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Emerging Pathogens of the *Candida* Species

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<http://dx.doi.org/10.5772/intechopen.80378>

Abstract

In recent years, opportunistic and nosocomial fungal pathogens have been dominated by yeasts of the genus *Candida*. Most of the research has focused on *Candida albicans* since it is the most prominent etiological agent. There are numerous publications that describe the biology, virulence factors, morphology, immunity, genomics, diseases, and laboratory aspects of *Candida albicans*. In this chapter we offer a historic perspective of *C. albicans* and focus on other non-albicans candida (NAC) that cause serious disease. We review the current knowledge of emerging NAC pathogens with useful graphics and current references. This chapter is laid out as an overview and is geared for students seeking basic information and may be superficial for an infectious diseases clinician.

Keywords: *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. guilliermondii*, *C. auris* and *C. krusei*, non-albicans candida (NAC), fungal pathogen

1. Introduction

By the end of the twentieth century, hospital-acquired fungal infections were on the rise. Infections by yeasts of the genus *Candida* have become one of the most common causes of bloodstream infections [1]. The increase in fungal infections is typically attributed to the longer survival of immuno-compromised individuals as well as the increase in the number of people in long term health care facilities undergoing, immunosuppressive therapy, long-term catheterization, broad-spectrum antibiotic use among others. This alarming increase in nosocomial fungal infections has alerted clinicians and scientist that yeasts, previously thought innocuous and relegated to plant pathology or industrial use were capable of causing serious illness.

While infections caused by *Candida* species are typically superficial and restricted to the urogenital or mucosal oral cavities, they are also capable of entering the bloodstream leading to deep-tissue infections [2].

The predominant yeasts in bloodstream infection remain restricted to the genus *Candida* [3] most of which, belong to the CTG clade, where the CTG codon is translated as Serine rather than Leucine [4]. Although the recent rise in the number of these infections [5] is mainly associated to *C. albicans*, non-albicans candida (or NAC) related diseases are also increasingly reported in different parts of the world [6]. The relative rates of infection among all *Candida* infections are shown in **Figure 1**. There are at least a dozen *Candida* species that can be pathogenic for humans, but more than 90% of reported invasive infections are associated with *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, and *C. tropicalis* [7].

The definition of a new or “emerging” pathogen is subjective at best. For example, how many independent isolations are required before an emerging pathogen is established as an infectious agent? Indications of emerging infections typically consist of case reports. The incidence of yeast infections is likely under-reported because it is dependent on clinical diagnosis and their desire to investigate, then confirm the novelty of the etiological agent, write a compelling report, and to withstand the critique and rigor of publishing the report. A close partnership between a research scientist and a clinical physician is critical for the most rigorous reports.

Furthermore, a single report describing several cases of infection by a novel microbe does not necessarily indicate that a new infection has emerged. Since these temporally separated clinical samples must be confirmed as being independent and not affected by laboratory practices, personnel and/or environmental factors [8]. For example, recent retrospective studies of blood stream infection caused by the genus *Candida*, reported *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. guilliermondii*, and *C. krusei*. This list closely resembles the list of known pathogenic *Candida* species in 1963 [3] suggesting that the emergence of other yeasts

