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# Growing role of non-Candida albicans *Candida* species in clinical disorders of humans and animals

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During the last two decades, fungi have been recognized as an important cause of serious infections with increased frequency. Among the fungi, *Candida* species are opportunistic agent, which are occurring as normal inhabitants of the digestive tract, oral cavity, and vagina of humans, and domestic animals. Twenty years ago, *C. albicans* represented 80% of *Candida* species recovered from patients with oral and systemic candidiasis. Although *C. albicans* continues to be the most frequently isolated species, the number of infections caused by non-*Candida albicans Candida* species (NCAC) such as *Candida glabrata, Candida tropicalis, Candida parapsilosis, Candida krusei, Candida guilliermondii, Candida lusitaniae, Candida kefyr, Candida famata,* and *Candida rugosa* have increased significantly over the last two decades. NCAC species accounted for 10%–40% of all systemic candidiasis from 1970 to 1990, and this proportion reached 35%–65% in the last two decades. This is mainly associated with the advanced diagnostic methods, the introduction and widespread use of better medical practices, the administration of broad-spectrum antibiotics, an increase in the number of invasive surgical procedures, the emergence of HIV and AIDS. Even though there is significant geographic variation in the frequency of NCAC species, *C. glabrata* remains the most common NCAC species, and *C. parapsilosis, C. tropicalis, and C. krusei* are also frequently isolated in most regions of the world. More studies are warranted to determine the clinical significance of NCAC in humans as well as in various species of animals.

**Key words:** Clinical disorders, domestic animals, non-*Candida albicans Candida* species, humans, yeast

## INTRODUCTION

Yeasts are unicellular fungi, which multiply mainly by budding. They are widely distributed in nature, and act as common saprophytic constituents of the normal human, and animal micro-flora. Among yeasts, *Candida* is the mostly encountered opportunistic agent. There are about 200 species of *Candida* of, which11 are implicated in clinical disorders of humans, and animals (Pal,2007).

The genus *Candida* belongs to the Family *Saccharomycetaceae*, Order Saccharomycetales, Class Saccharomycetes, and Division Ascomycota.

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They are opportunistic fungi, occurring as normal inhabitants of the digestive tract, oral cavity, and vagina of humans, and several domestic animals (Smith, 1967; Chengappa *et al.,* 1984; Pal, 2007). Fungal invasion resulting in disease has been associated with the intensive or prolonged use of antibiotics or steroids (Pal, 2007).

The infections due to *Candida* can lead to arrange of acute, sub-acute or chronic superficial or systemic disease (Eggimann *et al.*,2003).The frequency of *Candida* infection has been gradually increasing over the last several years, accompanied by a significant increase in morbidity, and mortality. *Candida albicans* is the most pathogenic *Candida* species, and is frequently identified in candidiasis lesions in humans (Pal and Desai,1998; Pal,2007. Twenty years ago, *C. albicans* represented 80% of the *Candida* species recovered from patients with oral and systemic candidiasis. Although *C. albicans* continues to be the most frequently isolated species, the number of infections caused by non-*albicans* species has increased significantly over the last two decades (Silva *et al.,* 2011). *Candida* species can be easily isolated on Sabouraud dextrose agar with chloramphenicol and also on Pal'sunflower seed medium (Pal,1997). The morphology of cultures can be easily studied in "Narayan" stain which was developed by Pal(2004).Therefore, this paper is dedicated to the memory of Dr. Ishwar Chand Vidyasagar, great Indian Scholar and reformer, fought for widow remarriage, higher education for women, and against child marriage.the objective of this paper is to review the increasing role of non- *Candida albicans Candida* species in clinical disorders of humans ,and domestic animals.

