

Clinical Manifestations of Candidiasis: Beyond *Candida albicans*

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Abstract

Fungal infections, including the *Candida*, species, are increasingly becoming problematic over the last two decades particularly in immunocompromised individuals. While there are over 150 different species only a few are pathogenic. The *Candida* species can evade the immune system and become pathogenic by a variety of factors including morphology, escaping phagocytosis, expression of adhesins and invasins, biofilm production due to contact sensing and thigmotropism, inhibition of the cytokine, interleukin 17, and production by the host. *Candida* infections produce both non-life, and life threatening manifestations and certain risk factors make infections more likely. Clinical manifestations include oral, genitourinary, gastrointestinal, and cutaneous candidiasis. Diagnosis of candidiasis can be problematic, however antigen testing, agar growth, and microscopic examination are available. Treatment of candidiasis rely on three principal antifungal agents; azoles, polyenes, and echinocandins. These three drug classes have specific drug target.

Keywords: Pseudohyphae; Chlamydo spores; Hyphal Cells; Albicans

Abbreviations: PAMPs: Pathogen-Associated Molecular Patterns; TLRs: Toll-like Receptors; CLR: C-type Lectin Receptors; MR: Mannose Receptor.

Introduction

The occurrence and prevalence of invasive fungal infections have been increasing over the past few decades, particularly in the immunocompromised patients and or individuals with predisposing conditions [1]. The increase of fungal infections over the past two decades is multifactorial, including patient demographics, higher occurrence of chronic diseases, and immunocompromised individuals, etcetera [2].

Fungal pathogens can be broadly grouped into three categories: opportunistic, true pathogens, and rare “emerging” opportunistic fungi. The difference between a

true and opportunistic pathogen is that a true pathogen is an infectious agent that causes disease in any susceptible host. In comparison, an opportunistic pathogen is a causative agent that generally only causes disease in the immunocompromised individuals and rarely in healthy patients. Lastly, rare “emerging” opportunistic fungi are pathogens that are not commonly seen and are generally reported in severely immunocompromised patients.

Fungal species generally grow in three main morphologies: yeast, hyphae, and pseudohyphae. However, *Candida* species have been noted to also produce chlamydo spores in vitro and rarely in infected tissues. Yeast cells are single cells that are spherical and can display both axial and bipolar budding patterns. Hyphae and pseudohyphae are also referred to as filamentous morphologies because the cells generally grow in a polarized manner and elongate. What

differentiates these two cell types is that hyphae cells are uniform in width and have true septa lacking constrictions, whereas pseudohyphae are ellipsoidal and have constrictions at the septal junctions. In both yeast and pseudohyphae, nuclear division occurs, and septum ring forms entirely across the mother-daughter bud neck. On the other hand, those events occur within the germ tube during the first cell division for hyphal cells. Additionally, the initial germ tube development happens before the G 1/S phase transition, whereas in yeast and pseudohyphae, in synchrony with the cell cycle. Upon finishing the first cell division, hyphal cells arrest in G1 cell phase until enough cytoplasmic mass has accumulated to move into the next cell cycle. As a result, hyphal cells have less branched compared to pseudohyphae cells. All these morphologies discussed are vegetative cell types. The final morphological structure is the chlamydospores. These are large, round, and thick-walled cells that customarily formed at the ends of hyphae filaments. Chlamydospores tend to form under stressful and poor nutrient environments. Two *Candida* species have been cited as forming chlamydospores: *C. albicans* and *C. dubliniensis*, along with other classical dimorphic fungi [3,4]. This cell structure is rare, and little is known about its function.

The *Candida* species are members of the kingdom Fungi, the phylum Ascomycota, class Hemiascomycota, and lastly the order Saccharomycetales [5,6]. There are more than 150 known *Candida* species; however, only 15 of those species are of clinical importance: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida guilliermondii*, *Candida lusitanae*, *Candida dubliniensis*, *Candida pelliculosa*, *Candida kefyr*, *Candida lipolytica*, *Candida famata*, *Candida inconspicua*, *Candida rugosa*, and *Candida norvegensis* [7]. Isolation frequencies vary among these species, but it has been determined that approximately 95% of *Candida* infections are caused by *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei* [7]. *Candida* species are either diploid or haploid. A few *Candida* species that are haploid include *C. glabrata*, *C. lusitanae*, and *C. guilliermondii* [8,9]. The other *Candida* species including *C. tropicalis*, *C. parapsilosis*, *C. albicans*, and *C. dubliniensis* are all diploid [8]. However, *C. albicans* has been seen in the diploid state; this state has been observed during periods of increased stress and during mating.

Candida albicans natural isolates are diploid and initially thought that it did not to have a sexual form of reproduction. While conventional meiosis has not been observed; *C. albicans* has two mating types (a and alpha).

These a and alpha stains have been shown to be capable of mating and form a tetraploid. This alternation of the cell type from diploid to tetraploid and then return to diploid without meiosis is termed 'parasexual.' Before undergoing the parasexual cycle, diploid cells must switch to an opaque phase. Once in the opaque phase, mating is like *Saccharomyces cerevisiae*.

Candida albicans is one of the most researched and clinically isolated opportunistic pathogens. Non-*albicans Candida* species (NAC) has been on the rise of being reported as colonizers and causative agents [5]. Many of these NAC infections account for approximately 50% of the non-superficial *Candida* infections; most commonly caused by *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* [5,10].

While specific aspects of *Candida* species have been discussed in previously published papers; they primarily focused on *Candida albicans*. This review focuses on complying with current knowledge of epidemiology and pathogenicity, clinical manifestations and therapeutic strategies beyond *Candida albicans* that are of clinical relevance.

Candida Species Distribution

There are over 150 species of *Candida* in nature, but only a small portion are human pathogens. Over the past few decades, the incidence of *C. albicans* has decreased and has begun to shift to non-*albicans* species. This shift has many factors and may be due to immunosuppression, increase the use of broad-spectrum antibiotics, and an increase in older infected patients. As the *Candida* infections shift more to non-*albicans* species, the concern increases.

In North America, *C. albicans* was isolated 64% in Canada and 48.9% in the USA in during the 1990's but has since decreased to 38% over the past two decades and shifted towards *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* [7]. Upon looking at *Candida* species causing invasive candidiasis, in Latin America *C. albicans* was isolated most often followed by *C. parapsilosis*. However, when compared to North America, *C. glabrata* was more common than in Latin America [7]. These results are assumed to be associated with poor maintenance of indwelling medical devices and infection control methods.

In European countries, the distribution of *Candida* species varies from country to country. For instance, in Finland *C. albicans* was found to be the most common species followed by *C. glabrata*; this distribution is similar to that of Sweden and Switzerland [7]. Whereas, in Spain

C. albicans was isolated less than half followed by *C. parapsilosis* being the most common non-*albicans* species. This distribution was like that of Italy. Other European countries, including Germany, Denmark, and the United Kingdom, *C. albicans* was isolated the majority of times followed by *C. glabrata* [7].

Until recently, *Candida albicans* was the predominant species worldwide causing at least 80% of the reported *Candida* infections. Nevertheless, over the past years, previous studies have shown a shift in the epidemiology from *Candida albicans* to non-*albicans Candida* which include *C. krusei*, *C. glabrata*, and *C. tropicalis* [11,12]. This shift may be due to immunosuppression, increase the use of broad-spectrum antibiotics, and an increase in infection of older patients. As the *Candida* infections shift more to non-*albicans* species, the concern increases. With the emergence of non-*albicans Candida* infection introduces antifungal resistance. *C. tropicalis* and *C. parapsilosis* are ordinarily susceptible to azole treatment; however, *C. tropicalis* is less vulnerable to fluconazole as compared to its more pathogenetic counterpart, *C. albicans*. Furthermore, *C. glabrata* is inherently more resistant to antifungal treatments, especially to fluconazole. *C. krusei* is naturally unaffected by fluconazole therapies. Lastly, *C. lusitaniae* is ordinarily able to be treated with azoles, but this species has a higher occurrence of amphotericin B resistance [1].

