INTRODUCTION

The fungal infections during the last decades are on the mount. The most common fungal infection, candidiasis can be defined as fungal infection which is caused by pathogenic fungus Candida albicans belonging to genus Candida. C. albicans is an opportunistic pathogen which is present as normal microflora in humans [1]. It can exist in unicellular yeast form to filamentous hyphal form and this switching between the two forms is an important virulence factor. It resides in commensal form on skin, gastrointestinal tract and mucosa of 30% to 50% healthy humans in natural conditions. But in immunocompromised conditions, it causes candidiasis which ranges from mucosal candidiasis to systemic infections resulting in 26-60% mortality rates [2, 3]. Candidiasis can be classified into three categories namely oropharyngeal/esophageal candidiasis (which develops in mouth and throat commonly called as thrush), vulvovaginal/genital candidiasis (which develops due to overgrowth of yeast in vagina) and invasive candidiasis (which occurs when Candida enters bloodstream) giving rise to candidemia. Moreover, with the ever increasing problem of multidrug resistance (MDR), the efficient therapeutics is facing numerous hurdles [4]. The pathogenicity of Candida and incidence of candidiasis depends on immune status of host cell through a delicate balance between the fungi and the host’s immune status which determines the commensal or parasitic relationship (Figure 1). The predisposing factors for candidiasis can be subdivided into immunologic and non immunologic factors according to occurrence. Considering the significance of C. albicans being the fourth most common cause of hospital acquired infections, here we review the predisposing factors which are responsible for this microorganism.

Figure 1 - The transition between commensal and pathogenic forms of Candida within the host cells depends on the CD4+ count which forms the basis of establishment of infection.
to cause a wide variety of infections ranging from mucosal to life threatening disseminated candidiasis.

**Predisposing factors**
Candida infections arise due to alteration in host defense system where both immunological and non immunological factors (Figure 2) play crucial roles making the conditions favorable for proliferation of *Candida* [5].

**Immunological factors**
The following section describes the immunological predisposing factor which contributes to enhanced susceptibility to candidal infections.

**HIV/AIDS**
According to the Joint United Nations Programme (2009) on HIV/AIDS and the National AIDS Control Organization (2008), there is an estimation of 2.4 million cases of HIV infection worldwide and 22.7 per 100,000 in India respectively. The immunocompromised or HIV infected patients are more prone to oral and pharyngeal candidiasis. It has been estimated that more than 90% of HIV patients suffer from fungal infections during the progression of disease [6]. The prevalence of candidal infections all over the world is 18% [7]. It has been found that HIV patients suffering from cutaneous candidiasis have low CD4+ lymphocyte count and elevation in RNA load [8]. Other than regular virulence factors in *Candida* necessary for pathogenesis such as secreted aspartyl proteases are also important for the same but its activity depends on host conditions [9]. Role of Natural killer cells (NK) in immune system against pathogens is well known. They work as immune effectors that directly bind to pathogen and kill them through perforin dependent mechanisms. The cascade involves the receptor NKp30.

![Figure 2 - Predisposing factors leading to Candida infections.](image-url)
receptor which is required for fungi and cell conjugate formation, phosphatidylinositol 3-kinase (PI3K) signaling and perforin release. But in case of HIV patients, NKp30 receptor have low activity which accounts for defective antifungal activity of NK cells [10]. Among the fungal pathogens, it has been found that C. albicans is the most prevalent species (68.5%) followed by C. tropicalis (7.4%), C. krusei (6.4%), C. parapsilosis (3.0%) and C. sake (2.5%) [11]. In HIV infected candidiasis patients, a Th17 functional subset of T helper cells is an important asset which is guarding against this fungus. The selective loss of T helper cells along with the progression of HIV infection causes the decay of fungal containment on the oral epithelium which in turn allows C. albicans to express its pathogenic potential [12]. Recent studies have shown that C. albicans inhibits the replication of HIV-1 in macrophages and dendritic cells. The inhibition is also contributed by host restriction factors which are able to block retroviral replication. The main cytidine deaminases are APOBEC3G and APOBEC3F that introduces G to A substitutions in the HIV-1 genome which inhibits viral replication. This can be used in antiretroviral therapy but the mucocutaneous candidiasis is also prevalent in HIV patients [13].

