Original Article

Comparative evaluation of prevalence and phenotypic variations of *Candida* species in patients of oral lichen planus and oral lichenoid lesions with healthy individuals - A prospective microbiological study

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Abstract

Context: *Candida* isolates might exaggerate the development and advancement of oral lichen planus (OLP) alone or together with other factors. There is a differing pathogenic potential of various *Candida* species. Since *Candida* species isolated from OLP and oral lichenoid lesions (OLL) have shown to be resistant to commonly used antifungal agents, identification of *Candida* species may play a pivotal role in its successful clinical management.

Aim: The aim of the study was to evaluate and compare the prevalence and phenotypic variations of *Candida* species in patients of OLP and OLL with healthy controls.

Subjects and Methods: This prospective microbiological study was conducted in the institution using indirect microscopic examination. The sample comprised of 40 clinicohistopathologically diagnosed cases of the study group (OLP and OLL) and 40 cases of control group (healthy individuals).

Statistical Analysis Used: The data collected was statistically analyzed using the Chi-square test and Fisher's exact test with the SPSS 20.00 software.

Results: The prevalence of *Candida albicans* was higher in the control group (28.10%) as compared to the study group (24.60%) and this difference was statistically significant. An increased frequency of non *C. albicans* species was seen in the study group, in decreasing order of *Candida glabrata* (40.70%), *Candida tropicalis* (22.20%), *Candida krusei* (22.20%) and *Candida guilliermondii* (3.70%), as compared to the control group.

Conclusion: Non *C. albicans* species were the predominant pathogens associated with the study (OLP + OLL) group. It is important to identify the infecting strains of *Candida* because isolates of *Candida* species differ widely, both in their ability to cause infection and also in their susceptibility of resistance to antifungal agents. Thus, phenotypic speciation of *Candida* is emerging as a necessary trend to highlight the need of administering appropriate antifungal therapy.

Keywords: Antifungal agents, *Candida albicans*, non-*Candida albicans*, oral lichen planus, oral lichenoid lesion

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INTRODUCTION

Oral lichen planus (OLP) is a T-cell mediated chronic inflammatory disorder of unknown etiology. The World Wide prevalence of OLP is approximately 2.2%[1] and in India, it is 2.6%.[2] OLP most commonly occurs at 30–80 years of age, with a female predilection. Two-thirds of OLP patients experience discomfort on having spicy and acidic foods.[3] There are varieties of lesions that resemble OLP, both clinically and histopathologically, which are referred to as oral lichenoid lesions (OLL).[4] If epithelial dysplasia is seen on initial diagnosis in cases of OLP and OLL, then, it is called as an oral lichenoid dysplasia (OLD). The overall rate of malignant transformation of OLP and OLL is reported to be 1.09% and 3.2%, respectively.[5] *Candida* isolates might exaggerate the development and advancement of OLP alone or together with other factors.[6] Besides *Candida albicans*, Non-*C. albicans* strains, such as *Candida parapsilosis*, *Candida tropicalis*, *C. dubliniensis*, *Candida krusei* and *Candida glabrata*, are frequently detected in OLP and OLL.[6-13] Various studies are done which have shown that there is a differing capability of various strains to promote dysplasia by catalyzing the production of nitrosamine (carcinogenic) and also because of metabolism of ethanol to the carcinogenic acetaldehyde and induction of proinflammatory cytokines.[14] As there is a differing pathogenic potential of various *Candida* species, identification of species may play a pivotal role in successful clinical management. Furthermore, Non-*C. albicans* species isolated from OLP lesions have shown to be resistant to commonly used antifungal agents.[7] Thus, the following study was undertaken to comparatively evaluate the phenotypic variation of Candida species in patients of OLP and OLL with healthy individuals using indirect microscopic examination.

SUBJECTS AND METHODS

This prospective study was carried out from December 2018 to December 2019 in the Department of Oral and Maxillofacial Pathology and Microbiology.

All the individuals visiting the institution were clinically screened for OLP and OLL, and biopsy sample was obtained after an informed consent. The sample comprised 40 clinicohistopathologically diagnosed cases of OLP and OLL (study group), using modified WHO criteria 2003[1] and 40 clinically diagnosed cases of healthy individuals (control group).