### *Pathogenic Non-Candida albicans Candida (NCAC) species*

The NCAC species are a heterogenous group of organisms and different from each other and from *C. albicans* (Moran *et al.,* 2002). Earlier, it was considered that *C. albicans* was the only species causing infection, and *C. parapsilosis, C. tropicalis and C. guilliermondii* were considered only as occasional pathogens (Moran *et al.,* 2002). The NCAC species are thought to cause candidiasis of less virulence explained by the fact that they lack, totally or partially, some virulence factors that the most virulent species *C. albicans* has. These are, for example, the ability to form hyphae, and the ability to perform phenotypic switching. They may also have a lower adherence capability to buccal epithelial and vascular endothelial surfaces, and lower secretion of proteinases (Moran *et al.*,2002).

The role of these NCAC species also referred to as non-albicans species have become increasingly important, especially in high risk patients (Meurman *et al.,* 2007). The increased prevalence of non-*albicans Candida* species found in human candidiasis can be partially attributed to advanced diagnostic methods, such as the use of primary culture media, which are able to differentiate between Candida species, and the introduction of molecular techniques for routine diagnosis. Other factors responsible for the increased prevalence of *Candida* species include the introduction, and wide spread use of better medical practices (such as immunosuppressive therapy), the administration of broad-spectrum antibiotics, an increase in the number of invasive surgical procedures (Silva *et al.,* 2011), treatments for cancer and the emergence of HIVand AIDS, (Moran *et al.,* 2002). Furthermore, the growing number of *Candida* species causing candidiasis may be a consequence of species selection in the presence of certain antifungal agents, resulting in the high level of antibiotic resistance found in non-*albicans* species (Silva et *al.,* 2011).

### *Epidemiology of pathogenic non-Candida albicans Candida species*

Global surveillance programs provide a tremendous amount of data regarding global trends in various aspects of NCAC candidiasis including geographical variation in the frequency of species, distribution by specimen type and patient age, as well as changes in the antifungal susceptibility of collected NAC isolates (Pfaller *et al.,* 2010) Due to the growing size of the population at special risk (due to neutropenia, immunosuppression metabolic dysfunction, and anticancer chemotherapy), candidiasis remains a persistent public health problem, and the proportion of NCAC species among *CANDIDA* isolates recovered from patients is increasing. Whereas NCAC species accounted for 10%–40% of all systemic candidiasis from 1970 to 1990, this proportion reached 35%–65% in the last two decades (Krcmery and Barnes, 2002). During recent decades, several countries around the world have witnessed a change in the epidemiology of *Candida* infections, characterized by a progressive

shift from a predominance of *Candida albicans* to non-*albicans Candida* species (including *C. glabrata* and *C. krusei*) (Krcmery and Barnes, 2002). There is growing evidence suggesting a role for increasing use of azole agents in this epidemiological shift (Oberoi *et al.,* 2012).

A recent ten-year analysis of the worldwide distribution of NAC species indicated that *C. glabrata* remains the most common NCAC species, and *C. parapsilosis, C.tropicalis, and C. krusei* are also frequently isolated. *C. guilliermondii* and *C. lusitaniae* have shown gradual emergence as a cause of invasive candidiasis, while C. *kefyr, C. famata, C. inconspicua, C. rugosa, C. dubliniensis,* and *C. norvegensis,* although rarely isolated, are now considered emerging NCAC species, as their isolation rate has increased between 2- and 10-fold over the last 15 years (Pfaller *et al.,* 2010).

Interestingly, significant geographic variation in the frequency of NAC species occurs. Among marked trends, *C. glabrata* is more prominent in North America than in Latin America. In addition, *C. tropicalis* is frequently isolated in Asia-Pacific, and less often encountered in the rest of the world, whilst *C. parapsilosis* remains 3-fold more commonly recovered in North America than in Europe. Finally, *C. guilliermondii* and *C. rugosa* are more prominent in Latin America, and *C. inconspicua* and *C. norvegensis* in Europe (Pfaller *et al.,* 2010) than in the rest of the world.

