Original Article

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Esophageal Candidiasis: Causative Species and their Antifungal Susceptibility Pattern in Hospital of Western U.P.

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Abstract

Esophageal candidiasis is more commonly presented in persons with immunocompromised conditions but it can also be seen in immunocompetent patients. There has been an epidemiological shift towards the predominance of candida spp. other than C.albicans such as C. glabrata C. parapsilosis, C. krusei, C. tropicalis, C. dubliensis etc. accounting for more than 50% of the Candida infections. The rampant misuse of antifungals has increased the antifungal resistance among C.albicans as well as non-albicans species and poses a challenge to clinicians for the management of such cases. The current study was aimed to understand the isolation of various Candida spp. in patients diagnosed with esophageal candidiasis attending a tertiary care center in western U.P. and to analyse its association with various predisposing factors. This study also extends to determine the susceptibility pattern of the isolated candida spp. against different antifungal agents. The study was conducted for 3 years in the hospital of western U.P. North India from July 2017 to June 2020. Candidial esophagitis was suspected when in endoscopy, whitish plaques are seen attached to the mucosa and these plaques were collected using biopsy forceps and sent to the microbiology laboratory for its fungal culture and speciation. In the current study, 60.1% were Candida albicans while 39.9% were other candida spp. Among NAC, the commonest species was C. parapsilosis (14.1%) followed by C. dubliensis (9.2%), C. glabrata (8.6%), C. tropicalis (4.9%) and C. krusei (3.1%). All isolates were found sensitive to AmphotericinB, however 3.1% of the isolates were resistant to Voriconazole and 7.4% to fluconazole. Fluconazole resistance is a serious issue as it is considered the drug of choice in cases with esophageal candidiasis. Such studies help clinicians to select appropriate antifungals for these patients and reduces patient's morbidity and mortality.

Keywords: Antifungal susceptibility, Esophageal Candidiasis, Candida albicans, Non-albicans candida.

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Introduction:

Hospital-acquired infections (HAI) due to Candida species are increasing since the 1980s, increasing morbidity and mortality rates along with an increase in hospital stay thereby increasing the overall treatment cost of the patients. Candida species can cause a variety of infections ranging from superficial, mucosal infections to complicated systemic infections like endocarditis, peritonitis, candidemia, systemic candidiasis etc.[1] Esophageal candidiasis (EC) was first observed in 1839 in a typhoid fever patient who later succumbed to his illness.[2] Esophageal candidiasis is more commonly presented in persons with immunocompromised conditions including persons suffering from AIDS, patients on chemotherapy or/and radiotherapy, organ transplantation, long-term steroid therapy or antibiotics, diabetes mellitus, intensive care unit (ICU) patients with various indwelling devices.[3,4] However, it is not a rare site to see EC in immunocompetent patients.[5,6]

The diagnosis of EC has improved drastically in recent decades due to the increased availability of flexible endoscopes and samples that can be obtained directly from the esophagus.[7,8] Fungal infections are mostly caused by C. albicans, however there has been an epidemiological shift in recent years and now non-albicans candida spp. (NACs) such as C. glabrata, C. parapsilosis, C. pseudotropicalis, C. vishwanathi, C.kefyr, C. dubliensis etc. accounting for above fifty percent of the total Candida infections.[9] EC is mostly treated using Fluconazole as it is safe, well-tolerated and produces a rapid clinical response.[10,11] However, species identification is extremely important to identify various strains of candida; as some strains are intrinsically resistant to certain antifungals like C. krusei for fluconazole.[12] The rampant misuse of antifungals has

increased the antifungal resistance among C.albicans as well as non-albicans species and pose a challenge to clinicians for the management of such cases.[13] The current study was aimed to understand the isolation of various Candida spp. in patients diagnosed with esophageal candidiasis attending a tertiary care center in western U.P. and to analyse its association with various predisposing factors. This study also extends to determine the resistance pattern of the various candida spp. isolated against common antifungals.

Subjects and Methods

A prospective observational study was carried out for 3 years in the hospital of western U.P. North India from July 2017 to June 2020. Candidial esophagitis was suspected when in endoscopy, whitish plaques are seen attached to the mucosa and these plaques were collected using biopsy forceps and sent to the microbiology laboratory for its fungal culture and speciation. All the patients included in the study were informed regarding the same and Informed consent was taken.

Sample processing

The collected sample was further processed and a wet mount was prepared for the appearance of budding yeast cells with or without pseudohyphae and cultured on Sabouraud Dextrose agar slants. Isolated colonies were identified based on cultural characteristics, gram stain, Reynold Braude phenomena, growth on chromogenic medium (CHROMagar), biochemical reactions in sugar fermentation and sugar assimilation test.[14] Antifungal drug testing of candida was done according to CLSI M 44A standards. Antifungals tested were fluconazole (25μg), voriconazole (1μg), and Amphotericin B (100 μg) procured from HiMedia laboratories, Mumbai. Confirmation of results was done by Minimum Inhibitory Concentration (MIC) using E- test as per manufacturer instructions. The incidence of various candida spp. was identified in frequency and percentage. Statistical analysis was done using recent SPSS software version 16.0 (IBMCorp., Armonk, NY, United States of America).