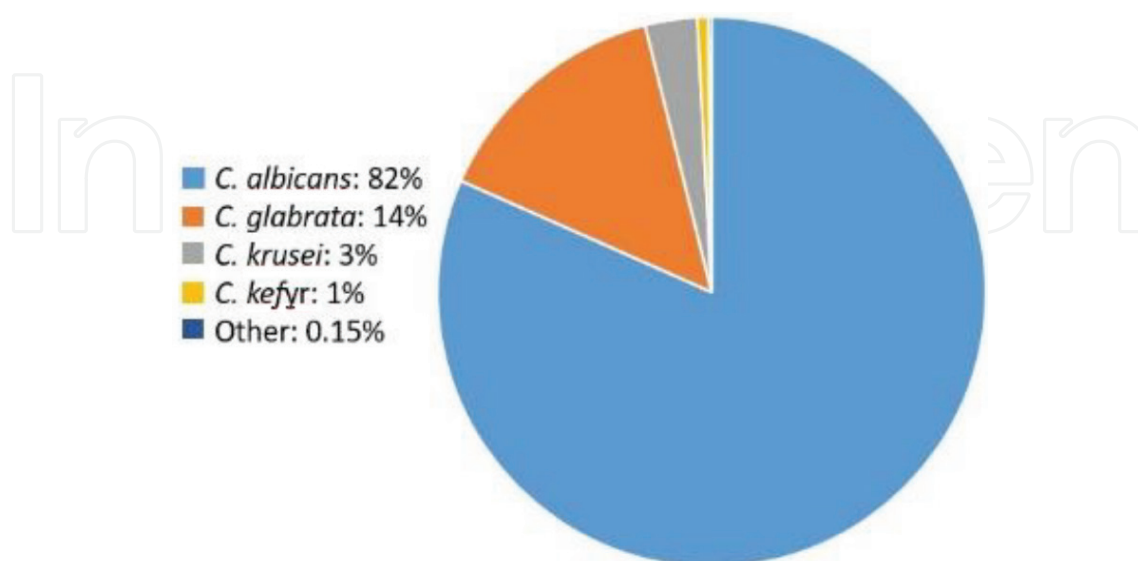


Figure 1. Relative rates of infection with *Candida* species.

as potential bloodstream isolates is a reflection of the changes in medical and laboratory practices since the early 1960s. Another important variable is that the advances in genomic tools coupled with the ability of contemporary blood culture systems and procedures to support the growth of the unusual yeast isolates have greatly accelerated the frequency of isolation and identification of novel (non-*C. albicans*) isolates as important pathogen.

For the purposes of this chapter we limit the definition of emerging pathogens to those that have recently appeared within a population or those whose incidence or geographic range is rapidly increasing or threatens to increase in the near future or those caused by previously undetected or unknown infectious agents.

2. Established pathogens of the Candida species

2.1. *Candida albicans*

The first description of a yeast infection was of thrush, by Hippocrates in the fifth century B.C. [9]. Since its first microscopic detection in thrush swabs by Langenbeck, subsequently Berg and Gruby [9] in 1839, *Candida albicans* has been confirmed to be the primary etiologic agent of thrush and cause of many other forms of mucosal disease. In fact, *C. albicans* is most frequently isolated species from human yeast infections [3]. Here we touch upon some of key features that make *C. albicans* a successful pathogen. The various morphological forms of *C. albicans* (**Figure 2**) have been associated with the shift from commensal or pathogenic states. The change from yeast to hyphae is thought to help cell adhesion and facilitate tissue infection, macrophage evasion and biofilm development [10].

C. albicans is a diploid polymorphic yeast (**Figure 2**) of human mucosal surfaces, a fungus that commonly found in the gastrointestinal (GI), respiratory, and urogenital tracts. It is generally commensal but able to turn into an opportunistic pathogen in immunocompromised or immuno-deficient individuals. It is the major species causing invasive candidiasis (46.3%), followed by *C. glabrata* (24.4%) and *C. parapsilosis* (8.1%) [11]. Systemic infections of *C. albicans* often cause death with a mortality rate of ~40% [12]. One reason leading to over growth of *C. albicans* is its ability to respond to a myriad of environmental imbalances such as changes in nutrition, temperature and pH [13]. Other important factors that increase the risk of *C. albicans* infection are prolonged treatment with broad spectrum antibiotics, surgical procedures, various diseases such as diabetes, trauma, and other genetic disease or congenital malformation. [2].

Candida albicans belongs to the CTG clade of fungal species and translates canonical leucine codons, CTG, to serine [14]. It prefers to use glucose as the carbon and has multiple approaches to transport and metabolize glucose. Nutritional changes alter virulence of *C. albicans* both during systemic infection as well as mucosal vaginitis, suggesting that alternative carbon sources within host environments are important during *C. albicans* infections [15].

Post-transcriptional mechanisms underlying this transition include mRNA stability, alternative transcript localization, and translation and influence *C. albicans* virulence processes. Below we highlight some key pathways but for details refer to book *Candida and Candidiasis* [16].

