Original Article

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Microbiology Section

Fluconazole Resistant *Candida* Oesophagitis in Immunocompetent Patients: Is Empirical Therapy Justifiable?

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ABSTRACT

Introduction: *C. albicans* (*Candida albicans)* is the foremost cause of fungal oesophagitis, however other species such as *Candida tropicalis, Candida krusei* and *Candida stellatoidea* have also been implicated to cause this condition. Although, numerous studies have identified risk factors for *C. albicans* oesophagitis, data for non- *C. albicans* species is still sparse.

Aim: To determine the aetiology of *Candida* oesophagitis in our medical centre over a two year period. Additionally, to investigate predisposing conditions for oesophageal candidiasis caused by different *Candida* species.

Material and Methods: All consecutive patients posted for upper gastrointestinal endoscopy at the endoscopy unit of a tertiary care hospital in north India with findings consistent with oesophagitis were screened for the presence of *Candida* oesophagitis by performing KOH (potassium hydroxide) examination and culture on SDA (Sabouraud's dextrose agar). Antifungal susceptibility testing as per CLSI guidelines was performed for fluconazole, a most common empirically prescribed antifungal for the condition.

Results: A total of 1868 patients with no known immune-compromised condition underwent upper gastroscopy at our centre during the study period. The prevalence of *Candida* oesophagitis was 8.7% (n = 163). *C. albicans* was recovered from majority of infections (52.1%), followed by *C. tropicalis* (24%), *C. parapsilosis* (13.4%), *C. glabrata* (6.9%) and *C.* krusei (3.6%). Alarmingly, among the *C. albicans* isolates 8.6% were resistant to fluconazole.

Conclusion: With rising reports of antifungal drug resistance among the isolates of *Candida* species, an increasing prevalence of this organism could have an impact on the treatment of *Candida*l oesophagitis and it should be approached with caution by the clinician.

Keywords: Antifungal susceptibility testing, Acid suppression therapy, Candidiasis

INTRODUCTION

Candida oesophagitis (OC) although, in the absence of predisposing factors is mainly a disease of the old age, possibly related to oesophageal dysmotility disorders, immune-suppression or defective carbohydrate metabolism. This disease is mostly observed in the immune-compromised host especially the debilitated patients who have received broad-spectrum antibiotics, corticosteroids or immune-suppressants [1,2]. However, with the improvement in flexible endoscopes and increase in its use, direct visualization and sample collection has become easier, and thus the diagnosis of new cases has enhanced [3]. The National Hospital Discharge Survey reports a rise in rates of oro-pharyngeal candidiasis by more than 4-fold between 1980 and 1989 in the United States [4].

Although *C. albicans* (*Candida albicans)* is the most common species implicated in *Candida* oesophagitis other *Candida* species like *C. glabrata (Candida glabrata), C. parapsilosis (Candida parapsilosis)*, *C. krusei (Candida krusei), C. stellatoideae* (*Candida stellatoideae)* and *C. tropicalis (Candida tropicalis)* are often reported to be the causative agents [5]. With growing concerns about the emerging resistance to azoles among *C. albicans* species, varying susceptibility among the non-albicans species huge importance is being attached to species and drug susceptibility profile of *Candida* [6].

Although, *Candida* oesophagitis is a well known entity worldwide but still the published Indian data evaluating OC is scarce. In addition, very little is known about infections caused by species other than *C. albicans.*

MATERIALS AND METHODS

In this descriptive study we have attempted to document the prevalence of *Candida* oesophagitis, predisposing factors, species distribution and susceptibility profile of isolated species over a 24-month period from January 2011 till December 2013 in a single medical centre. Patients posted for upper gastrointestinal endoscopy at the endoscopy unit of a tertiary care hospital in north India during two year period with findings consistent with *Candida* oesophagitis were included in the study. The study protocol was approved by the institutional ethics committee and proper informed consent was recorded from each of the recruited patients.

A presumptive case of *Candida* oesophagitis was defined as a patient who had whitish plagues adhered to the mucosa of oesophagus on biopsy, a finding suggestive of *Candida* oesophagitis. Recurrence of *Candida* oesophagitis in the same patient was defined as a new episode of *Candida* oesophagitis one month after the remission and was considered as a new case.

