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The Candida Genus Complex: Biology, Evolution, Pathogenicity Virulence and One Health Aspects, Beyond the *Candida albicans* Paradigm. A Comprehensive Review

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Review Article

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Abstract

Introduction: Yeast species of the genus Candida are important human pathogens and cause 90% of existing fungal infections. These pathogens within the One Health vision are closely linked to human, animal and environmental health.

Objective: To emphasize the importance of the status of Candida yeasts, as infectious, opportunistic and emerging agents.

Methodology: Databases and books relevant to the subject were used.

Results: Candidemia is the most hostile fungal infection in the studied populations. Several cases of superficial and invasive diseases involve isolation of these yeasts in various population groups. Parenteral nutrition, administration of broad-spectrum antibiotics, prolonged hospitalization, chemotherapy and vascular catheters were considered risk factors. *C. albicans* is the most prevalent species, followed by *C. parapsilosis*, *C. tropicalis* and *C. glabrata* and more recently by the appearance of a new pathogen *C. auris*. Yeasts of the genus Candida are associated with a high lethality rate in relation to hematological malignancies, mainly *C. albicans*.

Discussion: The pathogenic prevalence of *Candida* spp. is recognized all over the world. *Candida albicans* is the most commonly isolated species from clinical materials. The literature discusses methods used to differentiate strains in the study of the epidemiological relationship of members of the genus listed in this review. New Candida species isolated from clinical specimens continue to grow each year.

Conclusion: Candidemia is a prevalent pathology with high incidence, morbidity and mortality in the world. The taxonomy, mechanisms of action and status of this yeast genus are related to its virulence, adhesion and epidemiological characteristics, more suitable for treatments to control cases of fungal infections caused by yeasts of the genus Candida.

Keywords: *Candida* Species; Nosocomial Infections; Yeasts; Fungemia; Emerging Species; One Health

Introduction

Of the total number of eukaryotic species on planet Earth, recent records estimate that there are 8.7 million species; with fungi representing approximately 7% (611,000 species) of that number [1]. More data that are recent generated by Chinese researchers estimate that there are between 12 and 13.2 million fungal species on Earth and the estimative can change with the discovery of new specimens on the planet [2]. Of all fungi, about 600 species are considered human pathogens [1].

Within the One Health scope, human, animal and environmental health is integrated into seven priority topics to address the characteristics of fungi: environment, surveillance, antifungal resistance, transmission, diagnosis, therapeutics and potential interventions, which involve multiple factors and processes and their interactions over time at local, national and global levels.

Yeasts of the genus *Candida* are members of the phylum *Ascomycota*. This yeast-like fungal group is a heterogeneous group that contains about 1/4 of all yeast species, constituting approximately 200 different species of yeasts that can be pathogenic to humans and animals and were isolated from basically all of the body sites, among which, 40 species have been already associated with nosocomial fungal infections [3,4]. That include not only species of uncertain affiliation, but also unrelated lineages whose phylogenetic relationships are not resolved yet.

Candida yeast species are human constituents of the compatible microbiota and live symbiotically in buccal and gastrointestinal mucosa. Found as a ubiquitous and commensal microorganism present in skin and mucosa from other locations, such as rectal, vaginal, urethral, nasal, and aural, growing under aerobic conditions. Among the species of the genus, *Candida albicans* is the primary opportunistic yeast and the most commonly related to infections, and frequently isolated in humans. However, the prevalence of colonization and nosocomial fungal infections in which other species of *Candida* Non-*albicans* (NAC) have shown much higher rates of importance in the last decade, with rates above 50% of non-superficial infections by the genus [4-7]. Registries report that the incidence of bloodstream infections (BSI) has increased 15 to 20 times in recent decades, and candidemia is reported as the leading cause of healthcare-associated bloodstream infections (HAIs) in certain centers [8,9]. Among the NAC species isolated, the most commonly associated with candidiasis are *C. parapsilosis*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, *C. guilliermondii*, and *C. kefyr* [4,10].

Regarding the microbiological aspects, this eukaryotic microorganism can grow in an environment between 20ºC and 38°C, with a pH between 2-7.5, and these features favor the proliferation of the agent. These yeasts measure approximately 2 to 6 µm, and their shape can be spherical, ovoid, or elongated, presenting, in most species, pseudohyphae and hyphae formation in the tissues and the reproduction is by budding. Their colonies can be wet, creamy, the surface of the colony can be rough or smooth and the coloration can vary from white to cream, with a specific and characteristic odor, in Gram stain, they are colored purple [11,12].

Mycology experienced a time of ostracism, coming to re-emerge as an important medical area in the 1970s and 1980s [13,14]. However, with the ascension of new methods to identify species, the more traditional phenotypic methodologies have been replaced by techniques based on nucleic acid, which allowed the discovery of cryptic species, which lived hidden, imitating their original phenotypes, added to the list of human pathogens.

This study aimed to provide information on fungal infections of the genus Candida, including the disease candidemia, candidiasis and candiduria infections, focusing on important aspects of epidemiology, fungal-host interactions and laboratory diagnosis of emerging systemic infection, exploring and correlating the factors linked to human health in the inextricable “One Health” perspective, thus discussing the impact of these yeasts on the health of the planet, their influence on other vital elements. Therefore, it was possible to discuss current knowledge and information about the yeasts of this fungal genus, highlighting their role in human infections, thus providing a complete clinical picture to understand the importance of this yeast as an important pathogen.

Methodology

Bibliographical consultations and online articles from the last 23 years were carried out, using the databases BIREME

(Regional Library of Medicine), Highwire, PubMed (National Public Library), Scielo (Scientific Electronic Library Online), Lilacs (Latin American and Caribbean in Health Sciences), Web of Science, ScienceDirect and related books.

The following descriptors were chosen as inclusion criteria for scientific journals: Candidiasis, Vulvovaginal Candidiasis, Oral Candidiasis, Infection, Yeasts, and Yeasts-like. The analyzed articles were published from 2000 to 2023, related to the cited words. At the end of the survey, 285 references were duly used, and selected according to the proposed theme.

The confirmation of the current Yeast name was using the NCBI Master Express Configuration Database (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi). MycoBank Fungal Databases, Nomenclature & Species Banks (http://www.mycobank.org/) and Index Fungorum Partnership (http://www.indexfungorum.org), which are invaluable sources of up-to-date taxonomic information on taxonomic classifications suggesting fungi of medical importance and also as provided by Borman & Johnson; Brandt & Lockhart, Daniel and Hawsworth [3,13,15,16].

Pathophysiology

To be able to infect and colonize the animal, these microorganisms need to disrupt the mechanical barrier (epithelial tissue), biochemical, and extreme chemical resistance barriers (such as pH and mucus production) from the hosts, in addition to innate and acquired immunity [17,18].

The deregulation of the host organism can occur for several reasons and, among them, are stress, low immunity, use of medication, newborn patient, dental prosthesis, immunosuppression, neoplastic patient and HIV+ carriers (AIDS). In sexual behavior, although candidiasis is not considered a sexually transmitted infection, it is associated with sexual activity, especially in women in the beginning of sexual activity.

The usual form of *Candida* infection starts with the change of its habitual niche to the bloodstream or other tissues. The first attempt at host defense is phagocytosis and destruction by neutrophils, monocytes, and macrophages. Therefore, the mechanism that operates inside neutrophils and macrophages destroys the yeasts. Cellular immunity also has an active role in the defense against *Candida* infection, and cells are responsible for immunity against *Candida* on mucosal surfaces [19].

Virulence Factors and Resistance Mechanisms

The main virulence factors reported for *Candida* species include a series of attributes such as phenotypic switching (switches), a morphological transition between yeast and hyphae forms (pseudohyphae), mutations, dimorphism, polymorphism, the expression of adhesins and invasins on the cell surface, thigmotropism (filaments capable of invading tissue depth), biofilm formation, overexpression of efflux pumps, secretion of hydrolytic enzymes [17,20,21] (Figure 1).

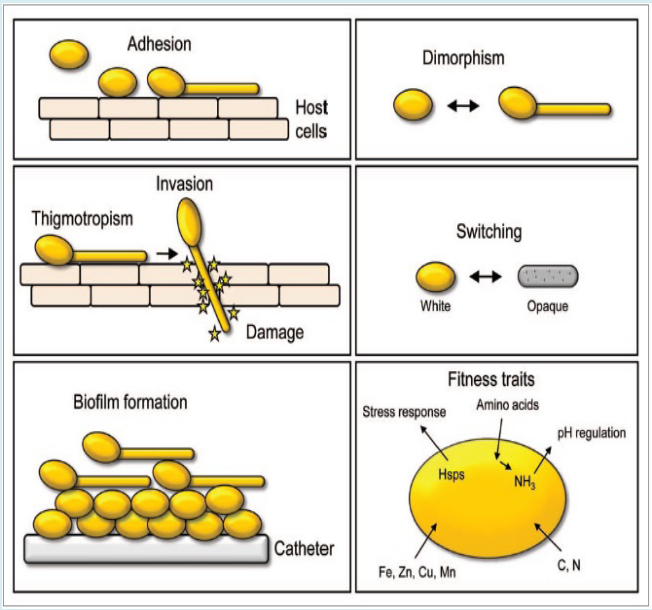

Figure 1: Schematic representation of the main virulence factors of the Candida genus [21].

Failure in antifungal therapy can occur due to several factors, such as intrinsic or natural resistance, a phenotypic characteristic that confers innate resistance to a given species to antifungal exposure, and acquired resistance/ clinical, which promotes mutations in the microorganism after exposure to the antifungal drug, causing a selection of more resistant cells [22].

The cell morphology of the species of this fungal genus is one of the main virulence factors since the different forms of cell presentation are involved in stages of the infectious process, where hyphae formation is directly related to the ability to invade the host tissue, the yeast form is associate with host-cell adhesion [21]. The infectious process and colonization begin with the adherence of the yeast to the epithelial cells. The presence of specific receptors on the cytoplasmic membrane is necessary for the attachment and penetration performed by the fungus.

The cell wall of this eukaryote is an essential mechanism for growth and survival, being a target for antifungal drugs and the immune system. The inner cell beta-glucans compounds are associated with glycosylated polymers and peptides that confer a range of hydrophobicity, adhesiveness, and chemical and immunological heterogeneity characteristics [23].

The ability to switch from the unicellular form of yeast to the filamentous form is term dimorphism. *Candida* spp. can reproduce by budding, and changing their shape, resulting in a conversion from the yeast form to a mycelium-shaped growth, with the production of hyphae and pseudohyphae and also in quorum sensing, characterized as a mechanism of intraspecies and interspecies microbial communication that provides microorganisms to express marked phenotypic changes when they are in high population densities [17,21,24].

According to Polke, the infectious process can also occur through phenotypic switching, which involves a cellular variation from "white, ovoid, cream" yeast cells to "opaque, elongated, grayish", this modification is characterized by the phenomenon called "switching" which occurs when cells are dividing by budding or forming biofilms, resulting from the stress that causes changes in cell surface behavior, making it more virulent and effective during infection [17].

Several species of *Candida* yeasts can produce biofilms. Biofilm formation by this fungal genus is a significative mechanism for the lack of action of antifungal [24]. Biofilms can form on a wide variety of surfaces, including living tissue, medical devices, drinking water piping systems, industrial environments, and natural aquatic systems. Although biofilms often adhere to solid surfaces, they can form in other locations as well, like at liquid-air interfaces, promoting better resistance to cells against chemical and physical aggression [17].

Biofilms have a well-consolidated structure, with substances called exopolysaccharides (EPS - extracellular polymeric substance) forming an extracellular matrix that promotes a strong bond between cells and aggregation, maintaining a stable mechanical barrier and excellent efficiency against UV rays' emission, phagocytosis, dehydration and resistance to antifungal drugs, consisting of carbohydrates, proteins, hexosamine, phosphorus and uronic acid [24,25].

The secretion of hydrolytic enzymes such as phospholipases, proteinases, and extra and intracellular lipases is involved in epithelial invasion and cellular penetration. Among the various enzymes produced, we highlight proteases, which hydrolyze peptide bonds of proteins present in host cells, and phospholipases, which degrade phospholipids in host membranes, which, in combination, are capable of promoting the destruction of cell membranes. Among the hydrolytic enzymes biosynthesized by the genus *Candida*, secreted aspartic proteases (SAPs) stand out, which are involved in processes that destroy, alter or damage the integrity of the membrane of infected cells leading to their dysfunction [26].