All the individuals were assessed clinicopathologically and confirmed cases of OLP and OLL were chosen for the study. During the conduct of the study, all human ethical principles as per the World Medical Association-Declaration of Helsinki and the guidelines of Good Clinical Practice (ICMR) were observed. The Institutional Ethical Committee approval was taken (MGM/DCH/IERC/11/2017), and an informed consent was obtained from all individuals participating in the study.

Before tissue sampling under aseptic conditions, a swab of the respective area was taken using a disposable swab stick [Figure 1]. The swab sample collected was immediately inoculated on Sabouraud's dextrose agar (SDA) medium (HiMedia). After getting positive cultures [Figure 2], a small inoculum was incubated in serum at 37°C for about 3 h, and a few drops of the suspension were then examined under light microscope to observe germ tube (GT) formation [Figure 3] for the detection of *C. albicans* species (Raynaud's phenomenon).[15]

For presence and speciation of non-*C. albicans* species, sugar fermentation test [Figure 4] and sugar assimilation test [Figure 5] were performed. Fermentation and assimilation test media were prepared with 2% sugar (Glucose, Sucrose, Lactose and Maltose) (HiMedia). Small inoculums were added into each tube and incubated for 48–72 h at 30°C. The ability to ferment sugar was shown by the presence of acid (indicator becomes pink) and gas trapped in the Durham tubes [Table 1a]. Sugar assimilation was depicted as a positive or a negative reaction for various sugars, as seen in [Table 1b].[16]

Data obtained were presented using descriptive statistics in SPSS Inc. Version 20.00, Chicago, Illinois,USA. Values for $P < 0.05$ were considered statistically significant.

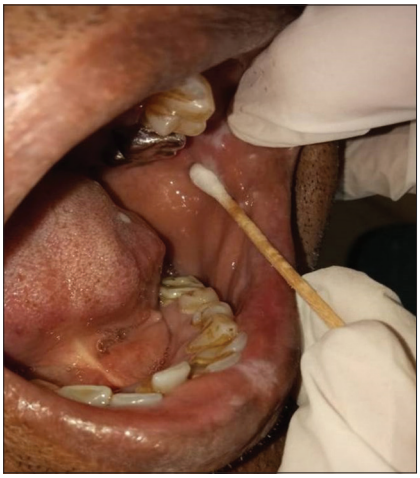


Figure 1: Swab culture from site of the lesion

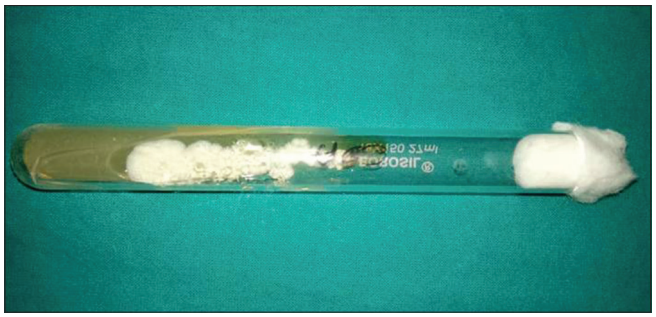


Figure 2: Swab culture inoculated on Sabouraud's dextrose agar media showing creamy white, convex colonies of *Candida* species after incubation

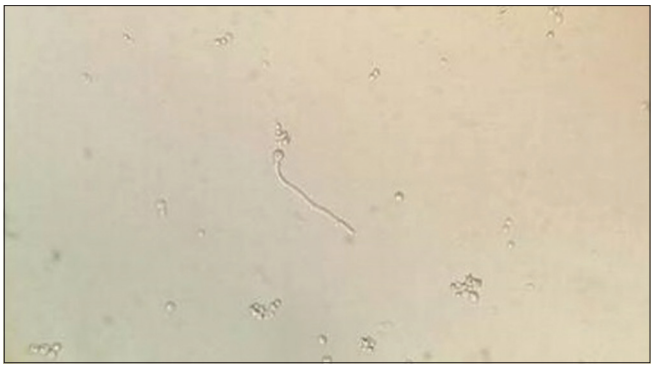


Figure 3: Germ tube test showing production of filamentous extension form yeast cell indicating positive for *Candida albicans*

Figure 4: Sugar fermentation test (positive for *Candida tropicalis* and C. kefyr)

