used as a platform for testing novel CARs. Jurkat cells were modified with M-CAR using a lentiviral vector, and M-CAR Jurkat cells were able to respond to soluble mannan and different forms of *Candida* species, which was demonstrated by high levels of CD69 expression and IL-2 production. These findings evidenced the high capacity of M-CAR to induce strong T cell activation against *Candida albicans* hyphae, *Candida tropicalis* hyphae, *Candida parapsilosis* pseudohyphae, and *Candida glabrata* yeast. Interestingly, M-CAR Jurkat cells expressed activation markers in the presence of *Rhizopus oryzae* spores [26]. Our group has advanced the effector function of M-CAR-T cells against *Candida* spp.

Our group also screened distinct scFvs against *Candida* spp. to generate a novel CAR specific to *Candida* species, and both T and NK cell lines were modified with CAR [25]. The distinct CARs generated to target *Candida* spp. were composed of CD8 as a hinge/transmembrane domain, CD137, and CD3ζ as intracellular signaling portions [25]. The antigen recognition domain consisted of different scFvs previously reported to recognize yeast and/or hyphae of *C. albicans*, as follows: scFv3 recognizes the adhesin Als3p [80]; scFv5 recognizes the SPT6 gene product [81]; scFv12 recognizes an unknown protein [82]; and scFvk3-1 binds to a carbohydrate, which is described below after characterization by our group [25].

In summary, scFv3-CAR and scFv12-CAR did not mediate cell activation against *C. albicans*, while scFv5-CAR mediated T cell activation only against *C. albicans* hyphae [25]. In contrast, scFvk3-1-CAR recognized both yeast and hyphal forms of *C. albicans*, as well as other clinically relevant species, including *C. glabrata*, *C. tropicalis*, and *C. auris*. In Jurkat cells, this receptor induced a strong response, marked by elevated expression of activation markers (CD69, CD25, ZAP-70), exhaustion markers (PD-1, TIM-3), and high IL-2 production [25]. Given this robust activation, scFvk3-1-CAR was subsequently expressed in NK-92 cells via lentiviral transduction, which resulted in reduced *C. albicans* viability alongside increased IFN-γ production and CD107a expression [25]. Glycan microarray analysis further revealed that scFvk3-1-CAR specifically recognizes *C. albicans* mannan, but not any other glycans [25]. *In vivo*, treatment of NOD scid gamma (NSG) mice infected with *C. albicans* using scFvk3-1-CAR-NK-92 cells led to a significant reduction in kidney fungal burden [25].

The development of novel CARs against *Candida* spp., reported by our group, opens an avenue to optimize CAR application for treating invasive candidiasis. The potential of M-CAR and scFvk3-1-CAR to redirect immune cells against *Candida* spp. instigates us to establish the current evaluation of the capacity of primary T cells expressing M-CAR or scFvk3-1-CAR to act as mediators of a cytotoxic effect capable of controlling the growth of *Candida* spp. Furthermore, several new strategies are being tested to improve the cytotoxic effect of M-CAR and scFvk3-1-CAR, such as the evaluation of other molecules, including costimulatory domains, and the association of treatment with CAR cells and antifungals.

4. Conclusion

The cell wall of *Candida* spp. represents the major target for immunotherapeutic strategies, given its critical role in virulence, immune evasion, and morphogenetic transitions. The immunotherapy approaches mentioned in this chapter, including CAR-T and CAR-NK cells, have shown promising results in preclinical studies, demonstrating the potential to enhance the host immune response, either in association with or without antifungal drugs currently available. Despite these advances, several challenges remain. The heterogeneity of *Candida* species, dynamic remodeling of cell wall components, and the need to selectively target fungal epitopes without cross-reactivity underscore the complexity of developing effective and safe immunotherapies. Future research should focus on optimizing antibody design and expanding the use of engineered immune cells to improve specificity and efficacy.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 5

Immunological Disorders Associated with Invasive and Noninvasive Candidiasis

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Abstract

This chapter will explore the genetic and immunological basis of *Candida* infections in individuals with immune genetic errors, focusing on defects in innate fungal sensing (e.g., CARD9 deficiency), Th17-mediated mucosal immunity (e.g., STAT1 gain-of-function variants and IL-17 pathway defects), and phagocyte function (e.g., chronic granulomatous disease and neutropenias), as well as T-cell deficiency. The chapter will describe the most common clinical presentations and current diagnostic and therapeutic approaches, providing insights into how host-pathogen interactions are disrupted in these disorders. Understanding these rare syndromes not only informs the management of affected patients but also reveals critical pathways in antifungal host defense.

Keywords: *Candida*, chronic mucocutaneous candidiasis, severe combined immunodeficiency, T-cell deficiency, CARD9 deficiency, neutropenia

1. Introduction

Fungal infections are recognized as an important global health problem, and in 2022, the World Health Organization published the high-priority list of fungal pathogens [1].

Candida spp. is considered the main cause of fungal infections worldwide. Approximately 200 *Candida* species have been described, but only about 20 are recognized as human pathogens. Even though *Candida albicans* is still one of the most frequent species, non-*albicans* species have been increasing in frequency in the last decades. The most frequent non-*albicans* species are *C. glabrata* (renamed as *Nakaseomyces glabratus)*, *C. krusei* (renamed as *Pichia kudriavzevii*), *C. parapsilosis* species complex, *C. tropicalis*, and *Candidozyma auris* [2]. Species distribution varies with geographical regions and specific risk factors. *C. auris* has become a concern worldwide with its capacity to cause outbreaks; it can be resistant to all three major classes of antifungals [2, 3].

Candida spp. is a human commensal microorganism found in the skin, oral mucosa, gastrointestinal, and genitourinary tracts. Candidiasis occurs when there is an increase in yeast inoculum and when defense and immune mechanisms fail [2, 4]. It can present as superficial infections compromising the skin and nails, it can cause deep mucosal infections, or it can lead to severe disease with fungemia and dissemination to distant organs and tissues. The host defense mechanisms and immunological state are the main factors that determine one presentation or the other [2].

2. Host defense against *Candida* species

Innate and adaptive immune responses are required to control *Candida* infections. Epithelial cells are considered the first line of defense against this fungus. Epithelial cells identify *Candida* and contribute to the interplay between innate and adaptive immunity [5] (**Figure 1**).

As part of the innate response, pathogen-associated molecular patterns (PAMPs) present in *Candida* species are recognized by different innate pattern recognition receptors (PRRs), including C-type lectin receptors (CLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), and Toll-like receptors (TLRs) [6, 7].

PAMPs are displayed in the fungal cell wall, and these molecules can be identical across different *Candida* species or even between other fungi. The cell wall can be divided into two main structures: an inner and an outer cell wall. The outer cell wall can prevent the recognition of the inner cell wall components. The type of proteins found in each cell wall is determined by the fungal morphology (yeast or hyphae) [8]. Relevant examples of PAMPs include β-glucans, N- and O-linked glycoproteins (mainly consisting of mannose), and phospholipomannans.

The PRRs are expressed by various host cells, including macrophages, monocytes, dendritic cells, neutrophils, T-cells, B-cells, and epithelial cells [7]. Each PRR has its own location within the cell. Most of them are located on the cell surface, whereas the rest can be found in the cytoplasm or endosomes. The recognition of PAMPs by their respective PRRs triggers downstream signaling pathways, such as nuclear factor kappa-light-chain-enhancer (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, resulting in the transcription of genes that induce the secretion of cytokines and chemokines to clear *Candida*. To better exemplify this process, the activation of dectin-1, a crucial and well-studied PRR, is described below.

After β-glucan binds to dectin-1, it activates the spleen tyrosine kinase pathway (Syk). Syk activates the protein kinase Cδ (PKCδ), inducing the formation of the caspase activation and recruitment domain-containing 9 (CARD9), B-cell lymphoma 10 (BCL10), and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) (CBM) complex. Upon assembly, the CBM complex activates the canonical and noncanonical NF-κB pathways. The former translocates to the nucleus and induces the transcription of Th1- and Th17-polarizing cytokines [5, 8]. The resulting polarization activates the adaptive immune response. Interleukin-6 (IL-6) and interleukin-23 (IL-23) are essential cytokines that induce Th17 cell differentiation. This differentiation also depends on the signal transducer and activator of transcription 3 (STAT3) [9]. Th17 cells and their effector cytokines, interleukin-17A and 17 F, have been widely described as critical elements of *Candida* immunity at mucosal sites [10, 11].

Figure 1.
Human immune response against Candida *spp. PAMPs recognition by their respective PRRs triggers downstream signaling pathways, resulting in the production of cytokines and chemokines for the elimination of* Candida. *Human immune response against* Candida *spp.*

Phagocytic cells are also activated through the recognition of PAMPs and contribute to the antifungal defense. Neutrophils have several antifungal mechanisms, such as the production of reactive oxygen species (ROS) by nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase and myeloperoxidase (MPO) systems, the formation of neutrophil extracellular traps (NETs), and neutrophil degranulation [12]. Whereas macrophages and dendritic cells sense and phagocytose fungal pathogens, these cells can also present fungal antigens to adaptive immune cells.

The presentation of fungal antigen to naive CD4 + T-cells generates a T-helper (Th) response that is essential for *Candida* infection at mucous membranes [13]. Additionally, the phagocytosis of *Candida* by dendritic cells stimulates the production of interleukin-12 (IL-12), which drives polarization to Th1. Th1 cells secrete interferon-gamma (IFN-ɣ), and its secretion upregulates the expression of the IL-12Rβ2 receptor, perpetuating the Th1 phenotype [13]. Th1 and Th17 immune responses are paramount against *Candida* infections [11].

In the last decades, the detection and description of immune responses against fungi have helped elucidate genetic mutations that lead to immunological disorders associated with invasive and noninvasive candidiasis [14].

Candida strains have evolved mechanisms to evade host immunity by proteolytic degradation of immune system components and interference with signaling pathways [15].

The ability to transform from yeast cells to filamentous hyphae is known as dimorphism and is used by some *Candida* species to invade tissues and evade the host immune response [2]. Adherence to biotic and abiotic surfaces is another important virulence factor mediated by adhesins. Hyphal formation and adhesion to an abiotic surface result in biofilm formation, which complicates the elimination of *Candida* by the immune system as well as by antifungal agents [2]. As mentioned before, proteolytic degradation by the hydrolytic enzyme candidalysin is another way to escape the immune response. This enzyme allows the fungus to invade deep tissues.

3. Candidiasis disease spectrum

Depending on the risk factors and on which component or pathway of the immune system is faulty, *Candida* infection can be classified as superficial, comprising skin and nails, as well as oral, esophageal, and/or genitourinary mucosa, and invasive disease manifested as candidemia and disseminated candidiasis with central nervous system (CNS) involvement, endophthalmitis, or osteoarticular infection [1, 2, 4, 9, 16].

3.1 Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) is characterized by persistent or recurrent episodes of oral, skin/nail, esophageal, or genital candidiasis caused more frequently, but not exclusively, by *C. albicans* [16, 17]. CMC was first described in 2001 by Kirk-Patrick *et al*., and no defined duration of illness or number of episodes in a year was established [18]. When studying a patient with persistent or recurrent episodes of mucocutaneous candidiasis, it is important to investigate the use of broad-spectrum antibiotics or prolonged steroid therapy, as well as secondary

immunodeficiency associated with HIV infection, diabetes mellitus, and chronic liver disease [16, 18]. If none of the above risk factors or diseases are identified, immunological congenital disorders need to be ruled out (**Table 1**). Quantification of T, B, and NK lymphocyte cell populations and subpopulations of T and B-cells is essential. Severe combined immunodeficiencies can present with chronic or recurrent mucocutaneous candidiasis. Other immunologic disorders where CMC is usually found are those associated with impaired IL-17 and IL-22 responses [19].

Although management is not well-standardized, administration of oral antifungal agents is usually required. Treatment with fluconazole can be administered for three to four weeks. Antifungal prophylaxis with triazoles or an oral cochleated amphotericin solution may be indicated in patients presenting with three or more episodes per year. Repeated oral and esophageal mucosa candidiasis events can lead to esophageal scarring, which can progress to strictures and stenosis [18].

3.2 Invasive candidiasis

Invasive candidiasis (IC) is one of the main causes of healthcare-associated infections; specifically, candidemia is situated in the top five causes of blood stream infections. IC is also recognized as the third cause of late-onset neonatal sepsis [4, 20]. Around 50% of these infections occur in critical care adult and pediatric units [4]. IC-associated mortality varies from 15–20% in adult patients, while in children and neonates, it has been reported to range between 9% and 37% [20]. Risk factors such as broad-spectrum antibiotics, the use of central venous catheters (CVC), total parenteral nutrition, and blood transfusions, along with *Candida* colonization, have been identified as crucial for the development of IC [21]. Genetic factors that predispose individuals to IC are associated with an impaired phagocytic function, either by altered quantity and quality of granulocytes, a defective oxidative burst for killing *Candida,* or recruitment of neutrophils to the site of infection. Congenital neutropenia, MPO deficiency, chronic granulomatous disease (CGD), CARD9 deficiency, and STAT1 gain of function are some of these immunodeficiencies [22].

Deep-seated infections with involvement of the liver, spleen, soft tissues, and lymph nodes are characteristic of IC in patients with CGD or MPO deficiency, whereas CNS involvement, without previous head surgery or ventricular devices, is highly suggestive of CARD9 deficiency [18, 19, 22].

Treatment of IC requires intravenous systemic antifungal therapy. Management guidelines recommend the use of echinocandins or Amphotericin B; the liposomal formulation is preferred, although the deoxycholate formulation is well tolerated in neonates and young infants [2, 4, 23]. Other important considerations in the treatment of IC are:

4. Candidiasis in inborn errors of immunity

A small number of Inborn errors of immunity (IEIs) have selective susceptibility to *Candida*. Nonetheless, susceptibility to *Candida* infection, along with other fungi or microorganisms, is much more common [10]. **Table 1** summarizes the IEIs associated with *Candida* infection [9, 10, 15, 18, 24, 25].

Interestingly, CARD9 deficiency and STAT1 gain-of-function are the only known IEIs that predispose to CMC and IC [24].

Inborn rrror of immunity	Gene(s)	*Candida* infection	Other fungal infections	Associatedclinical features	Antifungal immune defect
Dectin-1 deficiency[§]	*CLEC7A*	Vulvovaginal candi-diasis, onycho-mycosis	No	None	Impaired PRR activation
IL-17 RA deficiency	*IL17RA*	CMC	No	Folliculitis. May have *S. aureus* skin and soft tissue infections	Impaired IL-17RA signaling pathway
IL-17RC deficiency	*IL17RC*	CMC	No	None	Impaired IL-17RC signaling pathway
IL-17 F deficiency	*IL17F*	CMC	No	May have *S. aureus* skin and soft tissue infections	Impaired IL17F
STAT1 GOF	*STAT1*	CMC Invasive candidiasis	Yes	Bacterial and viral infections Autoimmunity (cytopenias, diabetes, thyroiditis) and enteropathy	Increased STAT1 phosphory-lation Impaired Th17 response
JNK1 haplo-insufficiency	*MAPK8*	CMC	No	May have *S. aureus* skin and soft tissue infections Connective tissue disorder (Ehlers-Danlos-like)	Impaired IL-17 and TGFβ1↓ signaling pathway
ACT1 deficiency	*TRAF3IP2*	CMC	No	Blepharitis, folliculitis, and macroglossia may have *S. aureus* skin and soft tissue infections	Impaired signaling of IL-17 receptor
APECED	*AIRE*	CMC	No	Endocrinopathies	Autoantibodies to IL-17A, IL-17F, and IL-22
Autosomal dominant-hyper-IgE syndrome	*STAT3*-Dominant negative	CMC	*Aspergillus* PJP TDEF *Cryptococcus*	Recurrent sino- Pulmonary and skin/soft tissue bacterial infections, “cold” cutaneous *S. aureus* skin abscesses Elevated IgE and eosinophilia, musculoskeletal abnormalities, characteristic facial features, and vascular anomalies	Impaired Th17 development

Inborn rrror of immunity	**Gene(s)**	***Candida* infection**	**Other fungal infections**	**Associatedclinical features**	**Antifungal immune defect**
ZNF341 deficiency	*ZNF341*	CMC	*Aspergillus* PJP TDEF *Cryptococcus*	Phenocopy of STAT3-DN	Impaired Th17 development
CARD9 deficiency	*CARD9*	CMC Invasive candidiasis*CNS candidiasis	*Aspergillus* Mucormycosis Deep derma-tophy-toses (tinea profunda)	Other fungal infections	Impaired CARD9 signaling pathway
Chronic granulomatous disease (CGD)	*CYBB* *CYBA* *CYBC1* *NCF1* *NCF2* *NCF4*	Invasive candidiasis	*Aspergillus* (more common than candida) Mucormycosis	Bacterial infections of the lung, liver, bone, skin, and/or lymph nodes Granulomatous inflammation	Impaired phagocyte oxidative burst
Mendelian Susceptibility to mycobacterial disease	*IL12RB1* *IL12B* *IL12RB2* *RORC* *IRF8*	CMC	No	Mycobacteria and *Salmonella* infections*RORC* RORC: mycobacteria only *IRF8* IRF8: mycobacteria ± EBV	Impaired IFN-ɣ sig naling pathway
Severe combined immuno-deficiency	Multiple genes+	CMC	No	Bacterial, viral, and opportunistic infections, and related complications NBS with TRECs allows early or asymptomatic detection	Severe T cell impairment
DOCK8 deficiency	*DOCK8*	CMC	No	Recurrent sinopulmonary and skin/soft tissue bacterial infections Cutaneous viral (molluscum, HSV) infections Severe atopy	Impaired Th17 development

Inborn rrror of immunity	Gene(s)	*Candida* infection	Other fungal infections	Associatedclinical features	Antifungal immune defect
Anhidrotic ectodermal dysplasia with immuno-deficiency	*IKBKG* *NFKBIA*	CMC	PJP	Recurrent sinopulmonary and NTM infections Anhidrosis, conical teeth, and sparse hair may be present in some patients	Impaired NF-κB pathway
LAD1	*ITGB2*	Invasive candidiasis	*Aspergillus*	Skin/soft-tissue infections with *Staphylococcus* and gram-negative bacteria, periodontitis	Neutrophils fail to migrate to infected tissues
Severe congenital neutropenia	*ELANE* *HAX1* *G6PC3*	Invasive candidiasis	*Aspergillus*	*HAX1* and *G6PC3* are syndromic forms of congenital neutropenia.	Impaired neutrophils function

[§]*Dectin-1 deficiency is not recognized as an IEI by the International Union of Immunological Societies' classification of 2024.*
[+]*ADA, AK2, CD247, CD3D, CD3E, CORO1A, DCLRE1C, IL2RG, IL7R, JAK3, LAT, LCP2, LIG4, NHEJ1, NUDCD3, PRKDC, PTPRC, RAC2, RAG1, RAG2, RMRP.*
APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; aka autoimmune polyglandular syndrome type 1 (APS1); CMC, chronic mucocutaneous candidiasis; LAD, leukocyte adhesion deficiency type 1; NBS, newborn screening; NTM, nontuberculous mycobacteria; PJP, Pneumocystis jirovecii *pneumonia; PRR, pattern recognition receptor; STAT1 GOF, signal transducer and activator of transcription 1 gain-of-function; TDEF, thermally-dimorphic endemic mycoses; TGFβ1, transforming growth factor beta-1; TRECs, T-cell receptor excision circles.*

Table1.
Inborn errors of immunity associated with Candida *infection.*

4.1 CARD9 deficiency and invasive candidiasis

CARD9 deficiency is an autosomal recessive disorder that consists of defective production of cytokines and chemokines, as well as a failure to recruit neutrophils and macrophages to the site of infection, resulting in ineffective fungal elimination [24].

CARD9 deficiency is recognized as one of the only IEIs with a specific susceptibility to fungi [22–24]. It was first described by Glocker et al. in 2009 in an Iranian consanguineous family that presented with CMC and deep dermatophytosis. Of the seven patients who presented with CMC, *Candida* CNS infection was diagnosed in three [26].

The CNS *Candida* disease predominance in CARD9 deficiency can be explained by a CARD9-dependent response in the microglia that generates interleukin IL-1β and the C–X–C motif chemokine, which stimulates neutrophil recruitment in the CNS at the signal of candidalysin [18, 22]. Other tissues and organs involved in IC of patients with CARD9 deficiency are the gastrointestinal tract (colon), eye, and bones.

A recent systematic review gathered information from 58 publications, including 89 CARD9 deficiency patients [27]. More than half of these patients presented with a fungal infection that led to the diagnosis of CARD9 deficiency before 18 years of age. The most frequent countries of origin for these patients were China, Algeria, and Iran. Different CARD9 gene mutations have been described; in this study, the most detected mutations were c.865C > T (18 cases), c.883C > T (14 cases), c.819–820insG (12 cases), c.1,118 G > C (9 cases), and c.820dupG (5 cases). All patients had deep infections (involving the dermis, subcutaneous tissues, bones, and internal organs); 32.8% were classified as invasive infections, and 67.18% as noninvasive.

For these cases, fungal infections were caused by *Candida* and *Trichophyton* species in the majority. Analysis developed by the authors indicated that the c.883C > T mutation (the second most common type of mutation found in this study) increased the likelihood of *Candida* infections ($p = 0.008$, OR = 10.421, 95% CI 1.849–58.748). *Candida* invasive infections were characterized by involvement of the CNS with brain abscesses, meningoencephalitis, and multiple masses [26, 27]. Endophthalmitis was another common presentation of IC in CARD9 deficiency, along with osteomyelitis and intraabdominal candidiasis.