Clinical Manifestations

The clinical manifestations caused by yeasts of the genus *Candida* are varied and can lead to a localized infection in the mucous membranes to a potentially fatal disseminated disease. The main factor that determines the type and extent of infection caused by *Candida* is mostly the immune response from the patient. Immunosuppressed patients (neutropenic, transplanted, diabetic, HIV carriers) who present the visceral dissemination of the infection, become risk cases [27].

The manifestations of candidiasis can be classified into three types: cutaneous, mucocutaneous, and systemic. Cutaneous candidiasis often occurs when there are humidity conditions and high body temperature, especially in regions with tropical climates and summer months; intertriginous manifestations occur (located in skin folds such as armpits, groin, intergluteal crease, submammary fold. In neonates, the use of diapers for a long period can cause eruptions, causing manifestations of cutaneous candidiasis in obese people in the folds of suprapubic and interdigital spaces and nail infections (onychomycosis and paronychias). Diabetes mellitus and HIV are also associated with these infections [27]. The lesions of cutaneous candidiasis are erythematous, pruritic, often pustular, with well-defined borders, and

almost always associated with smaller satellite lesions.

The form of disseminated candidiasis is rare and occurs in patients with debilitating diseases, or neoplastic, immunosuppressive diseases, after organ transplants and the use of suppressive drugs. In these cases, it can affect different organs and tissues such as the lungs, meninges, spinal cord, kidneys, bladder, joints, liver, heart, and eyes [27].

Mucocutaneous candidiasis affects the oral cavity and the vaginal canal and is the most common manifestation in humans. Mucosal infections are related to diabetics, pregnant women, and obese people. Systemic antibiotics, oral and inhaled corticosteroids, and oral contraceptive agents may contribute to triggering the lesions [28]. In the oral cavity can cause several manifestations such as oropharyngeal candidiasis, pseudomembranous candidiasis, erythematous candidiasis, chronic atrophic candidiasis (denture stomatitis), and esophageal candidiasis.

A very common manifestation in the elderly, but which can affect other ages, is called angular cheilitis, or angular commissuritis, popularly called mouthpiece, which is a small painful wound that occurs in the corner of the mouth, characterized by inflammation and fissure in the angle of the lips. The accumulation of saliva in the corner of the mouth seems to be the main triggering factor, facilitating skin maceration, fissure formation, and wound contamination by bacteria or fungi, in this case, caused by *Candida* yeasts [29].

Ocular manifestations by yeasts of the Candida genus are rare, when symptoms that appear as ophthalmological abnormalities are observed are ocular candidiasis, Candida endophthalmitis, Endogenous fungal endophthalmitis, Candida chorioretinitis. Endophthalmitis is difficult to treat with consequent ocular sequelae [29-34].

Vulvovaginal Candidiasis

The scientific literature has consecrated yeasts of the *Candida* genus as opportunistic agents often isolated from the skin and mucosa of healthy individuals, but which can lead to the development of infections called candidiasis, ranging from superficial infections to disseminated infections.

Candida vaginitis is a universally important disease with far-reaching effects on women's overall physical and mental health. Vulvovaginal candidiasis (VVC) is an infection of the vulva and vagina, caused by various species of *Candida*, which can become pathogenic under certain conditions that alter the vaginal environment. *Candida albicans* is acid tolerant, being found in approximately 10% to 20% of women of reproductive age, being considered highly vaginopathic [21].

This infection is characterized by itching, dyspareunia, and the elimination of vaginal discharge in lumps, similar to cream of milk. The vulva and vagina are often swollen and red, sometimes accompanied by a burning sensation when urinating. Lesions can extend through the perineum, perianal and inguinal regions. The discharge, which is usually white and thick, is odorless. In typical cases, small yellowish-white spots appear on the vaginal walls and cervix. Symptoms intensify in the premenstrual period when vaginal acidity increases [35].

Potential risk factors for VVC have been reported, such as the presence of irregular menstrual cycles, pregnancy, use of high-dose oral contraceptives, hormone replacement therapy, diabetes mellitus, HIV infection, use of systemic or topical antibiotics, habits of hygiene, use of tight and/or synthetic underwear, causing little aeration in the genital's organs, increasing humidity [35,36].

A comprehensive understanding of the immune response to *Candida* vaginitis is far from complete. The fields of mucosal biology and immunology are rapidly expanding and can provide insight into the complexity of this infection [36].

Balanitis/Balanoposthitis

In the male genital sphere, balanitis (acute or chronic inflammation of the glans penis) and balanoposthitis (inflammation of the foreskin region) can be asymptomatic, with only a slight itching, or symptomatic, starting with vesicles on the penis that evolve in severe cases, generating pseudomembranous plaques, generalized erythema, intense pruritus, fissures, ulcers, erosions, superficial pustules on the glans and balanopreputial sulcus, with purulent discharge from the urethra and pain in the glans when urinating and burning after intercourse [37].

Lesions may extend to the scrotum and skin folds, with pruritus, and in some cases, cause transient urethritis. *Candida* colonization of the penis occurs in 30 to 35% of men, with 1/3 of these men showing signs of candidiasis. There are several factors that predispose patients to develop balanitis, the infection is more common in uncircumcised individuals, associated with poor hygiene, sexual relations with partners infected with candidiasis, malnutrition, chemotherapy and drug use, the prolonged use of diapers (whether in babies or the elderly), and diabetic people, in some cases, penile candidiasis can be the first symptom of *diabetes mellitus* setting in [37-39].

However, several virulence factors may be associated with the ability of the microorganism to adapt to biological

niches, as this yeast is considered a "pleomorphic" organism, highly adaptable to the pH of the environment and even the human host; associating with cytoplasmic proteins and their various adhesion mechanisms.

The reports by Bhalani indicate that the use of tight underwear can greatly contribute to the permanence of the infection and even the incidence of infections in the feet, contributing when the underwear is contaminated by passing through the feet and afterward contacting the inguinal region and consequently reaching the genital organ [40].

Antifungals

Antifungals are drugs known for the treatment of systemic and superficial fungal infections, including the treatment of infections and lesions by yeasts of the genus *Candida*. These drugs are contained in the antifungal classes that include the Azoles (ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole), Echinocandins (caspofungin, anidulafungin and micafungin) and the Polyenes (amphotericin-B).

They are considered worldwide as essential and extremely important medicines for the treatment of invasive fungal infections, candidiasis, candidemia, and candiduria. For hospital treatments, fluconazole, itraconazole, and amphotericin B formulations are then used according to the National List of Essential Medicines in Brazil (RENAME) [41].

Azoles are fungistatic drugs and act through the inhibition of the enzyme lanosterol 14-alpha-demethylase, dependent on the cytochrome P450 system, acting through the inhibition of ergosterol biosynthesis. The inhibition of 14-α-demethylase, which acts in the C-14 demethylation step of lanosterol, results in intracellular accumulation of toxic products, leading to altered cell membrane permeability and, consequently, eventual cell death. As well as imidazole's (Ketoconazole and Miconazole); 5-Fluconazole and Itraconazole were the first drugs of the triazole family that began to be used in the treatment of invasive candidiasis and other fungal infections. Fluconazole is the main agent of this antifungal class that is used in the treatment of candidemia as well as in other invasive infections. Other available azoles include Voriconazole, Posaconazole, and Itraconazole [42].

Polyenes exert fungicidal activity, mainly in fungi that are in the stationary phase of growth, as they bind by hydrophobic interactions to ergosterol, the predominant sterol found in the cytoplasmic membrane of fungi. Nystatin (topical only) and amphotericin B (and its liposomal form) are polyene drugs of choice for the treatment of most systemic fungal infections. Amphotericin B, in its interaction with the ergosterol of the fungal membrane, results in the formation of pores, causing a change in cell permeability and consequent cell death, in addition, the oxidative stress resulting from the entry of this antifungal into the cell interior leads to the production of free radicals and intensifies this fungicidal effect. However, the administration of this drug to the patient can be complicated due to its nephrotoxicity, and it may be necessary to reduce the dose or even stop the therapy [43].

Echinocandins, led by the drugs caspofungin, anidulafungin, and micafungin, are fungicidal agents, non-competitive inhibitors of the synthesis of 1,3-beta-D-glucan (a component of the fungal cell wall), with excellent activity against almost all species of *Candida*. They have favorable toxicity profiles and are approved for the treatment of candidemia and other forms of invasive disease [44].

In addition to the three main classes of antifungal agents (azoles, polyenes, and echinocandins), other antifungal agents used in clinical practice, such as 5-Flucytosine, griseofulvin, and terbinafine, have different mechanisms of action, characteristics, and clinical indications. 5-Flucytosine is a pyrimidine analog that disrupts fungal DNA and RNA synthesis. 5-Flucytosine should always be given in combination with other antifungal agents and is indicated in the treatment of cryptococcal meningitis. Both griseofulvin and terbinafine act on the stratum corneum of the skin and are indicated in the treatment of dermatophytosis of the skin, hair, and nails [44].

The most traditional parameter to assess susceptibility to antifungal drugs is based on the minimum inhibitory concentration (MIC). This is defined as the lowest concentration of the drug capable of inhibiting fungal growth in the antifungal susceptibility test by dilution in agar or broth [45]. Historically, in 1997, was published a reference method (M27-A) for broth dilution tests recommended by the Clinical and Laboratory Standards Institute (CLSI) for determining susceptibility to antifungal drugs. In 2002, documents M27-A2 and M27-S2 were published dealing with the selection and preparation of antifungal agents, the implementation and interpretation of tests, and quality controls. In 2008, documents M27-A3 and M27-S3 were published, which include the cut-off points for echinocandins (anidulafungin, caspofungin, and micafungin) and for voriconazole. In 2012, a version of this document (M27-S4) was published that includes species-specific cutoffs for the five most common *Candida* species, and currently, a new document released (M27-M44S) [45].

Recently, mechanisms of drug resistance used by fungi were discussed by Hoenigl in a study evaluating mechanisms of action and pharmacokinetics in the most promising drugs to combat the fungal arsenal, including Fosmanogepix (inhibitor of the Gwt1 enzyme), ibrexafungerp (triterpenoid),

olorofim (dihydroorotate dehydrogenase enzyme inhibitor), opelconazole (triazole optimized for inhalation) and rezafungin (echinocandin) [46]. Cut-off points for the drug rezafungin are already available from the document (M27M44S) of the Clinical and Laboratory Standards Institute [45].

Phenotypic Morphology

The identification of yeasts is obtained through the analysis of their micromorphological characteristics and biochemical profile. The morphological characterization of most isolates of this genus consists of the observation of blastoconidium, pseudohyphae (sometimes true hyphae), and eventually chlamydoconidium. Pseudohyphae is another morphological structure observed in *C. albicans*, produced during its reproduction by budding, in which the buds do not detach from the parent cell, resulting in a chain of cells, whose shape resembles true hyphae [14].

The production of the germ tube (a continuous extension of the yeast mother cell produced at the beginning of the filament process, considered a transitional form between the yeast and the mycelium) at 37º C in blood or bovine serum, this test quickly shows the main feature for the differentiation between *C. albicans* and the other species. While, *C. albicans* produces the easily observable germ tube, that feature cannot be observed in other species. This ability of yeast to change its morphology depending on temperature and pH conditions is called cellular polymorphism [14].

Biochemical tests are based on nitrogen and carbohydrate assimilation (auxanogram), carbohydrate fermentation (zymogram), urea test, and germ tube test.

The CHROMagar *Candida*™ culture medium enables the presumptive identification of species of this genus, as well as facilitates the recognition of mixed cultures. Its principle is the production of color in colonies, by specific enzymatic reactions, with a chromogenic substrate in the medium.

Morphological changes are associated with the pathogenicity of this group of microorganisms, and it is believed that environmental factors can alter the physiological state of commensal yeasts, inducing morphogenetic alterations that result in the formation of mycelium, which is associated with the evolution of pathological states and adhesion mechanisms [47,48].

Main Species of The Genus *Candida*

From a taxonomic point of view, *Candida* species are described as belonging to the *Eukarya* Domain, *Ophistokonta* Clade, *Fungi* Kingdom, *Dikarya* Subkingdom, *Phylum* Ascomycota, Subphylum *Sacharomycotina*, Class *Saccharomycetes* (syn. *Hemiascomycetes*), Order *Saccharomycetales* and Family *Debaryomycetaceae* and Genus *Candida*, although some species are grouped in the *Ascomycotina* subdivision [49]. These microorganisms degrade proteins and carbohydrates to obtain carbon and nitrogen, essential elements for their development, surviving both in environments with oxygen and in anaerobic conditions.

