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Candida: A Clinico-mycological Study

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Abstract

Fungal infections caused by *Candida* spp. are a cause of morbidity and mortality, with *Candida albicans* being considered the prime suspect. Other species, *Candida tropicalis, Candida pseudotropicalis, Candida parapsilosis, Candida krusei, Candida guilliermondii,* and *Candida vishwanathii* are equally notorious and should be reported aggressively. The presence of fungal elements in clinical samples is sometimes low, making their detection challenging amidst the tissue elements and other bacterial presence. Therefore, mycological diagnostic methods need to be comprehensive with no less emphasis on any diagnostic step.

Keywords: Anti-fungal therapy, *Candida* spp., Debilitating diseases, Fungal infections.

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Background

Candida, the most common cause of human fungal infections, are opportunists and their severity is enhanced in the presence of predisposing factors. Isolation of *Candida* is not in itself diagnostic, as they occur as part of the commensal flora; therefore, interpretation of mycological results assumes significance in collaboration with clinical signs and symptoms and the existence of predisposing factors. *Candida albicans* accounts for the vast majority of infections. *Candida tropicalis*, *Candida pseudotropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida guilliermondii,* and *Candida vishwanathii* are also implicated in causing infections.[1-7]

Keeping the above facts in mind, the present study was undertaken with the aim of identifying the isolates of *Candida* to species level, in clinically suspected cases of fungal infections. The objective was to find out the clinicomycological correlation in patients from whom *Candida* species were repeatedly isolated and to study the antifungal susceptibility pattern of *Candida* isolates.

Materials and Methods

This prospective *in vitro* study was undertaken in a tertiary care teaching hospital in Mumbai, for 6 months. The study group comprised 100 patients from whom *Candida* species were repeatedly isolated from various sites or the same site at different times. Clinical data regarding underlying disease state, HIV status, and any predisposing iatrogenic conditions if present was noted. The samples comprised cerebrospinal fluid (CSF), pus, sputum, stool, urine, body fluids, swabs from throat, vagina and tracheostomy wound, scrapings from cornea and skin, and blood for culture which were processed using standard techniques.[8,9]

Wet mount and 10% KOH Mount was done to note for the presence of yeast cells with or without pseudohyphae. Primary gram-stained smear was done to note the Gram-positive budding yeast cells with or without pseudohyphae followed by culture on two slants of Sabouraud's dextrose agar with chloramphenicol (SDA), pH 5.4, and incubated at 37°C and 22°C. For urine, colony count of more than 100 was included. For fungal septicemia, 5–10 cc of blood was collected and inoculated aseptically into Hartley's broth. Subculture was done on two SDA slants at 24, 48, 72, 96 h, and every week for 30 days and incubated at 37°C and 22°C. Growth was noted after 48 h and thereafter, daily for 4 weeks, after which they were discarded. Creamy, smooth, pasty, opaque, shiny, or dull yeast colonies were confirmed by secondary gram-stained smear. Repeated isolates of *Candida* from various sites or the same site at different times, from the same patient, were included for further identification tests. Subculture on sugar-free nutrient agar was done thrice, to get isolates free of dextrose and eliminate errors in the carbohydrate fermentation and assimilation reactions.

Germ tube test was performed by emulsifying a portion of the colony in 0.5 ml of sterile human serum. In *C. albicans* and *Candida stellatoidea*, there was no constriction at the base of the extension, whereas, in *C. tropicalis,* there was constriction at the base of the extension.[9] Surface growth in Sabouraud's broth was observed in *C. tropicalis* and *C. krusei* as a climbing film on the sides of the test tube and regarded as presumptive evidence.[9] Dalmau culture done on corn-meal tween 80 agar was observed microscopically using compound microscope to see hyphae, blastoconidia, chlamydospores, and arthrospores. Pseudohyphae, due to pinching-off process of blastoconidiation and regular points of constriction or true hyphae breaking up into arthroconidia, was noted, with the former indicating toward genus *Candida*. Arrangement of blastoconidia was noted with differences in different species: (i) *C. albicans*: Compact clustering of blastoconidia at regular intervals along pseudohyphae with terminal chlamydospore, (ii) *C. tropicalis:* Sparse blastoconidia irregularly arranged along pseudohyphae, (iii) *C. pseudotropicalis*

