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CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES FOR OPPORTUNISTIC INFECTIONS CANDIDIASIS

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CANDIDIASIS

I) OROPHARYNGEAL CANDIDIASIS

Mucosal candidiasis, particularly oropharyngeal, has been the most common opportunistic infection, occurring in up to 90% of patients during the course of HIV disease in the pre-ART era[1]. It serves as a marker of immunosuppression, usually occurring when the CD4 count falls to less than 200 cells/μL. C. *albicans* accounts for most cases, although a significant proportion are caused by non-albicans species, such as C. *glabrata*, C. *dubliniensis*, and C. *tropicalis*[2,3].

a) Prophylaxis:

Primary. Specific antifungal agents are not recommended for this purpose (AIII).

Secondary (suppressive therapy). This is generally not recommended unless disease-free intervals between episodes are short (e.g. less than a month) or symptoms are severe (BIII) and the diagnosis has been confirmed (see Diagnosis below).

Preferred treatment:

- Fluconazole 100 mg PO daily or 3 times a week (BI)

Discussion. Immune reconstitution by initiation of antiretroviral therapy (ART) or revision of a failing regimen is essential for reducing the risk of recurrences of mucosal candidiasis. Factors to be considered in the decision regarding initiation of secondary prophylaxis include the frequency and severity of episodes, drug toxicities and interactions, and cost4. Both continuous and episodic use of fluconazole have been associated with a similar risk of ~4% for the development of fluconazole-refractory mucosal candidiasis after a median follow-up of 2 years[5]. Symptomatic episodes may be more frequent and difficult to control with topical therapy (see Treatment) in patients with marked CD4 lymphopenia.

b) Diagnosis. Oropharyngeal candidiasis clinical findings may include lesions which are white (also removable and curd-like), in addition to erythematous patches or angular cheilitis. Laboratory confirmation of the diagnosis is not necessary in the presence of typical appearing lesions; however, a potassium hydroxide (KOH) wet mount smear or Gram stain (with or without culture) demonstrating organisms compatible with *Candida* species is important in the setting of atypical lesions or lack of response to therapy. An oral cavity swab which is culture-positive for *Candida* species does not differentiate between mucosal candidiasis disease and *Candida* colonization, the latter being present in up to 82% of those who are HIV-positive[3]. However, in contrast to disease, colonization is usually associated with a relatively low number of organisms which is insufficient to detect on a smear or Gram stain.

c) Treatment.

SYSTEMIC THERAPY

- Fluconazole 100 mg PO daily for 7-14 days(AI), or

- Fluconazole 750 mg PO single dose (BI), or

TOPICAL THERAPY for 14 days

- Nystatin suspension 200,000-500,000 units swish and swallow, 4 times daily (BI), or
- Gentian violet 5 mL (0.00165%) swish and gargle for 2 minutes and then expectorate, twice daily (BI)

Discussion. Systemic therapy is preferable for moderate to severe or recurrent infection. While topical agents may not be as well tolerated and in general are less effective than systemic therapy[2,6,7], they may be less expensive and are free of potential drug interactions. There is less published experience with single dose fluconazole treatment using 750 mg, although the response rate appears to be similar to that achieved with a 14-day duration[8]. Alternative systemic regimens which have similar efficacy to fluconazole include itraconazole oral solution (not capsules) 200 mg daily for 7-14 days[9,10], or posaconazole oral suspension 400 mg PO twice daily for 1 day then 400 mg PO once daily for 13 days11. However, both of these antifungals are expensive and require a Pharmacare special authority request for funding in British Columbia.

Although four other topical antifungal formulations have demonstrated efficacy in clinical trials (nystatin pastilles[12], clotrimazole troches[6,12,13], amphotericin B oral solution or lozenges, and miconazole buccal tablets[13]), they are not currently marketed in Canada. However, on request they may be prepared by one of a few compounding pharmacies in British Columbia (see: Find A Compounder - PCCA - Professional Compounding Centers of America (pccarx.com)).