5. Conclusions

Candida infections usually develop in association with risk factors such as prolonged broad-spectrum antibiotics, steroid therapy, the use of intravascular devices, and total parenteral nutrition, among others. Chronic and recurrent events of oral and mucosal candidiasis urge the need to rule out immune disorders, including IEIs.

Invasive *Candida* infections, especially CNS candidiasis or other deep-seated presentations, should raise the suspicion of CARD9 deficiency.

Conflict of interest

The authors declare no conflict of interest.

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Section 3

Novel Therapeutic Strategies for Candidiasis Management

chapter 6

Emerging Role of Antifungal Peptides in Novel Therapeutic Strategies Against Candidiasis

Hadi Zare-Zardini, Zahra Salehi and Sima Sadat Seyedjavadi

Abstract

Candidiasis remains a significant public health challenge due to increasing antifungal resistance, biofilm formation, and limitations of conventional antifungal therapies. Antifungal peptides (AFPs), whether naturally occurring or synthetically engineered, have emerged as a promising class of therapeutic agents due to their unique mechanisms of action, including membrane disruption, inhibition of pathogenicity properties, and immune modulation. This chapter reviews the multifaceted role of AFPs in combating *Candida* infections, highlighting their structural diversity, sources, and broad-spectrum antifungal activity. Particular attention is given to their effectiveness against resistant strains and biofilms – areas where traditional agents often fail. Challenges such as peptide stability, cost-effective production, and optimization of drug delivery systems are critically discussed. Advances in peptide engineering, nanotechnology, and AI-based design are paving the way for next-generation AFP-based therapeutics. By transitioning these peptides from the laboratory to the clinic, they promise to transform antifungal treatment paradigms and address the urgent need for new strategies in the fight against drug-resistant candidiasis.

Keywords: candidiasis, antifungal resistance, novel therapeutics, antifungal peptides, mechanisms of action.

1. Introduction

1.1 Epidemiology and clinical relevance of candidiasis

Fungal infections pose a significant global health burden, and among them, candidiasis remains one of the most common and challenging clinical opportunistic infections. Candidiasis is mainly caused by species of the genus *Candida*, and *Candida albicans* is the most common pathogen isolated in mucosal and systemic infections. However, non-*albicans Candida* species such as *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and multidrug-resistant *Candida auris* have emerged as serious threats, particularly in immunocompromised individuals [1].

The prevalence of candidiasis has increased significantly in the past few decades due to the growing population of at-risk individuals, such as patients with hematological malignancies, recipients of organ or hematopoietic stem cell transplants, individuals undergoing chemotherapy or immunosuppressive therapy, and critically ill patients in intensive care units (ICUs) [2]. Invasive candidiasis, including candidemia, is associated with high morbidity and mortality, with reported mortality rates ranging from 40% to 60%, even with antifungal treatment [3].

Epidemiological data indicate that candidemia is the fourth most common bloodstream infection in hospitalized patients in the United States and a leading cause of hospital-acquired sepsis in many parts of the world [4, 5]. According to the Centers for Disease Control and Prevention (CDC), in 2023, more than 2,377 clinical cases of candidemia were reported in the United States alone, resulting in significant healthcare costs and prolonged hospital stays [5].

One of the most worrying aspects of candidiasis is the increase in multidrug-resistant strains, especially *C. auris*, which is capable of causing outbreaks in healthcare settings due to its persistence on surfaces and resistance to several classes of antifungal drugs [6]. The World Health Organization (WHO) has classified *C. auris* as a critical priority pathogen, highlighting the urgent need for novel therapeutic approaches [7].

Furthermore, *Candida* species are capable of forming biofilms on medical devices such as central venous catheters, urinary catheters, and prosthetic devices. These biofilms significantly enhance resistance to antifungal agents and contribute to chronic and recurrent infections [8]. The multifactorial pathogenicity of *Candida*, including its ability to undergo morphological changes, secrete hydrolytic enzymes, and evade host immune defenses, highlights the complexity of its pathogenesis and the difficulty of achieving effective and sustained eradication.

Given these challenges, the medical community is increasingly exploring alternative and adjunctive therapies to conventional antifungal agents. Antifungal peptides (AFPs), as a new class of therapeutic drugs, have attracted attention due to their potent antifungal activity, unique mechanisms of action, and lower tendency to induce resistance. Their potential role in reducing the burden of candidiasis represents a promising frontier in the development of antifungal drugs.

1.2 Limitations of current antifungal therapies

Despite the availability of several classes of antifungal drugs – including azoles, polyenes, and echinocandins – the treatment of candidiasis remains challenging. These therapies, although essential, suffer from significant limitations in terms of efficacy, toxicity, the development of resistance, and clinical outcomes.

The emergence of antifungal resistance is one of the most important issues in the management of *Candida* infections. Resistance to fluconazole, the most widely used azole antifungal, is particularly prevalent in non-*albicans Candida* species such as *C. glabrata*, *C. krusei*, and the recently emerged *C. auris* [9]. Resistance mechanisms include the overexpression of efflux pumps, mutations in target enzymes such as lanosterol 14-α-demethylase, and biofilm formation, which creates a physical and metabolic barrier to the penetration of antifungal drugs [10].

In addition to resistance, many conventional antifungals are associated with significant toxicity. Amphotericin B, though potent, is nephrotoxic and requires close monitoring and dose limitation [11]. Azoles, particularly itraconazole and voriconazole, can cause hepatotoxicity and have significant drug interactions, especially in patients on multiple drug regimens [12]. Echinocandins, although generally safer, are only available via intravenous injection and may cause hepatic effects in some patients [13].

Recurrence of the disease, especially in mucosal candidiasis such as oropharyngeal or vulvovaginal infections, is another major challenge. Recurrence often occurs due to incomplete eradication of the fungal reservoir or the persistence of biofilm-associated cells, which are highly resistant to antifungal agents [14]. In particular, biofilms are up to 1,000 times more resistant to antifungal agents than planktonic cells and are remarkably difficult to eliminate once established on medical devices or mucosal surfaces [8].

Furthermore, the lack of oral antifungal drugs with a broad spectrum of action and rapid fungicidal activity contributes to delays in therapeutic responses. Delays in diagnosis complicate the timely and effective initiation of treatment and often lead to poor clinical outcomes in patients with aggressive disease.

Given the increasing prevalence of resistant *Candida* species, the toxicity profiles of existing agents, and the recurrent nature of mucosal infections, there is an urgent need for innovative therapeutic approaches. These limitations highlight the necessity of investigating alternative agents with novel mechanisms of action – such as AFPs – that could overcome current therapeutic barriers and offer improved efficacy, safety, and resistance profiles.

1.3 The urgent need for novel therapeutic strategies

The convergence of antifungal resistance, limited therapeutic options, and the increasing global burden of candidiasis highlights the urgent need for innovative and effective treatment strategies. The growing ineffectiveness of conventional antifungal drugs – accompanied by biofilm-associated tolerance, multidrug resistance, and frequent clinical relapses – has exposed significant vulnerabilities in the current antifungal drug arsenal [8, 9].

Furthermore, the global emergence of *C. auris*, a multidrug-resistant and highly contagious pathogen, has challenged existing infection control and treatment frameworks and prompted warnings from the CDC and the WHO [6, 7]. The emergence of resistant *Candida* species has outpaced the development of new antifungal agents, leading to a growing gap in effective treatment coverage. Complicating matters further is the fact that antifungal drug discovery has significantly lagged behind antibacterial research in both the public and private sectors [15]. New therapeutic agents must meet several unmet criteria: they must be fungicidal, effective against biofilms, exhibit low toxicity to host tissues, have minimal potential for resistance development, and ideally be compatible with both systemic and topical drug delivery formats. In this context, alternative antifungal approaches, particularly those targeting novel cellular pathways or structural components, are being actively explored.

Meanwhile, AFPs have emerged as a promising therapeutic class. These natural or synthetic peptides exhibit broad-spectrum antifungal activity and unique mechanisms of action that differ significantly from traditional agents, making

them less susceptible to existing resistance mechanisms [16]. AFPs often disrupt fungal membranes, inhibit biofilm formation, and modulate immune responses, offering a multifaceted approach to combating fungal infections [17].

Given their potential to overcome many of the limitations associated with current treatments, AFPs are emerging as powerful candidates for the next generation of antifungal drugs. As research in this area accelerates, there is growing optimism that peptide-based agents may soon fill critical therapeutic gaps in the management of superficial and invasive candidiasis.

2. AFPs – an emerging class of therapeutics

In recent years, AFPs have emerged as a promising class of therapeutic agents in the fight against fungal infections. These natural or synthetic molecules are small, bioactive sequences that are often cationic and amphipathic and are capable of targeting fungal cells through diverse mechanisms. Their activity is not only limited to direct fungicidal effects but also includes biofilm disruption, immune system modulation, and synergistic interactions with conventional antifungal drugs [18, 19].

The increasing prevalence of antifungal drug resistance and the limitations of current antifungal drug treatments (e.g., toxicity, drug–drug interactions, and bioavailability issues) underscore the need for novel antifungal strategies. AFPs are of particular interest due to their broad-spectrum activity, low tendency to develop resistance, and potential for structural engineering to enhance selectivity and stability [20, 21].

This chapter reviews the biological properties, mechanisms of action, sources, and therapeutic potential of AFPs and lays the groundwork for their future clinical application.

2.1 Definition and fundamental concepts of AFPs

Antifungal peptides are a diverse group of short amino acid sequences, either naturally occurring or artificially engineered, that form an important part of the innate immune defense in many living organisms. AFPs, which are typically between 10 and 50 amino acids in length, are cationic, amphipathic, and often adopt structural configurations such as α-helices, β-sheets, or extended coils, which facilitate their interaction with microbial membranes [22].

These peptides account for a large part of antimicrobial peptides (AMPs) but are distinguished by their specific activity against fungal pathogens and emerging multidrug-resistant *Candida auris* [23]. AFPs can act through various mechanisms, in particular membrane permeability, as well as through intracellular targeting, production of reactive oxygen species (ROS), and modulation of host immune responses [24, 25].

One of the defining characteristics of AFPs is their selective toxicity toward fungal cells, which is largely attributed to the differences in membrane composition between host and fungal cells. For example, ergosterol, a key component of fungal membranes, provides a specific binding site for many AFPs, allowing for targeted disruption without harming mammalian cells [26]. This selectivity reduces the potential for systemic toxicity – a critical advantage over many conventional antifungal agents.

In addition to direct antifungal activity, AFPs have also demonstrated immunomodulatory properties. Certain peptides, such as human LL-37, not only kill fungal cells but also influence cytokine production, chemotaxis, and phagocyte activation, thereby enhancing the host's ability to clear infections [27]. This dual function positions AFPs as unique therapeutic agents capable of both pathogen eradication and immune system support.

In addition, AFPs possess structural and functional versatility, which makes them amenable to chemical modification, synthetic optimization, and target-specific engineering. This opens the door to the development of next-generation peptide therapeutics with improved pharmacokinetics, reduced immunogenicity, and increased antifungal potency [28].

2.2 Sources of AFPs: Natural and synthetic origins

Antifungal peptides exhibit extensive structural and functional diversity, a characteristic that stems from their wide range of origins in nature and advancements in synthetic biology. Understanding the sources of AFPs is essential to comprehending their potential as therapeutic agents, as their origin can influence their spectrum of activity, stability, and immunogenicity.

2.2.1 Natural origins of AFPs

Natural AFPs are evolutionarily conserved components of host defense systems in various species. These peptides are generally encoded in the genomes of the producing organisms and are rapidly deployed in response to pathogen invasion.

A. Microbial-derived AFPs

Microorganisms, including bacteria and fungi, produce AFPs as part of their competitive survival strategies in complex microbial ecosystems. Known AFP-producing bacteria include the genera *Bacillus*, *Lactobacillus*, *Streptomyces*, and *Burkholderia*. For example, iturin A, produced by *Bacillus subtilis,* exhibits significant antifungal activity [29]. Champacyclin, a head-to-tail cyclic octapeptide obtained from *Streptomyces champavatii*, inhibits the growth of the yeast *C. glabrata* [30].

B. Plant-derived AFPs

Plants express a wide range of pathogenesis-related proteins and peptides in response to fungal invasion. Based on sequence, cysteine residues, and function, plant AFPs can be divided into different families, including chitinases, defensins, and snakins, as well as hevein-type and glycine-rich peptides [31]. Chitinases are among the best-known and most-studied plant AFPs. They exhibit potent antifungal activity against a wide range of plant-pathogenic fungi [32].

C. Animal-derived AFPs

It has been found that many AFPs of animal origin are part of the innate immune responses of invertebrates and vertebrates. AFPs obtained from marine invertebrates include penaeidins, Cm–p1, and tachystatins. Melittin was isolated

from honey bee venom, which is present in the hemolysin phospholipase A. Melittin shows potent antifungal activity against various fungal species, including *Aspergillus* species and *Candida* species [17]. Protonectin was originally isolated from the venom of the neotropical social wasp *Agelaia pallipes pallipes*. Later, protonectin was shown to have potent antifungal and fungicidal activity against *C. glabrata*, *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* by disturbing membrane integrity and inducing ROS production in yeast cells [33].

2.2.2 Synthetic and engineered AFPs

With increasing interest in peptide-based therapeutics, the development of synthetic and engineered AFPs has gained momentum as an advanced strategy for combating invasive fungal infections. Natural AFPs from bacteria, fungi, plants, and animals have provided valuable structural and functional models, whereas synthetic AFPs offer greater control over peptide properties such as stability, specificity, spectrum of activity, and pharmacokinetics. Through rational design, high-throughput screening, and molecular engineering, synthetic AFPs can overcome many of the limitations associated with natural peptides, including protease sensitivity and suboptimal selectivity [34].

2.2.2.1 Rationale for peptide engineering

AFPs, despite exhibiting potent antifungal activity, often face limitations such as a short half-life in physiological environments due to enzymatic degradation and poor bioavailability. Artificial modifications have been employed to overcome these challenges and enhance the therapeutic potential of AFPs by improving protease resistance, increasing membrane selectivity, optimizing the charge–hydrophobicity balance, and enabling targeted delivery [18]. Common modification strategies include D-amino acid substitution to increase resistance to proteolysis [35], peptide cyclization (e.g. head-to-tail or side-chain cyclization) to stabilize secondary structures [36], PEGylation or lipidation to improve bioavailability and prolong systemic half-life [37], and glycosylation to enhance immune responses and target specificity, thereby improving the biological activity of peptide drugs [38]. Collectively, these approaches contribute to enhanced therapeutic efficacy, particularly in the treatment of systemic or biofilm-associated fungal infections, and facilitate the development of combinatorial therapies with existing antifungal agents [39].

2.2.2.2 Synthetic libraries and design approaches

Modern techniques such as solid-phase peptide synthesis (SPPS), computational modeling, and phage display allow for the rapid design and screening of synthetic peptide libraries [40]. High-throughput assays enable researchers to identify AFP candidates with optimal antifungal activity against a wide range of fungal pathogens [41].

Computational tools such as quantitative structure–activity relationship (QSAR) models, machine learning algorithms, and molecular dynamics simulations are increasingly used to predict peptide–membrane interactions, aggregation propensity, and target specificity [42]. These innovations reduce the time and cost

associated with experimental screening and improve the success rate of identifying prime candidates [43].

2.3 Mechanisms of action of AFPs

Antifungal peptides exert their effects through diverse mechanisms that target several structural and functional components of fungal cells. Unlike conventional antifungal drugs – which usually focus on a single pathway, such as ergosterol synthesis or β-glucan formation – AFPs employ a multi-target strategy. These mechanisms include membrane disruption, inhibition of cell wall biosynthesis, induction of oxidative stress, inhibition of pathogenic features such as morphogenesis and biofilm formation, and modulation of host immune responses. This multifaceted approach not only increases their fungicidal potential but also significantly reduces the risk of resistance development [22]. AFPs are typically cationic, amphipathic peptides that enable selective targeting of fungal membranes due to differences in membrane composition compared to mammalian cells. Their structural diversity, functional flexibility, and immune-modulation capacity make them highly promising candidates for next-generation antifungal therapies, especially in the context of drug-resistant fungal infections [41]. A schematic overview of these mechanisms is presented in **Figure 1**, which illustrates the multifactorial ways in which AFPs exert their antifungal activities.

2.3.1 Membrane targeting and disruption

One of the most basic and well-known mechanisms by which AFPs exert their activity is through direct targeting and disruption of the fungal cell membrane. AFPs are generally cationic and amphipathic, allowing them to selectively interact with negatively charged components of fungal membranes, such as phosphatidylserine and ergosterol-rich lipid bilayers [44, 45].

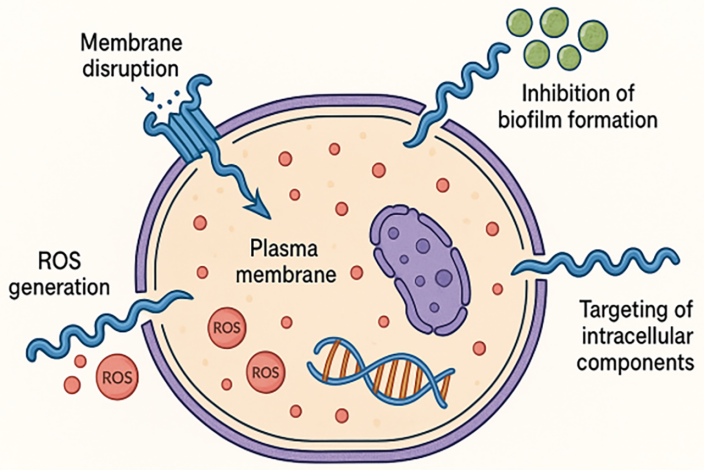


Figure 1.
Mechanisms of action of antifungal peptides (AFPs). AFP mechanisms include membrane disruption, intracellular targeting, induction of reactive oxygen species (ROS), inhibition of biofilm formation, and immune modulation. These actions collectively contribute to their effectiveness against resistant and biofilm-forming fungal pathogens.

After binding to the fungal membrane, AFPs adopt an active conformation – often α-helical or β-sheet – that enables them to enter the lipid bilayer. This interaction results in membrane permeability, which leads to ion imbalance, loss of membrane potential, leakage of essential intracellular contents, and ultimately cell lysis and death [46].

Several models have been proposed to explain this membrane-degrading activity. In the barrel-stave model, peptides insert vertically into the membrane to form transmembrane channels. In the carpet model, peptides align parallel to the membrane surface and disrupt the bilayer in a detergent-like fashion. In the toroidal pore model, peptides generate curved pores lined by both peptides and lipid molecules [47]. A well-known example is Histatin 5, a salivary peptide that targets *C. albicans* by binding to specific receptors and inducing membrane disruption and mitochondrial dysfunction [48]. Similarly, LL-37, a human cathelicidin, binds to fungal membranes and induces depolarization and pore formation [49].

Importantly, membrane-disrupting peptides are often rapid-acting, and their broad-spectrum activity makes them potent against planktonic fungal cells and biofilm-forming populations.

2.3.2 Inhibition of fungal cell wall biosynthesis

The fungal cell wall is a critical structural and functional component that maintains cell integrity, shape, and survival under stress. It is mainly composed of β-glucans, chitin, and mannoproteins, which are not found in human cells – making it an ideal target for antifungal therapeutics [50]. AFPs target fungal cell walls differently than conventional antifungal drugs, reducing toxicity to mammalian cells. Fungal walls are primarily composed of β-glucans, chitin, and mannans. Echinocandins (e.g. caspofungin, micafungin, anidulafungin) inhibit β-(1,3)-glucan synthase and weaken the cell wall structure [25]. Chitin-targeting agents, such as nikkomycin and polyoxin, block chitin synthase and disrupt cell integrity. Natural compounds such as cyclothiazomycin B1 and chromobactomycin also act by binding to chitin [51]. Mannan, found in the outer layer, helps with adhesion and evasion from the immune system. Pradimicin (PRM) binds to D-mannoside in fungal cell walls, damaging membrane integrity and inducing apoptosis [25].

2.3.3 Induction of oxidative stress and mitochondrial dysfunction

One of the key mechanisms through which AFPs exert their fungicidal effects is the induction of oxidative stress and mitochondrial dysfunction. This mode of action is particularly well-documented in *C. albicans* and other pathogenic fungi, where AFPs stimulate the overproduction of ROS, leading to cell damage and apoptosis-like cell death [52].

2.3.3.1 ROS production and cellular stress

AFPs, such as Histatin 5, a salivary peptide in humans, enter fungal cells and interact with mitochondrial components to significantly increase intracellular ROS

levels. This oxidative stress damages proteins, lipids, and nucleic acids, compromising cellular viability [48].

2.3.3.2 Mitochondrial dysfunction

Mitochondria are highly sensitive to redox imbalances. AFP-induced oxidative stress disrupts mitochondrial respiration and ATP synthesis, ultimately leading to the release of cytochrome c and other pro-apoptotic factors that mimic apoptosis in fungal cells [53]. Some plant defensins (e.g. RsAFP2) have also been shown to indirectly target mitochondrial pathways through interaction with glucosylceramides, key sphingolipids present in fungal membranes [54]. This multifaceted mechanism makes the induction of oxidative stress a potent and low-resistance strategy, contributing to the high efficacy of AFPs even against biofilm-forming and drug-resistant species of *Candida*.