The study on correlation between CD4+ counts and the prevalence of candidiasis suggests that CD4+ lymphocyte counts to be a marker of HIV disease progression [14]. The introduction of anti-human immunodeficiency virus drugs of the aspartic protease inhibitor-type (HIV PIs) can be used as a potent agent for inhibition of secretion of aspartic proteases (saps) which is a virulence factor in C. albicans. These enzymes can degrade critical host defense components like complement and epithelial defensive proteins such as histatin-5 and E-cadherin [15]. The two subunit vaccines which are based on antigens dominantly expressed by C. albicans in vivo are Als3 adhesin and Sap2 which have been recently undergone phase 1 clinical trial [12]. But much new insights are needed in order to combat the fungal infections during this immunocompromised condition.

Organ transplant

The fungal infections are predominantly prevailing in cases of organ transplantation. It has been reported that fungal infections are the second most common cause of mortality in kidney transplants due to immunosuppressive status of the patients. In organ transplantation, in order to prevent graft rejection, certain drugs are given to the patients as a part of immunosuppressive therapy to suppress the host immune status. The action of these drugs reduces the natural immune response resulting in increased susceptibility to fungal infections and particularly opportunistic organism like C. albicans [16]. The prevalence of candidiasis in organ transplants is 7% [17]. Mostly in case of renal transplantation, Candida can become more prevalent after organ transplantation and can lead to more severe infections in bloodstream leading to candidemia [18]. The most frequent form of oral candidiasis in renal transplantation patients is denture stomatitis which is followed by angular chelitis and pseudomembranous candidiasis. The chances of severe candidiasis increases after immediate post-transplantation period [19]. Invasive fungal infections are the most common causes of mortality in cases of renal transplantation and associated with parenteral nutrition, abdominal surgery and broad spectrum antibiotic therapy [20]. The most prevalent species of Candida is C. albicans (86.4%) as reported in a case study of kidney transplants in Brazil [21]. In case of liver transplantation, the prevalence of Candida species are C. albicans (50%), C. glabrata (12.5%), C. parapsilosis (12.5%), C. krusei (12.5%), C. lusitaniae (6.2%), C. tropicalis (6.2%) and multiple others (25%) [22]. The predisposing factors to fungal infection in patients of lung transplantation includes: preoperative chronic lung diseases and inherent palliative immunosuppression, intraoperative complications such as abnormalities in the bronchial anastomosis or lung injury, and postoperative complications such as enhanced immunosuppression for early rejection, graft dysfunction, concurrent viral and bacterial infections, and bronchiolitis obliterans syndrome.