Direct microscopy was done after keeping the tissue in 10% KOH solution overnight. Samples were inoculated on SDA with chlor-amphenicol (50mg/L) to prevent bacterial growth and additionally on Hi-Chrom *Candida* differential agar (CHROM agar) to improvise species identification, based on colored colony morphology. SDA slants and CHROM agar plates were incubated under 37°C for 48 hours. Isolates were further characterized by observing corn meal agar for chlamydospore production refining previous tests obtained with chromogenic media. Identification tests like germ tube test, sugar assimilation profile and sugar fermentation tests were employed for species identification. Differential growth on SDA at 37°C and 42°C for delineation of *C. albicans* from *Candida dubliniensis* was also performed.

The recovered *Candida* isolates were further purified in distilled water and subjected to antifungal susceptibility testing using commercially procured antifungal discs of fluconazole (Hi- media), as per standard CLSI guidelines (document M- 44A). For interpretation of sensitivity or resistance, zone size recommended by disc manufacturers was taken into consideration. A fluconazole disc of 25 µg was used. Standard ATCC strains, viz. *C. albicans* ATCC 90028, *C. parapsilosis*

22019 and *C. krusei* 6258 were used as control. Isolates resistant to fluconazole by disc diffusion method were further tested by broth macrodilution method as per CLSI guidelines (M27 A2) using fluconazole powder procured from Sigma-Aldrich.

RESULTS

Of 1868 patients referred to the endoscopy unit during the study period, 163 (8.7%) had findings compatible with *Candida* oesophagitis. Ages ranged from 24 years to 92 years, with a mean of 62 years, 95 (58.2%) of them were elderly. Hundred and ten patients (67.4%) were male and 53 (32.5%) females. *Candida* oesophagitis episodes were more frequent among elderly males (n=82, 50.3%).

Most common symptoms were heartburn (47.6%), odynophagia (23.1%), nausea and vomiting (16.4%) and (11.6%) patients were asymptomatic with the indication of endoscopy being malignancy, diabetes, long term steroid use etc. [Table/Fig-1] depicts the co-morbidities associated with the development of *Candida* oesophagitis in our study. The most frequent co morbidities were old age (63/95, 66.3%), COPD (Chronic obstructive pulmonary disease) (12/34, 35.3%), diabetes mellitus (6/14,43%), malignancies (0/1), chronic liver disease (0/2). It was noted that not even a single patient of gastro-oesophageal reflux disease had features of *Candida* oesophagitis.

[Table/Fig-2] shows the associations of the risk factors with the *Candida* oesophagitis. The putative conditions posing a risk of *Candida* oesophagitis were antibiotic usage (62/100, 62%), alcohol intake (4/16, 25%), acid suppression therapy (32/55, 58.2%) smoking (12/55, 21.8%), and inhaled steroid intake (15/22, 68.2%). Twelve of our patients had oesophageal dysmotility disorders and one patient was HIV positive. *C. albicans* (n=85; 52.1%) was the species most often isolated from biopsy samples, followed by *C. tropicalis* (n=39; 24%), *C. parapsilosis* (n=22; 13.4%), *C. glabrata* (n=11;6.9%,) and *C. krusei* (n=6, 3.6%).

