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Invasive Oesophageal Candidiasis

Current and Developing Treatment Options

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Abstract

Oesophageal candidiasis is frequently one of the first signs of HIV infection, and a marker of HIV disease. Approximately 10% of patients with AIDS or other immunodeficiency, whether due to an underlying disease, chemotherapy or radiation therapy, will experience oesophageal candidiasis during their lifetime. In addition, unless the underlying immunodeficiency is corrected, approximately 60% of patients will experience a relapse within 6 months of the initial infection. The systemic azoles have gradually replaced the use of amphotericin B for oesophageal candidiasis, and are generally safely used and effective agents for this infection. A concern in some of these patients is the appearance of antifungal-refractory oesophageal candidiasis, which frequently leads to a vicious cycle of poor oral intake, weight loss, malnutrition and wasting syndrome, with occa-

sional mortality due to malnutrition. Newer antifungals such as voriconazole and caspofungin, which are more potent *in vitro* and have a broader spectrum of activity, including activity against fluconazole-resistant *Candida* species are a welcome addition to the antifungal armamentarium that may be used in the management of refractory mucosal candidiasis.

Fungi are found ubiquitously in nature, in association with plants, mammals and insects. Accordingly, humans are continually exposed to multiple genera of fungi via various routes, but particularly by the ingestion of food allowing colonisation of the gastrointestinal tract. Depending on the interaction between host mucosal defence mechanisms and fungal virulence factors, colonisation may be transient or persistent, or local disease may ensue.

Of the various pathogenic fungi, yeasts of the *Candida* species constitute the dominant fungal genus responsible for human disease. Within the last three decades, *Candida* species have progressed from infrequent pathogens largely considered contaminants, to important and common human pathogens causing a wide spectrum of superficial and deep disease.

1. The Pathogen

Candida spp. are small (4–6μm), oval, thin-walled yeast-like fungi that reproduce by budding or fission. The genus *Candida* is comprised of over 200 species and constitutes an extremely diverse yeast genus whose common bond is the absence of a sexual cycle.[1] Only a few species cause disease in humans (table I).[2]

On culture media, *Candida* species form smooth, creamy white, glistening colonies.[6,7] In most situations, they do not require special conditions for growth. The different species of *Candida* are easily identified on the basis of growth characteristics and commercial kits that evaluate carbohydrate assimilation and fermentation reactions and provide species identification of *Candida* isolates within 2–4 days. The culture media, CHROMagar is used to rapidly identify many common *Candida* species,[8] employing a chemical colourimetric reaction on agar that allows distinction between *Candida albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, and other non-*albicans Candida* species.

2. Ecology and Epidemiology

The digestive tract, especially the oesophagus and the crop, is the most frequent source of yeast isolation in the majority of animals.[2] Although most species of *Candida* have been isolated from the GI tract of almost all animals, *C. albicans* has been recovered from a far wider range of animal hosts than any other *Candida* species. *C. albicans* is also the species with the highest prevalence among human yeast isolates and is the principal opportunistic yeast pathogen in most warm-blooded animals. Do-Carmo-Sousa concluded that *C. albicans* and *C. glabrata* (or *Torulopsis glabrata*) are obligatory animal saprophytes, whereas other non-*albicans Candida* species may function as facultative sapro-

Table I. Medically significant *Candida* species[3-5][a]

Candida species	Incidence (%)
C. albicans	50–60
C. glabrata	15–20
C. parapsilosis	10–20
C. tropicalis	6–12
C. krusei	1–3
C. lusitaniae	1–2
C. dubliniensis	<1
C. stellatoidea	<1
C. kefyr	<1
C. guilliermondii	<1

a Based on prevalence from blood stream, vaginal and rectal isolates.

phytes being recovered from sources other than animals.[9] *Candida* species are frequently found in the hospital environment in food, air and on floors and other surfaces.[10,11] Point prevalence studies reveal that at any given time 30–55% of participants have *Candida* spp. identified in the GI tract. One may reasonably conclude that *Candida* colonisation is almost universal.

Oesophageal candidiasis arises in individuals colonised with *Candida* spp. who are predisposed by illness, debility or local reduction in host resistance to an overgrowth of their own indigenous yeast flora. Carriage-rates vary according to anatomical site, a variety of local human host factors and sampling methods used to measure *Candida* colonisation. The overall prevalence of *Candida* colonisation in the GI tract is significantly lower in normal individuals than patients with a variety of disorders. A peak frequency of oral yeast colonisation is found in infants up to 18 months of age, with a lower frequency in older children and adults, increasing once more in healthy, middle-aged, and elderly individuals, which may relate to the wearing of dentures.[12,13]

Estimates of yeast concentrations indicate that healthy colonised individuals have on average 300–500 colony forming units (cfu)/mL of saliva, with a diurnal as well as day to day variation. Imprint culture techniques in dental patients show that the tongue is the oral site most densely populated with yeasts, followed by the palate and buccal mucosa. Enhanced yeast carriage is associated with poor oral hygiene.[14]

Yeast isolation from faeces is slightly lower than oral culture with a median of 23% in healthy individuals and 38% in hospitalised patients.[2] Some studies reveal a prevalence as high as 65%[15] and 60–80% of the isolated yeast are *C. albicans*. Estimates of yeast concentrations in faeces indicate a range of 10^1–10^3 cfu/g in healthy individuals,[15] which is sufficiently low to make isolation difficult. Higher concentrations (10^4/g) have been reported, with even higher concentrations when the patient is treated with antibacterials.[16] Most studies indicate a high carriage rate in the stomach and small intestine with point prevalence rates similar to that observed in the oropharynx.[2]

C. albicans accounts for 70–80% of oral isolates, and remains the major fungal pathogen of humans and the most common cause of mucosal and systemic fungal infection.[2] In addition, it is the best characterised species of *Candida*. *C. glabrata* and *C. tropicalis* each account for approximately 5–8% of infections, while other species occur only rarely.[17,18] *C. glabrata* has become important because of its increasing incidence worldwide and decreased susceptibility to antifungals. Its emergence is largely due to the increased incidence of candidiasis in the immunocompromised population and widespread use of antifungals.[19-21]

Of the non-*albicans Candida* species, *C. tropicalis* is either the 3rd or 4th most commonly recovered *Candida* sp. from either the bloodstream or mucosal surfaces.[21,22] *C. parapsilosis*, although a common cause of systemic infection, is an unusual cause of oesophageal candidiasis.[22-25] *C. parapsilosis* is of importance because of its ability to produce a form of 'slime' as a virulence factor, enabling it to adhere to environmental surfaces, skin and mucosal surfaces of hospital personnel.[24,26] *C. krusei*, although less common (1–2%), is of clinical significance because of its intrinsic resistance to fluconazole and reduced susceptibility to all antifungals.[21,27] It is generally recovered from the mucosal surfaces of patients with haematological malignancies, specifically neutropenic patients.[27-29] *C. dubliniensis* is a more recently identified species of *Candida* that was previously hidden among the germ tube positive strains of *C. albicans* and *C. stellatoidea*. Identified initially from the oral cavity of HIV-positive patients in Dublin, Ireland,[30,31] it has now been recovered from HIV-positive patients

throughout the world at rates ranging from 19–32%.[31] On the other hand, it has now been recovered from 3–14% of oral cavities of HIV-negative individuals, and has occasionally been associated with candidaemia and invasive disease.[32-34] *C. dubliniensis* is identified by germ tube and chlamydospore production, and the inability to grow at 45°C and by a specific colony colour on CHROMagar *Candida* medium.[8] It can now be identified using the commercially available yeast identification kits.[34] Other less commonly identified *Candida* species include: *C. kefyr*;[35] *C. guilliermondii*;[36] *C. lusitaniae*;[37,38] and *C. stellatoidea* closely related to *C. albicans*, by producing germ tubes *in vitro*, a morphologic characteristic only seen in *C. albicans* and some *C. dubliniensis* strains.[31,39-41]

It is not uncommon for a patient to harbour more than one *Candida* species from a single site. Furthermore, occasionally more than one *C. albicans* genotype has been reported from a single site, this is even more common in the HIV-positive population.[2,22,23] The prevalence of multiple species is usually <10%, and may include the combinations of *C. albicans* with either *C. glabrata*, *C. krusei* or *C. tropicalis*, which are the most commonly described combinations.

Epidemiological data of *Candida* spp. colonisation, transmission and infection was incomplete because of a lack of a reliable strain delineation (genotyping) system.[42] Genotyping has shown that most individuals who carry *C. albicans* as a commensal or pathogen, tend to carry the identical genotype simultaneously in different anatomical sites,[2,42] and most patients carry their own unique strains. However, not infrequently two or more different genotypes or strains are found at different sites in the same person.[43,44] No difference in the distribution frequency of genotypes is found when colonising organisms are compared with pathogenic isolates. Prospective molecular epidemiological studies of *C. albicans* using longitudinal cultures have shown that each patient tends to harbour the same genotype of *C. albicans* over long periods of time.[10,42,44] Additionally, genotyping has also confirmed the acquisition of *C. albicans* species from environmental and human sources.[10] Furthermore, identical strains of *C. albicans* were also recovered from patient foods prior to patient acquisition.[10,43,45]

3. Predisposing Factors for Oesophageal Candidiasis

A variety of local and systemic host and exogenous factors increase the prevalence of GI tract *Candida* spp. carriage and population levels, and enhance the transformation from the colonising/carrier blastoconidial phase to the more virulent hyphal phase. The severity and extent of candidal infections tend to increase with the number and severity of predisposing factors (table II).

