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THE RESISTANCE TO FLUCONAZOLE IN PATIENTS WITH ESOPHAGEAL CANDIDIASIS

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ABSTRACT – ***Context*** - Esophageal candidiasis is often observed in patients with risk factors for its development and fluconazole is the therapeutic choice for the treatment of this disease. ***Objectives*** - To determine its frequency, by performing upper digestive endoscopy; to determine *Candida* species involved in its pathogenesis and verify their distribution according with the predisposing factors and to determine susceptibility to fluconazole in the samples. ***Methods*** - From March 2006 to April 2007, all patients submitted to esophagogastroduodenoscopy at the Digestive Endoscopy Unit in the Oswaldo Cruz University Hospital, Recife, PE, Brazil, were eligible for the study. Samples were collected from patients who presented lesions consistent with esophageal candidiasis in order to identify *Candida* species and verify their susceptibility to fluconazole. The predisposing factors for the occurrence of esophageal candidiasis were described. ***Results*** - Of 2,672 patients referred to upper endoscopy at the Digestive Endoscopy Unit, 40 (1.5%) had endoscopic findings compatible with esophageal candidiasis. The average age was 49.1 years. Twenty one patients (52.5%) were less than 50 years old, of which 82.6% were infected with HIV. Most of them (52.5%) were males and 65.0% were inpatients. Diseases were identified in 90% of the patients and 21 (52.5%) were HIV positive. Concerning endoscopic findings, severe forms of esophagitis were found in 50% of the patients with CD4 count <200. *Non-albicans Candida* species were isolated in 22.7% of HIV positive and in 45% HIV negative patients. A total of 6 (14.28%) samples were resistant to fluconazole, while 2 (4.76%) samples had dose depending susceptibility to this drug. ***Conclusions*** - Esophageal candidiasis prevalence was low, although within the results described by other authors. Male and inpatients were the most affected. The species isolated varied according to the characteristics of each group studied. Both, resistance and dose-depending susceptibility to fluconazole were considered high.

HEADINGS - Candidiasis. Esophageal diseases. Fluconazole. Drug resistance, fungal.

INTRODUCTION

In 1839, a fungus was first described as the etiological factor of esophageal candidiasis (EC) in a patient who died due to typhoid fever. At that time no association was acknowledged between immunodepression and EC[13]. Nowadays, fungal esophagitis is well known to occur in immunocompromised hosts. Well-estabilished predisposing factors are AIDS, hepatic failure, neoplasms and diabetes mellitus[2, 5, 21, 22, 29]. EC has also been described in immunocompetent patients who underwent upper endoscopy[1, 6, 12]. Prolonged use of antibiotics, corticosteroids and immunosuppressors are related as risk factors for its development[5, 6, 11, 16, 21, 22, 29].

With the improvement of flexible endoscopes and the increase in their use, from the 70s on, samples obtained under direct vision of the digestive tract became possible[17] and thus, the diagnosis of EC was enhanced[5, 16, 21, 22, 29].

Since 1990, the introduction of a new generation of oral triazole antifungal agents marked an important advance in the management of candidal infections. Fluconazole is the drug of choice for the treatment of EC[3, 7, 26, 30]. It is generally safe, well tolerated and has been shown to produce a rapid clinical response. Moreover, fluconazole can be absorbed at any gastric pH and has minimal effects on steroid synthesis, which did not occur with the agents previously used[9]. However, certain *Candida* species are intrinsically (e.g., *Candida krusei* in 100%) or intermediately resistant (e.g. *C. glabrata* in 60%*)* to fluconazole in vitro[25, 34].

In Brazil, there are no studies describing the frequency of *Candida* species which cause EC. The knowledge of associated predisposing factors to esophageal infection, as well as *Candida* species and their susceptibility to fluconazole may facilitate the therapeutic guidance, especially in patients prone to relapse.

METHODS

Patient selection

All patients referred to upper gastrointestinal endoscopy at the Digestive Endoscopy Unit in "Oswaldo Cruz" University Hospital, Recife, PE, Brazil, between March 2006 and April 2007 were eligible for the study.

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Recurrence was defined as a new episode of EC 1 month after remission. When this happened, the patient was considered as another case.

