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Review

Comprehensive Insights into the Etiology, Diagnosis, and Treatment Strategies for Candidiasis

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Candida **species are the most common cause of opportunistic fungal infection worldwide.** ***Candida*** **is the major fungal pathogen of humans, causing diseases ranging from superficial mucosal infections to disseminated, systemic infections that are often life threatening. A striking feature of its pathogenicity is ability to grow in yeast, pseudohyphal and hyphal forms. The hyphal form has an important role in causing disease by invading epithelial cells and causing tissue damage. Among** ***Candida*** **spp.,** ***Candida albicans*** **is the most common infectious agent. This dimorphic yeast is a commensal that colonizes skin, the gastrointestinal and the reproductive tracts. Non-*C. albicans* species are also emerging pathogens and can also colonize human mucocutaneous surfaces. The pathogenesis and prognosis of candidial infections are affected by the host immune status and also differ greatly according to disease presentations.**

Key words: Candidiasis, types, diagnosis, identification and management.

INTRODUCTION

With changes in the medical and surgical management of patients over the past three decades, fungi have emerged as a major cause of human disease. Of the disseminated mycoses, candidiasis remains the most prevalent, with *Candida albicans* causing more invasive infections than any other fungus (Elizabeth, 2009). Candidiasis or thrush is a fungal infection (mycosis) of any of the *Candida* species, of which *C. albicans* is the most common, also referred to as yeast infection. Candidiasis is also technically known as candidosis, moniliasis and oidiomycosis (William et al., 2006). *Candida* spp. are the most common cause of fungal infections leading to a range of life-threatening invasive to non-life-threatening mucocutaneous diseases (Achkar and Fries, 2010). *Candida* infections can present in myriad ways. This dimorphic yeast is a commensal that colonizes skin, the gastrointestinal and the reproductive tracts. Non-*C. albicans* species are emerging pathogens and can also colonize human mucocutaneous surfaces. Consequently, they are also from the setting of candidiasis, albeit at a lower frequency. The pathogen-nesis and prognosis of candidial infections are affected by the host immune status and also differ greatly according to disease presentations. Therefore, diagnosis, management and treatment choices vary and need to be considered in the overall setting of the affected human host.

ETIOLOGY

C. albicans is the species most commonly isolated; probably, it is a commensal in humans. The other *Candida* species may be endogenous or exogenous, surviving on skin and on environmental surfaces. Table 1 shows the major, less common and rare species which are implicated in human infections (Johnson, 2009; Vazquez and Sobel, 2011).

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Table 1. *Candida* species implicated in human infections.

Common species	Less common species	Rare species
Candida albicans	*Candida dubliniensis*	*Candida blankii*
Candida glabrata	*Candida famata*	*Candida bracarensis*
Candida tropicalis	*Candida inconspicua*	*Candida catenulate*
Candida parapsilosis	*Candida lipolytica*	*Candida chiropterorum*
Candida krusei	*Candida metapsilosis*	*Candida ciferri*
Candida guilliermondii	*Candida norvegensis*	*Candida eremophila*
Candida lusitaniae	*Candida orthopsilosis*	*Candida fabianii*
Candida kefyr	*Candida pelliculosa*	*Candida fermentati*
	Candida rugosa	*Candida freyschussii*
	Candida zeylanoides	*Candida haemulonii*
		Candida intermedia
		Candida lambica
		Candida magnolia
		Candida membranaefaciens
		Candida nivariensis
		Candida palmioleophila
		Candida pararugosa
		Candida pseudohaemulonii
		Candida pseudorugosa
		Candida pintolopesii
		Candida pulcherrima
		Candida thermophila
		Candida utilis
		Candida valida
		Candida viswanathii

Table 2. Genomic features of *Candida* (Butler et al., 2009; Reiss et al., 2012).

Species	Genome size (Mb)	No. of genes	Ploidy	Pathogen
C.albicans	16	6,159	Diploid	++
C.glabrata	12.3	5283	Haploid	++
C.tropicalis	15	6,258	Haploid	++
C.parapsilosis	16	5,733	Diploid	++
C.krusei	11	-	Diploid	+
C.guilliermondii	12	5,920	Haploid	+
C.lusitaniae	16	5,941	Haploid	+

++, Strong pathogen; +, moderate pathogen.

DESCRIPTION OF COMMON SPECIES OF *CANDIDA*

These species span a wide evolutionary range and show large phenotypic differences in pathogenicity and mating, allowing us to study the genomic basis for these traits. Despite the genome size and phenotypic variation among the species, the predicted numbers of protein-coding genes are very similar, ranging from 5,733 to 6,318 (Table 2).

Candida albicans

It is a diploid yeast with two pairs of 8 chromosomes. Its genome size is about 16 Mb (Soll and Daniels, 2007). It possesses 6,159 coding genes. It is the predominant cause of invasive fungal infections. People at risk include those suffereing from HIV, cancer and intensive care unit patients for example those undergoing major surgery and organ transplants (Uwamahoro and Traven, 2010; Miceli

et al., 2011)

Candida glabrata (Torulopsis glabrata)

It is a small, haploid, monomorphic yeast with 13 chromosomes and a genome size of 12.3 Mb. It possesses 5283 coding genes. It has become important because of its increasing incidence worldwide and decreased susceptibility to antifungals. Its emergence is largely due to an increased immunocompromised patient population and widespread use of antifungal drugs. In many hospitals, *C. glabrata* is the second most common cause of candidemia (Pfaller and Diekema, 2007).

