Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)
ISSN: 2349-2759
Available online at www.jipbs.com

Review article

Candida spp., virulence, resistance, susceptibility to antifungals and their infections: A literature review of the last twenty years

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Received on: 12/04/2021, Revised on: 30/04/2021, Accepted on: 01/05/2021, Published on: 01/07/2021.

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Keywords: *Candida,* resistance, susceptibility.

Vol. 8 (3): 31-41, Jul-Sep, 2021.

Abstract

Yeasts of the genus *Candida* are part of the microbiota of the skin and mucous membranes. However, when there is a change in the normal microbiota or in the host's immune system they can become pathogenic. It causes infections called candidiasis, which can range from superficial lesions and, in more rare cases, can cause widespread infections, such as candidemia. The frequency of invasive mycoses caused by *Candida* spp. has been increasing significantly, becoming an important nosocomial fungal pathogeny. In this view, this study aims to review the literature of the last 20 years about vulvovaginal candidiasis, oropharyngeal candidiasis and candidemia, as well as aspects related to its virulence, susceptibility and antifungal resistance. Therefore, research was carried out in the databases: Pubmed, Scielo and Web of Science. For the research, the following keywords were used: "candidiasis" and "resistance" and "susceptibility" and "prevalence" and "virulence" "antifungal" and "age".

The present review updates health professionals in relation to vulvovaginal, oropharyngeal candidiasis and candidemia, focusing on the virulence of pathogens and susceptibility to antifungals. Updating and knowledge related to these infections are extremely important to help health professionals regarding the therapeutic conduct in the face of infections caused by *Candida* spp.

Introduction

The *Candida* genus is composed of several species capable of becoming pathogenic when there is a change in the normal microbiota or in the host's immune system [1]. *Candida* species naturally colonize the skin and mucosal surfaces of the genital and gastrointestinal tracts, as well as the oral cavity without causing damage [2, 3]. However, immunocompromised individuals, submitted to chemotherapy, with chronic diseases and newborns are vulnerable to the pathogenic action of these yeasts, presenting a high risk of serious infections [4, 5].

The epidemiology of infection and the distribution of *Candida* species vary between countries and regions, however, the species of clinical interest more frequently isolated in the literature have been *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. guilliermondii, C. krusei* and, less frequently, *C. dubliniensis, C. kefyr, C. rugosa, C. famata, C. lipolytica, C. norvegensis, C. inconspicua, C. auris* and *C. blankii* [6].

The frequency of invasive mycoses caused by *Candida* spp. has been increasing significantly, becoming an important nosocomial fungal pathogeny. The literature also describes the ability of yeasts of the genus *Candida* to form biofilm, which is an important virulence factor, since it is closely

related to resistance to antifungals [6]. Biofilms can be defined as a community microbial structure, adhered to a solid surface and covered by a matrix of exopolysaccharide material [7]. Its formation in hospitals occurs in medical devices implanted in patients, such as prostheses, endotracheal tubes and catheters [6, 8].

The clinical manifestations caused by *Candida* spp. vary and may generate an infection located in mucous membranes up to a potentially fatal disseminated candidiasis [9, 10]. The most observed types of candidiasis are: mucocutaneous, cutaneous and systemic. Mucocutaneous candidiasis affects the oral cavity, gastrointestinal tract and female genital tract, which is the most common form in individuals. Cutaneous candidiasis can affect moist areas of the human body such as interdigital spaces, breast regions, axillary folds, the inguinal region and nails. In neonates, the use of diapers can cause rashes, which results in skin candidiasis. The disseminated form of candidiasis is rare, occurring mainly in terminal patients with debilitating, neoplastic, immunosuppressive and post-organ transplant diseases. When it occurs, it may affect different organs and tissues such as the lungs, meninges, kidneys, bladder, joints, liver, heart, eyes and others [5, 11].

The species of the genus *Candida* most present in the microbiota of the oral cavity is *C. albicans.* However, other species have also been isolated such as *C. dubliniensis, C. glabrata, C. krusei, C. kefyr, C. parapsilosis* and *C. tropicalis.* The literature describes that the emerging species *C. dubliniensis* was isolated for the first time in the oropharyngeal region of an immunosuppressed patient in Dublin [12]. *Candida* spp. has been isolated in the oropharyngeal region in immunocompromised individuals, especially in HIV patients, occurring in 90% of these patients during the course of virus infection [13].