Fragments of whitish plaques adhered to the mucosa, compatible with *Candida* esophagitis, were collected with a biopsy forceps and sent for culture and species identification, without proceeding histopathological analysis.

Informed consent was obtained from each patient and approval for the study protocol was granted by the Ethics Committee of the Institution. Inclusion criteria consisted of diagnosis of EC and signature of informed consent.

Sample processing

When collected, samples were placed in Agar Sabouraud plates, a fungus selective medium, with cloranfenicol (50 mg/L), in order to prevent bacterial growth. After growth, colonies were again purified in distilled water and antibiotics and sowed in simple Agar Sabouraud plates. Hence, it was possible to isolate fungus specimens and proceed the biochemical tests for species identification.

The next step consisted in placing the samples in a chromogenic culture media which allowed instant pre-identification by eye of colonies of *Candida* (CHROMagar®). Through this presumptive technique, *C. albicans* colonies showed a greenish pattern, whilst other species presented distinct colours. Microcultive with corn meal Agar was further used to identify *Candida* species, refining previous tests obtained with chromogenic media[18].

Figure 1 describes Fluconazole susceptibility standards set by Disk-diffusion method (M44/NCCLS M27-A) for *Candida spp* used in this study.

Drug	Sensitive	Dose depending susceptibility (DDS)	Resistant
Fluconazole	≥19 mm	15–18 mm	<15 mm

FIGURE 1. Pattern of response to fluconazole

Endoscopic procedures were performed with Olympus (Exera 160) videoendoscopes and Medglobe® biopsy forceps, sterilized according to Brazilian Society of Digestive Endoscopy (SOBED) recommendations.

Study design and statistical methods

A descriptive, exploratory study – a series of cases – was conducted. Data were obtained prospectively by filling a specific formulary for each patient included in the research. The formulary was filled by interviewing the patient after endoscopy was performed. Some informations were acquired by reviewing medical records.

Data were typed in double entrance using EPI-INFO 6.0, which were then compared to avoid typing mistakes. The analysis was done by identifying the frequencies of variables. To demonstrate absolute values and their correlated proportions, tables were used.

RESULTS

Among 2,672 patients referred for endoscopy at "Oswaldo Cruz" Hospital, 40 (1.5%) had esophageal whitish plaques adhered to the mucosa, compatible with EC, according to Wilcox's endoscopic grading[33]. Mean age was 49.1 years, ranging from 31 to 66 years. Most of them (52.5%) were males and 65% were inpatients.

Predominant symptoms were dysphagia (47.5%), nausea and/or vomiting (32.5%), heartburn (32.5%), odynophagia (22.5%) and abdominal pain (20%). Five (12.5%) patients were asymptomatic. Of those, three had diabetes, one had neoplasm and none was HIV positive.

Table 1 describes cases according to age, predisposing factors, previous fluconazole use, CD4 count, grading of endoscopic esophagitis, isolated species of *Candida* and fluconazole susceptibility testing for each sample.

Associated diseases were identified in 36 (90%) patients: HIV in 21 (52.5%), diabetes mellitus in 6 (15%), chronic liver disease in 3 (7.5%), neoplasms in 2 (5%) and 4 (10%) had risk factors for EC, such as steroid use.

Most patients under 50 years of age (82.6%) were HIV positive. From that amount, 11 (52.4%) were in use of anti-retroviral therapy. Recent CD4 counting was known in 14 (66.7%) and its average was 157.7 (± 132.14/mm^3). Eight patients (57.2%) had CD4 count below 200 cells/mm^3, all of them in rescue scheme. Half of these patients were knowingly dead by the end of this study. Most severe presentations of esophagitis were in patients with greater immunologic compromise (Table 2).

Eighteen (45%) patients were taking antibiotics. Most of them were HIV positive (94.4%), and of this total 81% were in anti-retroviral therapy. Eight (20%) out of the HIV positive had previously used fluconazole.

Two cases of species association were detected: *C. albicans* with *C. krusei* and *C. glabrata* with *C. tropicalis*. The last case was a recurrence of EC, when the previous isolated agent was *C. albicans*.