The first time that the genus *Candida* was recognized as a human pathogen was in 1839, by Bernhard Von Langenbeck, when the species *C. albicans* was isolated from an oral infection (thrush) of a patient affected by typhus, and which is currently perhaps the most important pathogenic yeast for humans [49].

Candida species is one of the most important pathogens in medical mycology studies and research, and the incidence of this eukaryotic yeast in candidiasis cases in recent years seems to be increasing.

The correct analysis and identification of cryptic species in a clinical environment are relevant from a hospital and epidemiological point of view. The importance is to better understand the drivers and evolution of these fungal agents to antifungal resistance. Perhaps the most notable example of this importance for identifying species of Candida species, such as cryptic or fast-presenting *Candida auris.*

The introduction of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) in clinical and hospital laboratories has significantly improved the identification of this group of fungi with high precision and specificity. The results of the introduction of this system allowed the identification of most species, including cryptic species that are not possible to be identified by classical methodologies. However, this technology requires constant database updates, and its use is still restricted to high-income countries, without much room for hospitals and institutions in low-income countries.

Below, we describe a summary of the main genetic species, including emerging, methods focusing on epidemiological aspects, identification, virulence factors, and mechanisms of resistance to antifungal agents, to contribute to the understanding of the growing importance of this yeast. Changes in the names of the main species of this genus in the anamorphic phase (mitosporic stage, asexual stage) and teleomorphic (meiosporic stage, sexual stage) phase can be verified by consulting (Table 1).

Frequency	Anamorph Name	Teleomorph Name
Common species 2-70%	*Candida albicans* (37-70%)	
	Candida parapsilosis (20-30%)	
	Candida tropicalis (7-25%)	*Nakaseomyces glabrata*
	Candida glabrata (15-25%)	
Transient species (infrequent) 0,1-6,6%	*Candida auris*	-
	Candida dubliniensis	-
	Candida guilliermondii (0.6-6.6%)	*Meyerozyma guilliermondii*
	Candida krusei (2-4%)	*Pichia kudriavezevii*
	Candida lusitaniae (<1%)	*Clavispora lusitaniae*
	Candida metapsilosis	-
	Candida orthopsilosis	-
	Candida rugosa	*Diutina rugosa*
Rare species >0,1%	*Candida famata*	*Debaryomyces hansenii*
	Candida haemulonii	-
	Candida inconspicua	*Pichia cactophila*
	Candida kefyr (<1%)	*Kluyveromyces marxianus*
	Candida lipolytica	*Yarrowia lipolytica*
	Candida norvegensis	*Pichia norvegensis*
	Candida sake	-
	Candida zeylanoides	-
	Candida pelliculosa	*Wickerhamomyces anomalus*
	Candida fermentati	*Meyerozima caribbica* or *Pichia caribbica*
	Candida membranifaciens	*Kodamaea ohmeri*
	Candida fabianii	*Cyberlindnera fabianii*
	Candida lambica	*Pichia fermentans*
	Candida utilis	*Cyberlindnera jadinii*
	Candida bracarensis	*Nakaseomyces bracarensis*
	Candida catenulata	*Diutina catenulata*
	Candida eremophila	*Pichia eremophila*
	Candida etchellsii	*Starmerella etchellsii*
	Candida discreta	*Pichia cactophila*
	Candida sorbosivorans	*Starmerella sorbosivorans*
	Candida infanticola	*Wicherhamiella infanticola*
	Candida ciferrii	*Trichomonoascus ciferrii*
	Candida pseudorugosa	*Diutina pseudorugosa*
	Candida blankii	-
	Candida nivariensis	*Nakaseomyces nivariensis*
	Candida pararugosa	*Diutina pararugosa*
	Candida neorugosa	*Diutina neorugosa*
	Candida pintolopesii	-
	Candida viswanathii	-
	Candida pseudohaemuloni	-
	Candida palmioleophila	-
	Candida pulcherrima	*Metschnikowia pulcherrima*
	Candida freyschussii	-
	Candida magnoliae	*Starmerella magnoliae*
	Candida thermophila	*Ogataea polymopha*
	Candida colliculosa	*Torulaspora delbrueckii*

Table 1: Species of the genus *Candida* recognized incriminated as pathogens of medical importance [13,15,16].

Description of the Most Commonly Isolated Species of the Genus

Candida Albicans: Historical accounts describe that the first description of fungal infection was of thrush, by Hippocrates in the 5th century B.C. Langenbeck (1839) first described this yeast in a patient with typhoid fever who had stomatitis. It is currently the isolated species with the highest frequency of infections and is considered the most common opportunistic pathogen in humans, confirming to be the primary etiologic agent of candidiasis and cause of many other forms of the mucosal disease [50] (Table 2).

Specie	Specie Characteristic
Candida albicans	High adhesion capacity to abiotic surfaces, biofilm producer.
	Most prevalent species in human infections
	Specie that causes invasive disease and colonize mucous membranes.
	Diploid species, belonging to the CTG clade (translates serine instead of leucine).
	Resistance to Fluconazole and echinocandin.
	Currently appears resistant to caspofungin.
	Cryptic species *C. dubliniensis, C. africana* and *C. stellatoidea* (?)
Candida parapsilosis	Exogenous, ubiquitous pathogens, colonizing human skin, plants, water and soil.
	Diploid species, belonging to the CTG clade.
	Common species isolated from children, newborns and juveniles.
	It is closely related to the intravenous catheter, easily adhering to inanimate materials.
	Phenotypically indistinguishable from *C. orthopsilosis* e *C. metapsilosis.*
Candida tropicalis	Diploid, asexual and opportunistic species, belonging to the CTG clade.
	They undergo metamorphosis and adaptation to climatic variations.
	Easily adapts to human microenvironments.
	Species considered highly virulent, not associated with the microbiota but with the infection.
	Common in patients with hematological disorders.
	Has rare resistance.
Candida glabrata	Most common species of oropharyngeal and gastrointestinal (endogenous) colonization.
	Haploid species, not belonging to the CTG clade.
	Prevalence in the elderly and diabetics and predominantly nosocomial (except vaginal).
	Haploid genome has azole selection and cross-resistance.
	It has significant resistance to Fluconazole, susceptible to echinocandins and flucytosine.
	It is not dimorphic and does not have pseudohyphae, forming only blastoconidia.
	Phenotypically indistinct from *C. bracarensis* and *C. nivariensis.*
Candida krusei	Discovered by the 1st. time from a patient with typhus.
	It colonizes inert surfaces due to its hydrophobicity. Tolerates low pH (>3.5).
	Diploid species, not belonging to the CTG clade.
	Generally considered a transient commensal and is rarely isolated from mucosal surfaces.
	Pathogen of patients with hematologic malignancies and stem cell transplant recipients.
	It has an unusual feature in candidemias.
	Intrinsic resistance to fluconazole, susceptible to voriconazole, posaconazole and echinocandins.

Candida kefyr	Species found in food and dairy products.
	As a native of the human microbiota, this species is considered rare.
	It has been reported to colonize the oral cavities, gastrointestinal tract and urinary tract.
	Undefined ploidy does not belong to the CTG clade.
Candida guilliermondii	Emerging pathogen from Latin America, constituent of the normal human microbiota.
	Haploid species, belonging to the CTG clade.
	Show high antifungal resistance to azoles and echinocandins.
	Mainly reported as a cause of candidemia in cancer patients.
	Phenotypically indistinguishable *C. fermentati*, *C. xestobii, C. glucosophila, C. elateridarum,*
	C. athensensis, C. carpophila, C. smithsonii.
Candida auris	Named for being the 1st time isolated from the human ear canal.
	Haploid species, belonging to the CTG clade. Does not form pseudohyphae, but produces biofilm.
	Multiresistant yeasts, difficult to diagnose, can be confused with other species.
	Promotes serious and fatal infections.
	It remains viable for weeks and months in the environment. Likely transmission from
	an environmental source.
	Hypothesis of emergence due to global warming, presents thermal susceptibility.

Table 2: General summary of the characteristics of the mains pathogenic species of *Candida* yeasts of medical and clinical importance.

This yeast species, since its discovery, has presented more than 160 applied synonyms. It was first named *Oidium albicans* by Charles-Philippe Robin in 1853, then Friedrich Wilhelm Zopf in 1890 changed its name to *Monilia albicans* and after much study, Berkhout 1923 introduced the name *Candida albicans*, which became the accepted name for the species [12,51]. This fungal species is the most prevalent in the human microbiota that asymptomatically colonizes many areas of the body, particularly the gastrointestinal and genitourinary tracts of healthy individuals [52].

The polymorphic fungus *Candida albicans* is the most studied of all *Candida* species dispersed in the genus and is one of the most common opportunistic pathogens in humans [12,53]. According to reports by Moran, this species remains the most frequently isolated *Candida* species in the clinical setting [54].

The *Candida albicans* complex includes *C. albicans*, *C. dubliniensis*, *C. stellatoidea*, and *C. africana*, the latter being mentioned as an important emerging agent of vulvovaginal candidiasis (VVC) [55]. This complex is the most frequently isolated from clinical samples, as reported by Ortiz, however, cryptic species within this complex, such as *C. dubliniensis* and *C. africana*, are routinely misidentified or not identified [56].

Although superficial infections caused by *C. albicans* are not fatal, systemic yeast infections can lead to a mortality of 50% and it remains the main agent of nosocomial fungal infections [1]. The species remains widely accepted as the most pathogenic species of the genus with an increasing frequency of antifungal resistance worldwide [8,57,58].

C. albicans is a species of yeast, within the CTG clade that includes about 80 species that have a particular genetic code, grouped in this clade for being able to change the translation of the CUG codon, which traditionally encodes the amino acid leucine by a serine [59].

C. albicans is highly structured with compounds of various types of cellular structures wrapped in an extracellular matrix (Rlm1 and Zap1), producing biofilm, which acts as a physical barrier to drug penetration. A study reported that the treatment of biofilms with DNAse increases the activity of the drugs echinocandin (caspofungin) and polyene (amphotericin B) in the interruption of biofilms of *C. albicans* [60].

In hospitals, this yeast represents 39% of all sepsis cases, being the fourth most frequent cause of bloodstream infections in clinical settings, and biofilm formation by *C. albicans* can occur in a wide range of conditions and those genetic requirements likely vary from one condition to another [52,61,62].

This fungal species is predominant isolate from medical devices (urinary and central venous catheters, pacemakers, mechanical heart valves, joint prostheses, contact lenses, and dentures) which are structures susceptible to biofilm formation by this species, which spreads the infection and consequently leads to an invasive systemic infection to others tissues and organs [5,6,52,58]. And the production of an α-helical 31 amino acid peptide toxin cytolytic, Candidalisin, is released during hyphae formation, contributing to virulence during mucosal infections [63].

According to Ramage, *C. albicans* is not the only fungal species that can form biofilms in a mammalian host [59]. The closely related species *C. dubliniensis*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* have all been implicated in biofilm-associated infections. Although it is known that *C. albicans* is the fungal pathogen most frequently isolated from human infections, it is also the microorganism most commonly detected in association with bacteria [25]. Other *Candida* species were found together with *C. albicans* in polymicrobial biofilms from patients. These species include *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis*, *C.* guillermondii, *C. krusei*, and *C. glabrata* [59].

This pathogenic yeast-like specimen is a common cause of fungal infections in humans, and there is no great resistance to the antifungal drugs fluconazole, amphotericin B, and caspofungin, which are used in its therapy. However, repeated and prolonged use of fluconazole by patients with compromised immune systems can develop antifungal resistance [64]. *C. albicans* resistance can occur through several mechanisms, such as mutation and mitotic recombination, with the formation of antifungal target components with lower binding affinity to it, by overexpression of efflux pumps and biofilm formation [65].

In *C. albicans*, two major classes of efflux pumps modulate drug export: the ATP-binding cassette transporters superfamily (including CDR1, CDR2,) and the class of major facilitators (including MDR1) and enzyme expression (ERG11) [59,64].

Candida stellatoidea: Historical records indicate that *Candida stellatoidea* is classically distinguished from *C. albicans* by its ability to assimilate sucrose and that this *Candida* species probably resulted from a mutation in the sucrose gene of *C. albicans* [66].