Vulvovaginal candidiasis (CVV) is an inflammatory process caused, in 80 to 90% of the cases, by *C. albicans* [14]. This infection is characterized by itching, yellowish-white leucorrhea, dyspareunia, dysuria, edema and erythema in the inguinal region [5, 10]. In recent years an increase in the frequency of non-albicans species has been observed, mainly of *C glabrata, C. tropicalis* and C. *guilliermondii* [15]. The increased incidence may be associated with age, HIV infection, diabetes, use of hormonal methods of contraception, prolonged antimicrobial therapy and cytopathological changes [5, 10]. CVV is also an important cause of morbidity among pregnant women, however, it presents a low risk for the fetus [16].

Candidemia is a severe infection in the bloodstream caused by species of the genus *Candida.* This infection is an important inducer of hospital morbidity and mortality. It is believed that most cases of candidemia are acquired by endogenous route, due to the translocation of the pathogen through the gastrointestinal tract, colonized by *Candida* species [17]. The main risk factors for infection are exposure to broad-spectrum antibiotics, presence of central venous catheters, parenteral nutrition and previous surgeries [18].

Treatment of fungal infections by *Candida* spp. has been limited by the small number of antifungals, the lack of efficacy of pharmacological therapy and the acquisition of numerous mechanisms of yeast resistance. In recent years, the first-choice treatment for *Candida* spp. infections has been azoles such as fluconazole, itraconazole, voriconazole, in addition to amphotericin B. These two classes of medicines target the cell membrane of fungi. Azoles are the most used antifungals, since amphotericin B has its use restricted to hospital environment and has relevant adverse effects, such as nephrotoxicity and fever [19].

In recent years, the therapeutic success against yeasts of *Candida* spp. has been worsening and becoming increasingly difficult, in addition to the emergence of new pathogenic species. The success in the treatment of *Candida* spp. infections depends on the knowledge of the susceptibility profile of the fungus. Susceptibility tests are essential and the committees that standardize antimicrobial susceptibility and resistance tests are the *Clinical and Laboratory Standards Institute* (CLSI) and the *European Committee for Antimicrobial Susceptibility Testing* EUCAST [20].

In this view, the present study aims to conduct a search in the literature, in the period from 2000 to 2020, compiling the main infections caused by *Candida*, as well as aspects related to its virulence, susceptibility and antifungal resistance.

Methodology

The present study was based on a descriptive literature review in the online databases: PubMed, Scielo and Web of Science, using the following keywords: “candidiasis” and “resistance” and “susceptibility” and “antifungal” and “age”, for search on PubMed and Web of Science, and “candidiasis” and “resistance” and “susceptibility” and “antifungal” for search on the Scielo platform. The preestablished languages were Portuguese, Spanish and English.

The research was carried out according to the guidelines of the databases using Boolean operators (OR and AND), parentheses and quotation marks. Only a filter was used for the year of publication (2000 to 2020).

Results

In this work, 222 articles were found. Of these, 117 were from PubMed, 31 from Scielo and 74 from Web of Science. To select the articles, the title and abstract were initially analyzed, and when necessary, the full text, Figure 1. Subsequently, duplicate and triplicate articles were excluded, using the Zotero® management software, v. 4.0.29.10 (History and New Media Center, George Mason University, Fairfax, VA, EUA). In this stage, 90 articles were selected. The most used exclusion criterion was the failure to address the antifungal resistance and

susceptibility in a relevant way. After reading the selected articles, 43 were compiled that showed quality and relevance to the proposed theme (Figure 1).

In this work, 16 newspapers were found on the prevalence of vulvovaginal *Candida*, oropharyngeal and candidemia (table 1) and 16 articles on the *Candida* antifungal susceptibility profile (table 2).

