

An Overview to Candidiasis - Types of Candidiasis, Virulence Factors, Symptoms of Infection and Treatment

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ABSTRACT

Candida is a kind of yeast, is a fungus that infects the body. Candidiasis is known as yeast contagion because the infecting agent is a yeast, Candida albicans. Candida albicans are the pathogens that are of much significance which are present everywhere and mostly reside along side plentiful bacteria near mouth, gastrointestinal tract and vagina. Hippocrates was the first person to describe candidiasis in 1849. Candidiasis of the mouth is termed as Thrush. Cutaneous candidiasis is a skin infection that occurs in parts of the skin that have very little ventilation and are rarely moist. Deep Candidiasis occurs when fungi infiltrate the body, enter the bloodstream, and spread throughout the body. Treatment methodology are different for each case. Natural prevention is mandatory to safe yourself from being a victim to disease.

Keywords: *Candidiasis, Virulence Factors of Candida, Types of Candidiasis, Symptoms and Treatment.*

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INTRODUCTION

Candida fungi causes candidiasis. Almost 200 various species are included in the genus *Candida* but only minute quantity of them are harmful and can lead to infections which can either be external or internal (if it invades inside the body) which are more severe. *Candida albicans* are the pathogens that are of much significance which are present everywhere and mostly reside along side plentiful bacteria near mouth, gastrointestinal tract and vagina. The body's immune system and the present bacteria regularly monitors the candida and any impairment in the immune system or change in bacteria can result in candida causing an infection. Generally, these infections are mostly restricted to mouth, genital area and skin but a person with any other serious condition like cancer or HIV whose internal defence system is already much weakened can develop much severe one (Calderone & Clancy, 2011; Qadir & Asif, 2020).

Historical Overview of Candida:

The history of *Candida* dates back to the fourth century BC when Hippocrates described oral thrush (Anderson & Odds, 1985). Haussmann proved in 1875 that the causal organism in vulvovaginal candidiasis and oral candidiasis was the same (Lynch, 1994). Charles-Philippe Robin (1821-1885) called it *Oidium albicans* in 1853, but Zopf changed it to *Monilia albicans*

in 1890 (Vincent, 2012). Gruby identified the fungus that causes thrush as *Sporotrichum* by Robin in 1842, as *Oidium albicans* by Berkhout in 1923 (which means whiten). *Candida* comes from the Latin term "toga candida", referring to a specific white gown used by Roman Senate candidates. This term is most likely originated from white agar colonies or oral thrush sores (Acharya *et al.*, 2017; Kohli & Shinde, 2019).

What is Types of Candidiasis?

1. Superficial infection:

1.1 Oral Candidiasis:

Oral Candidiasis is a common fungal infection that affects the mucosa of the mouth. *C. albicans* are responsible for these lesions. This organism is believed to be a part of the normal oral microflora, and approximately 30% to 50% of people carry it (Singh et al., 2014). *C. albicans* is retrieved from the mouths of 60% of dentate patients over 60 years. Numerous *Candida* species are found in the oral cavity (Rao et al., 2013).

1.2 Vulvovaginal Candidiasis:

Vulvovaginal Candidiasis (VVC) is a severe worldwide health problem caused mainly by the polymorphic fungal pathogen *C. albicans*, continues to pose severe quality of life problems for immunocompetent women (Achkar & Fries, 2010) (Richardson et al., 2018). In one-third of cases, *Candida* species can cause vaginitis in women of childbearing age (Buggio et al., 2019). Itching, swelling, and painful feelings in the vaginal and vulvar tissue, frequently followed by odorless vaginal discharge, are symptomatic VVC. Several effective anti-*Candida* defense mechanisms in the vagina (including mannose-binding lectin associated with epithelial cells that activate complement) appear to tolerate long-term persistence of a low yeast concentration without initiating any symptoms (Cassone & Sobel, 2016).

1.3 Cutaneous Candidiasis:

Cutaneous Candidiasis is a type of superficial Candidiasis that affects wet, moist areas of the skin, particularly the intertriginous and axillary regions. Dark red itching and painful vesicles are the first signs of infection, followed by the development of dandruff on the skin (Chirac et al., 2014; Alter et al., 2018).