Cancer

Candida is being ranked among the ten prominent pathogen affecting leukemia patients, resulting in 25-60% mortality rates [23]. In blood tumors, candidemia caused by the Candida species affecting the patients are C. albicans (33%), C. guilliermondii (26%), C. parapsilosis (12%), C. krusei (8%), C. lusitaniae (5%), C. famata (4%), C. tropicalis (4%), C. glabrata (4%), and C. pelliculosa (4%). The incidence of candidiasis in cancer patients is around 43.2% [24]. Cancer and chemotherapy results in
immunosuppression which gives opportunity for emergence of fungal infection. The outcome is the cellular and humoral immune dysfunction and mucosal damage due to chemotherapy in ovarian and lung cancer. In a study, it has been observed that there is a deficiency of MPO (myeloperoxidase) which is an important risk factor for invasive candidiasis. The decreased level of TNF-α (Tumour Necrosis Factor) is also the result of Candida invasion only [25]. MMPs (matrix metalloproteinases) are involved in degradation of extracellular matrix and tumour cell evasion which leads to metastasis in cancer. The MMP2, 3, and 9 increase in breast cancer as they are involved in invasion, metastasis and tumor angiogenesis. The breast cancer patients are susceptible to candidiasis and there is a positive effect of candidiasis on the metastasis and tumor progression in breast cancer patients [26]. It has been found that Candida is involved in cell cycle arrest and blocks the proliferation of host cells, PGE2 (Prostaglandin E2) synthase expression (involved in eicosanoid proliferation of host cells, PGE2 (Prostaglandin is involved in cell cycle arrest and blocks the metastasis and tumor angiogenesis. The breast cancer patients are susceptible to candidiasis and there is a positive effect of candidiasis on the metastasis and tumor progression in breast cancer patients [26]. It has been found that Candida is involved in cell cycle arrest and blocks the proliferation of host cells, PGE2 (Prostaglandin E2) synthase expression (involved in eicosanoid and glutathione metabolism) and thus PGE2 production in patients suffering from HPV (human papillomavirus) 16 virus infections [27]. Interleukin is known to play a key role in mammalian immune system. The cancer patients who have deficient IL-17 receptor or low secretion of IL-17 are highly susceptible to systemic candidiasis [28]. More often, candidiasis is a common side effect of chemotherapy for malignant cancer. It has been found that thrombospondin-1 (extracellular matrix protein which is released at tissue injury sites) enhances the pathogenesis of disseminated candidiasis by creating an imbalance in the host immune response which leads to impaired fungal clearance, reduced phagocytic function and increased mortality [29]. Secreted aspartyl proteinase 2 (Sap2) is a virulence related trait of Candida and patients suffering from candidiasis have high titre values of Sap2. The candidiasis does not have significant clinical symptoms and hence its diagnostic methods have less sensitivity. For diagnostic purposes, Sap2 found in serum samples of cancer patients can be used for detection of Candida by an indirect competitive enzyme linked immunosorbent assay [30]. The antifungal drug echinocandin was used as a first line drug in candidemia affecting blood tumor patients [24]. Caspofungin and voriconazole drugs have shown immunomodulatory effect on human peripheral blood mononuclear cells (PBMC). The interaction between the drug and cells results in Th1-type cytokine secretion which assists in removal of fungal pathogen [31].

Genetic susceptibility

It has been believed that genetic factors must play an important role in determining the susceptibility to Candida infections (Figure 3). Mutations in single genes were found to be responsible for severe Candida infections in several primary immunodeficiencies that display the clinical picture of monogenetic disorders. The incidence of genetic susceptibility to candidal infections is 8.2% [32]. The monogenic disorder where CARD 9 gene codes for a protein Dectin-1, if there is a homozygous mutation then it can give rise to increased susceptibility to both mucosal and invasive Candida infections. The other monogenic disorder that results in an important primary immunodeficiency associated with Candida infections is CMC (chronic mucocutaneous candidiasis). The main cause of autosomal dominant CMC is the mutations in the CC domain of STAT 1 which is a signaling molecule of the type 1 and type 2 IFN receptor. Several mutations have been found in STAT3 a signaling molecule of the IL-23 receptor, which results in reduced IL-17 production [33, 34]. The mutations in genes coding for cytokines and their receptors have been described to be associated with Candida infections as in IL-12Rb1 deficiency which has been linked to mucocutaneous Candida infections and found to have increased susceptibility for invasive candidiasis [35]. Genetic variation in Toll like Receptors has also been associated with an increased susceptibility to fungal infections. Three single nucleotide polymorphisms (SNPs) in the TLR1 gene have been shown to influence susceptibility to candidemia [36]. It has been found that although there is a moderate effect on modulation of proinflammatory cytokine production, there is a minor impact of genetic variation in the autophagy genes ATG16L1 (autophagy related 16-like 1) and IRGM (immunity-related GTPase family, M) on the susceptibility to both mucosal and systemic Candida infections [37]. Several studies have been published showing a link between genetic variation and an increased risk for Candida infections, with different genetic pattern between mucosal and systemic candidiasis. So, it can be concluded that
Predisposing factors endorsing Candida infections

Nonimmunological Factors
The following section describes the non-immunological predisposing factors which contribute to enhanced susceptibility to candidal infections.