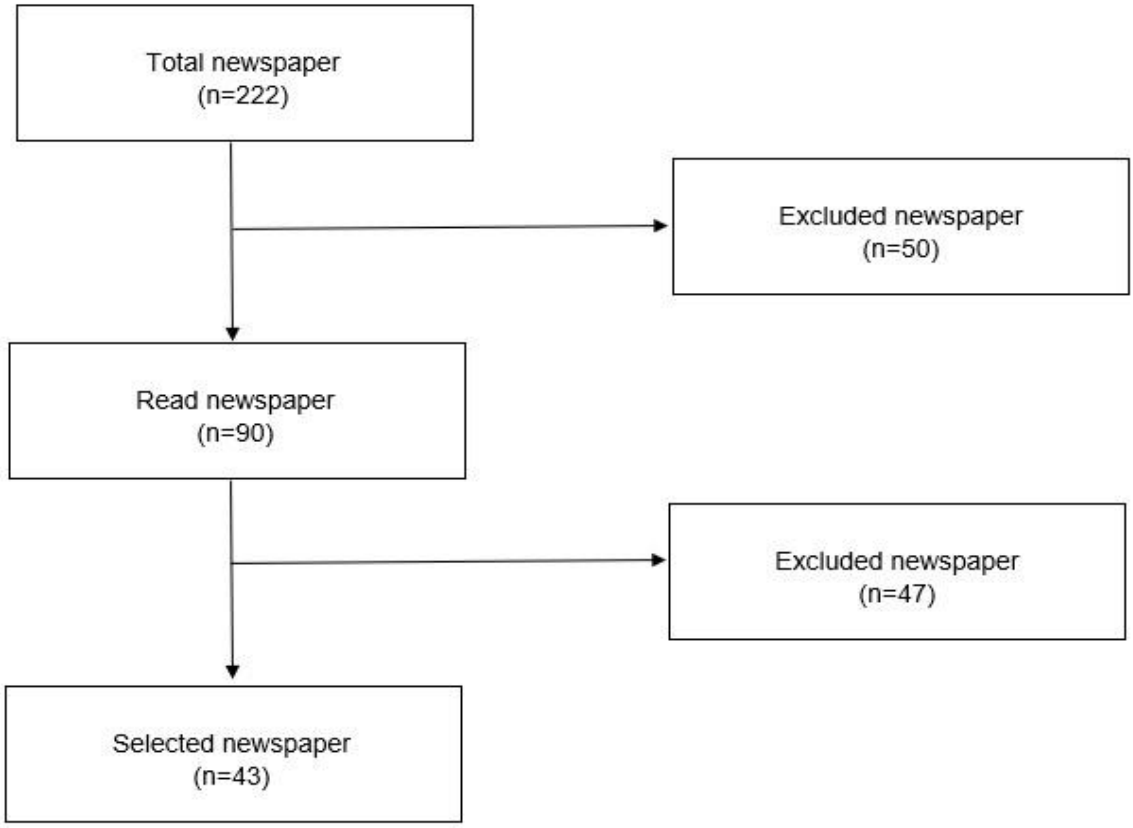

Figure 1. Flowchart of study selection.

Table 1. Articles about prevalence of vulvovaginal, oropharyngeal *Candida spp.* and candidemia.

Article	Author	Country	Year	Number of patients	Prevalence (%)
Prevalence and susceptibility of vaginal yeasts	Galle *et al.*	Brazil	2004	69	*C. albicans: 7* *C. glabrata: 15* *C. tropicalis: 7* *C. parapsilosis: 4*
Prevalence and susceptibility to fluconazole of *Candida* species that cause vulvovaginitis	Mohanty S. *et al.*	India	2007	111	*C. glabrata: 57* *C. albicans: 40* *C. tropicalis: 12* *C. krusei: 3* *C. parapsilosis:1*
Susceptibility of vaginal yeast to the most used antifungals in Maringá, Paraná, Brazil	Dalben Dota *et al.*	Brazil	2008	78	*C. albicans: 41* *C. glabrata: 9* *C. guillermondii: 5* *C. parapsilosis: 2* *C. lusitaniae: 1* *Saccharomyces cerevisiae: 2* *Trichosporon asahii: 1* *Rhodotorula* spp.*: 1*