### *Pathogenic non-Candida albicans Candida species of humans*

*Candida* species thereby rarely trigger infection in healthy people, but take advantage of a locally or systematically impaired immune system to proliferate in the host and cause diseases termed "candidiasis."Such fungal infections can be subdivided into three major groups: cutaneous (skin and its appendages), mucosal (oropharyngeal, esophageal, and vulvovaginal), and systemic (bloodstream infections, i.e., candidemia and other forms of invasive candidiasis. Superficial candidiasis (cutaneous and mucosal) is most commonly observed in AIDS patients, oropharyngeal thrush, and vaginitis are more frequently seen in immunocompetent infants and adult women, respectively. Candidemia and IC are common in cancer patients or in transplant individuals following immunosuppression. Candidiasis currently represents the fourth leading cause of nosocomial infections, at 8% to 10%, and mortality due to systemic candidiasis remains high, ranging from 15% to 35% depending on the infecting *Candida* species (Pfaller and Diekema, 2007).

Although *Candida albicans* remains the most frequently isolated agent of candidiasis, non-*abicans Candida* (NAC) species now account for a substantial part of clinical isolates collected worldwide in hospitals. NAC species of particular clinical importance include *Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei* , as well as the less-prominent species *Candida guilliermondii, Candida lusitaniae, Candida kefyr, Candida famata, Candida inconspicua, Candida rugosa, Candida dubliniensis, and Candida norvegensis* (Pfaller *et al.,* 2010).

### *Candida dubliniensis*

*C. dubliniensis* was first described in 1995, and is associated with oral lesions in HIV-infected individuals. This recently identified species is phenotypically and genotypically closely related to *C. albicans* (Coleman *et al.,* 1997). In vitro phenotypic studies have shown that *C. dubliniensis*has a few characteristics that distinguish it from *C. albicans* (Hazen *et al.,* 2001). Both produce germ tubes and chlamydospores. Unlike *C. albicans, C. dubliniensis* isolates grow poorly at 42°C (Coleman *et al.,* 1997). Despite the similarities with *C. albicans, C. dubliniensisis* not a common constituent of the oral microflora and only about 3.5% of healthy individuals carry *C. dubliniensis*in the oral cavity (Pinjon *et al.,* 2005). A prevalence of 15-30% of *C. dubliniensisin* the oral cavities of HIV-infected and AIDS patients has been reported (Pinjon *et al.,* 2005). It is not a common cause of bloodstream infection and the incidence in systemic infections is low. The reason for this seems to be the lower virulence of *C. dubliniensis* compared to the virulence of *C. albicans.* It has been suggested that the reason for the comparatively low virulence is its lower capacity to form hyphae compred to *C. albicans* (Stokes *et al.,* 2007). *C. dubliniensis is*, however, the only Candida species in addition to *C. albicans* that forms true hyphae. Decreased susceptibility or resistance has been reported in isolates recovered from HIV-patients receiving fluconazole therapy (Pinjon *et al.,* 2005). *C. dubliniensis* has been isolated from a wide range

of geographical locations, including Europe, North and South America and Australia (Willis *et al.*, 2000).

### *Candida glabrata*

Earlier *C. glabrata* was considered a pathogen that causes infection only when detected with *C. albicans*. However, there have been several reports on oropharyngeal *Candida* (OPC) infections due only to *C. glabrata* (Redding *et al.*, 2002) and it is now emerging as an important pathogen in both mucosal and bloodstream infections. It is commonly isolated from the oral cavities of HIV-infected individuals (Moran *et al.*, 2002). *C. glabrata* is the second-most common agent ofcandidemia in the United States since the early 1990s (Nucci and Marr, 2005). It is considered that *C. glabrata* associated OPC infections in HIV and cancer patients are more severe and more difficult to treat (Redding *et al.*, 2002). This is mainly due to the ability of *C. glabrata* to quickly develop resistance to fluconazole. Cross-resistance to the newer azoles has also been found to exist (Nucci and Marr, 2005). Resistance can be both innate and acquired. *C. glabrata* infections are difficult to treat and are associated with systemic infections having a high mortality rate. *C. glabrata* exhibits a lower oral keratinocyte-adherence capacity compared to *C. albicans*. The virulence factors, and host-parasite interactions of *C. glabrata* are not known (Redding, 2001).