Pathogenicity of *Candida* Species

Candida albicans remains to be the most common clinical isolate causative agent of candidiasis [13]. In most individuals, *Candida* is a harmless commensal. However, under certain conditions, *Candida* causes a wide range of infections. *Candida* pathogenetic potential is multifactorial. Below the pathogenetic mechanisms of *Candida* and host immune response are discussed.

Virulence Factors

Morphology

The yeast form of *Candida* is not necessary for virulence, but this morphology is known to play essential roles in virulence-related processes including colonization, rapid dissemination, cell-surface adhesion, and biofilm formation [4]. Yeast cells are thought to play a primary role in dissemination; whereas hyphal cells are primarily involved more in invasive infections. *Candida* will switch to pseudohyphae form to increase nutrition scavenging; in hyphal form serves to invade host tissues, lysis macrophages and neutrophils [4]. Seven clinically relevant *Candida* species have been documented forming pseudohyphae (*C. glabrata*, *C. lusitaniae*, *C. guilliermondii*,

C. parapsilosis, *C. tropicalis*, *C. dubliniensis*, and *C. albicans*); also only three species have been noted forming the main morphologies (*C. albicans*, *C. tropicalis*, *C. dubliniensis*) [4]. The ability to switch between various morphologies aids in adaptation and persistence in different niches inside a host.

Asteroid bodies (AB) have been described in *Candida*; these bodies are responsible for invasive mycosis [14]. The morphology of an AB is depicted as concentric layers and molded around a central yeast [14]. The AB protects the yeast cell from the host immune system and the surrounding environment. This structure is considered as an essential morphology because the central yeast is viable and capable of filamenting [14].

Escaping Phagocytes

C. tropicalis, *C. krusei*, *C. parapsilosis*, and *C. guilliermondii* are efficiently phagocytosed. However, these species filament inside and outside of macrophages to evade phagocytosis and alter macrophage recruitment [15]. *Candida* species unable to undergo dimorphic transitions have developed strategies to evade phagocytosis. For example, *C. lusitaniae* escapes macrophages by constructing cell chains, and *C. glabrata* proliferates within macrophages causing the host cell to lysis [16,17].

C. albicans has evolved strategies to allow survival by manipulating and escaping phagocytic cells. *C. albicans* promotes neutralization of the phagolysosome; this process involves the Stp2 transcription factor induction of the Ato5-mediated ammonia exporter [18]. This neutralization permits hyphae formation, therefore, facilitating escape from macrophages.

Candida species also evade phagocytosis by shielding the surface PAMPs. For the host to phagocytose pathogens, the pathogen must first be sensed; this process of sensing is achieved through recognizing the PAMPs of *Candida*. One study showed that the *Candida* β -glucans were shielded from Dectin-1 by external cell wall components [19]. The study also noted that during yeast budding and cell separation the β -glucans were not protected; whereas, during filament growth, the β -glucans fail to activate Dectin-1. As a result, the morphology directly contributes to the method by which phagocytes recognize the pathogen [19].

Adhesins and Invasins

Candida species have a set of proteins which mediate adherence between *Candida* cells to other materials, which includes microorganisms, surfaces, other fungal

cells and host cells. Agglutinin-like sequence (ALS) proteins have eight members (ALS1-7 and ALS9). The ALS gene encodes for glycosylphosphatidylinositol (GPI)-linked cell surface glycoproteins; these are located on the surface or wall of *C. albicans* [20]. Of the eight ALS proteins, ALS3 is vital for adherence of *C. albicans* in mucosal membranes including oral and vaginal [20]. ALS3 is hyphae specific and is required for endocytosis; also, ALS3 binds to host cell surface proteins N-cadherin on endothelial cells and E-cadherin on the oral epithelial cells.

Other crucial adhesins are HWP1 which is a hyphae-associated GPI-linked protein [20]. This protein is only expressed in the filamentous form. HWP1 acts as a substrate of mammalian transglutaminases in the epithelial cells which causes covalent bonding between host and fungi. HWP1 Δ/Δ mutants showed a decrease in adherence to buccal epithelial cells and reduced capabilities in causing systemic candidiasis [21].

Both ALS3 and HWP1 play an important and essential role in biofilm formation.

Contact Sensing and Thigmotropism

Candida has evolved to have an environmental cue that triggers hyphae and biofilm production. Upon encountering a surface, the *Candida* yeast cells will switch and begin to grow in hyphae form. When on a surface with ridges hyphae will grow directionally. This process is called thigmotropism. Thigmotropism begins when the cell encounters a ridge and causes the membrane to stretch which is detected by Mid1p. Followed by extracellular calcium uptake; this influx redirects the cell polarity machinery to a new growth axis. Evidence has been provided that thigmotropism is required for the invasion and damage of epithelial cells [22]. Consequently, contact sensing is essential for pathogenicity.

Biofilm Formation

Multicellular communities composed primarily of a polysaccharide matrix that adhere and grow on the surface of tissues or indwelling medical devices are termed biofilms [23-25]. Cellular biofilms exhibit drug resistance because of the heterogeneity of morphologies and the fungal metabolic state. A known property that contributes to drug resistance is the polysaccharide β -1,3-glucans. The biofilms extracellular matrix can sequester some antifungal drugs reducing the drug's effectiveness. The resistance is due to the up regulation of two efflux pumps: ATP-binding cassette (ABC) transporter and the major facilitator superfamily (MFS) [26]. ABC

transporters are a multigene family, including CDR genes, that plays a direct role in resistance; MFS has the MDR1 gene that encodes for a significant facilitator that has been linked to azole resistance and when overexpressed leads to fluconazole resistance entirely [27]. Biofilms also have a communication network that is composed of signaling processes, which includes quorum sensing [23]. This sensing process responds directly the cell density that affects growth and morphological changes; this most likely aids in survival [23]. Biofilm formation can be broadly categorized into three phases: adherence of yeast to a surface, the formation of a yeast-hyphae matrix, and an increase of matrix material [28]. Fully matured *Candida* biofilms have a complex network of yeast, hyphae, and pseudohyphae in a polysaccharide, carbohydrate, and protein environment. Following maturation yeast cells may disperse from the biofilm to seed at new, distal sites. The development of a biofilm is multifactorial. The chemical makeup of the surface has been documented to influence biofilm formation; also, high glucose mediums aid in biofilm formation [29]. Additionally, another study showed cell surface hydrophobicity, and gentle shaking promotes biofilm development [30].

Most *Candida* species have been shown to form a biofilm under various temperatures in vitro [28]. One study created a model system to investigate the growth of *Candida* biofilm on catheter material as determined by dry-weight, colorimetric, or radioisotopes assay. They showed three *Candida* species (*C. glabrata*, *C. parapsilosis*, and *C. pseudotropicalis*) grew significantly less biofilm compared to their more pathogenetic counterpart, *C. albicans* [29]. Another study confirmed these findings by using similar methods and determined that *C. albicans* form a more complex biofilm in comparison to *C. parapsilosis*, in which this biofilm consisted of only blastospore clumps [31]. Additionally, the *C. albicans* isolates showed minimal variation in biofilm production; also, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* showed less biofilm development [31]. *Candida* species vary in biofilm production capabilities. This highlights the importance of evaluating biofilms and *Candida* species wild phenotypes, both of which may contribute to pathogenicity.

Inhibition of IL-17 production

Interleukin 17 (IL-17) has been demonstrated to have an essential role in the host defense against fungal infections. A recent study showed that *Candida* could directly inhibit IL-17 production by altering the host tryptophan metabolism [32]. Tryptophan metabolism is monitored by two enzymes: indolamine-2,3-dioxygenase

(IDO) and tryptophan hydroxylase. *C. albicans* can shift tryptophan metabolism by inhibiting IDO expression, resulting in a reduced number of kynurenines and an increase in 5-hydroxytryptophan metabolites. The increase in the metabolites consequently inhibits the host production of IL-17 [32].

Farnesol

Farnesol was identified as a quorum-sensing molecule that represses yeast-hyphae transition of *C. albicans* [33,34]. It has been determined that farnesol may decrease macrophage function through ROS production. Additionally, farnesol has been suggested as a protective factor for *Candida* against oxidative stress by upregulating gene expression of CAT1, SOD1, SOD2, and SOD4 [33].