Table II. Factors predisposing to oesophageal candidiasis

Host factors
Age: infancy, elderly
Immunological
mucocutaneous candidiasis
acquired immunodeficiency syndromes
Depressed phagocytic function
quantitative (neutropenia)
qualitative (myeloperoxidase deficiency, CGD)
Diabetes mellitus and other endocrinopathies
Disruption of mucosal integrity
mucositis/ulceration (chemotherapy)
radiation
trauma/surgery
ischaemia
neoplasms
Debilitation
Exogenous factors
Antibacterial agents
Immunosuppressives
(corticosteroids and miscellaneous immunosuppressives)
Microbial synergy

CGD = chronic granulomatous disease.

3.1 Age

The association of thrush with neonates dates back to the time of Galen.[46] Studies by Taschdjian and Kozinn[47,48] showed that most cases of oral infection within the first few days of life arise primarily because of maternal contamination of the neonates with yeast from the birth canal.

Although the elderly are more likely to develop oral candidiasis, it is unclear whether this is the direct effect of age *per se*, since multiple other factors simultaneously interact or contribute to oral candidiasis.

3.2 Innate Immunity

The role of T cells in the normal gastrointestinal mucosal defence mechanism against *Candida* spp. is highlighted by the frequent occurrence of oral[49-52] and oesophageal[22,53] candidiasis in patients with AIDS. Following HIV infection, oral carriage of yeasts and risk of mucosal invasion increases in frequency in patients with progressive reductions in CD4+ cells.[54,55] The anti-*Candida* protective mechanism of T cells at a mucosal level is incompletely understood; however, investigations have shown that cytokines, especially interferon-γ, inhibit transformation of *Candida* blastoconidia to the more invasive hyphal phase.[56]

The role of phagocytic cells in GI tract mucosal defence against *Candida* spp. is emphasised by the high prevalence of candidal mucositis in patients with granulocytopenia.[39,57] Absence of neutrophils and monocytes not only predispose to mucosal candidiasis but also are associated with candidal invasion of the gut wall and subsequent candidiasis.

3.3 Diabetes Mellitus

Higher than normal frequencies of yeast carriage in the oral cavity[57,58] and faeces[57] have been reported in patients with diabetes. The mechanism by which diabetes increases host susceptibility to candidiasis is incompletely understood. Segal demonstrated increased *in vitro* adherence of *Candida* spp. to exfoliated buccal and vaginal epithelial cells facilitating colonisation.[59] Finally, insulin-deficient diabetics especially when acidotic, show impaired polymorphonuclear neutrophil phagocytic and fungicidal activity.[59,60]

3.4 Other Endocrinopathies

Mucosal candidiasis maybe associated with endocrine disorders other than diabetes including: hypothyroidism, hypoparathyroidism[61,62] and hypoadrenocorticism,[63] and paradoxically Cushing's syndrome, although oesophageal candidiasis is only rarely reported.[64]

3.5 Dietary Factors

Several investigators have suggested that a high carbohydrate diet, especially refined sugar, favours multiplication of yeast in the gut resulting in higher carriage rates,[65] particularly in the oral cavity.[66]

3.6 Local Trauma

Oral thrush and occasionally oesophageal candidiasis is a common complication after irradiation of head and neck cancer, and is a frequent complication of chemotherapy-induced mucositis.

3.7 Antibacterial Agents

The most commonly reported cause of higher gastrointestinal yeast carriage rate, population levels and symptomatic oral candidiasis is the use of antibacterials. No antibacterial is free from this common adverse effect, although certain broad-spectrum agents, most notably the tetracyclines and the β-lactam agents are considered at higher risk of enhancing yeast overgrowth.[67,68] The prevalence of symptomatic GI tract superinfection with *Candida* spp. is, however, generally low (<2%) following antibacterial use, even in hospitalised patients,

where it is often difficult to separate several contributory factors.[69,70]

3.8 Corticosteroids

Several surveys have shown a higher oral yeast prevalence in patients receiving corticosteroids,[71] and many experimental animal studies have found that corticosteroids enhance the susceptibility to local, superficial, invasive and disseminated candidal infections. In addition, *C. albicans* possesses an intracellular steroid-binding protein (receptor) with high specificity for corticosterone and progesterone.[72]

3.9 Malignancy

Gastrointestinal colonisation has been studied most extensively in patients with acute leukaemia and in bone marrow transplant recipients.[73] In a study of 91 patients with acute leukaemia, cultures taken upon admission revealed that 47% were colonised by *C. albicans*, 14% by *C. glabrata* and 18% by other *Candida* species.[74-76]

4. Virulence Factors

The biological features that contribute to the ability of *Candida* spp. to cause disease have previously been defined phenotypically. Total genome sequencing of *C. albicans* has allowed measurement of the effects of gene knockouts on the virulence of *C. albicans* in animal models. Genes required for virulence are regulated in response to environmental signals indigenous to the host environment.[77] These signals include temperature, pH, osmotic pressure, iron concentration and calcium ion concentrations. Adaptation to a changing environment facilitates the organism's ability to adapt and survive within the host niche.[78]

C. albicans undergoes reversible morphological transition between budding pseudohyphal and hyphal growth forms.[79] The ability to switch from one form to another appears to have a direct influence on the capacity of the organism to cause disease. At least 15 genes are recognised as playing a role in morphogenesis.[79]

The first step in any infection is epithelial surface colonisation, in turn dependent on microorganism adherence to epithelial cells and proteins, allowing them to withstand fluid forces that serve to expel particulates.[80,81] Adhesive ability of *C. albicans* has been correlated with pathogenesis of infection.

Invasion of host cells by *Candida* involves penetration and damage of the outer cell envelope. Phospholipids and proteins represent the major chemical constituents of the host cell membrane. Phospholipases, by cleaving phospholipids, induce cell lysis facilitating tissue invasion.[82] A family of at least nine genes makes up the secreted aspartyl proteinases (SAP) isoenzymes.[83] Several studies have now confirmed the importance of secreted aspartyl proteinases in pathogenesis of *C. albicans*-induced disease, particularly tissue invasion.[83]

5. Clinical Manifestations

Hippocrates[84] is credited with first describing oral thrush in debilitated individuals. Nineteenth-century authorities such as Trousseau[85] and Parrot,[86] recognised that thrush invariably arose as a consequence of pre-existing illness. The initial discovery of the organism causing thrush was not made until 1939, when Langenbeck[87] described a fungus in buccal aphthae in a patient with typhus. It was it left to Berg in 1846[88] to establish a cause-effect relationship between the fungus and oral lesions. In 1875, Haussmann[89] demonstrated that the causal agent of oral and vaginal thrush were the same. The taxonomic confusion accompanying the above observations continued until 1923 when Berkhout[1] proposed the genus name *Candida*, separating the genus from the universal *Monilia* genus moulds affecting fruit and vegetables.

In contrast to the skin, oral and enteric mucosa where infection is common, the oesophagus is an uncommon site of infection. Thus, candidal oesophagitis invariably occurs in predisposed individuals.

C. albicans is also the commonest cause of oesophagitis and after the oropharynx, the oesophagus is the commonest site of gastrointestinal candidiasis. Autopsy studies of patients with systemic candidiasis detected oesophageal involvement in 28–56% and gastric involvement in 23–35%.[57,90] The prevalence of candidal oesophagitis has increased because of AIDS, as well as the increased pool of transplanted, cancer and severely immunocompromised patients.

Candida microorganisms are frequently recovered from the oesophageal surface and reach the oesophagus in oral secretions. In contrast to oral candidiasis, little is known about host and yeast factors operative in the pathogenesis of oesophageal candidiasis and experimental models have not been established. However, it is likely that the usual yeast virulence factors and defects in host defence mechanisms also operate in the oesophagus.

Oesophageal candidiasis in an HIV-positive patient may be the first manifestation of AIDS.[91,92] In cancer patients, factors predisposing to oesophagitis include previous exposure to radiation, recent cytotoxic chemotherapy, antibacterial therapy, corticosteroid therapy and neutropenia.[93-95] The high prevalence of oesophagitis in patients with AIDS indicates the critical role of cell-mediated immunity in normally protecting the oesophagus from invasion by *Candida* spp. Candidal oesophagitis tends to occur later in the natural history of HIV infection and almost invariably in those with a low CD4+ count.[91,92,96] Histological sections of oesophagitis lesions reveal yeast hyphae forms in the mucosal epithelium, accompanied by a neutrophilic response as seen in oral thrush.[57]

Oesophageal candidiasis presents most commonly with dysphagia, odynophagia and retrosternal chest pain. Constitutional findings, including fever, only occasionally occur, and epigastric pain is rarely the dominant symptom. Even before AIDS, a male to female predominance was noted.[57,94,95] Most patients have underlying haematological malignancies, HIV infection or have undergone recent transplantation. Although oesophagitis may arise as an extension of oropharyngeal candidiasis, in more than two thirds of published reports, the oesophagus was the only site involved and more often in the distal two thirds than in the proximal third of the oesophagus. An occasional feature of oesophageal candidiasis in patients with AIDS is the complete lack of symptoms in spite of extensive objective oesophageal involvement.[96]

Physical findings are variable in distribution, character and severity. Kodsi classified oesophageal candidiasis on the basis of endoscopic appearance.[97] Type I refers to a few white or beige plagues, up to 2mm in diameter. In type II, the plaques are more numerous and larger than 2mm in diameter. In these milder grades, plaques may be hyperaemic or oedematous, but there is no ulceration. Type III involves confluent, linear and nodular elevated plagues with hyperaemia and frank ulceration, and Type IV additionally has increased friability of the mucosa and occasional narrowing of the lumen.

