


Candida lusitanae: Biology, Pathogenicity, Virulence Factors, Diagnosis, and Treatment

Diana F Mendoza-Reyes, Manuela Gómez-Gaviria*, Héctor M Mora-Montes 

Departamento de Biología, División de Ciencias Naturales y Exactas, Campus Guanajuato, Universidad de Guanajuato, Guanajuato, Gto, C.P. 36050, México

*These authors contributed equally to this work

Correspondence: Manuela Gómez-Gaviria; Héctor M Mora-Montes, Departamento de Biología, División de Ciencias Naturales y Exactas, Campus Guanajuato, Universidad de Guanajuato, Noria Alta s/n, col. Noria Alta, Guanajuato, Gto, C.P. 36050, México, Tel +52 473-7320006 Ext. 8193, Fax +52 473-7320006 Ext. 8153, Email m.gomezgaviria@ugto.mx; hmora@ugto.mx

Abstract: The incidence of fungal infections is increasing at an alarming rate and has posed a great challenge for science in recent years. The rise in these infections has been related to the increase in immunocompromised patients and the resistance of different species to antifungal drugs. Infections caused by the different *Candida* species, especially *Candida albicans*, are one of the most common mycoses in humans, and the etiological agents are considered opportunistic pathogens associated with high mortality rates when disseminated infections occur. *Candida lusitanae* is considered an emerging opportunistic pathogen that most frequently affects immunocompromised patients with some comorbidity. Although it is a low-frequency pathogen, and the mortality rate of *C. lusitanae*-caused candidemia does not exceed 5%, some isolates are known to be resistant to antifungals such as amphotericin B, 5-fluorocytosine, and fluconazole. In this paper, a detailed review of the current literature on this organism and its different aspects, such as its biology, possible virulence factors, pathogen-host interaction, diagnosis, and treatment of infection, is provided. Of particular interest, through Blastp analysis we predicted possible virulence factors in this species.

Keywords: biological aspects, candidiasis, multidrug resistance, opportunistic pathogens, virulence factors

Introduction

Candida spp. are often part of the normal microbiota that resides in non-sterile human tissues and as a such, are often found as part of the respiratory, gastrointestinal, urinary, and genital tracts, in the skin, fingernails, and oral cavity.^{1,2} Candidiasis is the name given to the infections caused by members of the *Candida* genus, and traditionally, the most frequently isolated species from clinical specimens is *Candida albicans*, which is associated with high morbidity and mortality rates.^{3–7} However, *C. albicans* is not the sole species of this fungal genus associated with human diseases.^{8,9} The emergent pathogen *Candida lusitanae* is an opportunistic haploid yeast that has been reported as the etiological cause of infection in humans, most frequently in immunocompromised patients who often have comorbidities.¹⁰ Even though it is considered a low-frequency emerging nosocomial pathogen and susceptible to conventional antifungal therapies, *C. lusitanae* has attracted attention because some isolates are resistant to amphotericin B, 5-fluorocytosine, or fluconazole.^{7,11–13} From the infections caused by *Candida* spp., *C. lusitanae* is responsible for approximately 19.3% of fungemia cases in cancer patients,¹⁴ and approximately 1.7% of all cases of genitourinary candidiasis in ambulatory patients.¹⁵

Before the fluconazole era, *C. lusitanae* infections were associated with high mortality rates; however, nowadays this is uncommon and mortality usually does not exceed 5%.¹⁰ Additionally to fungemia, *C. lusitanae* has also been associated with peritonitis, meningitis, and urinary tract infections.^{7,10} Thus far, the basic aspects of this organism have been poorly studied, and there is an increasing need to develop new alternatives to diagnose and treat this species and others belonging to the *Candida* genus. With no doubt, these facts make this fungal species of interest for both applied and basic science. Here, we offer a critical revision of the most relevant information on both *C. lusitanae* clinical and basic aspects and the caused infection.

Basic Biological Attributes of *Candida lusitanae*

C. lusitanae is a dimorphic organism that produces ovoid, ellipsoidal, or elongated yeast cells of a size of 2–6×2–10 µm, similar to other *Candida* species, such as *Candida tropicalis*,¹⁶ and colonies are creamy in color and appearance, soft and smooth.¹⁰ At the difference of *C. albicans*, the most studied species of this genus, *C. lusitanae* is not capable of developing true hyphae, only pseudohyphae, which is a blastoconidium with a constricted budding neck between conidium and the first compartment of the emerging germ tube.^{17,18} It is worthy to mention that the dimorphism in this organism has been related to the fungal resistance to amphotericin B.^{18–20} In addition, this morphological plasticity offers a possibility for a daughter cell to survive the host immune defenses.²⁰ In CHROMagar, the colonies generate a pinkish to purple color, allowing their differentiation from *C. tropicalis*, since both species are morphologically similar.¹⁹

The *Candida* genus once thought to gather asexual species, has now revealed some species with other reproductive cycles. *C. albicans* may go through parasexual and asexual cycles, while *C. lusitanae* shows asexual and sexual cycles, being its teleomorph *Clavispora lusitanae* and assuring meiosis during spore formation.^{21,22} The *C. lusitanae* mating-type (*MAT*) locus has been reported to be like the one found in *C. albicans*, and the sexual cycle is regulated by the biallelic locus *MATa* and *MATα*.²³ The strain *MATα* has four out of five genes homologs to *C. albicans* *MLTa*, whereas the *MATa* locus has a translocation that differentiates it from the *C. albicans* *MATa*.²¹ *C. lusitanae* genome contains the genes *MATa1* and *MATa2*, encoding for transcription factors required for cell mating and identity, and *MATa1* required for sporulation.²¹ The mating between α and a cells is performed when they are co-cultured and during stress by starvation.²¹ Then, the pheromones induce the conjugative tube, followed by cell and nuclear fusions, and finally, the formation of the asci that contains two spores.²¹

The recombination during the sexual cycle is *SPO11* dependent. This gene encodes for a meiosis-specific topoisomerase and is a homolog of *SPO11* found in other eukaryotes.^{21,23} In addition, *C. lusitanae* *CLS12*, a dispensable gene for filamentation, is involved in mating and is a homolog of the *Saccharomyces cerevisiae* *STE12*, a mating, and filamentation regulator.²⁴

Although the internal and external *C. lusitanae* structures and organelles are not very well characterized, it is known that like other *Candida* species it possesses a cell wall, cell membrane, endoplasmic reticulum, ribosomes, and Golgi apparatus.²⁵ The *C. lusitanae* cell wall has not been analyzed by transmission electron microscopy, but in nearby species such as *Candida krusei*, *Candida parapsilosis*, *C. tropicalis*, and *C. albicans*, it is known that the wall is uniform and with well-defined layers with different compositions.^{26–35} The outermost layer is observed as an electron-dense material of approximately 20 nm thick, corresponding to mannosylated glycoproteins, then, an electron-transparent layer in the middle, which has an appearance of being composed of spongy material and dispersion granules, and an inner layer of around 100 nm formed by a transparent matrix that contains filamentous structures.^{27,30,36–38} This innermost layer is generally composed of chitin and β-glucans in *Candida* spp.,^{29,31–34,39–44} while the outermost layer contains proteins modified with both N-linked and O-linked mannans.^{30,38,45–49} The *C. lusitanae* mannan structure is significantly different from other *Candida* species and closer to that described in *C. albicans*, showing β-1,2-mannose residues as part of the N-linked mannan side chains.⁵⁰ In *C. lusitanae*, the structural polysaccharides β-1,3-glucan and chitin, as in other *Candida* species, are located underneath the cell wall proteins, most of which are covalently linked to β-1,6-glucan by glycosylphosphatidylinositol anchors.⁵¹ In terms of immunological recognition by the host, the cell wall is the one that fulfills the most important function, since displays molecules that have a positive role in this immune sensing but also can disguise the interaction with immune effectors.^{41,51–53}

So far, the *C. lusitanae* metabolism has been poorly studied and scarce information is currently available. This organism is known to metabolize glucose, cellobiose, and cellotriose but fails to degrade cellobiose, a phenotypical trait that differentiates this species from *Candida guilliermondii*.⁵⁴ Moreover, *C. lusitanae* can also use galactose, sucrose, maltose, lactate, and trehalose as carbon sources.⁵⁵ Similar to other yeast-like species, it possesses a fermentative metabolism capable of producing ethanol from D-xylose under anaerobic conditions.⁵⁵ This ability to adapt its metabolism to assimilate different carbon sources has been linked to the resistance to some drugs, such as amphotericin B; cells growing in lactate are about 10 times more resistant to the drug than those growing in presence of glucose as a carbon source.⁵⁶ Based on these metabolic characteristics, this *Candida* species can be identified by the assimilation of sorbose, rhamnose, and 2-keto-D-gluconate.⁵⁵

The *C. lusitanae* genome is distributed in eight chromosomes and belongs to the *Candida* CTG clade.⁵⁷ This clade is composed of *C. albicans*, *C. lusitanae*, *Candida dubliniensis*, *C. tropicalis*, *C. guilliermondii*, and *C. parapsilosis*, and they

have in common the nonconventional use of the CUG codon to encode for serine instead of leucine.⁵⁷ Since *C. lusitaniae* has a sexual stage, it can go from haploid to diploid; being asexual cells often found as haploid organisms.⁵⁸

The *C. lusitaniae* (ATCC 42720) nuclear genome sequence contains 12.11 Mbp, with a GC content of 44.5%, a total of 6153 protein-encoding genes, and five pseudogenes.⁵⁹ A recent study reported the sequencing of five *C. lusitaniae* strains.⁶⁰ The strain DSY4606 (P1) contains 12.08 Mbp, the GC content is 44.53%, 5676 protein-encoding genes from a total of 5882 genes that have been predicted, along with nine rRNA genes and 197 tRNA genes.⁶⁰ The other strains analyzed in this study were P2 to P5 and the number of the genes varied from 5869 to 5892, suggesting small variations in the gene numbers and that the phenotypic plasticity could be due to recombination events during sexual reproduction.⁶⁰

The Virulence Factors Repertoire

Cell adhesion is essential in various biological processes and many fungi such as *Candida* spp. contain a family of cell wall glycoproteins named adhesins, which are responsible for offering unique adhesion properties.⁶¹ Adhesins are indispensable for fungal cell–cell interactions and to mediate the host–fungus interplay.⁶² The *Candida* spp. adhesion to host cells, in particular epithelial cells, is the first step in the infective process. *C. lusitaniae* also colonizes the host's epithelial cells as part of the first events of the infection but does not cause damage like other *Candida* species. It was reported that *C. albicans* is significantly more adherent (61.6%) to buccal epithelial cells than *C. lusitaniae* (2%),⁶³ and a similar trend was observed when the fungal ability to bind mucin was tested.⁶⁴ These low adhesion properties correlate with the low virulence reported for *C. lusitaniae*. Like other *Candida* species, *C. lusitaniae* can also adhere to plastic surfaces, such as indwelling catheters, cannulas, and drains.⁶⁵ The *ALS* gene family members, *EAP1*, *ECM33*, *HWPI*, *IFF4*, *INT1*, and *MP65*, are encoding for the major *C. albicans* adhesins.⁶⁶ Even though none of the putative orthologs of these genes have been characterized in *C. lusitaniae*, these can be found within its genome (Table 1), making it likely that adhesion occurs via these cell surface adhesins.