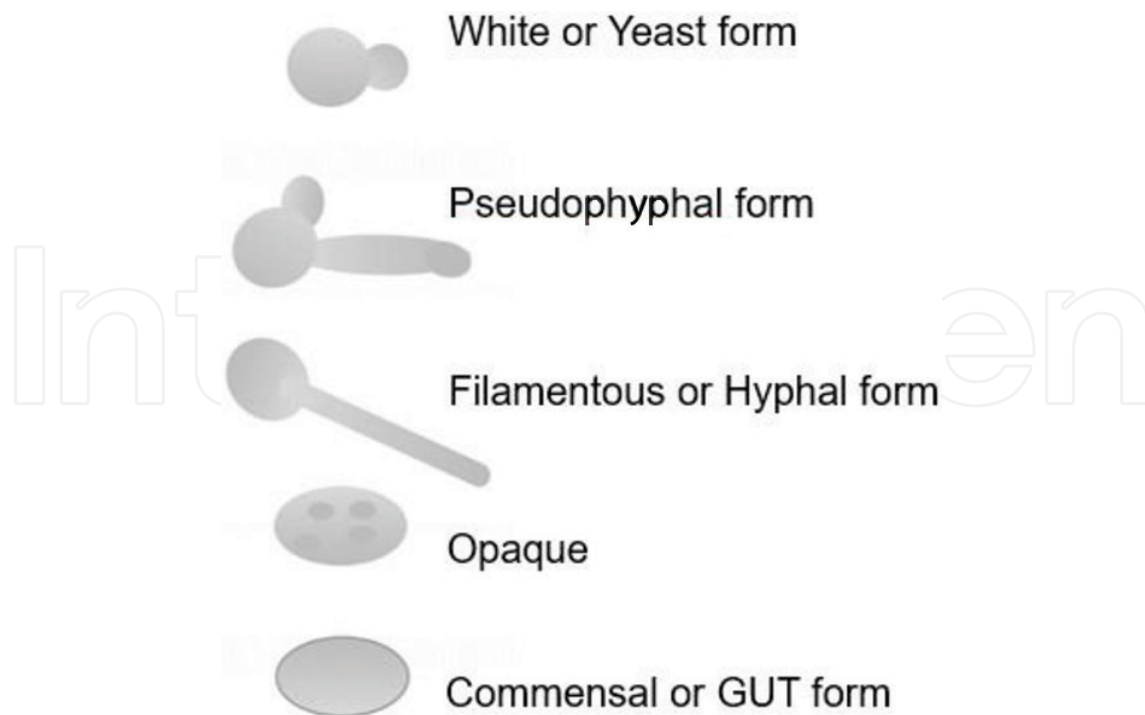


Figure 2. *Candida albicans* polymorphology.

At the transcriptional level, *C. albicans* fibrin Sac6 modulates morphogenesis and oxidative stress responses [17]. As mentioned above, metabolic adaptation a key virulence determinant is involved in the susceptibility of *C. albicans* to antifungal drugs as well as stress resistance and innate immune responses [18]. *C. albicans* typically infects epithelial cells through two specific mechanisms, active penetration and endocytosis. Before the infection, *C. albicans* transfer between commensal and invasive states through distinct genetic pathways to regulate the expression of hypha-specific and/or phase-specific genes. And these genes express proteins to regulate directly or indirectly to the pathogenesis and virulence of *C. albicans* [19]. The gastro-intestinally induced transition (GUT) highlights how these pathways are used [20]. Superficial candida infections require the interaction between fungal cell surface proteins or pathogen associated molecular patterns (or PAMPs) with host innate immune cells system or pathogen recognition receptors (or PRRs) (**Figure 3**). For example, cell-wall β -glucans can stimulate monocyte reprogramming as one of the main immunological responses in hosts [2].

When interacting with macrophages, the SPS system is stimulated in the nutrient poor host environment and is critical for resistance of *C. albicans* to macrophages. It consists of three components; an amino acid transporter, SSY1, a membrane associated protein PTR3 and a chymotrypsin-like serine endoprotease, SSY5. Under conditions of carbon deprivation, signaling through the Stp2 transcription factor triggers the use of amino acids as carbon source which helps neutralize the acidic environment of the phagosomes [21]. *C. albicans* employs several mechanisms to evade immune detection (**Figure 3**, [22, 23]).