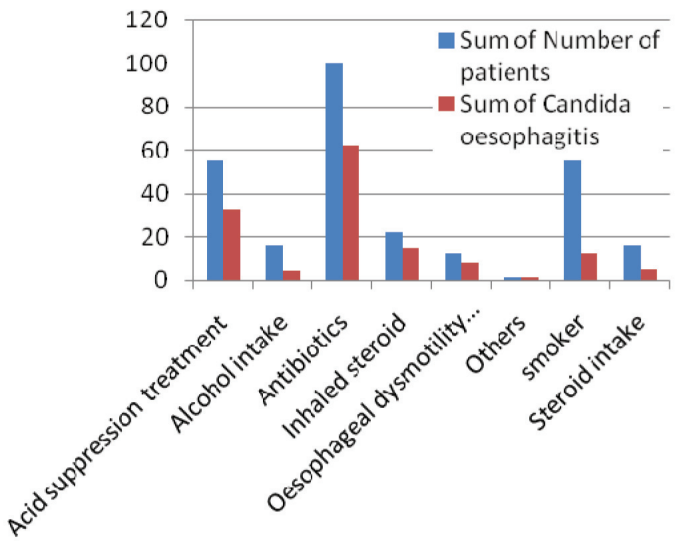
The results of in vitro antifungal susceptibility testing performed by Disc Diffusion technique on the recovered isolates revealed that 8.6% (13 out of 163) of the isolates were resistant to fluconazole [Table/Fig-3]. An alarming finding was that 50% of the isolates of *C. krusei* were resistant to fluconazole. Whereas resistance among other species varied, with 5/11 (45.4%) of isolates of *C. glabrata,* 1/39 (2.5%) and 3/85 (3.5%) isolates each of *C. tropicalis* and *C. albicans* respectively being resistant to fluconazole. Antifungal susceptibility testing of the resistant isolates by broth macrodilution method revealed 100% concordance with disc diffusion method except in case of one isolate of *C. parapsilosis* which was sensitive by disc diffusion method but resistant by broth macrodilution method.

DISCUSSION

Our study highlights the finding that *Candida* oesophagitis previously reported in immunocompromised persons is becoming more common among individuals with intact immune system as well. The frequency of *Candida* oesophagitis in this study involving 1868 immune-competent patients submitted to upper gastrointestinal endoscopy was 8.72%. An interesting finding was significant association of the condition in elderly. A possible reason to this may be an increase in oesophageal dysmotility, impairment of immunity or defective carbohydrate metabolism with rising age. Many authors have reported this in their studies and have proposed *Candida* oesophagitis a disease of elderly in the absence of other predisposing factors [7]. The second major association with *Candida* oesophagitis was found to be COPD. As suggested by Kesten et al., it is explained by the fact that patients of COPD during acute exacerbations are put on a combination of antibacterials and inhaled corticosteroids and usage of antibiotics eliminate bacterial competition for nutrients allowing overgrowth of *Candida*, inhaled corticosteroids on the other hand lead to mild immune compromise

Associated conditions	Number of patients	*Candida* oesophagitis
Old age	95	63(66.3%)
COPD	34	12(35.29%)
Reflux disease	29	0
Diabetes	14	6(42.85%)
Malignancy	1	0
Chronic liver disease	2	0

[Table/Fig-1]: Conditions associated with the development of *Candida* oesophagitis
COPD: Chronic obstructive pulmonary disease



[Table/Fig-2]: Risk factors associated with the development of *Candida* oesophagitis

Isolates	Number (%) N=163	Resistance (%) to Fu	
		DD	BM
C. albicans	85(52.1%)	3(3.5%)	3
C. tropicalis	39(24%)	1(2.5%)	1
C. parapsilosis	22(13.4%)	1(4.5%)	2
C.glabrata	11(6.9%)	5(45.4%)	5
C.krusei	6(3.6%)	3(50%)	3

[Table/Fig-3]: Antifungal sensitivity profile of the recovered isolates
Fu= Fluconazole; DD-Disc diffusion;BM-Broth macrodilution

[8]. Interestingly, GERD (Gastro-oesophageal reflux disease) was protective against colonization by *Candida* with none of the patient of GERD developing *Candida* oesophagitis.

We also noted that there was significant association of *Candida* oesophagitis with intake of histamine H2-receptor antagonists or proton pump inhibitors (PPIs) with higher yield in rate of isolation of *Candida* in patients on these medications. One reason for this might be that these agents raise the local pH of the oesophagus and make the environment more conducive to *Candida*l growth. As it is a known fact that gastric acidity is an essential barrier for control of most microorganisms, thus its inhibition can allow a number of infections to occur. In addition omeprazole is known to decrease the salivary secretion which can facilitate the growth of *Candida* in the mouth and can further help in its spread to the stomach [9,10].