### *Candida guilliermondii*

*C. guilliermondii* has been associated with poor clinical outcomes, and haematologic malignancies (Girmenia *et al.*, 2006). It may be found on human skin, and occur as part of the genitourinary and gastrointestinal tract flora. It can cause infection in patients undergoing surgical procedures, endocarditis in intravenous drug users, and fungemia in immunocompromised patients (Mardani *et al.*, 2000). *C. guilliermondii* has also been isolated in urinary tract infections.

### *Candida krusei*

*C. krusei* causes infection mainly in critically ill patients and is most often isolated in hematology patients with severe neutropenia. It is an uncommon pathogen causing candidemia. Isolates have been reported to be resistant to both fluconazole and itraconazole (Cartledge *et al.*, 1999), and there have also been some reports on resistant strains to amphotericin B (Ellis, 2002). The widespread use of fluconazole to prevent fungal infections in HIV infected patients has lead to a significant increase in *C. krusei*infections (Samaranayake and Samaranayake, 1994).

### *Candida lusitaniae*

The first descriptions of *C. lusitaniae* n 1959 were of a common isolate inhabiting the gastrointestinal tract, and the first reports on cases of human infection caused by *C. lusitaniae* were in 1979 (Holzschu *et al.*, 1979). It is a rare pathogen and few studies have been performed on it. It is less pathogenic than *C. tropicalis* and *C. parapsilosis* ,and causes infection mainly in immunocompressed hosts with prolonged administration of broad-spectrum antibiotics, prolonged hospitalization, cytotoxic or corticosteroid therapy, or granulocytopenia (Viudes *et al.*, 2002). It is also found to cause infections in low birth neonatal (Smith *et al.*, 2005). *C. lusitaniae* may develop resistance to amphotericin B, but the data are contradictory (Ellis, 2002).

### *Candida parapsilosis*

*C. parapsilosis* particularly affects critically ill neonates and surgical intensive care unit patients. Prematurity and low birth weight, have been recognized as risk factors (Sarvikivi *et al.*, 2005). Intravenous drug users have been reported to have fungemia or endocarditis caused *by C. paralopsilosis* and it is also connected to bone and joint infections (Moran *et al.*, 2002). The affinity of *C. parapsilosis*for medical devices such as intravascular catheters and prosthetic devices has been recognized. This has been explained by the findings on *C. palapsilosis* isolates from blood culture producing an extracellular polysaccharide, or slime, which may aid adherence and biofilm formation on plastic surfaces (Moran *et al.*, 2002). It is commonly recovered from human skin, and is quite often recovered from the hands of health care workers. *C. parapsilosis* is susceptible to azoles and polyenes. Tolerance to amphotericin B has, however, been reported (Hazen, 1995). Sarvikivi *et al.*, 2005, reported the emergence of fluconazole resistance in *C. parapsilosis* strains in a neonatal intensive care unit. Fluconazole prophylaxis was used in low doses, and this lead to resistant strains

over a 10-year period.

### *Candida tropicalis*

*C. tropicalis* is the most virulent of the NCAC species. This may be due to its ability to adhere to epithelial cells in vitro, and its ability to secrete moderate levels of proteinase (Moran *et al.,* 2002). It is usually isolated from the oral cavity and skin. It may also cause infections of the esophagus. The latter cases, however, have been shown to correlate with systemic diseases, in other words, poor general health makes the patient liable for candidemia caused by this strain. Pal (1987) is credited to elucidate the role of *C.tropicalis* in lung empyema of a patient in India.

