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Global Clinical Case Studies in *Candida* species: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author DN collected literature and prepared the first draft of the manuscript. Authors FHFF, GK and VP assisted planning, preparation of the whole manuscript. Author KV conceived the study, planned and prepared the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Candida species are a group of fungi that can cause infections in humans. These fungi are commonly found in nature and on human skin, but can cause infections in immunocompromised individuals. Candida can affect various areas such as the mouth, throat, vagina, and blood, leading to different clinical manifestations. Candida species include *C. albicans*, *C. glabrata*, and *C. tropicalis*, and many more. In the recent decade, several studies bring into light the Identification of Candida-specific drug targets which enables targeted therapies with minimal impact on the host, Effective drug targets can disrupt essential fungal processes, leading to efficient elimination of the infection, Specific protein targets in Candida to reduce the chances of off-target effects often associated with broad-spectrum antifungal agents. Common targets in Candida include fungal cell wall, ergosterol biosynthesis to disrupt fungal membrane integrity and protein synthesis pathways. Current challenges in antifungal therapy include resistance to antifungal drug candidates, host immune reactions and drug- induced toxic effects. Mechanism for antifungal drug resistance

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comprises drug efflux pump, target modification and drug catabolism, biofilm formation. To overcome these challenges, drug discovery approaches concentrate on quorum sensing and quorum quenching based anti-virulence and host-fungal interaction kinetics to improve treatment strategies. Future goals of anticandidal therapy would nano-based pharmacophores, immunotherapies, natural product-based antifungals and personalized medicine to minimize host reactions against drugs. Hence, in this paper, we will explore the importance of drug targets and the challenges in antifungal therapy.

Keywords: Candida spp.; anticandidal therapy; drug targets in candida; host-fungus interaction; biofilm.

1. INTRODUCTION

Candida, are dimorphic yeasts and a source of the opportunistic infection known as Candidiasis. In individuals with impaired immune systems, secondary infections like candidiasis are most frequent. The following Table 1 provides most common and clinically relevant *Candida* species known to cause infections in humans.

"Moniliasis, candidiasis, and thrush are all examples of synonyms for candidiasis. These are frequent occupants of the vaginal canal, gastrointestinal system, oral cavity, and other areas. Only in the presence of suitable circumstances do they become pathogenic. It may impact the vagina, penis, oral cavity, or other areas of the body. Thrush is the colloquial name for oral candidiasis. On the tongue, throat, and other parts of the mouth, it appears as white spots. Other signs and symptoms of thrush include soreness and trouble swallowing" [1]. Usage of antibiotics is frequently linked to candidiasis. Fungemia from *Candida albicans*, which results from fungal translocation across damaged mucosal barriers, may be brought on by cancer cytotoxic treatment. Depending on the quantity or makeup of the endogenous bacterial population and the host environment, fungal commensals in the upper and lower GI tract may develop into opportunistic pathogens [2]. " Although *Candida albicans* is the most common cause of candidiasis, non-Candida species have become much more common in recent years. Knowing about non-albicans species is crucial since it affects how they are treated. For certain drugs, such as fluconazole, species of candida other than *Candida albicans are also* resistant. *Candida albicans* was the most prevalent species (42/95; 44.21%), followed by *Candida lusitaniae* (18/95; 18.95%), *Candida parapsilosis* (13/95; 13.69%), *Candida glabrata* (8/95; 8.42%), *Candida kefyr* (6/95; 6.31%), *Candida famata* (5/95; 5.26%), *Candida africana* (2/95; 2.11%), and *Candida orthopsilosis* (1/95) [3]. "People with weakened immune systems are more susceptible to invasive and disseminative candidiasis, which has been on the rise internationally" [4]. Sections with candidiasis show spongiotic alterations in the epidermis along with acanthosis that is atypical, moderate spongiosis, and inflammatory changes. The stratum corneum and top layers of the epidermis contain neutrophils, which is the superficial epidermis' defining characteristic [5]. "Diabetes mellitus (DM) is a chronic metabolic and degenerative disorder that is characterized by chronic hyperglycemia and causes long-term complications like retinopathy, neuropathy, and nephropathy, generally accelerating macro- and micro-vascular changes. It is becoming one of the largest emerging threats to public health in the 21st century" [6,7]. "Glucose hemoglobin (hemoglobin A1c) is 5.7%. Because of antibody-mediated autoimmunity, exposure to environmental toxins, and genetic variations in the MHC Class II histocompatibility complex (HLA-DR/DQ), the pathophysiology of type 1 diabetes is multifactorial. These characteristics raise the risk of disease development as a result of the pancreas' ongoing loss of insulin-producing beta cells, which is brought on by the T cells' invasion through mitochondrial-driven apoptosis" [8]. "The World Health Organization and the International Diabetes Federation forecast that by the year 2045, there would be close to 629 million persons globally who have adult-onset diabetes, up from the estimated 425 million in 2017. Senior people with candidemia had greater rates of DM, cardiac, and pulmonary illnesses. Numerous studies have been conducted on the connection between diabetes and candidiasis, in part because people with diabetes are more susceptible to fungus infections than people without DM" [9,10,11]. "Significant consequences for morbidity and death arise from the development of medication resistance in Candida sp. isolates coupled with epidemiological variability in Candida sp. natural flora. As a result of shifting colonization to