Fluconazole is the best-tolerated azole antifungal drug, but may be associated with gastrointestinal symptoms and occasionally alopecia or hepatotoxicity. However, in comparative trials of 1-2 weeks of treatment, fluconazole and itraconazole had similar safety profiles[9,10]. In contrast to fluconazole, itraconazole has less reliable absorption and more drug interactions. Itraconazole capsules are less effective than the oral solution formulation for both oropharyngeal and esophageal candidiasis[2]. Itraconazole potential adverse effects include hepatotoxicity, peripheral neuropathy, occasional exacerbation of congestive heart failure due to its negative inotropic effect, and the triad of hypokalemia, peripheral edema and hypertension related to pseudohyperaldosteronism.

II) ESOPHAGEAL CANDIDIASIS

a) Prophylaxis:

Primary. Specific antifungal agents are not recommended for this purpose (AIII).

Secondary (suppressive therapy). As for oropharyngeal candidiasis, this is generally not recommended unless disease-free intervals between episodes are short (e.g. less than a month) or symptoms are severe (BIII) and recurrent symptoms are confirmed to be candidiasis with smear positive lesions (Gram stain, KOH smear, or cytology). Treatment options include:

Preferred therapy:

- Fluconazole 100-200 mg PO daily, or 200 mg three times weekly (BI)

Alternate therapy:

- Posaconazole oral suspension 400 mg twice daily (BII), or
- Itraconazole oral solution 200 mg once or twice daily (BIII)

Discussion: See the *Discussion, Secondary Prophylaxis of Oropharyngeal Candidiasis*. Fluconazole 200 mg 3 times weekly has been shown to reduce the recurrence rate for both oropharyngeal and esophageal candidiasis[5]. However, fluconazole 200 mg once weekly reduced the recurrence rate of both oropharyngeal and vulvovaginal, but not esophageal candidiasis[14].

b) Diagnosis. For immunocompromised HIV-positive patients, the presence of esophageal symptoms (odynophagia, dysphagia, or retrosternal pain) in association with clinical findings of oropharyngeal candidiasis has at least moderate predictive value for the presence of esophageal candidiasis[15,16] and can be treated presumptively without further investigations[17]. If a clinical response is not observed after 5-7 days of therapy, then upper gastrointestinal endoscopy should be performed with esophageal mucosal brushings with or without biopsies for cytology, culture, and histology. However, in one study of predominantly AIDS patients, 40% of those presenting with esophageal symptoms but without oropharyngeal candidiasis were confirmed to have esophageal candidiasis[16]. Viral infection due to cytomegalovirus (CMV) or *Herpes simplex* (HSV) frequently coexists with *Candida* esophagitis[16]. The endoscopic appearance of the mucosa in esophageal candidiasis is typically raised white plaques, whereas erosions and ulcers are usually due to viral infection or idiopathic ulcer[18]. When the predominant symptom is moderate to severe odynophagia rather than dysphagia, then the diagnosis is more often esophageal ulceration (e.g. viral or idiopathic) rather than candidiasis[17].

c) Treatment:

Preferred treatment:

- Fluconazole 200-400 mg orally daily (AI)

Alternate treatment:

- Itraconazole oral solution (not capsules) 200 mg daily (AI), or
- Voriconazole 200 mg (3 mg/kg) PO or IV twice daily (BI), or
- An echinocandin (e.g. micafungin 150 mg IV daily; or caspofungin 70 mg IV on day one, then 50 mg IV daily; or anildulafungin 100 mg IV on day one, then 50 mg IV daily) (BI), or
- Amphotericin B deoxycholate 0.3-0.7 mg/kg IV daily (BI), or
- Liposomal amphotericin B 3 mg/kg IV daily, (BIII), or
- Isavuconazole 200-400 mg PO loading dose, then 50-100 mg PO daily; or 400 mg PO once weekly for 3 doses; (BI) or 200 mg once daily IV