C. albicans has significant phenotypic and genetic diversity. It contains a diploid genome of 14.4 megabases arranged within eight chromosomes [24]. The heterozygosity and heterozygous

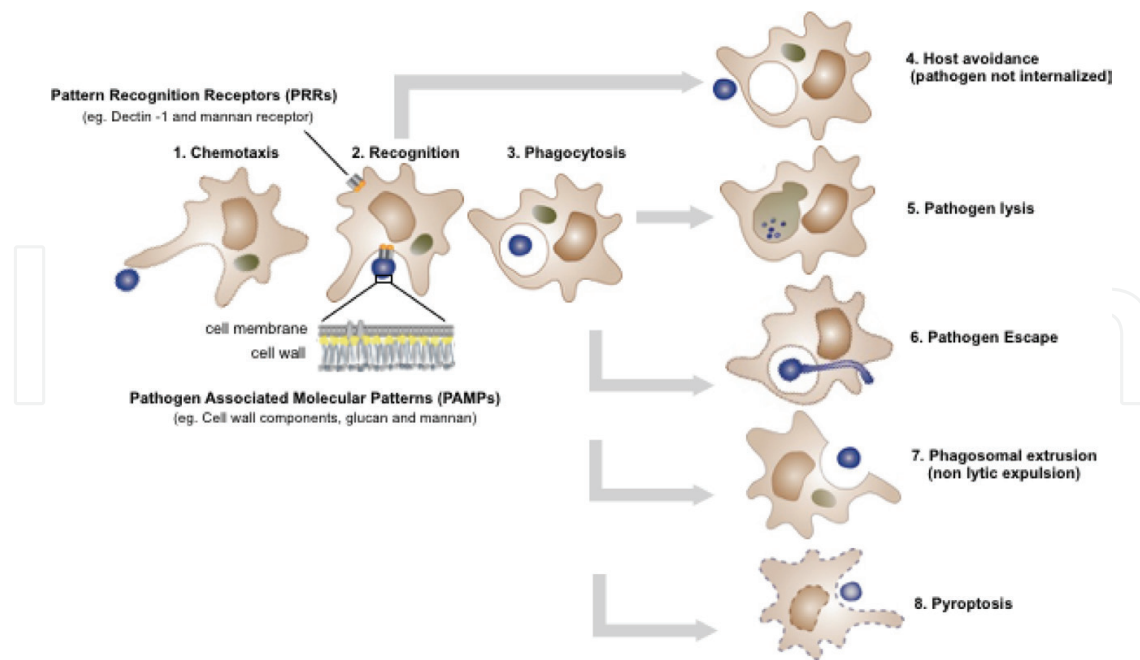


Figure 3. Host-Pathogen interactions. 1. Immune cells chemotax towards the pathogen, 2. fungal cell wall components pathogen associated molecular patterns (PAMPs) interact with macrophage via Pathogen Recognition Receptors (PRRs) such as Dectin-1 and Mannose Receptor that recognize β -(1,3)-glucan and mannan respectively, 3. Phagocytosis, 4. Host avoidance, 5. Pathogen lysis. 6. Pathogen escape, 7. Phagosomal extrusion where pathogen is expelled without lysis and 8. Pyroptosis.

of genome is thought to be related with *C. albicans* virulence and the genomic instability is crucial in its pathogenesis [2]. Differences specific to strains may contribute on the interaction of *C. albicans* and host [24].