Candida species that are more naturally resistant, such *C. glabrata*, *C. dubliniensis*, and *C. krusei*, the widespread use of medicines, notably azoles, has encouraged the selection of resistant species" [12,13].

"Currently, the epidemiology in the region is characterized by the global dispersion of Candida species, but it shows that *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* predominate" [14]. "One of the most prevalent fungal illnesses, vaginal candidiasis typically affects pregnant women and has been linked to systemic infections in newborns, especially those who were born prematurely or with low birth weight (LBW)" [15]. "In low birth weight newborns, candida is a significant risk factor for systemic infections and the associated fatalities" [16]. Amphotericin B has been shown to be effective in treating LBW preterm newborns with neonatal septicemia caused by *C. dubliniensis*.

When asymptomatic candidiasis was treated with clotrimazole in women, there was a trend for the number of preterm births to drop spontaneously. During pregnancy, checking for infection removal may lower your chance of giving birth prematurely [17,18]. In children hospitalized for invasive fungal infections, candidemia is the most common cause. Children under the age of one have been shown to have the greatest prevalence of candidemia among the various demographics of pediatric patients. Conversely, juvenile patients who have candidemia tend to respond to treatment more effectively than adults. Compared to the expenditures involved with treating adults, this improved result is associated with greater inpatient costs for neonates and early infants [19,20,21]. "Neonatal invasive candidiasis risk factors, especially in preterm born newborns, call for special attention". [79] Benjamin et al. [20] quantified "the risk factors predicting infection in high-risk premature infants in a study involving a prospective observational cohort of 1515 extremely low birth weight (ELBW) infants that was conducted over three years at 19 centers of the US Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network" [20]. "An opportunistic infection, candidiasis. Healthy people have *Candida albicans* colonizing their gastrointestinal, esophageal, and oropharyngeal mucosa. Candida albicans, which typically live in an immunocompromised host, can cause mucosal candidiasis in various locations. Due to a weakened immune system brought on by using corticosteroids or other cytotoxic medications, people with leukemia or lymphoma are more susceptible to candidal infection. major cutaneous candidiasis can occur and should be included in the differential diagnosis for immunosuppressed individuals presenting with cellulitis that does not respond to antibiotic treatment, even if it was not the major presentation in this instance. Deep skin infections caused by primary Candida spp. are relatively uncommon. Most cutaneous Candida spp infections are secondary to *Candida albicans* and appear in a number of ways, such as superficial dermatitis, intertrigo, and balanitis" [22]. Immunosuppressed patient groups, such as those taking intravenous cytotoxic chemotherapy, might have a larger range of fungal infections. It is usually advisable to look into and take into account probable fungal etiologies of the illness process when a patient with sepsis has an indwelling catheter or port-a-cath for cytotoxic treatment.

Table 1. Distribution of pathogenic *Candida* species

Name of the species	Type of infection	Target organs / Individuals
Candida albicans	Mucous Membrane and blood stream infections	Mouth – Oral Thrush; Vagina – Vaginal Candidiasis; Blood – Invasive Candidiasis
Candida glabrata	Blood stream infections	Candidiasis in Immunocompromised / Immunosuppressed individuals
Candida tropicalis	Blood stream infections	Candidiasis in Immunosuppressed patients
Candida parapsilosis	Catheter-related Candidiasis	Eyes – Ocular Keratitis; Neonates – Invasive Candidiasis
Candida krusei; *Candida lusitaniae*	Nosocomial Candidiasis	Candidiasis in Immunosuppressed patients
Candida dubliniensis	Mucous Membrane and soft tissue infection	Mouth – Oral Thrush; External Genitalia - Genital Candidiasis
Candida auris	Nosocomial Candidiasis	Candidiasis in Immunosuppressed patients

C. tropicalis is the pathogenic Candida species that is most common among non-albicans. This pathogenic yeast has significantly increased infection rates worldwide, and it is now posing a serious threat to those with impaired immune systems [23]. Patients with severe congenital neutropenia or leukocyte adhesion condition frequently develop invasive candidiasis, highlighting the crucial role granulocytes play in preventing widespread fungal infection [24].