Cell surface hydrophobicity and biofilm formation are known as relevant virulence factors in *Candida* spp. pathogenesis. The wall hydrophobicity is provided by the presence of hydrophobic proteins that are embedded within the *Candida* cell wall,⁶⁷ and several studies have linked the cell wall hydrophobicity with *Candida* adhesion to epithelial cells.^{68,69} A study involving 15 *C. lusitaniae* isolates showed that these had a higher wall hydrophobicity (37.52%), compared to *C. albicans* cells (8.48%).⁶⁸ Increased hydrophobicity has been related to cell adhesion; however, this is not the case for *C. lusitaniae*, where this species has been reported to be more hydrophobic but less adherent.⁶⁸ This result could be explained by the fact that there are other factors apart from hydrophobicity that are related to adherence, among these, fungal cells can switch between hydrophobic and hydrophilic phenotypes, due to changes in the environmental conditions such as the temperature, nutrient composition, growth phases, and culture medium used for cell propagation.^{70,71} This phenomenon has been reported in other *Candida* species, such as in *C. dubliniensis*.^{68,72}

Biofilm formation is an important factor that confers protection to the fungal cells, making them resistant to chemical or physical damage.⁷³ A study of mixed biofilms between *C. albicans* and *C. lusitaniae* showed this was not viable, but between *C. tropicalis* and *C. dubliniensis* was successfully established, suggesting that the hypha production by the two species was required for biofilm formation.⁷⁴ In another study, it was demonstrated that the ability of *C. lusitaniae* to form biofilms is influenced by the culturing media, being capable of doing so in YNB, but not in RMPI broth.⁵⁷ In *C. albicans*, biofilm formation is regulated by seven principal genes *BCR1*, *BRG1*, *EFG1*, *HSP90*, *NDT80*, *ROB1*, and *ZAP1*, which are likely to be within the *C. lusitaniae* genome (Table 1). However, research is needed to assess the contribution of these genes during *C. lusitaniae* biofilm formation.

During the pathogenic process, hydrolytic enzymes are paramount for success, and among them are the secreted aspartyl proteinase (SAP), phospholipase, and lipases. In *C. albicans*, lipases are described in some infection models but their function is not clear yet.⁷⁵ The putative orthologs of *C. albicans* genes encoding for lipases and phospholipases found within the *C. lusitaniae* genome are shown in Table 1. The SAPs have been described in *C. albicans* and some studies have focused on finding homologs in the other medically relevant *Candida* species. Here, Table 1 shows the putative SAPs orthologs found in *C. lusitaniae*, although the function is still unknown. SAPs help the pathogen penetrate the host and to evade the immune response, this way being an important element in pathogens' virulence.⁷⁶ When comparing the proteolytic activity of four different *Candida* species, *C. lusitaniae* showed the highest hydrolytic activity

Table 1 Prediction of the Most Important Virulence Factors in *Candida lusitanae*

Virulence Factor	<i>C. albicans</i> Protein	<i>C. lusitanae</i> Protein*	E- value	Similarity (%)	Putative Role
Adhesins	Als1-7 and Als9	CLUG_03274	1e ⁻⁴⁶	47	Adherence of the organism to the oral mucosa. ¹³⁸
		FOB63_002933	3e ⁻⁷⁴	47	
		EJF14_40078	7e ⁻⁴⁴	51	
	Ecm33	FOB63_002672	2e ⁻¹⁵⁰	75	Contributes to the integrity of the fungal cell wall. ¹³⁹
Biofilm formation	Iff4	FOB63_003688	4e ⁻²⁷	47	Involved in cell wall organization, hyphal growth, as well as in host-fungus interaction. ¹⁴⁰
	Mp65	FOB63_004871	4e ⁻¹¹⁹	78	Cell surface mannoprotein involved in cell wall glucan metabolism and adhesion. ¹⁴¹
	Bcr1	A9F13_15g00066	1e ⁻³⁹	87	Acts as a master regulator of biofilm formation. ¹⁴²
	Brg1	CLUG_05535	3e ⁻⁴⁷	61	Necessary for hyphal growth and biofilm formation. ⁷⁸
	Efg1	A9F13_02g02442	2e ⁻⁹¹	87	Transcriptional regulator required for filamentation. ⁷⁸
	Hsp90	A9F13_09g00462	0.0	95	Regulates several signal transduction pathways and temperature-induced morphogenesis; localizes to the surface of hyphae. ¹⁴³
	Ndt80	FOB63_000392	3e ⁻⁸¹	55	Necessary for hyphal growth and biofilm formation. ¹⁴⁴
Dimorphism	Rob1	E0198_003579	1e ⁻²⁰	45	Transcription factor involved in biofilm formation. ¹⁴⁵
	Zap1	CLUG_02564	7e ⁻¹³⁰	52	Negatively regulates the biofilm matrix production. ¹⁴⁵
	Cph1	CLUG_02576	1e ⁻¹¹⁹	60	A transcriptional regulator with a key role in controlling filamentous growth. ⁷⁷
	Hgc1	CLUG_00968	7e ⁻¹¹⁷	68	Essential for hyphal morphogenesis. ⁷⁹
Immune evasion	Nrg1	A9F13_05g02552	2e ⁻³²	82	Necessary for filamentation and virulence. ⁷⁸
	Tup1	A9F13_01g07271	0.0	85	Prevents filamentous growth in the absence of appropriate signals. ⁷⁸
	Hgt1	E0198_001093	0.0	81	Plays a non-canonical role by down-modulating phagocytosis and killing by human neutrophils. ¹⁴⁶
	Msb2	A9F13_12g01265	1e ⁻⁷¹	57	Signaling mucin that allows fungi survival and growth in the infected human host. ¹⁴⁷
	Pra1	No found	-	-	Encodes for an antigen associated with the cell wall, known as a fibrinogen binding protein. ¹⁴⁸

Proteinase and phospholipase	Lip5-8	EJF14_20550 E0198_001560	$3e^{-139}$ $7e^{-141}$	62 62	Required for virulence in different infection models. ⁶⁶
	Sap1-3 Sap5	EJF14_50044 FOB63_000850	$3e^{-45}$ $2e^{-45}$	49 51	Necessary for active penetration of host cells, neutrophil extracellular traps (NETs)-releasing response. Required for proteolysis. ⁶⁶
	Plb1-5	CLUG_01525 FOB63_000168	0.0 0.0	68 75	Important for host cell penetration and virulence in a mouse model of systemic infection. ¹⁴⁹
Thermotolerance	Hsp60	CLUG_00619	0.0	96	Acts as an immunogenic trigger in orchestrating <i>Candida</i> -related diseases under thermal stress. ⁸²
	Hsp104	CLUG_01501	0.0	90	Pro-survival mediator in response to increasing temperature. ⁸²
	Ssa1	CLUG_01400	0.0	94	Acts as invasin, facilitating host cell endocytosis. ¹⁵⁰

Notes: *Protein names are the accession codes of the sequences at the National Center for Biotechnology Information database (<https://www.ncbi.nlm.nih.gov/>). The putative protein sequence encoded by the *C. albicans* gene was subjected to a standard protein BLAST analysis at <https://www.ncbi.nlm.nih.gov/>. The best hit is reported in the *C. lusitanae* Protein column, and this was scored with the lowest E value. The similarity column refers to the comparison of amino acid sequences from the *C. albicans* encoded protein and the best hit.

but at the same time low enzyme secretion.⁷⁶ This observation may help to understand the low virulence of this species and its poor ability to kill laboratory animals.

As mentioned, *C. lusitaniae* belongs to the genus members that are not capable of forming true hyphae, only pseudohyphae. Dimorphism in fungi, such as *C. albicans* is related to the expression of some virulence factors that are morphology specific.²⁷ Among the main dimorphism regulators found in *C. albicans* are Cph1, a transcriptional regulator that controls filamentous growth; Hgc1, an essential protein for hyphal morphogenesis; and Nrg1/Tup1, transcriptional repressors that contribute to filamentation.^{77–79} According to our analysis, the *C. lusitaniae* genome contains putative orthologs of these genes (Table 1), suggesting that the process that controls dimorphism is differently regulated in *C. albicans* and *C. lusitaniae*.