Detection and identification of various yeasts has been a challenge. These yeasts can be distinguished morphologically on CHROMagar or spider media (**Figure 4**). However, genome sequencing is the most reliable method for species identification. In addition, detection of microsatellites also represents a reliable method for molecular typing and genetic analysis of *Candida*. A recent *Candida* distribution study conducted in a hospital, reported a clonal population including 62 identified genotypes among the tested isolates [25]. Beyond that, multilocus sequence typing (MLST) is another valuable method to understand the epidemiology of systemic *Candida* infections [2]. Here the DNA of seven housekeeping genes is sequenced. The results showed that MLST of *C. albicans* isolates are highly reproducible and sensitive. Comparative studies using MLST database of *C. albicans* are available online (<http://calbicans.mlst.net/>). These studies allowed further stratify the geographic isolation of *C. albicans*. For example, the most common MLST cluster within the *C. albicans* species is defined as clade 1. While, clade 2 is mainly located in the United Kingdom, clade 4 includes isolates from the Middle East and Africa, clade 11 includes isolates from continental Europe, and clades 14 and 17, where various gene clusters are regrouped include isolates from the Pacific region [26].

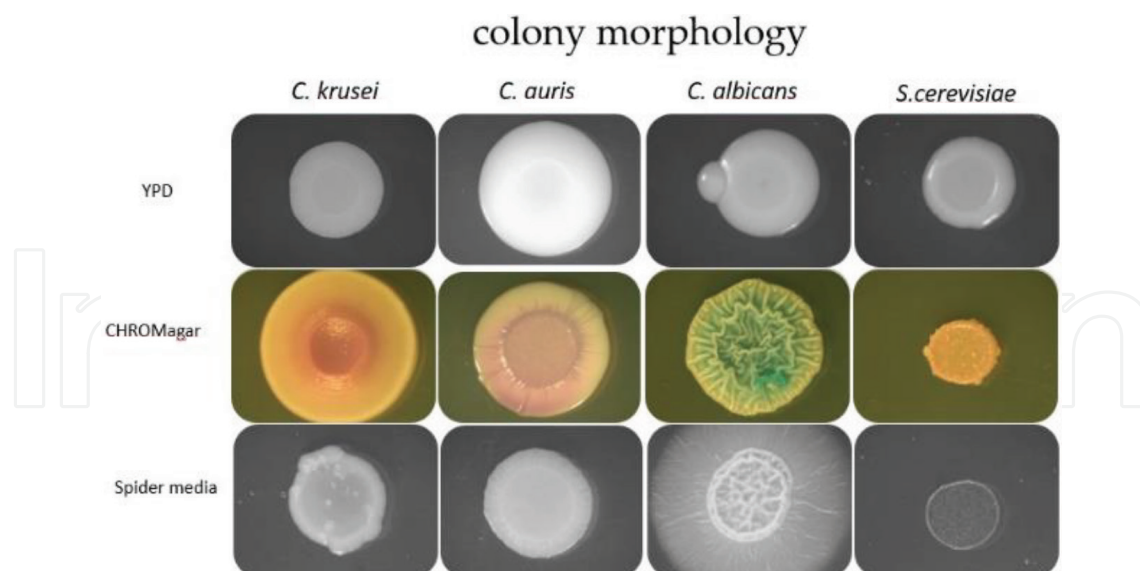


Figure 4. Colony morphology of *Candida krusei*, *Candida auris*, *Candida albicans* vs. *Saccharomyces cerevisiae*.

Pathogen profile: Diploid, belongs to the CTG clade, genome sequence available, antifungal resistance is moderate, molecular laboratory tools available.

2.2. *Candida glabrata*

Candida glabrata is often the second most common cause of candida infections after *C. albicans*. Historically, it has been considered nonpathogenic within the normal flora of healthy individuals without causing serious infection in humans. During the late 1990s, *C. glabrata* genetics was the most advanced among the non-*albicans* *Candida* (NAC) species due to its haploid status, its classical codon usage which allows direct usage of *S. cerevisiae* tools), and its high frequency of isolation in hospitals [27]. *C. glabrata* infections can be mucosal or systemic and often occur in immunocompromised persons or people with diabetes [28].

In contrast to most *Candida* species, *C. glabrata* is not dimorphic and exists as small blastoconidia under all environmental conditions both as commensal and pathogenic. In animal models *C. glabrata* is relatively nonpathogenic suggesting that it has few virulence attributes [28]. However, within the host environment, *C. glabrata* spreads rapidly, and is difficult to treat because it is resistant to many azole antifungal agents. Therefore, *C. glabrata* infections have a high mortality rate in compromised hospitalized patients [28].