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(keyfr): Elongated blastoconidia lying parallel to pseudohyphae giving a "*log-in stream*" appearance, (iv) *C. parapsilosis*: Spider-like satellite colonies distant from the site of inoculation, sparse blastoconidia seen on giant hyphae, classically called the "*sagebrush*" appearance', (v) *C. krusei*: Elongated blastoconidia with "*crossed matchstick*" appearance at points of separation, and (vi) *C. stellatoidea*: Large clusters of blastoconidia along pseudohyphae, but only rarely, a single chlamydospore.[9]

Carbohydrate fermentation test was performed in four carbohydrate fermentation broths of, glucose, sucrose, lactose, and maltose, incubated at 37°C for 48–72 h, and examined for a change in color from deep blue-green to faint green or yellow and gas production in Durham's tubes.[9] Carbohydrate assimilation test was done in the five assimilation slants, glucose, sucrose, lactose, trehalose, and raffinose, incubated at 22°C, and examined at 48–72 h for abundant growth and acid production, indicated by a change in color from blue to yellow.[9] Antifungal susceptibility testing was performed on all the isolates of *Candida* by Stoke's disk diffusion method on SDA (pH7.0–7.5) using a standard strain of *C. albicans, ATCC 10231*. Interpretation was done as sensitive (zone size equal to or wider than the zone size for the standard, or not more than 3 mm smaller than that of the standard), intermediate (zone size <3 mm, but smaller than the standard by more than 3 mm), and resistant (zone size 3 mm or less).[10]

Results

In 100 patients, 33 were above 50 years of age with 52 females and 48 males. Various debilities were present, such as pulmonary tuberculosis (21), post-operative state (17), chronic obstructive pulmonary disease (15), pulmonary tuberculosis with HIV infection (12), diabetes mellitus (09), renal disease (09), HIV infection (04), protein energy malnutrition (4), auto-immune disease (3), severe anemia (3), post renal transplant (1), cerebrovascular accident (1), and burns (1).

Of 320 clinical samples, the maximum numbers were of urine (70), followed by sputum (68), CSF (50), and pus (39). In 39.23% subjected to wet mount examination, yeast cells with mycelial forms could be detected. About 23.83% of samples examined by 10% KOH mount showed yeast cells with mycelial forms. About 41.06% of the gram-stained smears showed Gram-positive budding yeast cells with pseudohyphae. About 120 (39.73%) of the samples, excluding blood samples for blood culture, were detected by both microscopy and culture. One hundred and forty-six (45.62%) of 320 samples were culture positive for *Candida* spp. Various species of *Candida* were isolated, as shown in Table 1. Predisposing iatrogenic factors were noted, such as antibiotic treatment (36), antibiotic and steroid treatment (15), indwelling catheter and antibiotic treatment (15), indwelling catheter more than 1 week (14), an intravenous catheter (06), indwelling catheter and steroid treatment (04), indwelling catheter and anti-malignancy drugs (01), anti-malignancy drugs (01), an intravenous catheter with indwelling foley's catheter and antibiotics (07), and tracheostomy tube with antibiotics (01). In addition to *Candida* spp., 16 other fungi were also isolated such as *Aspergillus niger* (02 from CSF and 02 from pus), *Cryptococcus* spp. (04 from CSF), *Fusarium* spp. *(01 from corneal swab), Rhodotorula* spp (01 from CSF), *Rhizopus* spp. (01 from pus), *Torulopsis glabrata* (01 from pus), and *Geotrichum* spp. (01 from urine).