The phenotypic switching is strongly related to *C. albicans* virulence, allowing the fungus to adjust to different environmental conditions through the expression of different and selective genes.⁸⁰ *C. lusitaniae* undergoes phenotypic changes when cultured on YPD-CuSO₄ agar, generating white and light brown colonies containing exclusively yeast cells, and dark brown colonies containing pseudohyphae.⁸⁰ Light brown colonies showed a minimum inhibitory concentration (MIC) of 2–4 µg/mL for amphotericin B, the dark brown colonies of 8 µg/mL, and the white colonies of 256 µg/mL, underlining that this phenotypic switching is related to drug resistance.⁸⁰

Other virulence factors that play important roles in fungi are thermotolerance and immune evasion. Thermotolerance is responsible for facilitating the growth and colonization of the fungal cell once entering the host tissues. The host temperature is usually higher than the optimal for fungal growth, thus adaptation to this stressing milieu is essential for cell fitness and the ability to damage the host cells and tissues. Our bioinformatic analysis suggests that the *C. lusitaniae* genome contains putative orthologs of the genes for thermotolerance *HSP60* and *HSP104*, which encode heat shock proteins (Table 1). Hsp60 acts as an immunogenic trigger in the orchestration of diseases when there is thermal stress and Hsp104 is a survival mediator, in response to increased temperature.^{81,82} Immune evasion is a mechanism that involves many other processes, such as biofilm and protease production, morphological changes, and protein synthesis to overcome oxidative stress.⁴¹ Some of these processes have already been explained earlier in this section. For immune evasion, two possible orthologs of *C. albicans* Hgt1 and Msb2 were found in *C. lusitaniae*. However, no ortholog of the Pra1 gene was found (Table 1). However, the mechanisms of thermotolerance and immune evasion are probably similar in both fungi, due to the results obtained in our bioinformatics analysis (Table 1).

The *Candida lusitaniae*-Immune System Interaction

Currently, the most studied fungus–host interaction is that of *C. albicans*. However, although there are species-dependent variations in the way the host immune system recognizes *Candida* spp., the core processes may be similar and involve the recognition of the microorganism through pattern recognition receptors (PRRs). To the best of our knowledge, no study has explored the *C. lusitaniae*-host interaction; however, for *Candida guilliermondii*, the phylogenetically closest species within the *Candida* genus (Figure 1), the characteristics of this interaction have been more studied.³³ Therefore, it is possible to speculate that the current information we have regarding *C. guilliermondii* could be extrapolated to *C. lusitaniae*.⁸³

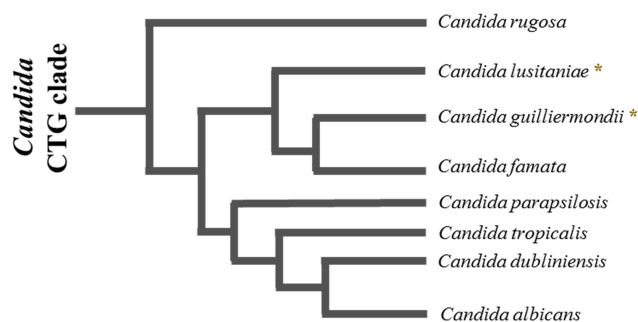


Figure 1 Schematic representation of the phylogenetic relationship between species of the *Candida* CTG clade. The species *C. rugosa*, *C. lusitaniae*, *C. guilliermondii*, *C. famata*, *C. parapsilosis*, *C. tropicalis*, *C. dubliniensis* and *C. albicans* are part of the CTG clade of *Candida*. (*) represents the species of our interest, *C. lusitaniae*, and *C. guilliermondii*, which are phylogenetically closer to each other. The lengths of the branches are arbitrary.

Immune detection of fungal species is an important process in establishing a protective antifungal immune response. For this interaction to take place, the components of the cell wall must be recognized.^{30,33,84} The fungal cell wall is a highly dynamic structure that provides protection, controls communication with the extracellular environment, maintains cell integrity, and functions as a molecular scaffold to display virulence factors.^{33,38,44,52} This structure has pathogen-associated molecular patterns (PAMPs), which are recognized by the immune system through PRRs, most of them located on the cell surface of immune cells.^{85–87} The main PAMPs found in the different *Candida* species, such as *C. guilliermondii*, are chitin, β -1,3- and β -1,6-glucans, and *N*-linked and *O*-linked mannans.⁵¹

It has been shown that during the immune response against *Candida* species, such as *C. guilliermondii*, murine neutrophils, and phagocytic cells can discriminate among species.^{88,89} Murine phagocytic cells, bone marrow cells, and spleen cells have a greater ability to kill *C. guilliermondii* when compared to the phagocytic rate of *C. albicans* cells.⁸⁸ Human monocytes differentially recognize some species of *Candida* such as *C. tropicalis* and *C. krusei*, but not *C. guilliermondii*, which is involved in increased stimulation of the complement components C3 and colony-stimulating factor of granulocytes and macrophages.⁸⁹ *C. guilliermondii* shows a limited ability to stimulate tumor necrosis factor α (TNF α) when coincubated with peritoneal macrophages.⁹⁰

Human peripheral blood mononuclear cells (PBMCs) are often used to evaluate pathogen–host interaction in different fungal species since they can produce different types of cytokines when the PRRs are activated by PAMPs. Although the different species of *Candida* show a similar cell wall composition, some differences could affect the interaction with components of innate immunity.^{33,44} In *C. guilliermondii* it has been observed that low levels of β -1,3-glucan induce lower cytokine levels when this polysaccharide is exposed to the cell surface.³³

C. guilliermondii cells stimulate higher levels of the cytokines TNF α , IL-6, IL-1 β , and IL-10, compared to *C. albicans* where stimulation is very low.³³ When cells are heat-inactivated (HK), higher levels of cytokines are stimulated than *C. guilliermondii* live cells; however, differences are observed when cytokine profiles are compared with those stimulated by *C. albicans*.^{39,73} *C. guilliermondii* stimulates a lower production of TNF α , IL-1 β , and IL-6 than *C. albicans* when the HK and β -elimination treatments are used, but the anti-inflammatory cytokine IL-10 is highly produced in presence of *C. guilliermondii* cells.³³ It is tempting to suggest that a similar cytokine profile may be stimulated by *C. lusitaniae* cells.

Blockade of receptors such as Dectin-1 with laminarin does not affect the ability of *C. albicans* to stimulate cytokine production; however, a significant reduction in cytokine levels is observed when HK cells are used.^{31–34,39,40,42,43,47} For *C. guilliermondii* though the presence of laminarin affects the cytokine stimulation by live or β -eliminated cells, indicating that a difference with *C. albicans*, *O*-linked mannans along with β -1,3-glucan sensing are key interactions for a strong cytokine stimulation.³³

Assays with macrophages revealed that most *Candida* species are uptake and internalized in acid phagolysosomes; however, the species that experienced this process in greater proportion are *C. tropicalis*, *C. guilliermondii*, and *C. krusei* at the difference of *C. albicans* and *C. auris*.³³

In addition to the responses mentioned above, complement proteins play an important role in the defense of the host against the pathogen, especially against members of the *Candida* species, since they promote phagocytosis and activate inflammatory responses.^{91,92} This system is a link between innate and adaptive immunity in such a way that a complete immune response against the pathogen is created.⁹³ In addition to *C. albicans*, species such as *C. lusitaniae*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* have also been reported to bind to complement proteins.⁹⁴

Once again, due to close phylogenetic relationship between *C. lusitaniae* and *C. guilliermondii*, we suggest that the immune response in both species is similar; however, this must be experimentally verified.

***Candida lusitaniae*-Caused Candidiasis**

C. albicans is the main species causing candidiasis in humans. However, other species of this genus have raised particular concern by exhibiting resistance to broad-spectrum antifungals commonly used to treat candidiasis.⁹⁵ This is the case of *C. lusitaniae* which, despite being a rare pathogen, has aroused special interest as a nosocomial pathogen due to its increased prevalence in recent years, being characterized by infecting immunocompromised patients, patients receiving prolonged antibiotic therapy, hospitalized, patients with underlying malignancies, and undergoing chemotherapies or bone marrow transplants.^{7,10,12,96} Another risk factor for candidiasis is the use of catheters, as they are major yeast reservoirs that promote

fungemia, and *C. lusitaniae* is no exception.^{97,98} Case reports in the literature have demonstrated the ability of *C. lusitaniae* to form biofilms, causing endogenous infections,^{99,100} and like other causative agents of candidiasis, the possibility of acquiring this species through person-to-person contact has been reported, at least in the intensive care unit.¹⁰¹

In a study conducted on patients with candidemia, it was shown that 43.5% of patients were infected by non-*albicans* species. Of this percentage, most patients were found to have a neutrophil count of fewer than 500 cells/ μ L.⁹⁵ Another study, conducted at a Texas cancer center between 1988 and 1999, reported that 75% of patients were neutropenic at the time of *C. lusitaniae* infection, with a mortality rate in these cases of 25%, which could be related to its high resistance to amphotericin B.⁷ In fact, most of the severe *C. lusitaniae* infections reported resistance to this antifungal drug.^{16,102–104}

C. lusitaniae has been isolated most frequently from the respiratory tract, followed by urine and blood samples. It has also been isolated from the peritoneum, vagina, and skin.^{11,12,103,105} In mouse models, kidney colonization by *C. lusitaniae* was found to be indifferent to the animal's immunocompetence.¹⁸ Unusually, cases of keratitis have been reported where *C. lusitaniae* was one of the etiological agents.^{106,107} The unusualness of these clinical cases was verified when a study published in 2012 reported that only 3 of 18 mouse models developed keratitis after being challenged with wild-type *C. lusitaniae* yeast cells.¹⁸

Clinical data on invasive infections caused by *C. lusitaniae* are scarce.¹⁰⁸ However, as mentioned, previous reports have shown that infections caused by *C. lusitaniae* usually appear in patients with hematological malignancies.^{108,109} A patient with acute lymphoblastic leukemia who underwent hematopoietic cell transplantation developed catheter-associated *C. lusitaniae* candidemia while undergoing amphotericin B therapy.¹⁰⁸ Similar to this case, there are several patients with malignant neoplasms, mainly leukemia, which are affected by this pathogen. Most patients have been reported to have both neutropenia and stem cell transplantation, known independent factors to develop this systemic infection.^{12,109,110} In 2003, 55 cases of *C. lusitaniae*-caused candidiasis were reported, predominantly bloodstream infections.¹⁰ Three-quarters of the studied population had underlying medical conditions, which led to a mortality rate of 5%.¹⁰