2. IN DIABETIC PATIENTS-CASE STUDY

“ Chronic hyperglycemia and other long-term consequences including retinopathy, neuropathy, and nephropathy are all symptoms of diabetes mellitus (DM), a metabolic and degenerative illness that typically speeds up macro- and micro-vascular alterations. One of the biggest new hazards to public health in the twenty-first century is growing” [25,26]. “Diabetes has been linked to several immunological changes, including cellular immunity that is more weakened and changes in polymorphonuclear cells, monocytes, and lymphocytes” [27]. “Glucose hemoglobin (hemoglobin A1c) is 5.7%. Because of antibody-mediated autoimmunity, exposure to environmental toxins, and genetic variations in the MHC Class II histocompatibility complex (HLA-DR/DQ), the pathophysiology of type 1 diabetes is multifactorial. These characteristics raise the risk of disease development as a result of the pancreas' ongoing loss of insulin-producing beta cells, which is brought on by the T cells' invasion through mitochondrial-driven apoptosis” [28]. “On the other hand, type 2 diabetes mellitus (DM) is characterized by insulin resistance, which is connected to alterations in mitochondrial metabolism, including decreased mitochondrial density, ATP generation, and levels of mitochondrial RNA (mtRNA), as well as elevated oxidative stress indicators. Circular mtDNA may undergo considerable tissue alterations as a result of repeated exposure to these effects in the pancreatic and endothelial cells. These modifications might result in secondary vascular disease and cardiac, renal, ophthalmic, and neurological problems” [28,29,30]. “To better understand the nutrition acquisition strategy and its potential connection to the hyperglycemic condition of diabetic patients, it was determined how quickly C. albicans grew in the presence of various amounts of glucose and fructose. The scientists found a clear correlation between glucose levels and C. albicans development, which may explain why non-controlled diabetic individuals frequently develop yeast infections. It's interesting to note that fructose has C. albicans inhibitory abilities. This suggests that foods high in fructose may help stop the growth of candidiasis. This is a crucial result in oral Candida sp. biofilms, especially for patients with prosthetic devices” [31]. “It was proven that AmB provided two hydrogen bonds and Vcz provided three crucial hydrogen bonds that stabilized the glucose. The same study's in vivo findings suggested that the physiologically significant increased blood glucose levels of mice with diabetes mellitus may interact with the existing selective antifungal drugs to reduce glucose activity through complex formation. In comparison to their pure molecules, Vcz-glucose and AmB-glucose complexes appear to be less effective. As a result, choosing the right medications for DM patients is crucial if we want to control infectious infections” [32]. “The first peptide toxin discovered in a human fungal pathogen, this enzyme is encoded by the hypha-associated ECE1 gene. In oral epithelial cells, candidalysin causes the release of lactate dehydrogenase (LDH), a sign of membrane instability and cell injury. Importantly, the research revealed that C. albicans mutants with the entire ECE1 gene or the candidalysin-encoding region deleted possess full invasive potential *in vitro* but are unable to cause tissue damage or cytokine release and are significantly weaker in mouse models of oropharyngeal candidiasis and zebrafish swim bladder mucosal models” [33]. “The risk factors for oral candidal infection are complicated, but it is known that tongue lesions, smoking, wearing dentures, and immunosuppression (such as diabetes mellitus) significantly affect oral Candida sp. carriage and the development of oral candidiasis” [34,35,36,37]. “Given that C. dubliniensis and C. albicans share many phenotypic traits, the divergence across research may be due to issues with identification methods. The same authors discovered that, as was seen in other investigations, the prevalence of C. tropicalis dramatically increased, exhibiting the greatest level of inflammation in DS” [38,39,40]. “18.8% of women with diabetes and 11.8% of women in the control group had vaginal yeast isolates. The diabetic group was shown to have more symptoms than colonized women (33.33%) and greater colonization, VVC, and RVVC than the controls (VVC + recurrent VVC (RVVC) = 66.66%). In attempt to identify the organisms responsible for VVC, Sherry et al. investigated the epidemiology of the disease in a cohort. The scientists found that NCAC was becoming more