Discussion: A systemic antifungal is recommended for 2-3 weeks (AI). There is a lack of evidence to support the use of topical agents which are not absorbed systemically (e.g. nystatin, clotrimazole tro-

ches) for the treatment of esophageal candidiasis. Fluconazole (oral or intravenous) is more reliably absorbed, at least as effective, equally or better tolerated, less expensive, and more readily available in British Columbia than any of the alternative antifungal drugs listed above[19,20,21,22,23,24,25]. Although itraconazole oral solution has been shown to have similar efficacy to fluconazole (endoscopic cure in 90% vs 80%, respectively)[20], the use of itraconazole capsules has been associated with lower endoscopic cure rates than fluconazole (66% vs 81%, respectively)[26]. Itraconazole oral solution is better absorbed than the capsule formulation (see the *Discussion* of the *Treatment* section of *Refractory Oral and Esophageal Candidiasis)*.

Other azole alternatives include voriconazole which appears to have similar efficacy compared to fluconazole (98% vs 95%, respectively), but more adverse effects[21]. In a recent clinical trial of immunocompromised patients (37% of whom were HIV-positive), similar high response rates were observed with isavuconazole compared to fluconazole (97% vs 95%, respectively), but with more adverse events in the isavuconazole 100 mg daily dosage arm of the study[25]. Posaconazole has been effective in the management of azole-refractory esophageal candidiasis (see the Discussion of the Treatment section of *Refractory Oropharyngeal and Esophageal Candidiasis*)[27].

For patients who are unable to swallow, all of the treatment options listed above have an intravenous formulation which is available in Canada, with the exception of itraconazole. Among the echinocandins, both micafungin22 and anidulafungin[24] have been shown to have similar efficacy and safety compared to fluconazole in clinical trials. Caspofungin had similar efficacy but was better tolerated than intravenous amphotericin B in a comparative trial[23]. A higher relapse rate has been reported with the echinocandins compared to fluconazole for esophageal candidiasis[22,24]. The somewhat lower response rate and major adverse events associated with intravenous amphotericin B make it the drug of last choice to be considered if alternatives are unavailable[23]. Currently in British Columbia, a Pharmacare special authority approval is required for funding itraconazole oral solution, voriconazole, posaconazole, and isavuconazole.

III) VULVOVAGINAL CANDIDIASIS

a) Prophylaxis (See above Oropharyngeal candidiasis)**:**

Primary. Specific antifungal agents are not recommended for this purpose (AIII).

Secondary (suppressive therapy). This is generally not recommended unless disease-free intervals between episodes are short (e.g. less than a month) or symptoms are severe (BIII) and the diagnosis has been confirmed.

Preferred treatment:

Fluconazole 150-200 mg once a week for 6 months (BI)

Discussion. See the *Discussion* section for *Secondary Prophylaxis of Oropharyngeal Candidiasis*. Fluconazole is the only antifungal drug recommended for suppressive therapy of recurrent vulvovaginal candidiasis[28,29,30]. In a double-blind clinical trial of HIV-positive women with CD4 counts of <300 cells/μL, fluconazole at a dose of 200 mg once weekly provided significant risk reduction

compared to placebo for the development of both vaginal (relative risk [RR] 0.64, 95% confidence interval 0.4-1.00; p=0.05) and oropharyngeal (RR 0.5, 95% confidence interval 0.33-0.74; p<0.001) candidiasis[14]. Most individuals with recurrent vulvovaginitis are HIV-negative with no known immunocompromise, and have been effectively managed with a 6-month course of fluconazole after which the frequency of recurrences can be reassessed[28]. Similarly, among HIV-positive persons with CD4 lymphopenia, initiation of ART in addition to a 6-month course of fluconazole may be effective in reducing the recurrence rate without having to continue the fluconazole indefinitely.