On the other, *Candida* has been cited to block farnesol production. A study investigated *C. albicans* mating; the results showed that farnesol blocks aerobic mating because morphological switching from yeast to opaque cells is required for mating [34]. They also determined that farnesol kill the opaque cells when under aerobic conditions. Also, under anaerobic conditions, the opaque cells were stabilized and blocked the production of farnesol, which permitted mating [34]. These findings suggest that anaerobic sites, for example, the gastrointestinal tract, are natural niches for ongoing colonization and mating for *C. albicans*.

Host response to *Candida* infections?

The fundamental aim of the host innate immune system is to distinguish between self and not self. Host recognition of invading microorganisms relies on evolutionarily conserved, germline-encoded pattern-recognition receptors (PRRs), which recognize highly conserved invariable molecular patterns, often essential for the survival of microorganisms, called pathogen-associated molecular patterns (PAMPs). *Candida* cell wall is composed of chitin, β -glucans, and mannoproteins [33]. These cell wall structures are recognized by two classes of membrane-bound PRRs: Toll-like receptors (TLRs) and C-type lectin receptors (CLRs). TLRs are transmembrane receptors; their engagement and induction send a signal to the nucleus of a cell causing gene expression of cytokines and chemokines. A major TLR that recognizes *C. albicans* is TLR2 which detects phospholipomannan; also TLR4 recognizes O-linked mannan [33]. Furthermore, by being able to recognize membrane-bound PAMPs, several PRRs identify *Candida* intracellularly. TLR9 has been shown to recognize *Candida* DNA and encourage cytokine production within dendritic cells [35]. Another study investigated how TLR9 modulated macrophage antifungal effector function. The results demonstrated the TLR9

deficiency was linked to resistance to murine candidiasis [36]. Macrophages lacking TLR9 were described to have normal phagosomal maturation; macrophage tumor necrosis factor alpha (TNF- α) was also increased when the TLR9 deficiency was present [36]. Macrophage effector response was increased by nitric oxide production. Moreover, TLR9 knockout had a more effective microbicidal activity against *C. albicans* [36]. An adaptor molecule termed MyD88-dependent of the TLR pathway is required for *Candida* and other fungal resistance; MyD88 signals through IL-1R, TLR2, TLR4, and TLR9.

A second major PRR family that identifies *Candida* PAMPs is the CLRs. There multiple PRRs associated with the CLRs family including Dectin-1, Dectin-2, Dectin-3, DC-SIGN, mannose receptor (MR) and mincle. β -glucans are identified by Dectin-1 and signals through Syk; N-linked mannan is recognized by mannose receptors. Dectin-2 and Dectin-3 bind to mannans and signals through Syk; DC-SIGN is found on dendritic cells and binds to high mannose carbohydrates. MR binds terminal mannan, and mincle binds α -mannose. In the Syk signaling pathway, CARD9 is signaled and induces cytokine induction. The current understanding of CLRs role in host defense is limited to *C. albicans*. One study investigated the potential role of Dectin-1 and Dectin-2 in host defense against *C. glabrata*. The study yielded results of the animal model becoming more susceptible to infection [37]. Dectin-1 was determined to be mandatory for myeloid cell recognition, killing of *C. glabrata*, and the development of Th1 and Th17 cell-mediated adaptive immune responses. Also, in Dectin-1 deficient mice, the host inflammatory responses were impaired. In conclusion, Dectin-1 plays a significant role in the host immune response against *Candida* pathogens [37].

(NOD)-like receptors (NLRs) are another PRRs family that recognize fungal PAMPs. NLRs are involved in recognizing intracellular pathogens. To date, there are 22 known NLRs, but only three have been seen to play a role in fungal recognition, this includes NLRP3, NLRP10, and NLRC4 [38,39]. NLRP3 is important for *C. albicans* induced inflammation; which is consistent because of NLRP3 signals through inflammasome formation and aids in the generation of Th17 responses [38,39]. Additionally, NLRP10 and NLRC4 have both been related to anti-*C. albicans* responses [40,41]. A study showed that when NLRP10 was deficient, there was an increase in susceptibility for disseminated candidiasis, no alternation in proinflammatory cytokine production, and defective Th1 and Th17 responses [40]. These results show the novel role of NLRP10 in the context of adaptive

fungal immune responses. In other respects, NLR4 was determined to function within the mucosal stroma to control oral candidiasis; also, NLR4 impacts inflammatory cell recruitment and protect against disseminated infections [41]. In conclusion, this study revealed the specific role of the NLR4 inflammasome in innate *Candida* immune responses.

Clinical Manifestations and Risk Factors

Candida species present as a commensal and an opportunistic pathogen; it is the most common cause of fungal infections [42]. These fungal infections range from non-life threatening mucocutaneous disease to invasive, life-threatening infections [43]. *Candida* infections commonly affect immunocompromised patients. Many factors affect clinical manifestations of candidiasis; also, there are many clinical presentations of candidiasis.

Risk factors for candidiasis

Even though *Candida* species are resident organisms of the human microflora, in the past couple of decades, abnormal overgrowth of *Candida* has been observed. This overgrowth is of importance because it has been noted to be the direct cause of a wide range of symptoms in healthy individuals [44]. Numerous factors contribute to yeast infections. These predisposing conditions include, but not limited to, decreased digestive secretions, nutritional deficiencies and dietary factors, impaired immune system, impaired liver function, drug and prolonged antibiotics use [7,44]. Risk factors for candidiasis can be divided into two general groups: host or health-care related factors. Immunosuppressive diseases, neutropenia, and age are the predominant host-related factors that are host-related that increases susceptibility to candidiasis [7]. Prolonged hospital or ICU visits are the most common health-care associated risk factor [45].

Altered Digestive Factors and Other Factors

In a healthy individual, digestive secretion directly contribute s to a healthy gut flora which includes preventing *Candida* overgrowth and its infiltration into the GI tracts surfaces. Pancreatic enzymes are responsible for maintaining the integrity of the small intestine; dysfunction of these enzymes can lead to food allergies and or formation of toxic substances [44]. A recent study investigated the prevalence of oral candidiasis and its association with malnutrition. The study finds determined that oral *Candidal* infections appeared to be related to malnutrition; therefore, mucosal lesions have a negative impact on the patient's nutrition and overall health [46]. Consequently, restoring and maintaining proper digestive secretions is of high importance to combat *Candida*.

All organisms need a balanced diet of right proportions; when that balance becomes unbalanced, the well-being of the body becomes compromised. Certain foods in our daily diet may favor *Candida* growth, for example, cheeses, alcoholic drinks, and milk; all these foods contain a higher content of yeast. Dairy products contain a high amount of lactose which may stimulate fungal growth, but they also have antibiotics [44]. Therefore, dietary factors should be monitored to ensure there is a balance. Also, common nutrient deficiencies in patients with chronic candidiasis include zinc, magnesium, selenium, fatty acids, folic acid, and vitamins B6 and A [44]. Also, iron is now considered an essential micronutrient. Multiple recent studies have documented irons role in fostering and colonization of *Candida* and other yeast [47,48].

Another factor is impaired liver function. When the livers functions are modified, toxins begin to accumulate. The accumulation can result in liver damage, changes in the mechanisms of detoxification, which in turn allows *Candida* to overgrow and can cause chronic candidiasis of the GI tract [44,49]. Maintaining the microflora balance is vital to keep the growth of *Candida* in check.

Immunocompromised patients

There are a plethora of mechanisms that are designed to protect the host from fungal pathogens; this protection is dependent upon an amalgamation of factors. Within immunocompromised individuals, alternations in phagocytic cells presence or function are the most common risk factor that puts the patients at a higher risk of fungal infections [50]. Maintaining the proper conditions for an appropriate immune function is critical to prevent infections from microorganisms and opportunistic pathogens. Therefore, any disease that affects the immune system function increases susceptibility infection. The most common predisposing diseases are diabetes, cancer, HIV/AIDS, and neutropenia [44].

Diabetes and Candidiasis

Diabetes is a prevalent disorder that is characterized by insufficient insulin secretion or insulin resistance to metabolic action on a target tissue in both men and women [49]. Oral candidiasis is common among diabetic patients; it has been shown that elevated blood glucose levels favor *Candida* growth but the mechanism which predisposes these patients is unclear [50]. The frequency of *Candida* infections among people with diabetes is approximately 31%; diabetic patients also have an increase in *Candida* colonization of the oral and vaginal cavity when compared to healthy patients [49,51,52].