Nosocomial infections
Nowadays, intensive care units (ICU) have emerged as epicenters for candidal infections. The incidence of candidiasis due to nosocomial infections or more commonly referred as hospital acquired infections is 59.7% (Figure 4) [38]. Secondary infections in sepsis are caused by Candida and candidiasis is the third most reason of blood infections in ICU in hospitals which results into 30-40% mortality rates [39]. As a matter of fact, widespread and prolonged usage of antifungals has led to the emergence of MDR in C. albicans. In a statistical study conducted in ICU in India, the incidence of candidemia was evaluated which clearly shows that the underlying reason for higher risk to candidemia is the use of broad spectrum antibiotics. The patients were given broad spectrum antibiotics and antifungals which resulted in antifungal resistance in turn giving more opportunity for candidal growth [40, 41]. The increased dose of drugs and antibiotics favors the overgrowth of Candida and other

Figure 3 - An overview showing the genetic susceptibility to Candida infections due to mutation and monogenic disorders. The mutations in TLR (Toll Like Receptors), IFN (Interferon) receptor, IL (Interleukin) receptor, CARD9 (caspase recruitment domain 9), STAT (Signal transducer and activator of transcription), MYD88 (Myeloid differentiation primary response gene 88) leads to changes in cascade which enhances the susceptibility to Candida infections.

the balance between pro- and anti-inflammatory cytokines represent an important component of host defense against both mucosal and systemic candidiasis.
Some drugs like ranitidine which are prescribed to patients suffering from ulcers in hospitals often favors the growth of Candida and patients become more susceptible to Candida infections in hospitals [42]. Thus reduction in antibiotic dosage could be one of the alternative way to minimize Candida infections.

The types of Candida infections are urinary tract infection, candidemia, surgical site infection and intra-abdominal infection [43]. There is an incidence of invasive candidiasis in neonates in neonatal ICU which results into mortality of low birth weight infants [44]. The underlying cause of candidal infections in neonatal ICU is the horizontal transmission of Candida colony from the newly born who had acquired congenitally and then transmitting to other neonates [45]. In invasive fungal infections in neonates, the predominant causes in ICU are third generation cephalosporin use, neutropenia in first week of life, abdominal surgery, central venous catheter insertion or incubation more than 6 days [46]. Persistent candidemia is the outcome of poor clinical facilities, drug resistance and host related factors on invasive fungal infection in neonatal ICU [47]. It has been studied that patients who have prior abdominal surgery and suffering from chronic PPI (proton pump inhibitor) are predisposed to Candida-associated intra-abdominal infections [48]. Candidemia is considered as a prevalent factor in nosocomial infections. The major causes are ileus, use of proton pump inhibitors, gastrointestinal bleeding, previous stay in the ICU, blood transfusion, vaspressors, requirement for antibiotics, and invasive medical procedures and it can also result in sepsis [49]. The risk factors for mortality are different in early onset candidemia (EOC)
and late onset candidemia (LOC). However there is need of improvement in diagnosis and treatment in early infections [50]. The use of catheters in hospitals is one of the causes of urinary tract infection (UTI) in ICU. \textit{Candida} species are well known for forming antibiotic resistant biofilms on medical equipment which is one of the major concerns of nosocomial infections. The use of catheters or intravenous devices is a good source for dissemination of biofilm forming fungi [51]. The biofilms are formed on indwelling devices in polymeric matrix and are resistant to the antifungal agents which in turn increase more infection [52]. The biofilms growing on devices like catheters provide a high risk for systemic candida infections as they provide entry site to \textit{Candida} directly into patients where they can flourish well. Due to complex structure, they can easily resist the effect of conventional antifungal drugs like amphotericin B and fluconazole [53-54].