Results

10,256 patients uderwent upper GI endoscopy in the department of gastroenterology for three years of which a total of 163 cases (1.6%) of esophageal candidiasis were detected. Out of these, 60.1% were Candida albicans while 39.9% were non-albicans candida. Esophageal candidiasis was more commonly seen in males (55.83%) compared to females (44.17%). The commonest age group affected was 31-40 yrs (25.8%) followed by 41-50 yrs (23.9%) and 21-30 yrs (15.9%) with a mean age of 38 yrs as shown in [Table 1]. In our study the most common underlying risk factor for EC was chronic liver disease responsible for 30% of cases followed by diabetes mellitus (20.2%), prolonged use of antibiotics (14.1%) and usage of steroid inhalers (4.9%) as shown in [Table 2]. Common complaints observed in cases with EC were dyspepsia accounting for 53.9%, dysphagia contributing to 48.5% cases followed by odynophagia (21.9%) as shown in [Table 3].

In the present study, 39.9% of cases accounted for non-albicans Candida (NAC). Among NAC, the commonest species isolated was C. parapsilosis (14.1%) followed by C. dubliensis (9.2%), C. glabrata (8.6%), C. tropicalis (4.9%) and C. krusei (3.1%) as shown in [Table 4]. In the current study, Amphotericin B was found sensitive in all cases. However 3.1% and 7.4% of the candida isolates were found resistant to Voriconazole and fluconazole respectively. Resistance to Voriconazole and fluconazole was more common among NAC especially C. dubliensis, C. krusei and C. glabrata compared to C. albicans as shown in [Table 5].

Table 1: Age-wise and sex-wise analysis of various Candida spp. isolated from patients of esophageal candidiasis:

Age group	No. of isolates	Males	Females
≤20 yrs	9 (5.5%)	6	3
21- 30 yrs	26 (15.9%)	19	7
31-40 yrs	42 (25.8%)	24	18
41-50 yrs	39 (23.9%)	23	16
51-60 yrs	25 (15.3%)	9	16
61-70 yrs	14 (8.6%)	5	9
>70 yrs	8(4.9%)	5	3
Total	**163**	**91 (55.83%)**	**72 (44.17%)**

Table 2: Association of esophageal candidiasis with predisposing factors:

Predisposing Factors	No. of patients (n=163)
Chronic Liver Disease	49 (30%)
Diabetes mellitus	33 (20.2%)
Prolonged use of antibiotics	23 (14.1%)
Steroid Inhaler	08 (4.9%)
Hepatitis C	06 (3.7%)
Hepatitis B	04 (2.4%)
Cancer patients	06 (3.7%)
Nil	34 (20.8%)

Table 3: Common complaints found in patients with Esophageal Candidiasis

Chief Complaint	No. of Patients (n-=163)	Percentage
Dyspepsia	88	53.9%
Dysphagia	79	48.5%
Odynophagia	35	21.5%
Other vague complaints	13	7.9%

Table 4: Distribution of various candida spp. in patients with esophageal candidiasis

Etiological agents	No. of isolates	Percentage
C.albicans	98	60.1%
C.parapsilosis	23	14.1%
C.dubliensis	15	9.2%
C.glabrata	14	8.6%
C.tropicalis	08	4.9%
C. krusei	05	3.1%
Total	163	

Table 5: Antifungal Susceptibility of various Candida Isolates

Clinical Isolates	Fluconazole (Flu)		Voriconazole (Vor)		Amphotericin B (Amp B)	
	S	R	S	R	S	R
C.albicans (98)	95 (96.9%)	03(3.06%)	97 (98.9%)	01 (1.1%)	98 (100%)	0 (0%)
C.parapsilosis (23)	23 (100%)	0 (0%)	23 (100%)	0 (0%)	23 (100%)	0 (0%)
C.dubliensis (15)	14 (93.3%)	01 (1.1%)	14 (93.3%)	01 (1.1%)	15 (100%)	0 (0%)
C.glabrata (14)	11 (78.6%)	03(21.4%)	13 (92.8%)	01 (7.1%)	14 (100%)	0 (0%)
C.tropicalis (08)	08 (100%)	0(0%)	08 (100%)	0 (0%)	08 (100%)	0 (0%)
C. krusei (05)	0 (0%)	05 (100%)	03 (60%)	02 (40%)	05 (100%)	0 (0%)
Total (163)	151 (92.6%)	12 (7.4%)	158 (96.9%)	05 (3.1%)	163 (100%)	0%