prevalent although C. albicans was still the most prevalent Candida species. There have also been reports of a heterogeneous biofilm-forming capability linked to decreased antifungal medication susceptibility" [41,42]. "They said that 14.9% of the individuals exhibited positive vaginal Candida sp. infection prior to beginning SGLT2 inhibitors. The colonization was substantially correlated with younger age and microangiopathy. In addition, 24 (36.9%) of the 65 people who tested negative for Candida sp. changed to a positive culture, and 18 (15.8%) of them experienced symptomatic vaginitis. The authors came to the conclusion that real-world practice appears to show greater rates of positive colonization and symptomatic vaginitis than clinical trial rates of 31% and 5-10%, respectively. Before and after using SGLT2 inhibitors, vaginal Candida colonization risk factors could change" [43]. "The advancement of microvascular illness, the lack of adequate host defenses, and diabetic vasculopathy—which exacerbates hypoperfusion and hyperglycemia and may result in neutrophil and lymphocyte dysfunction with decreased opsonization—are the most significant of these concerns" [44]. "The animal models of DM type 1 and type 2 (e.g., species, strain, gender, genetic) serve a variety of functions, and the study's objectives (e.g., employed for pharmacological or genetic investigations and understanding disease mechanisms) will determine which model is used" [45,46,47].

3. IN PREGNANT WOMEN-CASE STUDY

Three out of four women will have vulvovaginal candidiasis (VVC), sometimes known as a yeast infection, at some point in their lives.1 Pregnant women are more likely to get infected than other women, and more than 40% of afflicted women will experience two or more VVC episodes2,3 [48]. "The following antifungal medications are commercially available in Canada for the treatment of VVC: imidazole antifungals (such as butoconazole, clotrimazole, and miconazole), triazole antifungals (such as fluconazole and terconazole), and polyene antifungals (such as nystatin). These medications come in both oral and topically applied forms. Due to the safety evidence gathered from both animal and human studies, topical formulations of the antifungal imidazole and triazole, together known as azole antifungals, are regarded as the treatment of choice during pregnancy. Prospective and observational studies involving the use of topical antifungals did not reveal an increased risk of major malformations when mothers were exposed any time during pregnancy, and the authors considered them generally safe" [48]. "Systemic absorption of these topical medications is minimal, posing little risk of transfer to the unborn baby. Azole therapy should be recommended for 7 days instead of a shorter duration because of improved treatment success" [49,50]. "Research has been done on using boric acid to cure VVC. The antifungal drugs can be substituted by boric acid, despite the latter not being readily available commercially. There isn't a lot of information available on boric acid's safety in people. A recent retrospective case-control research from Hungary revealed a tenuous link between significant abnormalities and prenatal exposure to boric acid, although the link failed to approach statistical significance" [51]. "A non-significant higher odds ratio for total major malformations was seen for women who had been exposed to oral corticosteroids, according to a meta-analysis by Park-Wyllie et al. that included five prospective human investigations. In comparison to controls, there was a slight but statistically significant increase in the likelihood of having a cleft palate (odds ratio 3.35, 95% confidence range 1.97 to 5.69)" [52]. "About 3% of the dosage of topical corticosteroids that is administered to the skin is absorbed systemically. No higher incidence of significant abnormalities was reported in the offspring of pregnant women who used topical corticosteroids in two population-based investigations" [53]. "The *in vitro* activity of fluconazole was measured by the E-test (AB Biodisk, Solna, Sweden) in accordance with the manufacturer's instructions. The MIC values were read where the inhibition elapse intersected the strip which was interpreted as the lowest concentration at which 80% of the growth was inhibited. Interpretative susceptibility criteria recommended by the Clinical and Laboratory Standard Institute (CLSI) were used to evaluate the susceptibilities of isolates. Candidasis is regularly seen during a healthy pregnancy without posing a serious risk to the fetus. However, VVC may have a deleterious impact on pregnancy. If left untreated, vaginal candidiasis can culminate in pelvic inflammatory disease (PID), which can cause infertility in non-pregnant women as well as chorioamnionitis, which can cause abortion and preterm in pregnant women. VVC may increase the risk of candidemia in preterm infants during a healthy pregnancy. C. albicans is the most prevalent Candida species found in vaginal specimens, followed by other