Fluconazole resistance was observed in six (14.28%) samples, while dose-depending susceptibility occurred in two (4.76%). When two species were associated, one of them was resistant to this drug. Three (50%) out of the patients resistant to fluconazole had used this drug in the past, whereas no previous use of any kind of azoles was reported by the patients with dose-depending susceptibility.

DISCUSSION

A worldwide survey during the 90s showed that among all patients submitted to upper endoscopy EC frequency ranged from 1% to 8%[8]. In 2003, UNDERWOOD et al.[29] found that from the total of patients submitted to endoscopy during 1 year, 18 (0.8%) had EC. Likewise, in Argentina in 2005[21], 34 (2.6%) of such patients were found to have EC.

"Oswaldo Cruz" University Hospital is a reference unit for infectious diseases, oncology, hepatopathy, internal medicine and pneumology. This is probably the reason why a large number of EC patients were referred to endoscopy. In addition, considering that inpatients accounted for 65% of the subjects in this study, there was also a greater possibility that immunocompromised patients under antibiotics or steroid use were submitted to this exam. Moreover, previous knowledge of this study by the

TABLE 1. Case description according to age, predisposing factors, previous use of fluconazole, CD4 count, esophagitis degree, isolated species in culture and fluconazole susceptibility testing for each sample

Sample	Age (years)	Predisposing factors	CD4 count	Wilcox grading esophagitis	Isolated species	Response to fluconazole	Fluconazole use
1	33	HIV, CS, **ATB**	-	I	*C. tropicalis*	R	+
2	23	HIV, ATB	320	II	*C. albicans*	S	-
3	79	DM	-	I	*C. tropicalis*	S	-
4	32	HIV, ATB	34	II	*C. albicans*	S	-
5	68	DM	-	I	*C. albicans*	S	-
6	42	DM, CS	-	I	*C. albicans*	S	-
7	21	-	-	II	*C. tropicalis*	S	-
8	52	CLD , **CS**	-	II	*C. tropicalis*	DDS	-
9	38	HIV	93	I	*C. albicans*	S	-
10	41	HIV, ATB	282	II	*C. albicans*	S	-
11	30	HIV, ATB	43	IV	*C. albicans*	S	-
12	50	HIV, ATB	249	I	*C. albicans*	DDS	-
13	84	-	-	I	*C. tropicalis*	S	-
14	34	HIV, ATB	-	I	*C. albicans*	S	+
15	41	HIV, ATB	282	III	*C. tropicalis*	S	+
					C. glabrata	R	
16	24	HIV, ATB	10	II	*C. albicans*	S	+
17	64	-	-	I	*C. tropicalis*	S	-
18	39	HIV, ATB	91	III	*C. tropicalis*	R	+
19	-	HIV	-	I	*C. albicans*	S	-
20	43	CS	-	III	*C. albicans*	S	-
21	42	HIV, ATB	-	I	*C. glabrata*	S	-
22	60	DM	-	I	*C. tropicalis*	S	-
23	43	HIV, ATB	17	III	*C. albicans*	S	-
24	32	HIV, ATB	-	I	*C. albicans*	S	-
25	57	HIV	-	III	*C. albicans*	S	-
26	82	DM	-	I	*C. glabrata*	R	-
27	77	CLD	-	I	*C. krusei*	R	-
					C. albicans	S	
28	45	HIV	-	IV	*C. albicans*	S	-
29	64	Neoplasia	-	II	*C. albicans*	S	-
30	25	HIV, ATB	213	I	*C. albicans*	S	+
31	73	CLD	-	I	*C. albicans*	S	-
32	61	CS	-	I	*C. albicans*	S	-
33	35	HIV, ATB	161	II	*C. albicans*	R	+
34	70	CS	-	I	*C. albicans*	S	-
35	55	DM	-	I	*C. albicans*	S	-
36	54	Neoplasia	-	II	*C. albicans*	S	-
37	41	HIV, ATB	13	III	*C. albicans*	S	+
38	42	HIV, ATB	400	II	*C.parapsilosis*	S	-
39	44	CS, ATB	-	I	*C. albicans*	S	-
40	76	-	-	I	*C. albicans*	S	-