Many authors consider *C. stellatoidea* as a synonym of *C. albicans*, or even a variation within the *C. albicans* complex (*Candida albicans* var. *stellatoidea* - *C.*P. Jones & D.S. Martin) (Diddens & Lodder, 1942), and some studies show that *C. stellatoidea* is divided into two karyotypes (types I and II) and the yeast has mannan production. Furthermore, studies by Biswas indicate that *C. albicans* differs from *C. stellatoidea* by only three nucleotides and one amino acid in the cytochrome b gene sequence [67].

Serotype I, is considered by some authors to be the actual species *C. stellatoidea*. Serotype II is considered just a mutant from *C. albicans* because is sucrose-negative. There are authors who do not agree with the species status for *C. stellatoidea*, because in their studies this difference would be in only two base pairs [66,67].

More recently, UK researchers put an end to the controversy and confirmed that *C. stellatoidea* is a synonym of *C. albicans*, however, there is a marked genetic difference between isolates of *C. stellatoidea* type I and other *C. albicans* detected by the multilocus sequence typing (MLST) [68].

Candida dubliniensis: *Candida dubliniensis*, (identified in 1995 in Dublin, Ireland) was recognized as a new species whose morphological and biochemical characteristics are very similar to *C. albicans*, requiring the use of molecular methods to differentiate them.

In 1995, in Ireland, *Candida dubliniensis* was described, as predominantly associated with cases of candidiasis or being associated with oropharyngeal infections in HIV-positive individuals and diabetic patients. Although usually identified as a commensal in the oral cavity of a minority of healthy individuals [69]. Since its discovery, epidemiological analyzes have revealed that *C. dubliniensis* is much less prevalent than *C. albicans*, is comparatively rarely associated with systemic infection, and is considered less pathogenic than *C. albicans* which presents a variety of infection models [70].

The fungus reproduces optimally at 30-37°C, but not above 42°C. As *Candida dubliniensis*, no growth will occur in the prepared culture medium. *C. dubliniensis* usually has a diploid set of chromosomes, in which each chromosome appears twice, but the fungus can temporarily assume a haploid form. *C. dubliniensis* and *C. albicans* develop different colors in special culture media however, this process is not an easy task for human eyes, little trained [54,70]. Thus, the distinction between the two microorganisms, by biochemical techniques, is not successful.

Despite epidemiological variations, this yeast has presented itself as an important form due to its ubiquitous distribution and association with the development of mucosal candidiasis, especially in the oral mucosa, being an important pathogen in oropharyngeal candidiasis in HIV-positive individuals, and, more rarely, in systemic infections. *C. dubliniensis* is more likely to develop resistance to azoles, especially fluconazole [59].

Studies report that the vast majority of clinical isolates of *C. dubliniensis* seem to be susceptible to various antifungals such as voriconazole, fluconazole, itraconazole, amphotericin B, and 5-flucytosine [8,57]. Sullivan verified the development of resistance to azole components, in *C. dubliniensis* isolates, and observed that the CdCR1 and CdMDR1 genes, homologous to the CDR1 and MDR1 genes existing in *C. albicans*, would be responsible for the formation of efflux pumps of drugs in the yeast species [70].

Candida Africana: It was first described in 1993 as an atypical strain of *Candida* in patients from Madagascar, Angola, and Germany. *Candida africana* was previously proposed as a new species within the *Candida albicans* species complex, along with *C. albicans* and *C. dubliniensis.* This yeast was first described in 1995, as part of a study on the epidemiology of sexually transmitted diseases among prostitutes in Madagascar, as an atypical, chlamydospore-negative, germ-tube-producing strain of *Candida albicans*, and later proposed as a new species of *Candida* based on morphological, biochemical, and physiological characteristics [71,72].

Reports by Borman find that *C. africana* can be distinguished from *C. albicans* and *C. dubliniensis* by pyrosequencing a small region of ITS2, and reports indicate that *C. africana* has been isolated exclusively from genital regions in women [73]. Studies related that vaginal candidiasis in Iran identified as susceptible to azoles and echinocandins and resistant to azoles (clotrimazole, fluconazole, and itraconazole) were *C. Africana* [74,75]. The results of the susceptibility tests, carried out by Farahyar revealed that one isolate of *C. africana* was resistant to both clotrimazole and fluconazole and another had reduced susceptibility to itraconazole [55].

Two decades ago, *Candida africana* was proposed as a new species within the *Candida albicans* species comp lex, and since then it has raised a lot of controversy regarding its taxonomic status and its phylogenetic relationship with other *Candida* species, its status is still controversial, and remains, currently under debate.

***Candida tropicalis* (Castellani):** *Candida tropicalis* is a clinically relevant species that represents the second or third etiologic agent of candidemia, mainly in tropical regions. Virulence studies show experimental evidence that *C. tropicalis* is possibly the most pathogenic and virulent species among non-albicans *Candida* (NAC) and is closely associated with high mortality rates and associated with superficial, mucosal, invasive, and disseminated clinical manifestations [76]. It is considered the most frequently reported Candida species in India, the second most common species in Latin America, including Brazil and the third most common species in China, demonstrating its emerging nature [57].

With this, among the species of the genus *Candida*, *C. tropicalis* can be considered the second most clinically important species in tropical countries.

Candida tropicalis, phenotypically presents as a negative germ tube, does not produce chlamydospores, is a diploid yeast, which was believed to be just asexual, induced to undergo a parasexual cycle, which can oscillate between a yeast-like and filamentous morphological state (switching phenotypic), favoring the yeast adaptation to hostile environments. This alternation allows the species to have adaptive competence to survive the variations that occur in a host's microenvironments [77,78]. The species is also considered an important pathogen in animals and can be isolated from several veterinary sources such as swine, goats, sheep, horses, psittaciformes, rheiformes, sirenians, cetaceans, and decapods [79].

Favero report that in *C. tropicalis* isolates, one of the main ways of obtaining iron is related to the production and secretion of a cell wall mannoprotein called β-hemolysin, which can lyse erythrocytes and acquire iron from the heme group of hemoglobin [80].

Reports of studies indicate that *C. tropicalis* incorporates the constant development of resistance mechanisms to available pharmacotherapeutics. These studies report an exponential increase in resistance to amphotericin B and, in most cases, to azoles, especially fluconazole. Resistance to azoles occurs through mechanisms such as increased levels of the enzyme 14 α-lanosterol demethylases (Erg11p), a product of the ERG11 gene; upregulation of MDR1 and CDR1 genes that control drug efflux; alterations in the synthesis of sterols and decrease in the affinity of azoles for the cellular target and alterations in the biosynthesis of ergosterol mediated by the genes ERG3, ERG6 and ERG11, which enables the eukaryotic yeast to present resistance to the class of polyenes, such as amphotericin B, which is the third most applied antifungal in clinical practice, making this fact a matter of concern for clinical practice [6,77,81-83].

***Candida parapsilosis* (Ashford):** First isolated in 1928, studies on *C. parapsilosis* (*C. parapsilosis* stricto sensu) began in Puerto Rico, when Ashford isolated this yeast in the diarrheal feces of an unidentified patient, being classified as a species of *Monilia* incapable of fermenting maltose. Despite being considered a non-pathogenic agent, this species was later identified as the agent of a fatal case of endocarditis in an intravenous drug user, in 1940 [84]. Like the other species of the genus Candida, which are considered to participate in the microbiota of the epidermis, *Candida parapsilosis* is quite

common when it comes to skin isolations [85].

Because it is commonly found on the surface of the skin, *C. parapsilosis* presents better adhesion to materials such as acrylic in solutions containing glucose and parenteral nutrition solutions, and this species can be easily transmitted by the exogenous introduction of the pathogen from the environment, in current infections (ICS) caused in infants and neonates [86,87].

It is one of the species identified as causing nosocomial outbreaks, mainly among pediatric patients, with 1/3 of HF episodes in newborns caused in the USA and Australia [85]. Hospital outbreaks caused by this yeast were frequently described and were cited as the main sources of exogenous infection such as the hands of health professionals, infusions, biomaterials, infused solutions, vascular catheters, prosthesis implants [88,89].

Advances in the studies of *C. parapsilosis* allowed the separation of this species into three morphologically and physiologically indistinguishable groups until 2005. Studies based on genetic characteristics revealed that there were hidden characteristics of genetically distinct cryptic species in this species and allowed the classification by separating them. into distinct species closely related and named in *C. parapsilosis* stricto sensu, *C. orthopsilosis*, and *C. metapsilosis*. *C. parapsilosis* can produce pseudohyphae, also present in *C. orthopsilosis*, but absent in *C. metapsilosis*, a characteristic related to cell wall proteins [90].

Candida parapsilosis (*sensu stricto*) remains the main species of the complex, being the most isolated in infections. It is considered the second most isolated species in samples of candidemia in many regions of the world. This increase in the incidence of isolates has been explained, in part, by its considerable capacity to form biofilms and, therefore, its high affinity with intravascular and parenteral nutrition devices [91].

The agent is likely to be eliminated by common antifungal agents, because this fungal entity has resistance to fluconazole, amphotericin B and echinocandins, which is almost 3% for each drug presented [92].

Candida orthopsilosis: Formerly known as *C. parapsilosis* group II, *C. orthopsilosis* is morphologically indistinguishable from *C. parapsilosis* and *C. metapsilosis* [90]. *Candida orthopsilosis* is closely related to the pathogenic fungus *Candida parapsilosis*. However, while *C. parapsilosis* is the main cause of disease in immunosuppressed individuals and premature newborns, *C. orthopsilosis* is more rarely associated with infection [93]. According to reports in the literature, *C. orthopsilosis* can be considered an important causal agent of hospital outbreaks in patients over 60 years of age [91].

Candida metapsilosis: Formerly known as *C. parapsilosis* group III, *C. metapsilosis* is morphologically indistinguishable from *C. parapsilosis* and *C. orthopsilosis*. *C. metapsilosis* is a highly heterozygous diploid hybrid species, which indicates that its parent species were not pathogenic, and by sexual reproduction, a new opportunistic pathogen has been generated that spread worldwide [89]. *C. metapsilosis* is considered by researchers to be an undiagnosed species in adult patients with candidemia, only in the pediatric population [88].

***Candida glabrata* (Anderson):** *Candida glabrata* was first named *Cryptococcus glabrata* by Anderson in 1917. In 1938, Lodder and de Vries named it *Torulopsis glabrata*. The genus *Torulopsis* was described in 1894, while the genus *Candida* was only named in 1913, due to the lack of pseudohyphae production, *C. glabrata* was originally placed in the genus *Torulopsis* [51].

Until recently, *Candida glabrata* was considered a relatively non-pathogenic commensal fungal organism of human mucosal tissues, and more recently it is occupying the second or third place as an agent causing superficial (oral, esophageal, vaginal, or urinary) or systemic infections by candidiasis, which are often nosocomial [94].

Phenotypically, *C. glabrata* forms shiny, smooth, cream-colored colonies that are relatively indistinguishable from other *Candida* species, except for the relative size, which is quite small, has a haploid genotype, is non-dimorphic, has small blastoconidia, and does not form pseudo- hyphae at temperatures above 37°C, therefore, to colonize or cause infections, a breach in the host's natural barriers is necessary [51].

For this artifice, this yeast-like species needs all the virulence related to hyphal formation and phenotypic change, unlike *C. albicans*. This pathogen uses stealth and evasion of host defenses for its persistence, promoting a slowly evolving disease. High stress tolerance and rapid environmental adaptation also aid in its pathogenesis [95].

Candida glabrata is a species, which lies well outside the CTG clade, forming thin biofilms in vitro (without hyphal cells) on biotic and abiotic surfaces associated with the human host [59]. The cells of this species are ovoid and are characterized by not producing pseudohyphae. This yeast-like species is resistant to azoles [9,96].

Candida bracarensis: *Candida bracarensis* had its first isolated reports of vulvovaginal candidiasis in the United

Kingdom and Portugal in 2006 [97].

The knowledge of new yeast species to the phylogenetic clade of taxonomic groups represents the importance and a great impact on human health since modern medical therapy and improved methods to detect and differentiate yeasts have shown that many new and uncommon species have become clinically important.

Similar to other *Candida* yeast species; *C. bracarensis* was recovered from various body sites, especially mucosal surfaces (blood, abscess, vaginal cavity, throat, sputum) is associated with infection and colonization [91,97].

Candida nivariensis: The first isolates of *C. nivariensis* were reported in the Canary Islands in 2005, related to a lung abscess, blood, and urine [98]. Since then, specimens have been isolated from bloodstream infections around the world.