non-albicans Candida (NAC) species as C. glabrata, C. tropicalis, C. dubliniensis, and C. krusei" [54,55]. "Data on the frequency of VVC, its geographic distribution, and the *in vitro* antifungal susceptibility pattern of Candida isolates from vaginal swabs of pregnant women are few in Ghana. Studying the antifungal susceptibility of Candida species among pregnant women in the Ho Municipality is crucial due to the growing shift in Candida species populations from C. albicans to NAC and the quick emergence of drug resistance. The clinical circumstances of pregnant mothers and newborns may be improved by early detection and proper treatment" [56]. The capacity to distinguish pathogenic Candida isolates into their unique species using chromogenic medium has improved diagnostic techniques, which may be partially responsible for the rise in the identification of Candida species in human illnesses [57].

4. IN BABIES AND YOUNG CHILDREN-CASE STUDY

In children hospitalized for invasive fungal infections, candidemia is the most common cause. Children under the age of one have been shown to have the greatest prevalence of Candidemia among the various demographics of pediatric patients [58,59]. Conversely, juvenile patients who have candidemia tend to respond to treatment more effectively than adults. Compared to the expenditures involved with treating adults, this improved result is associated with greater inpatient costs for neonates and early infants. Additional comparisons of pediatric and adult secular trends are shown in the graph [60]. Between 2009 and 2015, the US Centers for Disease Control (CDC) started population-based surveillance in four US metropolises. Between 2012 and 2015, the total incidence of candidemia in neonates fell from 31.5 cases per 100,000 births in 2009 to 10.7 and 11.8 cases per 100,000 births, while it decreased in babies from 52.1 cases per 100,000 births in 2009 to 15.7 and 17.5 cases between the same years. In non-infant children, the incidence of candidemia fell in a similar manner, from 1.8 cases/100,000 births in 2009 to 0.8 cases/100,000 births in 2014. In keeping with these findings, a population-based observational research carried out in Atlanta, Georgia, found a decrease in the incidence of candidemia in patients under 1 year of age, from around 60 per 100,000 person-years in 2008-2009 to about 30 per 100,000 person-years in 2011 [57,58]. These consist of central line maintenance, guided insertion, and implementation packages for the whole hospital. These precautions highlight how crucial it is to use properly sterile barrier precautions, prepare the skin for central line insertion with chlorhexidine, take thorough care of the catheter and its insertion site, and regularly address the need for a central venous catheter. Neonatal invasive candidiasis risk factors, especially in preterm born newborns, call for special attention. 137 (9.5%) of the 1515 babies participated in the study had invasive candidiasis, which was confirmed by a positive culture from one or more of the following sources: blood (96), urine (52), CSF (9), or other sterile bodily fluids (10). A multivariable analysis of potentially modifiable risk factors associated with candidiasis identified the presence of an endotracheal tube, the presence of a central venous catheter, and the receipt of an intravenous lipid emulsion among the various predictive models that have been developed for invasive candidiasis in neonates. A second model anticipated candidiasis when blood cultures were performed. Vaginal birth, the week of gestation, and the appearance of Candida-like dermatitis were among the aspects of the history, physical examination, and preliminary laboratory analysis that indicated candidiasis [20]. In predicting newborn invasive candidiasis, the clinical prediction model outperformed clinician judgment (0.70) with an area under the receiver operating characteristic curve of 0.79. In this ground-breaking investigation, it was shown that invasive candidiasis increased the probability of neonatal mortality; for instance, 47 of 137 newborns with candidiasis died, compared to 197 of 1378 patients without candidiasis (14%) (p 0.0001). The babies from whom Candida was isolated from several sources had the greatest mortality rates. The death rate was 16 of 28 (57%) for baby patients with positive urine and blood or positive urine and CSF. The death rate was comparable in individuals who had *Candida* spp., underscoring the relevance of the recovery of Candida spp. from urine in newborns [20].

