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REVIEW

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

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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 lusitaniae* 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. lusitaniae*-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 lusitaniae* 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. lusitaniae* 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. lusitaniae* 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. lusitaniae* infections were associated with high mortality rates; however, nowadays this is uncommon and mortality usually does not exceed 5%.[10] Additionally to fungemia, *C. lusitaniae* 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. lusitaniae* clinical and basic aspects and the caused infection.

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Basic Biological Attributes of *Candida lusitaniae*

C. lusitaniae 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. lusitaniae* 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. lusitaniae* shows asexual and sexual cycles, being its teleomorph *Clavispora lusitaniae* and assuring meiosis during spore formation.[21,22] The *C. lusitaniae* 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 MLTα*, whereas the *MATa* locus has a translocation that differentiates it from the *C. albicans MATa*.[21] *C. lusitaniae* genome contains the genes *MATα1* 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. lusitaniae 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. lusitaniae* 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. lusitaniae* 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. lusitaniae* 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. lusitaniae*, 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. lusitaniae* 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 cellotetrose, a phenotypical trait that differentiates this species from *Candida guilliermondii*.[54] Moreover, *C. lusitaniae* 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. lusitaniae* genome is distributed in eight chromosomes and belongs to the *Candida* CTG clade.[57] This clade is composed of *C. albicans, C. lusitaniae, 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, HWP1, 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 lusitaniae*

Virulence Factor	*C. albicans* Protein	*C. lusitaniae* Protein*	E- value	Similarity (%)	Putative Role
Adhesins	Als1-7 and Als9	CLUG_03274 FOB63_002933 EJF14_40078	$1e^{-46}$ $3e^{-74}$ $7e^{-44}$	47 47 51	Adherence of the organism to the oral mucosa.[138]
	Ecm33	FOB63_002672	$2e^{-150}$	75	Contributes to the integrity of the fungal cell wall.[139]
	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]
Biofilm formation	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]
	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]
Dimorphism	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]
	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]
Immune evasion	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 *Candida*-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. lusitaniae* 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.

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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-$CuSO_4$ 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]

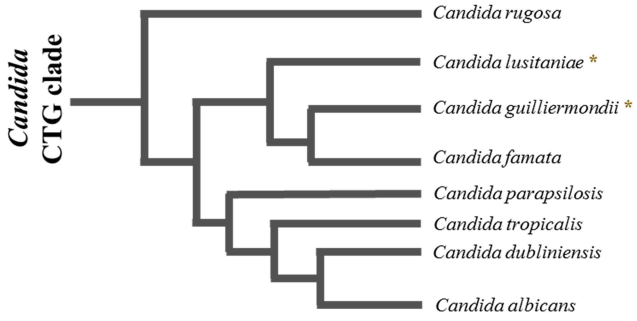

Figure 1 Schematic representation of the phylogenetic relationship between species of the *Candida* CTG clade. The species *C. rugosa, C lusitaniae, C guilliermondii, C famata, C parapsilosis, C tropicalis, C dubliniensis* and *C. albicans* are part of the CTG clade of *Candida*. (*) represents the species 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 (TNFα) 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 TNFα, IL-6, IL-1β, 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 TNFα, IL-1β, 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/μL.[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.

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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.

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