Candida tropicalis

It is a diploid, with 10 to 12 chromosomes and a haploid genome size of 15 Mb. It possesses 6258 genes. *C. tropicalis* is the third or fourth most commonly recovered *Candida* species from blood cultures. *C. tropicalis* has progressively been observed to be the commonest cause of invasive candidiasis in neutropenic patients such as those with acute leukaemia or those who have under-gone bone marrow transplantation (Kothavade et al., 2010).

Candida parapsilosis

It is a diploid or aneuploid with 14 chromosomes and a genome size of 16 Mb. It possesses 5733 genes. It is one of the principal causes of invasive Candidiasis. In most parts of the world, it is the third most common cause of candidemia especially in patients with intravenous catheters, prosthetic devices, and intravenous drug use. It is one of the most common causes of candidemia in neonatal intensive care units (Levy et al., 1998).

Candida krusei

It is a diploid, with 3-5 chromosomes and genome size of 11 Mb. It is the fifth most common bloodstream isolate, although, less common (1 to 2%), *C. krusei* is of clinical significance because of its intrinsic resistance to fluconazole and reduced susceptibility to most other antifungal drugs. It is frequently recovered from patients with hematological malignancies complicated by neutropenia tends to be associated with higher mortality rates (49 vs 28% with *C. albicans*), and lower response rates (51 vs 69% with *C. albicans*) (Hachem et al., 2008).

Candida guilliermondii (teleomorph-*Pichia guilliermondii*)

It is a haploid. It is reported to have genome size of 12 Mb and possess coding genes 5920. It has been isolated from environmental surfaces and from the skin and nails of healthcare workers. It has been shown to cause hematogenously disseminated candidiasis (Barchiesi et al., 2006; Medeiros et al., 2007).

Candida lusitaniae (teleomorph-*Clavispora lusitaniae*)

It is a haploid. It has genome size of 16 Mb. Among, the rare non-*albicans Candida* species, it has emerged during the last 20 years as an important nosocomial pathogen throughout the globe (Favel *et al*., 2004).

Candida kefyr

It consists of 18 chromosomes. *Candida kefyr* was only isolated from urine cultures (Weichert et al., 2012). It has been reported to cause systemic *Candida* infection in patients with neutropenic leukemia and in a woman with underlying heart disease. Very recently, it has been described as a pathogen causing invasive fungal enteritis in a patient with underlying haematological disease following bone marrow transplantation (Direkze et al., 2011).

EPIDEMIOLOGY OF *CANDIDA* SPECIES

Historically, *C. albicans* accounted for 70 to 90% of the isolates recovered from infected patients while other *Candida* species rarely isolated from clinical specimens (Anane et al., 2007). However, recently epidemiological data reveals a change in the patterns of infection with shift from *C. albicans* to non-*albicans Candida* species such as *C. glabrata*, *C. tropicalis, C. parapsilosis, C. krusei* (Ahmad and Khan, 2009). Table 3 represents epidemiological data of *Candida* spp. for the last 10 years. In India, *C. tropicalis* is the most common cause of nosocomial candidaemia. Epidemiological survey data from India showed that 67 to 90% of nosocomial candidemia cases were due to *Candida* non-*albicans* of which *C. tropicalis* was the most dominant (Kothari and Sagar, 2009).

In last few decades, there have been numerous reports of *Candida* infections in India. Sengupta et al. (1999), documented that out of sixty three isolates of yeasts (66.6%) were *C. albicans*, (14.3%) *C. tropicalis*, (6.3%) *C. parapsilosis*, (3.2%) *C. kefyr*, *C. krusei* and (1.6%) *C. guilliermondii.* In another study, Prasad et al. (1999) reported that *C. albicans* was the most predominant (47.6%) pathogenic species isolated from various clinical specimens followed by *C. tropicalis* (35.4%), *C. krusei* (4.9%), *C. glabrata* (3.7%), *C. zeylanoides* (2.4%), *C. guilliermondii* (2.4%), *C. kefyr* and *C. parapsilosis* (1%).

C. albicans is the major cause of serious fungal infections in the United States, and *Candida* species are

Table 3. Distribution of *Candida* species in epidemiological surveys of clinical isolates since the last 10 years.

Period of study	Region	*Candida albicans* (%)	*Candida tropicalis* (%)	*Candida glabrata* (%)	*Candida parapsilosis* (%)	Other *Candida* species (%)	References
1991-2000	India	14	38	3	2	26	Chakrabarti, 2005
2000-2003	Switzerland	64	9	15	1	2-9	Marchetti et al.,2004; Sandven et al., 2006
	Norway	70	7	13	6	1-3	
2001	US	55	9	21	11	2	Fenn , 2007
2001-2002	Paris ICU	54	9	17	14	2-4	Bougnoux et al., 2008
2001-2005	India	21.5	35.3	17.5	20	1-3.3	Xess et al., 2007
2003	India	45.8	24.7	1	10.5	10-38.4	Basu et al., 2003
2004	Japan	41	12	18	23	2	Takakura et al.,2004
2004	France	55	5	19	13	4	Talarmin et al., 2009
2004-2008	North America	46	8	26	16	1-3	Horn et al., 2009
2004-2007	Denmark	57	5	21	4	9	Arendrup et al., 2011
2007-2010	Brazil	34	15	10	24	17	Marra et al., 2011
2007-2011	India	30	50	20	-	-	Basu et al., 2011
2008-2009	Worldwide	48	11	18	17	4	Pfaller et al., 2011
	Europe	55	75	16	14	3-4	
	North America	43	11	24	17	2-4	
	Asia	57	12	14	14	2	
2009	Portugal	90	3	5	2	2	Fernandes et al., 2009
2010	Turkey	36	1	-	12	2	Altuncu et al., 2010
2010-2011	Worldwide	43	7	31	20	7	Das et al., 2011