5. IN SECONDARY INFECTION OF IMMUNOSUPPRESSED / IMMUNE COMPROMISED PATIENTS-CASE STUDY

Invasive Candida infections and candidemia (Candida species in the blood) are most frequently linked, especially in immunocompromised individuals and those who need urgent care. Patients who are

immunosuppressed, such as those with hematological malignancies (in patients who have recently recovered from an episode of neutropenia), recipients of hematopoietic cell transplants or solid organs, and those who are given chemotherapeutic agents for a variety of different illnesses, are particularly at risk for developing candidemia. Comprehensive gastrointestinal mucosal injury, broad-spectrum antibiotics, and central venous catheters are linked to additional risk factors. Although various Candida species other than *Candida albicans* have been found recently, *Candida albicans* is still the most common cause of candidiasis [60,61,62,63]. Infections of the bladder and kidneys, endophthalmitis, meningitis, osteoarticular infections, endocarditis, peritonitis, and intra-abdominal infections, as well as pneumonia, empyema, mediastinitis, and pericarditis, can all result from C. albicans getting into the bloodstream. Candida in the urine is referred to as candiduria. Patients with urinary system anomalies, most frequently urinary tract blockage, and/or those who have had a urinary tract operation are more likely to develop candiduria as a cause of candidemia. Although it is sometimes difficult to distinguish colonization from a bladder infection, it is typical in hospitalized individuals. When candiduria was present, renal transplantation was deemed to be a risk factor for ascending infection and candidemia. According to studies, isolated *Candida albicans* is present in more than 50% of hospitalized patients with candiduria [6,64]. Due to hematogenous seeding or inoculation following trauma, intra-articular injection, a surgical operation, or injectable medication usage, Candida species can infect bones and joints. Osteoarticular infections frequently show symptoms many months or even a year following a fungemia episode or surgical operation. At the same places, the symptoms are typically less obvious than bacterial infections. Long diagnostic delays are a result of both of these conditions, particularly in patients with vertebral osteomyelitis. discomfort and a reduced range of motion are the main signs of Candida arthritis, whereas local discomfort is the main sign of Candida osteomyelitis. A biopsy or aspirate culture of joint fluid or bone is only deemed pathogenic when one Candida colony is present [65,66,67]. The meninges are most frequently affected by central nervous system candidiasis (although they are all generally rare). Premature babies are most frequently the victims of this. Direct inoculation or hematogenous dissemination may have caused the infection. Neurosurgery, more recent antibiotics, and corticosteroids are risk factors. Localizing neurological symptoms, meningismus, increased cerebrospinal fluid pressure, and fever are frequently present. Compared to other Candida species, *Candida albicans* appears to be the most dangerous Candida species, increasing fatality rates in invasive infection [68,69]. The number of immunocompromised individuals is rapidly expanding due to the use of newer, more effective chemotherapy drugs and regimens. Due to their severely weakened immune systems and the external pressures from antibiotic use, these patient populations are incredibly vulnerable to invasive fungal infections, which explains why the burden of invasive fungal infections is regrettably rising in parallel with these medical advancements. This article examines the critical elements to take into account when dealing with the distinct patient populations afflicted by such illnesses and emphasizes recent changes in the epidemiology of invasive fungal infections [70]. The three most frequent cohorts of patients at risk of invasive fungal infections are those with acute leukemia, those who have undergone HSCT, and those who have undergone solid-organ transplants. Understanding the underlying immunologic deficiency (e.g., neutrophil, T cell, or B cell-mediated), the length, and the severity of the defect(s), as well as how to address these immunocompromised patients, is crucial. Intensity of immunosuppression (dose, duration, and temporal sequence of immunosuppressive regimen), extrinsic factors (radiation, drugs, or surgery, resulting in breaches in the body's mucocutaneous defensive surfaces), and environmental exposures (community or nosocomial) may all play significant roles and influence which pathogen may produce an invasive fungal infection. The total net infection risk affects the overall risk of infection [71]. The post-transplant course for HSCT recipients has a dynamic timeline due to the host, the graft (in terms of the length of neutropenia prior to engraftment), and procedural complications (such as the use of central venous intravascular catheters). Early on, invasive fungal infection risk is frequently influenced by host characteristics (such as older age) and transplant variables (such as human leukocyte antigen mismatch). To avoid graft-versus-host disease in particular, using immunosuppressive medications during the pre-engraftment period may severely deplete neutrophils, which increases the risk of developing invasive candidiasis and invasive aspergillosis. Alveolar macrophage phagocytic abnormalities and the propensity to develop

chronic graft-versus-host illness and Cytomegalovirus disease are the results of post-engraftment problems of the transplant, however [72].