Studies have shown that women with type 1 diabetes are more likely to be colonized with *Candida* species as compared to type 2 patients [51]. Female diabetic patients were commonly colonized in the vaginal cavity by either *C. albicans* or *C. glabrata* [11,51]. Patients with type 1 diabetes were predominately colonized by *C. albicans* whereas women with type 2 *C. glabrata* was more common [51].

HIV/AIDS and Candidiasis

The most common *Candidal* infection among the HIV/AIDS population is oropharyngeal [50]. *C. albicans* is the prevailing strain among these patients (68.5%) [49,50], followed by *C. tropicalis* (7.4%), *C. krusei* (6.4%), *C. parapsilosis* (3.0%), and lastly *C. sake* (2.5%) [49,53]. HIV/AIDS patients have an increase in risk for oral candidiasis due to the decreased function of Th17; these T helper cells are pivotal in guarding against *Candida* [49]. Because of this loss and the progression of HIV, this allows the fungus to no longer be contained by the oral mucosa, subsequently allowing *C. albicans* to become pathogenic [49,50].

A recent study has shown that *C. albicans* could inhibit the replication of HIV-1 within macrophages and dendritic cells [49,54]. This inhibition does not act alone; host restriction factors also contribute; primarily by stimulating interferon- α and restriction factors APOBEC3G and APOBEC3F production [54]. These two restriction factors introduce G to A substitutions of the HIV-1 genome resulting in viral replication inhibition [49,54]. Even though, *Candida* infection silences HIV-1 this could be problematic because this mechanism may help HIV-1 to evade the host immune responses and promote antiretroviral resistance [54].

Previous studies have shown there is a significant correlation between *Candida* colonization and CD4+ lymphocytes. These studies demonstrated a decreased count of CD4+ T lymphocytes is commonly correlated with the increased frequency of oral candidiasis [55-57]. T helper cell 17 has also been noted to become depleted as the HIV infection progresses resulting in *C. albicans* to overgrow and overcome the epithelial defenses [58]. However, new insights are needed to combat *Candida* and other fungal infections under immunocompromised conditions.

Cancer and Candidiasis

Cancer and chemotherapy predispose patients to opportunistic fungal infections because of the individual's immunosuppression. Altered immunological factors

correlate with increased susceptibility to *Candida* infections within cancer patients. Chemotherapy directly causes mucosal damage and impairs the cellular and humoral immune responses. This route of treatment tends to alter the host immune response. For example, a study showed that cancer patients had a deficiency in myeloperoxidase (MPO) and were at an increased risk for *Candida* infections [59]. More times than not *Candidal* infections are a common side effect of chemotherapy against malignant cancers. Another study determined that thrombospondin-1 enhance *Candida* ability to disseminate due to the imbalance of the host immune system; this results in decreased fungal clearance, dissemination, and increased mortality [60].

Studies have shown that patients with candidiasis may have an increase in developing cancer later in life. In one study conducted a nationwide population-based cohort study to evaluate whether *Candida* infections is are related to increased cancer risk. The study concluded that patients with *Candida* infections had a significantly higher risk of cancer overall [61]. Other recent findings have reported that *C. albicans* is capable of promoting cancer through various mechanisms: producing carcinogenic byproducts, promoting inflammation, and induction of Th17 response [62].

Currently, there is insufficient data that supports *Candida* species can promote cancer. However, there is an acceptable hypothesis about the carcinogenic effects of *Candida* species. Studies published years ago implied that *C. albicans* might contribute to oral carcinogenesis because of its ability to produce nitrosamines [63,64]. As a result, carcinogenic lesions may develop because of the activation of specific proto-oncogenes [63]. These findings were supported by another research study that concluded that *C. albicans* acted as a promoter for carcinogenesis on rat tongues followed by repeated application of nitroquinoline [65]. Besides, a more recent study showed that *C. albicans* also produces high levels of acetaldehyde in low oxygen conditions [66]. These findings are of importance because acetaldehyde is carcinogenic and has been associated with cancers of the upper digestive tract [66]. Better More insights are needed in this field to obtain a better understanding of the carcinogenic byproducts *Candida* produces and its downstream effects.

Inflammation and cancer have had a recognized relationship for years. Inflammation is necessary for the progression of cancer and the malignant phenotype. *Candidal* infections are responsible for pro-inflammatory cytokines to be secreted. The effects of this fungal

infection to endorse metastasis appears to be based on inflammation [62]. It has been noted experimentally that following the recognition of *Candida* contributes to tumor adhesion and metastasis in correlation with TNF- α and IL-18 [67,68]. This is critical because patients are commonly treated with chemotherapy and are immunosuppressed meaning their leukocyte population is substantially reduced or eliminated. As a result, cancer cells may not be adhering to the leukocytes but instead attaching to endothelium and consequently metastasizing.

Another mechanism proposes that *C. albicans* may promote cancer progression. Th17 produces IL-17 which is a known requirement for resistance against *Candida*. However, other cytokines like IL-23 are also involved in angiogenesis, tumor incidence, and growth [69]. IL-23 antagonizes IL-12 and IFN- γ ; both are required cytokines for a cytotoxic immune response. When IL-23 is being expressed within a tumor environment, IL-17 can be induced by tumor resident immune cells. The IL-17 expression induces neutrophils and macrophage infiltration [69]. Consequently, these cells produce matrix metalloproteinase (MMPs) which endorses tumor growth [69]. Additionally, IL-23 might induce cytotoxic T lymphocytes (CTLs) which produce IL-17 resulting in tumor progression rather than tumor elimination [69]. Although the roles of IL-23 and IL-17 are still being investigated, inappropriate expression of these cytokines has been linked to cancer.

There are numerous studies reporting mechanisms by which viruses and bacteria can impact cancer directly, but there is limited research in the context of fungi. To obtain a vast knowledge and to develop appropriate treatments more research is needed to understand better how *Candida* species promotes cancer.

Prolonged use of Antibiotics and Drugs

Antibiotics have been determined to play a significant role in the development of *Candida* infections [44]. Overgrowth of *Candida* occurs because the mode of action for antibiotics is to eliminate bacteria; which has the role of preventing the overgrowth of fungal species [44]. *C. albicans* is the primary species that overgrows [44,50]. Antibiotics with a narrow spectrum are less likely to cause fungal overgrowth due to these therapies are more specific in their mode of killing. The fact that fungal growth increases with the broad-spectrum antibiotic are of importance for hospitals because of nosocomial resistant infections that have the potential of leading to lethal complications [44]. Consequently, a reduction in the usage of antibiotics can be utilized as a valid alternative to control or diminishing resistance [44].

Other drug usages also favor the growth of *Candida* species, especially *C. albicans*, are oral contraceptives, corticosteroids, and antiulcer drugs [44]. Corticosteroids mode of action is to promote anti-inflammatory and immunosuppressive properties; this can result in lower host resistance to infection and put the individuals at risk for candidiasis [50]. Corticosteroids often reduce the response of macrophages to T cell mediators [50]. Lastly, patients tend to have higher levels of salivary glucose; therefore, *Candida* growth, proliferation, and adhesion are promoted [70].

Pregnancy, Neonates and Childhood

Pregnancy can serve as a risk factor for vulvovaginal candidiasis [49]. Episodes of VVC and recurrent VVC often occur during pregnancy or the luteal phase of the menstruation cycle due to the elevated levels of estrogen and progesterone [71]. During pregnancy, the risk of developing VVC is increased due to the changes in hormone production which increases glycogen [49]. Pregnant women are commonly affected by *C. albicans* when suffering from VVC [49]. It has been shown in a study that pregnant women have an increased occurrence of vaginal *Candida* colonization compared to non-pregnant women [49].