the fourth most commonly cultured microbe from blood. The attributable mortality from bloodstream *C. albicans* infections in adults is at least 15% (Noble et al., 2010). In North and South America, non-*albicans Candida* species account for more than half of the bloodstream isolates: *C. glabrata* and *C. parapsilosis* are the predominant non-*albicans* species, respectively. Whereas, in Europe, *C. albicans* remains the most frequent species, epidemiological trends suggest that non-*albicans Candida* species, in particular *C. glabrata,* are emerging. In addition to differences in the fungal ecology of the different continents, the large use of azoles antifungal agents may have contributed to this progressive shift of the epidemiology of candidemia (Eggimann et al., 2011). These infections are associated with a high mortality rate that ranges from 46 to 75%, reflecting the severity of this illness (Pfaller and Diekema, 2007). As a result of high mortality rates and prolonged length of hospital stays, *Candida* infections also have their impact on health care costs, which is estimated at one billion dollar per year in the US alone (Rentz et al., 1998). However, in European study the frequency is slightly lower at 0.5 to 0.7 cases per 10,000 patients a day (Machetti et al., 2004).

Major types of candidiasis

Candidasis is an acute or chronic infection produced by *Candid*a, generally limited to the skin and mucous membranes, but it could produce a serious systemic disease (Gamboa et al., 2006).

Mucosal candidiasis

Candidal infections are restricted to non-sterile mucosal surface for example oropharyngeal and vulvuvaginal candidiasis (Shao-hua et al., 2008).

Oropharyngeal candidiasis (OPC)

Oral candidiasis is one of the most common, oral mucosal infections seen in persons with HIV (Dangi et al., 2010). *Candida* is commensal organism and part of normal oral flora in about 30 to 50% of the population (Scardina et al., 2007). There are three general factors that may lead to clinically evident oral candidiasis : immune status of host, oral mucosal environment and particular strain of *C. albicans* (hyphal form is usually associated with pathogenic infection) (Ugun et al., 2007). The appearance of OPC in HIV-positive patients heralds the onset of AIDS, corresponding to the decrease in the CD4+ T-lymphocyte count below 200/µL and plasma viral loads of more than 100,000 copies/ml (Reiss et al., 2012). However, other yeast species have been increasingly identified, such as non-*C. albicans Candida* (NCAC) species (*Candida glabrata, C. parapsilosis, C. krusei, C. tropicalis, C. dubliniensis,* and *C. guilliermondii*) (Martins et al., 2010).

The ability of the yeasts to overcome host clearance mechanisms and to colonize surfaces can be considered as a risk factor for oral infection. The balance between *Candida* colonization and candidiasis relies on the balance between pathogen characteristics (e.g. production of adhesins, secreted aspartylproteinases) and host factors (Henriques et al., 2006). Host local predisposing conditions comprise: (i) reduced saliva secretion, (ii) epithelial changes and local mucosal diseases, (iii) changes in commensal flora, (iv) high carbohydrate diet (v) denture wearing. There are different types of oropharyngeal candidiasis including acute pseudomembranous, acute atrophic, chronic hyper-plastic, chronic atrophic, median rhomboid glossitis, denture stomatitis and angular cheilitis Figure 1 and 2. The most discrete lesion represents conversion from benign colonization to pathological overgrowth (Akpan and Morgan, 2010).

Vulvovaginal candidiasis (VVC)

Vaginal candidiasis is the most frequent reason for gynecology consultation in primary health care services (Gonzalez et al., 2011). Disease is usually associated with considerable morbidity, healthcare cost, discomfort, pain and sexual functioning; however, it is seldom life threatening. The symptoms associated with VVC are eczematoid dermatitis lesions that sometimes show vesicular and grey-white psuedomembrane, vulval pruritis, burning, erythema and curd like discharge Figure 3. It is a significant problem affecting 75% of women at least once during their lifetime (Paul and Fidel, 2004). *C. albicans* is both the most frequent colonizer and responsible for most cases of VVC. Nevertheless, over the last decades there have been reports demonstrating an increment in the frequency of cases caused by non-albicans species with *C. glabrata* consistently being the leading species while other species are *C. glabrata*, *C. tropicalis*, *C. krusei* and *C. parapsilosis* (Beigi et al., 2004; Ray et al., 2007). *C. dubliniensis* is a new species that has been recently reported from vaginal disease in the world. *C. albicans* possesses the ability to survive and proliferate in physiological extremes of pH, osmolarity, availability of nutrients and temperature (Hube, 2004). This versatility may account for the successful behavior of *C. albicans* both as a commensal colonizer of the vagina and as a pathogen.