b) Diagnosis. Typical symptoms may include vulvar pruritis, pain, swelling, external dysuria, and discharge in association with examination findings of vulvar edema, excoriations and whitish curd-like discharge. Since the clinical presentation is non-specific, laboratory confirmation is required for the diagnosis with KOH wet mount smear (or Gram stain) of vaginal discharge demonstrating the presence of yeast forms, with or without pseudohyphae. Vaginal culture is usually not necessary, but may be considered if the smears are negative and other causes are unlikely. However, 10-20% of the general population, and a higher proportion of HIV-positive women have vaginal colonization with *Candida* species, which in the absence of symptoms or signs does not warrant treatment[31]. Self-diagnosis is inaccurate in more than half of women who choose over-the-counter antifungal drug therapy, regardless of whether or not there was a prior history of clinically diagnosed vulvovaginal candidiasis[32]. *Candida albicans* accounts for the majority of cases, and susceptibility testing is seldom required.

Lack of response to treatment or recurrent disease requires culture confirmation including the *Candida* species identification. C. *glabrata* is the most frequent non-albicans *Candida* causing vulvovaginitis[33]. Infections due to non-albicans Candida species have lower response rates to treatment[34]. The presence of only yeast forms on KOH smear or Gram stain suggests the presence of C. glabrata, which does not form hyphae or pseudohyphae. Despite there being some evidence of *Candida* transmission by sexual activity, *Candida vulvovaginitis* is not considered to be a sexually transmitted infection, and testing and treatment of sexual partners is not recommended[29,30].

c) Treatment:

Uncomplicated vulvovaginitis

- Fluconazole 150 mg PO single dose (AII), or
- Topical azole "over-the-counter" (OTC) (AII)
  - Clotrimazole 2% cream 5g intravaginally once daily for 3 days, or
  - Miconazole 4% cream 5g intravaginally once daily for 3 days, or
  - Miconazole 2% cream 5g intravaginally once daily for 7 days, or
  - Miconazole 1200 mg vaginal suppository single dose, or
  - Miconazole 200 mg vaginal suppository once daily for 3 days, or
  - Miconazole 100 mg vaginal suppository once daily for 7 days

Severe vulvovaginitis

- Fluconazole 150 mg PO, followed by 1-2 repeat doses at 3-day intervals (AI), or
- Topical azole (as above) for 7-14 days duration. If using the miconazole 1200 mg vaginal suppository, then the first dose is given on day 1 followed by a second dose on day 4.

Fluconazole-refractory vulvovaginitis

Preferred treatment:

- Topical azole (as for Severe vulvovaginitis above), or
- Topical nystatin vaginal suppositories 100,000 units once daily for 14 days

Alternative treatment:

- Boric acid 600 mg gelatin capsule intravaginally once daily for 14 days, or
- Itraconazole 200 mg PO daily for 3-7 days (BII)

Recurrent vulvovaginitis

- Topical azole (as above) for 7-14 days, or fluconazole (100 mg, 150, or 200 mg) PO for 3 doses (days 1, 4, and 7), before considering starting secondary prophylaxis (see above). If using the miconazole 1200 mg vaginal suppository, then the first dose is given on day 1 followed by a second dose on day 4.

Discussion. Treatment for both uncomplicated and complicated vulvovaginitis in HIV-positive women is the same as for those who are HIV-negative[29]. Uncomplicated vulvovaginitis is defined as being infrequent, mild, and likely due to *Candida albicans* in non-immunocompromised women. Complicated vulvovaginitis is defined by any one of the following: recurrent (defined as 4 or more symptomatic episodes in 1 year) or severe disease, infection caused by non-*albicans Candida*, or the host being immunocompromised, diabetic, or debilitated[29].