After being described in 2005, and verifying its genetic relationship with *C. glabrata, C. nivariensis,* was isolated in cases in a Spanish hospital for a period of 3 years, being suggested as a new opportunistic pathogen [98]. Before its description, Lachance, analyzing the strain isolated from flowers in Canada, suggested that *C. nivariensis* infections, which occurred in hospital patients in Spain, could have been acquired from environmental sources, where there were potted plants, associated the description with the environmental flats [99]. Thus, it was proposed that *C. nivariensis* be considered a clinically important emerging pathogenic yeast.

***Candida guilliermondii* (Castell.):** Currently, this yeast has received a new name in its teleomorphic state *Meyerozyma guilliermondii* (Wick.). Kurtzman & M. Suzuki 2010*,* basionymy *Pichia guilliermondii* Wick*.,* 1966. Many lineages of *C. guilliermondii* present characteristics similar morphologically and biochemically to *C. famata* and methods based on molecular biology are used to distinguish the two species [100,101].

However, molecular analysis of the genomic DNA allows the differentiation of 7 distinct species in this complex: *C. guilliermondii* stricto sensu (teleomorph *Meyerozyma guilliermondii*), *C. fermentati* (teleomorph *Meyerozyma carribicca*), *C. xestobii, C. smithsonii, C. athensensis, C. elateridarum, C. carpophila*, and *C. glucosophila*. So far, only three species of the complex have been associated with infections in humans: *C. guilliermondii*, *C. fermentati e C. carpophil* [100,101].

Meyerozyma guilliermondii is commonly isolated from clinical specimens such as sputum, wounds, and blood. For this reason, this species and its anamorphic state *Candida guilliermondii* are listed among the 15 yeasts most commonly related to human disease and are responsible for conditions such as otitis, endocarditis, and joint infections. Invasive infections by *C. guilliermondii* are still considered infrequent and have been described as an emerging agent, especially in cancer patients. As with *C. lusitaniae*, there are reports of in vitro resistance to amphotericin B, as well as a description of poor clinical response in patients treated with polyenes [89].

In addition to its presence in healthy humans, *M. guilliermondii* is a widely studied microorganism, being described in clinical and environmental samples, being a species of clinical importance, and being used in biotechnological applications and potential for biological control [102]. In 2022, Pinto, in research carried out in Rio de Janeiro/Brazil, isolated the etiological agent in breast infection, isolated from the milk of a puerperal woman with mastitis [103].

Candida haemulonii: *Candida haemulonii* is a species well associated with animals. It was first isolated in 1962 from the intestine of trematode fish (*Haemulon scirus*) [104]. After records of this fungal entity isolated from seawater and dolphin skin in Portugal from mites (*Ornithodoros moubata*) in the Czech Republic and marine cnidarians (*Palythoa caribaeorum*, *Palythoa variabilis*, and *Zoanthus sociatus*) collected in Brazilian coral reefs. Records of the first human clinical isolate of this species were described in 1984, collected from the blood of a patient with renal failure, and, since then, isolates of *C. haemulonii* have been regularly reported in patients causing wounds and other types of infections [105].

Candida haemulonii emerged as an opportunistic pathogenic fungus associated with nail infections, onychomycosis, paronychia, vaginal candidiasis, blood infections, and several fungemia related to catheters, osteitis, and outbreaks in ICUs; considered resistant to amphotericin B, low susceptibility to azoles (fluconazole, itraconazole, voriconazole), caspofungin and 5-flucytosine), resulting in difficulty in treating deep infections.

More recently, *C. pseudohaemulonii* and *C. duobushaemulonii* were identified in 2006 and 2012, respectively, as distinct lineages within the *C. haemulonii* species complex based on phylogenetic analyzes of the intragenic spacer region of rDNA (ITS) [105].

Finally, in 2016, *C. vulturna* was identified as a distinct species most closely related to *C. duobushaemulonii* based on phylogenetic analysis of the rDNA locus. The first isolate of this species was isolated from flowers in the Philippines and later isolated as a cause of human candidemia [106].

Emerging fungal pathogens comprising the *C. haemulonii* complex and the recent emergence of a multidrug-resistant yeast, *Candida auris*, have drawn attention to the closely related species of the *Candida haemulonii* complex that include *C. haemulonii*, *C. duobushaemulonii*, *C. pseudohaemulonii*, *C. vulnera* and *C. vulturna* recently identified.

Gade, analyzed, through whole genome sequencing, the multidrug-resistant properties of this group of yeasts, working with samples from Panama, Venezuela, Israel, Guatemala, Colombia, and the United States, demystifying species that were housed in the isolates of these places [47].

Candida kefyr: Currently, this yeast is called *Kluyveromyces marxianus* (E.C. Hansen) Van der Walt, 1971. Previously it was known as *C. pseudotropicalis*. The latter was first isolated from kefir in 1909 and reported under the obsolete name *Saccharomyces fragilis*.

The ecology of this yeast is not fully understood, but it seems to be extremely rare in diseases, but its presence can cause fungemia, esophageal infections in immunosuppressed patients, with hematogenous diseases, leukemias and cancer. It survives in diverse habitats, and thrives very well in industrialized dairy products, natural habitats such as kefir grains, fermented dairy products, industrial sewage and plants [107].

A study carried out in the Middle East, determined the prevalence of *C. kefyr* among yeast isolates collected during 2011-2018 in Kuwait. Antifungal susceptibility testing and genotypic heterogeneity were evaluated [108]. In 69 isolates of *C. kefyr* from the bloodstream, urine and respiratory samples of patients analyzed; some strains showed reduced susceptibility to amphotericin B and one isolate to all antifungals (amphotericin B, fluconazole, voriconazole, caspofungin and micafungin) tested with isolates with synonymous mutations in ERG11 and FKS1. IGS1 sequencing identified seven haplotypes among 27 selected isolates.

C. kefyr is an emerging pathogen among patients with hematologic malignancies. Dufresne, studied colonization and infection by *C. kefyr* in patients with hematological malignancies over a period of six years and found that 83 patients were colonized and/or infected by *C. kefyr* presenting with invasive candidiasis [109].

Candida krusei: Currently, this yeast is called *Pichia kudriavzevii* Boidin, Pignal & Besson, 1965. It has phenotypic characteristics of forming pseudohyphae with elongated blastoconidia, giving the appearance of crossed matchsticks or trees, a species also known as *Issachenkia orientalis* [110].

Candida krusei also appears as an occasional hospital pathogen, occurring mainly in patients with hematological malignancies, bone marrow transplant recipients, prolonged neutropenia, and patients previously exposed to azoles, since this species is intrinsically resistant to fluconazole.

Candida krusei form pseudohyphae with elongated blastoconidia, giving the appearance of crossed matchsticks or trees. This fluconazole resistant yeast due to decreased 14α-desmethylase susceptibility and yet there is an energy-dependent efflux mechanism. Reduced affinity for ERG11 and ABC1 underexpression lead to azole resistance, although it varies by drug and site. *Candida krusei* and *C. glabrata* infections can cause serious complications, as they have higher crude mortality than other Candida species, such as *C. albicans* or *C. parapsilosis* [62].

Candida inconspicua: *Candida inconspicua* was first described as *Torulopsis inconspicua* in Lodder and Kreger-van Rij (1952) and later reclassified as Candida (Yarrow and Meyer, 1978). Currently this eukaryotic specimen was named *Pichia cactophila* (Starmer, Phaff, M. Miranda & M.W. Mill. 1978).

Many studies maintain that *C. inconspicua* can often be found in dairy products, including milk, cheese, or butter [12]. *C. inconspicua* s reported in immunosuppressed patients with viral infections, oral or esophageal infections, vaginal infections, and in patients with diabetes mellitus, osteomyelitis, oropharyngeal and esophageal candidiasis in HIV-positive patients, as well as candidemia in patients with hematologic malignancies [8].

C. inconspicua, was tested on fluconazole, amphotericin B, fluorocytosine, and caspofungin by different methods. For fluconazole, a high susceptibility to the different methods used was observed [56]. This researcher, depending on the isolation site, the frequency of fluconazole-resistant strains can vary between 26.1% (skin and soft tissues) and 62.9% (genital tract), indicating a high phenotypic heterogeneity among *C. inconspicua* isolates.

Candida ciferrii: This yeast is called *C. ciferrii, Stephanoascus ciferii* and *Trichomonascus ciferrii* (M. Th. Smith, van der Walt & E. Johannsen) (Kurtzman & Robnett, 2007).

This yeast is considered rare in human clinical isolation, *C. ciferrii* can be isolated from soil and animals, and the first description of this yeast was made in 1965. This yeast assimilates inositol almost exclusively. In humans, cases of onychomycosis, candidemia, infections in immunocompromised patients, and a disseminated form in a patient with acute myeloid leukemia have already been described. Case reports demonstrate that *C. ciferrii* is resistant to fluconazole [111,112].

By sequencing the 18S rRNA gene, they divided *S. ciferrii* into three groups and proposed the *S. ciferrii* complex, which consists of *Stephonoascus ciferrii, Candida allociferrii* e Candida mucifera [113].

***Candida famata*:** Currently, this yeast is called *Debaryomyces hansenii* or *Torulopsis candida*. It is a *hemiascomycete* yeast commonly found in natural substrates and usually found in some foods, including dairy products. *C. famata* is an opportunistic pathogen that inhabits the human oral cavity as a commensal [114].

Candida famata was previously considered a non-pathogenic yeast to man, however, clinical cases of this yeast have been reported as onychomycosis, fungemia, alveolitis, peritonitis, endophthalmitis (retinopathies), infections in the mediastinum and central nervous system Isolates collected worldwide show that *D. hansenii* (*C. famata*) is responsible for 0.08 to 0.5% of the isolates recovered during invasive candidiasis. *C. famata* is a rare cause of invasive candidiasis that showed reduced susceptibility to echinocandins and azoles, potentially in the context of previous exposure to antifungals [8,56].

***Candida lusitaniae*:** Currently, this yeast is called *Clavispora lusitaniae* Rodr. Mir., 1979. Species isolated for the first time in Portugal from the alimentary canals of blooded animals. Recognized since the 1980s as an opportunistic species, found in blood, urine, and respiratory tract, it differs in its ability to ferment cellobiose and assimilate rhamnose. *C. lusitaniae* is generally a low-virulence yeast and may be resistant to amphotericin B and sensitive to triazoles [110].

Candida lusitaniae is an infrequent yeast as a causative agent of invasive disease, but it has been reported as an agent of candidemia in immunocompromised patients, mainly cancer patients, however, it is an uncommon yeast in the hospital environment, and the reported cases occur more in patients immunocompromised by malignant neoplasms. Characteristically, this Candida species is naturally resistant to amphotericin B or acquires it quickly, but they are sensitive to triazoles [89].

In 2012, Tragiannidis associated this species with hematological malignancies and cancer patients undergoing chemotherapy, reporting that invasive *C. lusitaniae* infections were also reported in the pediatric population, constituting 4-7% of all cases of candidemia [115]. Unlike adults, the risk factors for HF by the yeast species among pediatric patients were indwelling venous catheter, broad-spectrum antibiotics, and immunocompromised status.

***Candida lipolytica*:** Currently, this yeast is called *Yarrowia lipolytica*. *C. lipolytica* is a ubiquitous organism, it has been isolated from refrigerated meats, petroleum derivatives, agricultural materials, plants, and soil, and it is not a frequent agent of opportunistic infection. *C. lipolytica* can cause catheter-associated candidemia, due to its power to produce viscosity and better adhesion, it has even less virulence, which can generate asymptomatic infections, and the pathogen is already found in the oral cavity, lungs (bronchial secretion), urine, in the esophagus, in the female genital tract, and the intestines. Previous studies show that *C. lipolytica* is susceptible to amphotericin B and azole derivatives [116].

***Candida viswanathi*:** Considered a rare pathogen, was first isolated from the cerebrospinal fluid of immunosuppressed patients and in a patient with meningitis in 1959, but despite this, this species is more commonly found in animals and environmental sources and in a few reports of clinical manifestations [117].

The species was re-isolated in 1962 from sputum by Sandhu and Randhawa, who provided a detailed description of the fungus isolated from a sputum sample, including the Latin diagnosis and validated its taxonomic nomenclature [118]. Despite being a rarely reported species as a cause of candidemia; *C. viswanathii* gained importance and prominence after 23 cases of Bloodstream Infections, reported between 2013–2015 in a tertiary hospital in Chandigarh, India with strains resistant to fluconazole [119].