2.3.4 Biofilm disruption

Biofilms are structured microbial communities enclosed in a self-assembled extracellular matrix (ECM) that makes them up to 1,000-fold more resistant to antifungal agents [55]. AFPs can also act by preventing the formation of fungal biofilms and eradicating preformed biofilms through mechanisms related to cell wall disruption, inhibition of planktonic fungal cell adhesion to surfaces, gene regulation, and generation of ROS.

2.4 Comparative analysis of AFPs and conventional antifungal drugs

While conventional antifungal drugs have improved the management of fungal infections, their effectiveness has been limited by issues such as resistance, toxicity, and poor activity against biofilms. In contrast, AFPs offer a promising alternative with unique properties and potential advantages, as summarized in a comparative analysis with conventional antifungal agents in **Table 1**.

2.4.1 Mechanism of action

Conventional antifungal drugs target specific components of fungal cells — such as ergosterol synthesis (azoles), membrane integrity (polyenes), or cell wall synthesis (echinocandins) – but their narrow-spectrum mechanisms make them susceptible to resistance through point mutations or overexpression of efflux pumps [12]. In contrast, AFPs exert multi-targeted actions, including membrane permeabilization, mitochondrial disruption, and biofilm inhibition [56]. Their amphipathic nature causes selective destabilization of the fungal membrane, while some AFPs, such as histatins and plant defensins, can also induce ROS production and apoptosis-like cell death in fungi [24].

2.4.2 Antifungal spectrum and biofilm activity

Another important limitation of current antifungal therapies is their limited effectiveness against fungal biofilms, which are notorious for being resistant to treatment and are implicated in chronic infections, particularly those associated with

Feature	AFPs	Traditional antifungal drugs
Mechanism of action	Membrane disruption, ROS induction, intracellular targeting, immunomodulation	Ergosterol synthesis inhibition (azoles), membrane binding (polyenes), and cell wall inhibition (echinocandins)
Spectrum of activity	Broad-spectrum (*Candida* spp., molds, resistant strains)	Variable; some are narrow-spectrum (e.g. fluconazole)
Biofilm activity	Effective against biofilms; disrupts the matrix and inhibits adhesion	Generally weak against mature biofilms
Resistance potential	Low; multiple, rapid-acting targets reduce resistance development	Increasing resistance, especially in Candida and Aspergillus
Toxicity	Generally low; some off-target effects at high doses	Dose-limiting toxicity is common (e.g. amphotericin B nephrotoxicity)
Pharmacokinetics	Short half-life; poor oral bioavailability (improved via engineering)	Well-characterized; varies across classes
Combination potential	High synergy with azoles and echinocandins	Often used in combination, but there is a risk of drug–drug interactions
Manufacturing cost	High (peptide synthesis/ engineering); decreasing with new technologies	Lower cost; well-established production pipelines
Clinical maturity	Mostly preclinical or early clinical stage	Widely approved and used in standard care

Table 1.
Comparative overview of antifungal peptides (AFPs) and conventional antifungal drugs.

implanted medical devices. Conventional drugs often show poor penetration and lower activity in mature biofilms, necessitating high doses or combination therapy. In contrast, several AFPs have demonstrated strong anti-biofilm properties, both *in vitro* and *in vivo* [57]. The ability of AFPs to destroy biofilms lies in their physicochemical properties, which enable them to penetrate and damage fungal cells and the ECM.

2.4.3 Toxicity and host compatibility

Conventional antifungals, especially polyenes such as amphotericin B, pose risks of systemic toxicity and drug interactions that complicate treatment [58]. In contrast, AFPs often exhibit less cytotoxicity, selectively targeting fungal membranes without killing mammalian cells. Furthermore, synthetic AFPs can be optimized for greater stability and reduced immunogenicity, enhancing their safety profile [59].

2.4.4 Resistance development

Perhaps one of the most attractive advantages of AFPs is their low tendency to develop resistance. Unlike small-molecule drugs that act on single targets, the multifaceted modes of action of AFPs pose a major obstacle to the evolution of resistance. *In vitro*, fungi exposed to sublethal levels of AFPs rarely develop stable

resistance, a phenomenon attributed, in part, to the physical, rather than enzymatic, nature of the membrane disruption [16].

Moreover, AFPs can synergize with conventional antifungal drugs, restoring activity against resistant isolates and reducing the required doses of both agents. Such synergy has been demonstrated between defensin PvD_1 and amphotericin B [60].

2.4.5 Stability, delivery, and formulation

One area where traditional drugs still excel is formulation stability and oral bioavailability. Many AFPs are subject to proteolytic degradation *in vivo* and require encapsulation or structural modification for systemic administration. However, advances in peptide engineering – such as cyclization, D-amino acid substitution, and nanoparticle drug delivery systems – are rapidly overcoming these obstacles [61].

3. AFP efficacy against *candida* species

The increase in antifungal resistance in *Candida* species, particularly *C. albicans*, *C. glabrata*, and *C. auris*, has led to increased interest in AFPs as alternative therapies. AFPs have unique mechanisms of action, broad-spectrum activity, and the ability to overcome resistance to conventional drugs. They effectively target both planktonic and biofilm-associated cells by disrupting membrane integrity, inducing oxidative stress, and interfering with intracellular processes [61–63]. Unlike traditional antifungals that act on limited targets such as ergosterol or β-glucan synthesis, AFPs act on multiple cellular sites, reducing the risk of resistance [45]. Many AFPs also show strong activity against azole-resistant strains, making them valuable in combating multidrug resistance [64].

3.1 *In vitro* and *in vivo* studies of AFPs against *candida* spp.

AFPs have emerged as promising therapeutic candidates in the ongoing battle against *Candida* infections, offering a broad spectrum of activity and a lower likelihood of developing resistance. Their efficacy has been confirmed in both *in vitro* and *in vivo* models, ranging from simple broth microdilution assays to complex mammalian infection systems. This body of evidence confirms their potential as next-generation antifungal agents.

3.1.1 In vitro studies

In vitro experiments have played an important role in elucidating the mechanisms of action, minimum inhibitory concentrations (MICs), and synergistic interactions of AFPs with conventional antifungal drugs. These studies usually use standardized methods such as those established by the Clinical and Laboratory Standards Institute (CLSI) [65]. For example, histatin 5 (Hst5), a salivary peptide, is capable of inhibiting the growth of Candida albicans at concentrations between 25 and 800 μg/mL [66]. Similarly, synthetic derivatives such as P-113, a truncated analog of Hst5, have retained their activity under physiological

salt conditions and have demonstrated greater resistance to proteolytic degradation [67].

Synthetic peptides, such as NP339, a cationic peptide, have demonstrated broad-spectrum activity *in vitro* against *C. albicans* and *C. auris*. NP339 exhibited rapid fungicidal effects within less than one hour of exposure against *C. albicans* [68].

Furthermore, synergy studies have shown that AFPs can enhance the efficacy of azoles and polyenes. For example, LL-37 and its analogs have demonstrated synergistic effects with fluconazole against *Candida* strains [69].

Importantly, *in vitro* biofilm models have highlighted the potential of AFPs to disrupt *Candida* biofilms. Peptides, such as Ctn [15–34] derivatives, effectively reduced viable biomass and disrupted ECM integrity [70].

3.1.2 *In vivo* studies

In vivo assessments provide fundamental insights into efficacy, toxicity, pharmacokinetics, and host responses in the context of complex biological systems. Murine models of candidiasis have been widely used to study the therapeutic potential of AFPs. For example, histatin-5 has been shown to be effective in a murine model of vulvovaginal candidiasis and to reduce the fungal burden in the vagina [71].

In a systemic candidiasis model, intravenous administration of NP339 resulted in a significant reduction of fungal CFUs in the kidney and spleen, accompanied by a favorable safety profile and no observable histological damage [72].

3.2 AFPs and their effects on *candida albicans* biofilms

Biofilm formation by *C. albicans* is a major clinical challenge due to its contribution to antifungal resistance, persistent infections, and high recurrence rates, particularly in infections associated with medical devices such as catheters, dentures, and prosthetic implants [73]. Biofilms are complex, structured microbial communities embedded in a self-assembled ECM that protect fungal cells from host immunity and conventional antifungal treatments. The biofilm phenotype is characterized by increased tolerance to azoles, polyenes, and echinocandins, necessitating the development of new drugs that can penetrate and disrupt these resistant communities [74].

AFPs, as part of the innate immune defense in many living organisms, have emerged as promising alternatives due to their broad-spectrum activity and unique modes of action. Importantly, several AFPs have demonstrated potent anti-biofilm activity against *C. albicans*, both at the early stages of adhesion and at the mature stages of biofilm formation.

3.2.1 Mechanisms of AFP action against biofilms

AFPs inhibit fungal biofilm formation and persistence through different mechanisms and target various stages of biofilm development. AFPs, such as OSIP108 and Tn-AFP1, reduce biofilm formation by *C. albicans* during the cell adhesion stage. Tn-AFP1 can inhibit biofilm formation by interfering with adhesion-related genes, such as *ERG*11 and *MDR*1, thereby blocking the initiation of biofilm

formation. Many AFPs directly disrupt fungal membranes, increasing permeability and causing cell lysis. Peptides such as KP, Protonectin, and Polybia-MPI are known for their ability to damage fungal membranes in this way. Several AFPs also increase the production of ROS, which damage fungal cells and play a role in biofilm inhibition. KP and Battacin analog 13 are examples of peptides with ROS-mediated activity. AFPs, such as Tn-AFP1, destabilize fungal membranes and biofilm structure by targeting ergosterol biosynthesis pathways, such as downregulating *ERG*11. AFPs, such as ApoEdpL-W, bind ECM components, such as β-glucans, while echinocandins reduce ECM content, making biofilms more vulnerable to disruption. Some peptides, such as EntV68, block the transition from yeast to hyphal growth, which is crucial for the maturation of *Candida* biofilms. The effectiveness of AFPs can vary depending on the stage of biofilm development. Early-stage inhibitors, such as ApoEdpL-W, act during initial biofilm formation, whereas others, such as KP, can target mature biofilms at higher concentrations. In addition, AFPs can modulate the expression of genes related to biofilm formation and hyphal growth, also influencing fungal morphology and matrix production [57].

4. Challenges in the development and application of AFPs

Peptide-based antifungal therapies face several critical challenges that limit their clinical application. A major issue is poor stability and bioavailability, as peptides are highly susceptible to enzymatic degradation and have a short half-life, especially when administered orally. Toxicity and lack of selectivity also raise concerns, as some peptides may damage human cells due to their amphipathic nature. High production costs and complex synthesis methods further hinder scalability and accessibility. Furthermore, effective delivery remains a challenge, as peptides struggle to cross biological barriers such as the skin and blood–brain barrier and are often degraded before reaching the site of infection.

Ongoing research focuses on overcoming these obstacles through peptide modification, protective formulations, and advanced drug delivery systems. These innovations aim to increase peptide stability, selectivity, and cost-effectiveness, making them more suitable for future clinical use [75].

5. Future perspectives in the development of AFPs

The future of AFP therapy is shaped by significant technological and scientific advances aimed at improving efficacy, stability, and drug delivery. One of the key areas of innovation is the rational design and molecular engineering of peptides. Synthetic peptides with enhanced antifungal activity and reduced toxicity are being developed by modifying amino acid sequences, altering hydrophobicity, and incorporating unnatural residues. Strategies such as cyclization and disulfide bond formation are widely used to increase peptide stability against proteolytic degradation and prolong their therapeutic half-life *in vivo* [76].

In addition, advances in peptide drug delivery systems are critical to overcoming the pharmacokinetic limitations of AFPs. Drug delivery carriers such as nanoparticles, liposomes, and hydrogels have shown great potential in protecting peptides from enzymatic degradation and facilitating targeted delivery to sites of

infection. These carriers also allow for controlled and sustained release, extending the therapeutic window. Transdermal systems and mucosal formulations, including nanoemulsions and bioadhesive patches, are actively being developed for the treatment of localized fungal infections such as oral, vaginal, or cutaneous candidiasis [77, 78].

Combination therapies represent another promising frontier. Co-administration of AFPs with conventional antifungal agents (e.g. azoles, echinocandins) has been shown to produce synergistic effects, increasing the efficacy of fungal killing and reducing the likelihood of resistance. Moreover, the combination of AFPs with immunomodulatory compounds, such as cytokines or immune checkpoint inhibitors, may enhance host immunity and improve treatment outcomes, especially in immunocompromised individuals [75].

Finally, computational biology and artificial intelligence (AI) are transforming the development of AFPs. Bioinformatics tools are utilized for structure-based design and optimization, enabling accurate prediction of peptide–target interactions and antimicrobial efficacy. Machine learning algorithms, trained on databases of AMPs, can identify key features associated with antifungal activity. These AI-based approaches significantly reduce the need for extensive experimental screening and expedite the discovery of novel and potent AFPs [79, 80].

Overall, the integration of synthetic biology, smart drug delivery systems, combination strategies, and computational tools offers a promising roadmap for overcoming current challenges and expanding the clinical applicability of AFPs in the near future.

6. AFPs in preclinical and clinical development

Several AFPs have progressed into clinical development for treating fungal infections, particularly those caused by *Candida* species and biofilm-associated conditions. NP213 (Novexatin®) is a synthetic cyclic peptide designed for the topical treatment of onychomycosis, demonstrating strong efficacy and safety, with over half of patients clearing the infection after daily use. Similarly, HXP124, a plant-derived defensin, has shown broad antifungal activity and good nail penetration, significantly reducing infection in early trials. CZEN-002, a synthetic peptide for vulvovaginal candidiasis, combines antifungal and anti-inflammatory effects and has achieved high cure rates in initial studies. P113, derived from histatin 5, exhibits potent activity against *Candida* and bacteria and has proven to be safe in clinical trials for oral infections. Omiganan, a broad-spectrum synthetic peptide with immunomodulatory properties, is safe for topical use, though its clinical antifungal efficacy remains unconfirmed. hLF1- 11, derived from human lactoferrin, shows antifungal and immune-enhancing actions with demonstrated safety, yet its clinical effectiveness against fungal infections is still being evaluated. Finally, Iseganan (IB-367), a protegrin-derived peptide, offers broad antimicrobial activity and effectively reduces oral fungal loads; however, clinical outcomes on mucositis and pneumonia treatment have been mixed. Overall, these AFPs present promising safety and antifungal activity profiles, highlighting their potential as new topical or systemic antifungal therapies [68].

7. Conclusion

Fungal infections, particularly those caused by drug-resistant *Candida* species, continue to be a major clinical challenge, especially in immunocompromised individuals. The limitations of conventional antifungal therapies – such as resistance, toxicity, and limited-spectrum activity – have highlighted the need for alternative therapeutic strategies.

Antifungal peptides have emerged as promising therapeutic candidates due to their rapid fungicidal activity, broad-spectrum efficacy, and unique mechanisms of action. Their ability to disrupt fungal membranes and modulate immune responses, coupled with the potential for structural optimization, makes them attractive for the development of next-generation antifungal drugs. Advances in drug delivery technologies, including nanoparticles and mucosal systems, are further enhancing their clinical potential.

Despite these advantages, AFPs face several challenges, including instability, high production costs, potential immunogenicity, and drug delivery problems. Addressing these obstacles requires ongoing interdisciplinary research and innovation in peptide engineering, computational modeling, and combination therapies.

Ultimately, the successful clinical application of AFPs depends on integrated scientific, regulatory, and economic efforts. With sustained research and investment, AFP-based therapies could significantly advance the prospects for treating resistant fungal infections, including invasive candidiasis.

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Conflict of interest:

The authors have no conflicts of interest.

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Chapter 7

Novel Chemical Strategies for Targeting Candidiasis

Mohammad Shafiei and Atefeh Akbari

Abstract

Across the landscape of fungal infections, invasive candidiasis remains a pressing clinical challenge, driven by rapid resistance to azoles among non-albicans species such as *Candida glabrata*, *Candida krusei*, and *Candida auris*. This chapter reviews contemporary medicinal chemistry innovations aimed at countering azole resistance and expanding the antifungal spectrum. The introduction situates the problem within the limitations of traditional antifungal classes – azole antifungals, echinocandins, polyenes, and flucytosine – and underscores the urgent need for agents that combine potent activity with favorable safety profiles. Next, under the heading "Exploring the Known Targets," the discussion focuses on structural modifications of existing drugs to explore known targets, optimize new interactions, and mitigate human side effects. This is followed by a description of dual-mechanism or hybrid designs that simultaneously target two or more fungal proteins to disrupt resistance pathways and broaden antifungal coverage, representing a new strategic approach. A section on computational discovery highlights the pivotal role of virtual screening, docking, quantitative structure–activity relationships, molecular dynamics, and the growing influence of artificial intelligence and machine learning in guiding lead identification and optimization. Ultimately, we underscore the importance of integrating medicinal chemistry with advanced computational tools to develop potent, low-toxicity therapeutics capable of confronting resistant *Candida* strains and reducing global fungal disease mortality.

Keywords: candidiasis, medicinal chemistry, azole, fungal resistance, hybrid inhibitors, *in silico*

1. Introduction

Invasive fungal infections caused by *Candida* species continue to pose a formidable challenge in clinical settings, particularly among immunocompromised patients. With an estimated 1.5 million cases annually and mortality rates often surpassing 40% in high-risk groups, candidiasis is not only prevalent but often deadly [1]. The clinical landscape has been further destabilized by the emergence of resistant non-albicans species such as *Candida glabrata*, *Candida krusei*, and the highly problematic *Candida auris*, which has demonstrated multidrug resistance and

outbreak potential in healthcare environments, underscoring the urgent need for novel therapeutic strategies [2].

While antifungal drug classes such as azoles, echinocandins, polyenes, and flucytosine have underpinned therapy for decades, their limitations are increasingly evident. Azoles suffer from resistance due to efflux pump activation and target mutations; polyenes are constrained by nephrotoxicity; and echinocandins, though generally safer, show reduced activity against biofilms and certain *Candida* strains. These factors threaten to diminish the efficacy of existing agents and highlight the critical necessity for innovative antifungal drugs with improved safety profiles and broader activity [3, 4].

Recent insights into fungal cell biology have paved the way for more selective therapeutic strategies. Targeting fungal-specific elements – such as ergosterol biosynthesis enzymes, stress response pathways, and virulence factors – offers the potential for improved selectivity and reduced host toxicity. A prime example is the development of next-generation tetrazoles like oteseconazole, which leverage structural differences between fungal and human lanosterol 14α-demethylase to minimize off-target effects. Such advances illustrate how molecular precision can be translated into safer, more effective antifungal agents [1].

Beyond target specificity, a multifaceted approach is gaining traction. Hybrid molecules that combine two or more mechanisms of action are being designed to simultaneously overcome resistance, enhance potency, and extend spectrum. For instance, conjugating ergosterol biosynthesis inhibitors with histone deacetylase (HDAC) moieties has shown promise in preclinical models. Still, these strategies come with challenges – including stability, bioavailability, and potential toxicity – that require careful optimization [5].

Complementary to wet-lab innovation, computational drug discovery tools now play a central role in antifungal development. Quantitative structure–activity relationship (QSAR), molecular docking, pharmacophore modeling, and machine learning (ML)–driven compound prioritization are shortening the timeline from hit discovery to lead optimization. Yet, these technologies are not without limitations: *in silico* predictions must be validated biologically, and they depend on the availability of high-quality structural data – a particular hurdle in fungal research [6].

This chapter explores the current frontier of chemical strategies for addressing candidiasis. Section 2 reviews established and emerging molecular targets specific to *Candida* species. Section 3 examines the rationale, design principles, and challenges of hybrid antifungal molecules. Section 4 highlights the role of computational tools in accelerating drug discovery and guiding rational design. Finally, we discuss how these strategies may converge to meet the urgent clinical need for safer, more robust anti-candidiasis therapies. These approaches are summarized in **Figure 1**, which outlines the integrated framework guiding next-generation antifungal development.

2. Exploring the known targets

With the rise of resistant isolates of fungal pathogens, research has increased in finding new targets, especially those involved in the resistance

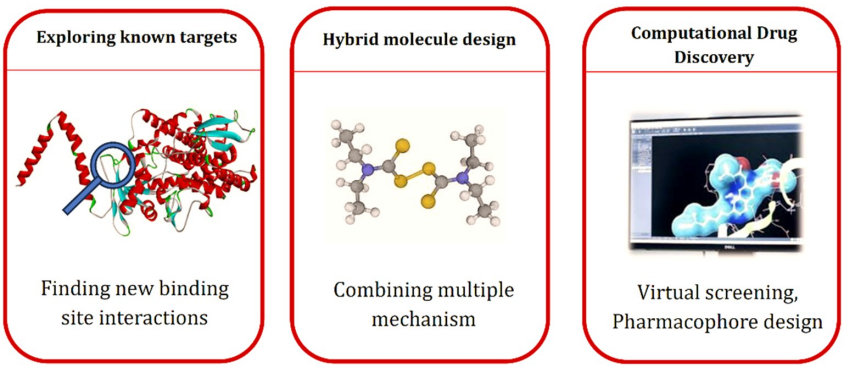


Figure 1.
New strategies to design novel chemical compounds.

process. The druggability of these targets and their potential to treat resistant fungal infections has been tested. Innovative strategies for the next generation of antifungal therapy include heat shock protein 90 (HSP90) inhibitors, HDAC inhibitors, other protein–protein interactions, and immune response-based proteins like c-Jun N-terminal kinase 1 (JNK-1). While designing novel drugs for these targets is very useful, the challenge still exists in the selectivity of these agents due to the eukaryotic nature of fungal cells, which is very important in terms of potential side effects [7, 8].