Neonates *Candida* colonization results from vertical transmission from the infected mother [49,72]. Colonization may be the first step toward *Candida* infections at the rectum in neonates [49]. In one study investigated what *Candida* isolate in neonates were similar to that of their mothers. The study determined that the mothers colonized with *C. albicans* give birth to neonates also colonized with *C. albicans* primarily in the anal region [72]. With the study's findings suggest that vertical transmission plays a vital role in neonates *Candida* colonization. Another study suggested that an increased risk of CCC occurs when the neonate's birth weight is below 1500 grams, received antibiotic treatment, and if extensive instruments were used during delivery [73].

Another risk for pregnant women and neonates is *Candida* chorioamnionitis. This infection is rare and characterized by inflammation of the amniochorion membrane; the membrane generally ruptures prematurely [74,75]. *C. albicans* (71.3% of cases) is the most common species that has documented to cause this infection followed by *C. glabrata* [75]. One case study reported chorioamnionitis caused by *C. glabrata* followed by in vitro fertilization (IVF). This case study confirms that there is a strong association between fertilization techniques and chorioamnionitis [76]. More research is

needed to deepen our knowledge about *Candida* infections and chorioamnionitis.

Indwelling Medical Devices

Approximately half of the nosocomial infections are associated with indwelling medical devices [28]. The consequence of having indwelling devices can lead to life-threatening illness and device malfunction. A proportion of device-related infection is caused by *Candida* species; particularly the blood and urinary tract are involved. Also, biofilm formation insignificantly involved in these infections. The presence of a biofilm on the medical device poses another complication for treatment that was previously discussed as a virulence factor.

Common medical devices that have been associated with *Candida* infections include central venous catheters, cardiovascular devices, and urinary catheter. Most cases of urinary tract infections are catheters related, and *Candida* species accounted for approximately one-third of those infections [28]. *Candida* infections have a strong correlation with the presence of urinary catheters; *C. albicans* is the most commonly isolated species followed by *C. glabrata* [28].

Candida infections are also commonly associated with cardiovascular devices, including heart valves, pacemakers, implantable cardioverter defibrillators, and ventricular assist devices. Prosthetic valve endocarditis (PVE) is a rare but a severe complication; fungi have been reported to cause up to 10% of all cases of PVE and *Candida* species accounts for up to 90% of these infections [28]. Fungal PE has a higher mortality rate compared to bacterial PVE [28]. *C. albicans* is the most common species accounting for 56 – 66% of all *Candida* PVE; *C. glabrata* and *C. parapsilosis* have also been isolated [77,78].

Another cardiovascular device that has been cited to have *Candida* infection complications are pacemakers; most often this complication is caused by *Staphylococcus* species [28]. *Candida* infections associated with pacemaker have been noted mostly as case studies or single case reports. Currently, cases have reported three *Candida* species as causative agents: *C. albicans*, *C. glabrata*, and, less often, *C. tropicalis* [79-81].

Implantable cardioverter defibrillators (ICD) are used to manage cardiac arrhythmias [28]. Infection rates for ICDs are low and have only been reported to reach about 7% [82]. One case study showed that of the seven infected patient, only one patient was infected with *C. albicans* and *C. glabrata* in conjunction with a bacterial infection [82].

Therefore, fungal ICD infections are sporadic and commonly coincide with a bacterium.

Ventricular assist devices (VADs) provide temporary support for cardiac circulation [28]. Fungal colonization or infection have been documented in approximately 37 % of patients with VADs [83]. A recent study found that 38% of VAD patients developed *Candidaemia* (13.5% of all cases) [84]. Furthermore, VADs directly affects the host immune system; the interaction between the device and blood activates T cells resulting in cell death; also B cells become hyperactive with dysregulated immunoglobulin synthesis [83]. These alternations in cellular immunity consequently increase the risk of fungal infections.

Central venous catheters are placed into large veins generally located on the neck, chest, or groin. Central venous catheter-related infection caused by fungi commonly manifests itself as fungemia [85]. *Candidaemia* is frequently among immunocompromised patients with underlying malignancy, hematologic disorders, GI diseases, burn, and critical illness [86]. *C. albicans* accounts for at least 60% of candidemia cases; *C. glabrata* and *C. tropicalis* have also been isolated in hospital settings [87]. One case report cited that nearly half of *Candidaemia* were caused by non-*albicans* species [88]. Another single case reported *C. membranaefaciens* as a causative agent [85]. This species is widely considered non-pathogenic and associated with drink spoilage.

Recent or prolonged hospitalization

Intensive care units (ICUs) have emerged as a hub for *Candida* infections. When admitted in the hospital, whether it be a short or long-term stay, one is at risk for a nosocomial infection. A cohort study was conducted over the course of 10 years of patients in ICUs. This study investigated the frequency of *Candida* infections in the context of IUCs. The most frequent infection was of the bloodstream (53% of cases) and of those infections *C. albicans* was isolated 63.6% [89]. Additionally, in this study, it noted other non-*albicans* species were also causative agents of *Candidaemia*, which included *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*, and *C. zeylanoides* [89]. These infections were all related to hospital-borne infections. Therefore, it is vital that risk factors be followed up to prevent *Candida* based infections. This also brings up the controversy of if patients, who are in ICUs or going to have a prolonged stay at a healthcare facility, should be treated with antifungals as a prophylactic.

Clinical Manifestations

Oral Candidiasis

Candida is readily isolated from the oral cavity, but this isolation is not a good predictive factor for the development of infection [90]. Oral candidiasis is commonly termed oral thrush; it frequently presents as a superficial infection. The oral manifestation of candidiasis is caused by the same species that commonly cause vaginal candidiasis. There is not one single form of oral candidiasis but rather three primary forms that are categorized according to their presentations.

Pseudomembranous Candidiasis

This manifestation of candidiasis is generally an acute infection, but if this infection is recurrent, then the term chronic pseudomembranous candidiasis is used. On the oral surfaces, a superficial layer of white to whitish-yellow velvety confluent plaques that resemble cottage cheese is apparent; this layer can easily be sloughed off [90-92]. The plaques consist of the accumulation of desquamated epithelial cells, yeast and hyphal form of *Candida*, keratin, fibrin, and necrotic cells [90-92]. Other surfaces that may be involved include labial and buccal mucosa, tongue, soft and hard palate, and oropharynx [90]. Patients with HIV/AIDS are prevalent to have both the oral and esophageal mucosa involved [90]. Individuals with the acute form report a mild tingling to a burning sensation and changes to taste perception [90,92]. Whereas patients with chronic pseudomembranous candidiasis the esophageal mucosa may be involved which then results in dysphagia and chest pains [90].

Erythematous Candidiasis

Erythematous candidiasis infections are not as standard; it manifests in an acute and chronic form [90,92]. Clinically, patients chief complaint is a localized painful sensation of the erythematous area [90]. Physical appearance includes lesions on the dorsum of the tongue with de-papillated areas [90]. Lesions may also appear on the palate; this is presented more common among HIV/AIDS patients [90]. Erythematous candidiasis does not have a constant appearance; there are several variations if this oral candidiasis.

Acute atrophic candidiasis appears as red patches generally on the palate; these patches may also occur on the buccal mucosa or dorsal tongue [92]. Atrophy of the lingual papillae may accompany this infection [92]. Patients generally have complaints about a burning sensation of the mouth and soreness of the lips and tongue [92]. Clinically, this infection is generally localized within the erythematous regions [90]. Acute atrophic candidiasis is also known as antibiotic sore mouth

because after prolonged use of broad-spectrum antimicrobials there is a possibility the overgrowth of *C. albicans* with the oral mucosa [50,92].

Chronic atrophic candidiasis is also known as denture stomatitis; it is characterized by lesions that are erythematous, edematous, and infection is localized to the oral mucosa that in contact with dentures [92]. Generally, this infection is asymptomatic, but patients may have complaints of a burning sensation and or a sore mouth [90,92]. The infected area is typically restricted to the palate, but the mandibular mucosa may also be affected [90]. Studies have previously shown patients that wear dentures are at higher risk for oral colonization and or infection caused by *C. glabrata* [93].

Angular stomatitis physical appearance is redness and fissure lesions restricted to the commissures of the mouth, and often the fissures are bilateral. The primary complaint is a pain in the infected area. *C. albicans* is often isolated from the corners of the mouth in combination with *Staphylococcus aureus* and *Streptococcus* [90-92]. Although *C. albicans* is often isolated, cases have been reported of angular stomatitis being caused solely by bacteria along alone [90,94].