Uncommon complications of oesophagitis include bezoar formation, perforation,[98,99] aortic-oesophageal fistula formation[98,99] and, rarely, extensive necrosis destroying the entire oesophageal mucosa.[57] In neutropenic patients, oesophageal candidiasis may lead to candidaemia and disseminated candidiasis, and when extensive ulceration is present, may provide a portal of entry for bacteria, resulting in bacteraemias.

Table III. *In vitro* susceptibility of the medically relevant *Candida* species against seven antifungals[3,38,102]

Candida species	Fluconazole	Itraconazole	Voriconazole	Flucytosine	Caspofungin	Micafungin	Amphotericin B
C. albicans[a]	S	S	S	S	S	S	S
C. glabrata[a]	S-DD	S-DD	S	S	S	S	S to S-DD
C. tropicalis[a]	S	S	S	S	S	S	S
C. parapsilosis[a]	S	S	S	S	S to S-DD	S to S-DD	S
C. krusei[a]	R	S-DD to R	S to –S-DD	I-R	S	S	S to S-DD
C. lusitaniae[ab]	S	S	S	S	S	S	S to R
C. dubliniensis[c]	S	S	S	S	S	S	S

a On the basis of blood stream isolates.[3]

b Clinical isolates.[38]

c Based on oral isolates.[102]

I = intermediate resistance; **R** = resistant; **S** = susceptible; **S-DD** = susceptible dose-dependent.

6. Diagnosis

A reliable diagnosis can only be made by histological evidence of tissue invasion in biopsy material. Nevertheless, antifungal therapy is frequently initiated empirically with minimal criteria in a high-risk patient. However, the mere association of the presence of *Candida* spp. within an oesophageal lesion by smear or culture does not provide sufficient evidence to distinguish *Candida* spp. as a commensal, from *Candida* spp. as an invasive pathogen. While oesophageal brushings are highly sensitive in diagnosing oesophagitis, specificity is not high and neither is the positive predicative value.[93] This is because the presence of *Candida* hyphae in oesophageal brushings is just as compatible with colonisation as it is with infection.

In the absence of biopsy material, radiological features previously formed the basis for diagnosis. A barium contrast upper GI radiograph in oesophageal candidiasis may reveal shaggy mucosal irregularities and nodular filling defects.[100,101] As severity increases, the nodular pattern becomes extensive giving a cobblestone appearance. Peristaltic abnormalities are also common.[100] Infrequently, discrete ulceration and stenosis may be observed. Unfortunately, the sensitivity of barium swallow is relatively low and radiological abnormalities are often absent in mild to moderate oesophagitis, especially in patients with AIDS.[22,57,91,92] Accordingly, radiology has been replaced by endoscopy which not only provides a rapid and highly sensitive diagnosis, but is also the only reliable method of differentiating among the various causes of oesophagitis.[93] The characteristic endoscopic appearance is described as yellow-white plaques on an erythematous background, with varying degrees of ulceration. White plaques and pseudomembranes are not exclusive to infection with *Candida* spp. and erythema in the absence of plaques may be due to *Candida* spp. Radionuclide tests are of little value in the diagnosis of oesophageal candidiasis and no serological tests reliably diagnose invasive oesophageal candidiasis

Differential diagnosis includes radiation oesophagitis, reflux oesophagitis, cytomegalovirus or herpes simplex virus infection. In the patient with AIDS, it is not uncommon to identify more than one aetiological agent causing oesophagitis.[22,23]

7. Management

The principal systemic agents with anti-*Candida* activity include amphotericin B, ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole, caspofungin, micafungin and flucytosine. The activities of these agents against *Candida* spp. are predictable and vary with species (table III).

It is important to recognise that the endpoint or goal of antimycotic therapy in oral thrush is rapid relief of symptoms, and prevention of complications and early relapse immediately following cessation of therapy. The goal is not to achieve sterilisation of the mucosal surface. Mycological eradication is rarely achieved, although routine cultures may become negative towards the end of a standard course of therapy. In the latter patients, low numbers of yeast persist in numbers below the threshold of detection of swab cultures.

The drug of choice depends on the infecting species and the clinical setting. *C. albicans* isolates are the most susceptible to all of the antifungal agents. The pattern for *C. tropicalis* and *C. parapsilosis* is quite similar, with just slightly higher minimum inhibitory concentrations (MICs) for fluconazole. *C. parapsilosis* tends to have higher MICs for all of the echinocandin agents, including caspofungin, micafungin and anidulafungin.[21,103] *C. glabrata* tends to have fluconazole MICs that are 16–32-fold higher than those for *C. albicans*. *C. krusei* isolates have the highest fluconazole and flucytosine MICs of any of the species, whereas *C. lusitaniae* isolates frequently have elevated amphotericin B MICs and failure of amphotericin B therapy is well described.[38,104,105]

Interpretation of the MIC results shown in table IV is controversial in spite of the use of National Committee for Clinical Laboratory Standards M27-A methodology.[105] The most extensive correlation data are available for fluconazole, itraconazole and flucytosine versus *Candida* spp.[3,106-108] Tentative interpretive breakpoints for these three drugs when tested have been proposed and are summarised in table IV.[3] For fluconazole and itraconazole, the novel category S-DD, implies that susceptibility is dependent on obtaining the maximal possible drug concentration. For fluconazole, this implies the use of doses ≥400 mg/day in adults with normal renal function. For itraconazole, it implies that measures should be taken to ensure that enough drug is absorbed to produce a measurable blood concentration, preferably one of least 0.5 μg/mL. Large datasets correlating MICs with outcomes are not available for flucytosine and this situation is further complicated by the fact the drug is only rarely used as monotherapy.[109]

Table IV. Definition of interpretive breakpoints for *Candida* species[3]

Antifungal agent	MICs (μg/mL)		
	susceptible	susceptible-DD	resistant
Fluconazole	≤8	16–32	>32
Itraconazole	≤0.125	0.25–0.5	>0.5
Flucytosine	≤4.0	8–16	>16
Amphotericin B[a]	<1.0		>1.0

a Not approved by National Committee for Clinical Laboratory Standards M27-A methodology.

DD = dose dependent; **MIC** = minimum inhibitory concentration.

Using these breakpoints, *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. lusitaniae* are susceptible to fluconazole, whereas isolates of *C. glabrata* typically have an MIC that places them in the S-DD category for fluconazole. For itraconazole, *C. glabrata* and *C. krusei* often have MICs in the S-DD category, while the other major *Candida* species are generally susceptible. In general, virtually all azoles, including the latest generation azoles, voriconazole and posaconazole, are 10–100 times less active against *C. glabrata* and *C. krusei* strains when compared to *C. albicans*. Finally, all species but *C. krusei* are generally susceptible to flucytosine.

The choice of an antifungal agent for the management of oesophageal candidiasis is based on the integration of multiple factors such as drug efficacy, drug toxicity, patient status and microbiological information (table V). Amphotericin B is fungicidal *in vitro* for most *Candida* species.[3,106,110,111] Both the deoxycholate and lipid-based derivatives of amphotericin B are similarly active against *Candida* species,[111-113] although higher doses of the lipid-based formations are required. The azoles in general are generally fungistatic against most *Candida* spe-

Table V. Antifungals for management of oesophageal candidiasis

Antifungal agent	Formulations	Strengths	Dosages
Amphotericin B	IV	50 mg/vial	0.3–0.5 mg/kg/day
Ketoconazole	Tablet	200mg	1–2 tablets od–bid
Fluconazole	Tablet/IV	100mg	1 tablet od
	Solution	10 mg/mL	10mL od
Itraconazole	Capsule/IV	100mg	200mg od
	Solution	10 mg/mL	10–20mL od–bid
Voriconazole[a]	Tablet	50mg, 200mg	1 tablet (200mg) bid
Caspofungin	IV	50mg	50mg od
Micafungin[a]	IV	50–100mg	50–100mg od

a Not approved by US FDA for oesophageal candidiasis.
bid = twice daily; **IV** = intravenous; **od** = once daily.

cies.[114-116] The echinocandin antifungal group is fungicidal and broad spectrum against *Candida* species.[103,117]

Oesophageal candidiasis requires systemic therapy, topical preparations are of no value.[118] Generally, either fluconazole or itraconazole have been demonstrated to be efficacious.[22,119,120] Occasionally parenteral fluconazole may be required initially if the patient is unable to take oral medications.