C. glabrata has haploid genome, in contrast to the diploid genome of *C. albicans* and some NAC species [29]. It is distinguishable from *C. albicans* by its small-subunit rRNA [28]. *C. glabrata* only use glucose and trehalose. Such unique sugar utilization among *Candida* species can be applied to identify yeast to the level of genus and species. Now commercial kits (API 20C, Uni-Yeast-Tek, and YeastIdent) are available to identify *C. glabrata* in mixed cultures [28].

Both *C. glabrata* and *C. albicans* are commensal suggesting that similar host mechanisms such as suppressing expression of pathogenic determinants may be at play to effectively prevent

infection of both microorganisms. However, the relatively low virulence of *C. glabrata* in animal models compared to *C. albicans* suggests genes controlling the virulence of *C. glabrata* may be different from those in *C. albicans* [28].

C. glabrata isolates are often associated with high resistance to the azole class of antifungal agents and less susceptibility to most other antifungal agents including amphotericin B [30]. Several mechanisms of azole resistance of *C. glabrata* have been identified, such as increased P-450-dependent ergosterol synthesis, an energy-dependent efflux pump of fluconazole and possibly via a multidrug resistance-type transporter [28].

Pathogen profile: Haploid, does not belong to the CTG clade, genome sequence available, antifungal resistance is high, several molecular laboratory tools available.

3. Emerging pathogens of the Candida species

3.1. *Candida auris*

Fluconazole-resistant *Candida* has been identified as a serious public health threat (www.cdc.gov). Among these, *Candida auris* has simultaneously and independently emerged on three continents in several countries as a multi drug resistant fungal pathogen with high mortality [31]. Phylogenetic analysis and polymorphism typing indicate that *C. auris* strains are clonal suggesting likely transmission from an environmental source.

Candida auris, as the name suggests, was first isolated from the drainage of the external ear of a Japanese patient [31] and 15 Korean patients in 2009 [32]. Identification of it is challenging with standard microbiologic techniques. It frequently exhibits multidrug-resistance. Ever since these initial cases, *C. auris* has become an emerging global health threat causing massive invasive infections and outbreaks in healthcare facilities. Cases have already been identified in India, South Africa, Kuwait, the United Kingdom, Venezuela, Brazil, the United States, Colombia, Pakistan, Spain, Germany, Israel, Norway, and Oman [33].

Phylogenetically, *C. auris* is closer related to *Candida haemulonii* and *Candida ruelliae* [31] while distantly related to other more common pathogens *C. albicans* and *C. glabrata* [34]. Four distinct clades have been identified from geographic separate origins, suggesting almost simultaneous emergence of populations [35]. Susceptibility to antifungal reagents and survival from phagocytosis is largely different among four clades (CDC report).

Risk factors for *C. auris* infection appear to be similar to infections from *Candida* in general. *C. auris* is reported to grow at temperatures ranging from 35 to 42°C. It forms pink colonies on chromogenic media. *C. auris* does not form pseudohyphae (**Figure 4**) but capable of forming biofilms [36] and adhering to catheter material, although to a lesser degree as compared to *Candida albicans* [37]. Some *C. auris* strains produce phospholipase and proteinase, which may account for the variability in pathogenicity in a murine model [37].

The genomes of several isolates have been sequenced and they appear to parse into four distinct clades by geographic region [35]. Clades were separated by thousands of single-nucleotide

polymorphisms, but within each clade isolates were typically clonal. Various mutations in *ERG11*, the gene encoding for lanosterol 14- α -demethylase and induced upon prolonged growth with antifungal drugs were shown to be associated with azole resistance in each geographic clade.

Again, while whole genome sequencing is the most reliable method for species identification, PCR and real-time PCR assays have shown excellent accuracy and have been effective for diagnosis, to rapidly identify *C. auris* [38]. The development of new antifungal medications with activity against *C. auris* will be vital to controlling *C. auris* as therapeutic options are already limited. Also aggressive infection control measures are critical to reducing the spread of *C. auris* [33].

Pathogen profile: Haploid, belongs to the CTG clade, Genome sequence available, antifungal resistance is high, several minimal molecular laboratory tools available.