HIV = human immunodeficiency syndrome virus infection; DM = diabetes mellitus; ATB = antibiotics use; CE = corticosteroids use; CLD = chronic liver disease; S = susceptible; R = resistant; DDS = dose-depending susceptibility

TABLE 2. Patients distribution according to endoscopic findings, infection by HIV and CD4 count

EC grading	HIV positive						HIV negative		Total	
	CD4<200		CD4≥200		Unkown CD4					
	n	%	n	%	n	%	n	%	n	%
Wilcox 1-2	4	50	5	83.3	5	71.4	18	94.7	32	80
Wilcox 3-4	4	50	1	16.7	2	28.6	1	5.3	8	20
TOTAL	8	20	6	15	7	17.5	19	47.5	40	100

greater intensity of endoscopic findings. WERNECK-SILVA and PRADO[32], in 2007, however, did not support this observation. On the other hand, MOCROFT et al.[19], in 2005, found that HIV medical staff might have contributed to an increase in referrals for acknowledgement of digestive complaints, especially those of patients refractory to clinical treatment. The frequency of 1.5% of EC found in this study was relatively low, although within the expected variation mentioned in most recent publications.

AIDS patients represented over half the cases. Most severe forms of EC were more frequent in patients with greater immunologic compromise, expressed by CD4 count below 200 cells/mm^3. This fact may suggest that the more severe are the endoscopic findings, the more intensive is the magnitude of immunodepression.

However, most HIV patients with CD4 count below 200 were also in use of antibiotics, which might have contributed to a

positive patients had a decline in EC frequency once immunity was restored by use of anti-retroviral drugs. Comparative studies with appropriate samples are needed to investigate the accuracy of this observation.

The endoscopic finding of EC in patients without digestive complaints must be valued. In this study, among the five asymptomatic patients, three had diabetes and one had neoplasm. Glycemic control in diabetic patients may help or even resolve esophageal infection[29]. On bearers of neoplasm, EC might represent a progressive immunity decline. A case-control study settled in the United Kingdom found out that 70% of EC patients aged over 65 were submitted to endoscopy due to weight loss and anemia. The authors concluded this to be a limited survival marker, since elders tend to naturally loose their innate immunity[31]. Once EC is found in patients with possibilities of recovering their immunity conditions, this may lead to indicate the need for correction of the predisposing factors. However, in patients whose immunity might not be restored, EC could represent a poor prognosis marker. This might also be valid for HIV positive patients with inadequate response to potent anti-retroviral therapy. Half of the patients with CD4 count below 200 from our series were knowingly dead by the end of this study. This outcome also matches that of a study done by MACROFT et al.[19], which indicates short life expectancy for patients with EC and low levels of CD4.

REDAH et al.[24] reported a high endoscopic yield for the endoscopic diagnosis of *C. albicans*, detecting sensitivity, specificity, positive and negative predictive values of 100%, 83%, 88% and 100%, respectively. They emphasize, however, the importance of identifying species for better characterization of the diseases' behavior. LYMAN et al.[15] also studied the importance of identifying *Candida* species involved, since the in vivo response to fluconazole is related to its in vitro response as well as to its mucosa adhesion ability.

Eight (20%) samples in this study would have been improperly treated if the endoscopic aspect was the only one considered, that is, samples that showed to be resistant or to have dose-depending susceptibility to fluconazole.

Table 2 shows patients' distribution according to endocopic findings, infection by HIV and CD4 count.

Candida albicans frequency amongst HIV positive patients in this study (77.3%) is coincident with that found in the literature, which describes *C. albicans* as the most frequently identified agent in esophageal disease, varying from 42% to 79% of the infected patients[20]. Non-*albicans Candida* species were found in 22.7% HIV-positive and in 45% uninfected patients. Hence, the last group hosted almost twice as much the amount of non-*albicans* species as the first group. There was no statistically significant difference between them, probably due to the reduced size of the sample.

The pattern of species association described in this study may have clinical implications due to empirical treatment with fluconazole. The latter may have eradicated the species susceptible to the drug, namely, *albicans* and *tropicalis,* thus tending to perpetrate esophageal infection through selective growth of *krusei* and *glabrata* species, which are both resistant, in vitro, to fluconazole.