Vulvovaginal candidiasis in Mato Grosso, Brazil: pregnancy status, causal species and drug tests	Dias Brasili *et al.*	Brazil	2011	*70* *no pregnant* *80* *pregnant*	*C. albicans: 73* *C. parapsilosis: 14* *C. tropicalis: 4* *C. glabrata: 3* *C. albicans: 92* *C. kusei: 3* *C. glabrata: 2* *C. parapsilosi: 1* *C. tropicalis: 1*
Clinical characteristics of Turkish women with *Candida krusei* vaginitis and antifungal susceptibility of *C. krusei* isolates	Guzel Baril *et al.*	Turkey	2013	560	*C. albicans: 43* *C. glabrata: 28* *C. krusei: 5* *C. kefyr: 4* *More the one specie of Candida: 21*
Phenotypic characterization and antifungal susceptibility pattern to fluconazole in *Candida* species isolated from patients with vulvovaginal candidiasis in a tertiary hospital	Ragunathan *et al.*	Índia	2014	40	*C. albicans: 65* *C. glabrata: 23* *C. tropicalis: 8* *C. parapsilosis:5*
Molecular identification and antifungal susceptibility of 186 isolates of vulvovaginal candidiasis in southern China	Shi *et al.*	China	2015	186	*C. albicans: 91* *C. glabrata: 4* *C. tropicalis: 3* *C. parapsilosis: 1*
Changing trends of candida isolates and their antifungal susceptibility pattern in vulvovaginal candidiasis cases of tripura north east India	Mullick Basu *et al.*	Índia	2015	58	*C. albicans: 38* *C. tropicalis: 26* *C. glabrata: 21* *C. krusei: 12* *C. parapsilosis: 2* *C. guilliermondii: 2*
Epidemiology, species distribution, antifungal, and ERG11 mutation of *Candida* species isolated from pregnant chinese of woman	Yan *et al.*	China	2016	124	*C. albicans: 70* *C. tropicalis: 12* *C. glabrata: 10* *C. parapsilosis: 5* *C.krusei: 3*
Susceptibility and molecular characterization of *Candida* species in patients with vulvovaginitis	Fornari *et al.*	Brazil	2016	40	*C. albicans: 83* *C. glabrata: 8* *Saccharomyces cerevisiae:5* *C. dubliniensis: 3* *C. guilliermondii: 3* *C. kefyr: 3*
Prevalence of *Candida* spp. in cervical-vagina samples and in vitro susceptibility of isolates	Brandolt *et al.*	Brazil	2017	36	*C. albicans: 74* *C. glabrata: 9* *C. parapsilosis: 3* *C. tropicalis: 3*
Susceptibility pattern to *Candida* spp. antifungals. isolated from the female genital tract at Yaoundé Bethesda Hospital in Cameroon	Kengne *et al.*	Cameroon	2017	94	*C. albicans: 46* *C. glabrata: 20* *C. tropicalis: 7* *C. dubliniensis: 5* *Others yeasts: 21*
Susceptibility test to antifungals of vulvovaginal species of *Candida* spp. among women cared for in the prenatal clinic at tertiary hospitals in Peshawar	Khan *et al.*	Pakistan	2018	108	*C. albicans: 41* *C. tropicalis: 17* *C. krusei: 17* *C. glabrata: 15* *C. dubliniensis: 10*

Vulvovaginal candidiasis: distribution of *Candida* species and their susceptibility pattern to antifungals	Bitew *et al.*	Ethiopia	2018	87	*C. albicans: 59* *C. krusei:17* *C. dubliniensis: 9* *C. glabrata: 3* *C. inscospicua: 1* *C. tropicalis: 2* *C. kefyr: 2* *C. guilliermondii: 2* *C.l usitaniae: 1* *C. parapsilosis: 2*
The occurrence of vulvovaginal *Candida* spp. species and their antifungal susceptibility pattern in HIV seropositive women in Ahvaz, Southwest Iran	Varnasiri *et al.*	Iran	2020	29	*C. albicans: 62* *C. glabrata: 21* *C. dubliniensis: 14* *C. krusei: 3*

Table 2. Newspaper about *Candida* antifungal susceptibility profile.

Author	Specie	Method	Antifungal	Susceptibility profile
Galle *et al.* Brazil 2004	*C.albicans* *C.glabrata,* *C.tropicalis,* *C.parapsilosis*	Microdilution in broth	Fluconazole Itraconazole Amphotericin B	9.8% of *C. albicans* were resistant to fluconazole and 17.6% to itraconazole. 11.7% of other species of candida were resistant to itraconazole
Mohanty S. *et al.* India 2007	*C.glabrata,* *C.albicans,* *C.tropicalis,* *C.kruse* *C.parapsilosis*	Microdilution in broth	Fluconazole	70% were sensitive to Fluconazole and 30% were SDD.
Dalben Dota *et al.* Brazil 2008	*C.albicans,* *C.glabrata,* *C.guillermondi* *C.parapsilosis* *C.lusitaniae* *Saccharomyces cerevisiae* *Trichosporon asahii* *Rhodotorula sp.*	Microdilution in broth	Ketoconazole Fluconazole Itraconazole Nystatin Amphotericin B	5.7% of *Candida* no *albicans* were resistant to amphotericin B, 8% to fluconazole and 20% to itraconazole. The strains of *C. albicans* were more sensitive to antifungal tested.
Dias Brasili *et al.* Brazil 2011	*C.albicans* *C.krusei* *C.glabrata* *C.parapsilosis* *C.tropicalis*	Microdilution in broth	Ketoconazole Fluconazole Itraconazole Amphotericin B	1.25% were resistant to fluconazole
Guzel *et al.* Turkey 2013	*C.krusei*	Microdilution in broth	Amphotericin B 5-flucitosin Caspofungin Itraconazole Voriconazole Econazole Ketoconazole Miconazole Sulconazole Fluconazole	All strains were sensitive to amphotericin B, ketoconazole, miconazole and sulconazole. 52.9% were resistant to itraconazole, 27% to voriconazole and 57.1% to fluconazole.
Ragunathan *et al.* India 2014	*C.albicans* *C.glabrata* *C.tropicalis* *C.parapsilosis*	E-test	Fluconazole	2.5% resistant to fluconazole
Shi *et al.* China 2015	*C.albicans* *C.glabrata* *C.tropicalis* *C.parapsilosis*	Neo-sensitabs	Caspofungin Miconazole Itraconazole Voriconazole Fluconazole	All strains were sensitive to caspofungin,12.5 % were resistant to miconazole and itraconazole, 18% were resistant to voriconazole, 31.2 % were resistant to fluconazole, 75%