Another study conducted by the International Pediatric Fungal Network, between 2007 and 2011, showed that *C. lusitaniae* was found in 8 out of 201 isolates collected from 196 non-neonatal pediatric patients.¹¹¹ The University Children's Hospital Münster obtained data on infections caused by different *Candida* species between 1998 and 2006. Among these, *C. lusitaniae* was found to be the causal agent of 7.1% of candidemias in patients under 20 years old.^{108,112} Most of these patients were immunocompromised, had an indwelling venous catheter, and were receiving broad-spectrum antibiotic treatment.¹¹² These three conditions are shared with another clinical study, where 12 patients showed fungemia due to *C. lusitaniae*.⁷ Ten of these patients had received cytotoxic drugs and nine patients were neutropenic.⁷ A case study reported the presence of *C. lusitaniae* in an immunocompetent patient with intraperitoneal infection after undergoing laparoscopic hydrosalpinx surgery.¹¹³ Intra-abdominal infections are a morbidity cause in patients undergoing abdominal surgery and are commonly caused by *Candida* species.¹¹³

Diagnosis of *Candida lusitaniae* in Clinical Samples

The effective *Candida* strains identification at the species level in the clinical area has become very important due to the high incidence of candidiasis in recent years. Different strategies have been used over time to differentiate and identify the different *Candida* species. Chromogenic agars, such as *Candida* ID agar and CHROMagar *Candida* agar,^{114–116} have been used for the detection and presumptive identification of *Candida* spp., especially *C. albicans*. *Candida* ID agar is based on a chromogenic substrate of indolyl glucosaminide that is hydrolyzed by the different *Candida* species and generates different colors in the colonies. In the case of *C. lusitaniae*, the colonies appear pink in this agar; however, although the color could be informative for identification, other species such as *C. tropicalis* and *C. guilliermondii* develop colonies of this same color.¹¹⁶ *C. lusitaniae* identification on CHROMagar *Candida*, a medium that also uses a chromogenic substrate of β -glucosaminidase, shows purple and white colonies, however, these colonies have the same colors as *C. krusei* and *C. parapsilosis*, which could not ensure the correct *C. lusitaniae* identification.¹¹⁶ In corn meal agar, *C. lusitaniae* shows ovoid yeast cells, which are arranged in pairs and chains, also, abundantly branched and curved pseudohyphae can be seen. Some strains of this species have rudimentary or null pseudohyphae.¹¹⁷

In recent years, methods have been developed to allow early identification of the different *Candida* species, trying to reduce morbidity and mortality of infected patients.¹¹⁸ *Candida* spp. identification by traditional methods such as

morphology analysis can take 3–5 days or even longer for unusual species.¹¹⁹ The design of *Candida* species-specific probes has helped identify more than 18 species of this genus, including *C. lusitaniae*.¹¹⁹ For this, universal fungal primers, multicopy genetic targets, and species-specific probes are used, which are directed to the *ITS2* region of the gene that encodes rRNA.¹²⁰ The API 20C carbohydrate assimilation system is also a gold standard for phenotypic characterization of non-*albicans* species.^{116,119}

For *C. lusitaniae* identification, the ability of the API *Candida* system (bioMérieux, France) to identify isolates of this species has been evaluated.¹²¹ Of 52 clinical isolates that had been previously identified based on their morphology, 48 of these were identified as *C. lusitaniae* at 48 hours. Subsequently, 44 of the isolates were identified as *C. lusitaniae* at 24 hours, and the other four were discarded because they assimilated cellobiose more slowly.¹²¹ The morphological identification determined that the strains corresponded to the species *C. lusitaniae*; however, this identification was verified using the ID 32C system, which was chosen for its extensive database.¹²¹ By this system, all the strains were identified as *C. lusitaniae*, two of these by applying complementary tests and reincubating for another 24 hours.¹²¹ Using the API *Candida* system, only 12 strains were identified as *C. lusitaniae* at 24 hours. In other words, the API system is not effective for the identification of this species and it is proposed that it is necessary to include morphological characteristics to avoid misidentification of *C. lusitaniae* as *Candida famata*.¹²² Although API *Candida* is considered a promising system for the identification of *Candida* species, it is not the most adequate to identify *C. lusitaniae*.¹²¹

Molecular taxonomic methods have also been used for *C. lusitaniae* identification.¹¹⁰ Using these methodologies, it was determined that the DNA bases of two clinical isolates were 45.1% guanine plus cytosine molecules from one strain, compared to 44.7% guanine plus cytosine molecules from the second strain. DNA/DNA reassociation experiments showed that there was a complementarity greater than 95% between the DNA of the two *C. lusitaniae* clinical isolates.¹¹⁰

Therapeutic Options to Treat Infections Caused by *Candida lusitaniae*

Four classes of antifungal drugs are currently used to treat systemic candidiasis: azoles, such as fluconazole, itraconazole, posaconazole, and voriconazole; polyenes, like conventional amphotericin B and its lipid formulations; the echinocandins caspofungin and micafungin; and the pyrimidine analog flucytosine.¹²³ Several non-*albicans* *Candida* species are inherently resistant or less susceptible to various classes of antifungals, and the introduction of new azoles such as fluconazole has increased the frequency of multidrug-resistant strains.¹²³

C. lusitaniae is known to develop resistance to amphotericin B; however, this species is considered susceptible to flucytosine and azoles.¹²⁴ Although in most cases this pattern is consistent, several studies have shown that this species can develop resistance to flucytosine and azoles, classifying it as a species difficult to manage due to the variation in antifungal susceptibilities.^{7,124–127} Echinocandins are the most widely used antifungal drugs for the treatment of *C. lusitaniae*-caused candidemia, which targets the β -1,3-D-glucan synthase encoded by the *FKS* genes,¹²⁸ but their use has resulted in reported emerging resistance in several strains.¹²⁹ Mutations in the *FKS* genes specifically *FKS1* and *FKS2* are responsible for the increased MIC in some species. In *C. lusitaniae*, it is reported that a nonsense mutation occurs in the *FKS1* hot spot 1 at position 645 (S645F), which leads to an increase in the MIC for several echinocandins.¹²⁹ Caspofungin resistance correlates with three new *FKS1* mutations (S638Y, S638P, and S631Y); which correspond to positions Ser645 and Ser643 of *C. albicans* Fks1, and have been related to echinocandins resistance.^{127,129} Furthermore, resistance to fluconazole in this species is thought to be associated with the overexpression of a major facilitator gene (*MFS7*), and mutations in the transcriptional activator *MRR1* in *C. albicans*.¹³⁰

Clinical cases of neonates with kidney infections caused by *C. lusitaniae* have shown that changes in colony morphology are associated with resistance to amphotericin B and azoles.¹²⁶ Previous reports have indicated that initial therapy is based on the use of amphotericin B and that it is used mainly as monotherapy.¹³¹ However, due to increased resistance to this antifungal, therapy began to be replaced by fluconazole or combined therapy. This therapy seemed to work in 85% of patients, who were cured, and the mortality rate decreased, presenting only 12% mortality in patients treated under this scheme.⁷ The response appears to be different for clinical cases, and largely depends on the patient's immunity. In a study of 46 patients, one-third were cured with amphotericin B, one-third with fluconazole, and one-third with flucytosine.¹²⁶ Although exclusive therapy with amphotericin B is not ruled out, an initial combination with flucytosine is recommended.¹²⁶ Fluconazole therapy is effective in many cases and is recommended for treating disseminated candidiasis caused by *C. lusitaniae*.^{7,132} However, it is

necessary to carry out in vitro tests as soon as the presence of this species is identified, to determine the most appropriate treatment for each patient.¹²⁶

Clinical reports have described that *C. lusitaniae* can generate multiresistant isolates when fluconazole antifungals are combined with amphotericin B.¹²⁹ This type of combined treatment can be counterproductive and it is suggested that should be avoided, especially when *C. lusitaniae* is involved in deep-seated infections in immunocompromised patients.^{126,129}

Something that has attracted attention in this species is the phenotypic change that it can develop in the culture medium. Two colony color variations have been demonstrated in CHROMagar *Candida*, causing the phenotype of full-size colonies and small colonies, both of which are included in the *MATa* genotype.^{20,126,133,134} These phenotypical switching affected susceptibility to amphotericin B.^{20,126} Moreover, changes in phenotype are observed when cross-resistance to fluconazole and itraconazole develops. This phenomenon had been already reported in different clinical cases that had documented acquired resistance to amphotericin B.¹³⁵ It seems that this change is influenced by the adaptation of the organism to environmental changes.¹²⁶ Similar findings have been reported also in *Candida glabrata*.¹³³ These events of resistance to antifungals such as amphotericin B appear to be correlated with decreased ergosterol levels as a result of a defect in sterol isomerase.¹³⁶ Although it is not ruled out that the resistance may be mediated by other mechanisms, such as the alteration of other steps in the biosynthesis of sterols, changes in the plasmatic membrane phospholipids, modifications in the cell wall structure, and the increase in the catalase activity.¹³⁷

Finally, the correct treatment of infections caused by *C. lusitaniae* requires early control of susceptibility to antifungal drugs and an exhaustive examination of cultures to evaluate the possible morphological changes above mentioned.

Concluding Remarks

In recent years, research on candidiasis has been increasing but most of the work has been focused on understanding the biological, epidemiological, clinical, and biological aspects of species such as *C. albicans* and to a lesser extent on other species such as *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. krusei*.²⁷ *C. lusitaniae* is perhaps a forgotten pathogen because of the low frequency of isolation in healthcare centers. However, the infection caused by this species can be fatal in immunocompromised patients and the microorganism can develop resistance to antifungal drugs such as amphotericin B, and azoles, making it a difficult species to treat.

Bioinformatic tools have been key to understanding basic aspects of neglected species like this one since they allow us to generate gene predictions, which help to detect differences and similarities in terms of virulence, drug resistance, and relevant biological information when compared to thoroughly studied species like *C. albicans* and *C. tropicalis*. This information could be useful to develop new techniques for diagnosis, and treatment and to find other therapeutic targets against *C. lusitaniae*.

The information collected in this work highlights that there is still a lack of information about this species, which could be an opportunity area to develop more exhaustive studies that allow the scientific community to elucidate important aspects of this species' biology. It would be interesting to develop new methodologies that allow the rapid and efficient identification of *C. lusitaniae* strains since the methodologies currently used are not very specific and could give false negatives or false positives, as is the case of the morphological evaluation in *Candida* ID agar and CHROMagar *Candida*. Finally, the study of the interaction with humoral and cellular components of the host immunity results paramount to understanding the *C. lusitaniae*-host interaction and proposing immunomodulatory options to treat the caused infections by this *Candida* species.