Recently, these efforts led to the design and discovery of a novel and selective fungal HSP90 inhibitor (see **Figure 2**) [9]. HSP90 is known as the Achilles heel of drug resistance across diverse pathogenic fungal species, so it is considered to be a new strategy to mitigate resistance and counter the threat posed by drug-resistant fungi. This compound exhibited potent synergistic effects with fluconazole *in vitro* and *in vivo*. Additionally, it reversed FLC resistance by downregulating the expression of related genes. In particular, it could avoid the potential mammalian toxicity of HSP90 inhibitors based on key residue differences that were established between humans and fungi [9]. These data support the feasibility of targeting fungal HSP90 as a promising antifungal strategy [5, 10].

Although the discovery of new key targets in fungi offers promising avenues for novel antifungal therapies, the process of designing lead molecules

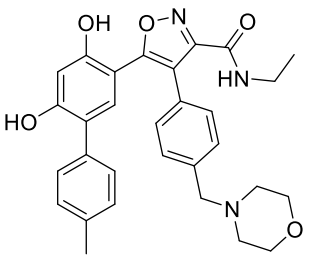


Figure 2.
Novel species-selective fungal HSP90 inhibitor.

that can be effectively converted into safe and potent drug candidates remains a complex, long-term endeavor. Current state-of-the-art methods for drug development against novel targets are time-consuming and resource-intensive.

On the contrary, many recent research efforts have focused on exploring new binding sites within old fungal targets, aiming to discover innovative interactions that can be exploited for therapeutic benefit. Medicinal chemists are actively modifying known drugs to enhance their affinity and selectivity for fungal targets. Such structural modifications aim to improve drug efficacy, stability, and pharmacokinetic properties, ultimately leading to more effective antifungal therapies with fewer side effects.

A notable illustration of this approach is the innovation of the tetrazole framework within the azole antifungal class. A primary challenge with azole drugs is their propensity to interfere with other medications due to their inhibition of the human CYP3A4 enzyme, which metabolizes many drugs. This issue primarily stems from the metal-binding site of azole molecules, which is responsible for CYP3A4 inhibition. To overcome this, scientists replaced the imidazole ring with a triazole ring, increasing the compound's selectivity for the fungal target, although some issues persisted [1, 11].

Recently, Viamet Pharmaceuticals has achieved notable advancements through strategic medicinal chemistry. They engineered three new azole derivatives that exhibit high specificity for fungal CYP51, along with enhanced potency, improved pharmacokinetic profiles, and better physicochemical characteristics compared to earlier compounds. These improvements involved substituting highly metal-affinic, potent triazole rings with tetrazole rings, which have less affinity for metals, and compensating for any reduction in potency by exploring binding site interactions and modifying side chains. This systematic approach led to the development of a fourth-generation azole with superior selectivity and efficacy (see **Figures 3** and **4**) [1, 12, 13].

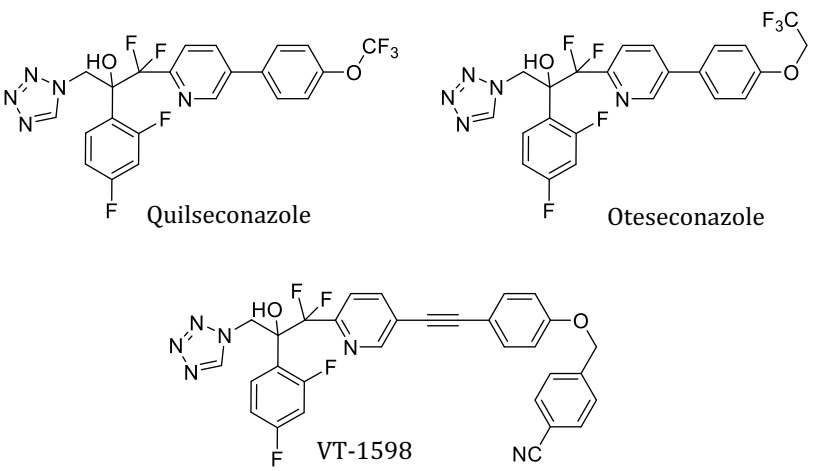


Figure 3.
Fourth-generation azole structures.

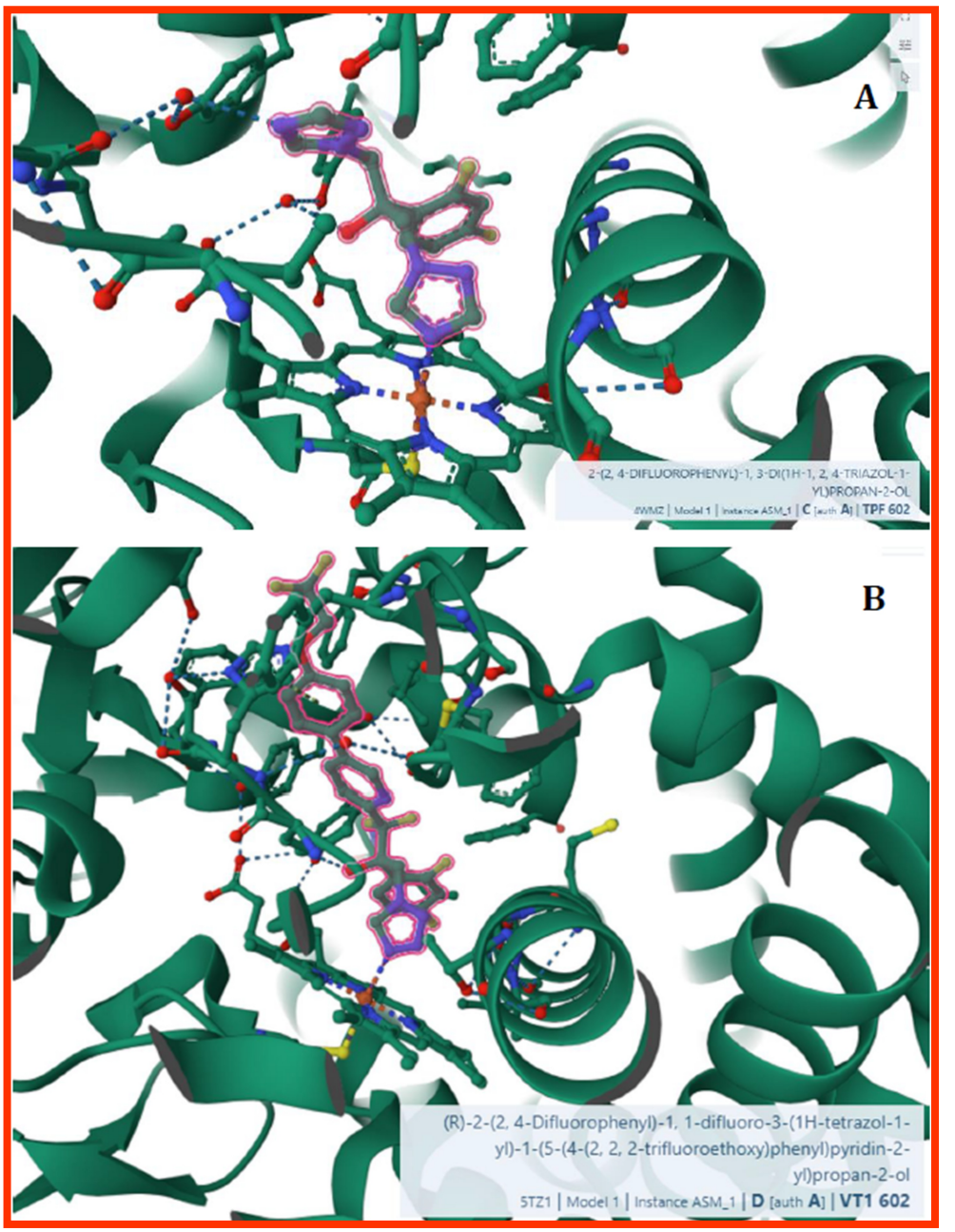


Figure 4.
(a) 3D structure of S. cerevisiae *CYP51 complexed with fluconazole in the active site (PDB: 4WMZ). (b) 3D structure of* C. albicans *CYP51 complexed with oteseconazole in the active site (PDB: 5TZ1), obtained from rcsb.org.*

One such candidate, quilseconazole (VT-1129), is in early-phase clinical trials targeting cryptococcal meningitis. Preclinical studies in mice demonstrated promising results, with better survival rates after one month compared to traditional

drugs like fluconazole. In June 2016, Quilseconazole was granted fast track designation by the FDA as an orphan drug for treating cryptococcal meningitis [14, 15].

Another tetrazole-based compound, oteseconazole (VT-1161), showed success in Phase III clinical trials for vulvovaginal candidiasis in March 2019. It became the first FDA-approved medication for this condition [16–18]. The most recent candidate, VT-1598, also offers the broadest antifungal activity within the tetrazole class and has exhibited potent *in vitro* effects against *Coccidioides* species. Currently, VT-1598 is undergoing Phase I trials for treating candidiasis, coccidioidomycosis, and cryptococcosis [19–21].

The binding site interactions of fourth-generation azoles are unique in comparison to older structures like voriconazole, which was first used as a lead structure for designing these new structures (see **Figure 4**).

Overall, these developments underscore the importance of fine-tuning side-chain structures and exploring binding pocket interactions to boost drug potency. Furthermore, modifications to the metal-binding tetrazole group have played a crucial role in enhancing both the selectivity and efficacy of these antifungal agents.

3. Hybrid molecule design

Molecular hybrids of structures with known mechanisms are now gaining momentum worldwide and may be a key tool in the arsenal of medicinal chemistry efforts for drug discovery. Hybrid or dual-mechanism molecules are defined as combinations of two or more chemical scaffolds that act on different targets to create more specific and powerful drugs. In addition, this strategy could effectively combat resistance development by targeting different biological pathways. Recently, efforts have increased to introduce one molecule with at least two different mechanisms against fungal infections. Following this, we will discuss some of these studies.

3.1 CYP51/HDAC inhibitors

Fungal HDACs play a key role in the regulation of stress adaptation, morphogenetic changes, and virulence in fungal pathogens. On the contrary, azoles have been known as the first-line therapy for invasive fungal infections for decades, and azole resistance includes the overexpression of CYP51. Therefore, co-targeting HDAC and CYP51 has been considered a potential antifungal strategy. In order to combine azole as CYP51 inhibitor with SAHA, an HDAC inhibitor, Han and coworkers merged key pharmacophores of both CYP51 and HDAC inhibitors directly and through linkers. In this work, docking studies confirmed the formation of appropriate interactions similar to posaconazole. The most active compound (see **Figure 5**) showed significant *in vitro* and *in vivo* activities through the inhibition of ergosterol biosynthesis and downregulation of the expression of CYP51 and the efflux pump [22, 23].

3.2 HDAC/ HSP90 inhibitors

Ganetespib, a known HSP90 inhibitor, when used against azole-resistant *C. albicans*, was found to have m-diphenol and triazolone moieties necessary

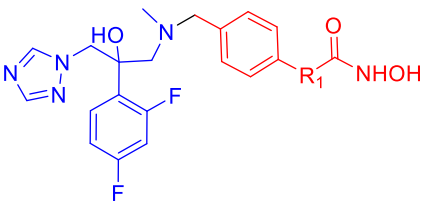


Figure 5.
CYP51/HDAC inhibitor.

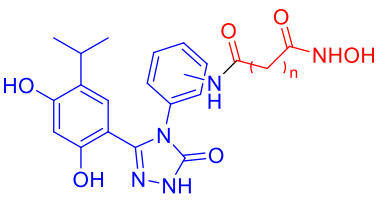


Figure 6.
HDAC/HSP90 inhibitor.

for effective hydrogen bonding in fungal HSP90. Therefore, this part was linked to the hydroxamic acid key structure for HDAC inhibition through alkyl amides. The compound with para-hydroxyaminooxobenzamide and a six-carbon atom linker (see **Figure 6**) showed significant synergistic potency in treating fluconazole-resistant candidiasis. Besides its anti-*Candida* activity, fungal-selective inhibitory activity on HSP90/HDAC, low toxicity, and excellent *in vitro* (FICI = 0.266) and *in vivo* synergistic antifungal potency were also observed [23].

3.3 Janus kinase-2/HDAC inhibitor

Some studies successfully demonstrated the synergistic effects of dual Janus Kinase-2 (JAK2)/HDAC inhibitors and fluconazole to treat resistant *C. albicans* infections. 2-aminopyrimidine-based compounds (an important pharmacophore of JAK2 inhibitors) and hydroxamic acid or benzamide (zinc-binding group of HDAC) hybrid structures were synthesized and evaluated. Among them, one exhibited moderate activity and synergistic effects with FLC (see **Figure 7**) [5].

3.4 Squalene epoxidase/CYP51 inhibitor

In another study, the key ergosterol bio-synthetic enzymes (Squalene epoxidase [SE]; 14 alpha-demethylase, CYP51) were selected as dual-target receptors to guide the construction of novel antifungal compounds, which could achieve the purpose of improving drug efficacy and reducing drug resistance. Most of the designed compounds displayed obvious biological activity against different *Candida* spp. and *Aspergillus fumigatus*. Among them, two compounds not only possessed excellent broad-spectrum anti-fungal activity (MIC50, 0.125–2 mg/mL) but also maintained anti-drug-resistant fungal activity (MIC50, 1–4 mg/mL; see **Figure 8**). Preliminary

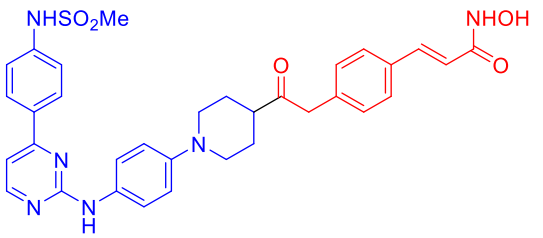


Figure 7.
JAC/HDAC inhibitor.

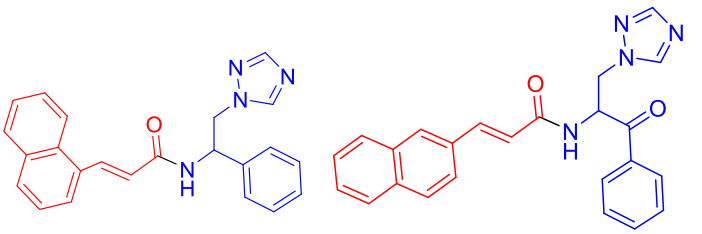


Figure 8.
SE/CYP51 inhibitor.

mechanism studies revealed that the compounds could block the bio-synthetic pathway of ergosterol by inhibiting the dual-target (SE/CYP51) activity, and this finally caused the cleavage and death of fungal cells. In addition, they also discovered that compounds with low toxicity and side effects could exert excellent therapeutic effects in a mouse model of fungal infection, which was worthy of further in-depth study [24–26].

3.5 Cycloxigenase-2/CYP51 inhibitor

In the study aimed at designing novel dual-target (cycloxigenase-2 [COX-2]/CYP51) inhibitors, three series of compounds were constructed through the pathway of skeleton screening and combination; their molecular structures were synthesized and evaluated. Most of the compounds exhibited significant antifungal ability. Among them, some with excellent antifungal and anti-drug-resistant fungal ability (MIC50, 0.125–2.0 μg/mL; see **Figure 9**) were selected

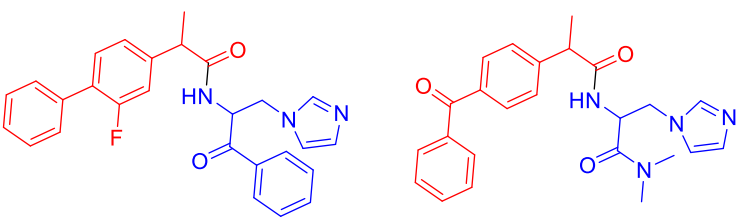


Figure 9.
SE/CYP51 inhibitor.

for the subsequent mechanistic study. They could block the ergosterol biosynthesis pathway by inhibiting CYP51 and also effectively showed COX-2 inhibition ability, eliminated the inflammatory reaction of the infected region, and activated the body's immune function [27].

4. Computational methods

4.1 Introduction to computational tools in drug discovery

Computational tools have revolutionized drug discovery by enabling a more efficient and systematic approach to understanding biological systems and chemical interactions. These technologies reduce reliance on traditional laboratory experiments, which are often costly and time-consuming, by allowing scientists to simulate molecular processes using advanced algorithms and high-performance computing. Virtual screening techniques, such as molecular docking and QSAR, enable rapid evaluation of large chemical libraries, prioritizing promising lead compounds for experimental testing. This accelerates the transition from initial discovery to drug development, saving both time and resources. Beyond screening, computational modeling guides rational drug design by providing detailed insights into the structure and dynamics of target proteins and potential ligands. Techniques like molecular dynamics (MD) simulations help optimize drug–target interactions, improving binding affinity and specificity, while *in silico* Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) models predict pharmacokinetic properties to refine candidate molecules. Looking ahead, integrating artificial intelligence (AI) and ML promises to further streamline all stages of drug development, uncover hidden patterns in complex datasets, and facilitate personalized treatments. Following this, we will discuss some important computational tools [28, 29].

4.2 Protein data bank

The Protein Data Bank (PDB) is a key global resource dedicated to storing three-dimensional (3D) structural information of biological macromolecules, such as proteins and nucleic acids. Since its inception in 1971, the PDB has provided open access to a comprehensive collection of experimentally derived molecular structures. These structures are primarily determined using techniques like X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy. Each entry, with a unique code, contains detailed atomic coordinates along with associated experimental data and descriptive metadata, offering a precise view of the molecular architecture.

The PDB is critically important for computational research within the biological sciences. Its data underpins a variety of computational approaches, including molecular docking, virtual screening, structure-based drug design, and simulations of MD. Scientists use these structural datasets to analyze how biomolecules function, explore their dynamic behaviors, locate potential drug-binding pockets, and design new molecules with therapeutic potential. Access to this extensive library of structural data greatly enhances the ability of researchers to develop insights into

PDB code	Organism	Ligand	Method	Released time	Reference
5V5Z	*C. albicans*	Itraconazole	X-RAY	March 29, 2017	[31]
5FSA	*C. albicans*	Posaconazole	X-RAY	March 15, 2017	[32]
5TZ1	*C. albicans*	VT-1161	X-RAY	March 15, 2017	[32]
5JLC	*C. glabrata*	Itraconazole	X-RAY	May 25, 2016	[31]

Table 1.
Fungal CYP51 drug–target complexes in the PDB databank, as assessed in August 2025.

biological processes and accelerate drug discovery efforts. For instance, several complex structures of fungal lanosterol 14-alpha demethylase (CYP51) protein with inhibitors are available from PDB (rcsb.org). The information on CYP51 structures of some *Candida* species is presented in **Table 1** and could be used in computational antifungal drug discovery projects [30].

In essence, the PDB serves as a vital link between experimental structural biology and computational modeling, fostering advances across multiple disciplines within molecular and structural biology.

4.3 Molecular docking

Molecular docking is a computational technique that models the interaction between a small molecule, such as a potential drug, and a target protein, aiming to predict the most favorable binding orientation and estimate the strength of the interaction. Docking algorithms generate multiple binding poses by exploring different orientations and conformations of the ligand within the binding site. These poses are scored based on predicted binding affinity, which reflects how well the molecule fits and interacts with the target. In virtual screening, molecular docking is a cornerstone because it allows rapid evaluation of millions of compounds, ranking them according to their predicted binding potentials. This method helps identify candidates that are most likely to interfere with the biological function of the target, thus streamlining the early stages of drug discovery [28, 33].

4.4 Quantitative structure–activity relationship

QSAR modeling applies mathematical algorithms to relate the chemical structure of compounds to their biological activity. By analyzing datasets of known molecules with measured activities, QSAR creates predictive models that can estimate the activity of new, untested compounds based on their structural descriptors. These models are extremely valuable for guiding chemical modifications that enhance potency or reduce toxicity. In virtual screening, QSAR is often used in conjunction with docking: compounds predicted by QSAR to have high activity are prioritized for further docking studies, thereby reducing the number of molecules that need intensive computational evaluation. This integrated approach enhances efficiency by focusing efforts on the most promising candidates early in the discovery process [28, 34].

4.5 MD simulations

MD simulate the physical movements of atoms in a molecule over time, providing a dynamic picture of molecular interactions rather than a static snapshot. MD simulations assess the stability of drug–protein complexes under physiological conditions, revealing conformational flexibility, binding site adaptability, and potential induced-fit effects. When applied after docking, MD helps validate and refine the predicted binding poses by observing how the complex behaves over time, offering insights into the durability and strength of the interaction. Additionally, MD can identify the most stable conformations and inform modifications to improve ligand binding or reduce off-target effects, thus refining virtual screening results and guiding experimental validation [28, 29].

4.6 *In silico* ADMET modeling

The pharmacokinetic and safety profile of a drug candidate – collectively called ADMET – are critical determinants of its success in clinical development. *In silico* ADMET modeling uses ML algorithms trained on experimental data to predict how compounds behave in the human body, including ADMET. Incorporating ADMET predictions into virtual screening pipelines allows researchers to filter out compounds with undesirable pharmacokinetic properties early, preventing costly late-stage failures. This integrated filtering ensures that the shortlisted candidates not only bind effectively but also have a higher likelihood of being safe and effective in humans [35, 36].

4.7 AI and ML

AI and ML techniques process and analyze large, complex datasets – such as genomic data, chemical libraries, and previous drug trial results – to discern patterns and make predictions with high accuracy. In drug discovery, these algorithms can predict the likelihood of compound activity, identify new therapeutic targets, or suggest modifications for better efficacy and safety. In virtual screening, AI models enhance the precision of binding affinity predictions, reduce false positives, and prioritize candidates for experimental testing. Additionally, AI-driven approaches can simulate clinical trials, forecast adverse reactions, and facilitate personalized medicine strategies, making them among the most promising tools to transform traditional drug development timelines [34, 37].