Ketoconazole 200 mg/day was the first oral systemic imidazole antifungal agent used in the management of oesophageal candidiasis, and is effective even in debilitated immunocompromised patients, including those with malignancy or AIDS.[22,57] In addition, ketoconazole has also been effective in patients with chronic mucocutaneous candidiasis,[121] with cure rates in excess of 80% with daily ketoconazole administered for 10–14 days.[114,121-123] However, ketoconazole has now been replaced by the newer triazoles (fluconazole and itraconazole) because of its limitations and adverse effect profile. Ketoconazole therapy has been limited by fears of hepatotoxicity and concerns about the reliability of gastric absorption, especially in patients receiving histamine H_2-receptor blockers. In addition, a parenteral form of ketoconazole is not available for patients unable to swallow.

In general, fluconazole has become the standard of care in the management of oesophageal candidiasis. Oral fluconazole at a dose of 100–200 mg/day for 14–21 days enjoys a superior safety profile, excellent gastric absorption with >92% bioavailability and, when necessary, can be given parenterally.[120] Clinical trials of fluconazole compared with ketoconazole reveal high cure rates superior to those encountered with other imidazoles, along with a more rapid onset of action.[119,120] A striking feature of fluconazole is the rapidity of response, usually within 10 days.

Itraconazole oral solution is also being used with increased frequency. The itraconazole cyclodextrin solution is currently used for therapy, since it has a greater bioavailability than do the capsules. In several clinical studies, patients treated with itraconazole oral solution 100–200 mg/day had clinical response rates comparable to that of patients treated with fluconazole tablets 100–200 mg/day (94% and 91%, respectively).[124-126] Both regimens were well tolerated without any significant adverse events. In addition, the mycological cure rates were not statistically different at, 92% and 78%, respectively.

Several concerns have been raised about the widespread use of the more potent oral triazoles. These concerns include drug interactions, adverse effects, increased expense and risk of resistance. In addition, several studies have documented the selection of *C. glabrata* and *C. krusei*, which are either resistant or less susceptible to the azole antifungals.[28,29,127] *C. albicans* resistance to azoles is still uncommon; however, both clinical failure and *in vitro* resistance has been observed in HIV-positive patients receiving prolonged and often indiscriminate therapy with fluconazole.[22,128]

Given the high success rate achieved with fluconazole and itraconazole, amphotericin B is generally reserved for patients with endoscopically proven oesophageal candidiasis who have failed standard doses of azole therapy. Low-dose amphotericin B (0.3–0.5 mg/kg or 10–20 mg/day for

10 days) is often sufficient for moderate disease, but higher doses may be necessary for patients with AIDS and refractory mucosal candidiasis.[22,123,129,130] Oral flucytosine 100–150 mg/kg/day in four divided doses is effective, but is rarely prescribed alone because of the tendency for resistance to develop.

In spite of the rapid responses to antimycotic therapy, patients with AIDS are at high risk of developing symptomatic recurrences of either oropharyngeal or oesophageal candidiasis.[91,124-126,131-133] Approximately 60% of patients who experience one episode of oesophageal candidiasis will relapse within 3 months.[22] Accordingly, some clinicians will begin secondary prophylaxis with oral therapy using either fluconazole or itraconazole after a single episode of oesophageal candidiasis.

Suppressive antifungal therapy with fluconazole 100–200mg either daily or weekly is effective in preventing recurrent episodes, but it should only be used if the recurrences become frequent or are associated with malnutrition as a result of poor oral intake and wasting syndrome.

8. Management of Refractory Oesophageal Candidiasis

Development of resistance to azole antifungal agents is not uncommon following prolonged therapy of recurrent mucocutaneous candidiasis in HIV-positive patients.[22] Emergence of resistance during a course of therapy in other settings is uncommon[21] but has occasionally been reported.[134,135] Primary infection with a resistant strain of *C. albicans* also has been described.[136] Resistance to amphotericin B is relatively uncommon, but has been described for all *Candida* species. Resistance to amphotericin B implies that the isolate is also likely to be resistant to the newer lipid-based formulations of amphotericin B.[112]

Intrinsic or primary resistance to flucytosine may be present in any species of *Candida*.[109] More importantly, acquisition of resistance by susceptible isolates during flucytosine monotherapy is common and flucytosine should not be used as monotherapy for this reason.[137]

Routine susceptibility testing of all *Candida* isolates is not indicated, although all invasive isolates should be identified to the species level. Testing is justified in patients with refractory disease (e.g. refractory oropharyngeal or oesophageal candidiasis in patients with AIDS or persistent candidaemia while receiving antifungal therapy).

The combination of flucytosine with either amphotericin B or an azole has been used previously, and these combinations often appear with at least additive activity *in vitro*.[137] The use of amphotericin B and azoles in combination for treatment of candidiasis is extremely controversial. The overlapping mechanisms of action of these agents raise the possibility of antagonism and the little available information has not excluded this theoretical possibility. Antagonism has been occasionally seen in some circumstances, especially when ketoconazole or itraconazole are combined with amphotericin B.[138-141] Sugar[140,141] concluded that interactions ranging from antagonism to synergy have been reported depending on dose, experimental model and design, and organism studied.

The clinical impact of antifungal resistance in patient with AIDS was recently demonstrated in patients who failed standard antifungal therapy for oropharyngeal candidiasis.[142] After the onset of fluconazole-refractory thrush, patients had a median survival of 184 days. Moreover, after the onset of clinical resistance to amphotericin B, the patients had an astonishing 83-day median survival rate. Although mucosal candidiasis does not produce death directly, clinical failure is probably a comorbidity factor in the rapid demise of these patients. However, clinical failure is also probably a

marker of severe immunosuppression and a non-functional immune system.

Antifungal resistance can be divided into two categories, clinical and *in vitro*. Clinical resistance signifies failure of the antifungal to eradicate the infection in the absence of *in vitro* resistance. Such resistance may occur for a variety of reasons. *In vitro* resistance can also be subdivided into either primary (innate or intrinsic) or secondary (acquired) resistance.[22]

Investigators have reported antifungal success and failures in patients with oropharyngeal candidiasis and *Candida* isolates with both low and high MIC values.[143] In fact, one group reported that several HIV-infected patients with documented *in vitro* fluconazole-resistant mucosal candidiasis were able to respond to fluconazole therapy.

Investigators have identified several key risk factors for the development of fluconazole-resistant mucosal candidiasis in patients with AIDS.[133] These risk factors include: greater number of episodes of oropharyngeal candidiasis (6.1 vs 1.8), lower median CD4+ cell count (11 vs 71 cells/mm^3), longer median duration of all antifungal therapy (419 vs 118 days), and longer duration of systemic azole administration (272 vs 14 days). When the authors used two controls matched by CD4+ cell count, resistant cases continued to have a greater median exposure time to azoles (272 vs 88 days; $p = 0.005$) as the significant risk factor.[128,133]

Management of fluconazole-resistant mucocutaneous candidiasis is frequently unsatisfactory and response is short-lived, with periodic and rapid recurrences.

Generally, many patients with refractory mucosal candidiasis will improve by simply increasing the dose of fluconazole (table VI).[22] For example, if patients fail to respond to a dosage of fluconazole 200 mg/day, a dosage increase to 400 mg/day will frequently produce a good clinical response, at least for a short period of time. However, the symptomatic improvement is generally transient and mucosal candidiasis quickly reappears. In some patients with fluconazole-refractory mucosal candidiasis, use of the fluconazole suspension may be beneficial. Several reports describe improvement in these patients, possibly because of increased salivary levels obtained when the suspension is taken with the swish-and-swallow technique.[144,145]

Table VI. Alternative therapy for the management of antifungal-refractory mucosal candidiasis[a]

Antifungals	High-dose fluconazole (400–800 mg/day) PO/IV
	Fluconazole suspension 200–400 mg/day PO
	Itraconazole oral solution 200mg bid PO
	Voriconazole 200mg bid PO
	Voriconazole 3–4 mg/kg bid IV
	Caspofungin acetate 50mg IV
	Parenteral amphotericin B 0.3–1.0 mg/kg/day
	Lipid preparations of amphotericin B 3–5 mg/kg/day
Combination therapy	Amphotericin B + flucytosine
	Amphotericin B + fluconazole
	Fluconazole + flucytosine
	rhuGM-CSF + fluconazole[146]
	Fluconazole + terbinafine[147]
Investigational antifungal agents[148-153]	Micafungin – Fugisawa Healthcare Inc, Deerfield, IL, USA
	Anidulafungin (VER-002) – Versicor Inc (now Vicuron Pharmaceuticals), Fremont, CA, USA
	Posaconazole (SCH-56592) – Schering-Plough, Kenilworth, NJ, USA
	Ravuconazole – Bristol-Myers Squibb, Princeton, NJ, USA

a Many of the alternative therapies are not US FDA approved and are not supported by adequate clinical trials.

bid = twice daily; **IV** = intravenous; **PO** = orally; **rhuGM-CSF** = recombinant human granulocyte-macrophage colony-stimulating factor.