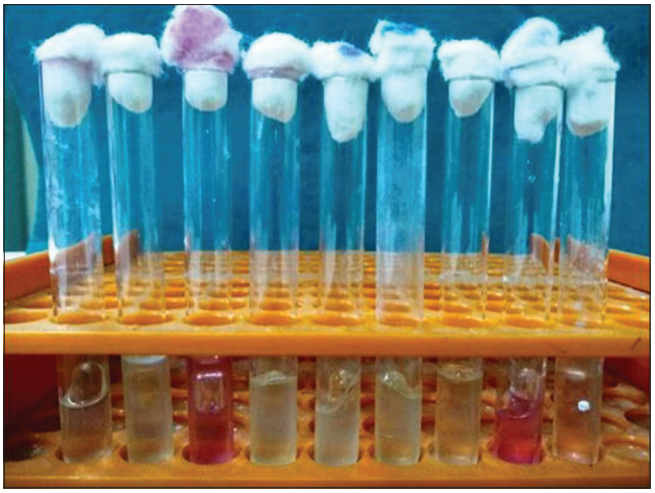


Figure 5: Sugar assimilation test (positive for *Candida glabrata*)

RESULTS

In the present study, the clinicohistopathological evaluation of the study group was done by using modified WHO criteria 2003.[1] The details of the evaluation of the cases of OLP, OLL and OLD are shown in [Table 2]. Microbiological evaluation for *candida* species of control group and study (OLP + OLL) group was done by indirect microscopic examination (SDA culture, GT test, sugar fermentation and sugar assimilation) as elaborated in Table 3.

SDA swab culture showed 100% cases of study group ($n = 40$) and 42.5% cases of control group ($n = 17$) were positive for *Candida* species. On statistical comparison [Table 3a], out of total cases in the present study ($n = 80$), the frequency of presence of *Candida* species was higher in study (OLP + OLL) group (50%) and absence of *Candida* species in control group (28.75%) and this difference was statistically significant ($P < 0.0005$) [Graph 1].

GT test showed that 40% cases ($n = 16$) of study (OLP + OLL) group were positive for *C. albicans* and the remaining 60% cases ($n = 24$) were non *C. albicans*. In the control group, 35% cases ($n = 14$) were *C. albicans* and only 7.5% cases ($n = 3$) were non *C. albicans*. On statistical comparison [Table 3b], out of total positive cases ($n = 57$) in the present study, frequency of *C. albicans* (24.60%) was higher in control group and non *C. albicans* species (42.10%) in study (OLP + OLL) group and this difference was statistically significant ($P < 0.0003$) [Graph 2].

Sugar fermentation test and sugar assimilation test done for speciation of *Candida* showed 40% cases ($n = 16$) were *C. albicans* and 60% cases ($n = 24$) were non *C. albicans*. The non *C. albicans* included 45.8% cases ($n = 11$) of *C. glabrata*, 25% cases ($n = 6$) of *C. tropicalis* and *C. krusei*, 4.1% case ($n = 1$) of *Candida guilliermondii*. In control group 7.5% cases ($n = 03$) of non *C. albicans* species included 2.5% cases each one of *C. glabrata* ($n = 01$), *C. tropicalis* ($n = 01$) and *C. krusei* ($n = 01$). On statistical comparison [Table 3c], species such as *C. glabrata*, *C. tropicalis*, *C. krusei* and *C. guilliermondii* were higher in study (OLP + OLL) group as compared to control group with statistically insignificant difference ($P > 0.05$).

DISCUSSION

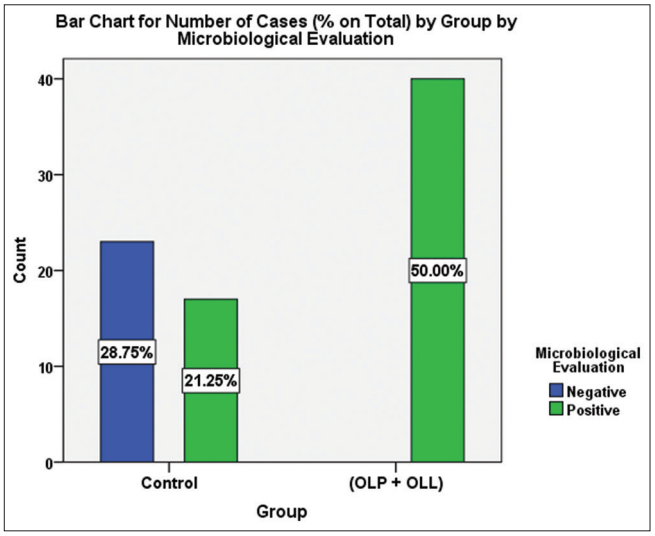
Candida species are implicated as one of the risk factors in epithelial dysplasias in oral potentially malignant disorders such as leukoplakia, lichen planus and submucous fibrosis as well as in oral carcinogenesis.[17] Studies show an association of *Candida* species with OLP. Other than *C. albicans*, non-*C. albicans* strains, such as *C. parapsilosis*, C. tropicalis, *C. dubliniensis*, *C. krusei* and *C. glabrata*, are frequently detected in OLP. Furthermore, Non-*C. albicans* species isolated from OLP lesions have shown to be resistant to commonly used antifungal agents. A proper identification of the specific candidial strains should be performed due to the variable degree of invasiveness and antifungal sensitivity of the different species of *Candida*.[6] Emergence of drug-resistant strains of *Candida* has highlighted the need for reliable methods of candidial isolation and identification.[16] Thus, the above study was undertaken to comparatively evaluate the phenotypic variation of *Candida* species in patients of OLP and OLL with healthy individuals using indirect microscopic examination.