Although *Candida* spp. are a natural component of the skin's flora, the studies are estimated that between 20% and 25% of the world's population suffers from fungal skin infections, the most common of which is *C. albicans* (Havlickova et al., 2008). Symptoms of skin infection include thickening, flaking, and redness (Kashem & Kaplan, 2016).

2. Systemic Infection:

2.1 Alimentary Tract Infection:

Esophageal Candidiasis is the most prevalent cause of esophagitis. Many patients suffer from gastro-esophagitis with a prevalence of up to 88 % due to *C. albicans*, and since *Candida* yeasts are part of the natural flora present in the mouth, but when the host defense mechanisms are compromised, this causes *Candida* yeasts to spread over the esophageal mucosa (Alsomali et al., 2017). The incidence of esophageal Candidiasis ranged from 0.32 to 6.0% in humans, and it seems that the prevalence of esophageal Candidiasis in patients with AIDS is due to diseases that accompany diabetes or from the frequent use of drugs such as antibiotics (Pappas et al., 2016).

2.2 Respiratory Tract Infection:

The respiratory channels are infected with *Candida* yeasts, particularly the lung and respiratory bronchioles, causing chronic bronchitis infections (Vidigal & Svidzinski, 2010). However, in human *Candida* yeast infections are rare in the respiratory system due to the difficulty of recognizing them, except through their development in certain materials such as cerebrospinal fluid or blood or special culture media (M. Patel et al., 2015).

2.3 Urinary Tract Infection:

Candidiasis is one of the infectious agents that have been diagnosed in people with urinary tract infections (Bongomin et al., 2017). *C. albicans* is the primary pathogen isolated from most urine samples (Kalantar et al., 2015). *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. guilliermondii*, and *C. kefir* are also isolated from UTIs (Tan & Chlebicki, 2016).

Virulence Factors :

Candida has the capacity to infect a wide range of organisms due to a variety of virulence factors. These features, which include structural changes between yeast and hyphal forms, adhesin expression, cell invasion, thigmotropism, biofilm formation, phenotypic switching, and the production of hydrolytic enzymes, are referred to as virulence factors [Figure 1]. Furthermore, suitable characteristics include quick adaptability to pH variations in the environment, metabolic flexibility, strong food collecting systems, and stress response devices (Nicholls et al., 2011).

1. Adherence:

The cell wall of *Candida albicans* is vital for the pathogen's pathogenicity because it includes mannoprotein derivatives that aid *Candida* in defending itself against the host's immune system. (Nasution, 2013). *C. albicans* cells can form complexes with host cells and abiotic surfaces, facilitating colonization and biofilm formation (Zordan & Cormack, 2011; de Groot *et al.*, 2013; Lohse *et al.*, 2018). Three domains include ALS adhesins: the ligand-binding domain at the N-terminus (Lin *et al.*, 2014). In *C. albicans*, nine members of the ALs gene family (Nobile *et al.*, 2008) (Hoyer & Cota, 2016). Als3 acts as an invasion factor, allowing the fungal invasion to the host tissue (Phan *et al.*, 2007) and iron uptake (Almeida *et al.*, 2008). Als3 plays a key role in biofilm generation (Vandermeulen *et al.*, 2006) (Czuban, 2020). In *C. albicans*, the hyphal wall protein 1 (Hwp1) is the founder of a second family of five adhesins expressed exclusively during hyphal development (de Groot *et al.*, 2013). Both virulence and mating include the Hwp family. Yeast wall protein 1 (Ywp1) prevents yeast cells from adhering to surfaces, enabling them to escape and possibly helping fungal spread during systemic Candidiasis (Granger, 2012). The HYR gene family has twelve members and encodes a third group of putative adhesins (de Groot *et al.*, 2013).