4.8 Virtual screening

Virtual screening is an overarching computational approach that integrates multiple techniques – such as molecular docking, QSAR, MD simulations, ADMET predictions, and AI/ML models – to evaluate and prioritize large compound libraries efficiently. It begins with the structural characterization of the target protein, often derived from experimental data or homology modeling. The screening process employs molecular docking to identify initial hits, filters candidates using QSAR and ADMET profiles, and further refines promising molecules through MD simulations and AI predictions. This combination of methods allows researchers to rapidly identify high-potential candidates that are likely to bind effectively, be safe, and

have appropriate pharmacokinetic properties. The ultimate goal is to intelligently narrow down extensive chemical databases to a manageable number of candidates for laboratory testing, dramatically accelerating the early phases of drug discovery while reducing costs and resources [28, 38].

4.9 Recent computational works in anti-*Candida* drug discovery: Key studies and advances

In recent years, multiple computational studies have employed diverse methods to identify promising candidates for treating candidiasis, utilizing known drug repositories and innovative modeling approaches.

For instance, Chakraborti et al. [39] conducted an *in silico* drug repurposing analysis by comparing targets of FDA-approved drugs with proteins from *C. albicans*. They identified 26 drugs with potential antifungal activity that could be repurposed against 31 *C. albicans* protein targets. Additionally, chemical similarity searches highlighted 33 more approved drugs that might inhibit *C. albicans* [39].

Building on similar *in silico* approaches, Verma et al. [40] modeled the structures of three drug targets – TRR1, TOM40, and YHB1 – and performed high-throughput virtual screening of 8,815 FDA-approved drugs. Among the top binders, arbutamine, hydroxychloroquine, and carindacillin demonstrated notable binding affinities. MD simulations identified critical residues involved in stable drug–target interactions, and the study indicated that arbutamine (see **Figure 10**) could be effective against multiple *Candida* species due to conserved regions, providing valuable insights into antifungal development [40].

In the realm of structure–activity relationship modeling, Maurya and Mishra [41] developed a 3D-QSAR model based on the activity of 40 coumarin derivatives against *C. albicans*. The model facilitated the design of new coumarin derivatives, which were validated through molecular docking and dynamics simulations, marking a creative avenue for novel antifungal compounds [41].

Jabeen et al. [42] utilized pharmacophore modeling, molecular docking, ADMET analysis, DFT calculations, and MD to identify inhibitors targeting mutant CYP-51, a key enzyme linked to antifungal resistance in *C. albicans*. Out of over 11,000 compounds screened, CP-3 (see **Figure 11**) showed promising binding affinity and drug-like properties, and MD simulations confirmed its potential as an effective antagonist of resistant fungal strains [42].

In another study, Das et al. [43] employed protein homology modeling, virtual screening, and MD simulations, resulting in the identification of Indacaterol (see **Figure 12**) as a candidate drug based on suitability, binding affinity, and stability analyses. These findings underscore its potential as an anti-*Candida* agent [43].

There are many other computational works exploring various aspects of anti-*Candida* drug discovery, and the volume of such research continues to grow rapidly. The increasing reliance on computational approaches highlights their crucial role in

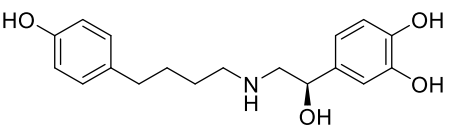


Figure 10.
Arbutamine structure.

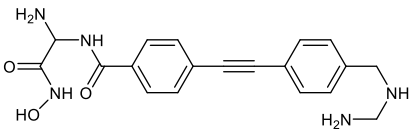


Figure 11.
CP-3 structure.

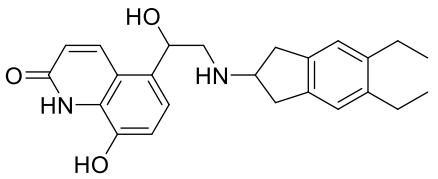


Figure 12.
Indacaterol structure.

accelerating drug discovery processes, reducing costs, and enabling more targeted and effective antifungal therapies. As technology and methodologies advance, the future of this field promises even more significant contributions toward combating resistant and invasive fungal infections.

5. Conclusion

The ongoing rise of resistant *Candida* species and the limitations of existing antifungal therapies demand innovative, safe, and broadly effective treatments. This chapter has framed antifungal discovery through a medicinal chemistry lens, illuminating the challenges and opportunities that shape contemporary research. Resistance mechanisms – ranging from efflux pump upregulation and CYP51 mutations to biofilm formation – necessitate interventions that anticipate fungal adaptability and maintain therapeutic efficacy. Targeted selectivity remains essential; fungal-specific processes such as ergosterol biosynthesis and virulence pathways offer compelling but demanding avenues for high therapeutic indices, as demonstrated by the evolution of fourth-generation azoles and their nuanced binding profiles.

Hybrid, dual-mechanism strategies present a particularly promising path to outpace resistance by co-targeting complementary pathways or pairing single-enzyme inhibition with other antifungal actions. These designs require careful optimization to balance potency with stability, bioavailability, and safety. Computational methods have become integral to this effort, enabling structure-based docking, QSAR, MD simulations, and AI-guided design that accelerate lead identification while maintaining rigorous evaluation of pharmacokinetic and safety properties. Yet, the strength of computational predictions hinges on robust *in vitro* and *in vivo* validation, ensuring that *in silico* insights translate into real-world efficacy and tolerability. As the field advances, the synergy between medicinal chemistry and computational pipelines, guided by up-to-date structural data and translational studies, will be pivotal in delivering safer, more effective antifungal therapies for resistant candidiasis.

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Section 4

Pathobiology of Clinical Candidiasis

Chapter 8

Candidiasis Endocarditits: From Surgical Approach to Artificial Intelligence and Minimally Invasive Techniques

Dario Buioni

Abstract

Candida endocarditis represents a challenging situation for cardiac surgery. It is characterized by high morbidity and mortality, and current diagnostic procedures and surgical approaches need to be improved. This type of fungal infection is constantly increasing. The continuing advances in artificial intelligence (AI) and its growing use in the treatment of infectious diseases allow for improved management by analyzing and linking clinical data, images, microbiological, and genomic aspects, to offer the best therapeutic option. They often affect patients who have already been operated on or are difficult to treat. New methods of diagnosis and management are available. The use of minimally invasive surgical techniques and percutaneous approaches is now widely used and allows us to offer an effective therapeutic option even for patients at high risk or even incurable with traditional techniques. In our opinion, the use of AI combined with minimally invasive or percutaneous techniques allows us to treat these highly fatal diseases, improving outcomes.

Keywords: Candida, minimally invasive approach, artificial intelligence, percutaneous techniques, heart valve disease

1. Introduction

Fungal endocarditis accounts for 1–6% of endocarditis cases [1], and this patient population presents a significant challenge for cardiac surgeons [2, 3]. They often have valves and prosthetic cardiac devices and require a longer postoperative recovery period. They can cause severe ventricular failure, despite targeted antibiotic therapy at even high doses for a long time; furthermore, they can create pathologies that are very complex from a surgical point of view. Among the various species, Candida species is characterized by a substantial increase in hospital morbidity and mortality [4, 5]. These types of infections are very complex, and therefore, it is necessary to improve our knowledge to understand which factors favor valvular infections and how they manage to be aggressive, unlike bacterial endocarditis. It is still being studied which clinical or pathophysiological condition or risk factor may

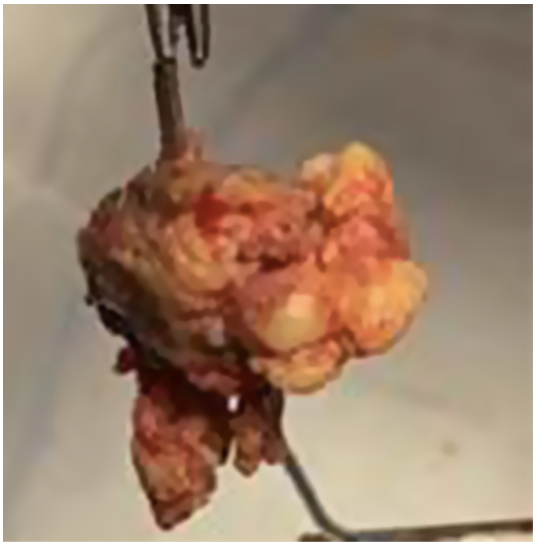


Figure 1.
Tricuspid vave vegetation.

increase the risk of this type of infection [6, 7]. Recently, analyzing non-Candida albicans Candida (NCAC) infections involving prosthetic devices and hemodialysis catheters, it appears that these may constitute an independent risk factor for candidiasis [8]. Given the significant increase in IVDU use and the rise in candidemia, it is necessary to address these issues. Cases of Candida endocarditis are increasing, becoming a major global problem, especially because it affects vulnerable populations such as the elderly and immunocompromised (**Figure 1**). The patients most exposed to these types of infections are the most fragile, those with prolonged hospital stays, and those requiring indwelling devices and/or catheters. These patients very often develop fatal nosocomial fungal infections. Several factors contribute to their prevalence: anatomical, genetic, and lifestyle; therefore, improved diagnostic and treatment pathways are needed. Great efforts are being made for early diagnosis, pharmacological therapy, and evolution in surgical approaches to improve the outcomes of this type of patient. The use of artificial intelligence (AI) in diagnostic pathways, in the types of surgical approaches, and the use of minimally invasive or percutaneous techniques allows for the reduction of the risk of mortality or morbidity.

2. Clinical aspects

Anatomically, Candida infections mostly affect the mitral and aortic valves, which are usually replaced or repaired due to age-related degeneration. Patients who have undergone previous cardiac surgery may have immunosuppression that favors the onset of infection. Case reports also show candidal infections affecting patients undergoing percutaneous procedures such as TAVR. In addition to the Albicans subgroup, other Candida subspecies can also cause destructive infections, such as C. parapsilosis, which appears to affect TAVR patients more frequently; C. tropicalis

in defibrillator infections or young patients; C. glabrata in immunosuppressed patients; and even C. dublinensis. These agents can create large vegetations that can obstruct the ventricular outflow tract, such as the mitral-aortic junction or abscesses/fistulas; they very often cause salvage procedures. However, the location and association with a particular valve depend on a wide range of risk factors. The literature has numerous cases of patients with subcutaneous catheter devices in which the valve was not affected, while the right atrial septum appeared to be involved. Several clinical cases have highlighted the ability of C. albicans to infect any site on the endothelium. Rare cases of prosthetic heart infection by C. tropicalis have been particularly aggressive, causing damage to cardiac structures and requiring heart transplantation. Candida species develop in patients with central venous catheters, approximately 15% of whom develop the disease, as do those who inject drugs, causing endocarditis that primarily affects the right-sided valves.

3. AI applications and imaging modalities

Using machine learning (ML) models [9, 10] such as SABIER and SYSUPMIE, these have demonstrated encouraging results for high predictive accuracy in the early diagnosis of IE, analyzing embolic risk stratification and postoperative mortality, more effectively than traditional clinical scoring systems. AI allows for the combination of echocardiographic images (preferably TEE and 3D imaging) with advanced imaging such as positron emission tomography (FDG-PET)/computed tomography (CT), allowing for greater sensitivity, specificity, and reduced interobserver variability, thus facilitating the best clinical approach through the analysis of different types of imaging. Furthermore, AI-based microbiology techniques, including MALDI-TOF mass spectrometry combined with ML and metagenomic classifiers based on neural networks, have shown promising results in the rapid identification of pathogens and the prediction of antimicrobial resistance. These approaches are still being improved, but initial results are positive, and they may be increasingly used in the future. Some drawbacks need to be addressed, such as small data samples, difficulties in interpreting the data, potential ethical issues, and the need for universally accepted validation. Generative AI appears to have a significant role in clinical counseling in the coming years, although its functions will need to be limited and carefully monitored. AI, particularly ML, offers new tools to improve AI-based healthcare by cross-referencing and analyzing complex clinical data, images, and genomic information to facilitate diagnosis and treatment. In this chapter, we examine the applications of AI and the growing use of minimally invasive approaches in IE caused by Candida species through early identification, diagnostic imaging, microbiological analysis, and treatment optimization, integrating evidence from IE-specific studies. The use of AI is becoming increasingly popular because early identification and accurate risk stratification of Candida IE are crucial to the outcomes of these patients, who are characterized by a high risk of mortality and morbidity. Delays in diagnosis or an underestimation of the severity of the disease can lead to a very complex clinical picture, leading to more complex types of interventions with limited options for patients. In recent years, several clinical models have used traditional ML techniques, such as multivariate logistic regression, to improve the ability to predict the risk of potential IE.

3.1 Echocardiography images

For example, in patients with Staphylococcus aureus bloodstream infection (BSI), risk scoring systems could be used to define the profile of patients requiring transesophageal echocardiography (TEE) (**Figure 2**). The PREDICT and VIRSTA scores assign point values to specific risk factors, identifying patients at low risk of IE. It has been established that a VIRSTA score <3 demonstrated a negative predictive value (NPV) of approximately 98%, allowing TEE to be avoided in low-risk subjects. Some studies, such as Lai et al. (2024), have developed the ML-based "SABIER" risk score using a random forest ML algorithm applied to an 11-year dataset of over 15,000 S. aureus BSI episodes. The SABIER score achieved an area under the receiver operating characteristic curve (AUC-ROC) of approximately 0.74 and maintained a similarly high NPV (~98%); AUC-ROC quantifies a model's ability to discriminate between true and false positives over a range of thresholds. Scores above 0.7 are considered indicative of good performance. The most important aspect of SABIER is its ability to exclude subjective clinical assessments. While the SABIER model awaits validation, scoring typologies such as this allow us to explore new uses of ML in promoting early diagnosis. AI can help prevent potential complications of IE.

Vegetations with a diameter >10 mm on echocardiography are one of the criteria for indicating surgical treatment to prevent embolism, but with AI we will not be able to define which type of vegetation has characteristics of greater embolization even if less than 10 mm and therefore anticipate surgical intervention to avoid stroke or cerebral hemorrhages that increase the risk of mortality and morbidity of IE. Some centers, for example, in Spain, are using computer vision on echocardiographic images to identify morphological characteristics (beyond simple diameter) that predict a high risk of embolism [11, 12]. Furthermore, by adding simpler tests, the electrocardiogram (ECG) could be combined with echocardiographic and/or CT images to predict other dangerous complications, such as abscesses, conduction system abnormalities that cause heart block, or severe cases of heart failure. For example, one study applied AI to a panel of 27 inflammatory cytokines in patients with IE. It identified IL-15 and CCL4 levels as

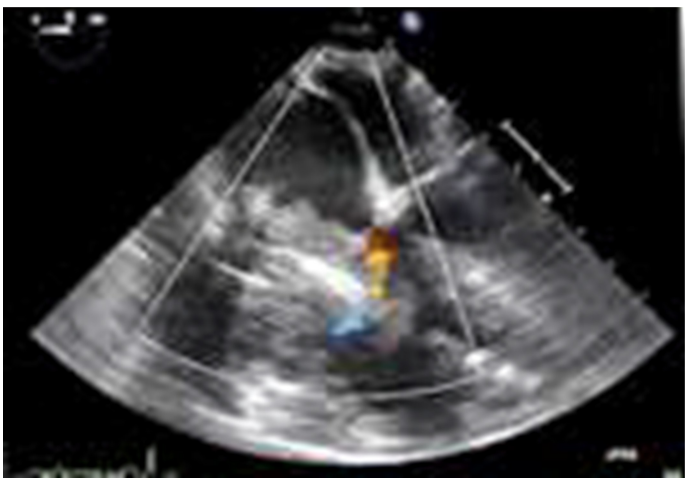


Figure 2.
Echocardiography image.

key predictors of mortality, achieving an accuracy of approximately 91% in predicting death when combined with C-reactive protein. Such biomarker-based AI models could be useful for early surgical approaches or to improve pharmacological therapy. Another study developed and validated a risk model ("SYSUPMIE") using an XGBoost ML algorithm to predict early mortality after IE surgery. The model appears to have good predictive accuracy (AUC: ~0.81), allowing it to surpass existing risk models such as EUROSCORE or STS score, creating a more specific model for endocarditis and, in the future, for various germs. AI will optimize echocardiography images. This is the gold standard for the rapid diagnosis of IE and poses no particular risks to the patient, even with TEE; however, it depends on the operator's experience and the patient's anatomy. Early diagnosis of IE can be difficult in cases of prosthetic valves or poor acoustic windows, and vegetations can often be confused with small thrombi or calcifications. AI can reduce the risk of false positives by improving image quality, analysis consistency, and highlighting subtle features. Sineglazov et al. developed a DL computer vision system to automatically segment and detect valvular vegetations in echocardiographic images. By analyzing information pixel-by-pixel throughout the cardiac cycle, these models can potentially distinguish vegetations from any artifacts or normal structural features. By combining echocardiographic images with AI, this could allow clinicians to detect small vegetations that are difficult to detect due to artifacts that could delay treatment. Based on initial reports in the literature, the integration of AI allows for more standardized ultrasound interpretation in IE, especially 3D TEE, when it is equivocal or nondiagnostic. Future ML models could also leverage large-scale data mining from echocardiographic reports using natural language processing (NLP) to help determine risk and predict prognosis for IE. Several studies have shown that these applications are already available with good accuracy [13, 14].

3.2 CT scan

Cardiac CT is often used as a supportive examination when echocardiographic images are unclear or when it is necessary to define anatomical features in cases of redo or to define specific anatomical features (abscesses, fistulas, aneurysms). CT images are often nondiagnostic for various reasons, such as the interpretation of subtle perivalvular changes, which can be complex and are sometimes characteristic of native valves and/or prosthetic valves, which are not indicative of endocarditis (**Figure 3**). AI algorithms can extract CT data to identify patterns that are imperceptible to radiologists, for example, to distinguish sterile postoperative changes from true abscess cavities around a prosthetic valve. AI could integrate ultrasound and CT images to confirm or better define features present in both ultrasound and CT images (e.g., a valvular defect on CT corresponding to vegetation on echocardiography). Early studies have shown increased sensitivity for structural complications of IE by leveraging the strengths of each modality [15].

3.3 Nuclear imaging studies

For nuclear imaging studies, such as FDG-PET/CT, AI has demonstrated improved diagnostic performance. These techniques are highly useful for defining peripheral hemorrhages, prosthetic valve endocarditis (PVE), and cardiac device

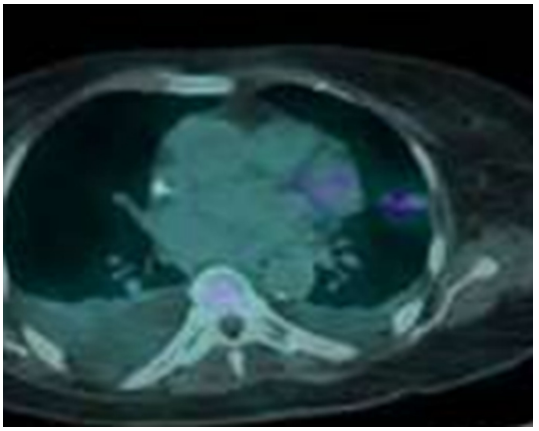


Figure 3.
CT scan.

infections (PMK, endografts, vascular grafts) by identifying metabolically active foci of infection. In a proof-of-concept study, ML algorithms combined PET/CT results with other diagnostic components of the 2015 modified Duke/ESC criteria, achieving greater diagnostic specificity without compromising sensitivity. Among the four ML modeling approaches, an ensemble model achieved the highest AUC, at 0.41 compared to 0.917 for conventional criteria. In another 2023 study, a radiomics-based ML approach to FDG-PET/CT for suspected VEP increased diagnostic sensitivity from 59% to 72%. Through AI, PET images can identify most forms of IE earlier and reliably. Another nuclear technique, leukocyte SPECT/CT, appears to have higher specificity than PET for the detection of IE in some series. Currently, these tests are very expensive and require specialized technicians. With the help of AI, in addition to the previous or reliable diagnosis of EI, it can optimize the recognition of vegetations or aggressive infections of the cardiac skeleton (abscesses, fistulas, or device infections). It can integrate echocardiogram images with PET/SPEC in order to have more precise, objective analyses and reduce individual interpretation [16]. AI can be very useful in identifying pathogens and drug resistance. By analyzing images, it can identify the growth path of a growth or the increased aggressiveness, creating more aggressive lesions despite seemingly appropriate therapy. This could help us operate on a patient earlier to avoid embolization or more complex interventions. For example, advanced ML algorithms have been integrated with matrix-assisted laser inference ionization and MALDI-TOF mass spectrometry, and associated combination software to improve identification accuracy. While traditional MALDI-TOF approaches, which inherently depend on reference libraries and software matching, reliably identify organisms to genus, accuracy can decrease for closely related species. ML can analyze subtle differences in mass spectral patterns. For example, on the species Brucella, a set of ML classifiers achieved 100% accuracy in differentiating three Brucella species based on their MALDI spectra, while standard methods struggled to go beyond genus-based identification [17, 18]. This method may also be useful for fungal infections. Achieving improved pathogen identification from ML could improve clinical outcomes through more precise microbial diagnosis and enable earlier and less complex interventions [19]. Cultures are often nondiagnosable and

negative; therefore, additional tests, such as polymerase chain reaction (PCR) and, especially, analysis of valve tissue, are necessary. New neural network-based tools, such as transformer-based classifiers, will allow us to analyze this large data sample, enabling us to identify pathogens even when they are absent from reference databases. This will allow us to identify rare or unrecognized pathogens that cause BCNE, increasing diagnostic accuracy and early diagnosis [20].