Acknowledgments

This work was supported by Consejo Nacional de Ciencia y Tecnología (ref. FC 2015-02-834 and CF-2019-6380), and Red Temática Glicociencia en Salud (CONACYT-México).

Author Contributions

All authors made a significant contribution to the work reported, in the conception, design, execution, acquisition of data, analysis, and interpretation, critically reviewed the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare no conflict of interest.

References

1. Aguiar Cordeiro R, de Jesus Evangelista AJ, Serpa R, et al. β -lactam antibiotics & vancomycin increase the growth & virulence of *Candida* spp. *Future Microbiol.* **2018**;13(8):869–875. doi:10.2217/fmb-2018-0019
2. Goncalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, Silva S. Vulvovaginal candidiasis: epidemiology, microbiology and risk factors. *Crit Rev Microbiol.* **2016**;42(6):905–927. doi:10.3109/1040841X.2015.1091805
3. Pfaller MA, Diekema DJ, Mendez M, et al. *Candida guilliermondii*, an opportunistic fungal pathogen with decreased susceptibility to fluconazole: geographic and temporal trends from the ARTEMIS DISK antifungal surveillance program. *J Clin Microbiol.* **2006**;44(10):3551–3556. doi:10.1128/JCM.00865-06
4. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. *Diagn Microbiol Infect Dis.* **1998**;30(2):121–129. doi:10.1016/S0732-8893(97)00192-2
5. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance[®]) registry, 2004–2008. *Diagn Microbiol Infect Dis.* **2012**;74(4):323–331. doi:10.1016/j.diagmicrobio.2012.10.003
6. Andes DR, Safdar N, Baddley JW, et al. The epidemiology and outcomes of invasive *Candida* infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Transpl Infect Dis.* **2016**;18(6):921–931. doi:10.1111/tid.12613
7. Minari A, Hachem R, Raad I. *Candida lusitanae*: a cause of breakthrough fungemia in cancer patients. *Clin Infect Dis.* **2001**;32(2):186–190. doi:10.1086/318473
8. Fakhim H, Vaezi A, Dannaoui E, et al. Comparative virulence of *Candida auris* with *Candida haemulonii*, *Candida glabrata* and *Candida albicans* in a murine model. *Mycoses.* **2018**;61(6):377–382. doi:10.1111/myc.12754
9. Fakhim H, Vaezi A, Javidnia J, et al. *Candida africana* vulvovaginitis: prevalence and geographical distribution. *J Mycol Med.* **2020**;30(3):100966. doi:10.1016/j.mycmed.2020.100966
10. Hawkins JL, Baddour LM. *Candida lusitanae* infections in the era of fluconazole availability. *Clin Infect Dis.* **2003**;36(2):e14–18. doi:10.1086/344651
11. Baker JG, Nadler HL, Forgacs P, Kurtz SR. *Candida lusitanae*: a new opportunistic pathogen of the urinary tract. *Diagn Microbiol Infect Dis.* **1984**;2(2):145–149. doi:10.1016/0732-8893(84)90010-5
12. Sanchez V, Vazquez JA, Barth-Jones D, Dembry L, Sobel JD, Zervos MJ. Epidemiology of nosocomial acquisition of *Candida lusitanae*. *J Clin Microbiol.* **1992**;30(11):3005–3008. doi:10.1128/jcm.30.11.3005-3008.1992
13. Zhang H, Ran Y, Li D, et al. *Clavispora lusitanae* and *Chaetomium atrobrunneum* as rare agents of cutaneous infection. *Mycopathologia.* **2010**;169(5):373–380. doi:10.1007/s11046-009-9266-9
14. Jung DS, Farmakiotis D, Jiang Y, Tarrand JJ, Kontoyiannis DP. Uncommon *Candida* species fungemia among cancer patients, Houston, Texas, USA. *Emerg Infect Dis.* **2015**;21(11):1942–1950. doi:10.3201/eid2111.150404
15. Obisesan OJ, Olowe OA, Taiwo SS. Phenotypic detection of genitourinary candidiasis among sexually transmitted disease clinic attendees in Ladoke Akintola University Teaching Hospital, Osogbo, Nigeria. *J Environ Public Health.* **2015**;2015:401340. doi:10.1155/2015/401340
16. Hadfield TL, Smith MB, Winn RE, Rinaldi MG, Guerra C. Mycoses caused by *Candida lusitanae*. *Rev Infect Dis.* **1987**;9(5):1006–1012. doi:10.1093/clinids/9.5.1006
17. Boissard S, Ruprich-Robert G, Florent M, Da Silva B, Chapeland-Leclerc F, Papon N. Role of Sho1p adaptor in the pseudohyphal development, drugs sensitivity, osmotolerance and oxidant stress adaptation in the opportunistic yeast *Candida lusitanae*. *Yeast.* **2008**;25(11):849–859. doi:10.1002/yea.1636
18. Zhang J, Silao FG, Bigol UG, et al. Calcineurin is required for pseudohyphal growth, virulence, and drug resistance in *Candida lusitanae*. *PLoS One.* **2012**;7(8):e44192. doi:10.1371/journal.pone.0044192
19. McClenney NB, Fei H, Baron EJ, et al. Change in colony morphology of *Candida lusitanae* in association with development of amphotericin B resistance. *Antimicrob Agents Chemother.* **2002**;46(5):1325–1328. doi:10.1128/AAC.46.5.1325-1328.2002
20. Yoon SA, Vazquez JA, Steffan PE, Sobel JD, Akins RA. High-frequency, *in vitro* reversible switching of *Candida lusitanae* clinical isolates from amphotericin B susceptibility to resistance. *Antimicrob Agents Chemother.* **1999**;43(4):836–845. doi:10.1128/AAC.43.4.836
21. Reedy JL, Floyd AM, Heitman J. Mechanistic plasticity of sexual reproduction and meiosis in the *Candida* pathogenic species complex. *Curr Biol.* **2009**;19(11):891–899. doi:10.1016/j.cub.2009.04.058
22. Gargeya IB, Pruitt WR, Simmons RB, Meyer SA, Ahearn DG. Occurrence of *Clavispora lusitanae*, the teleomorph of *Candida lusitanae*, among clinical isolates. *J Clin Microbiol.* **1990**;28(10):2224–2227. doi:10.1128/jcm.28.10.2224-2227.1990
23. Francois F, Noel T, Pepin R, et al. Alternative identification test relying upon sexual reproductive abilities of *Candida lusitanae* strains isolated from hospitalized patients. *J Clin Microbiol.* **2001**;39(11):3906–3914. doi:10.1128/JCM.39.11.3906-3914.2001
24. Young LY, Lorenz MC, Heitman J. A STE12 homolog is required for mating but dispensable for filamentation in *Candida lusitanae*. *Gene.* **2000**;155(1):17–29.
25. Leite de Andrade MC, Soares de Oliveira MA, Santos F, et al. A new approach by optical coherence tomography for elucidating biofilm formation by emergent *Candida* species. *PLoS One.* **2017**;12(11):e0188020. doi:10.1371/journal.pone.0188020
26. Diaz-Jimenez DF, Mora-Montes HM, Hernandez-Cervantes A, Luna-Arias JP, Gow NA, Flores-Carreon A. Biochemical characterization of recombinant *Candida albicans* mannosyltransferases Mnt1, Mnt2 and Mnt5 reveals new functions in O- and N-mannan biosynthesis. *Biochem Biophys Res Commun.* **2012**;419(1):77–82. doi:10.1016/j.bbrc.2012.01.131
27. Gomez-Gaviria M, Mora-Montes HM. Current aspects in the biology, pathogeny, and treatment of *Candida krusei*, a neglected fungal pathogen. *Infect Drug Resist.* **2020**;13:1673–1689. doi:10.2147/IDR.S247944