In a study evaluating 250 isolates recovered from 93 HIV-infected patients with acute oropharyngeal candidiasis, *in vitro* ketoconazole and itraconazole resistance was less than 15% for *C. albicans* strains which were resistant to fluconazole.[154]

Several studies evaluating itraconazole oral solution demonstrated promising results in patients with AIDS who had failed to respond to fluconazole at doses of 200 mg/day.[155-157] Clinical cure or im-

provement occurred in 55–70% of patients. As expected, mycological cure rates were low (<30%) and relapses following treatment cessation were rapid, usually within 14 days.

In patients with severe disease, parenteral amphotericin B at dosages of 0.4–0.6 mg/kg/day are required to achieve response. After the clinical response is achieved, it is essential to continue suppressive amphotericin B therapy in an attempt to increase disease-free intervals.

Several new systemic antifungal compounds have recently been approved for use. Voriconazole is in the azole family of compounds, and is structurally similar to fluconazole except with a broad-spectrum of antifungal activity.[148-150] It is a lipophilic azole and available in both the parenteral and oral forms. However, because of its excellent bioavailability of 96%, the oral formulation is extremely useful as step down therapy. *In vitro* susceptibility studies have demonstrated efficacy against most *Candida* species, including fluconazole-resistant *C. albicans*, *C. glabrata* and *C. krusei*.[148-150] Unlike fluconazole, it has minimal renal excretion and is metabolised primarily by the liver. It has US FDA approval as primary therapy of invasive aspergillosis and for refractory fungal infections, specifically due to *Fusarium* spp. and *Scedosporium apiospermum*. As with other azoles, voriconazole is metabolised by the cytochrome P450 (CYP) enzymes 3A4, 2C19, and 2C9. Thus, the potential exists for interactions with other drugs metabolised by these specific enzymes (table VII).

Table VII. Voriconazole drug-drug interactions[148]

Interaction	Drugs
These drugs decrease voriconazole concentrations	Rifampin, barbiturates (long-acting), carbamazepine, rifabutin, phenytoin
Voriconazole increases concentrations of these drugs	Sirolimus, cyclosporin, tacrolimus, astemizole, cisapride, pimozide, quinidine, ergot alkaloids, warfarin, sulfonylurea, omeprazole, HMG-CoA reductase inhibitors (statins)

Although not yet approved for mucosal candidiasis in the US, voriconazole appears to be a useful compound in patients with oropharyngeal or oesophageal candidiasis. In a randomised, double-blind, multicentre trial comparing voriconazole to fluconazole for the treatment of oesophageal candidiasis in 391 immunocompromised patients, voriconazole 200mg twice daily was as effective as, but no better than, fluconazole 200mg daily with clinical cure rates of 98.3 and 95.1%, respectively.[151] In addition, because of its broad spectrum of activity and its excellent *in vitro* activity against fluconazole-resistant *Candida* species, voriconazole may also prove to be a useful agent in the management of fluconazole-refractory mucosal candidiasis in patients with AIDS.[152]

Caspofungin was approved by the US FDA in 2001 for the treatment of refractory aspergillosis and in 2002 for the management of oesophageal candidiasis.[148,153] It is a new class of antifungal compound called the echinocandins. The echinocandins mechanism of action is the specific and non-competitive inhibition of the (1,3)-β-D-glucan synthase enzyme complex that is essential for the formation of glucan polymers of fungal cell walls.[103,117] Fortunately, mammalian cells do not have (1,3)-β-D-glucan, thus these antifungals provides the advantage of selective toxicity.[148,153] Caspofungin is active against a variety of fungal pathogens, including most *Candida* spp., including azole-resistant *Candida* spp., *Aspergillus* spp., *Histoplasma encapsulatum* and *Blastomyces* spp. Unfortunately, this compound only has a parenteral formulation and is administered once daily. Caspofungin has minimal renal excretion (~2%), and minimal hepatic metabolism. Because of this, there are rare drug-drug interactions, and its primary adverse effect is hepatotoxicity in approximately 10% of patients.

A recent clinical trial with caspofungin evaluated two different caspofungin dose administration regi-

mens versus amphotericin B for the treatment of oesophageal candidiasis. Overall, both caspofungin regimens were equivalent to amphotericin B 0.5 mg/kg/day in 123 immunocompromised patients with oesophageal candidiasis. Clinical success was achieved in 74 and 89% of patients receiving caspofungin at 50 and 70 mg/day, respectively, and in 63% of patients receiving amphotericin B.[158] In addition, because of its potent *in vitro* activity against fluconazole-resistant *Candida* species, caspofungin may also be a reasonable alternative to amphotericin B in patients with fluconazole-refractory mucosal candidiasis.

Two new antifungals are currently in phase III of development and also appear encouraging in early in clinical trials.[148,153] Posaconazole, is an extended spectrum azole, similar to voriconazole. It also has excellent *in vitro* activity against fluconazole-resistant isolates.[148,153] In addition, a new echinocandin, micafungin has also recently been submitted to the US FDA for approval and is being evaluated in several clinical trials. *In vitro* results and early clinical trials are promising against many *Candida* species, including the fluconazole-resistant *C. albicans*, *C. glabrata*, and *C. krusei*.[148,153]

In addition to the use of antifungals in these severely immunocompromised patients, it is also important not to underestimate the significance of the dysfunctional immune system in patients with AIDS and refractory fungal infections.[22] The addition of highly active antiretroviral therapy (HAART) along with the addition of a new antifungal may prove extremely beneficial in resolving these recalcitrant fungal infections. HAART alone has the potential to lower HIV viral loads, increase CD4+ cell counts and, theoretically, improve immune function of a patient with advanced HIV-infection. Thus, treatment with aggressive HAART therapy alone without antifungals has eradicated antifungal-refractory oropharyngeal candidiasis in patients with advanced HIV-infection.[159]

The classic management of infections in the compromised host has always depended on antimicrobial agents, without taking into account host defects. Several cytokines developed and produced by recombinant technology also show promise in assisting the host response to eradicate a fungal infection.[160] There have been several reports recently on the use of human recombinant granulocyte-macrophage colony stimulating factor (rhuGM-CSF) in patients with oropharyngeal or oesophageal candidiasis refractory to either fluconazole or amphotericin B.[146,161] Although no large studies have been published, the few case reports describe good response rates with rhuGM-CSF in patients with advanced HIV-infection and refractory mucosal candidiasis.[22,146,161]

9. Conclusion

In conclusion, recent progress in antifungal research has resulted in two newly approved antifungal compounds and four more antifungals in either phase II or III of development.[148-153,158] These newer antifungal agents have an extended spectrum of activity, ease of administration, and fewer adverse events than older antifungals. The impressive results of these new compounds make them attractive in the management of fungal infections in the compromised host. However, difficulties in managing these infections should remind us that we can not rely solely on antifungals alone. We must also continue to strive to find ways to improve the function of the body's dysfunctional immune system in order for it to work synergistically and eliminate opportunistic fungal infections.