2. Invasion mechanisms:

C. albicans is the most prevalent fungal pathogen that infiltrates host cells (Naglik *et al.*, 2011; Wächtler *et al.*, 2012). The fungal proteins Ssa1 and ALs3 are responsible for endocytosis. These proteins can be located on the cell membrane. The interaction of these proteins with "E- and N-cadherins" on epithelial and endothelial cells, as well as epithelial growth factor receptors on oral epithelial cells, allows fungal cells to invade, resulting in a remodelling of the host's cytoskeleton (Sun *et al.*, 2010). (Solis *et al.*, 2017). Active penetration occurs when hyphae extend into host tissue. This is the most frequent mechanism for fungi to infect oral epithelial cells and the only way discovered in enterocytes (Dalle *et al.*, 2010); (Wächtler *et al.*, 2010). It has also been hypothesized that secreted aspartic proteases contribute to active penetration (Dalle *et al.*, 2010).

C. albicans uses hyphal development and released virulence proteins to exert physical force against host cell membranes (Wächtler *et al.*, 2012). In the meanwhile, host cells use a variety of processes to expand and repair damaged membranes (Westman *et al.*, 2019). As a result, a "invasion cavity" forms in which the invading hypha is enclosed by the host membrane (Moyes *et al.*, 2016). The squeezed space enclosing the hypha inside the invasion pocket permits *C. albicans* produced virulence agents to aggregate to high local concentrations, causing additional injury and tension to the host (Moyes *et al.*, 2016). (Allert *et al.*, 2018).

3. Biofilm formation:

Biofilms are a popular source of nosocomial infection (Nobile & Johnson, 2015). Additionally, they exacerbate clinical difficulties due to antifungal drug resistance (Taff *et al.*, 2013). The attachment of *C. albicans* cells to the surface initiates the formation of biofilms. Contact with the surface promotes hyphal growth (see Cellular polymorphism), biofilm formation, and the formation of extracellular matrix, and the biofilm matures into a well-organized and stable structure (Nobile & Johnson, 2015). Biofilm formation is a complex process that involves adhesin expression, cellular morphogenesis, and extracellular matrix formation, all of which are regulated by a network of transcription factors. As a result, the formation of biofilms is regulated by a complex transcriptional network containing over 1000 genes (Nobile *et al.*, 2012) (Lohse *et al.*, 2018). ALS family members are among the target genes, as they are necessary for biofilm formation and promote fungal cell aggregation through amyloid formation (Dehullu *et al.*, 2019).

4. Hyphal Formation:

Environmental factors such as a lack of nitrogen, which causes malnutrition and stimulates the mitogen-activating protein kinase (MAPK) kinase cascade, and the cAMP-PKA pathway, which promotes hyphal development, are among the factors that regulate hyphal formation in *C. albicans* (Gow *et al.*, 2012).

Temperatures above 35°C and natural pH cause hyphae to form, but pseudohyphae form when

phosphate levels are high. The hyphae do not have a narrowing of the neck of the mother cell and have parallel arms, which distinguishes them from pseudohyphae, which have a constricted neck of the mother cell (Sudbery et al., 2004).

5. Hydrolytic enzymes:

Extracellular hydrolytic enzymes tend to play a critical role in host tissue adherence, infiltration, invasion, and degradation (Silva et al., 2012). *C. albicans* hydrolase secreted 3 significant classes of hydrolase: protease, phospholipase, and lipase. These hydrates aid successful pathogen penetration into host cells and extracellular absorption of nutrients from the atmosphere. Around ten aspartic proteins (Sap1-10) are identified, although their precise contribution to pathogenicity is debatable, and there are four main groups of phospholipases (A, B, C, and D), with all five members of class B active in disturbing the host cell membrane. Lipase comprises ten different enzymes (LIP1-10) that have been shown to suppress virulence in experiments (Wächter et al., 2012).

6. Polymorphism:

C. albicans is a polymorphic microorganism that may form elongated ellipsoid yeast cells or elongated cells with parallel-walled walls and septal compressions (Sudbery et al., 2004). Dimorphism refers to the transition between yeast and hyphal forms, and it has been claimed that both growth forms are required for pathogenicity (Jacobsen et al., 2012). There is a major change in gene expression patterns, cell wall composition, and the expression of many virulence factors during the transition from yeast to hypha (Jacobsen et al., 2012; Meyer et al., 2013). 2020 (Chen et al.). Physiological temperatures (>36°C), hunger, an ambient pH more than 7, the presence of serum, N-acetylglucosamine, or high CO₂ levels can all cause morphological alterations in the host niche (Meyer et al., 2013).