3.2. *Candida krusei*

Candida krusei was first discovered in 1839 by Langenbeck from a patient with typhus, 75 years later Castellani proposed the suggestion that *C. krusei* may cause disease in humans [39]. Since then, it has been generally considered as a commensal in warm-blooded animals with low pathogenicity and virulence. In humans, *C. krusei* is generally considered to be a transient commensal and is infrequently isolated from mucosal surfaces. However, since 1960s there has been an increase in the number of reports of *C. krusei* as a human pathogen.

In contrast to most other ovoid shaped *Candida* spp., *C. krusei* cells are generally elongated in a feature similar to *C. kefyr* (formerly known as *C. pseudotropicalis*) among clinically important *Candida* spp. *C. krusei* has various colony morphologies. It has a multilayered cell wall consisting of an outer irregular coat of flocculent material, an electron-dense zone, a granular layer, a less granular layer, a thin layer of dense granules and another sparsely granular layer outside the cell membrane. The mannan component of the *C. krusei* cell wall has been shown to be different from other *Candida* spp. in containing (1–2) and (1–6) side chains in the ratio of 3:1 as being lightly branched [40]. Such differences may account for the variable behavior of *C. krusei* in biological fluids such as saliva and bronchial lavage fluid comparing with other *Candida* spp.

C. krusei has two basic morphological forms, yeast and pseudohyphae and both are often present simultaneously in growing cultures and not easily separated. *C. krusei* grows at a 37°C but can withstand temperature up to 45°C. *C. krusei* can grow in vitamin-free media even though most common *Candida* spp. require biotin or additional vitamin for growth. *C. krusei* ferments and assimilates glucose only as carbohydrate [39].

Like *C. auris*, *C. krusei* can adhere to abiotic surfaces but not to the same extent as *C. albicans*. Although adhesion to host surfaces is essential for colonization and invasion, *C. krusei* is able to colonize readily to inert surfaces such as implants and catheters by virtue of its cell surface hydrophobicity. Less pathogenic species—*C. parapsilosis*, *C. pseudotropicalis* (now *C. kefyr*) and *C. glabrata*—usually produce significantly less biofilm than the more pathogenic *C. albicans*,

but *C. krusei* produced the most extensive biofilm on the surfaces of polyvinyl chloride catheter disks regardless of the growth medium. This could demonstrate the very high cell surface hydrophobicity, and adherence of *C. krusei* to inert plastic surfaces, which may then have other species, facilitated biofilm development [39]. *C. krusei* does not adhere to buccal epithelial cells whereas *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*, and *C. kefyr* do.

The susceptibility to lysozyme, an antimicrobial enzyme produced in phagosomes has been used as a method to assess the microbial virulence. Such tests indicate that the susceptibility to lysozyme of *C. krusei* > *C. parapsilosis* > *C. tropicalis* > *C. guilliermondii* > *C. albicans* > *C. glabrata*, the latter being the most resistant to lysozyme [41]. Interesting when pre-incubated in sucrose-supplemented media, *C. krusei* becomes highly sensitive to lysozyme as compared to *C. albicans*.

Pathogen profile: Diploid, does not belong to CTG clade, genome sequence available, antifungal resistance is high, minimal molecular laboratory tools available.

3.3. *Candida kefyr*

C. kefyr was first found in dairy products such as fermented milk, cheese, and yoghurt [42]. It was first isolated from a *C. kefyr* sample in 1909, named *Saccharomyces fragilis* at first, then *C. pseudotropicalis* and was reclassified as *Kluyveromyces marxianus* [43].

C. kefyr is rarely associated with disease [44] representing ~1% isolates of *Candida* spp. from clinical specimens [7, 45] (**Figure 1**). The first case of invasive *C. kefyr* (*C. pseudotropicalis*) was identified in a 58-year-old female with metastatic adenocarcinoma of the breast [46]. It has been reported to colonize oral cavities, gastrointestinal tract, and urinary tract. All infected patients were immunocompromised and had several potential risk factors [43]. There are only a few published cases of invasive *C. kefyr* infections.