### *Pathogenic non Candida albicans Candida species of domestic Animals*

Mycoses of domestic animals caused by yeast have been recorded for approximately 150 years, since Eberth described candidiasis in poultry in 1858. Numerous yeasts are potential agents of animal mycoses. The majority of these infections are cutaneous and superficial, and are of minor clinical significance but fatal systemic infection are also reported. Currently, most common pathogenic yeasts of domestic animals are included in the genera *Candida*, *Cryptococcus* and *Malassezia* (Pal, 2007; Cabaries, 2010).

There is an increased incidence of *Candida* species isolation from cervical mucus of cows with fertility problems (Panangala *et al.,* 1978 .*Candida* endometritis has been reported in horses and has been implicated as a cause of early embryonic death and infertility. Pregnancy is known to alter the host immune response, and pregnant women have an increased incidence of vaginal candidiasis (Gentry and Price, 1985 ; Seelig, 1966).

In the past, *C. albicans* was assumed to be the only pathogenic yeast of the genus *Candida*. Some of the major non-*Candida albicans Candida* species cited as opportunistic pathogens in domestic animals are summarized in Table-1. *Candida albicans, C. krusei, C. tropicalis*, and *C. parapsilosis* represent 71 % of the *Candida* spp. isolated from domestic animals (Chengappa *et al.,* 1984).The etiologic role of *C.tropicalis* in bovine abortion, and mastitis of dairy cows, and buffaloes has been established (Wohlegemuth and Knudtson,1973; Pal and Lee,1991; Pal,1997).Cutaneous candidiasis in a dog due to *C.guilliermondii* has beenreported by Mueller and co-workers(2002).

### *Antifungal resistance among NCAC species*

Several of these non- *Candida albicans Candida* species exhibit resistance to traditional triazole antifungals like fluconazole, and may also demonstrate cross-resistance to newer triazoles (Magill *et al.*, 2006). This makes it imperative to perform both speciation and antifungal susceptibility testing of all yeast fungi isolated from bloodstream or otherwise.

The most commonly used antifungal agents are azoles (fluconazole, itraconazole, and ketaconazole) and polyenes (amphotericin B). Some Candida species have intrinsic resistance and some develop resistance to azoles. The widespread use of fluconazole and itraconazole as therapeutic or prophylactic doses has increased recently (Moran *et al.,* 2002) and is most often associated with the HIV infected with oropharyngeal candidiasis (Sanglard and Odds, 2002). This has lead to the increase of reports of resistance. *C. krusei, C. inconspicua, and C. norvegenesis* are by nature resistant to fluconazole and *C. glabrata* possess the ability to rapidly develop resistance to fluconazole (Moran *et al.,* 2002). It is believed that prolonged or repeated exposure to low-dose fluconazole may be associated with resistant isolates of *C. albicans,* and to the selection of resistant non-*Candida albicans* species in the patient (Richardson, 2005). Antifungal drugs should be used as high doses only for the treatment of oral candidiasis, not for prophylaxis. In a recent study by Bagg and others (2005), of the 270 *Candida* isolates from patients receiving treatment for advanced cancer 25% were not susceptible to fluconazole at standard doses and 66% of the *C. glabrata* solates were fluconazole-resistant. However, in a study by Kuriyama *et al.*,2005, from a total of 618 clinical *Candida* isolates from patients with different oral diseases almost all were susceptible to fluconazole. Only 6.8% of the *C. glabrata* strains and none of the *C. krusei, C. paralopsilosis, and C. tropicalis* strains were resistant to fluconazole. Itroconazole resistance was found in 23.7% of the *C. glabrata* 3.14% of the *C. krusei*, 7.7% of the *C. tropicalis* and 1% of the *C. albicans* strains.