Candida viswanathii is a fungus that efficiently produces long-chain dicarboxylic acids, which are useful in petrochemical and biodiesel production, is then found in places enriched with petroleum hydrocarbons, used in biotechnological applications, such as the production of reductase, lipase, enzymes, biodegradation of petroleum and biodiesel, the production of polyunsaturated fatty acids. And it is closely related to *Candida tropicalis*, a prominent human fungal pathogen [120].

***Candida utilis*:** Currently, this yeast is called *Cyberlindnera jadinii* (Sartory, R. Sartory, Weill & J. Mey.). Studies carried out by Czech researchers detected a species *Candida fabianii*, synonymous with *Cyberlindnera fabianii* (Wick.) Minter 2009; Studies carried out by Czech researchers, detected *Candida fabianii*, synonymous with *Cyberlindnera fabianii* (Wick.) Minter 2009; erroneously described *C. pelliculosa* and *C. utilis*, in clinical samples after identification in MALDI-TOF, and will describe that after observations, *C. fabianii* appears to be a significantly important emerging yeast species, with the same frequency *as C. lusitaniae* and *C. guilliermondii* [121].

In 2019, Park, in Korea, isolated the clinical specimen in urine samples, identifying the same problem of identification of the fungal specimen [122].

***Candida pelliculosa*:** *Candida pelliculosa,* also known as *Pichia anomala* (E. *C.* Hansen) Kurtzman 1984 or *Hansenula anomala* (Hansen) H. and P. Sydow. This yeast was recently renamed to *Wickerhamomyces anomalus* (E.*C.* Hansen) Kurtzman, Robnett & Basehoar-Powers, 2008 [12]. In 1965 it was renamed *Candida beverwijkiae* E.K. Novák & Vitéz, however, current medical literature prefers the 1925 name of *C. pelliculosa*, as all current case reports and outbreak reports are listed under this nomenclature.

It is a species of environmental fungus often isolated from soil, plants, fruits, or organic compounds, as it is an ecological fungal species, it can cause infections in immunocompromised individuals.

Studies show that *C. pelliculosa* infects newborns. Clinical analyzes reveal that infants, children, and individuals with compromised immune systems, including those in hematologic disease units, surgical ICUs, and neonatal intensive care units, are more susceptible to *C. pelliculosa* bloodstream infections that often lead to high morbidity and mortality [123].

The information describes that the biofilm of *C. pelliculosa* consists mainly of yeast cells; however, very little is known about the molecular nature of its biofilm formation process [121].

Candida norvegensis: Currently, this yeast is called Pichia *norvegensis* Leask & Yarrow, 1976. *Candida norvegensis* has been an uncommon cause of infection in humans. It was first isolated in Norway from the sputum of three patients with asthma almost 60 years ago [124].

Candida norvegensis is an emerging fluconazole-resistant pathogen isolated in most cases from the skin and mucous membranes of immunocompromised patients. *Candida inconspicua* e *Candida norvegensis* are two closely related species rarely involved in invasive infections. They belong to emerging species less susceptible to fluconazole and seem to be more frequently isolated from human samples [57].

Wicherhamomyces anomalus has become an agent of concern as several large outbreaks in neonatal wards have been reported worldwide in the past 5 years [125]. A study in northern India in 2001 reported that 379 newborns and children with low birth weight and prolonged hospitalization, developed fungemia due to *C. pelliculosa* in an outbreak that lasted for 23 months [126]. The outbreak possibly occurred from the contaminated hands of a healthcare worker. Adhering to strict hand hygiene practices and contact precautions is key to preventing such outbreaks [127].

Invasive candidiasis documented by *C. norvegensis* has been rarely reported, therefore, the clinical characteristics of patients at risk for this pathogen are poorly defined. This species is isolated in most cases from the upper respiratory tract and wound specimens [124,128].

***Candida rugosa*:** Currently, this yeast is called *Diutina rugosa* (H. W. Anderson) Khunnamwong, Jindamorakot, Limtong & Lachance, it has also been called *Candida cylindracea* Koichi Yamada & Machida ex S. A. Mey. & Yarrow 1998.

Candida rugosa, although it is a rare pathogen to cause invasive fungal infection, it is observed as a possible emerging fungal entity. Fungemia due to this *Candida* species was recognized before 1985. *C. rugosa* frequently colonizes high-risk patients and exhibits reduced sensitivity to polyenes and fluconazole, which can be transmitted from person to person in a hospital environment and are endemic at certain institutions. This yeast is a versatile biocatalyst and applies to a variety of biotechnologies in the pharmaceutical and food industries, as flavoring agents [129].

***Candida auris*:** This important yeast has emerged as a global pathogen in the last decade, *Candida auris* was isolated for the first time in Japan in 2009 from the external auditory canal of a patient, simultaneously other records of 15 cases of infection in the ear canal, have been recorded in South Korea [104,130]. In the same year, Lee and their collaborators recorded the first cases of this yeast in cases of nosocomial fungemia [131].

In Brazil, first positive case in a patient admitted to the ICU, a catheter tip sample from a patient admitted to the ICU of a hospital in Salvador/BA, in an outbreak of 15 cases. The second outbreak, also occurred in a urine sample in Salvador/BA, in total there were 16 outbreaks in this region of Bahia/Brazil with two deaths [132,133]. A third outbreak with notifications referring to two possible cases of Candida auris in patients admitted to a hospital in Pernambuco/ Brazil [132,133]. In the period between november 2021 and february 2022, the capital of Pernambuco, Recife, 48 cases of yeast infection were recorded. The State of São Paulo confirmed the first case of contamination by *Candida auris*, bringing concern to public health entities.

There have been reports on all continents except Antarctica, with most cases associated with ICU outbreaks and high mortality rates and hospital outbreaks with clonal isolates [134,135].

The enigma involving *Candida auris*, perhaps, lies in the simultaneous emergence of genetically different clonal populations, involving three continents, which has sharpened the interest of researchers in its multiple distinct clades

(South Asia (Clade I), East Asia (Clade II), African continent (Clade III) and South American (Clade IV) and more recently the emergence of a fifth clade (Clade V), isolated from the swab of the ear canal of an Iranian patient, was proposed by Chow [136,137].

The simultaneous emergence of genetically unrelated clades of this organism has sparked thoughts on how this drug-resistant yeast originally manifested, with theories about its emergence only recently being proposed, linked to some new biological traits [138]. Casadevall hypothesized that environmental climate changes caused by human action and intervention led to the selection of thermally tolerant fungal species that can breach the protective thermal restriction zone (Figure 2) [138].

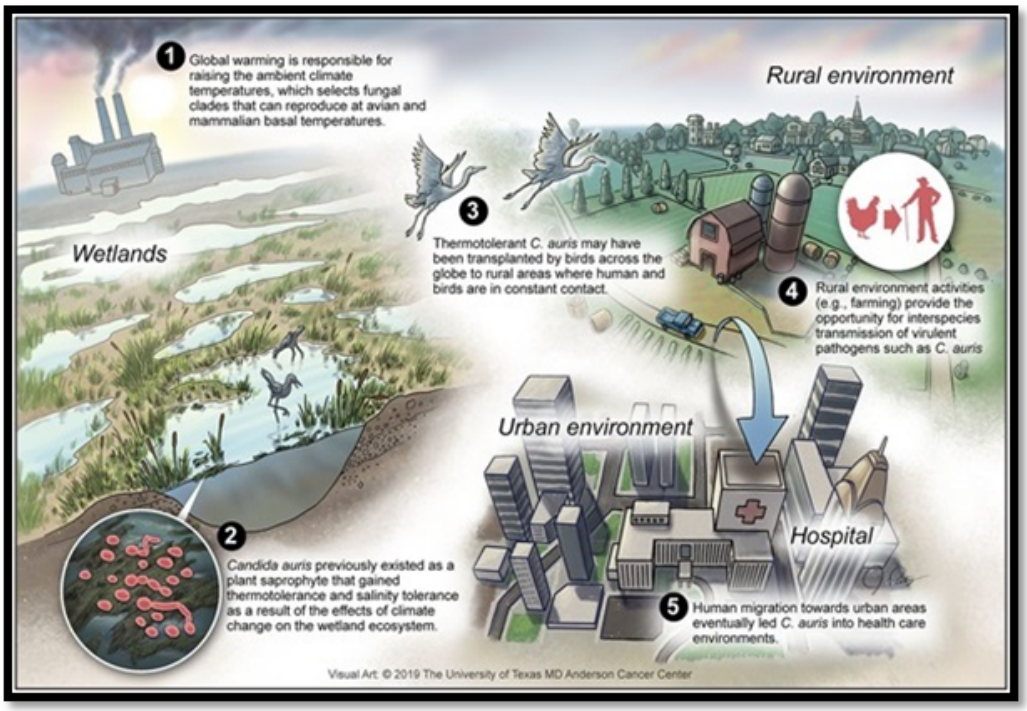

Figure 2: Schematic representation of the appearance of *Candida auris* [138].

The ability of this yeast to survive the typically unfavorable conditions to which many microorganisms do not survive, such as adaptation to environmental responses, tolerance to high temperatures, salinity, virulence, and resistance to multiple drugs, are the primary factors that may allow the survival of this yeast e in hostile environments.

If these factors related to the existence of this new human pathogen, within this theory proposed by Casadevall for its emergence are correct, it emerged with the help and interference of man, causing it to become yeast that demonstrates characteristics pathogens of a successful pathogen, and a phenotype promoted by high temperatures [138].

Incredibly among *Candida* species, the high transmissibility of this pathogen is highlighted in hospital outbreaks with clonal isolates, resulting in the closure of intensive care units [135]. Sanyaolu point out that this eukaryotic agent behaves more like a bacterium than a yeast and that its pathogenic attributes include easily transmissible, causes severe infection and high mortality 67%, contaminates the environment quickly, is not easily identified, a pathogen that is resilient to disinfectants and desiccation and develops resistance very quickly [139].

C. auris spreads easily, persisting on surfaces and medical-hospital environments, remaining for a long period, and also facilitated by person-to-person contact, showing a high capacity to be potentially influenced by the ability of yeast to produce genes involved in biofilm formation [140].

Some strains of *C. auris* are resistant to all three major classes of antifungal drugs and their identification require specific laboratory methods. *C. auris* is generally intrinsically resistant to fluconazole with variable resistance to echinocandins and polyenes, with reports of isolates reported as multidrug-resistant and with strains that are pan-

resistant to azoles, polyenes, and echinocandins [134,136].

***Candida blankie*:** The genus Candida has several known species that can become pathogenic in certain situations. *Candida blankii* is a pathogenic fungus, first identified in 1968, isolated from a mink in Canada; currently being considered a newly recognized emerging species that, in the last decade, has been identified as an agent of systemic diseases. There is still no specific treatment protocol, although in the few cases reported in the literature, the adopted therapy was effective [141].

A case report involving an immunocompromised adult patient with *C. blankii* endocarditis. Treatment of candidiasis caused by this opportunistic pathogen has been successful using a combination of polyene and echinocandins [142].

Vietnamese researchers evaluated the biodiversity of marine ecosystems, on the coastlines of Vietnam, and isolated this species considered the most abundant in marine habitats and which was not considered a pathogenic specimen [143]. *C. blankii* is not a regular component of the human skin/mucosa microbiota and is less virulent than C. albicans. In 2015, reports of an outbreak in a hospital in India were documented, involving *C. blankii* in bloodstream infections (BSI) leading to newborn deaths due to multidrug-resistant candidemia [144].

Results

A total of 285 references addressing infections related to yeasts of the genus Candida and the infections produced by this eukaryotic agent, involving: Candidemia/fungemia (56.9%), vaginal candidiasis (11%), Oral candidiasis (7.3%) with tumors and neoplasms, Candiduria (10.1%), endogenous fungal endophytalmitis and ocular candidiasis (5.5%) in addition to other diverse superficial manifestations (9.2%). In the ranking of prevalent species, 107 species were highlighted in the records found, with the species *C. albicans* (77.8%) as the most prevalent in general infections, receiving the percentage of 41.7% only in bloodstream infections. Followed by *C. parapsilosis* (10.2%), *C. tropicalis* (8.3%) and then *C. glabrata* (2.8%) and *C. africana* (0,9%) with a single record. These sequential orders of prevalence of the species are consistent with the reports of several authors in their series, mentioned above in this review.