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References

1. Berkhout CM. De Schimmelgeschlachter Monilia, Oidium, Vospora, en Torula [dissertation]. Utrecht: University of Utrecht, 1923
2. Odds FC, editor. Candida and candidosis. 2nd ed. London: Bailliere Tindall, 1988
3. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. Clin Infect Dis 2000; 30 (4): 662-78
4. Vazquez JA, Sobel JD, Peng G, et al. Evolution of vaginal Candida species recovered from human immunodeficiency virus-infected women receiving fluconazole prophylaxis: the emergence of *Candida glabrata*? Clin Infect Dis 1999; 28 (5): 1025-31
5. Sobel JD, Ohmit SE, Schuman P, et al. The evolution of Candida species and fluconazole susceptibility among oral and vaginal isolates recovered from human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. J Infect Dis 2001; 183 (2): 286-93
6. Kwon-Chung KJ, Bennett JE, editors. Medical mycology. Philadelphia (PA): Lea & Febiger, 1992
7. Rippon JW, editor. The pathogenic fungi and pathogenic actinomycetes. 3rd ed. Philadelphia (PA): WB Saunders, 1988
8. Pfaller MA, Houston A, Coffmann S. Application of CHROMagar candida for rapid screening of clinical specimens for *candida albicans*, *candida tropicalis*, *candida krusei*, and *candida (torulopsis) glabrata*. J Clin Microbiol 1996; 34 (1): 58-61
9. Do-Carmo-Sousa L. Distribution of yeasts in nature. In: Rose AH, Harrison JS, editors. The yeasts. London: Academic Press, 1969: 79-105
10. Vazquez JA, Sanchez V, Dmuchowski C, et al. Nosocomial acquisition of *Candida albicans*: an epidemiologic study. J Infect Dis 1993; 168 (1): 195-201
11. Wade JC, Schimpff SC. Epidemiology and prevention of Candida infections. In: Bodey GP, Fainstain V, editors. Candidiasis. New York: Raven Press, 1985: 111-33
12. Marples MJ. Microbiological studies in Western Samoa: II. The isolation of yeast-like organisms from the mouth. Trans R Soc Trop Med Hyg 1960; 54: 166-70
13. Smith BJ, Pman AP, Arblasto PG. Incidence of Candida in hospital in-patients and the effects of antibiotic therapy. BMJ 1966; 1: 208-10
14. Kennedy MJ. Regulation of *Candida albicans* populations in the gastrointestinal tract. In: McGinnis MR, editor. Current topics in medical mycology. New York: Springer-Verlag, 1989: 315-402
15. Cohen R, Roth FJ, Delgado F, et al. Fungal flora of the normal human small and large intestine. N Engl J Med 1969; 280: 638-41
16. Sakata H, Fujita K, Yahioka H. The effects of antimicrobial agents on the fecal flora of children. Antimicrob Agents Chemother 1986; 29: 225-9
17. Mackenzie DWR. Yeast from human sources. Sabouraudia 1962; 1: 8-15
18. Cambon M, Petavy AF, Guillot J, et al. Etude de la frequence des protozoaires et des levuires isoles du parodonte chez 509 sujets. Pathol Biol (Paris) 1979; 27: 603-6
19. Fidel Jr PL, Vazquez JA, Sobel JD. *Candida glabrata*: review of epidemiology, pathogenesis, and clinical disease with comparison to C. albicans. Clin Microbiol Rev 1999; 12: 80-96
20. Gumbo T, Isada CM, Hall G, et al. *Candida glabrata fungemia*: clinical features of 139 patients. Medicine 1999; 78: 220-7
21. Pfaller MA, Diekema DJ, Jones RN, et al. International surveillance of bloodstream infections due to Candida species: frequency of occurrence and *in vitro* susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol 2001; 39 (9): 3254-9
22. Vazquez JA. Therapeutic options for the management of oropharyngeal and esophageal candidiasis in HIV/AIDS patients. HIV Clin Trials 2000; 1 (1): 47-59
23. Stenderup A, Schonheyder H. Mycoses complicating AIDS. Microbiol Sci 1984; 1: 219-23
24. Girmenia C, Martino P, De Bernardis F, et al. Rising incidence of *Candida parapsilosis fungemia* in patients with hematologic malignancies: clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. Clin Infect Dis 1996; 23 (3): 506-14
25. Levy I, Rubin LG, Vasishtha S, et al. Emergence of *Candida parapsilosis* as the predominant species causing candidemia in children. Clin Infect Dis 1998; 26 (5): 1086-8
26. Sanchez V, Vazquez JA, Barth-Jones D, et al. Nosocomial acquisition of *Candida parapsilosis*: an epidemiologic study. Am J Med 1993; 94 (6): 577-82
27. Abbas J, Bodey GP, Hanna HA, et al. *Candida krusei fungemia*: an escalating serious infection in immunocompromised patients. Arch Intern Med 2000; 160 (17): 2659-64
28. Merz WG, Karp JE, Schron D, et al. Increased incidence of fungemia caused by *Candida krusei*. J Clin Microbiol 1986; 24: 581-4
29. Wingard JR, Merz WG, Rinaldi MG, et al. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. Antimicrob Agents Chemother 1991; 37: 1847-9
30. Sullivan D, Coleman D. *Candida dubliniensis*: characteristics and identification. J Clin Microbiol 1998; 36: 329-34
31. Sullivan DJ, Westerneng TJ, Haynes KA, et al. *Candida dubliniensis* sp. nov.: phenotypic and molecular characterization of a novel species associated with oral candidosis in HIV-infected individuals. Microbiology 1995; 141 (7): 1507-21
32. Hidalgo JA, Brown W, Vazquez JA. Invasive C. dubliniensis in an HIV-negative patient: a new opportunistic fungal pathogen. Infect Dis Clin Pract 2000; 9: 176-9
33. Sebti A, Kiehn TE, Perlin D, et al. *Candida dubliniensis* at a cancer center. Clin Infect Dis 2001; 32 (7): 1034-8
34. Jabra-Rizk MA, Baqui AA, Kelley JI, et al. Identification of *Candida dubliniensis* in a prospective study of patients in the United States. J Clin Microbiol 1999; 37 (2): 321-6
35. Hazen KC. New and emerging yeast pathogens. Clin Microbiol Rev 1995; 8 (4): 462-78
36. Vazquez JA, Lundstrom T, Dembry L, et al. Invasive *Candida guilliermondii* infection: *in vitro* susceptibility studies and

molecular analysis. Bone Marrow Transplant 1995; 16 (6): 849-53
37. Sanchez V, Vazquez JA, Barth-Jones D, et al. Epidemiology of nosocomial acquisition of *Candida lusitaniae*. J Clin Microbiol 1992; 30 (11): 3005-8
38. Yoon SA, Vazquez JA, Steffan PE, et al. High-frequency, *in vitro* reversible switching of *Candida lusitaniae* clinical isolates from amphotericin B susceptibility to resistance. Antimicrob Agents Chemother 1999; 43 (4): 836-45
39. Bodey GP, Anaissie EJ, Edwards JE. Definitions of Candida infections. In: Bodey GP, editor. Candidiasis: pathogenesis, diagnosis, and treatment. New York: Raven Press Ltd, 1993: 407-8
40. Kwon-Chung KJ, Riggsby WS, Uphoff RA, et al. Genetic differences between type I and type II *Candida stellatoidea*. Infect Immun 1989; 57 (2): 527-32
41. Rikkerink EH, Magee BB, Magee PT. Genomic structure of *Candida stellatoidea*: extra chromosomes and gene duplication. Infect Immun 1990; 58 (4): 949-4
42. Soll DR. The ins and outs of DNA fingerprinting the infectious fungi. Clin Microbiol Rev 2000; 13 (2): 332-70
43. Odds FC. *Candida albicans*, the life and times of a pathogenic yeast. J Med Vet Mycol 1994; 32 Suppl. 1: 1-8
44. Pfaller MA, Cabezudo I, Hollis R, et al. The use of biotyping and DNA fingerprinting in typing *Candida albicans* from hospitalized patients. Diagn Microbiol Infect Dis 1990; 13 (6): 481-9
45. Berger C, Frei R, Gratwohl A, et al. Bottled lemon juice: a cryptic source of invasive Candida infections in the immunocompromised host. J Infect Dis 1988; 158 (3): 654-5
46. Galen 130-ca. 200. Des remedius parabilibus I-III. In: Kuhn CG. Opera Omnia. Hildersheim: George Olms, 1965
47. Taschdjian CL, Kozinn PJ. Laboratory and clinical studies on candidiasis in the newborn infant. J Pediatrics 1957; 50: 426-33
48. Kozinn PJ, Taschdjian CL, Dragutsky D. Therapy of oral thrush; a comparative evaluation of gentian violet, mycostatin, and amphotericin B. Monogr Ther 1957; 2: 16-24
49. Rothschild H, Wilson M, Lopez M, et al. An immunological investigation of a family with chronic mucocutaneous candidiasis. Int Arch Allergy Appl Immunol 1976; 52: 291-6
50. Sams Jr WM, Tomzzo JL, Snyderman R, et al. Chronic mucocutaneous candidiasis. Am J Med 1979; 67: 948-59
51. Beta PG. Pathology of some of the opportunistic infections in acquired immune deficiency syndrome (AIDS). Pathologica 1985; 77: 67-75
52. Chandler FW. Pathology of the mycoses in patients with the acquired immune deficiency syndrome (AIDS). Curr Top Med Mycol 1986; 1: 1-23
53. Jaffe HW, Bergman DJ, Selik RM. Acquired immune deficiency syndrome in the United States, the first 1000 cases. J Infect Dis 1983; 148: 339-45
54. Melbye M, Schonheyder H, Kesters L, et al. Carriage of oral C. albicans associated with a high number of circulating suppressor T Lymphocytes. J Infect Dis 1985; 152: 1356-7
55. Schnheyder H, Melbye M, Biggar RJ, et al. Oral yeast flora and antibodies to *Candida albicans* in homosexual men. Mykosen 1984; 27: 539-44
56. Kalo-Klein A, Witkin SS. Prostaglandin E_2 enhances and gamma interferon inhibits germ tube formation in *Candida albicans*. Infect Immun 1990; 58: 260-2
57. Sobel JD, Vazquez JA. Fungal infections of the gastrointestinal tract. In: Surawicz C, Owen T, editors. Gastrointestinal and hepatic infections. Philadelphia (PA): WB Saunders, 1995: 219-45
58. Topper-James L, Aldred MJ, Walker DM. Candidal infections and populations of *Candida albicans* in mouths of diabetics. J Clin Pathol 1981; 4: 706-11
59. Segal E, Sotoka A, Schechter A. Correlative relationship between adherence of *Candida albicans* to human vaginal epithelial cells *in vitro* and candidal vaginitis. J Med Vet Mycol 1984; 22: 191-200
60. Wilson RM, Reeves WG. Neutrophil phagocytosis and killing in insulin-dependent diabetes. Clin Exp Immunol 1986; 63: 478-84
61. Sutptin A, Albright F, McCure DJ. Five cases of idiopathic hypoparathyroidism associated with moniliasis. J Clin Endocrinol 1943; 3: 625-30
62. Spinner MW, Blizzard RM, Childs B. Clinical and genetic heterogeneity in idiopathic Addison's disease and hypoparathyroidism. J Clin Endocrinol 1968; 28: 795-804
63. Podolsky S, Ferguson BD. Fatal systemic candidiasis following treatment of Addisonian crisis in a juvenile diabetic. Diabetes 1970; 19: 438-44
64. Giombetti R, Hagstrom JWC, Landey S, et al. Cushing's syndrome in infancy: a case complicated by monilial endocarditis. Am J Dis Child 1971; 122: 264-6
65. Cormane RH, Goolings WRO. Factors influencing the growth of *Candida albicans*. Sabouraudia 1963; 3: 52-63
66. Samaranayake LP. Nutritional factors and oral candidosis. J Oral Pathol 1986; 15: 61-5
67. Seelig MS. The role of antibiotics in the pathogenesis of Candida infections. Am J Med 1966; 40: 887-917
68. Fitzpatrick JJ, Topley HE. Ampicillin therapy and Candida overgrowth. Am J Med Sci 1966; 252: 310-3
69. Caldwell JR, Cluff LE. Adverse reactions to antimicrobial agents. JAMA 1974; 230: 77-80
70. Winner HI, Hurley R. *Candida albicans*. London: Churchill, 1964
71. Johnston RD, Chick EW, Johnston NS. Asymptomatic quantitative increase of *Candida albicans* in the oral cavity: predisposing factors. South Med J 1967; 60: 1244-7
72. Loose DS, Feldman D. Characterization of a unique corticosterone-binding protein in *Candida albicans*. J Biol Chem 1982; 257: 4925-30
73. Sanford GR, Metz WG, Wingard JR, et al. The value of fungal surveillance cultures as predictors of systemic fungal infections. J Infect Dis 1980; 142: 503-9
74. Kleinegger CL, Lockhart SR, Vargas K, et al. Frequency, intensity, species and strains of oral Candida vary as a function of host age. J Clin Microbiol 1996; 34: 2246-54
75. Walsh TJ, Merz WG. Pathologic features in the human alimentary tract associated with invasiveness of *Candida tropicalis*. Am J Clin Pathol 1986; 85: 498-502