Another form of oral candidiasis is median rhomboid glossitis. This infection causes symmetrical, red, and elliptical shaped lesions that are generally located on the posterior dorsal surface of the tongue [94]. *Candida* hyphae penetrate the superficial layers of the parakeratotic epithelium [94]. Also, the lesions are caused by the atrophy of the filiform papillae [92,94]; patients are ordinarily asymptomatic [90,92,94]. This manifestation is rare with a documented prevalence of less than 1% occurrence [92].

Lastly, linear gingival erythema was previously known as 'HIV-gingivitis' because it occurred in HIV in suffers and served as a clinical marker for the disease progression; although children have been reported with this condition [90,92]. Clinically, this infection manifests itself with erythematous bands on the marginal gingiva of one or more teeth; at times bleeding may occur [90,92]. Commonly *C. albicans* is associated with this infection, but *C. dubliniensis* has also been noted as an emerging pathogen [90,91].

Hyperplastic candidiasis

Hyperplastic candidiasis previously was referred to as 'Candidal leukoplakia'; this was due to the difficulty to differentiate between leukoplakic and hyperplastic candidiasis [90,92]. Clinically, this *Candida* infection

presents itself in a chronic form [90]. Also, if clinically manifest itself in two variations: homogenous adherent plaque-like/smooth or as erythematous multiple nodular forms [90,91]. A primary characteristic of this form of candidiasis is the *C. albicans* hyphae penetrate the oral epithelium [91]. Lesions frequently form bilaterally in the commissural region of the buccal mucosa; the lesions less often form on the lateral border of the palate and tongue [90]. Hyperplastic candidiasis differs from pseudomembranous infections because the lesions from this form of infection cannot be gently removed by slouching sloughing [90-92]. Lacerations may be small to large translucent milky plaques, or they can be nodular or freckled upon looking at viewing [90-92]. Studies have shown another important distinguishing feature of this candidiasis is studies have shown a possible connection with malignant transformation [91]. An established association between oral cancer and *Candida* has not been determined. However, in vitro studies have demonstrated that *Candida* organisms could generate carcinogenic nitrosamine [63,91].

Genitourinary Candidiasis in Males and Females

Candida species are commonly found within the vaginal tract and preputial space [95,96]. The sole presence of *Candida* and the absence of immunosuppression and injured mucosa is not usually correlated; thus this is referenced as colonization [43]. The most frequent manifestation of genitourinary candidiasis is vulvovaginal candidiasis (VVC) followed by *Candida* balanitis and candiduria [43,96,97]. VVC is common among women in their childbearing years as well as patients who are on prolonged antibiotic therapy. The typical vaginal environment is maintained through the interactions of *Lactobacillus acidophilus* and resident flora, a hormonal and pH balance [12]. The vagina has a natural process in which it gains protection against reproductive tract infections; the lactobacilli breaks down into lactic acid creating an acidic environment that is toxic and inhibits the growth of other microorganisms including *Candida* species [12,98]. When this process experiences alterations to its equilibrium, such as antibiotic treatment, this can lead to vaginitis [12]. With this imbalance, *Candida* can over-proliferate; depending on the severity of this imbalance this infection can range from a mild yeast infection to disseminated infection in severely immunosuppressed patients [12,43].

The healthy microflora of the preputial space is diverse, complex and changing as a result of type/presence of bacteria that is dependent on age, hygiene and sexual relations [95]. Similarly, to females, the simple presence of *Candida* species does not allow for a clinical diagnosis.

Vulvovaginal Candidiasis (VVC) and Recurrent VVC

VVC is characterized as the inflammation of the vulva and vaginal tract that is caused by *Candida* species [12,43]. Clinical symptoms of VVC vary among the cases and are nonspecific; also, the symptoms can be associated with other vaginal and sexual transmitted diseases [43]. Hallmark symptoms include itching, inflammation, burning, and thick curdy vaginal discharge with or without foul odor. *C. albicans* generally cause VVC albicans, but non-*C. albicans* species have been isolated in clinical cases as a causative agent, most commonly *C. glabrata* [96]. It has been widely assumed that the clinical presentation of VVC would be identical; however, subtle variances have been reported in clinical cases of *C. glabrata* VVC [11,99]. Women presenting symptoms of VVC caused by *C. glabrata* had a lower frequency of abnormal discharge when compared to *C. albicans* [11]. Patients also reported a burning sensation more regularly than itching [11]. In cases of VVC caused by *C. glabrata*, the patients were more likely to have elevated pH levels [11,99]. Since the frequency of vaginitis caused by *C. glabrata* is small, no large-scale studies have been conducted [11].

C. tropicalis is generally termed as the third most predominant *Candida* species, preceded by *C. albicans* and *C. glabrata* [100]. Vaginitis caused by *C. tropicalis* presents like a typical yeast infection. VVC infections caused by *C. tropicalis* is not commonly isolated in the United States and Europe regions but more commonly in the Nigeria regions [43]. Also, the patients' demographic effects and increase the probability of a NAC species infections.

Most VVC infections that are caused by non-albicans *Candida* are commonly caused by *C. glabrata* (5% - 10% of cases) or *C. tropicalis* (<5% of cases) [101]. *C. krusei* has been reported being the causative agent of approximately 1% of vaginal candidiasis infections [102]. Vaginal candidiasis caused by *C. krusei* is unusual and questioned whether it is a true vaginal pathogen [101]. VVC caused by *C. krusei* appeared to have the same signs and symptoms from other vaginal candidiasis cases caused by other *Candida* species [102]. *C. krusei* is a rare causative agent for vaginal candidiasis but is of clinical importance due to its natural resistance to fluconazole [101,102]. Furthermore, there is limited research and literature experience with *C. krusei* vaginitis.

Candida parapsilosis is not frequently isolated from vaginal cultures, and its role as a VVC pathogen remains unstudied [103]. Women infected by *C. parapsilosis* reported signs and symptoms similar to a typical VVC infection caused by *C. albicans* [103].

Recurrent VVC is defined as having four or more vaginal yeast infections in a year [104]. Patients with recurrent VVC are predominantly infected by *C. albicans* or *C. glabrata* but determining the species is clinically essential for proper treatment and management [105]. It has been hypothesized that patients that have been experiencing recurrent VVC and are who are treated with short-term antifungals repeatedly may be the cause of the emergence of NAC vaginitis [106]. A higher percentage of NAC species have been clinically isolated from women with recurrent VVC [43]. Patients who present with unremarkable and challenging vaginitis yeast speciation is of importance. For example, patients who are infected with *C. lusitanae* tend to report minimal symptomatology with less to no swelling or redness of the vaginal region; primarily report a burning or itching sensation [106]. Also, upon examination of these patients, the vaginal pH is healthy and have no external presentation of a yeast infection [106].

Candida Balanitis

Candida balanitis is associated with inflammation of the glans penis and regularly including the prepuce in the presence of *Candida* species [43,95]. Sole inflammation of the glans penis is referenced as balanitis, while inflammation of the prepuce is termed posthitis; if inflammation is involved in both areas, then it is coined balanoposthitis [95].

Candiduria

Candiduria is common among hospitalized patients but rare in healthy individuals [107]. Urinary tract infections (UTIs) caused by *Candida* species are on the rise mainly as nosocomial infections due to the increase in at-risk patients [107,108]. Urine samples with the presence of *Candida* species pose a challenge for physicians in determining if the candiduria denotes colonization, urinary tract infection which has the possibility of leading to renal candidiasis with sepsis [108].

Gastrointestinal candidiasis

Candida species commonly colonize the human gastrointestinal tract as a commensal organism [109]. As an intestinal fungus is it believed that it directly influences gut health [110]. However, the direct influence of fungal colonization and its effects on the gastrointestinal tract has not been thoroughly studied. However new studies are coming out showing the results of an interaction between the intestinal immune system and the gut microbiome [111].

Candida colonization and GI tract diseases

Inflammatory bowel disease (IBD) is a blanket term used to describe a heterogeneous group of chronic inflammatory diseases that involve the gastrointestinal (GI) tract [109,111,112]. IBD consist of two clinical manifestations: ulcerative colitis (UC) and Crohn's disease [111,112].