In our study the commonest species isolated was *C. albicans* (n=85, 52.1%), followed by *C. tropicalis* (n=39, 24%), *C. parapsilosis* (n-22, 13.4%), *C. glabrata* (n=17, 6.9%) and *C. krusei* (n=6, 3.6%). Similar findings have been reported by authors with *C. albicans* being the commonest species identified in patients with *Candida* oesophagitis world over [11-14]. What is alarming is that 8.6% of our isolates were resistant to fluconazole. As fluconazole is a drug of choice for the treatment of *Candida* oesophagitis, its irrational and empirical use might be the reason of high fluconazole resistance. This is similar to data published in recent years in which azole resistance

has been found to be higher among isolates of *Candida* isolated from *Candida* oesophagitis [12,15].

CONCLUSION

Candida oesophagitis among immunocompetent is becoming a common entity and fluconazole is empirically prescribed in these group of patients. The finding of 8.6% of fluconazole resistance among the *Candida* isolates in the present study underscores the importance of routine testing of antifungal susceptibility among *Candida* oesophagitis patients. Other antifungals like ketoconazole and voiconazole which could not be included in the present study due to financial constraints should also be tested for efficacy against the resistant isolates.

REFERENCES

[1] Baher PH, McDonald GB. Oesophageal infections: risk factors, presentation, diagnosis, and treatment. *Gastroenterology.* 1994;106:509-32.
[2] Simon MR, Houser WL, Smith KA, *et al*. Oesophageal candidiasis as a complication of inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 1997;79:333-38.
[3] McCloy RF. Endoscopy. *Curr Opin Gastroenterol*. 1987;3:967-70.
[4] Banerjee SN, Emori TG, Culver DH, Gaynes RP, Jarvis WR, Horan T, et al. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. National Nosocomial Infections Surveillance System. *Am J Med.* 1991;91:86S–89S.
[5] Naito Y, Yoshikawa T, Oyamada H, et al. Oesophageal candidiasis. *Gastroent Jap.* 1988;23:363-70.
[6] Kotwal A, Biswas D, Sharma JP, Gupta A, Jindal P. An observational study on the epidemiological and mycological profile of Candidemia in ICU patients. *Med Sci Monit.* 2011;17(11):663-68.
[7] Weerasuriya N, Snape J. *Candida* oesophagitis in elderly patients: risk factors, prevention and management. *Drugs Aging*. 2008;25(2):119-30.
[8] Kesten S, Hyland RH, Pruzanski WR, Kortan PP. Oesophageal candidiasis associated with beclomethasone dipropionate aerosol therapy. *Drug Intell Clin Pharm*. 1988;22(7-8):568-69.
[9] Karmeli Y, Stalnikowitz R, Eliakim R, Rahav G. Conventional dose of omeprazole alters gastric flora. *Dig Dis Sci.* 1995;40:2070-73.
[10] Kochhar R, Talwar P, Singh S, Mehta SK. Invasive candidiasis following cimetidine therapy. *Am J Gastroenterol.* 1988;83:102-03.
[11] Kliemann DA, Pasqualotto AC, Falavigna M, Giaretta T, Severo LC. *Candida* oesophagitis: species distribution and risk factors for infection. *Rev Inst Med trop S Paulo*. 2008;50(5):261-63.
[12] Maninder J, Usha AJ. Isolation, characterization and antifungal susceptibility pattern of *Candida* species causing oropharyngeal candidiasis in HIV positive patients. *Commun Dis*. 2008;40(3):177-81.
[13] Lunel FV, Koeleman JG, Spanjaard L, et al. Trends in fungaemia and antifungal susceptibility in the Netherlands. *Neth J Med*. 2006;64(7):236–42.
[14] Narain S. Neonatal systemic Candidiasis in a tertiary care center. *Ind J Med Microbiol*. 2003;21:56–58.
[15] Nadagir SD, Chunchanur SK, Halesh LH, Yasmeen K, Chandrasekhar MR, Patil BS. Significance of isolation and drug susceptibility testing of non-*Candida* albicans species causing oropharyngeal candidiasis in HIV patients. *Southeast Asian J Trop Med Public Health*. 2008;39(3):492-95.

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