Cutaneous candidiasis

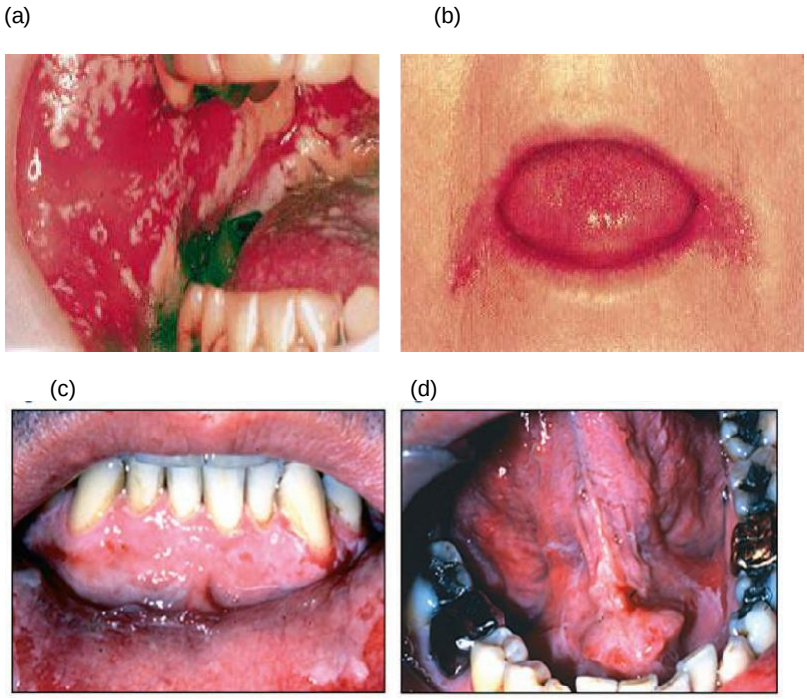
Cutaneous candidiasis is usually secondary infection of skin and nail (body folds) in predisposed patients. It occurs as a sub-acute or chronic infection. Disease involvement may be localised or generalised to the skin or nails. The spectrum of cutaneous candidiasis includes diaper rash, intertrigo candidiasis, *Candida* folliculitis, Otomycosis, Onychia and Paronychia Figure 4 (Mahmoudabadi, 2006). It usually occurs in warm, moist and creased area, such as axillary folds, inguinal or intergluteal areas. It is fairly common opportunistic disease and usually lead to maceration and trauma in skin. It is commonly found in diabetics and obese people. Other predisposing factors are antibiotic and oral contraceptives become macerated (Xiao-dong et al., 2008).

Invasive candidiasis

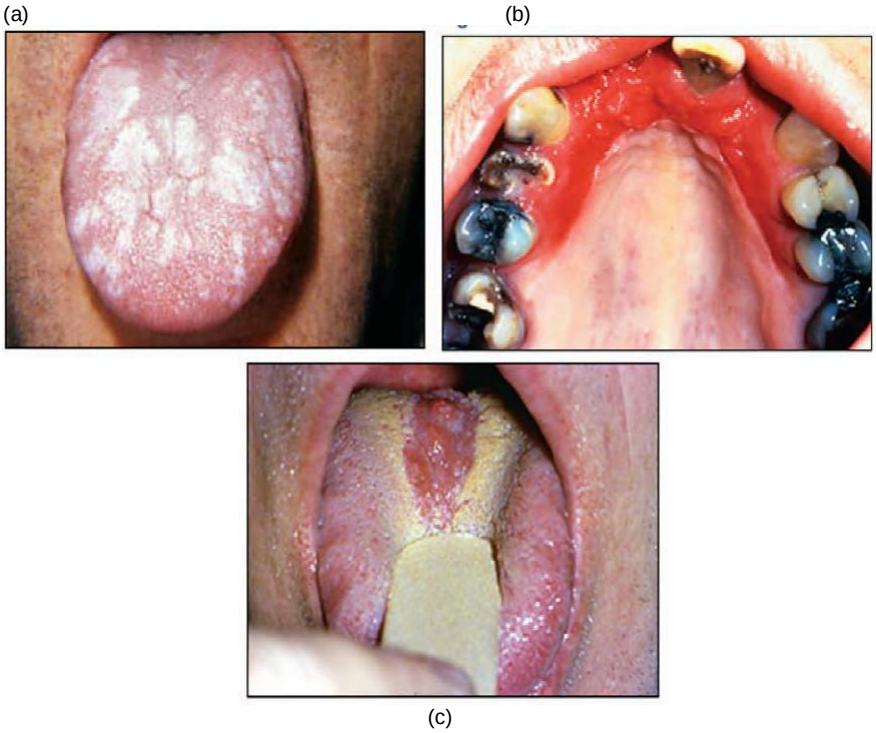
Invasive infections can involve virtually any organ. *C. albicans* continue to account for the majority of invasive fungal infections, there has been a recent increase in disease due to non-*albicans Candida* species (and antifungal-resistant *Candida* isolates) (Arora et al., 2011).