28. Mora-Montes HM, Ponce-Noyola P, Villagomez-Castro JC, Gow NA, Flores-Carreón A, Lopez-Romero E. Protein glycosylation in *Candida*. *Future Microbiol.* **2009**;4(9):1167–1183. doi:10.2217/fmb.09.88
29. Estrada-Mata E, Navarro-Arias MJ, Perez-Garcia LA, et al. Members of the *Candida parapsilosis* complex and *Candida albicans* are differentially recognized by human peripheral blood mononuclear cells. *Front Microbiol.* **2015**;6:1527. doi:10.3389/fmicb.2015.01527
30. Gómez-Gaviria M, García-Carnero LC, Tamez-Castrellón AK, Mora-Montes HM. The cell wall of medically relevant yeasts and molds. In: Zaragoza Ó, Casadevall A, editors. *Encyclopedia of Mycology*. Oxford: Elsevier; **2021**:12–22.
31. Hernandez-Chavez MJ, Clavijo-Giraldo DM, Novak A, et al. Role of protein mannosylation in the *Candida tropicalis*-host interaction. *Front Microbiol.* **2019**;10:2743. doi:10.3389/fmicb.2019.02743
32. Hernandez-Chavez MJ, Franco B, Clavijo-Giraldo DM, Hernandez NV, Estrada-Mata E, Mora-Montes HM. Role of protein phosphomannosylation in the *Candida tropicalis*-macrophage interaction. *FEMS Yeast Res.* **2018**;18(5). doi:10.1093/femsyr/foy053
33. Navarro-Arias MJ, Hernandez-Chavez MJ, Garcia-Carnero LC, et al. Differential recognition of *Candida tropicalis*, *Candida guilliermondii*, *Candida krusei*, and *Candida auris* by human innate immune cells. *Infect Drug Resist.* **2019**;12:783–794. doi:10.2147/IDR.S197531
34. Perez-Garcia LA, Csonka K, Flores-Carreón A, et al. Role of protein glycosylation in *Candida parapsilosis* cell wall integrity and host interaction. *Front Microbiol.* **2016**;7:306. doi:10.3389/fmicb.2016.00306
35. Toth R, Nosek J, Mora-Montes HM, et al. *Candida parapsilosis*: from genes to the bedside. *Clin Microbiol Rev.* **2019**;32(2). doi:10.1128/CMR.00111-18
36. Joshi KR, Wheeler EE, Gavin JB. The ultrastructure of *Candida krusei*. *Mycopathologia.* **1975**;56(1):5–8. doi:10.1007/BF00493575
37. Grigor'eva A, Bardasheva A, Tupitsyna A, et al. Changes in the ultrastructure of *Candida albicans* treated with cationic peptides. *Microorganisms.* **2020**;8(4):582.
38. Gómez-Gaviria M, Vargas-Macias AP, García-Carnero LC, Martínez-Duncker I, Mora-Montes HM. Role of protein glycosylation in interactions of medically relevant fungi with the host. *J Fungi.* **2021**;7(10):875. doi:10.3390/jof7100875
39. Navarro-Arias MJ, Defosse TA, Dementhon K, et al. Disruption of protein mannosylation affects *Candida guilliermondii* cell wall, immune sensing, and virulence. *Front Microbiol.* **2016**;7:1951. doi:10.3389/fmicb.2016.01951
40. Navarro-Arias MJ, Dementhon K, Defosse TA, et al. Group X hybrid histidine kinase Chk1 is dispensable for stress adaptation, host-pathogen interactions and virulence in the opportunistic yeast *Candida guilliermondii*. *Res Microbiol.* **2017**;168(7):644–654. doi:10.1016/j.resmic.2017.04.009
41. Hernandez-Chavez MJ, Perez-Garcia LA, Nino-Vega GA, Mora-Montes HM. Fungal strategies to evade the host immune recognition. *J Fungi.* **2017**;3(4):51. doi:10.3390/jof3040051
42. Gow NA, Netea MG, Munro CA, et al. Immune recognition of *Candida albicans* beta-glucan by dectin-1. *J Infect Dis.* **2007**;196(10):1565–1571. doi:10.1086/523110
43. Mora-Montes HM, Netea MG, Ferwerda G, et al. Recognition and blocking of innate immunity cells by *Candida albicans* chitin. *Infect Immun.* **2011**;79(5):1961–1970. doi:10.1128/IAI.01282-10
44. Walker LA, Munro CA. Caspofungin induced cell wall changes of *Candida* species influences macrophage interactions. *Front Cell Infect Microbiol.* **2020**;10:164. doi:10.3389/fcimb.2020.00164
45. Shibata N, Kobayashi H, Suzuki S. Immunochemistry of pathogenic yeast, *Candida* species, focusing on mannan. *Proc Jpn Acad Ser B Phys Biol Sci.* **2012**;88(6):250–265. doi:10.2183/pjab.88.250
46. Klis FM, de Groot P, Hellingwerf K. Molecular organization of the cell wall of *Candida albicans*. *Med Mycol.* **2001**;39(Suppl 1):1–8. doi:10.1080/mmy.39.1.1.8-0
47. Mora-Montes HM, Bates S, Netea MG, et al. A multifunctional mannosyltransferase family in *Candida albicans* determines cell wall mannan structure and host-fungus interactions. *J Biol Chem.* **2010**;285(16):12087–12095. doi:10.1074/jbc.M109.081513
48. Mukaremera L, Lee KK, Mora-Montes HM, Gow NAR. *Candida albicans* yeast, pseudohyphal, and hyphal morphogenesis differentially affects immune recognition. *Front Immunol.* **2017**;8:629. doi:10.3389/fimmu.2017.00629
49. Munro CA, Bates S, Buurman ET, et al. Mnt1p and Mnt2p of *Candida albicans* are partially redundant alpha-1,2-mannosyltransferases that participate in O-linked mannosylation and are required for adhesion and virulence. *J Biol Chem.* **2005**;280(2):1051–1060. doi:10.1074/jbc.M411413200
50. Shibata N, Kobayashi H, Okawa Y, Suzuki S. Existence of novel beta-1,2 linkage-containing side chain in the mannan of *Candida lusitanae*, antigenically related to *Candida albicans* serotype A. *Eur J Biochem.* **2003**;270(12):2565–2575. doi:10.1046/j.1432-1033.2003.03622.x
51. Gow NAR, Latge JP, Munro CA. The fungal cell wall: structure, biosynthesis, and function. *Microbiol spect.* **2017**;5(3). doi:10.1128/microbiolspec.FUNK-0035-2016
52. Díaz-Jiménez DF, Pérez-García LA, Martínez-álvarez JA, Mora-Montes HM. Role of the fungal cell wall in pathogenesis and antifungal resistance. *Curr Fungal Infect Rep.* **2012**;6(4):275–282. doi:10.1007/s12281-012-0109-7
53. Gow NA, van de Veerdonk FL, Brown AJ, Netea MG. *Candida albicans* morphogenesis and host defence: discriminating invasion from colonization. *Nat Rev Microbiol.* **2012**;10(2):112–122. doi:10.1038/nrmicro2711
54. Freer SN. Fermentation and aerobic metabolism of cellodextrins by yeasts. *Appl Environ Microbiol.* **1991**;57(3):655–659. doi:10.1128/aem.57.3.655-659.1991
55. Lachance M-A. Chapter 21 - *Clavispora* Rodrigues de Miranda (1979). In: Kurtzman CP, Fell JW, Boekhout T, editors. *The Yeasts*. 5th ed. London: Elsevier; **2011**:349–353.
56. Ene IV, Adya AK, Wehmeier S, et al. Host carbon sources modulate cell wall architecture, drug resistance and virulence in a fungal pathogen. *Cell Microbiol.* **2012**;14(9):1319–1335. doi:10.1111/j.1462-5822.2012.01813.x
57. Priest SJ, Lorenz MC. Characterization of virulence-related phenotypes in *Candida* species of the CUG clade. *Eukaryot Cell.* **2015**;14(9):931–940. doi:10.1128/EC.00062-15
58. Sherwood RK, Scaduto CM, Torres SE, Bennett RJ. Convergent evolution of a fused sexual cycle promotes the haploid lifestyle. *Nature.* **2014**;506(7488):387–390. doi:10.1038/nature12891
59. Butler G, Rasmussen MD, Lin MF, et al. Evolution of pathogenicity and sexual reproduction in eight *Candida* genomes. *Nature.* **2009**;459(7247):657–662. doi:10.1038/nature08064