			Ketoconazole Terbinafine	resistant to terbinafine and more than 50% resistant to ketoconazole .
Mullick *et al.* India 2015	*C.albicans* *C.tropicalis* *C.glabrata* *C.krusei* *C.parapsilosis* *C.guilliermondii*	E-test	Fluconazole Voriconazole Ketoconazole Amphotericin B	50% were sensitive to ketoconazole and 80% were sensitive to others antifungal
Yan *et al.* China 2016	*C.albicans* *C.tropicalis* *C.glabrata* *C.parapsilosis* *C.krusei*	Fungi test kit 3	Amphotericin B Fluconazole Itraconazole	60% of *C.tropicalis* and *C.glabrata* were resistant to fluconazole and more of 85% to itraconazole. 100% of *C. krusei* were resistant to itraconazole...
Fornari *et al.* Brazil 2016	*C.albicans* *C.dubliniensis* *C.guilliermondii* *C.kefyr* *C.glabrata* *Saccharomyces cerevisiae*	Microdilution in broth	Amphotericin B Ketoconazole Itraconazole Fluconazole Nystatin	100% of *C. guilliermondii* were resistant to amphotericin B and 100% of *C. kefyr, C. albicans* and *C. glabrata* were SDD to nystatin.
Brandolt *et al.* Brazil 2017	*C.albicans* *C.glabrata* *C.tropicalis* *C.parapsilosis*	Microdilution in broth	Fluconazole Itraconazole	50% of *C. albicans* and *C. glabrata* were resistant to itraconazole, more than 60% these species were SDD or resistant to fluconazole. 50% to *C. parapsilosis* were resistant to itraconazole. All *C. troipicalis* were sensitive to fluconazole and itraconazole.
Kengne *et al.* Cameroon 2017	*C.albicans* *C.glabrata* *C.tropicalis* *C.dubliniensis*	Disk diffusion	Fluconazole Miconazole Itraconazole Nystatin Ketoconazole	13.5% were resistant to fluconazole, 31.1% to itraconazole, 17.5% to nystatin and 2.7% to miconazole and ketoconazole.
Khan *et al.* Pakistan 2018	*C.albicans* *C.tropicalis* *C.krusei* *C.glabrata* *C.dubliniensis*	Disk diffusion	Fluconazole Voriconazole Itraconazole Nystatin Clotrimazole	62% were resistant to fluconazole, 10.2% to voriconazole, 40.7% to itraconazole, 58.3% to nystatin and 59.3% to clotrimazole
Bitew *et al.* Ethiopia 2018	*C.albicans* *C.krusei* *C.dubliniensis* *C.glabrata* *C.inscospicua* *C.tropicalis* *C.kefyr* *C.guilliermondii* *C.lusitaniae* *C.parapsilosis*	VITEK 2	Fluconazole Voriconazole Caspofungin Micafungin Moscacitosin	17.2% were resistant to fluconazole and 5.7% to moscacitosin.
Maraki *et al.* Greece 2019	*C.albicans* *C.lusiataniae* *C.lipolytica:* *C.parapsilosis* *C.kefyr* *C.dubliniensi* *C.ciferri* *C.inconspicua* *C.famata* *C.norvegensis* *C.rugosa*	VITEK 2	Amphotericin B Voriconazole Flucytosine Fluconazole	0.2% of species were resistant to amphotecin B, 1.4% were resistant to voriconazole, 2.1% to flucytosine and 6.6% to fluconazole
Varnasiri *et al.* Iran	*C.albicans* *C.glabrata* *C.dubliniensis*	Microdilution in broth	Amphotericin B Caspofungin Itraconazole	100 % of *C. albicans* and *C. krusei* were resistant to amphotericin B. All species were sensitive to caspofungin.

2020	*C.krusei*	Fluconazole

Vulvovaginal candidiasis

Yeasts of the genus Candida are characterized by being unicellular, eukaryotic and heterotrophic. Yeasts develop in the presence of oxygen or in the absence of it. The components of the genus *Candida* are very diverse, so they can grow as yeasts (blastospores) and also in filamentous forms, pseudohyphae and pseudomycelium [20]. According to Goulart *et al.*, the presence of *Candida* in the vagina, in the absence of symptoms and immunosuppression, is not commonly associated with disease and is called colonization. In contrast, vulvovaginal candidiasis is defined as inflammation of the vulvovaginal mucosa in the presence of *Candida* and the absence of other infectious etiologies [13].