Systemic or disseminated candidiasis

Severe organ invasive or systemic hematogenously disseminated candidiasis is characterized by spreading of the *Candida* cells into almost the entire body with a tendency to create abscesses in vitally important organs Figure 5, inducing their failure which leads to mortality in ~50% of all cases, irrespective of administration of intensive antifungal therapy (Pappas et al., 2003; Zaoutis et al., 2005; Pachl et al., 2006). Clinical signs of ongoing systemic candidiasis are hyper- and/or hypothermia, tachycardia, hypotension, high white blood cell counts, the need for vasopressor, etc. It occurs predominantly as a consequence of some invasive medical procedures, immunosuppressive therapy and aging. Principal predis-posing factors are severe neutropenia and a variety of



Figures 1. Different types of OPC with symptoms (a) Acute pseudomembanous candidiasis; (b) Angular cheilitis; (c) and (d) Pseudomembranous candidiasis as a consequence of the extended use of a broad-spectrum antibacterial agent (Akpan and Morgan, 2010).



Figures 2. (a) Hyperplastic candidiasis (candidal leukoplakia) of the buccal mucosa and tongue due to heavy smoking; (b) *Candida*-associated denture stomatitis; (c) Median rhomboid glossitis (Terezhalmy and Huble, 2011).

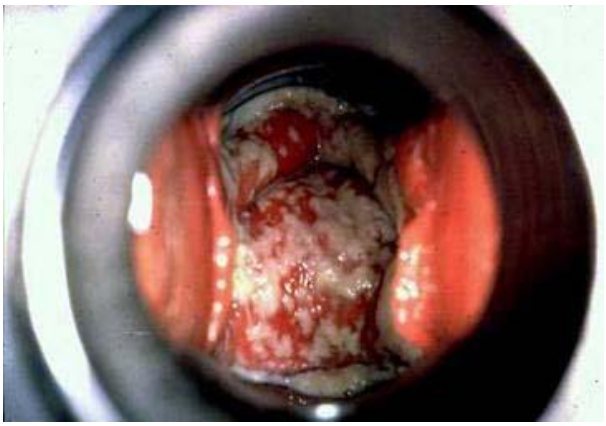


Figure 3. Vulvovaginal candidiasis showing typical cottage cheese appearance of white clumpy vaginal discharge (Vazquez and Sobel, 2011).

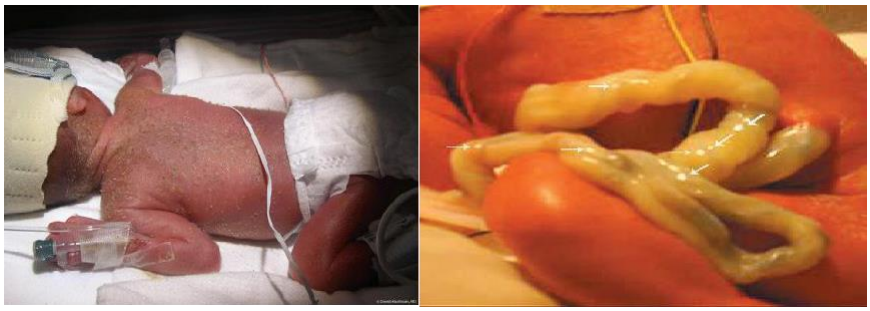


Figure 4. Congenital cutaneous candidiasis (a) with flaky skin in an extremely low birth weight infant; (b) Focal pearly lesions noted in cord (some arrowed). (Kaufman, 2012; www.archdischild.com).

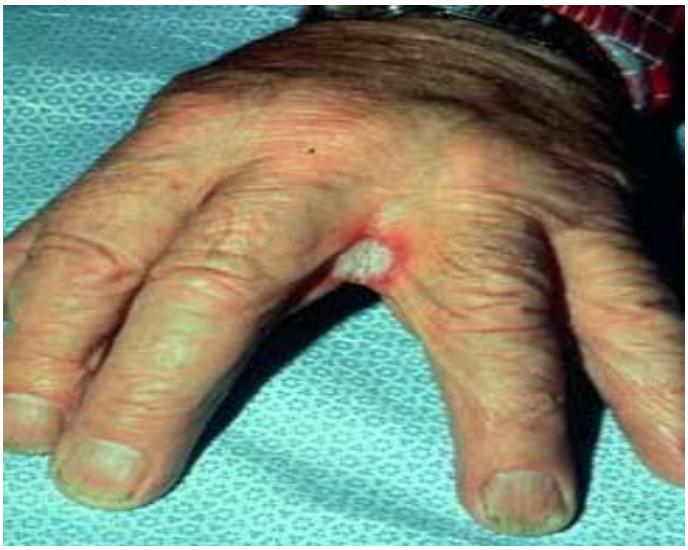


Figure 5. Erosio Interdigitalis Blastomycetica (http://overcoming*candida*.com/images).

neutrophil dysfunctions. Beside the innate immunity (neutrophils, phagocytes, complement), the host protection is associated with the patient's ability to produce *Candida*-specific antibodies, as demonstrated by those recovered from systemic candidiasis (Matthews and Burnie, 2005; Kalkanci et al., 2005).

Candidemia or (blood stream infections) BSI

Candidemia is not only associated with a mortality of about 30 to 40% but also extends the duration of hospital stay and increases the cost for medical care. *Candida* species are the 4th leading cause of hospital acquired BSIs reaching 8 to 10% of all BSIs acquired in hospitals (Pfaller and Diekema, 2007). In recent years, *Candida* species associated with candidemia have shifted from *C. albicans* to non-*albicans Candida* species (NAC). Approximately half of the reported cases of candidemia are now caused by NAC candidemia has become an increasingly important infection. The mortality rate of candidemia is higher (range from 13 to 90%) (Fang et al., 2005). The main entry is the gastro-intestinal tract (Bouza and Muñoz, 2008; Singhe and Deep, 2009). The main risk factors for candidemia are serious alteration in cutaneous and mucous barriers (because of surgery

wounds, intubation or vascular catheters) and colonization of these barriers due to the use of broad spectrum antibiotics (Mensa et al., 2008; Picazo et al., 2008).