The bacterial infections may also play as a predisposing factor for candidal infections. The \textit{Clostridium difficile} infection (CDI) in patients in hospitals is a risk factor for development of candidemia and CDI may predispose for the translocation of \textit{Candida} [55]. The KPC-producing \textit{Klebsiella pneumoniae} (KPC-Kp) colonization or infection is also associated with candidemia in hospital acquired infections. Thus the gastrointestinal tube plays as key role in dissemination of Multi Drug Resistant (MDR) microorganisms like \textit{C. difficile} and \textit{K. pneumoniae} and also reservoir for \textit{Candida} [56, 57]. One of the ways to lessen the candida colonization in patients undergoing extensive abdominal surgery is early antifungal prophylaxis [58]. It has been mentioned in a study on management of intraabdominal candidiasis (IAC) in clinical settings, that there is urgent need to elaborate the recommendations for IAC management suggested by multidisciplinary expertise panel [59].

It has also been suggested that the restricted use of central venous catheters in hospitals and shortening the stay in ICU may help in reducing the development in invasive candidiasis.

\textbf{Diabetes}

Diabetes is a multisystemic disorder which is characterized by insufficiency of insulin secretion or resistance to the metabolic action of insulin on target tissues. Poor glycemic control in diabetic patients increases susceptibility to candidal infections [60]. The incidence of diabetic population is expected to increase from 171 million in 2000 to 366 million by 2030 [61]. The prevalence of candidiasis in diabetic patients is 31.4% [62]. Diabetic patients have increased \textit{Candida} colonization in oral mucosa in comparison with normal individuals [63]. It has been estimated that diabetic patients have highly glycosylated hemoglobin which can play as important factor for candidal infections and there is a formation of chemically reversible glycosylated products with salivary glucose and proteins in tissues during hyperglycemic episodes. The accumulation of glycosylation products on buccal epithelial cells may result in increasing the number of available receptors for \textit{Candida} and thus candidiasis [64]. The main factors contributing to oral \textit{Candida} colonization in case of diabetes mellitus are diabetic type, glycemic control and salivary pH [65]. The secreted acid proteinase might play a role in the pathogenesis of vulvovaginal candidiasis and improvement in the glucose control may reduce the risk of \textit{Candida} colonization and potentially symptomatic infection [66]. The prevalence of fungal infections in diabetic patients is also a result of immune dysfunction including low complement factor 4, decreased cytokine response after stimulation in humoral innate immunity and decreased functions (chemotaxis, phagocytosis and killing) of diabetic polymorphonuclear cells and diabetic monocytes/macrophages in cellular innate immunity [67].

It has been found that antifungal agent fluconazole shows alternation in phospholipase production, modification of buccal epithelial cells and reduction in adhesion of \textit{C. albicans} to human buccal epithelial cells in diabetic patients suffering from oral candidiasis [68]. The use and addition of the iron chelator, deferasirox used in the treatment of zygomycosis in diabetic patients, can be a promising compound but additional agents with new targets of action are also needed [69].

\textbf{Burn}

Nowadays, \textit{C. albicans} is emerging as a major fungal infection in burn wounds in hospitals, which can result in sepsis as one of the principle causes of death after a severe burn. The incidence of \textit{Candida} infections in burn wounds is 35.6% [70]. The burn wound represents a favorable site for fungal...
infections as they are exposed and serves for opportunistic colonization of fungal infections. The other factors which can favor for infection are age of the patient, extent of injury and depth of the burn wound along with the type, number of microbe attacking the patient, enzyme and toxin production, and motility which determines the likelihood of invasive burn wound infection. The risk factors for invasion are severity of illness, total parenteral nutrition, antibiotics, burns, central venous lines, and immunosuppression [71]. The prevalence of invasive candidiasis in burn cases varies widely and accounts for 3-23% of severe infection with 14 to 70% mortality rate [72]. The detection of fungal infection usually occurs after 14 days of injury [73]. In a study by Kobayashi et al. it has been suggested that burn-associated CD301 type 2 T cells may play a role on the increased susceptibility of burned patients to C. albicans infection [74].