4. Surgical approach

We have seen how the use of AI in both diagnosis and pharmacological strategies is gaining more and more ground, even in surgical strategies, it can have ample space, allowing surgeons to improve patient outcomes, especially if integrated with minimally invasive techniques or, more importantly, with the robotic approach. In fact, it is possible to analyze the images of instrumental examinations (3D echocardiography, CT, angiography) in order to plan the intervention for that specific clinical case. This will allow, in the future, to make even the most complex cases less difficult. The conventional surgical approach (**Figure 4**) still remains the first choice approach in many centers [20, 21].

4.1 Minimally invasive cardiac surgery

According to the guidelines, surgical approach is urgent for three reasons: 1) in case of vegetation >10 mm to prevent embolization or its recurrence; 2) there is severe heart failure refractory to pharmacological therapy; and 3) if there are severe cases of infection with abscesses, fistulas, pseudoneurysms/aneurysms. Therefore, data in the literature recommend, whenever possible, intervening as early as possible to avoid clinical complications or complex surgical procedures. Minimally invasive cardiac surgery (MICS) is gaining increasing importance to improve outcomes.



Figure 4.
Conventional approach.

Valve surgery has also been shown to have excellent long-term results in cases of IE, as well as to be repeatable and safe; even with regard to repair techniques, data show, considering the type of patients, similar to those for nonendocarditis cases [21–23]. Several studies have compared traditional surgery with less invasive techniques. In favor of MICS, a lower use of transfused blood products has been observed (shorter postoperative ventilation time, shorter intensive care unit stay, and similar survival during follow-up between the two groups. These data are encouraging; especially in the treatment of mitral valve IE, especially when combined with repair. It could become the gold standard for selected cases. It must be said that in very complex cases, such as severe mitral annulus involvement with concomitant annular calcification, or in cases involving the aorto-mitral continuity, requiring complex annular reconstruction or double-valve surgery, the conventional approach still appears to yield the best results. In these specific cases, various ML techniques can be helpful in analyzing images and assisting the surgeon in planning the procedure. Based on previous studies that have identified Candida subspecies as a major risk factor for 30-day mortality and increased morbidity after surgery due to endocarditis, especially in right heart infections. Caballero et al. [24], in their review, analyzed the use of AI in MICS, and various studies have been examined, including the use of simulators. It has been noted that AI can help surgeons improve surgical planning and technical skills. This will help surgeons improve outcomes, reducing mortality and morbidity, especially in complex cases. This review, which evaluated various studies on the application of AI in MICS, found the main disadvantages to be potential ergonomic deficiencies during lengthy surgical procedures, high levels of stress in some procedures, and a long and demanding learning curve. Furthermore, the limited number of participating surgeons, limited data availability, and the lack of validation in most of the studies were also noted. Another disadvantage highlighted in this review is the incompatibility between some AI processes and MICS surgical training, which prevents the use of potential solutions [25–27]. The minimally invasive approach combined with possible repair offers a significant advantage, especially for young patients. Unfortunately, this type of infection is common in patients with multiple medical conditions and immunosuppressed conditions, thus posing a high surgical risk. Rajkar et al. demonstrated that MICS for IE is a valid alternative to sternotomy. They confirmed that hospital stays are reduced and that the reduced surgical trauma leads to reduced blood transfusions. Longer surgical times are often required, but with the aid of AI and increased cases, these times are reduced. For example, in IE of MV, the MICS approach was associated with a higher repair rate at their center. In multivariate analysis accounting for baseline risk and acuity, the MICS approach was not found to be a predictor of adverse outcomes. This indicates that in experienced centers, the MICS approach for IE may become common in selected patients, such as young or particularly frail patients. MICS is becoming increasingly widespread, both due to patient preference and surgeon expertise. These data support the use of MICS in IE without increased morbidity or mortality [28, 29]. Mikus et al. [30] performed a single-center study comparing the outcomes of isolated mitral valve surgery for infective endocarditis performed via conventional complete sternotomy or minimally invasive right minithoracotomy. They analyzed 134 patients who underwent isolated mitral valve surgery for infective endocarditis between January 2010 and March 2024. Although the mortality rate did not show statistically significant improvements (although there was a positive trend and both

approaches reported a mortality rate consistent with those reported in the literature), MIMVS showed several advantages, including shorter intensive care unit stays and reduced incidences of renal failure, stroke, and sepsis. The overall valve repair rate was 31 of 34 cases (23%). The most interesting finding of this study was that patients treated with MICS (18 of 40; 45%) underwent valve repair compared to those with traditional sternotomy (13 of 94; 13.8%).

4.2 Robotic approach

In recent years, the robotic approach has gained popularity in selected cases (**Figure 5**). This technique could also be useful in cases of IE, especially when complex valve reconstruction is required. The literature contains cases in which centers with over 10 years of experience with robotic MVR use this method for selected cases of IE. Among the advantages, it can facilitate repair surgery and ensure a more rapid recovery [31]. It's clear that this type of approach requires extensive experience, especially in the robotic setting, and that these approaches must increasingly be recognized in guidelines [32]. It's important to note that these approaches have excellent results in high-volume centers and require careful patient selection, even though this is not easy in this setting. Therefore, greater use of ML systems for data entry and processing will be crucial to define the best patient approach and achieve improved outcomes. In the future, the integration of AI algorithms, together with the robotic approach, represents a valid option for the treatment of even the most complex cases. Surgical devices like the da Vinci and others, AI-assisted navigation platforms, and computer vision itself can enable surgeons to perform complex procedures with greater precision. AI algorithms analyze vast data sets and can provide surgeons with real-time information to improve intraoperative decision-making. Furthermore, AI could aid in preoperative planning and, through the use of simulators, allow surgeons to optimize surgical techniques to predict potential complications and even customize the procedure based on the patient's clinical and anatomical characteristics. Ethical issues, data confidentiality, regulatory constraints, and the need for clinical validation continue to pose obstacles to its widespread adoption. It is necessary to establish standardized protocols and evaluate the long-term impact of AI-based interventions in conjunction with robotic approaches. The use of robotics and AI in surgery is an extraordinary development for surgical patients, including those with EI, allowing for improved surgical outcomes with less impact. The increased use of AI-based

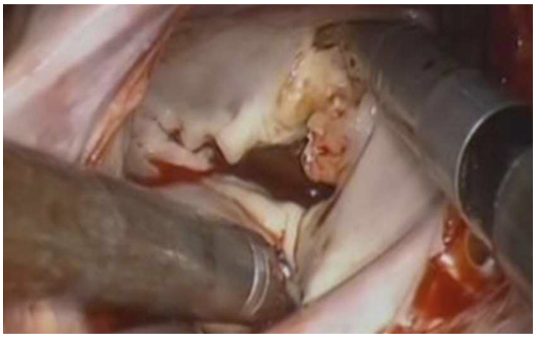


Figure 5.
MICS.

technologies (ML, computer vision, and visual computing), integrating them with robotic approaches, has already impacted numerous surgical specialties, with significant benefits. Literature findings show significant progress in robotic surgery across a variety of medical specialties, meaning this approach will also be possible in EI.

4.3 Percutaneous system

In some cases, the patients' conditions are particularly critical (high frailty, elderly patients, or those with recurrent heart failure), and surgery, even in MICS, carries excessive risk. These patients previously faced a risk of failure to resolve their clinical condition and thus a fatal outcome. Today, new devices allow for a percutaneous solution. The AngioVac system is gaining increasing popularity, proving highly effective in treating right-sided IE by debulking vegetation, reducing periprocedural risk, and avoiding embolization. A meta-analysis demonstrated its efficacy in high-risk surgical cases, with rates of 89.2% and 79.1%, respectively. Vegetation elimination rates greater than 50% were achieved in 90% of cases, with reduced bacteremia and a lower risk.

The AngioVac® system consists of a wide-lumen catheter, initially available to clinicians for the removal of large thrombi from the vena cava, right atrium, and pulmonary arteries (**Figure 6**). Its usefulness has been demonstrated in the removal of right-sided vegetations, especially the native tricuspid valve or active prosthetic valves, and in right ventricular pacing/ICD lead infections. In some high-risk cases, this represents a valid option when surgery is not feasible, allowing the procedure to be performed relatively quickly. This method currently has some disadvantages: two large-bore venous access cannulas must be placed, which can expose the patient to the risk of vascular or hemorrhagic complications. To limit the vascular access problem, systems such as Perclose Proglide (Abbott Vascular) are available. This device is inserted into the vessel and allows for effective percutaneous closure without requiring invasive surgical procedures. Unfortunately, due to the large size of the catheters, this device does not appear to be suitable for small or pediatric patients. Furthermore, during its action, due to the mobilization of vegetations, there may be a risk of pulmonary embolization of the clot or vegetation in the right

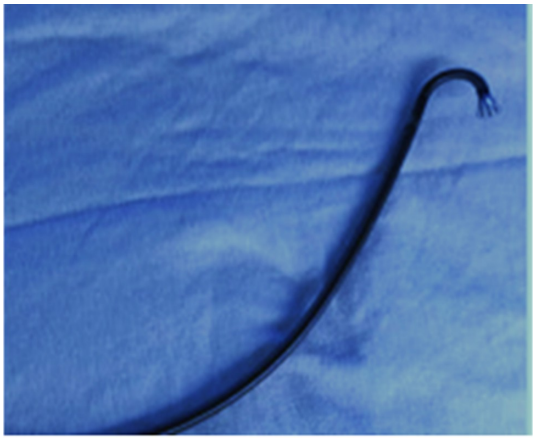


Figure 6.
AngioVac.

atrium. Data in the literature indicate that particular attention must be paid to patients with severe respiratory impairment or reduced pulmonary reserve, as even small emboli can cause severe respiratory failure with the patient's death. It has been used in patients with distal thrombi, such as areas of the right ventricle, the outflow tract, and the pulmonary artery. In these cases, there remains a high risk of damaging vessels or very delicate structures. In fact, it should be performed by experts to reduce the risk of trauma, due to the characteristics of the device [30, 31]. Initial cases have also been performed along the left sides of the heart, especially for vegetations on the mitral valve or prosthesis. In this case, the risk of cerebral embolism is very high; therefore, a multidisciplinary approach is always necessary in these cases. Initial data, however, confirm the effectiveness of this procedure even for large vegetations on the left side of the heart, in patients with a prohibitive surgical risk [32].

5. Discussion

AI, along with minimally invasive techniques and robotics, is accelerating the discovery of new surgical strategies for patients with candidal endocarditis. A robotics-assisted digital approach could identify a personalized surgical approach for each patient, thus optimizing outcomes. Initial reports are very promising, but integrating generative AI into clinical care for IE carries significant risks. Current LLMs have limitations, a lack of true contextual awareness, and a tendency to generate inaccurate information. There needs to be greater awareness of both the strengths and limitations of generative AI, especially in IE cases, which are characterized by high mortality and morbidity. Above all, ethical issues must be overcome, which remain the major limitation, especially when using AI with a robotic approach. Large datasets from simulators are still needed to improve the vast amount of data from so many centers. Standardization of procedures is necessary to reduce potential errors. Methods like ANN require multidisciplinary teams to analyze high-quality experimental data and analyze it effectively. A multidisciplinary approach is essential because various types of imaging must be integrated with surgical strategies and initial pharmacological therapy. In recent years, new methods using AI and ML have been applied to endocarditis, but greater progress is needed for Candida cases, as they affect more fragile and higher-risk patients. Among the various AI systems, it is necessary to identify the most effective one to avoid errors in the diagnostic process. With increasing data, its analysis, process optimization, data processing, and greater experience with robotic techniques, it will be possible to treat increasingly complex patients. We are convinced that the robotic approach associated with AI will allow for better outcomes and increasingly greater valve repair possibilities [31]. Robotic cardiac surgery is still evolving, despite having been used for over a decade. Tissue telemanipulation and less invasive methods will become an important part of our surgical field in the future. Mitral, tricuspid, and even aortic repair in degenerative diseases is described much more frequently than infective endocarditis in the literature and in clinical practice. Infective mitral endocarditis is complex, due to the variable severity of the disease and the variety of valvular conditions [32–35]. Debridement of the infected tissue is mandatory in the surgical treatment of infective endocarditis, followed by restoration of the function and size of the valve

leaflets. For this reason, prosthetics are often preferred over repairs. Patches are often needed to increase the size of the anterior mitral leaflet. For posterior leaflet lesions, we have preferred to use artificial chordae to preserve as much leaflet tissue as possible. According to data from the United States of America, approximately 25% of mitral valve surgeries have been performed with minimally invasive techniques, and only half of these have been performed with a robotic approach. Even today, mitral valve repair using robotic procedures is rare and is performed by specialized centers, but we are witnessing an increase in cases, with improved results and operating times [36]

6. Conclusion

By 2025, managing candidal endocarditis with traditional surgery alone appears outdated. MICS represent a valid alternative; in fact, they are now widely used and included in guidelines. The use of robotic techniques represents a major revolution [37, 38]. AI is increasingly used, especially in surgical planning. The integration of various types of imaging, improved early diagnosis, combined with the use of mini- or robotic techniques, will allow for personalized surgical treatment. It is necessary to improve the various AI systems, optimize data processing, and standardize procedures. This will optimize results. Important issues to address include ethical issues, increased knowledge of the systems, and greater experience with robotic techniques. Initial reports appear to show encouraging data and are opening a new avenue, especially for treating the most complex cases.

Conflict of interest

The author declares no conflict of interest.

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Chapter 9

Vulvovaginal Candidiasis

Vaishali Walke

Abstract

Candida albicans is the most common etiological agent for vulvovaginal candidiasis (VVC); however, other *Candida* species may also occasionally be responsible for this disease. The classical signs and symptoms include intense pruritus, curdy vaginal discharge, dyspareunia, sometimes dysuria, genital discomfort, pain, diminished sexual pleasure, and psychological suffering. An estimated disease burden suggests that around 75% of women may have experienced at least one episode of VVC, while 40%–45% will have two or more episodes. The predisposing factors include pregnancy, poor hygiene, diabetes, immunosuppressive therapy, vaginal dysbiosis after antimicrobial treatment, and human immunodeficiency virus (HIV). The diagnosis can be made either by wet mount (saline, 10% KOH), Pap smear, which can aid in demonstrating the budding yeasts, hyphae, or pseudo-hyphae, and culture examination to confirm the pathogenic species. If fungal culture cannot be performed, empirical treatment can be considered for these patients with VVC. The disease is known to significantly cause morbidity, which hampers the quality of life and comfort of daily functioning in young and active female patients. Therefore, a correct diagnosis and the right treatment is the need of the hour considering the burden of disease in the young female population. There is also a high incidence of recurrent VVC and challenges faced while managing it with the standard treatment regimens. This background provides a strong and rational basis for the development of immunological treatments, particularly vaccines, to address recurrent VVC.

Keywords: vulvovaginal infection, *Candida albicans*, fungal infection, Torulopsis gabrata, Candidiasis, Torulopsis

1. Introduction

Candida vulvovaginal infection is a common fungal infection caused by *Candida* species. The literature mentions that approximately 75% of all women experience at least one episode of vulvovaginal candidiasis (VVC) during their reproductive years of life [1]. An acute inflammatory condition of the vulva and vagina, VVC is induced by the overgrowth of *Candida* organisms, clinically characterized by white curdy discharge, associated with a burning sensation and itching in the vulva and vagina, and dyspareunia [2]. There is a wide range of predisposing factors or triggering events, such as medications like antibiotics, oral contraceptives, hormone replacement therapies, immunosuppressive therapy or pregnancy, uncontrolled

diabetes mellitus, sexual activities, and poor hygiene. Additionally, an estimated 8% to 10% of women are also susceptible to recurrent VVC (RVVC), which is defined as four or more episodes of VVC in a year. Unlike episodic or sporadic VVC, recurrent disease requires maintenance therapy that includes the long-term use of antifungal drugs over several months. One recent global study has reported a worldwide annual prevalence of RVVC of approximately 138 million, and an additional 372 million over one's lifetime, resulting in substantial morbidity and economic burden due to the recurrent disease [3]. A multinational internet panel-based study quoted a lifetime prevalence rate of 9% by the age of 50, with the majority of episodes occurring between the ages of 19 and 35 years [4]. Regardless of the extensive global literature on disease prevalence, the current knowledge about VVC is vital for reporting on various aspects of vaginal infections, including diagnostics and therapeutic approaches, understanding the nature of host immunity and pathogenesis, and behavioral factors associated with disease etiology [5–9].

2. Etiopathogenesis

2.1 Etiology

Candida albicans is a eukaryotic microorganism with an exceptional ability to adapt to different environmental and host niches. This unique strength allows the organism to behave not only as a commensal but also as an opportunistic pathogen for humans. This dual property exhibits a morphological correspondence that enables it to undergo a morphogenetic change from a round-ovoid yeast cell to a hyphal mycelial growing organism. This transformation is of great significance for the pathogenicity of *C. albicans*. The yeast forms can be observed as commensals in the intestine and vagina in more than 50% of healthy asymptomatic individuals, while the hyphal forms are seen in the pathological specimens obtained from invaded smears and tissue specimens from women with signs and symptoms of VVC or RVVC. Its incidence is said to be highest in young women in the age group of 20–40 years [1, 4]. Higher estrogen levels are considered to make these females more susceptible to infection; the increased incidence is also reported during pregnancy and the postmenopausal period in women who are on hormone replacement therapy. Estrogen levels increase the glycogen content of the epithelium, which is associated with a direct effect on *Candida* growth and an increase in its adherence to the vaginal epithelium. The literature quotes that among symptomatic women, *C. albicans* was isolated in approximately 86.6% [7] in one American study and 77.1% in an Italian study among the positive cultures [8].

2.2 Predisposing factors

In VVC, either host or microbial factors are considered to play an important role in the sporadic or recurrent category. The host factors include the use of antibacterials or systemic corticosteroids, as well as the patient's immune status, such as uncontrolled diabetes, lupus erythematosus, thyroid disease, and/or human immunodeficiency virus (HIV) infection. The behavioral factors that are also considered to trigger episodes of VVC include sexual practices and genital hygiene [10, 11]. The microbial factors mainly consist of *Candida* species, most commonly *C. albicans*, while rare species such as *C. glabrata*, *C. parapsilosis*, and *Saccharomyces*

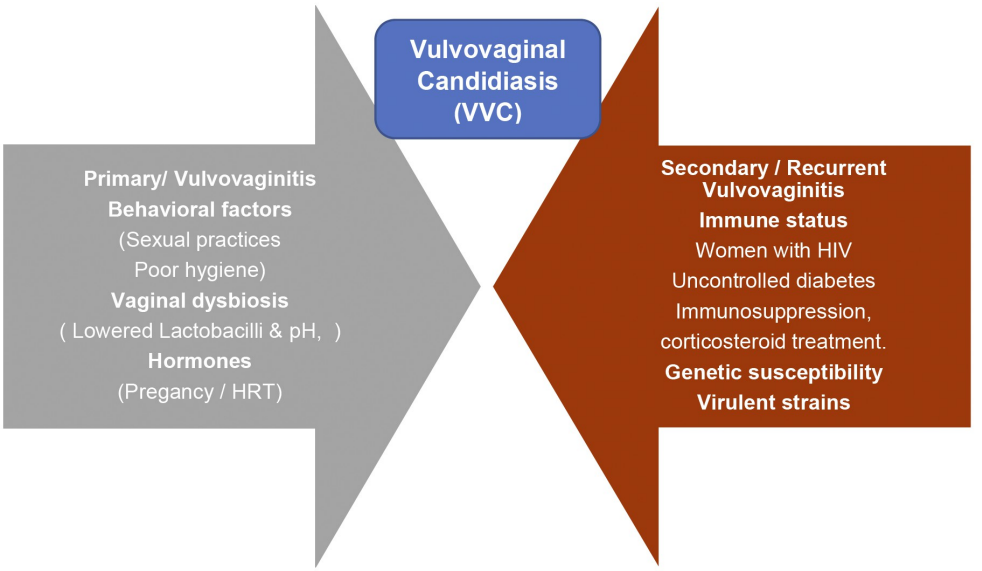


Figure 1.
The factors contributing to both primary and recurrent vulvovaginal candidiasis (RVVC) [12, 13].

cerevisiae are also responsible for up to 33% of recurrent infections. There may be inherent differences between *C. albicans* and non-*C. albicans* infections; hence, a positive fungal culture, which specifies the infecting microorganism, is an essential first step in the management of RVVC [3, 11] (see **Figure 1**).

2.3 Pathogenesis

The vaginal milieu has its own microbiome that prevents various genital infections caused by different microorganisms. *Lactobacillus* and *Candida* are two key players, where *Lactobacillus* keeps the vagina healthy and checks the pathogenic trait of *Candida*, which is the causative agent for VVC. The interplay between *Candida* species and *Lactobacillus* is regulated via various biomolecules released from *Lactobacillus* that modulate the immune response, thereby offering protection against the microorganism. *Lactobacillus* secretes compounds such as organic acids, biosurfactants, and hydrogen peroxide (H_2O_2), through which it regulates the growth and colonization of *Candida* species. The vaginal pH, in the range of 3.5 to 4.5, is maintained through the varying amounts of short-chain aliphatic organic acids, lactic acid, and acetic acid released by different species of *Lactobacillus,* thus keeping microbial growth in check. However, this symbiotic association gets altered due to some non-microbial factors like physical injury, gynecological procedures, and/or hormonal therapies [14].