Among the various clinicohistopathological parameters evaluated as per modified WHO criteria 2003, study group included 35% cases ($n = 14$) of OLP and 65% cases ($n = 26$) of OLL in which 34.6% cases ($n = 09$) showed epithelial dysplasia. Shivhare *et al*. in 2016[17] believed that the modified classification of OLP 2003 is more practical and aids in the diagnosis of OLP better but it also has dysplasia as exclusion criteria for OLP. Patil *et al*.[18] in 2014 assumed that if OLP manifested bilaterally (clinically typical) and histologically only compatible (shows dysplasia), according to 2003 modified criteria, it should be labeled as an OLL. In fact, exclusion of all lesions that resemble OLPs but exhibit epithelial dysplasia may lead to an underestimation of the rate of malignant transformation of OLP. This fact was restated by Arora S *et al*. in 2006,[6] where they reported severe epithelial dysplasia and carcinoma *in situ* in their series of OLP. Rejecting a diagnosis of OLP

Table 1a: Sugar fermentation of Candida species

Species	Fermentation of sugar			
	Glucose	Maltose	Sucrose	Lactose
C. albicans	AG	AG	-	-
C. tropicalis	AG	AG	AG	-
C. kefyr	AG	AG	AG	-
C. guilliermondii	AG	-	AG	-
C. krusei	AG	-	-	-
C. parapsilosis	AG	-	-	-
C. glabrata	AG	-	-	-
C. dubliniensis	AG	AG	-	-

A: Acid production, G: Gas production, -: Negative reaction



Graph 1: Graphical representation of comparison (frequency %) between control group and study (oral lichen planus + oral lichenoid lesions) group for presence or absence of candida species using Sabouraud's dextrose agar culture

Table 1b: Sugar assimilation of Candida species

Species	Sugar assimilation of								
	Sucrose	Lactose	Trehalose	Raffinose	Cellobiose	Melibiose	Galactose	Xylose	Maltose
C. albicans	+	+	+	–	+	–	–	+	+
C. glabrata	–	–	+	–	–	–	–	+	–
C. krusei	–	–	–	–	–	–	–	+	–
C. tropicalis	+	–	+	–	+	–	+	+	+
C. guilliermondii	+	–	+	+	+	+	+	+	+
C. dubliniensis	+	–	–	–	–	–	–	–	+

+: Positive reaction, -: Negative reaction

Table 2: Clinicohistopathological evaluation of study group (oral lichen planus and oral lichenoid lesions) by using modified WHO criteria 2003

	OLP		OLL		
Criteria	Clinically typical of OLP + histopathologically typical of OLP	Clinically typical of OLP + histopathologically only compatible with OLP	Histopathologically typical of OLP + clinically compatible with OLP	Clinically compatible with OLP + histopathologically only compatible with OLP	Total
Number of cases (*n*)	14	8	11	7	40

Epithelial dysplasia is seen in 9 cases of OLL: Lichenoid dysplasia. OLP: Oral lichen planus, OLL: Oral lichenoid lesions

Table 3: Microbiological evaluation of control group and study (oral lichen planus + oral lichenoid lesions) group