76. Bennet JE. Diagnosis and management of candidiasis in the immunosuppressed host. Scand J Infect Dis 1978; 16 Suppl.: 83-6
77. Mekalanos JJ. Environmental signals controlling expression of virulence determinants in bacteria. J Bacteriol 1992; 174 (1): 1-7
78. De Bernardis F, Muhlschlegel FA, Cassone A, et al. The pH of the host niche controls gene expression in and virulence of *Candida albicans*. Infect Immun 1998; 66: 3317-25
79. Brown AJ, Gow NA. Regulatory networks controlling *Candida albicans* morphogenesis. Trends Microbiol 1999; 7 (8): 333-8
80. Sundstrom P. Adhesins in *Candida albicans*. Curr Opin Microbiol 1999; 2 (4): 353-7
81. Staab JF, Bradway SD, Fidel PL, et al. Adhesive and mammalian transglutaminase substrate properties of *Candida albicans* Hwp1. Science 1999; 283 (5407): 1535-8
82. Leidich SD, Ibrahim AS, Fu Y, et al. Cloning and disruption of caPLB1, a phospholipase B gene involved in the pathogenicity of *Candida albicans*. J Biol Chem 1998; 273 (40): 2678-86
83. Monod M, Togni G, Hube B, et al. Multiplicity of genes encoding secreted aspartic proteinases in Candida species. Mol Microbiol 1994; 13 (2): 357-68
84. Hipocrates CA, Adams F. Epidemics 460-377 BC, Book 3. Baltimore (MD): Williams and Wilkins, 1939
85. Trousseau A. Lectures on clinical medicine, delivered on the Hotel-Dieu, Paris, Vol. 2 [Cormack JR, translated from 1865 edition]. London: New Sydenham Society, 1869
86. Parrot J. Cliniques des Noruvea-n s L'athrepsie., Lecons Recuellies par Dr. Paris: Troisier G. Masson, 1877
87. Langenbeck B. Auffingung von pilzer aus der schleimhaut der speiserohre einer typhus-leiche: neue not geb. Natur-u-Heilk 1939; 12: 145-7
88. Berg FT. GM Torsk hos Barn. Stockholm: LJ Hjerta, 1846
89. Haussmann D. Parasites de organes sexuals femeil-les de l'homme et de quelques animaux avec une notice sur development de l'Oidium albicans Robin. Paris: JB Bailliere, 1875
90. Eras P, Goldstein MJ, Sherlock P. Candida infection of the gastrointestinal tract. Medicine 1972; 51 (5): 367-79
91. Stevens DA. Fungal infections in AIDS patients. Br J Clin Pract Suppl 1990; 71 (44): 11-22
92. Coleman DC, Bennett DE, Sullivan DJ, et al. Oral Candida in HIV infection and AIDS: new perspectives/new approaches. Critical Rev Microbiol 1993; 19 (2): 61-82
93. Wheeler RR, Peacock Jr JE, Cruz JM, et al. Esophagitis in the immunocompromised host: role of esophagoscopy in diagnosis. Rev Infect Dis 1987; 9 (1): 88-96
94. Jensen KB, Stenderup A, Thomsen JB. Esophageal moniliasis in malignant neoplastic disease. Acta Med Scand 1964; 175: 455-9
95. Minoli G, Terruzzi V, Rossini A. Gastroduodenal candidiasis occurring without underlying disease: report on 2 cases. Endoscopy 1979; 11: 18-22
96. Clotet B, Grifol M, Parra O, et al. Asymptomatic esophageal candidiasis in the acquired-immunodeficiency-syndrome-related complex [letter]. Ann Intern Med 1986; 105 (1): 145
97. Kodsi BE, Wickremesinghe C, Kozinn PJ, et al. *Candida esophagitis*: a prospective study of 27 cases. Gastroenterology 1976; 1 (5): 715-9
98. Lefkowitz M, Elsas LJ, Levine RJ. Candida infection complicating peptic esophageal ulcer: infection in an aortic-esophageal fistula. Arch Intern Med 1964; 113: 672-5
99. Sehhat S, Hazeghi K, Bajoghli M, et al. Oesophageal moniliasis causing fistula formation and lung abscess. Thorax 1976; 1 (3): 361-4
100. Athey PA, Goldstein HM, Dodd GD. Radiologic spectrum of opportunistic infections of the upper gastrointestinal tract. Am J Roentgenol 1977; 129 (3): 419-24
101. Pagani JJ, Libshitz HI. Radiology of Candida infections. In: Bodey GP, Fainstain V, editors. Candidiasis. New York: Raven Press, 1981: 71-84
102. Pfaller MA, Messer SA, Gee S, et al. *In vitro* susceptibilities of *Candida dubliniensis* isolates tested against the new triazole and echinocandin antifungal agents. J Clin Microbiol 1999; 37 (3): 870-2
103. Vazquez JA, Lynch M, Sobel JD. *In vitro* activity of a new pneumocandin antifungal agent, L-733,560 against azole-susceptible and -resistant Candida and Torulopsis species. Antimicrob Agents Chemother 1995; 39 (12): 2689-91
104. Minari A, Hachem R, Raad I. *Candida lusitaniae*: a cause of breakthrough fungemia in cancer patients. Clin Infect Dis 2001; 32 (2): 186-90
105. Bhargava P, Vazquez JA. Amphotericin B-resistant *Candida krusei*?. A comparison of standardized testing and time kill studies. Proceedings of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, 924
106. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts: approved standard M27-A. Wayne (PA): National Committee for Clinical Laboratory Standards, 1997
107. Rex JH, Pfaller MA, Galgiani JN, et al. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of *in vitro-in vivo* correlation data for fluconazole, itraconazole, and Candida infections. Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards. Clin Infect Dis 1997; 24 (2): 235-47
108. Quereda C, Polanco AM, Giner C, et al. Correlation between *in vitro* resistance to fluconazole and clinical outcome of oropharyngeal candidiasis in HIV-infected patients. Eur J Clin Microbiol Infect Dis 1996; 15 (1): 30-7
109. Stiller RL, Bennett JE, Scholer HJ, et al. Susceptibility to 5-fluorocytosine and prevalence of serotype in 402 *Candida albicans* isolates from the United States. Antimicrob Agents Chemother 1982; 22 (3): 482-7
110. Witt MD, Imhoff T, Li C, et al. Comparison of fluconazole and amphotericin B for treatment of experimental *Candida endocarditis* caused by non-C. albicans strains. Antimicrob Agents Chemother 1993; 37 (9): 2030-2
111. Law D, Moore CB, Denning DW. Amphotericin B resistance testing of Candida spp.: a comparison of methods. J Antimicrob Chemother 1997; 40 (1): 117-9
112. Karyotakis NC, Anaissie EJ. Efficacy of escalating doses of liposomal amphotericin B (AmBisome) against hematogenous *Candida lusitaniae* and *Candida krusei* infection in neutropenic mice. Antimicrob Agents Chemother 1994; 38 (11): 2660-2