7. Host adaptation:

Rather of direct contact with the host, adaptation increases virulence by increasing the physiological strength of fungus in the host's ports. Adaptation in *Candida albicans* involves metabolic flexibility, powerful nutrition acquisition systems, and robust stress response mechanisms (Meyer et al., 2013). (Brown,

Budge, et al., 2014). These features contribute to *C. albicans*' success as both a commensal and a human disease (d'Enfert et al., 2020).

8. Host damage:

C. albicans obtain cytoplasmic nutrients by causing damage to host cells, and fungi possess a complex set of weapons for this purpose. The host-secreted hydrolase, including phospholipase B1, lipase, and secreted aspartic protease (Saps), accumulate in the invasion pocket and the host's membranes, proteins, and extracellular matrix degrade, releasing nutrients (Schofield et al., 2005). It also produces candidalysin, a pore-forming toxin encoded by the ECE1 gene (Moyes et al., 2016).

9. Metabolic adaptation:

Metabolic adaptation is needed for commensalism and virulence, which are intimately linked to other characteristics of pathogenicity (Brown, Brown, et al., 2014). *C. albicans* prefers glucose as a carbon source but changes the metabolism to depend on other carbon sources in glucose-limited environments, such as the colon or after entrapment in the phagosome (Barelle et al., 2006). Even when glucose is inaccessible, *C. albicans* may simultaneously use alternative carbon sources through multiple pathways (Childers et al., 2016). The metabolic adaptation of fungi allows them to thrive in a wide variety of host niches. In addition, it affects the tolerance of *C. albicans* to antifungal medications and environmental stressors (Ene et al., 2012).

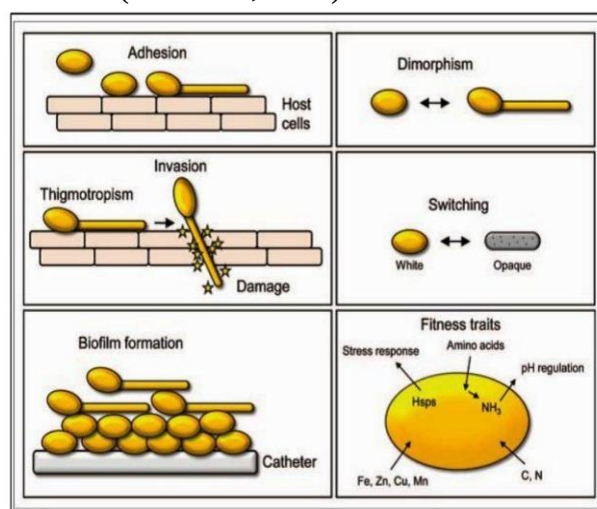


Figure 1: Virulent factors contribute to the pathogenicity of *Candida* Spp. (Mayer et al., 2013).

Symptoms of Infection:

The symptoms of candidiasis vary differently according to area of infection as oral thrush, exhaustion due to magnesium loss, urinary tract infections, digestive system consequences like cramps, constipation, gas etc. Skin and nail infections (Qadir & Asif, 2020).

Treatment:

For Thrush, anti-fungal medicines are usually prescribed like nystatin and clotrimazole. If the infection is not severe then fluid form of nystatin or clotrimazole lozenge can be orally swallowed. In case of severe infections, Fluconazole is prescribed to take one tablet in a day. For the treatment of Cutaneous Candidiasis, blend of lotions, creams and ointments are prescribed, and the patient is directed to keep the affected area dry and clean. For Vaginal candidiasis, creams and ointments for direct applying or oral medicines like prescribed butoconazole, clotrimazole, nystatin, tioconazole or fluconazole can be prescribed. Deep Candidiasis required

intravenous antifungal dosage for treatment. It can be series of antifungal doses until fully treated (Jennings & Brush, 2013) (Wall et al., 2019).

CONCLUSION:

Candidiasis is a fungal infection caused by a yeast (a kind of fungus) called *Candida*. *Candida albicans* is the most prevalent *Candida* species that may infect humans. *Candida* generally resides on the skin and within the body, in locations including the mouth, throat, intestine, and vagina, without creating any difficulties. *Candida* may cause infections if it develops out of control or penetrates the body deeply.

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