Topical azoles are more effective than nystatin. Systemic therapy is recommended for patients who do not tolerate or respond to topical therapy. Oral itraconazole capsules were as effective as topical clotrimazole for vaginitis[35]; however, itraconazole's role in fluconazole-refractory mucosal candidiasis has only been reported in oropharyngeal and esophageal disease. Azoles may be unreliable for non-*albicans Candida* species infection, which may respond to boric acid 600 mg or nystatin[29,34]. Nystatin vaginal suppositories and boric acid gelatin capsules are not marketed in Canada, but on request may be prepared by one of a few compounding pharmacies in British Columbia (see: Find A Compounder - PCCA - Professional Compounding Centers of America (pccarx.com)).

IV) REFRACTORY MUCOSAL CANDIDIASIS

Treatment.

Preferred treatment (for either oropharyngeal or esophageal candidiasis):

- Itraconazole oral solution (not capsules) 200 mg daily for 4 weeks (AI), or
- Posaconazole oral solution 400 mg PO twice daily for 4 weeks (AI)

Alternative treatment:

Oropharyngeal candidiasis (2 weeks):

- Nystatin suspension 200,000-500,000 units swish and swallow, 4 times daily (BII), or
- Compounding pharmacy options (see Discussion):
- Amphotericin B oral solution 100 mg/mL, 5 mL swish and swallow 4 times a day; or amphotericin B prepared from the IV formulation: 5 mL (1 mg in 5mL dextrose 5% in water (D5W) with cherry syrup) swish and swallow 4 times a day (BII) or
- Nystatin oral tablets (500,000 units) dissolve in the mouth or liquid suspension (0.5-1.0 million units) swish and swallow, 3-5 times a day (BIII), or
  - Clotrimazole troches 10 mg orally, 4-5 times daily (BIII), or
- Any of the treatment options listed below for esophageal candidiasis.

Esophageal candidiasis (2-4 weeks):

- Posaconazole oral solution 400 mg PO twice daily for 2 weeks (AI), or
- An echinocandin (e.g. micafungin 150 mg IV daily; or caspofungin 70 mg IV on day one, then 50 mg IV daily; or anildulafungin 100 mg IV on day one, then 50 mg IV daily) (BII), or
- Voriconazole 200 mg (3 mg/kg) PO or IV twice daily (BII), or
- Liposomal amphotericin B 3 mg/kg IV daily, (BIII), or
- Amphotericin B deoxycholate 0.3-0.7 mg/kg IV daily (BII)

Discussion. Azole-refractory mucosal candidiasis has been defined as clinical failure to respond to a 14-day course of treatment with either fluconazole 200 mg daily, or itraconazole oral solution 200 mg PO twice daily[36]. Azole-refractory disease was most prevalent in the pre-ART era, often recurrent, and associated with advanced HIV disease and significant prior fluconazole exposure. Most reports involved oropharyngeal rather than esophageal or vulvovaginal *candidiasis*[37]. Most of the oropharyngeal cases had been due to *Candida albicans*[37]; whereas refractory vulvovaginitis is often caused by non-*albicans Candida* species, particularly C. *glabrata*[31,33,34]. The *Candida* isolates in the oropharyngeal cases usually have reduced susceptibility in vitro to fluconazole (Minimum Inhibi-

tory Concentration for 80% [MIC80] > 32 µg/mL)37 and varying degrees of cross-resistance to other azoles. Refractory cases should have a smear (KOH or Gram stain) and culture collected for species identification for confirmation of the diagnosis.

Clinical response rates for fluconazole-refractory oropharyngeal *candidiasis* have been in the range of 55-80% with itraconazole oral solution36,38,39, 83% with voriconazole40, 64% with caspofungin[41], 75-86% with posaconazole[27,42] and 43% with amphotericin B oral solution[43,44]. Excluding fluconazole-refractory disease, among patients with either oropharyngeal or esophageal candidiasis the response rate with intravenous amphotericin B has only been 63%[23,45]. The association of refractory mucosal candidiasis with advanced HIV disease and short median survival time of 33 weeks in the pre-ART era[37] requires prompt initiation or revision of ART, which has been successful in eradicating azole-refractory mucosal candidiasis without antifungal therapy[46].