Amphotericin B is the most commonly used poly-

**Table 1:** Etiologic role of some non- *Candida albicans Candida* species in various clinical disorders of domestic animals

| Candida species | Animal species | | Clinical disorders |
|---|---|---|---|
| *C. cariosilignicola* | Horse | - | Keratomycosis |
| *C. catenulaa* | Poultry | - | Alimentary tract infection |
| *C. famata* | Horse | - | Arthritis |
| *C. glabrata* | Cat and dog | - | Urinary tract infection |
| | Cattle | - | Abortion |
| | Horse | - | Keratomycosis |
| | Pig | - | Alimentary tract infection |
| *C. guilliermondii* | Cat and dog | - | Cutanous and urinary tract infection |
| | Cattle | - | Abortion and mastitis in cattle |
| | Horse | - | Keratomycosis in Horse |
| | Poultry | - | Alimentary tract infection in poultry |
| *C. hellenica* | Cattle | - | Mastitis |
| *C. keyfr* | Cattle | - | Abortion and mastitis |
| *C.krusei* | Cat and dog | - | Urinary tract infection |
| | Cattle | - | Abortion and mastitis |
| | Horse and poultry | - | Alimentary tract infection |
| *C. lusitaniae* | Cattle | - | Abortion and mastitis |
| | Horse | - | Keratomycosis |
| *C. parapsilosis* | Cat and dog | - | Cutaneous and urinary tract infection |
| | | - | Abortion and mastitis |
| | Cattle | - | Arthritis, endocarditis and keratomycosis |
| | Horse | - | Alimentary tract infection |
| | Poultry | | |
| *C. pellicullosa* | Cattle | - | Mastitis |
| *C. pintolopesii* | Swine | - | Alimentary tract infection |
| *C. rugosa* | Cat and dog | - | Urinary tract infection in cat and dog |
| | Cattle | - | Mastitis in cattle |
| | Horse | - | Genital tract infection in horses |
| *C. sake* | Poultry | - | Alimentary tract infection |
| *C. sloofiae* | Pig | - | Alimentary tract infection |
| *C. tropicalis* | Cat and dog | - | Urinary tract infection in cat and dog |
| | Cattle | - | Mastitis in cattle |
| | Horse | - | Arthritis and keratomycosis in horses |
| | Poultry | - | Alimentary tract infection in poultry |
| *C. zeylanoides* | Swine | - | Keratomycosis |

Source: Cabaries (2010)

ene antifungal. It has been in use since the 1950s (Moran *et al.,* 2002). It has a broad spectrum of activity. There have only been few reports on resistant *C. albi*cans isolates. Recently there have been reports on resistant *C. glabrata* and *C. krusei* isolates (Moran *et al.,* 2002). Resistant isolates have also been found in *C. tropicalis, C. parapsilosis, and C. lusitaniae. C. glabrata* is considered as intermediate or susceptible dependent upon dose. Voriconazole is a wide-spectrum azole, which is susceptible to most of the isolated strains but reduced susceptibility to this antifungal has also been reported by Bagg and co-investigators (2005).

### *Conclusion*

Several of these non-*albicans Candid*a species exhibit resistance to traditional antifungals treatments, and may also demonstrate cross-resistance to newer triazoles. This makes it imperative to perform both speciation, and antifungal susceptibility testing of all yeast fungi isolated from bloodstream or otherwise. NCAC have been identified in increasing numbers in patient samples. These species pose a threat in the future due to commonly used antifungal drugs. The pathogenesis and the role of NCAC species in clinical disorder of man and animals are still incompletely understood. New virulence factors, and the mechanisms of virulence in the NCAC species are not fully understood.

It is emphasized that comprehensive epidemiological studies on the role of the different non- *Candida albicans Candida* species in various clinical disorder of humans and animals including their pathogenesis and virulence factors must be conducted. In addition, the further studies on the resistance level of the NCAC species to the present traditional antifungal drugs should be carried out. Finally, the research initiations should be encouraged on the innovation of new drugs against NCAC species.

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