Ulcerative colitis is defined by chronic continuous and superficial inflammation that affects the colon solely. A study was conducted to determine the effects of *Candida* colonization on the course of UC. The study yielded results that showed *C. albicans* (approx. 91% of cases) was the predominant species followed by *C. glabrata* (approx. 6.7% of cases) and *C. inconspicua* (approx. 1.6% of cases) [112].

In comparison, Crohn's disease (CD) is characterized by patchy inflammation that may affect unspecified parts of the gastrointestinal tract and the entire thickness of the bowel wall. The specific cause of this disease is currently unknown but is hypothesized that there is an abnormal response to gut the microbial antigens [111,113]. One study observed the fungal changes of the gastrointestinal tract in the context of CD patients. From this study, it showed that patients diagnosed with CD had an increased abundance of *C. tropicalis* in correlation with *Escherichia coli* and *Serratia marcescens* [113]. Furthermore, there was also a high correlation with anti-saccharomyces cerevisiae antibodies (ASCA) titers in individuals that were heavily colonized [113,114].

In conclusion, high levels of *Candida* colonization are associated with diseases of the gastrointestinal tract. The presence of *Candida* species, primarily *C. albicans*, is associated with delayed healing of gastric ulcers; also, inflammation and the ulceration aid in the colonization of the GI tract [109]. Future studies are needed to develop a more in-depth knowledge base of how these changes in the fungal population of the gastrointestinal tract result in IBD.

Cutaneous Candidiasis

Congenital Cutaneous Candidiasis (CCC)

Congenital cutaneous candidiasis (CCC) is an immensely rare disorder that first appears within the first week of life [73,115]. Neonates generally acquire candidiasis during the birthing process, but the reasons that explain the route of transmission and pathogenesis remains unknown [73]. It is currently being hypothesized that the development of chorioamnionitis is the mechanism of fetal infection [116]. CCC has a wide range of clinical manifestations [73,115,116]. Diagnosing CCC is

challenging due to the various rash presentations [117]. Congenital cutaneous candidiasis cases from 2004 and 2015 were reviewed and concluded that 100% of the cases *C. albicans* was isolated [117]. Generally, skin findings consist of an extensive maculopapular rash [73,117]. This neonate cutaneous infection manifestations also include erythema, pustules, abscesses, and or desquamation [73,115-117]. Typical areas of skin involvement are the face, scalp, trunk, and extremities [73,117]. CCC infections do have the ability to disseminate; generally, the patient presents with respiratory distress, and *Candida* species are isolated from the gastrointestinal tract; in rarer cases to the blood and cerebrospinal fluid [117].

Congenital cutaneous candidiasis is rare, and less than 100 cases have been reported in the literature over the past two decades. Therefore, little research and knowledge are known of this disorder.

Chronic Mucocutaneous Candidiasis (CMC)

Chronic mucocutaneous candidiasis is rare and characterized by recurrent *Candida albicans* infections of the skin, nails, mucous membranes and hyperkeratosis [118]. This disorder commonly manifests itself in early childhood, and there is some familial linkage. CMC disease is linked with inborn errors of the interleukin-17 (IL-17) immunity [118-120]. In 2011, two genetic etiologies were reported with this *Candida* disease: an autosomal recessive deficiency and an autosomal dominant deficiency [119]. Two separate cases of genetic deficiencies in genes for interleukin-17 signaling molecules have been noted [119]. The first patient presented an autosomal recessive deficiency of the interleukin-17 receptor A which eradicated the cellular responses downstream to IL-17A and IL-17F cytokines [119]. The second patient had an autosomal dominant deficiency in IL-17F cytokine resulted in a partial defect of the IL-17 dimer molecule [119]. Patients with an autosomal dominant deficiency commonly present with mutations of the signal transducer and activator of transcription 1 (STAT1) and caspase-associated recruitment domain (CARD9) [118,120]. STAT1 is a protein-coding gene that mediated cellular responses to signaling molecules including interferons and cytokines. Mutations in STAT1 leads to defective helper-T (Th) cell 1 and 17 responses, which potentially explain this fungal infection [118,120]. CARD9 is an adaptor molecule that mediates signals from C-type lectin-like receptors (CLRs) to induce the transcription and production of proinflammatory cytokines [118,121]. Patients with CARD9 deficiencies present with two immunological phenotypes that include decreased IL-17 producing T

cells and impaired *C. albicans* killing by neutrophils [118,121].

Candidal Onychomycosis

Onychomycosis is a fungal infection of the nails; 80% of the toenail infections and at least 50% of fingernail infections are caused by dermatophytes [122,123]. However, *Candida* species have been emerging as a causative agent [123,124]. *Candida* species are not considered a part of the nail flora [44]. *Candida* onychomycosis is primarily found in individuals with defective immune responses consequentially due to aging, diabetes mellitus, and an immune suppressive disease. On the other hand, individuals that are not immunocompromised may also contract *Candidal* onychomycosis because of the persons' occupation. *Candidal* nail infections are more common among women than men who may be a result of self-inoculation from the vaginal flora [122,124]. Although some studies have shown that men are more likely to develop onychomycosis, then than women due to men increased lifestyle and occupation hazards [125]. This form of infection may manifest itself as paronychia and onychia [44, 122]. *Candida* onychomycosis can be divided into three broad categories: *Candidal* paronychia, *Candidal* granuloma, and *Candidal* onycholysis [122,124].

Candidal Paronychia

This manifestation is the most common form of a *Candidal* nail infection and is characterized by initial inoculation of the soft tissue surrounding the nail which is then followed by the invasion of the nail plate [122,124]. The affected soft tissue is inflamed; generally appears red and edematous [124]. "Beau's lines," which are transverse depressions, commonly appear when the nail matrix is infected [122,124]. If the infection progresses this may result in a coarse, irregular, bowed, and finally dystrophic nail [122,124]. Paronychia presents either as an acute or chronic ailment [126]. The difference between these two presentations is the duration of the infection, acute paronychia is an infection that is last less than six weeks, and chronic is where the duration is longer than six weeks [126]. *Candidal* onychomycosis accounts for 95% of chronic paronychia, and the remaining clinical cases are caused by atypical mycobacteria and gram-negative rods [124,126]. A present study showed that *Candida parapsilosis* and *Candida guilliermondii* surpassed *Candida albicans* as the most commonly isolated pathogen from patients [127]. Within the same study, it showed the distribution of onychomycosis among *Candida* species might be dependent upon geographical location [127]. *C. krusei*, *C. glabrata*, *C. tropicalis*, and *C. lusitaniae* have also

been isolated as causative agents for onychomycosis [125,127].

Candidal Granuloma

Candidal granuloma exclusively appears in patients with CMC. The fungal organism directly invaded the nail plate, and when the infection is advanced, the soft tissue surrounding the nail is engorged until the digit develops a pseudo-clubbing appearance [122,124].

Candidal Onycholysis

Onycholysis is defined as the separation of the nail plate from the nail bed that occurs on the finger and toes [128]. Initially, onycholysis appears at the distal subungual hyperkeratosis with a yellow to gray mass that lifts off from the nail plate [124]. As this infection progresses, the nail begins to lysis or separate [122,124]. This clinical manifestation is more common on the hands rather than the feet; also occurs mainly due to direct trauma to the nail of the fingers and toes [122,124,128]. Patients with this form commonly have psoriasis and or pustular psoriasis [122,124,128]. Either sex can be affected, but it is more common among women, potentially because of occupational hazard that allows the nails to be exposed to continuous moisture [128]. Finger onycholysis among women has been associated with *C. albicans* colonization [128].

Invasive Candidiasis

Clinical syndromes associated with invasive candidiasis caused by non-*albicans* species is difficult to differentiate from *C. albicans*. Manifestations range from fever in a hemodynamically stable patient to sepsis and septic shock [10]. Invasive candidiasis is a primary cause of disease and death in patients with hematologic malignancies and a frequent cause of failed remission induction chemotherapy [129]. At least 15 species of *Candida* causes diseases, but only about 5 of those are causative agents for invasive candidiasis: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis* [130]. Also, in certain parts of the world, including Asia, the UK, Spain, and the United States, *C. auris* has been emerging as a pathogen. This is of concern because *C. auris* is a multidrug-resistant fungus [130].