The groundbreaking research conducted on human volunteers, in which intravaginal challenging with live *C. albicans* organisms was performed, revealed that VVC is mediated through innate immune responses. The research concluded that neutrophil recruitment into the vagina was positively correlated with the disease symptoms experienced by participants. The recognition of the importance of innate immunity in driving the inflammatory responses observed in patients with VVC

postulated numerous insights about the disease pathogenesis. Neutrophils release TNF-α, which amplifies the expression of Toll-like receptors (TLRs) present on the epithelial surface, and recognize *Candida* cells via direct interaction with mannan and β-glucan moieties through pattern recognition receptors (PRRs). The immune system activation thereafter activates the MAPK and Syk signaling pathways, which augment the inflammatory process to hinder *Candida's* proliferation. The current knowledge supports the pathogenesis of VVC as multifactorial, with an interplay of several factors such as vaginal microbiome dysbiosis, epithelial invasion by *Candidal organisms*, their colonization, and the immune escape phenomenon. The holistic understanding of the exact pathogenesis of VVC is progressive, and several studies are being conducted to discover the unknown factors or molecules responsible for the disease processes [15].

2.4 Clinical features

The clinical diagnosis of VVC is most of the time based on clinical features alone; however, its presentation may not be specific and is therefore liable to misdiagnosis. Although women with vaginal yeast colonization are asymptomatic, many may experience varying degrees of vaginal itching, while some may also complain of vaginal soreness, swelling, dyspareunia, dysuria, or increased discharge [16].
A detailed clinical history should include questions regarding vaginal discharge – its nature, quantity, color, and odor. The history should also include variations in symptoms with menses; apart from this, attempts at over-the-counter treatment options, if availed, and the responses to prior such therapies. Information should also be obtained regarding whether the patient is sexually active, any associated experience of dyspareunia, and the age at the initiation of sexual activity. If needed, a local examination should be conducted to inspect the vagina and vulva for the presence of any evidence of congestion, edema, ulceration, or chronic skin changes; this can be combined with palpation, for which a cotton-tip applicator can be used to elicit areas of tenderness. The vagina and cervix should be inspected thoroughly, and specimens should be obtained from the lateral vaginal wall for laboratory evaluation [17, 18].

3. Laboratory approach

The cornerstone for the diagnosis of VVC includes clinical features, microscopic examination, and yeast culture. The detailed examination of the sample obtained from vaginal secretions involves a battery of tests, including pH testing, the amine (whiff) test, saline wet preparation, and a 10% potassium hydroxide (KOH) mount for microscopy and culture examination. The finding of normal pH (less than 4.5) on physical examination effectively excludes the possibility of bacterial vaginosis, while a pH greater than 4.5 has a limited differential. A whiff test for the presence of amines should be performed by placing a drop of 10% KOH onto the vaginal secretions and checking for a fishy odor [11].

3.1 Wet mount

Saline wet mount microscopic examination enables the visualization of trichomonads, their motility, and the presence of clue cells. By adding 10% KOH to

the slide, the epithelial cells undergo lysis, which increases the ability to identify hyphae or blastospores – an added advantage of the wet mount smear [1].

3.2 Pap smear

In the conventional Pap smear, the organisms can be seen as budding yeasts (3–7microns) and pseudohyphae, which are round to oval eosinophilic to gray-brown structures (see **Figure 2a,b**) The background shows fragmented

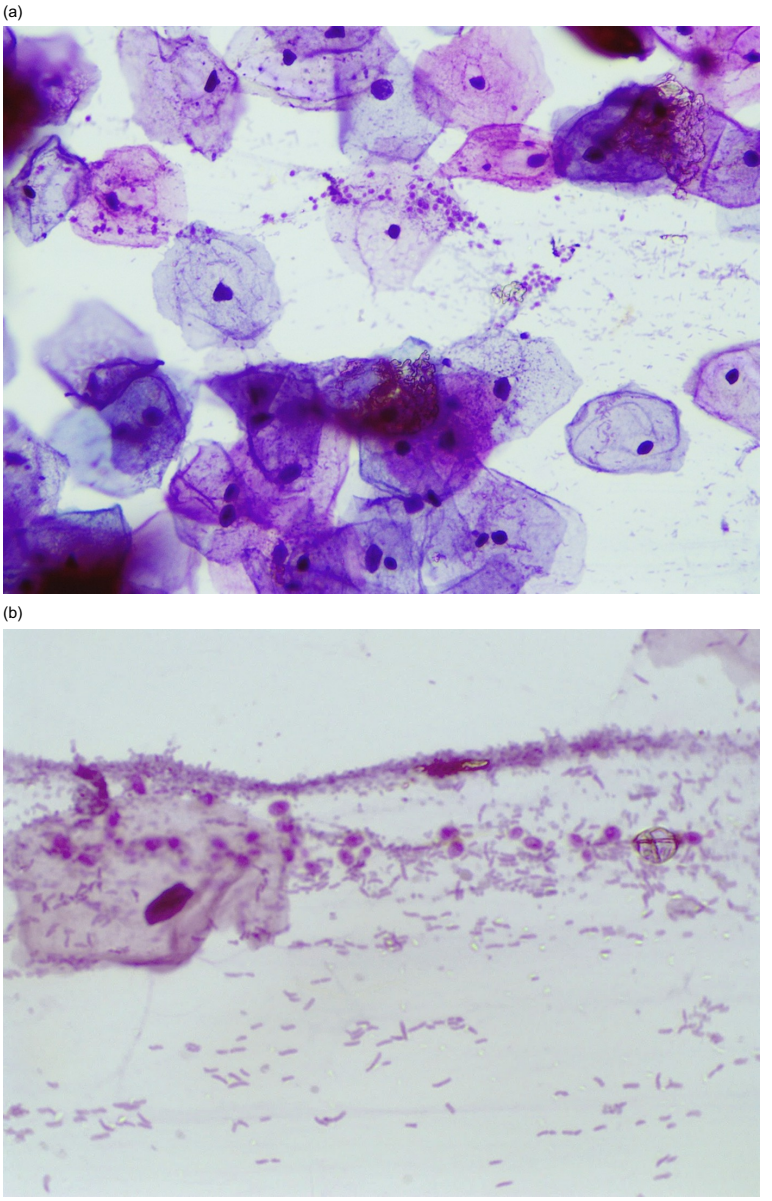


Figure 2.
(a) Pap smear displaying yeast forms of Candida *species with focal budding. [Pap × 10×]; (b) Pap smear displaying yeast forms of* Candida *species with evident budding. [Pap × 40×].*

leukocyte nuclei and spiculation of squamous epithelial cells, which is better seen in liquid-based preparations. The species *C. glabrata* (formerly Torulopsis) conventionally exhibits small, uniform, round budding yeast forms surrounded by a clear halo [19]. Normal secretions, when examined, may reveal the occasional presence of leukocytes. However, a ratio of more than one white blood cell to epithelial cell can point toward an underlying infection. Assessment of the presence of bacterial flora (lactobacillus-dominant or not) can help rule out whether a patient has bacterial vaginosis, where a shift in flora and a coccobacillary-dominant smear background may be observed [3, 11].

3.3 Fungal culture

Approximately 15% to 20% of women are asymptomatic and are colonized with yeast species as part of their normal vaginal flora, and they generally do not need any kind of therapy. However, symptomatic women with chronic complaints should be further investigated. The performance of fungal culture in these scenarios will be of added value because it corroborates not only the diagnosis of VVC but also allows for species identification and increases the sensitivity of KOH preparation. In these patients, the successful treatment of a positive fungal culture, corroborated by a negative follow-up culture result, results in the resolution of symptoms in ~90% of cases [20, 21]. In some patients with evidence of vulvar/vaginal ulcerations, which can be elicited on local examination, the culture for Herpes simplex virus is also warranted. If chronic skin changes are evident or ulcers exist, a tissue biopsy may be of additional help to identify the disease process, such as lichen sclerosus, squamous epithelial hyperplasia, other vulvar dermatoses, or pre malignant conditions. Cultures for infections like trichomoniasis, gonorrhea, and chlamydia are indicated if the vaginal secretions reveal many white blood cells but no underlying cause is found [22].

4. Treatment

The uncomplicated VVC, which *C. albicans* generally causes, is responsive to all types of conventional antifungal drugs in approximately 80% of patients. Therefore, according to the 2021 Centers for Disease Control and Prevention guidelines, uncomplicated VVC should be treated with topical preparations of short duration. This modality is more beneficial than oral azoles, as topical agents avoid systemic side effects. However, in approximately 50% of patients treated with oral fluconazole, VVC recurs after six months. Hence, the American Society for Infectious Diseases recommends the concurrent use of topical and oral azoles. The non-*C. albicans Candida* species may be resistant to standard azole treatment at times; hence, it becomes essential to have knowledge about the species type, and it is recommended to request azole sensitivity testing on culture. For the treatment of RVVC, the control of underlying disease is of utmost importance [23, 24]. For recurrent infection with *C. albicans*, a 14-day oral azole therapy to induce clinical remission and a negative fungal culture has to be followed by a six-month maintenance regimen that consists of ketoconazole (Nizoral), 100 mg daily; itraconazole (Sporanox), 100 mg daily; and fluconazole (Diflucan), 100 to 200 mg weekly [11]. Follow-up of these patients by examination and reculture after the initial two weeks of regimen initiation, and then at three and six months during the

maintenance regimen, will help ensure that the antimycotic therapy is effective and working well [25, 26]. Fluconazole, if taken during pregnancy, is said to be associated with spontaneous abortion and birth anomalies such as craniofacial and heart defects. Women with HIV infection, with lower CD4 + T-cell counts, may experience increased rates of VVC, which is also accompanied by increased viral shedding. The treatment modalities in women with HIV infection are similar to those without evidence of HIV infection [27]. The best treatment modality depends on the patient's medical conditions and the etiological agent. Moreover, factors such as drug resistance in the causative agents and various mutations in immunity-related genes can affect treatment outcomes [28].

5. Role of vaccines

The high incidence of RVVC and the challenges faced while managing it with conventional therapy provide a strong recommendation for the development of immunological treatments that complement the current antifungal treatment plan. The use of exogenous cytokines, antibodies, and immunomodulators can be a potential consideration; however, the mainstay regarding the application of immunotherapy appears to be progress and advancement toward an effective and safe anti-*Candida* vaccine. At the same time, the vaccine should possess the ability to mount an immune response against the virulence traits of *Candida* without influencing the delicate balance of the vaginal microenvironment. In contrast to immunocompromised subjects who are at risk of invasive *Candida* infection, immunocompetent patients can mount vaccine-induced immune responses, thereby being capable of controlling, if not eliminating, the fungal infection [29]. To date, only two anti-*Candida* vaccines have passed phase 1 clinical trials for safety and immunogenicity, while one is still in phase 2 clinical trials. Both vaccines have shown strong evidence of protection against *C. albicans* vaginal infection in rat and mouse models, although with a likely different mechanism of immunological protection [30–32].

6. Conclusion

Candida vulvovaginitis is a common disease generally caused by *C. albicans*, a dimorphic fungus, which can be challenging for treating physicians due to treatment failure and recurrences associated with it. It considerably alters the quality of life and comfort of daily functioning in the young female population. Despite these facts, an accurate diagnosis using available diagnostic tools can alleviate the patient's morbid symptoms. For patients for whom conventional treatment fails, it is essential to reestablish the diagnosis with an emphasis on completely eliminating the symptoms and improving the quality of life among these women.

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Conflict of Interest

The authors declare that there exists no conflict of interest for this chapter.

Declaration

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Chapter 10

Superficial, Subcutaneous, and Deep Cutaneous Fungal Infections

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Abstract

Cutaneous mycoses are caused by a wide variety of fungi. Depending on their classification, they can be superficial, subcutaneous, or deep, and are more common in countries with tropical climates. Diagnosis is initially clinical and is complemented by the use of direct or indirect tests. For example, subcutaneous infections invade the skin and subcutaneous cellular tissue. Treatment can be either local or systemic. The management of systemic or deep mycoses is essential, as some infections can cause generalized forms in immunosuppressed patients, leading to severe cases of lesions in the skin, lungs, bones, brain, or other organs, with high mortality if not diagnosed early. This chapter is justified by the need to review the latest advances in cutaneous mycoses.

Keywords: cutaneous fungi, mycosis fungoides, cutaneous candidiasis, cutaneous drug administration, invasive mycoses

1. Introduction

This chapter highlights the importance of mycoses as neglected diseases. They must be recognized and treated early to prevent progression to invasive mycoses. The most common pathologies and their treatments are analyzed.

Dermatophytes are fungi that parasitize the skin and its appendages, causing infections such as scalp ringworm, ringworm of the skin, ringworm of the hands, feet, and onychomycosis. Recurrent and refractory dermatophytosis includes recurrent generalized tinea corporis, secondary to *Trichophyton rubrum*, which may be resistant to terbinafine. In this case, treatment should be initiated with 50 mg of oral itraconazole for five days, accompanied by ciclopirox and combined topical miconazole cream [1].

Onychomycosis is an infection of the nail caused by fungi, including dermatophytes, non-dermatophytes, mycelial fungi, and yeasts, accounting for 50% of all nail-related diseases. According to a meta-analysis of 26 clinical trials, the treatment consists of terbinafine 250 mg daily for 12–16 weeks or itraconazole 200 mg daily for 12 weeks in monotherapy, which achieves significantly greater cure rates than topical treatments [2]. However, local antifungals, such as topical terbinafine 10%, have a mycological cure rate of 69.9%, with negative culture and potassium hydroxide microscopy, showing statistical significance ($p < 0.001$) [3]. Currently, new laser therapies are available that show promising results in the treatment of mycoses [4].

Regarding *Candida sp.,* cutaneous candidiasis can affect the skin or mucous membranes in susceptible populations [5, 6].

Interdigital tinea pedis is treated with topical miconazole gel and may require 6–12 months of treatment [7].

2. Mycoses located on the skin and mucous membranes

Mucormycosis is an infection caused by fungi of the order Mucorales, such as *Rhizopus*, *Mucor,* and *Rhizomucor*, that can colonize dressings used for wounds, causing invasive skin infections with the possibility of becoming severe cases, mainly in immunosuppressed patients or those who have received organ transplants [8]. In a review conducted with 958 patients infected with COVID-19, researchers observed the development of cutaneous mucormycosis eight days after hospitalization, representing less than 1% of hospitalized patients [9].

Primary cutaneous coccidioidomycosis presents as a suppurative granulomatous disease and can form skin abscesses, ulcers, plaques, nodules, blisters, and cellulitis; diagnosis is made through direct examination or biopsy [10, 11].

Paracoccidioidomycosis is a fungal infection caused by *Paracoccidioides brasiliensis*, considered an endemic disease in Latin America. It can affect the skin, lungs, mouth, throat, and lymph nodes [12]. Treatment is administered for 10 months with itraconazole, ketoconazole, and sulfadiazine [13]. Another therapeutic option is the use of amphotericin B (AmB), a drug of the polyene class that has a fungicidal effect, accompanied by sulfamethoxazole-trimethoprim, which is also used as a maintenance drug [14].

3. Subcutaneous mycoses

Sporotrichosis is a subcutaneous mycosis caused by a dimorphic fungus of the genus *Sporothrix*, whose invasion occurs through penetration via wounds. It manifests as a chronic granulomatous subcutaneous mycosis, affecting the skin and lymph nodes [15], and has been observed in 69.47% of immunosuppressed patients [16]. A systematic review showed that, in countries like Brazil, the most frequent agent in isolations was *Sporothrix brasiliensis* [17], followed by *S. schenckii*. Its clinical manifestations were characterized by lymphocutaneous involvement in 56.14% of cases, systemic involvement in 14.34% – especially in the lungs – and hypersensitivity reactions in 4.55% of cases [18]. The least reported species were *S. globosa, S. luriei, S. mexicana, S. pallida,* and *S. chilensis* [19]. Treatment consists of

itraconazole, terbinafine, amphotericin, or fluconazole and depends on the sensitivity of the pathogen [20, 21].

Chromomycosis, also known as chromoblastomycosis or verrucous dermatitis, is a chronic subcutaneous infection that forms verrucous and papillomatous lesions. Fungal isolates associated with this disease include 80.9% *Fonsecaea spp*., 14.5% *Cladophialophora spp.,* and 1.5% *Phialophora spp.* [22]. The average duration of the disease is 10.8 years, with the most frequent clinical forms being warty formations in 46.4% of cases and tumorous formations in 21.7% of cases [23].

The most active antifungals against granulomatous and suppurative dermatoses are terbinafine, voriconazole, itraconazole, and 10% potassium hydroxide. Combinations with itraconazole (200 mg/day) + terbinafine (250 mg/day), as well as acitretin, can also be used [24, 25].

Mycetomas are inflammatory tumors or granulomas caused by filamentous fungi that produce punctate lesions of different colors, located in the subcutaneous cellular tissue, causing deformity and chronic evolution fistulas, whose main characteristic is painless inflammation, generally caused by *Streptomyces somaliensis* and *Madurella mycetomatis* [26].

Eumycetomas account for 70.7% of cases and are caused by true fungi, while actinomycetomas represent 29.3% and are caused by the genera *Nocardia* and *Streptomyces,* with a mortality rate of 1% and a recurrence rate of 40% [27].

There are forms of massive actinomycetoma in the head and neck that present as giant tumors. Treatment consists of itraconazole 200 mg three times a day for three days, followed by 200 mg twice a day. In cases of resistance, there are other alternatives such as voriconazole 200 mg orally every 12 hours, posaconazole 300 mg in oral capsules once a day, in addition to surgical treatment with excision [27].

4. Deep mycoses

Fungi associated with deep cutaneous infections include *Candida spp., Aspergillus spp., Fusarium spp.*, and dermatophytes, especially *Trichophyton rubrum* and *T. mentagrophytes*. The lesions are superficial and erythematous, developing into firm subcutaneous nodules, ulcers, abscesses, and, in advanced cases, can cause osteomyelitis and bone loss [28].

Deep mycoses are caused by various species of fungi. A systematic review determined that, in Nigeria, histoplasmosis and eumycetoma are the two most frequent infections, and they are associated with other factors such as skin carcinoma, cutaneous tuberculosis, neurofibromatosis [29], acquired immunodeficiency syndrome, and chronic use of corticosteroids [30].

Cutaneous aspergillosis represents the initial kidney manifestation of a systemic infection in immunosuppressed patients with liver transplants, as well as [31, 32], angioinvasive dermatophytosis with necrotizing fasciitis secondary to Trichophyton rubrum infection. This condition presents as a rare complication of skin infections, requiring early surgical treatment, at least 12 weeks of oral terbinafine, and reduction of immunosuppression. Deep cutaneous fungal infections (DFFI) can cause significant morbidity, with rates as high as 75% [33].

Invasive fungal infections cause high morbidity and mortality, triggering chronic infections and generalized multisystem invasive mycoses.

The objective of this chapter is to describe the advances in superficial, subcutaneous, and deep cutaneous fungal infections.

5. Methodology

A search was carried out for articles published in the last five years, for which a research question was generated: What are the advances in superficial, subcutaneous, and deep cutaneous fungal infections? Databases such as Latindex, PubMed, and Google Scholar were used. The following search terms were used: cutaneous mycoses, mucormycosis, paracoccidioidomycosis, sporotrichosis, deep mycoses, and superficial mycoses, yielding a total of 38 articles that addressed the research question for analysis.

Elaboration: Dr. Javier Aquiles Hidalgo Acosta.

Description: **Table 1**. The etiology of skin infections depends mainly on the geographical distribution, with a predominance of Candida infections and *Trichophyton spp*. These were distributed across all study regions. *Malassezia spp*. was reported in Iran as the second most common cause, while Brazil ranked third in frequency, along with a series of fungi causing cutaneous mycoses [34–38].

Table 1 demonstrates that cutaneous mycoses are widely distributed, with a high incidence in several regions of the world, regardless of the location of the study. New resistance mechanisms have been observed, including genetic alterations and previously known host factors such as immunosuppression and diabetes mellitus.

Figure 1. Recurrent genital candidiasis resistant to azole treatment that produces an alteration in quality of life and requires additional treatment. Resistant mycoses are important for health because they threaten the effectiveness of antifungal treatments, increasing the risk of infections becoming more severe and difficult to treat.

Description: **Figure 1.** Chronic fungal infection resistant to current antifungal treatments. The image shows recurrent vulvovaginal candidiasis and fungal plaques of *Candida albicans* resistant to short-term treatment, which generate chronic cervicitis, dyspareunia, and pelvic pain.

Elaboration: Dr. Javier Aquiles Hidalgo Acosta.

Description: **Table 2** illustrates advances in treatment, mechanisms of fungal resistance, emerging species, fungal genetics, new molecular diagnostic tests, and risk factors associated with infection.

Elaboration: Dr. Javier Aquiles Hidalgo Acosta.

Description: **Table 3** demonstrates current advances in the management of subcutaneous and deep cutaneous mycoses, as well as associated risk factors and various genetic factors that influence treatment and outcomes in exceptional cases.

6. Results

The results of the evidence synthesis on skin infections show significant advances over the past five years in areas such as treatment comparisons, laser therapy, and new mechanisms of fungal resistance to various drugs.

Coinfections detected with the presence of other germs, such as Aspergillus and the SARS-CoV-2 virus, have been identified during the COVID-19 pandemic; the identification of unknown risk factors will allow for better understanding.