Discussion

Opportunistic fungal infections, particularly caused by commensal Candida species, have gained serious concern worldwide. Esophageal candidiasis is amongst the most common opportunistic infections in a patient with immunocompromised status. Esophageal candidiasis develops in two steps: colonization and then the invasion of epithelium. Mostly EC remains undiagnosed and after colonization there is the invasion of superficial epithelium of the esophageal wall further progressing to tissue necrosis and later ulceration leading to serious complication of esophageal perforation which is difficult to treat and also dreadful for the patient. In the current study, the prevalence of esophageal candidiasis was 1.6% which is higher compared to Naito et al,[15] and Underwood et al,[16] showing esophageal candidiasis in 0.71% and 1.17% of upper GI endoscopy respectively. Our center is a tertiary center and cases are referred from all nearby areas which might be the reason for the higher prevalence in our study. In the current study, males (55.83%) were more commonly involves as compared to females (44.17%) which are in accordance with findings in other studies.[17,18] In our study, the commonest affected age group was 31-40 yrs (25.8%) followed by 41-50 yrs (23.9%) and 21-30 yrs (15.9%). The same pattern was also observed in another study conducted by Lakshmy et al.[18] This could be due to various factors including the presence of immunocompromised patients, diabetes mellitus, liver diseases, use of antibiotics, steroids etc.

In our study the most common underlying risk factor for EC was chronic liver disease observed in 30% of cases followed by diabetes mellitus (20.2%), prolonged use of antibiotics (14.1%), usage of steroid inhalers (4.9%), associated malignancy (3.7%) and chronic Hep C infection (3.7%). In a related study held by Choi JH et al,[3] Diabetes mellitus and malignancy were the most common concomitant

diseases associated with esophageal candidiasis. Diabetes mellitus is an important risk factor associated with esophageal candidiasis due to impaired immunity and stasis of esophageal contents in the esophagus. In our study, dyspepsia was the most common complaint accounting for 53.9% followed by dysphagia (48.5%) and odynophagia (21.9%). However a similar study conducted by Choi JH et al,[3] showed dyspepsia in 13.5% of cases and in 12% of cases typical esophageal symptoms like dysphagia and odynophagia were observed. Many cases of EC are missed as they do not have any symptoms and we might find EC as an incidental finding, many patients can also present with complications like hemorrhage or perforation making it a life-threatening event.

Candida albicans was the leading pathogen accounting for 60.1% of yeast infection compared to NACs similar to the studies conducted by Nadagir SD et al,[19] and Baradkar VP et al,[20] showing Candida albicans in 66.6% and 70% of cases respectively. However the isolation of C. Albicans was much higher in other studies like Sajith et al,[21] (97.4%) and Badarinarayanan et al,[22] (87.5%). In the present study, 39.9% of cases accounted for non-albicans Candida (NAC). Among NAC, the most common species were C. parapsilosis (14.1%) followed by C. dubliensis (9.2%), C. glabrata (8.6%), C. tropicalis (4.9%) and C. krusei (3.1%). In another study conducted by Kakati B et al, the commonest species isolated was C. Albicans accounting for 52.1% followed by C. tropicalis (24%), C. parapsilosis (13.4%) and C. glabrata (6.9%).[23] However the most alarming finding in our study was that 7.4% of our cases were resistant to fluconazole. Other studies also showed resistance to fluconazole (8.6% cases).[23] Fluconazole resistance is a serious issue as it is considered the drug of choice in cases with esophageal candidiasis and this high resistance could be due to its empirical and irrational use. A high level of resistance to commonly used antifungals in these species poses a serious threat for society as well as clinicians in treating such patients. Also certain species like C. krusei and C.glabrata are found inherently resistant to common azoles like fluconazole. Increasing resistances of candididiasis against common azoles have also been reported in many articles published in a decade.[19,24]

Many new and advanced antifungal agents have been introduced in recent decades and their efficacy, effectiveness and sensitivity to treat fungal infections is required. Hence antifungal sensitivity testing is important in an isolated strain of candida for better management of patients. In our study, all isolates were sensitive AmphotericinB was found sensitive in all the isolates. Voriconazole was found more effective compared to itraconazole and fluconazole, but voriconazole resistance is also seen in many isolates due to cross-resistance with other azoles.

Conclusion

Esophageal candidiasis incidence has been increased throughout the world especially among immunocompromised patients. C.albicans is the common isolate in our hospital; however the incidence of NAC has also increased considerably. The NAC species has changes in their sensitivity pattern to various antifungal agents used commonly in clinical practice which is a common cause of concern. Thus it is important for both clinicians and microbiologists to be vigilant and contribute to the proper implementation of antifungal therapy and the antifungals should be used judiciously to prevent resistance against common antifungals.

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