According to Brandolt *et al.*, vulvovaginal candidiasis is an infection of the genital mucosa that mainly affects the vulva and vagina. The most recurrent symptoms of the infection are itching, burning, cracking, erythema, leukorrhea and whitish plaques on the vaginal mucosa. VVC is considered the second cause of genital infection in women of reproductive age, and its exact incidence is still unknown [21].

According to Kengne *et al.*, some predisposing factors for VVC include pregnancy, antibiotic consumption, decompensated diabetes, chronic anemia, unprotected sex, contraceptives with a high level of estrogen, among others [22].

In 2014, Ragunathan and collaborators isolated *Candida* spp. in 40 women and the predominant risk factor for VVC was pregnancy (55%), followed by the use of broad-spectrum antibiotics (20%), diabetes mellitus (15%), oral contraceptive pills (7.5%) and tuberculosis (2.5%) [23]. Candidiasis in pregnant women can lead to severe complications that include abortion, chorioamnionitis and premature birth. Transmission can occur from the infected mother's vagina to the newborn, leading to a congenital yeast infection [24].

It is estimated that 75% of adult women are affected by at least one episode of VVC in their lifetime, 40-50% will have recurrence and 5% will present recurrent vulvovaginal candidiasis (RVVC). RVVC is defined as the presence of four or more symptomatic episodes of infection in one year. [15]. A study published in 2014, carried out at the tertiary hospital in Puducherry, included a study group of 180 women aged between 15 and 45 years. The authors stated that the reason for the high incidence in this age group includes low levels of protective cervical antibodies, increased sexual activity and the influence of reproductive hormones that can lead to increased susceptibility to reproductive tract infections. [23].

The diagnosis of vulvovaginitis is made through microscopic analysis of vaginal secretion to search for microbiological agents such as protozoa (*Trichomonas vaginalis*), bacteria (*Gardnerella vaginalis*) or fungi (*Candida* spp.), followed by culture of the fluid to confirm the diagnosis. The confirmatory diagnosis based on culture is not performed routinely and is not commonly recommended in many regions, since the procedures are expensive and time-consuming [16]. Many clinicians require that vaginal discharge be sown for specific identification of the species and to better define the best therapy to use.

Candida albicans continues to be the most prevalent CVV agent, however, in recent years there has been an increase in non-albicans species, also becoming important pathogens [25]. In a study carried out in Brazil, 69 strains from 250 samples of vaginal fluids subjected to culture were isolated and found that *C. albicans* was the most isolated yeast with a prevalence of 74%, followed by *C. glabrata* (14.5%), *C. tropicalis* (7.2%) and *C. parapsilosis* (4.3%) [26]. Dalben Dota *et al.* (2008) also found that *C. albicans* was the most isolated yeast, followed by *C. glabrata, C. guilliermondii, C. parapsilosis* and *C. lusitaniae* [15]. According to a research carried out in Turkey in 2013, of the 560 vaginal yeast isolates, *C. albicans* was the most prevalent (43.2%), followed by *C. glabrata* (27.7%), *C. krusei* (5.0%) and *C. kefyr* (3.6%) [22]. Another study found *C. albicans* as the most prevalent (65%), followed by *C. glabrata* (22.5%), *C. tropicalis* (7.5%) and *C. parapsilosis* (5%) [21].

A study carried out in India, published in 2007, with the participation of 601 sexually active women with suspected CVV, obtained 111 isolates of *Candida* spp., in which there was a prevalence of *Candida glabrata*, a non-albicans species, with about 56.5 %, followed by *C. albicans*, *C. tropicalis* and *C. krusei*. In this sense, an increase in the prevalence of non-albicans species may require vigilance, as it may imply a therapeutic change in the treatment of *Candida* non-albicans vaginitis. [27].

According to Dias *et al.*, (2011), many Brazilian women self-diagnose and, consequently, self-medicate for the treatment of vulvovaginal candidiasis, using vaginal preparations of butoconazole, clotrimazole, miconazole, tioconazole, medications that are sold over the counter. However, the findings demonstrate that many women who self-medicate to treat candidiasis do not have a diagnosis of CVV. [16].