Analyzing the 285 references evaluated in this article, the records indicate that the male population (49.6%) were the most affected by infections of this fungal genus presented in the series, involving yeast-like agents, mainly in cases of candidemia. Females followed (25.7%), followed by reports involving children (8.9%) and other unspecified records (15.8%). The information reported in the different series indicates a percentage for publications involving international registries (59.4%) and publications of Brazilian registries (40.6%).

Discussion

The tenuous boundary that differentiates and demarcates the species of microorganisms on the planet is a very controversial subject and for yeasts, it would be no different. Phylogenetic and cladistic analyses, DNA sequencing, and, more recently, the advent of MALDI-TOF, have brought great advances and questions that are constantly being reassessed, in species delimitations, as occurred with *Candida albicans* and *C. dubliniensis* [69,70], *Coccidioides posodasii* and *C. immitis*, or even the genetic diversity between *Cryptococcus neoformans* and *C. gattii* [145,146]. Also, questions about cryptic species such as *C. parapsilosis, C. methapsilosis, C. orthopsilosis* and *Lodderomyces elongisporus* [90,91] e *C. albicans, C. dubliniensis* and *C. africana* [147].

Candida spp. continues to be the predominant cause of invasive fungal infections [6,148]. The genus *Candida* includes about 200 species, but many species are endosymbionts of humans. The main species of clinical interest are *Candida albicans, C. parapsilosis, C. tropicalis, C. glabrata, C. krusei, C. guilliermondii* and *C. lusitaniae.*

However, increasing numbers of cases of related superficial and invasive diseases and emerging *Candida* species have been described, involving isolations of *C. dubliniensis, C. kefyr, C. rugosa, C. famata, C. utilis, C. lipolytica, C. norvegensis, C. inconspicua* and the more recent pathogen *C. auris*.

The genus *Candida* spp. is responsible for about 80% of fungal infections in the hospital environment and is a relevant cause of bloodstream infections, with 40 to 60% of cases of fungemia. This yeast genus can be found living symbiotically in the microbiota of the reproductive and gastrointestinal mucosa of 50-70% of individuals [9,21]. Globally, *Candida* spp. is responsible for 400,000 cases each year and about 90% of AIDS patients suffer from *Candida* infections [149].

The identification of yeasts at the species level is a challenge for clinical microbiologists working in health centers in low-income countries due to the lack of appropriate technologies. Conventional methods based on phenotypic or biochemical characteristics are sometimes insufficient to provide accurate identification of the etiologic agent of infection.

The incidence of invasive fungal infections caused by *Candida* spp. continue to increase, in part due to the increase in the population of immunocompromised patients and

those undergoing invasive procedures [21,150].

The WHO (World Health Organization) recently published a report highlighting actions and strategies aimed at improving the prevention of fungal pathogens that pose threats to public health. The *Candida* genus received prominence, being classified as invasive, resistant, and wide geographic range agents. Among the critical priority group, *C. albicans* and *C. auris* were considered extreme organisms and received prominence due to their high degree of infection; *C. parapsilosis, C. tropicalis*, and *C. glabrata* stand out in the high priority group and, finally, *C. krusei*, tops the list of medium priority pathogen agents [150].

Guinea, emphasizes that *Candida albicans, C. glabrata, C. tropicalis, C. parapsilosis e C. krusei*, are the most frequently isolated species in cases of Candidemia, and that *C. albicans* is more frequent in patients with ages up to 18 years [11]. The frequency of *C. parapsilosis* decreases with age and *C. glabrata* is more common in the elderly; however, its distribution varies in population-based studies carried out in different geographic areas, and is responsible for 11% to 16% of all candidemias.

However, as Toda say the species *Candida albicans, C. parapsilosis, C. tropicalis* e *C. glabrata,* are the four *Candida* species most frequently isolated from cases of *Candida* invasion, results which are similar to those found by Chang [152,153]. Candidemia is a bloodstream infection caused by yeasts of the genus *Candida* spp. is considered the fourth most common microbial infection in hospitalized patients.

A study carried out by Pfaller Pappas and Pal described that only five species of *Candida* were responsible for >90% of candidemia cases worldwide, the species *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis e C. krusei* [9,57,149].

Globally, the frequency of *C. albicans* prevails in clinical research, *C. glabrata* and *C. krusei* are stable in research, but *C. parapsilosis* and *C. tropicalis* increase their frequency of isolation, depending on the region and anatomical sites researched. The challenges for this fungal group include the high variability of clinical manifestations, pathogenic nature, and rapid growth that the genus can present, in addition to the scarcity of controls in diagnostic tests and the use of antifungal drugs, side effects, relapses, recurrences, and complications that arise due to the inadequate control of the variability of the species, thus making it a serious problem for the health service that may not be familiar with the various manifestations of infections that the etiological agent can cause.

C. albicans, even over the years, continues to be the predominant species on both sides of the Atlantic, with infections by this species being recorded with a percentage that varies from approximately 70% in Finland to more than 56% in studies involving countries such as France, Sweden, United Kingdom, Germany and Austria and approximately 50% in the United States and Spain [7,128,154,155].

According to several studies in the USA, Brazil, Europe, Asia, Africa, and Australia, the *Candida albicans* species remains prevalent in various infections, when the etiological agent of the *Candida* genus is identified. Estimates by researchers around the world point to a higher incidence of fungal diseases in the USA than in Europe, with incidence records of reversal in cases [152,156,157]. Most epidemiological data on bloodstream infections caused by *Candida* yeasts (ICS's) are recorded in the Americas, and a large part of studies carried out in the USA [148,152,158-162].

Recent epidemiological studies have reported an increasing incidence of non-albicans candidemia. While *Candida parapsilosis* is the most prevalent non-albicans species in Latin America, Southern Europe and Asia. *Candida glabrata*, which is less susceptible to antifungal drugs, ranks second in the US, northern Europe and Australia [5,58,96]. A SENTRY surveillance study, analyzing information regarding *C. glabrata*, informs that 11% of the strains of this species present mutirresistance to both fluconazole and echinocandin, implying the emergence of this species [5,8,57].

In Brazil, the genus *Candida* was reported as the seventh etiological agent causing blood infections, with *C. albicans* (34.3 %) being the most prevalent species of these infections, followed by *C. parapsilosis* (24.1 %), *C. tropicalis* (15.3%) and *C. glabrata* (10.2%), with a mortality rate of 72.2% [163]. This species ranking is in agreement with the research related in this article and we can observe that in Brazil, *C. albicans* is the most isolated yeast species in blood infections in many regions of the country and even in other regions of the globe [96,163-180]. This fact can be explained due to the high plasticity that this yeast presents in adaptation, adhesion factors, and enormous versatility to environments and even as a human host, where its pathogenic behavior prevails.

However, the bibliographic survey from 2010 onwards shows an alternation between the *C. parapsilosis* species *C. parapsilosis* and *C. tropicalis* showing that *C. parapsilosis* was the second most prevalent species in blood infections, after *C. albicans*, and *C. tropicalis* in the third position [76,171,181-192]. This observation refers to information provided by Menezes who describe that *C. parapsilosis* is the second or third most prevalent species in blood infections and Zhang emphasize the ability of *C. tropicalis* to present a phenotypic mutation, which favors its adaptation to environments,

survives climatic variations and is easy to adapt to human microenvironments [77,184].

Historically, *Candida glabrata* had been considered a relatively non-pathogenic saprophyte of the normal microbiota of healthy individuals, rarely causing infections in humans; however, this yeast species is currently considered the second leading cause of invasive candidiasis in immunosuppressed patients in hospital settings; as reported by a group of jordanian researchers [193]. In research carried out in 22 sentinel hospitals participating in the ARTEMIS project, *C. glabrata* was identified in samples of blood, urine, and body fluids showing resistance to antifungal agents and more frequently in Poland, the Czech Republic, Venezuela and Greece [57]. Prompt species identification and fluconazole susceptibility testing are necessary to optimize therapy for invasive candidiasis.

However, in our records, we can observe, that *C. glabrata* appeared in prevalence, above *C. albicans* only in the records of infections described in candiduria, candidemia and vulvovaginal candidiasis [194-196].

In this review, we can observe that *C. albicans* proved to be the most prevalent etiological agent in different types of environments and infections, being cited as predominant (77.9%) in the studies cataloged in this report, from the year 2000 to the year 2022. Several records of this fungal entity were reported, as prevalent, in collections and causing oral, vaginal, post-COVID infections and mainly blood infections, except for some records in which *Candida parapsilosis* (*sensu stricto*) remained the main isolated species in infections, being considered the second most prevalent species in samples of candidemia in many regions of the world and the third position *C. tropicalis* and three records of *C. glabrata* in cases of candidemia in patients with cancer, vaginal candidiasis and candiduria [171,181-189,191,195-200].

What is observed is that the three most prevalent species in various infections cataloged and distributed across the globe, *C. albicans, C. parapsilosis, and C. tropicalis*, were recorded in this study, having them as etiological agents of infections, in agreement with the data found by several researchers. Currently, the species report, highlighting the fungal genera, shows *C. albicans* and *C. auris* as critical species, which deserve extreme attention [151].

Several microorganisms can cause infections and proliferation in the female genital region, such as *Gardnerella vaginalis, Mobiluncus, Mycoplasma hominis, Staphylococcus,* and *Streptococcus*, including *Candida* yeasts, causing vaginitis or vaginosis. It is estimated that 75% of all women of childbearing age will be afflicted with VVC at least once in their lifetime [36]. About 50% of them will have at least one-second episode and 40-45% of all women will have recurrent vulvovaginal candidiasis, with two or more episodes, ≥4 episodes per year. About 80% to 92% of cases are due to *C. albicans* and 10% to 20% to other species (*C. tropicalis, C. glabrata, C. krusei, C. parapsilosis*) [201,202].

In the United States, vaginosis is currently the most common cause of vaginitis, accounting for 40% to 50% of cases in women of childbearing age. Among women, about 20 to 30% of vaginal infections are colonized by *Candida* [89]. Candidiasis is associated with life stages and is influenced by estrogens, such as childbearing age and pregnancy [55,203,204].

In vaginal infections, the prevalence in Brazil is 18%, and the species *C. albicans* is the most frequent species, the other species account for 80 to 90% of cases [205]. In the records cataloged in this study, we can see that VVC cases were reported in different parts of the world: in Brazil, Malaysia, Austria, Argentina, in Ethiopia, Iran and Algeria with *C. albicans* as the predominant species [165,168,198,201,203,206-214].

In 2001, *C. albicans* isolated from African and German patients with atypical phenotypes were described as a new species, *C. Africana* [147]. Although later phylogenetic analyses better support its status as an uncommon variant within *C. albicans*. This recently described opportunistic yeast has been associated with vaginal candidiasis, with this site being considered a niche pathogen for this genital infection, and more prevalent than the *C. dubliniensis* in genital samples, as previously reported in Berlin and Germany [71,147]. This fact is similar to the findings on the African continent, Nigeria, in suspected vulvovaginitis, in cases of vulvovaginitis in Biscay, in Spain [215,216]. And records of five isolations of *Saccharomycetaceae* isolated from glans infection, causing balanoposthitis, in patients in Shanghai, China [217].

Studies involving genital infections, with recovered *C. africana* as the causative agent of vaginal candidiasis (VVC) and the record of Chinese researchers in samples collected from the penile region, show that this yeast species is not very relevant in the records of genital infections, and in the cited works, *C. albicans* appears as the most prevalent species [74,75,147,211,213-218].

Most cases reported to date are from seven countries in Africa, especially Madagascar and Angola. Because it is closely related to *C. albicans*, and routine phenotypic identification methods often fail to differentiate the species; cases may be underreported [142]. Fakhin reports that identification results for this species may be mistakenly identified as *C. albicans* or *C. dubliniensis* [214].

It is important to emphasize that this disease is usually linked to women, being commonly reported and publicized as a disease that affects only females, through vaginal candidiasis, but can also affect male patients. Genital candidiasis in men is a condition caused by excessive colonization by yeasts of the genus *Candida* in the region of the male genital sphere. The prevalence in men of all ages is between 12 to 20%, which, despite being less common, 90% of cases were by *C. albicans* infections [219]. Findings in Brazil, indicated a high prevalence of infections in the genito-crural region by *C. albicans*, mainly in young men (18-20 years) [220]. Another study carried out in the USA with a prevalence of *C. tropicalis*, having the male military as the target audience, and also a work with genital infection in the male population, causing balanoposthitis isolating *C. africana* [200,217].