The drug of choice for EC treatment is fluconazole[3, 7, 23, 26, 30]. Studies have demonstrated that fluconazole prophylaxis reduces the chances of both colonization and invasive fungi infections in high risk patients[4]. However, randomized clinical assay evidences suggest that its use increases the risk for colonization by resistant, dose-depending susceptible[4, 27, 30] and non-*albicans* species[4].

In this series of cases, fluconazole resistance occurred in six (14%) samples and dose-depending susceptibility in two (4%). Half the patients who presented drug resistance related previous fluconazole use, which is considered the most important factor for this outcome[4, 14]. Most were HIV positive under 50 years of age, and CD4 count <200 was found in 34%, which also might sign a possible indicator for resistance[14].

Two (66.7%) out of three patients who had previously used fluconazole in this study had non-*albicans* species. An increase in colonization by non-*albicans* species was demonstrated by BRION et al.[4] in a systematic review of randomized clinical assays.

Resistance to fluconazole found by GOLDMAN et al.[10] was 4.1% in patients on continuous and 4.3% on sporadic fluconazole intake. All patients had a CD4 count <150 and both groups showed no difference in overall survival rates. Hence, fluconazole resistance in this study represents almost three and a half times the rates found in the literature review.

Despite the high frequency of resistance found, one should not diminish the role of fluconazole in EC treatment. Patients without previous episode of EC or without previous use of fluconazole, immunocompromised or not, will possibly respond well to this drug, since the proper management of existing predisposing factors is provided.

In cases of recurrence of the esophageal infection, species identification and susceptibility testing for fluconazole are indicated. Both measures might indicate distinct approaches to conduct the disease. In case of resistant species, another drug therapy will be needed. Fluconazole, however, remains useful in dose-depending susceptibility, in which case only the dose adjustment will be enough to resolve EC.

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RESUMO – ***Contexto*** - A candidíase esofágica é comumente observada em pacientes com fatores de risco para seu desenvolvimento. ***Objetivos*** - Determinar a freqüência da candidíase esofágica, por meio da endoscopia digestiva alta; identificar as espécies de *Candida* envolvidas na patogênese da candidíase esofágica e sua distribuição de acordo com o fator predisponente; determinar a susceptibilidade ao fluconazol nas amostras coletadas. ***Métodos*** - De março de 2006 a abril de 2007, os pacientes submetidos a esofagogastroduodenoscopia no Hospital Universitário Oswaldo Cruz, Recife, PE, foram considerados elegíveis para o estudo. Aqueles que apresentaram lesões compatíveis com candidíase esofágica tiveram amostras coletadas para a identificação das espécies de *Candida*, de sua sensibilidade ao fluconazol e descritos os fatores de risco para a doença. ***Resultados*** - Dos 2.672 pacientes encaminhados para endoscopia, 40 (1,5%) apresentaram achados compatíveis com candidíase esofágica. A média de idade foi de 49,1 anos. Vinte e um pacientes (52,5%) tinham menos que 50 anos, dos quais 82,6% eram infectados pelo HIV. A maioria (52,5%) era homens e 65,0% encontravam-se internados. Fatores predisponentes foram identificados em 90% da amostra, sendo que 21 (52,5%) eram HIV positivos. As formas mais graves de esofagite foram encontradas em 50% dos pacientes com CD4 <200. Espécies de *Candida* não-*albicans* foram detectadas em 22,7% dos pacientes HIV positivos e em 45% dos pacientes não infectados. A resistência ao fluconazol foi observada em seis amostras (14,28%) e a sensibilidade dose-dependente em duas (4,76%). ***Conclusão*** - A prevalência de candidíase esofágica foi baixa, embora dentro de variação esperada. Pacientes homens e que estavam internados foram os mais acometidos. Houve variação nas espécies encontradas, de acordo com as características dos grupos estudados. Tanto a resistência ao fluconazol como a sensibilidade dose-dependente foram consideradas altas.

DESCRITORES - Candidíase. Esofagiopatias. Fluconazol. Farmacorresistência fúngica.

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