6. VIRULENCE Factors Studied IN *Candida* sp.

"One group of virulence factor causes colonisation to take place and the other help to spread the infection. Polymorphism implies the transition of C. *albicans* from a commensal form to a pathological one, which depends on changes in the environment in which it is located. It is characterized by the morphological transition of blastospores into hyphae, and the transitional form between are pseudohyphae. The morphological transition of *C. albicans* begins with the budding of blastospores and the formation of new cells. The nuclei separate at the mother–daughter cell junction via the septum. The nuclei of hyphal forms divide in the germ tube but outside the septum region. After division, one nucleus returns to the mother cell, and the other moves toward the center of the germ tube. *C. albicans* is present in the form of yeast in the human microbiome. Several signaling pathways are involved in hyphal formation. The most important is cAMP-dependent protein kinase A (cyclic adenosine monophosphate PKA). It has been shown that a hypha-specific toxin, candidalysin, is crucial for the occurrence of candidiasis. Candidalysin is a cytolytic 31-amino acid α-helical amphipathic peptide. It is produced by the *C. albicans* hyphae, and it is crucial in damaging the host cells. It is thought that it contributes to establishing a systemic infection and mortality. Candidalysin is capable of directly damaging the epithelial membrane, by intercalation, permeabilization, and creating pores, causing the cytoplasmic contents to weaken". [79].

"Factors that contribute to the pathogenic potential of *Candida albicans* are the expression of proteins important for adhesion and invasion. The process of adhesion is affected by various factors, such as the types of protein in the cell wall, and the physical and chemical properties of the cell surface. Adhesins of *C. albicans* recognize ligands such as proteins, fibrinogens, and fibronectins and bind to them. Since adhesins such as Als3 and Hwp1 are mainly expressed during hyphae creation, they play an important role in the adhesion of *C. albicans* to the host cells". [79]

"Formation of biofilm is a property of *C. albicans* pathogenesis. Most infections caused by *C. albicans* are related to the creation of a biofilm on the surface of the host or on abiotic surfaces (implants), which leads to high morbidity and mortality. Because *C. albicans* can transition from yeast to hyphae morphologically, its biofilm is a complex structure of different morphological forms. The biofilm develops through several consecutive phases. In the first phase, the individual cells of *Candida albicans* adhere to the substrate, which forms the basal layer of the biofilm. After that comes the phase of cell proliferation and filamentation, in which the cells form elongated protrusions, which continue growing into filamentous hyphal forms. The production of hyphae is a sign of the initiation of the creation of the biofilm. In the maturation phase, the accumulation of an extracellular polysaccharide matrix follows. The final phase involves the dispersion of non-adherent cells, which results in the possibility of the inception of new biofilms and the possibility of dissemination in the tissue" [79].

"The extracellular polysaccharide matrix comprises extracellular polymers. Essential part of the extracellular matrix are β-1,3-glucans, which significantly contribute to the biofilm's resistance to antifungal drugs because they prevent contact with target cells. *C. albicans* cells in biofilm release more β-1,3-glucans into the extracellular matrix than planktonic cells. The transcription network that regulates biofilm formation consists of six major transcription regulators (Efg1, Tec1, Bcr1, Ndt80, Rob1, and Brg1) that regulate the expression of 1000 genes. Bcr1 transcription factor (Biofilm and Cell wall Regulator 1), whose main target is Hwp1 (Hyphal Wall Protein), is necessary to form biofilm on mucosal surfaces. The Hwp1 protein binds to transglutaminases on host cells in biofilms on mucosal surfaces. While on abiotic surfaces, it is expressed as an independent enzyme of the host and has an adhesion function. Several different gene products control biofilm development on abiotic surfaces transcription factors (Efg1, Bcr1, Tye7), cell wall proteins (Hwp1, Als3), protein kinases (Ire1, Cbk1). The two essential regulators of biofilm on abiotic surfaces are Efg1 and Bcr1. These transcription factors are needed for the expression of different genes for cell adhesion and filamentation in biofilms on abiotic surfaces. Additionally, the adhesin Als3 which is the target of Bcr1 plays a crucial role in the formation of biofilm on the abiotic surface. During the

Table 2. Distribution of Virulence proteins and the encoding genes to target specific cell types