Given itraconazole's uncertain absorption and numerous drug interactions, therapeutic drug monitoring (TDM) may be considered if prolonged therapy is planned, but is not routinely required in the management of mucosal candidiasis. If necessary, itraconazole TDM is available at the St. Paul's Hospital (Vancouver) chemistry laboratory. A trough itraconazole level (EDTA plasma sample) should be obtained after 4-7 days of treatment and periodically thereafter. The observation of prolonged salivary itraconazole concentrations and clinical responses with the oral solution in some patients who have had undetectable itraconazole blood levels due to drug interactions indicates the presence of a significant topical effect, at least in oropharyngeal disease[47]. Itraconazole adverse effects include hepatotoxicity, peripheral neuropathy, occasional exacerbation of congestive heart failure due to its negative inotropic effect, and the triad of hypokalemia, peripheral edema and hypertension related to pseudohyperaldosteronism.

V) MUCOSAL CANDIDIASIS IN PREGNANCY

Both systemic azole antifungals and echinocandins should be avoided in pregnancy due to concerns related to teratogenicity, abortion, or inadequate safety data (AIII).

Treatment

Oropharyngeal and vulvovaginitis

- Topical antifungals as outlined above (except miconazole)

Esophageal candidiasis

- Liposomal amphotericin B IV or amphotericin B IV or as outlined above

Discussion. In the general population, about 10% of pregnant women are affected by vulvovaginal candidiasis[48]. During pregnancy, topical antifungals are the preferred agents for both oropharyngeal and vaginal candidiasis. An intravenous amphotericin B formulation is required for esophageal candidiasis[49] given the lack of evidence to support topical therapy for this indication.

In regard to the risk associated with various antifungal drugs in pregnancy, topical azoles are not ab-

sorbed or minimally absorbed and are considered safe in any trimester. The one exception is topical miconazole which has the FDA pregnancy drug category C designation (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well -controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite risks)[50]. In pregnancy, amphotericin B and liposomal amphotericin B are the safest among the systemically administered antifungal drugs, both being listed as FDA pregnancy drug category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women). Neonates born of mothers who have received extended courses of amphotericin B formulations should be evaluated for renal dysfunction and hypokalemia.

Fluconazole is an FDA category D drug (evidence of human fetal risk; however, the potential benefit may warrant its use despite the risk). In the Danish Medical Birth Registry, tetralogy of Fallot was observed with greater frequency among infants whose mothers received fluconazole during the first trimester[51]. A subsequent study based on the same registry also demonstrated an increased risk of spontaneous abortion among women exposed to any dose of fluconazole between weeks 7-22 of pregnancy[52]. This latter finding was confirmed in the recent Quebec Pregnancy Cohort study (1998-2015)[53]. An additional observation of the Quebec study was that high dose fluconazole, defined as a cumulative dose of >150 mg during the first trimester was associated with cardiac anomalies[53]. A recent study based upon the national pregnancy registries for Sweden and Norway showed no association between fluconazole use in pregnancy and any increased risk of either stillbirth or neonatal death[54].

Itraconazole, posaconazole, and the echinocandins are all FDA pregnancy drug category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite risks)[50]. Voriconazole is also not recommended in pregnancy and has an FDA pregnancy drug category D designation (evidence of human fetal risk; however, the potential benefit may warrant its use despite the risk). The paucity of human studies regarding the safety of posaconazole, voriconazole, and the echinocandins in pregnancy support the recommendation to avoid all of these antifungals in pregnancy. Although itraconazole is an FDA category C drug, no increased rate of congenital abnormalities has been observed in 3 studies of women who received itraconazole during pregnancy[51,55,56]. However, in a study of 1st trimester itraconazole exposure, there were higher rates of both spontaneous and induced abortion compared to the control group[55], making it another systemic azole to avoid in pregnancy, particularly during the 1st trimester.

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