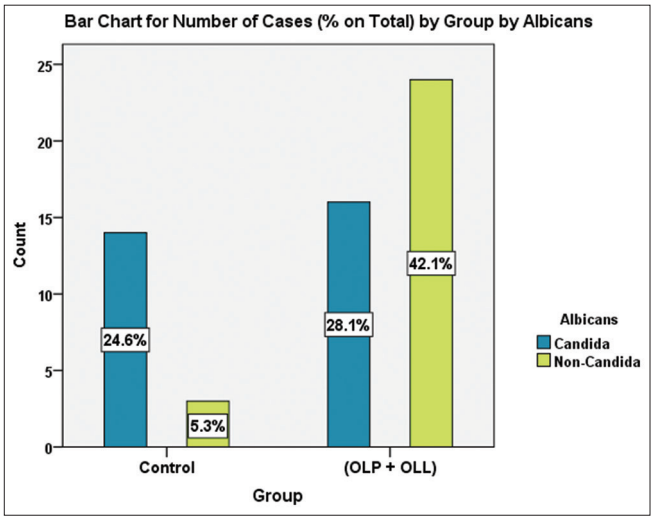
	Total (*n*)	Negative cases	Positive cases	Candida albicans	Candida nonalibicans					Total
					C. glabrata	C. tropicalis	C. krusei	C. guilliermondii	C. dubliniensis	
Control group, *n* (%)	40	23 (58)	17 (42)	14 (35)	1 (2.5)	1 (2.5)	1 (2.5)	0	0	3 (7.5)
Study (OLP + OLL) group, *n* (%)	40	0	40 (100)	16 (40)	11 (45.8)	6 (25)	6 (25)	1 (4.1)	0	24 (60)

OLP: Oral lichen planus, OLL: Oral lichenoid lesions

Table 3a: Statistical comparison (frequency %) between control group and study (oral lichen planus + oral lichenoid lesions) group for presence or absence of candida species using Sabouraud's dextrose agar culture

Group	Frequency, *n* (%) for microbiological evaluation			*P*
	Negative	Positive	Total for row	
Control group	23 (28.75)	17 (21.25)	40 (50.00)	<0.0005
Study (OLP + OLL) group	0	40 (50.00)	40 (50.00)	
Total for Column	23 (28.75)	57 (71.25)	80 (100.0)	

Pearson Chi-Square $_{(1)}$ (two-sided) =32.281, Exact *P* value is <0.0005, indicating significant results. OLP: Oral lichen planus, OLL: Oral lichenoid lesions



Graph 2: Graphical representation of comparison (frequency %) between control group and study (oral lichen planus + oral lichenoid lesions) group for candida species using germ tube test

solely due to the presence of dysplasia, therefore, requires consideration.[18]

In our study, on SDA swab culture, frequency of positive *Candida* species was higher in study (OLP + OLL) group and negative *Candida* species in control group. Several studies done by Arora S *et al.* 2016,[6] Lundström *et al.* 1984,[8] Zeng *et al.* 2009,[9] and Jainkittivong *et al.* 2017.,[10] show variable results in OLP and control group. The reason of such findings could be attributed to candidal growth on many preexisting pathological processes by inducible enzyme system that allows them to replicate using polycyclic aromatic hydrocarbon as their source of energy.[19] Negative culture in controls (28.75%) in our study indicates their absence in healthy host. Because microorganisms are continuously removed from the oral cavity by host clearance mechanism, *Candida* survival may not be always possible.[20]

On performing GT test for differentiation into *C. albicans* and non *C. albicans* species,[16] the frequency of *C. albicans* was higher in control group and non *C. albicans* species in study (OLP + OLL) group. To the best of our knowledge, no other studies show an increased number of non *C. albicans* in OLP and OLL as compared to healthy controls. Several studies were done by Mehdipour *et al.*[11] and Ebrahimi *et al.*[12] show variable results in OLP and control group. The formation of germ tubes is influenced by various environmental factors (temperature, concentration of inoculum, composition of the medium, pH and bacterial contamination) which may account for false readings.[16] One possible concern about this technique is that 95% of *C. albicans* isolates or some non *C. albicans* (*C. dubliniensis*, *C. tropicalis* and *C. parapsilosis)* can also generate germ tube or pseudohyphae in serum, leading to misidentification if only perfunctory tests are performed.[15]