60. Kannan A, Asner SA, Trachsel E, Kelly S, Parker J, Sanglard D. Comparative genomics for the elucidation of multidrug resistance in *Candida lusitanae*. *mBio*. 2019;10(6):e02512–02519. doi:10.1128/mBio.02512-19
61. de Groot PWJ, Bader O, de Boer AD, Weig M, Chauhan N. Adhesins in human fungal pathogens: glue with plenty of stick. *Eukaryot Cell*. 2013;12(4):470–481. doi:10.1128/EC.00364-12
62. Willaert RG. Adhesins of yeasts: protein structure and interactions. *J Fungi*. 2018;4(4):119. doi:10.3390/jof4040119
63. Biasoli MS, Tosello ME, Magaró HM. Adherence of *Candida* strains isolated from the human gastrointestinal tract. *Mycoses*. 2002;45(11–12):465–469. doi:10.1046/j.1439-0507.2002.00793.x
64. de Repentigny L, Aumont F, Bernard K, Belhumeur P. Characterization of binding of *Candida albicans* to small intestinal mucin and its role in adherence to mucosal epithelial cells. *Infect Immun*. 2000;68(6):3172–3179. doi:10.1128/IAI.68.6.3172-3179.2000
65. Dorko E, Kmet'ová M, Marossy A, Dorko F, Molokáčová M. Non-albicans *Candida* species isolated from plastic devices. *Mycopathologia*. 1999;148(3):117–122. doi:10.1023/A:1007178806720
66. Staniszevska M. Virulence factors in *Candida* species. *Curr Protein Pept Sci*. 2020;21(3):313–323. doi:10.2174/1389203720666190722152415
67. Nordin MA, Wan Harun WH, Abdul Razak F. An *in vitro* study on the anti-adherence effect of *Brucea javanica* and *Piper betle* extracts towards oral *Candida*. *Arch Oral Biol*. 2013;58(10):1335–1342. doi:10.1016/j.archoralbio.2013.07.001
68. Muadcheingka T, Tantivitayakul P. Distribution of *Candida albicans* and non-albicans *Candida* species in oral candidiasis patients: correlation between cell surface hydrophobicity and biofilm forming activities. *Arch Oral Biol*. 2015;60(6):894–901. doi:10.1016/j.archoralbio.2015.03.002
69. Panagoda GJ, Ellepola AN, Samaranayake LP. Adhesion to denture acrylic surfaces and relative cell-surface hydrophobicity of *Candida parapsilosis* and *Candida albicans*. *APMIS*. 1998;106(7):736–742. doi:10.1111/j.1699-0463.1998.tb00220.x
70. Bujdaková H, Didiášová M, Drahovská H, Černáková L. Role of cell surface hydrophobicity in *Candida albicans* biofilm. *Open Life Sci*. 2013;8(3):259–262. doi:10.2478/s11535-013-0136-y
71. Krasowska A, Sigler K. How microorganisms use hydrophobicity and what does this mean for human needs? *Front Cell Infect Microbiol*. 2014;4:112. doi:10.3389/fcimb.2014.00112
72. Blanco MT, Morales JJ, Lucio L, Pérez-Giraldo C, Hurtado C, Gómez-García AC. Modification of adherence to plastic and to human buccal cells of *Candida albicans* and *Candida dubliniensis* by a subinhibitory concentration of itraconazole. *Oral Microbiol Immunol*. 2006;21(1):69–72. doi:10.1111/j.1399-302X.2005.00260.x
73. Gulati M, Nobile CJ. *Candida albicans* biofilms: development, regulation, and molecular mechanisms. *Microbes Infect*. 2016;18(5):310–321. doi:10.1016/j.micinf.2016.01.002
74. Pathirana RU, McCall AD, Norris HL, Edgerton M. Filamentous non-albicans *Candida* species adhere to *Candida albicans* and benefit from dual biofilm growth. *Front Microbiol*. 2019;10:1188. doi:10.3389/fmicb.2019.01188
75. Schaller M, Borelli C, Korting HC, Hube B. Hydrolytic enzymes as virulence factors of *Candida albicans*. *Mycoses*. 2005;48(6):365–377. doi:10.1111/j.1439-0507.2005.01165.x
76. Pichová I, Pavlicková L, Dostál J, et al. Secreted aspartic proteases of *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis* and *Candida lusitanae*. Inhibition with peptidomimetic inhibitors. *Eur J Biochem*. 2001;268(9):2669–2677. doi:10.1046/j.1432-1327.2001.02152.x
77. Braun BR, Johnson AD. *TUPI*, *CPH1* and *EFG1* make independent contributions to filamentation in *Candida albicans*. *Genetics*. 2000;155(1):57–67. doi:10.1093/genetics/155.1.57
78. Cleary IA, Lazzell AL, Monteagudo C, Thomas DP, Saville SP. *BRG1* and *NRG1* form a novel feedback circuit regulating *Candida albicans* hypha formation and virulence. *Mol Microbiol*. 2012;85(3):557–573. doi:10.1111/j.1365-2958.2012.08127.x
79. Zheng X, Wang Y, Wang Y, Hgel, a novel hypha-specific G1 cyclin-related protein regulates *Candida albicans* hyphal morphogenesis. *EMBO J*. 2004;23(8):1845–1856. doi:10.1038/sj.emboj.7600195
80. Miller NS, Dick JD, Merz WG. Phenotypic switching in *Candida lusitanae* on copper sulfate indicator agar: association with amphotericin B resistance and filamentation. *J Clin Microbiol*. 2006;44(4):1536–1539. doi:10.1128/JCM.44.4.1536-1539.2006
81. Sanchez Y, Lindquist SL. *HSP104* required for induced thermotolerance. *Science*. 1990;248(4959):1112–1115. doi:10.1126/science.2188365
82. Gong Y, Li T, Yu C, Sun S. *Candida albicans* heat shock proteins and Hsps-associated signaling pathways as potential antifungal targets. *Front Cell Infect Microbiol*. 2017;7(520):520. doi:10.3389/fcimb.2017.00520
83. Papon N, Courdavault V, Clastre M, Bennett RJ. Emerging and emerged pathogenic *Candida* species: beyond the *Candida albicans* paradigm. *PLoS Pathog*. 2013;9(9):e1003550.
84. Martinez-Alvarez JA, Perez-Garcia LA, Flores-Carreón A, Mora-Montes HM. The immune response against *Candida spp.* and *Sporothrix schenckii*. *Rev Iberoam Micol*. 2014;31(1):62–66. doi:10.1016/j.riam.2013.09.015
85. Netea MG, Brown GD, Kullberg BJ, Gow NA. An integrated model of the recognition of *Candida albicans* by the innate immune system. *Nat Rev Microbiol*. 2008;6(1):67–78. doi:10.1038/nrmicro1815
86. Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against *Candida* fungal infections. *Nat Rev Immunol*. 2015;15(10):630–642. doi:10.1038/nri3897
87. Reid DM, Gow NAR, Brown GD. Pattern recognition: recent insights from Dectin-1. *Curr Opin Immunol*. 2009;21(1):30–37. doi:10.1016/j.coi.2009.01.003
88. Vecchiarelli A, Bistoni F, Cenci E, Perito S, Cassone A. In-vitro killing of *Candida* species by murine immunoeffectors and its relationship to the experimental pathogenicity. *Sabouraudia*. 1985;23(5):377–387. doi:10.1080/00362178585380541
89. Högåsen AK, Abrahamsen TG, Gaustad P. Various *Candida* and *Torulopsis* species differ in their ability to induce the production of C3, factor B and granulocyte-macrophage colony-stimulating factor (GM-CSF) in human monocyte cultures. *J Med Microbiol*. 1995;42(4):291–298. doi:10.1099/00222615-42-4-291
90. Aybay C, Imir T. Tumor necrosis factor (TNF) induction from monocyte/macrophages by *Candida* species. *Immunobiology*. 1996;196(4):363–374. doi:10.1016/S0171-2985(96)80059-3
91. Killick J, Morisse G, Sieger D, Astier AL. Complement as a regulator of adaptive immunity. *Semin Immunopathol*. 2018;40(1):37–48. doi:10.1007/s00281-017-0644-y
92. Singh DK, Tóth R, Gácsér A. Mechanisms of pathogenic *Candida* species to Evade the host complement attack. *Front Cell Infect Microbiol*. 2020;10:94. doi:10.3389/fcimb.2020.00094

93. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Res*. 2010;20(1):34–50. doi:10.1038/cr.2009.139
94. Meri T, Hartmann A, Lenk D, et al. The yeast *Candida albicans* binds complement regulators factor H and FHL-1. *Infect Immun*. 2002;70(9):5185–5192. doi:10.1128/IAI.70.9.5185-5192.2002
95. Chi HW, Yang YS, Shang ST, et al. *Candida albicans* versus non-albicans bloodstream infections: the comparison of risk factors and outcome. *J Microbiol Immunol Infect*. 2011;44(5):369–375. doi:10.1016/j.jmii.2010.08.010
96. Khan Z, Ahmad S, Al-Sweih N, Khan S, Joseph L. *Candida lusitanae* in Kuwait: prevalence, antifungal susceptibility and role in neonatal fungemia. *PLoS One*. 2019;14(3):e0213532. doi:10.1371/journal.pone.0213532
97. Luzzati R, Amalfitano G, Lazzarini L, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. *Eur J Clin Microbiol Infect Dis*. 2000;19(8):602–607. doi:10.1007/s100960000325
98. Chow JK, Golan Y, Ruthazer R, et al. Factors associated with candidemia caused by non-albicans *Candida* species versus *Candida albicans* in the intensive care unit. *Clin Infect Dis*. 2008;46(8):1206–1213. doi:10.1086/529435
99. Raja A, Park J. Disseminated *Candida lusitanae*: nosocomial acquisition secondary to an indwelling urinary catheter. *Case Rep Infect Dis*. 2021;2021:6632730. doi:10.1155/2021/6632730
100. Simitsopoulou M, Kyrpitzis D, Velegraki A, Walsh TJ, Roilides E. Caspofungin at catheter lock concentrations eradicates mature biofilms of *Candida lusitanae* and *Candida guilliermondii*. *Antimicrob Agents Chemother*. 2014;58(8):4953–4956. doi:10.1128/AAC.03117-14
101. Fowler SL, Rhoton B, Springer SC, Messer SA, Hollis RJ, Pfaller MA. Evidence for person-to-person transmission of *Candida lusitanae* in a neonatal intensive-care unit. *Infect Control Hosp Epidemiol*. 1998;19(5):343–345. doi:10.2307/30141376
102. Guinet R, Chanas J, Goullier A, Bonnefoy G, Ambroise-Thomas P. Fatal septicemia due to amphotericin B-resistant *Candida lusitanae*. *J Clin Microbiol*. 1983;18(2):443–444. doi:10.1128/jcm.18.2.443-444.1983
103. Merz WG. *Candida lusitanae*: frequency of recovery, colonization, infection, and amphotericin B resistance. *J Clin Microbiol*. 1984;20(6):1194–1195. doi:10.1128/jcm.20.6.1194-1195.1984
104. Blinkhorn RJ, Adelstein D, Spagnuolo PJ. Emergence of a new opportunistic pathogen, *Candida lusitanae*. *J Clin Microbiol*. 1989;27(2):236–240. doi:10.1128/jcm.27.2.236-240.1989
105. Desnos-Ollivier M, Moquet C, Chouaki T, Guérin AM, Dromer F. Development of echinocandin resistance in *Clavispora lusitanae* during caspofungin treatment. *J Clin Microbiol*. 2011;49(6):2304–2306. doi:10.1128/JCM.00325-11
106. Parentin F, Liberali T, Perissutti P. Polymicrobial keratomycosis in a three-year-old child. *Ocul Immunol Inflamm*. 2006;14(2):129–131. doi:10.1080/09273940500328487
107. Huynh N, Chang HY, Borboli-Gerogiannis S. Ocular involvement in hospitalized patients with candidemia: analysis at a Boston tertiary care center. *Ocul Immunol Inflamm*. 2012;20(2):100–103. doi:10.3109/09273948.2011.646383
108. Apsemidou A, Füller MA, Idelevich EA, Kurzai O, Tragiannidis A, Groll AH. *Candida lusitanae* breakthrough fungemia in an immuno-compromised adolescent: case report and review of the literature. *J Fungi*. 2020;6(4):380. doi:10.3390/jof6040380
109. Atkinson BJ, Lewis RE, Kontoyiannis DP. *Candida lusitanae* fungemia in cancer patients: risk factors for amphotericin B failure and outcome. *Med Mycol*. 2008;46(6):541–546. doi:10.1080/13693780801968571
110. Holzschu DL, Presley HL, Miranda M, Phaff HJ. Identification of *Candida lusitanae* as an opportunistic yeast in humans. *J Clin Microbiol*. 1979;10(2):202–205. doi:10.1128/jcm.10.2.202-205.1979
111. Steinbach WJ, Roilides E, Berman D, et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. *Pediatr Infect Dis J*. 2012;31(12):1252–1257. doi:10.1097/INF.0b013e3182737427
112. Tragiannidis A, Fegeler W, Rellensmann G, et al. Candidaemia in a European Paediatric University Hospital: a 10-year observational study. *Clin Microbiol Infect*. 2012;18(2):E27–E30. doi:10.1111/j.1469-0691.2011.03720.x
113. Wawrysiuk S, Rechberger T, Futyma K, Miotła P. *Candida lusitanae* - a case report of an intraperitoneal infection. *Prz Menopauzalny*. 2018;17(2):94–96. doi:10.5114/pm.2018.77310
114. Baumgartner C, Freydiere AM, Gille Y. Direct identification and recognition of yeast species from clinical material by using albicans ID and CHROMagar *Candida* plates. *J Clin Microbiol*. 1996;34(2):454–456. doi:10.1128/jcm.34.2.454-456.1996
115. Odds FC, Bernaerts R. CHROMagar *Candida*, a new differential isolation medium for presumptive identification of clinically important *Candida* species. *J Clin Microbiol*. 1994;32(8):1923–1929. doi:10.1128/jcm.32.8.1923-1929.1994
116. Cooke VM, Miles RJ, Price RG, Midgley G, Khamri W, Richardson AC. New chromogenic agar medium for the identification of *Candida* spp. *Appl Environ Microbiol*. 2002;68(7):3622–3627. doi:10.1128/AEM.68.7.3622-3627.2002
117. Deorukhkar SC, Roushani S. Identification of *Candida* species: conventional methods in the era of molecular diagnosis. *Ann Microbiol Immunol*. 2018;1(1):1002.
118. Essendoubi M, Toubas D, Bouzaggou M, Pinon JM, Manfait M, Sockalingum GD. Rapid identification of *Candida* species by FT-IR microspectroscopy. *Biochim Biophys Acta*. 2005;1724(3):239–247. doi:10.1016/j.bbagen.2005.04.019
119. Elie CM, Lott TJ, Reiss E, Morrison CJ. Rapid identification of *Candida* species with species-specific DNA probes. *J Clin Microbiol*. 1998;36(11):3260–3265. doi:10.1128/JCM.36.11.3260-3265.1998
120. Fujita S, Lasker BA, Lott TJ, Reiss E, Morrison CJ. Microtitration plate enzyme immunoassay to detect PCR-amplified DNA from *Candida* species in blood. *J Clin Microbiol*. 1995;33(4):962–967. doi:10.1128/jcm.33.4.962-967.1995
121. Michel-Nguyen A, Favel A, Chastin C, Selva M, Regli P. Comparative evaluation of a commercial system for identification of *Candida lusitanae*. *Eur J Clin Microbiol Infect Dis*. 2000;19(5):393–395. doi:10.1007/PL00011231
122. Campbell CK, Davey KG, Holmes AD, Szekely A, Warnock DW. Comparison of the API *Candida* system with the AUXACOLOR system for identification of common yeast pathogens. *J Clin Microbiol*. 1999;37(3):821–823. doi:10.1128/JCM.37.3.821-823.1999
123. Arendrup M, Horn T, Frimodt-Møller N. *In vivo* pathogenicity of eight medically relevant *Candida* species in an animal model. *Infection*. 2002;30(5):286–291. doi:10.1007/s15010-002-2131-0
124. Lockhart SR, Iqbal N, Cleveland AA, et al. Species identification and antifungal susceptibility testing of *Candida* bloodstream isolates from population-based surveillance studies in two U.S. cities from 2008 to 2011. *J Clin Microbiol*. 2012;50(11):3435–3442. doi:10.1128/JCM.01283-12
125. Barchiesi F, Tortorano AM, Di Francesco LF, Cogliati M, Scalise G, Viviani MA. In-vitro activity of five antifungal agents against uncommon clinical isolates of *Candida* spp. *J Antimicrob Chemother*. 1999;43(2):295–299. doi:10.1093/jac/43.2.295