Nitric oxide nanoparticle has been shown to have antifungal activity and can be used for treatment of cutaneous burn infections and wounds [73]. Nowadays, Serum (1→3)-β-D-glucan (BG) is increasingly used as diagnostic marker for invasive fungal infections [75].

Pregnancy
This condition can serve as a risk factor for vaginal candidiasis. It has been found that there is more prevalence of Candida vaginal colonization in a comparative study on Candida infections in pregnant and non-pregnant women. This colonization can result in complications related to delivery [81]. The incidence of Candida infections in pregnancy is 27.8% [82]. The most dominant Candida is C. albicans which has 66.3% prevalence when isolated from Tanzanian pregnant women suffering from vaginal candidiasis [83]. The main cause of prevalence of candidiasis is the disruption of vaginal normal flora [84]. During pregnancy the risk of vaginal thrush increases, possibly due to changes in hormone production, leading to increased glycogen content in the vagina. The effect of vaginal candidiasis in pregnancy is the abnormal vaginal discharge [82]. The promising treatment of vulvovaginal candidiasis during pregnancy is antifungal testing and determination of virulence factors [85]. It has been suggested that application of gynazol can be recommended in case of recurrent vaginal Candida infection [86]. It has also been reported that C. albicans isolated from vaginal exudates in pregnant women is more susceptible to antifungal drugs [87].

Other factors
Hydrochloric acid, bile juices and pancreatic enzymes are digestive secretions which play an important role in digesting the food in the gastrointestinal tract of humans. They maintain the integrity of small intestine and prevent the growth of microorganisms such as Candida into the absorptive sites in gastrointestinal tracts. But due to intake of antacids, antiulcer drugs and decreased secretion of digestive juices, Candida gets opportunity to overgrow in the stomach [88]. The other factor is the impaired liver function in which the liver is not able to perform its function of detoxification. The accumulated toxins are absorbed by intestine and make the individual more sensitive to chemicals. This stimulates the overgrowth of Candida and causes chronic candidiasis in digestive tract [89]. Sucrose, honey, maple syrup, refined sugars, fruit juice, has an important
role in functioning as growth enhancers for microbes. Foods with high content of yeast and fungi like cheeses, alcoholic beverages and dried fruits favor the growth of Candida. Essential nutrients like magnesium, vitamins A and B6, selenium, zinc, folic acid and essential fatty acids are found to be deficit in chronic candidiasis [42]. The use of drugs and chemical compounds hampers the functioning of liver which results in toxin accumulation thereby altering the bowel microflora. The balance of microflora is important in maintaining the nutritional status, cholesterol metabolism, immune system function, carcinogenic agents and aging. The hormonal imbalance, chronic stress also favors the above mentioned conditions which results in overgrowth of Candida [90].

CONCLUSION

It can be concluded that all the predisposing factors responsible for causing candidal infections can cause mild infections to severe life threatening infections. The incidence in mortality rates due to candidiasis, invasive fungal infections and candidemia are opening the gateway for new insights in research of more potent antifungal drugs. The better understanding of mechanisms or factors involved in pathogenesis in fungal infections can serve better for combating resistance in fungal pathogens. Thus, there is urgent need of further research and well programmed management in hospital settings which can reduce the mortality due to fungal infections in hospital acquired infections.

AUTHORS CONTRIBUTION

The authors contributed equally to the present study.

CONFLICT OF INTERESTS

None to declare.

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