Name of the *Candida* species	Target organ/tissue/cell	Name of the virulence protein and gene	Role of the virulence protein	References
C. lusitaniae	host's epithelial cells	CLUG_03274FOB63_002933E JF14_40078	Adherence of the organism to the oral mucosa	Kamai, *et al.*, 2002 [72]
C. albicans	mucosal cells	EJF14_50044FOB63_000850 aspartyl proteinases (SAP) and phospholipases (PL)	Necessary for active penetration of host cells, neutrophil extracellular traps (NETs)-releasing response. Required for proteolysis.	Staniszewska. *et al*, 2020 [73]
C. lusitaniae	activates cell-surface protein and adhesin genes	A9F13_15g00066 Bcr1p	Acts as a master regulator of biofilm formation.	Nobile *et al.*, 2005 [74]
C. tropicalis	Candida interaction with endothelium using porcine whole blood vessel.	ALS gene	Adhesion to biotic surface and infection	Klotz, 1983 [75]
C.parapsilosis	Dendritic cells	Lipase CpLIP1 and CpLIP2	Promotes the fungal cell in macrophages and mitigate the inflammatory response in host	Toth *et al*., 2017 [76]
C.glabrata	Mucous membrane epithelial surface of the host	proteases, phospholipases, and hemolysins *Epa* proteins CBS138 *C*	*in vitro* as it regulates the interaction between yeast and the host's epithelial cells. In addition, it is involved in biofilm formation	Olson *et al*, 2017 [77]
C. auris	Epithelial cells	MRL 31102 and MRL 31103(phospholipase and proteinase)	ability to form biofilms on biotic surfaces such as skin and non-biotic surfaces such as medical devices	Larkin *et al*., 2017 [78]

formation of a biofilm, besides the change in expression of genes directly involved in its formation, the expression of genes indirectly related to different characteristics of the biofilm also changes. The expression of genes involved in the metabolism of sulfur-containing amino acids is increased, which is characteristic of cells in the biofilm's deeper layers. This metabolism allows cells to survive starvation and oxidative stress because sulfur amino acids are involved in the synthesis of antioxidants. The biofilm cells form a hypoxic environment and increase the expression of genes involved in glycolysis, fatty acid metabolism, and ergosterol synthesis". [79]

Thigmotropism of the hyphae of *C. albicans* is regulated by the extracellular intake of calcium through calcium channels. It is an important mechanism in the enhancement of the virulence of *Candida spp.* Thigmotropism aids in creating a biofilm on abiotic surfaces and the spread in the host tissue.

Among virulence factors of *C. albicans* is phenotype transition between white and opaque cells. Phenotype diversity provides a quick response to changes in the environment. It is extremely important for the life of many microbe species. In *Candida albicans* cells, switching between two phenotype states, white and opaque, leads to differences in filamentous growth and interactions with immunological cells in vitro. Morphological changes and phenotypic switches are stabilized transcriptionally and are stable for many generations.

"Secretion of hydrolytic enzymes are present in *Candida albicans.* Hydrolytic enzymes facilitate the commensal and pathogenic characteristics such as attachment to host tissue and causing the host cell membrane's rupture. Because of these enzymes, invasion into the surfaces of mucous membrane and blood vessels is possible, and they also participate in avoiding the host's immune response. There are three main enzymes produced by *C. albicans* are SAP (secreted aspartyl protease), phospholipase, and hemolysin" [71] (Talapko *et al.,* 2021).

Fungal diseases are severe and have very high morbidity as well as up to 60% mortality for patients diagnosed with invasive fungal infection. In this review, *in vitro* and in vivo studies provided us with the insight into the role of Candida virulence factors that mediate their success as pathogens, such as: membrane and cell wall (CW) barriers, dimorphism, biofilm formation, signal transduction pathway, proteins related to stress tolerance. The following Table 2 explores the distribution of various *Candida* species and the putative virulence proteins with role and genes coding the virulence proteins which targets specific tissues or cells in the host.

7. CONCLUSION

Medical professionals handling these patients face a significant challenge due to the epidemiologic shifts in the prevalence of invasive fungal infections in a rapidly growing group of immunocompromised individuals. Despite the expanding range of antifungal medication, the morbidity and fatality rates related to these infections remain chronically high. To combat the pervasive fungi that cause invasive fungal diseases, it may be desirable to create less harmful forms of immune suppression. We could have an advantage over these complex eukaryotes if we can reduce the length of neutropenia and enhance immune suppression treatments to better establish immunological tolerance of the allograft.

DATA AVAILABILITY

All datasets analyzed in this study are included in the manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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