Disseminated candidiasis can be either acute or chronic and commonly occurs in patients with leukemia who have received cytotoxic chemotherapy [129]. Clinically acute disseminated candidiasis (ADC) presents as neutropenic fever unresponsive to antibacterial, skin lesions, pneumonia, and shock. Common infection sites include the skin, lungs, GI tract, kidneys, liver, and spleen [129]. Chronic disseminated candidiasis (CDC) manifest

as a non-neutropenic fever, unresponsive to antibacterial, abnormal liver function test; also, in this form of infection, the spleen and liver are predominantly the sites of infection [129].

Candidemia is generally viewed as the most common manifestation of candidiasis. Candidemia appears to be age-specific, with the highest occurrences at the extremes of age [131]. Deep-seated candidiasis commonly arises from direct inoculation or hematogenous dissemination. Common sites for deep-seated candidiasis include bone, muscle, joints, eyes, and the central nervous system (CNS) [131]. One possible way invasive candidiasis occurs when *Candida* species colonize the gut and invades through translocation to distal regions of the host. In patients with indwelling medical devices, candidemia that originated from colonization may lead to colonization of the device and the formation of a biofilm [131]. Once candidemia has been established, the fungi may disseminate to other regions. Signs and symptoms of candidemia are dependent upon the site of infection .

C. tropicalis is a frequent causative agent of candidemia in Latin America [132]. Patients who have this manifestation caused by *C. tropicalis* commonly central venous catheters and are on a broad-spectrum antibiotic [132]. Few reports of this infection exist, and the information is limited.

Also, *C. glabrata* has been reported as the cause of meningitis and endocarditis as a late complication of candidemia [133]. *Candida* infection of the CNS is a rare manifestation of invasive candidiasis. CNS infections caused by *Candida* species commonly includes meningitis, parenchymal abscesses, and vasculitis. Most cases are due to *C. albicans* [133].

Diagnosis & Therapeutic Treatment Options

Summary on Diagnosing Candidiasis

Diagnosing *Candida* infections can be problematic because *Candida* species can grow in various morphological forms depending on their environment. Another challenge for diagnosing candidiasis is due to this infection presents itself in many manifestations; also, the manifestations may be dependent upon the patient's demographic. However, some tools can be applied to screen and determine the presence of fungal cells. Techniques include antigen testing, CHROMagar media, and microscopic examination [134].

Antigen testing for candidiasis is commercially available in enzyme-linked immunosorbent assay (ELISA) kits which are suitable for specificity but variable

sensitivity [134]. ELISA detects the mannans for the *Candida* species. Serum 1,3- β -D-glucan (BDG) is increasingly used as a diagnostic marker for invasive fungal infections [135]. Mannans and BDG are the most successful targets for these assays because they are the most abundant constituents of the cell wall. Serology testing is standard in diagnosing invasive candidiasis [136]. One primary concern with anti-*Candida* antibody assays is their sensitivity, which may be reduced in immunocompromised patients and a positive result may not differentiate previous infections [136].

CHROMagar is an agar plate that distinguishes between various *Candida* species by color because of a chemical reaction. This chromogenic media yields rapid identification of yeast. Currently, three *Candida* (*C. albicans*, *C. tropicalis*, and *C. krusei*) species can be detected and differentiated. *C. albicans* growth is described as light-medium green colonies. *C. tropicalis* colonies are blue with a purple-like pigmentation in the surrounding agar. Lastly, *C. krusei* colony growths are large, fuzzy, and rose-like in color with white edges. Other *Candida* species can grow on this media and typically present as white-beige colonies (e.g., *C. glabrata*). Additionally, CHROMagar is commonly used to aid in identifying *Candida* involved in genitourinary infections [43]. This method of identification for *Candida* species is important because it is rapid and cost-effective.

Direct microscopic examination of smears is another approach for identifying *Candida* species. This approach is commonly used in *Candida* infections that involve the mucosal membranes (e.g., oral and genitourinary candidiasis) [43,137]. This method involves taking a sample from the infected area and viewing it under the microscope. Prior to examination, the sample is ideally treated with potassium hydroxide (KOH), Gram stain, or periodic acid Schiff (PAS) stain [137]. Generally, when a *Candida* infection is suspected the samples are prepared with KOH; KOH allows *Candida* to stand out and not be obscured by organic materials. *Candida* hyphae and pseudohyphae are visible in a KOH wet mount preparation [137]. Additionally, hyphae and yeast cells under Gram staining preparation will appear dark blue, whereas when in a PAS stain they will be red to purple [137].

Summary of the Treatment of Candidiasis

Currently, to date, there are three principal antifungal agents to treat candidiasis which includes azoles, polyenes, and echinocandins. Each of these drug classes has a specific drug target.

Azoles target 14- α -demethylase which mediates the conversion of lanosterol to ergosterol. This class directly targets the biosynthesis of ergosterol. Azoles are metabolized by cytochrome p450, which can cause a drug to drug interactions [138]. A common azole that is prescribed is Fluconazole. Fluconazole commonly treats candidemia and non-critically ill patients without prior exposure to azoles and colonization of the strain with reduced susceptibility to the azoles (e.g., VVC and candiduria) [138]. Fluconazole is generally well tolerated but has a limited spectrum; Voriconazole is the new azole on the market is the new and improved Fluconazole because of its increased spectrum.

Polyenes antifungal agents bind directly to ergosterol and destabilize the fungal cell membrane. Amphotericin B (AmB) is classified as polyene; AmB binds to the fungal cell membrane causing pores to form and subsequently the leakage of intracellular cations resulting in cell death. AmB is effective in killing fungal cells, but nephrotoxicity is a significant concern with this drug. Currently, there are three lipid formulations of AmB: liposomal amphotericin B (L-AmB), amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD); all have a higher tolerance level and decrease toxicity [138]. Of the three lipid amphotericin B formulations, L-AmB is widely used and most favorable due to pharmacokinetics. L-AmB is also preferred because of its high intracellular penetration in the cerebral spinal fluid [138]. Commonly the first line of therapy for disseminated candidiasis is L-AmB and used as the second line against invasive candidiasis [138].

Echinocandins directly targets the cell wall by inhibiting 1,3- β -D-glucan (BDG) synthesis; the loss of the cell wall glucans results in osmotic fragility. This is a fungicidal agent against *Candida* species including non-albicans isolated resistance to Fluconazole. Echinocandins are generally well tolerated with limited side effects, also has excellent pharmacokinetics and pharmacodynamics. To date, three echinocandins (anidulafungin, caspofungin, and micafungin) are used as a treatment against invasive candidiasis, primarily candidemia [138]. Even though echinocandins have a strong safety profile, therapeutic concentrations are low in some tissues (e.g., eye, CNS, urine, endocardium, and peritoneum) also the pharmacodynamics and pharmacokinetics are poor in critically ill patients [138]. Echinocandins are concerned as a treatment option for invasive candidiasis in critically ill individuals and or when colonization of a *Candida* strain is evident with reduced susceptibility to azoles [138].

5-fluorocytosine (Flucytosine) is another antifungal, and it inhibits nucleic acid synthesis. This therapy method is not commonly used as monotherapy because resistance easily develops. When is used flucytosine is used it is typically used in combination with another antifungal agent. Flucytosine use should be considered in cases of endophthalmitis, endocarditis or CNS infections because this drug distributes well among the tissues [138].

Conclusion

Candida species are an opportunistic fungal pathogen that causes infections ranging from superficial to invasive. The occurrences of opportunistic fungal infections have increased significantly over the past few decades, mainly contributes to morbidity and mortality in immunosuppressed patients. Although *C. albicans* may be the most prevalent species as of right now, the species distribution in the recent has begun to shift towards non-albicans species. The NAC are emerging pathogens and are of clinical importance. These species have been largely ignored, and our current knowledge of pathogenicity, epidemiology, host immune response, and treatment of NAC infections is incomplete. Nevertheless, if NAC infections are to be adequately managed in the future comprehensive studies of these *Candida* species must be performed.

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