Diagnosis

Yeast isolates are routinely identified by different phenotypic methods comprising examination of their morphological features, analysis of their ability to assimilate and/or ferment different carbohydrate substrates, and their ability to assimilate different nitrogen compounds (Elizabeth and Johnson, 2009).

Direct examination

Mounts of smear, scrapings and biopsy specimens are suitable for direct examination of yeast. The laboratory methods are direct microscopy with 10% KOH (Shenoy et al., 2008). KOH serves to digest the protein debris and clears keratinised tissue and increases the visibility. KOH can be supplemented by Lactophenol-Cotton-Blue stain or the fluorochrome Calcofluor-White for easier demonstration of the fungal elements (Segal, 2004).

Examination of stained specimens (Fenn, 2007)

Specimens stained with the following stains are also used in the clinical mycology laboratory:

Gram stain

Young *Candida* organisms are Gram-positive, oval or round in shape showing budding yeast cells, psuedohyphae and short elements of true hyphae.

Calcofluor white

Calcofluor white stain fluoresces under filtered UV light to enhance the detection of fungus as it binds to polysaccharides in chitin in the cell wall showing as bright green. A drop of calcofluor white can be added at the time of mounting in KOH (Harrington et al., 2007).

Identification by culturing on different media

Several media are available for culturing *Candida* for example: Sabouraud dextrose agar, proposed in 1894, is still the medium most frequently employed in the primary isolation of pathogenic fungi. Nowadays, chromogenic media have recently been developed to facilitate rapid identification. Chromogenic media contain chromogenic substrates which react with enzymes secreted by the target microorganisms to yield colonies of varying colors for example- CHROMagar *Candida,* Biggy agar, CandiSelect 4 (Hospenthal et al., 2006; Adam et al., 2010). Other media used are, malt yeast extract, corn meal agar, Tween 80 agar (Yucesoy and Marol, 2003).

Non-culture based methods for diagnosis

Serological assays include testing for *Candida* antibodies and antigens. Polymerase chain reaction (PCR) and DNA probes have the advantage of being able to detect small amounts of *Candida* DNA in either blood or tissues. PCR amplification of the hypervariable D1/D2 or ITS 1 and two regions of the large ribosomal subunit (26S) is followed by automated sequencing (Linton et al., 2007). More recently, pyrosequencing (Qiagen, Hilden, Germany) of just a small fragment (20 bp) of the ITS 2 region has also proved discriminatory for most pathogenic yeast, including cryptic species (Borman et al., 2009). The *C. albicans* peptide nucleic acid fluorescent *in situ* hybridization (PNA FISH) assay was first introduced in 2002 for rapid identification of yeast directly from blood cultures. The assay uses PNA probes targeting *C. albicans*-specific rRNA. The test has been shown to have high specificity and sensitivity (Wilson et al., 2005). A more advanced kit is now available, the *C. albicans*/*C. glabrata* PNA FISH, which distinguishes between *C. albicans* and *C. glabrata* from blood culture bottles that have signaled positive and demonstrate yeast on Gram staining (Shepard et al., 2008). A shortened version (1.5 h) has recently been described (Gherna and Merz, 2009).

Management of different candidiasis

Oral candidiasis

Oropharyngeal candidiasis may be treated with either topical azoles (clotrimazole troches), oral azoles (fluconazole, ketoconazole, or itraconazole), or oral polyenes (such as nystatin or oral amphotericin B (Shokohi et al., 2010). In patients who are HIV-positive, OPC infections tend to respond more slowly, and about 60% of patients experience a recurrence within 6 months of the initial episode (Vazquez, 2000). The goal of antifungal therapy in OPC is rapid relief of symptoms, prevention of complications and early relapse following cessation of therapy.

Multiple randomized prospective studies of oropharyngeal candidiasis have been performed in patients with AIDS and patients with cancer. Most patients respond initially to topical therapy (Pappas et al., 2004). In HIV-infected patients, symptomatic relapses may occur sooner with topical therapy than with fluconazole and resistance may develop with either regimen (Pelletier et al., 2000). Fluconazole is superior to ketoconazole. Itraconazole capsules are equivalent in efficacy to ketoconazole. A dosage of itraconazole solu-

tion of 2.5 mg/kg twice daily has been recommended as suitable for treating oropharyngeal candidiasis in pediatric patients less than 5 years of age.

One study found that a fluconazole dosage of 200 mg/day was superior to that of 400 mg/week for prevention of symptomatic oropharyngeal disease in HIV-infected patients. Long-term suppressive therapy with fluconazole in HIV-infected patients has been shown to reduce the incidence of invasive fungal infections but has no effect on overall survival (Pankhurst et al., 2009). In a recent large study, long-term suppressive therapy with fluconazole was compared with episodic use of fluconazole in response to symptomatic mucosal disease. Continuous suppressive therapy reduced the relapse rate relative to intermittent therapy and was associated with an increased rate of development of *in vitro* microbiological resistance, but the frequency of clinically refractory disease was the same for the 2 study groups (Goldman et al., 2002). Oral polyenes, such as amphotericin B or nystatin, are less effective than fluconazole in preventing this infection. In a placebo-controlled study of HIV-infected patients itraconazole (200 mg/day) was no more effective than placebo for preventing development of mucosal candidiasis.