In recent years, there has been an increase in the number of cases of mycosis caused by emerging candida species, involving the isolation of *C. dubliniensis*, *C. kefyr, C. rugosa, C. famata, C. lipolytica, C. norvegensis*, and others [21]. However, there seems to be great differences regarding the species of isolated vaginal yeasts and geographic location. [22]. Fornari *et al.*, conducted a study in Brazil, in which the following species were

isolated: *C. albicans, C. glabrata, C. dubliniensis, C. guilliermondii and C. kefyr* [28]. Bitew and collaborators published, in 2018, a study in which they obtained isolates *of C. albicans, C. krusei, C. dubliniensis, C. glabrata, C. inconspicua, C. tropicalis, C. kefyr, C. guilliermondii, C. lusitaniae* and *C. parapsilosis* [29].

The treatment of vulvovaginal candidiasis varies considerably, however, the most widely used drugs are azoles. Nevertheless, the prophylactic and exacerbated use of these drugs have been associated with the selection of less susceptible *Candida* strains, resulting in a difficulty in the treatment of the infection [22].

Antifungal resistance has presented itself as a challenge for public health, since the chance of microbiological resistance should be considered if the patient has already been in contact with a drug from the azole group. The sensitivity test is essential, as it can specify the clinical response, predict treatment failure and develop local antibiograms, helping in the empirical choice of the antifungaln [24].

A study by Khan *et al.* determined the *in vitro* susceptibility of *Candida* spp. using the disk diffusion method, as recommended by document M44A from the Clinical Laboratory Standard Institute (CLSI). They observed a resistance of 62% for fluconazole, 59.3% for clotrimazole, 10.2% for voriconazole and 40.7% for itraconazole [24]. According to a study conducted by Brandolt *et al.*, carried out in Brazil, 50 isolates of *Candida* spp. underwent susceptibility testing *in vitro*, using the broth microdilution test, standardized by protocol M27-A2 CLSI (2002), where 74% of *Candida albicans* isolates showed resistance to fluconazole and 56.8% to itraconazole. In this study, 12% of *Candida glabrata* isolates showed no resistance to fluconazole and 50% were resistant to itraconazole. *C. tropicalis* was 100% susceptible to fluconazole and itraconazole [21]. The literature describes *C. krusei* as intrinsically resistant to fluconazole, which corroborates the data found in this literature review. [16, 30-32].

The therapeutic arsenal available for the treatment of fungal infections is limited. Amphotericin B is an antifungal of the polyene class highly effective against yeasts, however its use is limited to severe conditions and restricted to the hospital, due to its high toxicity [22]. A study by Fornari *et al.* observed that all strains *of C. albicans, C. glabrata and C. kefyr* were susceptible to amphotericin B, however *C. guilliermondii* showed intrinsic resistance to the polyene derivative [28].

Candidemia

Another important infection caused by *Candida* yeasts is candidemia, responsible for serious complications in hospitalized patients, leading to sepsis and high mortality rates [25]. In the past two decades, Zhang *et al.* list candidemia as the fourth and seventh most common blood infections in the USA and Europe, respectively [18].

The prevalence of *Candida* species varies depending on the geographic location. In the present study, there was a higher prevalence of the species *C. albicans* in Europe (53.7%), followed by Oceania (46.5%), Asia (45.7%) and North America (45.1%), while Africa (43%) and South America (39.9%) had slightly lower rates. Brazil showed an average of 35.4% in the prevalence of *C. albicans* [33, 34].

Although *Candida albicans* remains the most prevalent in blood infections worldwide, it is interesting to observe studies with a predominance of other species. An example is the study by Pinhati *et al.*, which reports a 70% prevalence of cases of candidemia by *C. parapsilosis* in an Intensive Care Unit of a Brazilian tertiary hospital. [35].

In the present study, it was observed, in relation to non-albicans *Candida* species, a predominance of *C. parapsilosis* in Africa (30%), South America (26.7%), Oceania (21.6%) and Europe (18%). In North America, *C. glabrata* (20.5%) was the second most prevalent species, while in Asia, *C. tropicalis* (16.7%) occupied the second position, following *C. albicans*. As for the susceptibility and resistance profiles of the different species that cause candidemia, a general and common change can be observed in most studies. Susceptibility to azole derivatives and polyenes is relatively high, while in most studies, *C. glabrata* and *C. tropicalis* emerge as species resistant to many antifungals [35, 36].

A global study, carried out by Pfaller *et al.*, showed that isolates of *C. albicans, C. parapsilosis* and *C. tropicalis* were susceptible to anidulafungin, caspofungin and micafungin in all age groups tested, while isolates of *C. krusei, C albicans* and *C. parapsilosis* were completely susceptible to posaconazole and voriconazole [26]. In this study, *C. glabrata* was the species with the highest resistance values, showing considerable rates (16.7%) of resistance to anidulafungin, caspofungin, micafungin and fluconazole [30].