These emerging pathogens of the *Candida* species themselves are typically not more virulent than *C. albicans*. It is generally thought that their conversion from commensalism to parasitism is largely determined by the host immune status [39]. In some cases these pathogens are resistant to multiple antifungal agents. For example, >90% of the recently emergent *C. auris* isolates are resistant to fluconazole, >30% are resistant to amphotericin B, and >5% to echinocandins, and >40% are resistant to classes of antifungal agents, while 4% are resistant to all three classes of antifungals available [35].

Pathogen profile: Ploidy is not determined, does not belong to CTG clade, Genome sequence available, antifungal resistance is moderate, few molecular laboratory tools available.

4. Other *Candida* species

Candida lusitanae was firstly isolated from warm-blooded animals and was shown to cause opportunistic infections in humans in 1979 [47]. It is distinguished from other *Candida* species by its resistance to Amphotericin B however resistance profile *in vivo* is similar to

other *Candida* species. Like most pathogens of the *Candida* species, *C. lusitaniae* has similar ability to colonize individuals but can opportunistically infected in immune-compromised patients [48].

Pathogen profile: Haloid, belongs to CTG clade, genome sequence available, antifungal resistance is moderate—high, few molecular laboratory tools available.

Candida tropicalis is another prevalent NAC pathogen in *Candida* species. In immunocompromised mice and human patients, *C. tropicalis* isolates appeared to have increased virulence. Secreted aspartyl proteinase 5 and 9 (Sap5 and Sap9) antigens are expressed by *C. tropicalis*. Invasive *C. tropicalis* infections were found more frequently in acute leukemia or bone marrow transplants patients may indicate that polymorphonuclear leukocytes are the first defense line against of *C. tropicalis* [49]. Overexpression of *ERG11* gene mutations in *C. tropicalis* likely causes resistance to azoles.

Pathogen profile: Diploid, belongs to CTG clade, genome sequence available, antifungal resistance is moderate, several molecular laboratory tools available.

Candida dubliniensis is a species of chlamydospore- and germ tube-positive yeast, primarily recovered from HIV-infected individuals and AIDS patients. It has been shown to grow well at temperatures ranging between 30 and 37°C but not 42°C. *C. dubliniensis* is unable to express beta-glucosidase activity [50].

Pathogen profile: Diploid, belongs to CTG clade, genome sequence available, antifungal resistance is moderate, several molecular laboratory tools available.

Candida parapsilosis has increased in significance and prevalence over the past 2 decades. The infections are mainly associated with prosthetic devices and catheters, especially in the nosocomial spread. Risk factors of *C. parapsilosis* infections include the hydrolytic enzymes secretion, prosthetics adhesion, and biofilm formation [51].

Pathogen profile: Diploid, belongs to CTG clade, genome sequence available, antifungal resistance is moderate-high, several molecular laboratory tools available.

Candida guilliermondii is the sixth frequently isolated *Candida* species, an emerging pathogen in Latin America that rarely causes invasive candida infections. However, it has been reported to exhibits reduced susceptibility to fluconazole [52] thus further study of the anti-drug mechanism is required.

Pathogen profile: Haploid, belongs to CTG clade, genome sequence available, antifungal resistance is high, several molecular laboratory tools available.

Candida lipolytica (also known as *Yarrowia Lipolytica*) isolates formed narrow, multi-branched, true hyphae on cornmeal-Tween 80 agar [53]. *C. lipolytica* is a weakly virulent pathogen that is most clearly vascular catheter-related. It is sensitive to Amphotericin B and Ketoconazole *in vitro*.

Pathogen profile: Haploid, does not belongs to CTG clade [54], genome sequence partially available, antifungal resistance is moderate [55], few molecular laboratory tools available.

Candida rugosa rarely causes invasive infections; however, recently, isolates have been shown to be an increasing cause of fungal infections especially in Latin America. Besides, *C. rugosa* appears decreased susceptibility to fluconazole with various patterns following geographic regions [56].

Pathogen profile: Haploid, belongs to CTG clade, genome sequence is not available, antifungal resistance is high, few molecular laboratory tools available.

Acknowledgements

This work was supported by Worcester Polytechnic Institute.

Conflict of interest

There is no conflict of interest concerning this chapter.

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