However, a second study found that itraconazole (200 mg/day) was effective as suppressive therapy for up to 6 months after a course of oral or esophageal candidiasis. Between 64 and 80% of patients with fluconazole-refractory infections will respond to treatment with itraconazole solution. Intravenous caspofungin is a reasonable alternative. Oral or intravenous amphotericin B is also effective in some patients. Itraconazole oral solution has also proven to be effective in cases of fluconazole-refractory oral candidiasis. Oral solution of amphotericin B has also been successfully used to treat fluconazole-resistant thrush.

Much of the information on the microbiology of esophageal candidiasis is extrapolated from studies of oropharyngeal candidiasis. However, it is known that in patients with either AIDS or esophageal cancer, *C. albicans* remains the most common etiological agent. The presence of oropharyngeal candidiasis and symptoms of esophagitis (dysphagia or odynophagia) is predictive of esophageal candidiasis. A therapeutic trial with fluco-nazole for patients with presumed esophageal candidia-sis is a cost-effective alternative to endoscopy; most patients with esophageal candidiasis will have resolution of their symptoms within seven days after the start of therapy. Fluconazole is superior to ketoconazole, itraconazole capsules and flucytosine for the treatment of esophageal candidiasis. Itraconazole capsules plus fluky-tosine are as effective as fluconazole. Up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution. Voriconazole (200 mg for a median duration of 14 days) is as efficacious as fluco-nazole (400 mg loading dose followed by 200 mg/day for a median duration of 15 days) but is associated with a higher rate of treatment-related adverse events. Voriconazole has shown success in treatment of cases of fluconazole- refractory disease (Walsh et al., 2002). Intravenous amphotericin B is also effective. Caspofungin acetate has shown activity and safety equivalent to fluconazole, including good responses in individuals with fluconazole-refractory disease. In the cases of both oropharyngeal and esophageal candidiasis, the vast majority of infections are caused by *C. albicans,* either alone or in mixed infection. However, symptomatic infections caused by *C. glabrata* and *C. krusei* alone have been described.

Vulvovaginal candidiasis

Topical agents including azoles (all are used for 1 to 7 days depending on risk classification: over-the counter (OTC) clotrimazole, OTC butoconazole, OTC miconazole, OTC tioconazole, terconazole), nystatin [100,000 U per day for 7 to 14 days], oral azoles (ketoconazole (400 mg for five days), which is not approved in the United States); itraconazole (200 mg for 1 day, or 200 mg per day for three days), which is not approved in the United States; and fluconazole (150 mg) (Nyirjesy, 2008). Boric acid administered vaginally (600mg gelatin capsule, once per day for 14 days) is also effective. Treatment of VVC predominantly involves use of the imidazole and triazole agents available as topical or oral formulations. Azoles achieve higher success rates even over shorter duration of therapy than nystatin vaginal suppositories or creams. Topical agents pre-viously prescribed for 7 to 14 days are now available as single dose or short course (three to five days) regimens. Topical azoles when appropriately prescribed are remarkably free of systemic side effects and toxicity especially in pregnancy (Canuto and Rodero, 2002). The oral azoles used for systemic therapy are ketoconazole, itraconazole and fluconazole, but only fluconazole (150 mg given as a single dose) is approved by the FDA for this indication in the United States. Oral azoles have been shown to be at least as effective as topical agents, are more convenient and more popular among users and are free of local side effects (Nurbhai et al., 2007).

In selecting an antifungal agent, it is useful to define VVC as uncomplicated or complicated disease (Dekker et al., 2005). The majority of episodes of VVC are uncomplicated (90%). These are sporadic, mild-to-moderate infections caused by *C. albicans* that occur in normal hosts who lack predisposing factors. Uncomplicated infections can be successfully treated with any of the available topical or oral antifungal agents, including short course and single dose regimens. Complicated infections are defined as those that have a moderate to severe clinical presentation (Macphail et al., 2002) are recurrent in nature (4 episodes per year), are caused by non-*albicans Candida* species, or occur in ab-

normal hosts, e.g., diabetic patients with poor glucose control. Complicated infections are far less likely to respond to reduced courses of therapy and should be treated more intensively for 7 to 14 days in order to achieve a clinical response.

In a study of almost 500 women with complicated VVC, prolonging fluconazole therapy by adding a second dose of 150 mg fluconazole 72 h after the initial dose resulted in significantly higher clinical and mycological cure rates in women with severe VVC. Non-*albicans Candida* species, especially *C. glabrata*, are less susceptible *in vitro* to azoles, and VVC caused by these species is less likely to respond clinically, especially to short course azole therapy. Encouraging results have been obtained with boric acid 600 mg capsules given vaginally daily for 14 days or topical 17% flucytosine (Sobel et al., 2003). Vulvovaginal candidiasis in HIV-infected women is incompletely understood. One large study showed it behave in a fashion similar to that in seronegative women. Vaginal carriage of *Candida* is more common in HIV seropositive women, but symptomatic VVC was not more frequent or modestly increased only and did not increase with progressive immunosuppression. Others have, however, noted increased rates of VVC with increasing immunosuppression (Sobel et al., 2001). The differences in results may be due to differences in study design and diagnostic criteria. Longitudinal cohort studies of vaginal candidiasis in HIV-positive women did show a progressive increase in colonization with *C. glabrata* and diminished fluconazole susceptibility (Shann and Wilson, 2003).