Swedish researchers in 2008, conducted research involving balanoposthitis records in 100 patients and 26 patients in the control group. Among patients with balanoposthitis there was a frequency of *Candida albicans* (18%) [221]. In the control group *C. albicans* was found in 7.7% of patients. Aridogan found 65.5% of yeasts of the genus Candida in 245 men [222]. *Candida albicans* was identified as the most common non-lipophilic yeast (46.0%), isolated among the other yeasts colonizing patients in the residual microbiota of the penis.

In previous research carried out by German researchers1, they isolated atypical samples of *C. albicans*, suggesting that the fungal specimens are a variant of the genus, collected from clinical samples of patients with vaginal infections in Madagascar and Angola and oral, perianal, penis (balanitis) and skin (dermatomycosis) regions in Germany, this variant being named *C. africana*, showing that this new species has a close relationship with the genital regions [147,217].

As it deals with genital infection and is considered rare in the male population, we observed in published articles, in cases of yeast infections of the *Candida* genus causing cases of Candidemia, candiduria, candidiasis and eye infections were more prevalent in the male population (51.4%), excluding jobs where aspects of studies were directly linked to female genital conditions.

Even over the years, Candidemia records stand out, maintaining the prevalent species, as observed in studies of candidemia incidence in Finland and Iceland [154,156,157,223]. The records indicate an increase in cases, but the analyzes indicate that the etiological agents involved in the cases of infection may have reached a state of balance, proven by the resistance to antifungal drugs, observed by the researchers. The same situation can be observed in studies by American researchers, who found a significant decline in the incidence of candidemia and an increase in echinocandin-resistant *Candida*, suggesting greater surveillance of the species of *Candida*, less sensitive to the drug class [159,160].

In a study carried out by Miranda in comparison with results from surveillance cultures, this researcher found that *C. albicans* isolates from blood and surveillance cultures of the gastrointestinal tract showed identical genotypes, suggesting that colonization of the gastrointestinal tract had blood infection as its source and caused by an exogenous source, mainly caused by the hands of health professionals and catheter tips [224].

In comparison with other *Candida* species, *C. parapsilosis* has a wide distribution in nature and is not an obligate human pathogen, having been isolated from non-human sources such as domestic animals, insects, soil, and marine environments [9,225]. Isolation of *C. parapsilosis* is increasing worldwide. In data from the SENTRY Antimicrobial Surveillance Program, *C. parapsilosis* was considered the second most common yeast species of the genus *Candida* isolated from normally sterile places in the body of hospitalized patients [5,58]. Outbreaks of this yeast-like species, with antifungal resistance, were found by several Brazilian researchers, Turks, Mexicans and Greeks reinforcing the need for surveillance in this species [5,171,181-183,185,188].

Two classes of antifungal agents (amphotericin B and echinocandins) seem to be effective against biofilms formed by *Candida* spp [226]. However, increasing records of the incidence of infections caused by *C. glabrata* and *C. rugosa* may be because they are often less susceptible to the azole antifungals currently used. Other studies emphasize the classification of *C. tropicalis* and the *C. parapsilosis* complex as more frequent than the *C. glabrata* complex [4,10,11]. Classification differences are observed when institutions, geographic regions, or single patient groups are studied [6,11,81].

In the process of biofilm formation formed by yeasts of the genus *Candida*, the increase in antimicrobial resistance seems to be quite observed, mainly among non-*albicans* species.

Recent studies, based on antifungal susceptibility, advocate that it is necessary, for there to be an improvement in the administration of antifungals, to act against the increase in resistance to drugs used in clinical practice [227]. Fluconazole and amphotericin B are the antifungal drugs of choice used in the prophylaxis and treatment of Candida yeasts that affect newborns. Echinocandins, Azoles and Amphotericin B are the drugs used in the treatment of candidemia. With the emergence of intrinsically resistant

strains such as *C. krusei*, specimens that show reduced sensitivity as in the case of *C. glabrata*, or even to fluconazole and echinocandins such as *C. parapsilosis*, it is essential to know the species and monitor the resistance to antifungals of isolates of this cosmopolitan fungal group [9,62].

This is in line with the pertinent relationship and the recent emergence of *C. auris*, which demonstrates high resistance to antifungal drugs. Another recent study, based on data collected in the USA, suggests that even if there is no statistical improvement in the patient's outcome, adequate antifungal administration allows a significant reduction in the use of antifungals [228].

More recently, Brazilian researchers report the clinical and epidemiological characteristics of patients colonized by *C. auris* isolated from urine, axillary region and inguinal region, in the largest outbreak in Brazil and showed the biofilm formation capacity of the yeast strains [229].

Several genes have been tested for drug susceptibility in vitro, and cells in biofilms are intrinsically resistant to conventional antifungal therapies, the host's immune system, and other environmental perturbations, making biofilm-based infections a significant clinical challenge. Rajendran observed the formation of biofilms, the secretion of hydrolytic enzymes involved in the lysis of proteins, and Sacristán observed the formation of biofilms in samples producing proteinase and phospholipase isolated from bronchial aspirate samples [230,231].

The FKS gene encodes the enzyme 1,3-β-glucan synthetase, an important component of the cell wall, which is the target of action of inhibitory drugs (echinocandins) [25]. These FKS gene mutations may be related to stress caused by prolonged exposure, repeated exposure to drugs, or a combination of these two factors. However, the natural polymorphism of certain species, such as *C. parapsilosis* and *C. guilliermondii*, characterizes much higher values of minimum inhibitory concentrations when compared to strains susceptible to this class [25,27].

However, resistance mediated by efflux pumps is one of the most common, and they play a major role in these mechanisms. Efflux pumps are composed of MFS (Major Facilitator Superfamily) proteins, which use energy expenditure, such as ATP degradation or concentration gradients of protons present in biological membranes, which can lead to overexpression, promoting drug expulsion to the outside of the microorganism [232].

Finally, another resistance mechanism reported is the reduction of antifungal sensitivity in an adaptive response to oxidative stress induced by the action of drugs and mutations in the ERG11 gene, associated with resistance to azoles, which modify the affinity of lanosterol-14-a- demethylase and mutations in the ERG3 gene, which lead to the formation of ergosterol and incorrect functioning of efflux pumps, which also lead to increased resistance to antifungal agents [233].

Like the of *Candida auris*, reported as isolated from the ear canal of a woman in Japan, a record of *Candida infanticola,* was described by Kurtzman of the isolation of this yeast from the ear canal of a child in Germany [234]. The emerging pathogen *C. auris* has recently become a problem due to its significant resistance to antifungal agents, such as: resistance to fluconazole in 93% of patients; amphotericin B in 35% and in 7% resistant to echinocandins.

In 2003, Colombo and Guimarães, emphasize that the general mortality of fungemia by Candida spp is around 40 to 60%. This information is in line with the information provided by Canela, that in Brazil, mortality rates from the infection can exceed 50%, depending on the patient's health status, a value higher than those reported in Europe and North America [89,174]. More currently, Pappas, emphasize that the overall in-hospital mortality rate of *C. auris* candidemia ranges from 30% to 60%, and infections typically occur several weeks after hospital admission and especially when there is prolonged hospitalization [9].

Studies indicate that analyzes carried out by an ophthalmologist suggest that up to 16% of patients have candidemia, with 2 to 9% of cases of chorioretinitis and 1% of cases of endophthalmitis. All ocular structures can be affected, promoting ophthalmological disorders [235]. Case series report that *C. albicans* is the prevalent species involving cases of eye infections [29-34,236].

With regard to yeast species, Caggiano, in their series observed that *Candida albicans* was the dominant species in Europe and America; and other non-albicans species predominate in Asia with percentages of 75% [237]. In Brazil, a study carried out by Doi [163], showed that in 16 hospitals evaluated, *Candida* spp. ranked seventh in prevalence and the mortality rate was 72.2%. In this same country, Lamoth, estimated the incidence of Candida species isolated from bloodstream infections in 1,265 ICUs in 79 countries, finding *C. albicans* as the most frequent species (70.7%) and the highest incidence of this species was found in Europe (71.7%), while the lowest was in Latin America (57.1%) [238].

This information raises the alarm that this infectious complication is becoming a major challenge for clinicians working in tertiary hospitals in different countries. *C. albicans* continues to be the main pathogen of candidemia worldwide,

but a shift in favor of other species has been taking place in recent years, with highlights for *C. parapsilosis, C. tropicalis* and *C. glabrata.*

In recent years, with the advent of the pandemic, invasive fungal infections associated with the severe respiratory syndrome called COVID-19 (SARS-COv-2) have reached a new level with important complications, involving fungi and hospitalized patients; receiving highlights for three specific groups reported in a study by Mariscal [239]. Of the fungal groups; the Aspergillus, presented the first reports of pulmonary aspergillosis occurred in China in 2020 with devastating results; followed in 2021 by cases of infections caused by Mucorales starting in India and later in other countries, involving USA, Pakistan, Russia, Iran, Mexico, Austria, Bangladesh, Chile, Germany, Turkey, Italy, Lebanon, United Kingdom, including Brazil [240-245] and yeasts of the genus Candida, with emphasis on *Candida auris*, involving serious comorbidities with a global alert signal for future pandemics [188,242,246].

According to reports by Pfaller and Machado, regarding the problem of COVID-19 and taking into account the classic example of the increased incidence of infection by C. auris, the species commonly isolated from infections, there may be a considerable increase in resistance of *C. tropicalis* and *C. parapsilosis* to fluconazole and voriconazole during the COVID-19 pandemic [247,248].

When choosing antifungals, the MIC should be the guide for the correct choice of antifungals to be recommended. Echinocandids are the first-choice therapy for most species of Candida yeasts. Fluconazole can be substituted for *C. albicans*, *C. parapsilosis* and *C. tropicalis*, while *C. krusei, C. glabrata, C. auris* can respond to the prophylactic use of amphotericin B [249].

Recently available antifungal agents such as fasmanogepix, rezafungin and tetrazol provided hope for better management of bloodstream infections, fasmanogepix did not show action against *C. krusei* while Ibrexafungerp exhibited potent activity against several species of Candida spp. including isolates resistant to fluconazole/ echinocandins, however some strains of *C. glabrata* and *C. auris* showing FKS mutations, may be resistant to Ibrexafungerp [46,247,249-251].

More recently, a study by American researchers, showed the association of *Candida* yeasts linked to the expression of pro-inflammatory immune pathways, involving the presence of the species in tumors, colon cancers, metastatic disease, and cell adhesions attenuated [252-285]. These records show the reality and specific role of the microbiota in the interaction of cancer pathogenesis, and the close relationship with fungal pathogens, suggesting that tumor-associated fungal DNA can serve as diagnostic or prognostic biomarkers.

Conclusion

This article presents an approach to the virulence factors of Candida yeasts, contextualizing their impact on the genesis and development of infectious processes caused by the group of these microorganisms.

Understanding these mechanisms has a relevant impact not only on studies of the relationship between microorganisms and the host, but also on the development of innovative techniques for modulating these mechanisms by drugs associated with antimicrobial therapy that can provide therapeutic tools for the control of persistent infections of these organism's fungal agents.

In view of the world scenario, without a doubt, resistance to antifungals is the most significant benefit for this group of yeasts, which coexist daily with humans and which, combined with the attributes of resistance, thermotolerance, adaptability and biofilm, become efficient arsenals of war.

The medical and scientific community must pay attention to the importance of the implications of the species of the genus *Candida* spp., especially its species that receive greater prominence and prevalence, *C. albicans* and future species that are emerging, in the selection of target antifungal drugs. Although in most studies little significant difference is observed in the results with the use of different classes of antifungals, that is, it is worrying since this increase in the main species can cause risk factors that interfere with the use of certain antifungals.

Often, the lethality found in some studies demonstrates the enormous need for more continuous surveillance in the management of invasive fungal diseases so that there is an optimization of prevention and control policies and antifungal prophylaxis.

It is difficult to predict the future of this enigmatic species of fungus, but we can be sure that it will continue to concern the scientific community in the coming decades, as has been demonstrated with the multidrug-resistant fungi that presented themselves to SARS-CoV-2 (COVID-19), and demonstrated their multiple abilities to infect and cause clinical emergency damage.

Authors Contributions

DPLJ (leader) idealized, contributed to the study design, data analysis, data interpretation, revision and editing of the manuscript. GMO, MRA and MSCM read and revised

the manuscript. All other co-authors collected the data, organized the information and helped with the writing of the manuscript. All authors read and approved the final version of the manuscript. All authors had full access to all study data and had final responsibility for the decision to submit for publication.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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