Regarding the resistance mechanisms detected in cutaneous mycoses, **Table 2** highlights the genetic polymorphism between species that cause diagnostic failures, see **Table 2**. The presence of little-known yeasts, recently discovered in cutaneous infections caused by *C. africana*, was identified. These yeasts are indistinguishable

Author/population	Etiological agents	Outcomes	Type of research/ Country
de Albuquerque et al., [34]/ 3,316 fungal species identified in eight years	Las especies de *Candida* fueron las más aisladas (79.8%), *Trichophyton sp.* representó el 5.6%, *Trichophyton rubrum* el 3.3%, *T. tonsurans* el 2.8%, *T. mentagrophytes* el 1.9%, y *Malassezia spp*. correspondió al 1.5%. Otros hongos menos frecuentes incluyeron *Trichosporon sp. (1.1%), Geotrichum spp*., *Rhodotorula spp*., *Microsporum sp*., *Microsporum canis*, *Epidermophyton sp*., *Fusarium sp.* y *Aspergillus sp.*	Higher incidence of candidiasis, onychomycosis, and dermatophyte infections.	Retrospective and descriptive study/Brazil
Khodadadi et al. [35] studied 750 patients diagnosed with superficial fungal infections	*Candida spp*. was the most frequent, accounting for 70.3%, followed by *Malassezia spp.* at 28.47% and *Rhodotorula spp.* at 1.1%. Filamentous fungi comprised 34.8% dermatophytes and 7.5% non-dermatophytes. The dermatophytoses diagnosed included tinea unguium, ringworm of the head, ringworm of the foot, ringworm of the body, and tinea cruris. Among the isolated non-dermatophyte fungi obtained were *A. flavus, A. niger, Aspergillus spp., Penicillium, Fusarium, Mucor, Stemphylium, and Alternaria.*	Higher incidence of candidiasis, onychomycosis, and dermatophytosis.	Retrospective and descriptive study/Iran
Mäntyniemi et al. [36] studied 573 patients with superficial fungal infections in adults	*Trichophyton rubrum, T. interdigitale, T. mentagrophytes, T. tonsurans, Epidermophyton floccosum, Candida albicans, Cryptococcus and Fusarium spp., and Candida parapsilosis*.	The most frequent infection was tinea pedis (51.5%) and tinea unguium (48.0%). The most frequent pathogen causing a fungal infection was Trichophyton rubrum.	Retrospective study/Finland
Shaw et al. [37], 587 patients with dermatophytosis	*Trichophyton indotinea*	A is most effective when it extends from 8 to 12 weeks ($p < 0.001$). The best antifungals were itraconazole (Odds Ratio: 15.5) or terbinafine (Odds Ratio: 4.34).	Retrospective Analysis/India
Wang et al. [38] reported 160 individual cases of invasive dermatophytosis	*T. rubrum* was the most common germ at 53.1%, followed by *T. mentagrophytes at* 7.5%, *Microsporum canis* at 6.9%, *T. tonsurans at* 5.6%, *T. interdigitale* at 5.0%, and *T. violaceum* at 3.8%.	Overall mortality was 7.9%. Solid organ transplantation was associated as a risk factor in 26.9% of cases. Individuals using topical immunosuppressants had a risk of cutaneous mycosis of 15.6%. Patients with genetic mutations had a probability of infection of 14.4%, a history of diabetes mellitus was associated with 14.4%, and trauma with 6.9%. Mortality was 17.4% in patients with CARD9 or STAT3 genetic mutations.	Systematic review; no region reported.

Table 1.
Most frequent etiological agents of skin infections.

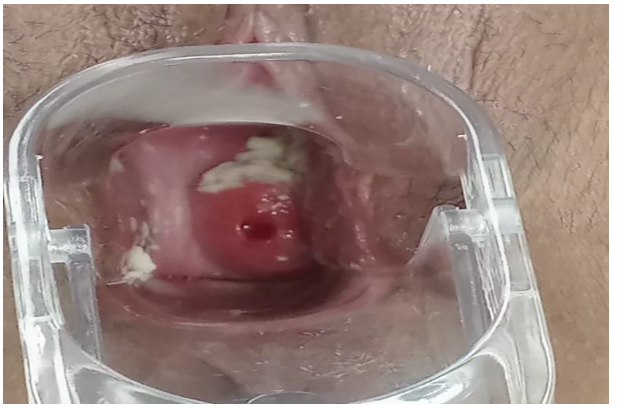


Figure 1.
Recurrent Candida albicans *infection. Sources: Dr. Javier Aquiles Hidalgo Acosta*, recurrent albicans *infection*.

from other species using conventional methods, representing a growing problem for public health and necessitating the implementation of molecular identification methods such as PCR and PCR-RFLP, a technique that combines PCR with restriction fragment length polymorphism (RFLP) to analyze variations in DNA. Additionally, antifungal susceptibility studies and sequencing of hyphal wall protein 1 (HWP1) genes are required.

The results of sporotrichosis demonstrate a rapid worldwide expansion, with an increase in cases of cutaneous forms, previously considered endemic to some regions, now showing greater transmission. These resistance mechanisms, driven by genetic overexpression of efflux pumps, decrease the efficacy of antifungals, causing treatment failure, with high, intermediate, and low minimum inhibitory concentrations across all lines of treatment, which is considered a growing health problem. For example, in Brazil, outbreaks of the disease associated with domestic pets have been observed, contributing to its expansion and being linked to genetic variability with marked epidemiological changes (see **Table 2**).

There are studies investigating the action of antifungals in sporotrichosis with other drugs, such as NSAIDs, that have demonstrated synergistic effects, even observing the reversal of resistance, which would represent a significant achievement on the path to improving the efficacy of treatments (see **Table 2**).

Cutaneous manifestations were observed as an initial sign of invasive mycosis in solid organ transplant patients. Subcutaneous and deep infections presented high mortality, with the need for biopsy to rule out neoplasia. Treatment of these cases included surgery, amputation of the affected limb with debridement, microsurgeries, and intraoperative biopsy for management (see **Table 3**).

7. Discussion

The review provides important data regarding clinical, histopathological, and molecular diagnosis, resistance, susceptibility, advances in treatment, including nanotechnology, the use of surgery to remove lesions that do not respond to antifungals, drug repurposing, and new approaches.

Author/population	Management	Results
Nenoff et al. [1]: An 82-year-old patient, 30 years infected with generalized tinea corporis for 30 years.	Treatment consisted of itraconazole, 50 mg each day for 5 days weekly in the long term, which completely suppressed dermatophytosis; topical treatments included ciclopirox and miconazole.	*T. rubrum,* isolated from skin flakes, exhibited terbinafine resistance due to mutations in the squalene epoxidase gene. Sequencing revealed an isoleucine codon mutation resulting in an amino acid substitution of isoleucine 479 to threonine, along with an additional mutation leading to an amino acid substitution of isoleucine 479 to valine.
Gupta et al. [2]: Patients with toenail onychomycosis – 8,136 patients across 77 randomized controlled trials.	Superior mycological cure was achieved with oral terbinafine 250 mg/day (odds ratio: 16.41, 95% CI: 6.49–41.47) or oral itraconazole 200 mg/day (odds ratio: 18.61, 95% CI: 7.40–46.81).	Continuous administration of terbinafine 250 mg achieved a cure rate of 48.9%, while itraconazole 200 mg achieved a cure rate of 29.0%.
Gupta et al. [3]: Distal subungual onychomycosis in 365 patients.	Topical terbinafine 10% solution achieved mycological cure, with a negative culture result in 69.9% of cases at week 52, compared to placebo at 27.7% ($P < 0.001$).	Complete healing was observed from week 24.
Meretsky et al. [4], Onychomycosis in 533 people.	Laser treatment achieves higher mycological cure rates in patients who received laser treatment compared to those treated with terbinafine (OR = 3.19; 95% CI: 1.39–7.29; $p > 0.05$) and was also higher than other drugs (odds ratio = 3.13; 95% CI: 1.39–37.34; $p > 0.05$). Treatment was maintained for a minimum of 3 months and a maximum of 6 months.	More local adverse events were observed following laser treatment compared to terbinafine (odds ratio = 2.60; 95% confidence interval: 0.01–617.14; $P > 0.01$).
Gharehbolagh et al. [5]: Antifungal susceptibility and prevalence of the *C. albicans* complex and *C. africana* in 167 isolates.	*C. africana* is susceptible to 16 drugs, with low rates of resistance to fluconazole, voriconazole, anidulafungin, caspofungin, and micafungin.	*C. africana* accounted for 0.6% of all infections, and strains resistant to itraconazole, 5-flucytosine, terbinafine, fluconazole, and clotrimazole were detected.
Faridi et al. [6] investigated cryptic species of the Candida albicans complex by subculturing in the chromogenic medium CHROMagar Candida. Among 112 clinical samples studied, 9 samples corresponded to skin.	DNA isolation, molecular identification: PCR-RFLP detected genetic variability of the strains, PCR-HWP1, and antifungal susceptibility testing.	*C. albicans* was the most frequent germ, followed by the *C. glabrata complex, the C. parapsilosis complex,* and *C. krusei*. Within the C. albicans complex, the isolates consisted of *C. albicans (*94%), *C. dubliniensis* (4%), and *C. africana (*2%). Between 6.7% and 8.9% of the isolates were resistant to fluconazole and itraconazole.

Author/population	Management	Results
Sinha et al. [7]: Interdigital gel treatment for tinea pedis in 224 patients	Gel composed of 2% naftifine hydrochloride (n = 112) was compared with 2% miconazole gel (n = 112) in patients with mild or moderate interdigital tinea pedis.	78.18% and 76.36% mycologically confirmed cures at 12 weeks of treatment
Chaves et al. [8]: Management of a post-surgical mucormycosis flare after kidney transplantation	Sterile bandages to secure wound dressings in patients undergoing kidney transplants.	The incidence of post-renal transplant cutaneous mucormycosis decreased from 25% to 0% post-intervention (0/49), with a relative risk of 0 (P = 0.003).
Özbek et al. [9], Mucormycosis associated with COVID-19 in 958 cases.	Advanced age, comorbidities, aspergillosis, use of tocilizumab, immunosuppression, diabetes mellitus, malignancy, and the use of corticosteroids increase the risk of mucormycosis.	Cutaneous mucormycosis accounts for less than 1% of cases; the overall mortality rate is 38.9%.
Reyna-Rodríguez et al. [10], Primary cutaneous coccidioidomycosis in 82 reported cases.	First-line treatment consists of azoles	Polymerase chain reaction (PCR) allows differentiation between species.
Policepatil et al. [11], Cutaneous coccidioidomycosis in 40 patients.	The characteristic lesions of the disease include ulcers, plaques, nodules, blisters, cellulitis, and abscesses.	In 75% of cases, the diagnosis was initially incorrect.
Sato et al. [12] studied Paracoccidioidomycosis (PCM) in 149 patients with acute, chronic multifocal, or chronic unifocal presentations, as well as 110 individuals without the disease who served as a control group.	Role of genetic polymorphism in acute and multifocal forms of the disease	Polymorphism in the promoter region of the IL18 gene increases the risk of acute infection [p = 0.015; odds ratio = 3.10 (95% confidence interval: 1.24–7.77)] and increases the risk of chronic multifocal or unifocal infection [p = 0.023; odds ratio = 2.61 (95% confidence interval: 1.14–5.96)].
Shikanai-Yasuda et al. [13]: Paracoccidioidomycosis in 42 patients.	Comparison of itraconazole, ketoconazole, and sulfadiazine	Four to six months of continuous treatment yielded significant results (P = 0.0001) with itraconazole, (P = 0.017) with ketoconazole-based management, and (P = 0.0012) for sulfadiazine-based treatment.
Seki et al. [14] discuss advances in antifungal therapy for *Paracoccidioides*, highlighting the use of 10 drugs.	Nanotechnology as an approach to alternative therapies.	Three groups of drugs were used: polyenes for amphotericin B (AmB) induction; liposomal forms of amphotericin B (LAmB); sulfonamide derivatives such as sulfamethoxazole-trimethoprim (SMX-TMP) for maintenance; and azoles with similar therapeutic effects, including itraconazole, ketoconazole, and sulfadiazine.

Author/population	Management	Results
Pinto-Almazán et al. [15] reported sporotrichosis in 37 patients infected with HIV/AIDS.	Characteristics of sporotrichosis	Sporotrichosis presents in a more severe and disseminated form, with a predominance in patients with lower CD4
Uemura et al. [16]: Coinfection of sporotrichosis with human immunodeficiency virus in 131 diagnosed patients.	Amphotericin B with an azole or azole monotherapy resulted in 51.15% (67/131) of patients surviving, while 37.4% (49/131) experienced mortality.	The infection had a systemic disseminated presentation in 69.47%, while cutaneous dissemination represented 13%. The average CD4 + lymphocyte count was 154.07 cells/μL.
Rabello et al. [17] reported on emerging zoonotic sporotrichosis in Brazil, documenting 10,400 cases of human sporotrichosis.	83.65% of patients received monotherapy with itraconazole, which was the most commonly used drug in 63% of cases; potassium iodide was used in 30%; terbinafine in 4.5%; and local heat or cryosurgery in 0.9%. Other treatments accounted for 1.6%, including amphotericin B, posaconazole, fluconazole, and ketoconazole.	13 Environmental Strains of *Sporothrix spp*. Diagnosed with Human Sporotrichosis in Brazil
Gonçalves et al. [18], Human sporotrichosis in a center in Brazil: analysis of 142 samples.	Genetic differentiation, diversity, and antifungal susceptibility of *Sporothrix* species.	Significant variability ($P < 0.0001$) was observed between isolates of *S. brasiliensis* with different genotypes, forming subgroups within the same population, such as *S. brasiliensis* and *S. schenckii*. The presence of *S. brasiliensis* constituted 100% of cases during outbreaks associated with domestic cats.
Rodrigues et al. [19] demonstrated in vitro antifungal activity against fungal-resistant *Sporothrix*.	Emergence of resistance to azoles and polyenes, diagnosis by DNA detection in clinical samples through multiplex assay. In severe cases, amphotericin B deoxycholate and liposomal formulations were used.	Treatment failure, low sensitivity to itraconazole, resistance mechanisms developed by the species – such as overexpression of efflux pumps – and high rates of minimum inhibitory concentration for some antifungals, including pyrimidine, echinocandins, voriconazole, fluconazole, and albaconazole.
Xavier et al. [20] reported *S. brasiliensis* in five countries: Paraguay, Chile, Argentina, the United Kingdom, and the United States, based on data from 573 articles published.	Drugs used in vivo as monotherapy or in combination therapy with itraconazole (200–400 mg/day), amphotericin B, potassium iodide, and terbinafine are the drugs used.	Description of the inhibitory activity of 28 drugs against *S. brasiliensis* with fungal inhibition.

Author/population	Management	Results
Seibert et al. [20], "Itraconazole Resistance in *Sporothrix brasiliensis* and *Sporothrix schenckii*: A Synergistic Approach with NSAIDs in Nine Resistant Isolates."	Ibuprofen was the most effective nonsteroidal anti-inflammatory drug, followed by aspirin.	The combination of an anti-inflammatory with itraconazole demonstrated synergistic antifungal activity; itraconazole combined with aspirin, diclofenac sodium, or ibuprofen resulted in a reversal of resistance.
Santos et al. [21], Chromoblastomycosis across five continents in 7,740 patients.	Treatment consisted of surgical excision, cryotherapy, thermotherapy, photodynamic therapy, and surgical debridement. Itraconazole was the most commonly used antifungal therapy. Other treatments included terbinafine, fluconazole, ketoconazole, flucytosine, and systemic or intralesional amphotericin.	Total cure was achieved in 302 patients, and partial cure was observed in 188 cases. Amputation of the affected limb was necessary in 14 cases.

Table 2.
Systematic summary of evidence on advances in cutaneous mycoses.

Author/population	Management	Results
Guevara et al. [23], Chromoblastomycosis in 2,081 patients	Treatment consisted of itraconazole as monotherapy or in combination with other antifungals, and surgery and cryosurgery were required in several cases.	Immunosuppression after kidney transplantation was the most frequent risk factor, and leprosy was the most commonly associated concomitant infectious disease. *Fonsecaea pedrosoi* and *Cladophialophora carrionii* emerged as the predominant etiologic agents.
Guevara et al. [24] reported on chromoblastomycosis in Mato Grosso, Brazil, in 10 patients with a mean disease duration of 8.6 years.	Antifungals with greater activity include terbinafine, voriconazole, and itraconazole.	*F. pedrosoi* has moderate genetic diversity.
Belda et al. [25]: chromoblastomycosis clinical case presentation of one patient with an infection lasting 11 years.	Combination of oral itraconazole and terbinafine, plus topical imiquimod and oral acitretin as adjuvant therapy.	Five months of treatment resulted in the regression of the warty plaques. The use of adjuvants with classic antifungal drugs, specifically itraconazole plus terbinafine, demonstrated a positive response to treatment.
Ali et al. [26]: host genetic susceptibility to mycetoma in 53 patients.	Genetic susceptibility to mycetoma as targets for new mycetoma treatments.	Thirteen genes with allelic variants are associated with mycetoma. The affected genes are found in different pathways of the immune, hormonal, and adaptive systems.
Hoogervorst et al. [27], Mycetoma caused by Madurella mycetomatis in immunosuppressed patients: report of one case from Somalia.	The patient required several treatments for recovery. Initially, he received itraconazole in several doses without a response. He was then switched to voriconazole 200 mg orally, which was discontinued due to adverse effects. Finally, he was continued on posaconazole 300 mg orally once a day, followed by surgical excision.	Long-term posaconazole treatment was continued for 4.5 years, and three surgeries were needed to resolve the infection.
Cassalia et al. [28]: deep cutaneous mycoses eumycetoma case report	Topical antifungal therapy with efinaconazole applied twice daily and oral therapy with itraconazole 100 mg.	Incisional biopsy allowed the diagnosis to be determined. The pathological study showed hyperkeratosis, dyselastosis, and pseudoepitheliomatous hyperplasia accompanied by chronic inflammation and fungal spores. After two weeks of treatment, the clinical picture resolved.
Bassey et al. [29]: deep cutaneous mycoses in Nigeria based on a systematic review of 137 cases.	Histopathological diagnosis is the gold standard in cutaneous mycoses.	15.3% of patients were misdiagnosed with cancer, and 0.7% were misdiagnosed with cutaneous tuberculosis or neurofibromatosis, causing treatment delays.

Author/population	Management	Results
Tsai et al. [30]: the most common subcutaneous and systemic fungal infections in Taiwan.	The identified patients had risk factors such as hematological malignancies, acquired immunodeficiency syndrome, and prolonged use of corticosteroids, and they presented severe forms.	*Fonsecaea sp.,* aspergillosis, mucormycosis, and disseminated cryptococcosis were identified through tissue culture and were associated with the highest mortalityrates.
Park et al. [31], "Cutaneous aspergillosis as a cause of systemic infection: presentation of one case in a patient with immunosuppression."	Treatment consisted of amphotericin B and voriconazole.	Mortality due to disseminated mycosis was observed six weeks after the initial diagnosis, with invasion, brain abscess, and pulmonary mycosis. Despite treatment, mortality occurred without a response.
Patel et al. [32], "Cutaneous and renal aspergillosis after orthotopic liver transplantation."	*Aspergillus fumigatus* is the most common germ in solid organ transplant infections, presenting with an initial clinical picture of skin lesions.	Need for close clinical monitoring of patients with skin infections in solid organ transplant cases.
Anwaier et al., 2025: Mohs micrographic surgery for the treatment of deep cutaneous fungal infections – review of 8 patients.	Mohs micrographic surgery in the management of cutaneous mycoses allows for the surgical removal of the infection.	The most prevalent fungal infections were phaeohyphomycosis (62.5%) and mucormycosis (25%).

Table 3.
Current approaches to the management of superficial and subcutaneous cutaneous mycoses.

A systematic review identified 39 cases of patients with leukemia and Fusarium cutaneous infection in Brazil, Japan, and the United States of America, classifying it as a cosmopolitan disease [39].

Sporotrichosis is the most common subcutaneous mycosis in countries such as Mexico. Epidemiological data on cutaneous and subcutaneous infections are unknown in some countries, which necessitates further research [40].

8. Conclusion(s)

The treatment of superficial mycoses is based on the application of cutaneous antifungals and, to a lesser extent, systemic treatment. For cases of subcutaneous or deep mycoses, systemic treatment is the treatment of choice, often accompanied by surgery or combined treatment. In cases of resistance or lack of remission, several treatments can be used, including oral drugs, cutaneous applications, and azole derivatives such as itraconazole, posaconazole, and voriconazole. Other drugs, such as terbinafine and Amphotericin B, are also utilized. It is necessary to obtain results from cultures or biopsies in cases of chronic evolution or lack of remission of a cutaneous mycosis.

The chapter describes various mycoses as causes of neglected skin infections, mainly induced by *Candida* species. Chronic infections resistant to current antifungal treatments, such as recurrent vulvovaginal candidiasis, have been especially highlighted.

Acronyms and abbreviations

DFI	Deep cutaneous fungal infections

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Conflict of interest

The authors declare no conflicts of interest.

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Candidiasis is a major fungal infection with increasing clinical and therapeutic challenges worldwide. The emergence of drug-resistant *Candida* species and limitations of current antifungal therapies demand new perspectives in diagnosis and treatment. This book, comprising 10 chapters, presents recent advances in understanding candidiasis, highlighting emerging clinical challenges and novel therapeutic approaches. It serves as a valuable resource for clinicians, researchers, and healthcare professionals involved in the management of fungal infections.

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