Recurrent VVC is usually caused by susceptible strains of *C. albicans*, and resistance is rarely encountered. Although more intensive prolonged induction therapy lasting up to 14 days invariably induces remission, the fungistatic nature of the available agents combined with persistence of the underlying defect makes relapse within three months almost inevitable unless a maintenance antifungal regimen is employed. The regimen used most often is fluconazole, 150 mg weekly (Sobel et al., 2004). Male genital candidiasis presents in two forms, and most commonly as a transient pruritic and erythematous penile cutaneous reaction that may follow unprotected intercourse with exposure to *Candida* antigens present in the partner's vagina and represents a hypersensitivity reaction. Successful treatment entails eradication of yeast in the vagina. True superficial penile *Candida* infection, the second form, occurs infrequently and usually in diabetic and uncircumcised males who develop balanoposthitis that responds promptly to topical or systemic azole therapy.

Cutaneous candidiasis

Cutaneous candidiasis infections may be treated with any number of topical antifungal agents (clotrimazole, econazole, miconazole, ketoconazole, ciclopiroxolamine, sulconazole and oxiconazole). Oral itraconazole is the drug of choice as a pulse therapy. Initial therapy for diaper rash should promote local dryness, avoid occlusion and provide good hygiene (Mistiaen and van Halm-Walters, 2010). *Candida* paronychia requires drainage of the abscess, followed by oral therapy with either fluconazole or itraconazole. However, *Candida* folliculitis, onychomycosis and extensive cutaneous infections in patients who are immunocompromised require systemic antifungal therapy. For *Candida* onychomycosis, oral itraconazole appears to be the most efficacious, either 100 mg daily for 3-6 months or as a pulse dose regimen that requires 200 mg twice daily for 7 days, followed by three weeks off therapy. The cycle is repeated every month for three to six months (Pappas et al., 2004).

Invasive candidiasis

Systemic candidiasis or disseminated candidiasis: For clinically stable patients, start treatment with either an echinocandin or fluconazole. Fluconazole (6 mg/kg per day) is generally preferred for clinically stable patients (B-III). Amphotericin B deoxycholate (0.6 to 0.7 mg/kg per day) or a lipidassociated formulation of amphotericin B (3 to 5 mg/kg per day) may be used in acutely ill patients or patients with refractory disease. Some experts recommend an initial one to two-week course of amphotericin B for all patients, followed by a prolonged course of fluconazole (Edwards et al., 1997). Therapy should be continued until calcification or resolution of lesions, particularly in patients receiving continued chemotherapy or immunosuppression.

Premature discon-tinuation of antifungal therapy may lead to recurrent infection. Patients with chronic disseminated candidiasis may continue to receive chemotherapy, including ablative therapy for recipients of bone marrow and/or stem cell transplants. Treatment of chronic disseminated candidiasis in such patients continues throughout chemotherapy. Adjuvant glucocorticoids may have a role in achieving a prompt resolution of fever, abdominal pain and the inflammatory response in patients refractory to antifungal therapy but prolonged antifungal therapy is still required (Legrand et al., 2008). Additional studies are still needed before this form of therapy can be recommended.

Candidemia: Fluconazole (400 mg/day) and amphotericin B deoxycholate (0.5-0.6 mg/kg per day) are similarly effective as therapy. A large randomized study has demonstrated that caspofungin (70 mg on the first day followed by 50 mg/ day) is equivalent to amphotericin B deoxycholate (0.6 to 1.0 mg/kg per day) for invasive candidiasis (mostly candidemia) (Mora-Duarte et al., 2002). Caspofungin was better tolerated and had a superior response rate in a predefined secondary analysis of evaluable patients. A comparison of flucona-

zole (800 mg/day) with the combination of fluconazole (800 mg/day) plus amphotericin B deoxycholate (~0.7 mg/kg per day for the first 5-6 days) as therapy for candidemia was confounded by differences in severity of illness between the study groups, but the study found the regimens to be comparable and noted a trend toward better response (based principally on more-effective bloodstream clearance) in the group receiving combination therapy (Piarroux et al., 2004).

Conclusion

Candidiaisis has emerged as a significant medical problem throughout the globe. The increase of *Candida* infections might be related to several factors such as the:
(1) Human Immunodeficiency Virus; (ii) neutropenic persons due to anticancer treatments; (iii) the abusive use of extended spectrum antibiotics; (iv) metabolic disorders such as diabetes mellitus. The need of the hour is to understand every aspect of Candidal infections. Early and specific diagnosis is crucial and the decision to treat a patient with these unusual infections is often based on little clinical and microbiological information. Treatment decisions need careful consideration of the epidemiological factors and the immune status of the population at risk. Thus, large prospective epidemio-logical surveys using a common database and methodologies are needed to monitor the increasing trends in incidence and changes in species distribution, to identify new at-risk patients and to evaluate the impact of the introduction of new antifungal agents into the market.

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