Corroborating this research, a study by Xiao *et al.* found out that *C. glabrata* and *C. tropicalis* demonstrated resistance rates of 53.8% and 25% to itraconazole, respectively, whereas *C. albicans*, *C. parapsilosis* and *C. krusei* were susceptible to most tested drugs (fluconazole, itraconazole, voriconazole, amphotericin B) in other studies analyzed [31].

Oropharyngeal candidiasis (COP) is the opportunistic fungal infection that more often affects seropositive individuals (50 to 95% of those infected), with no distinction of sex and age. In general, it affects more patients diagnosed late and/or with no response to treatment with antiretrovirals [13, 37].

According to HIV-infected rates worldwide, India and Nigeria top the rankings, while Brazil and Mexico occupy the top positions in Latin America. One study described

that there was a correspondence between the number of people infected with HIV and a higher prevalence of COP infection. Additionally, there has been a decrease in opportunistic infections in developed countries since the introduction of highly active antiretroviral therapy (HAART) [37-40].

Oropharyngeal candidiasis

The more prevalent species observed in the studies regarding oropharyngeal candidiasis were *Candida albicans*, *Candida glabrata, Candida tropicalis, Candida parapsilosis and Candida krusei*. Only in one of the studies involving HIV-positive pediatric population, *Candida glabrata* was highlighted and *Candida lipolytica* was considered an emerging pathogen [41]. In another study conducted in Norway with children undergoing treatment with broad-spectrum antibiotics (due to severe neutropenia and cystic fibrosis), it was expected that there would be a greater predisposition to *Candida* colonization, however there was no significant difference in the rates between the group of sick children and the healthy control group. Three species are also highlighted in particular in this study: *Candida famata* (the two isolates showed resistance to amphotericin B), *Candida magnoliae* (reduced susceptibility to fluconazole) and *Candida sphaerica* (resistant to fluconazole) [42]. In addition, *Candida famata* appeared in two other studies, diverging the findings among them regarding the resistance to antifungals. While the former showed resistance to AMB, two other isolates from *Candida famata*, in northeastern Brazil indicated susceptibility to AMB and total resistance to fluconazole [43]. On the other hand, for HIV-infected patients studied in India, *Candida famata* did not show resistance to azoles [37]. *Candida kefyr, Candida lusitaniae* and *Candida sake* were noted in other articles, also considered as emerging species [38, 40-42]. Susceptibility to azoles and AMB was observed for *Candida lusitaniae* and *Candida kefyr*, in an article with seropositive individuals in Nigeria [38].

Nevertheless, C. *krusei* was the species with the highest resistance to almost all antifungal agents, being observed only 100% susceptibility to voriconazole [39, 43]. As mentioned earlier, *C. parapsilosis* and *C. glabrata* were seen more frequently in the articles that addressed COP; both showed low resistance to the antifungals used: itraconazole (11.1%) for *C. parapsilosis*, and fluconazole (13.43%), voriconazole and amphotericin B (12.5%) for *C. glabrata*. *C. albicans* showed resistance of 12.83% for fluconazole and 10.73% for itraconazole. The antifungals observed in common in the studies were: fluconazole, voriconazole, 5-FC, amphotericin B, ketoconazole and itraconazole, and susceptibility tests were performed by the broth microdilution method, and Etest [37, 38, 40, 43].

Brazilian Health Regulatory Agency (ANVISA) notified the identification of a possible case of *Candida auris* in Brazil, called an emerging fungus that presents a series of threats to public health, because it presents resistance to antifungal agents used in clinical practice to treat *Candida* infections, besides the need for specific laboratory methods to identify this yeast. The literature describes some strains of *C. auris* as resistant to the three main classes of antifungal drugs: polyenes, azoles, echinocandins. The emerging fungus can cause hematological and systemic infections, especially in patients with comorbidities [44].

Conclusion

This bibliographic review provides an important update for healthcare professionals on the susceptibility to *Candida* spp. infections. *Candida* is a fungal genus of high importance in public health, as it causes many pathologies. The diagnosis is fundamental for the adequate treatment, since, in recent years, the prevalence of emerging yeasts and strains resistant to therapy has been increasing. The species of *Candida* that presented greater resistance in the literature were *C. krusei* against fluconazole and itraconazole, *C. tropicalis* and *C. parapsilosis* against ketoconazole, fluconazole and terbinafine, *C. guilliermondii* against amphotericin B and *C. glabrata* against nystatin, clotrimazole and itraconazole. The antifungal susceptibility profile review supports health professionals in the management of antifungal therapy, allowing for a better quality of life for the patient and reducing the chances of its recurrence.

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