113. Ng TT, Denning DW. Liposomal amphotericin B (AmBisome) therapy in invasive fungal infections: evaluation of United Kingdom compassionate use data. Arch Intern Med 1995; 155: 1093-8
114. Anaissie E, Paetznick V, Bodey GP. Fluconazole susceptibility testing of *Candida albicans*: microtiter method that is independent of inoculum size, temperature, and time of reading [published erratum appears in Antimicrob Agents Chemother 1992 May; 36 (5): 1170]. Antimicrob Agents Chemother 1991; 35 (8): 1641-6
115. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. Drugs 1990; 39: 877-916
116. Hughes CE, Beggs WH. Action of fluconazole (UK-49,858) in relation to other systemic antifungal azoles. J Antimicrob Chemother 1987; 19: 171-4
117. Kurtz MB, Rex JH. Glucan synthase inhibitors as antifungal agents. Adv Protein Chem 2001; 56: 423-75
118. Ginsburg CH, Braden GL, Tauber AI, et al. Oral clotrimazole in the treatment of esophageal candidiasis. Am J Med Sci 1981; 71 (5): 891-5
119. Dewit S, Urbain D, Rahir F, et al. Efficacy of oral fluconazole in the treatment of AIDS-associated esophageal candidiasis. Eur J Clin Microbiol Infect Dis 1991; 10: 503-5
120. Darouiche RO. Oropharyngeal and esophageal candidiasis in immunocompromised patients: treatment issues. Clin Infect Dis 1998; 26 (2): 259-72
121. Horsburgh CR, Kirkpatrick CH. Long term therapy of chronic mucocutaneous candidiasis with ketoconazole; experience with 21 patients. Am J Med 1983; 74 Suppl. 1B: 23-9
122. Hughes WT, Bartley DL, Patterson GG, et al. Ketoconazole and candidiasis: a controlled study. J Infect Dis 1983; 147 (6): 1060-3
123. Fazio RA, Wickremesinghe PC, Arsura EL. Ketoconazole treatment of *Candida esophagitis*: a prospective study of 12 cases. Am J Gastroenterol 1983; 78 (5): 261-4
124. Wilcox CM, Darouiche RO, Laine L, et al. A randomized, double-blinded comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis. J Infect Dis 1997; 176: 227-32
125. Barbaro G, Barbarini G, DiLorenzo G. Fluconazole compared with itraconazole in the treatment of esophageal candidiasis in AIDS patients: a double-blind, randomized, controlled clinical study. Scand J Infect Dis 1995; 27 (6): 613-7
126. Barbaro G, Barbarini G, Calderon W, et al. Fluconazole versus itraconazole for *Candida esophagitis* in acquired immunodeficiency syndrome. Gastroenterology 1996; 111: 1169-77
127. Wingard JR. Importance of Candida species other than C. albicans as pathogens in oncology patients. Clin Infect Dis 1995; 20 (1): 115-25
128. Maenza JR, Merz WG, Romagnoli MJ, et al. Infection due to fluconazole-resistant Candida in patients with AIDS: prevalence and microbiology. Clin Infect Dis 1997; 24 (1): 28-34
129. Medoff G, Dismukes WE, Meade III RH, et al. A new therapeutic approach to Candida infections, a preliminary report. Arch Intern Med 1972; 130: 241-5
130. Scott BB, Jenkins D. Gastro-oesophageal candidiasis. Gut 1982; 23: 137-9
131. Tavitian A, Raufman JP, Rosenthal LE, et al. Ketoconazole resistant *Candida esophagitis* in patients with acquired immunodefieiency syndrome. Gastroenterology 1986; 90: 443-5
132. Glatt AE, Chirgwin K, Landesman SH. Treatment of infections associated with human immunodeficiency virus. N Engl J Med 1988; 18: 1439-48
133. Maenza JR, Keruly JC, Moore RD, et al. Risk factors for fluconazole-resistant candidiasis in human immunodeficiency virus-infected patients. J Infect Dis 1996; 173 (1): 219-25
134. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood 2000; 96 (6): 2055-61
135. Mori T, Matsumura M, Kanamaru Y, et al. Myelofibrosis complicated by infection due to *Candida albicans*: emergence of resistance to antifungal agents during therapy. Clin Infect Dis 1997; 25: 1470-1
136. Xu J, Ramos AR, Vilgalys R, et al. Clonal and spontaneous origins of fluconazole resistance in *Candida albicans*. J Clin Microbiol 2000; 38 (3): 1214-20
137. Polak A. Multicenter study of the standardization of sensitivity testing of fungi to 5-fluorocytosine and amphotericin B. Mykosen 1987; 30 (7): 306-8, 311-4
138. Schaffner A, Bohler A. Amphotericin B refractory aspergillosis after itraconazole: evidence for significant antagonism. Mycoses 1993; 36 (11-12): 421-4
139. Scheven M, Schwegler F. Antagonistic interactions between azoles and amphotericin B with yeasts depend on azole lipophilia for special test conditions *in vitro*. Antimicrob Agents Chemother 1995; 39 (8): 1779-83
140. Sugar AM. Use of amphotericin B with azole antifungal drugs: what are we doing? Antimicrob Agents Chemother 1995; 39 (9): 1907-12
141. Sugar AM, Hitchcock CA, Troke PF, et al. Combination therapy of murine invasive candidiasis with fluconazole and amphotericin B. Antimicrob Agents Chemother 1995; 39 (3): 598-601
142. Fichtenbaum CJ, Koletar S, Yiannoutsos C, et al. Refractory mucosal candidiasis in advanced human immunodeficiency virus infection. Clin Infect Dis 2000; 30 (5): 749-56
143. Revankar SG, Dib O, Kirkpatrick WR, et al. Clinical evaluation and microbiology of oropharyngeal infection due to fluconazole-resistant Candida in Human immunodeficiency virus-infected patients. Clin Infect Dis 1998; 26: 960-3
144. Martins MD, Rex JH. Fluconazole suspension for oropharyngeal candidiasis unresponsive to tablets. Ann Intern Med 1997; 126 (4): 332-3
145. Parving H. Fluconazole suspension for oropharyngeal candidiasis unresponsive to tablets. Ann Intern Med 1997; 126: 332-3
146. Vazquez JA, Gupta S, Villanueva A. Potential utility of recombinant human GM-CSF as adjunctive treatment of refractory oropharyngeal candidiasis in AIDS patients. Eur J Clin Microbiol Infect Dis 1998; 17 (11): 781-3

147. Vazquez J, Lamarca A, Schwartz R, et al. Management of fluconazole-refractory oropharyngeal candidiasis using high-dose terbinafine in patients with AIDS. Proceedings of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto, 1418

148. Ernst EJ. Investigational antifungal agents. Pharmacotherapy 2001; 21 (8 Pt 2): 165S-74S

149. Sheehan DJ, Hitchcock CA, Sibley CM. Current and emerging azole antifungal agents. Clin Microbiol Rev 1999; 12 (1): 40-79

150. Ghannoum MA, Kuhn DM. Voriconazole-better chances for patients with invasive mycoses. Eur J Med Res 2002; 7: 242-56

151. Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis 2001; 33 (9): 1447-54

152. Ruhnke M, Schmidt-Westhausen A, Trautmann M. *In vitro* activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with human immunodeficiency virus infection. Antimicrob Agents Chemother 1997; 41 (3): 575-7

153. Hussain MA, Reyes GH, Ghannoum MA. Newer antifungal agents and treatment strategies. Rev Med Microbiol 2001; 12 Suppl. 1: S3-S12

154. St-Germain G, Dion C, Espinel-Ingroff A, et al. Ketoconazole and itraconazole susceptibility of *Candida albicans* isolated from patients infected with HIV. J Antimicrob Chemother 1995; 36 (1): 109-18

155. Eichel M, Just-Nubling G, Helm EB, et al. Itraconazole suspension in the treatment of HIV-infected patients with fluconazole-resistant oropharyngeal candidiasis and esophagitis. Mycoses 1996; 39 Suppl. 1: 102-6

156. Cartledge JD, Midgley J, Gazzard BG. Itraconazole cyclodextrin solution: the role of *in vitro* susceptibility testing in predicting successful treatment of HIV-related fluconazole-resistant and fluconazole-susceptible oral candidosis. AIDS 1997; 11 (2): 163-8

157. Phillips P, Zemcov J, Mahmood W, et al. Itraconazole cyclodextrin solution for fluconazole-refractory oropharyngeal candidiasis in AIDS: correlation of clinical response with *in vitro* susceptibility. AIDS 1996; 10 (12): 1369-76

158. Villanueva A, Arathoon EG, Gotuzzo E, et al. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. Clin Infect Dis 2001; 33 (9): 1529-35

159. Zingman BS. Resolution of refractory AIDS-related mucosal candidiasis after initiation of didanosine plus saquinavir. N Engl J Med 1996; 334: 1674-5

160. Vecchiarelli A, Monari C, Baldelli F, et al. Beneficial effect of recombinant human granulocyte colony-stimulating factor on fungicidal activity of polymorphonuclear leukocytes from patients with AIDS. J Infect Dis 1995; 171 (6): 1448-54

161. Swindells S, Kleinschmidt DR, Hayes FA. Pilot study of adjunctive GM-CSF (yeast derived) for fluconazole-resistant oral candidiasis in HIV-infection. Infect Dis Clin Pract 1997; 6: 278-9

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