In the present study, the frequency of non *C. albicans* species such as *C. glabrata*, C. tropicalis, *C. krusei* and *C. guilliermondii* was higher in study (OLP + OLL) group as compared to control group. Among non *C. albicans* species in study (OLP + OLL) group, the frequency of *C. glabrata* was higher and *C. dubliniensis* showing phenotypic similarity to C. albicans was not detected. The control group, however, showed the presence of only *C. glabrata*, *C. tropicalis* and *C. krusei*. Non *C. albican* species were also isolated in various other studies done by Lundström *et al.*[8] in 1984, Masaki *et al.*[13] in 2010, Mehdipour *et al.*[11] in 2010, Arora S *et al.*[6] in 2016 and Jainkittivong *et al.*[10] in 2017. All these studies isolated different types of non *C. albican* species in OLP cases such as *C. glabrata*, *C. parapsilosis*, *Candida dubliniensis*, *C. krusei* and C. fukuyamaensis, but unlike our study, all other studies showed higher frequency of *C. albicans* than non *C. albican* species. This variability could be attributed to different methodology used in various studies like PCR analysis and Chromagar culture isolation.[6,7]

These non *C. albicans* species lack many of the virulence factors present in *C.* albicans, i.e., the ability to form hyphae and phenotypic switching. They have low adherence capacity

Table 3b: Statistical comparison (frequency %) between control group and study (oral lichen planus + oral lichenoid lesions) group for candida species using germ tube test

Group	Frequency (%) for microbiological evaluation of all positive cases in control and study group (*n*=57)			
	C. albicans	Candida nonalbicans	Total for row	*P*
Control group	14 (24.60)	3 (5.30)	17 (29.8)	<0.0003
Study (OLP + OLL) group	16 (28.10)	24 (42.10)	40 (70.20)	
Total for Column	30 (52.60)	27 (47.40)	57 (100.0)	

Pearson Chi-Square (1) (two-sided) = 8.584a, Exact *P* value is <0.0003, indicating significant results. OLP: Oral lichen planus, OLL: Oral lichenoid lesions

Table 3c: Statistical comparison (frequency %) between control group and study (oral lichen planus + oral lichenoid lesions) group for candida nonalbican species using sugar fermentation test and assimilation test

Group	Frequency (%) for microbiological evaluation (candida nonalbicans)					
	C. glabrata	C. tropicalis	C. krusei	*C. guilliermondii*	Total for row	*P*
Control group	1 (3.70)	1 (3.70)	1 (3.70)	0	3 (11.10)	1
Study (OLP + OLL) group	11 (40.70)	6 (22.20)	6 (22.20)	1 (3.70)	24 (24.60)	
Total for column	12 (44.40)	7 (25.90)	7 (25.90)	1 (3.70)	27 (100.0)	

Fisher's exact test=1.56, *P*=1, indicating not significant result. OLP: Oral lichen planus, OLL: Oral lichenoid lesions

to buccal epithelial and vascular endothelial surfaces. They secrete less proteinases.[21] However, *C. glabrata* is less susceptible to killing by human beta-defensins than is *C.* albicans and exhibits various degrees of resistance to the antifungal activity of salivary histatins and mucins.[19] In addition, *C. glabrata* possesses both innate and acquired resistance against antifungal drugs, due to its ability to modify ergosterol biosynthesis, mitochondrial function or antifungal efflux. This resistance allows for its relative overgrowth over other susceptible species. Furthermore, in a study, it was noted that biofilm-forming ability in *C. tropicalis* was greater as compared to *C. albicans*. Biofilm formation is implicated as an important virulence attribute of Candida species as it increases the ability to withstand host defenses and also confers significant resistance to antifungal therapy.[16,21] Thus, although less virulent in nature, non *C. albicans* need to be differentiated and identified to emphasize the initiation of adequate and appropriate therapeutic modalities in treating OLP and OLL cases. Identification of different candida species may be the need of the hour as there are significant differences in their susceptibility to antimycotic drugs.[19,21,22]

CONCLUSION

A constant rise in immuno-suppressed patients, widening range of recognized pathogens and resistance to antifungal drugs are contributing factors which stresses the need for species identification of Candida, an opportunistic pathogen. Therefore, it is important to identify the infecting strains of *Candida* because isolates of *Candida* species differ widely, both in their ability to cause infection and also in their susceptibility to antifungal agents. Furthermore, it is important for successful clinical management and for determining appropriate control measures to prevent transmission of resistant candidal pathogens. Thus, phenotypic speciation of candida is emerging as a necessary trend to highlight the need of administering appropriate antifungal therapy. Studies with larger sample size are required to be done to substantiate this hypothesis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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