126. Favel A, Michel-Nguyen A, Peyron F, et al. Colony morphology switching of *Candida lusitanae* and acquisition of multidrug resistance during treatment of a renal infection in a newborn: case report and review of the literature. *Diagn Microbiol Infect Dis*. 2003;47(1):331–339. doi:10.1016/S0732-8893(03)00094-4
127. Pfaller MA, Diekema DJ, Andes D, et al. Clinical breakpoints for the echinocandins and *Candida* revisited: integration of molecular, clinical, and microbiological data to arrive at species-specific interpretive criteria. *Drug Resist Updat*. 2011;14(3):164–176. doi:10.1016/j.drug.2011.01.004
128. Abruzzo GK, Flattery AM, Gill CJ, et al. Evaluation of the echinocandin antifungal MK-0991 (L-743,872): efficacies in mouse models of disseminated aspergillosis, candidiasis, and cryptococcosis. *Antimicrob Agents Chemother*. 1997;41(11):2333–2338. doi:10.1128/AAC.41.11.2333
129. Asner SA, Giulieri S, Diezi M, Marchetti O, Sanglard D. Acquired multidrug antifungal resistance in *Candida lusitanae* during therapy. *Antimicrob Agents Chemother*. 2015;59(12):7715–7722. doi:10.1128/AAC.02204-15
130. Dunkel N, Blass J, Rogers PD, Morschhäuser J. Mutations in the multi-drug resistance regulator *MRR1*, followed by loss of heterozygosity, are the main cause of *MDR1* overexpression in fluconazole-resistant *Candida albicans* strains. *Mol Microbiol*. 2008;69(4):827–840. doi:10.1111/j.1365-2958.2008.06309.x
131. Krcmery V Jr, Oravcova E, Spanik S, et al. Nosocomial breakthrough fungaemia during antifungal prophylaxis or empirical antifungal therapy in 41 cancer patients receiving antineoplastic chemotherapy: analysis of aetiology risk factors and outcome. *J Antimicrob Chemother*. 1998;41(3):373–380. doi:10.1093/jac/41.3.373
132. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. *Clin Infect Dis*. 2000;30(4):662–678. doi:10.1086/313749
133. Bouchara JP, Zouhair R, Leb S, et al. *In-vivo* selection of an azole-resistant petite mutant of *Candida glabrata*. *J Med Microbiol*. 2000;49(11):977–984. doi:10.1099/0022-1317-49-11-977
134. Vargas K, Messer SA, Pfaller M, et al. Elevated phenotypic switching and drug resistance of *Candida albicans* from human immunodeficiency virus-positive individuals prior to first thrush episode. *J Clin Microbiol*. 2000;38(10):3595–3607. doi:10.1128/JCM.38.10.3595-3607.2000
135. Odds EC. Switch of phenotype as an escape mechanism of the intruder. *Mycoses*. 1997;40(Suppl 2):9–12. doi:10.1111/j.1439-0507.1997.tb00556.x
136. Peyron F, Favel A, Calaf R, Michel-Nguyen A, Bonaly R, Coulon J. Sterol and fatty acid composition of *Candida lusitanae* clinical isolates. *Antimicrob Agents Chemother*. 2002;46(2):531–533. doi:10.1128/AAC.46.2.531-533.2002
137. Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. *Clin Microbiol Rev*. 1999;12(4):501–517. doi:10.1128/CMR.12.4.501
138. Kamai Y, Kubota M, Kamai Y, Hosokawa T, Fukuoka T, Filler SG. Contribution of *Candida albicans* *ALS1* to the pathogenesis of experimental oropharyngeal candidiasis. *Infect Immun*. 2002;70(9):5256–5258. doi:10.1128/IAI.70.9.5256-5258.2002
139. Gil-Bona A, Reales-Calderon JA, Parra-Giraldo CM, Martinez-Lopez R, Monteoliva L, Gil C. The cell wall protein Ecm33 of *Candida albicans* is involved in chronological life span, morphogenesis, cell wall regeneration, stress tolerance, and host–cell interaction. *Front Microbiol*. 2016;7:64. doi:10.3389/fmicb.2016.00064
140. Kempf M, Apaire-Marchais V, Saulnier P, et al. Disruption of *Candida albicans* *IFF4* gene involves modifications of the cell electrical surface properties. *Colloids Surf B: Biointer*. 2007;58(2):250–255. doi:10.1016/j.colsurf.2007.03.017
141. Gomez MJ, Torosantucci A, Arancia S, Maras B, Parisi L, Cassone A. Purification and biochemical characterization of a 65-kilodalton mannoprotein (MP65), a main target of anti-*Candida* cell-mediated immune responses in humans. *Infect Immun*. 1996;64(7):2577–2584. doi:10.1128/iai.64.7.2577-2584.1996
142. Nobile CJ, Mitchell AP. Regulation of cell-surface genes and biofilm formation by the *C. albicans* transcription factor Bcr1p. *Curr Biol*. 2005;15(12):1150–1155. doi:10.1016/j.cub.2005.05.047
143. Burt ET, Daly R, Hoganson D, Tsurulnikov Y, Essmann M, Larsen B. Isolation and partial characterization of Hsp90 from *Candida albicans*. *Ann Clin Lab Sci*. 2003;33(1):86–93.
144. Chen CG, Yang YL, Shih HI, Su CL, Lo HJ. CaNdt80 is involved in drug resistance in *Candida albicans* by regulating *CDR1*. *Antimicrob Agents Chemother*. 2004;48(12):4505–4512. doi:10.1128/AAC.48.12.4505-4512.2004
145. Araújo D, Henriques M, Silva S. Portrait of *Candida* species biofilm regulatory network genes. *Trends Microbiol*. 2017;25(1):62–75. doi:10.1016/j.tim.2016.09.004
146. Kenno S, Speth C, Rambach G, et al. *Candida albicans* factor H binding molecule Hgt1p – a low glucose-induced transmembrane protein is trafficked to the cell wall and impairs phagocytosis and killing by human neutrophils. *Front Microbiol*. 2019;9:3319. doi:10.3389/fmicb.2018.03319
147. Swidergall M, Ernst AM, Ernst JF. *Candida albicans* mucin Msb2 is a broad-range protectant against antimicrobial peptides. *Antimicrob Agents Chemother*. 2013;57(8):3917–3922. doi:10.1128/AAC.00862-13
148. Marciel A, Gadoury C, Ash J, Zhang J, Nantel A, Whiteway M. Analysis of *PRA1* and its relationship to *Candida albicans*- macrophage interactions. *Infect Immun*. 2008;76(9):4345–4358. doi:10.1128/IAI.00588-07
149. Leidich SD, Ibrahim AS, Fu Y, et al. Cloning and disruption of *caPLB1*, a phospholipase B gene involved in the pathogenicity of *Candida albicans*. *J Biol Chem*. 1998;273(40):26078–26086. doi:10.1074/jbc.273.40.26078
150. Sun JN, Solis NV, Phan QT, et al. Host cell invasion and virulence mediated by *Candida albicans* Ssa1. *PLoS Pathog*. 2010;6(11):e1001181. doi:10.1371/journal.ppat.1001181

Infection and Drug Resistance

Dovepress

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>