Bacterial growth was seen in 19 samples in addition to the growth of *Candida*. *Acinetobacter* spp. in CSF (01), coagulase-negative *Staphylococci* in urine (01), *Escherichia coli* in urine (01), *Klebsiella* spp. in sputum (07), CSF (02) and broncho-alveolar lavage (01), *Pseudomonas* spp. in sputum (02), and urine (02) samples.

All four isolates of *C. albicans* in cutaneous candidiasis were susceptible to clotrimazole, nystatin, and amphotericin B. In 17 cases of mucosal candidiasis, sensitivity to clotrimazole was the highest (70.58%), followed by nystatin (64.7%), amphotericin–B (58.82%), and fluconazole (52.94%). In 125 systemic candidiasis cases, sensitivity to amphotericin-B (72%) was higher than to fluconazole (61.6%).

Discussion

Fungal infections are progressive and sometimes life-threatening, if not nipped in the bud at an early stage. Microscopy indicates the presence of yeasts, quite significant in sterile fluids. The presence of budding yeast cells, mycelia, and inflammatory cells, with the growth of *Candida* in culture, is suggestive of candidiasis. However, the presence of budding yeasts with no mycelia, with or without inflammatory cells, and the growth of *Candida* in culture is suggestive of colonization. In contaminated material such as feces and sputum, observation is much less conclusive, unless mycelial forms are also seen. The relative importance of mycelial forms as opposed to yeast forms in oral or enteric specimens has been emphasized by Toala *et al*.[11]

Table 1: Species wise and sample distribution of *Candida* spp. (n=146)

S. No.	*Sample types*	*Total isolates*	*C. tropicalis*	*C. albicans*	*C. stellatoides*	*C. pseudotropicalis*
1.	Urine	54	37	15	1	1
2.	Sputum	47	25	21	1	-
3.	CSF	3	1	2	-	-
4.	Pus	7	5	2	-	-
5.	Corneal scraping	0	-	-	-	-
6.	Blood	3	1	2	-	-
7.	Stool	4	-	2	-	2
8.	Throat swab	5	-	5	-	-
9.	Gastric lavage	6	2	4	-	-
10.	Ascitic fluid	5	5	-	-	
11.	Broncho-alveolar lavage	1	1	-	-	
12.	Vaginal swab	2	-	2	-	-
13.	Skin scraping	4	-	4	-	-
14.	Pleural fluid	4	3	1	-	-
15.	Tracheostomy swab	1	1	-	-	
	Total	146	81 (55.48%)	60 (41.09%)	02 (1.36%)	03 (2.05%)

C. tropicalis: Candida tropicalis, C. albicans: Candida albicans, C. stellatoides: Candida stellatoides, C. pseudotropicalis: Candida pseudotropicalis

Wet and 10% KOH mount examination showed 30.46% positivity in the present study. This can be attributed to less amount of *Candida* in the sample. Milne LJR reported that fungi are less abundant than bacteria in clinical material. Hence, smear examination and culture, for the isolation of *Candida* have their own importance.[12] Differentiating fungi from artifacts, especially in unstained films, is challenging. Gram-stained primary smears are relied on, therefore, to capture the false negatives. In this study, gram-stained primary smears showed the presence of Gram-positive budding yeast cells with mycelial forms in 41.06% of the samples, showing a higher rate of detection than wet and 10% KOH mount preparation. About 47.35% of samples were culture positive, of which 39.73% were positive by both microscopy and culture and 7.61% were positive only in culture. This false negativity can be due to less amount of *Candida* in the sample. About 4.63% were positive by microscopy and negative in culture, which can be attributed to the difficulty in differentiating fungal elements from artifacts.[13] *Candida* spp. isolated were 146 (45.62%), of which 81 (55.48%) were *C. tropicalis,* 60 (41.09%) *C. albicans*, 2 (1.37%) *C. stellatoidea,* and 3 (2.05%) *C. pseudotropicalis*.

About 33% of the patients in the present study were above 50 years of age. Age as a predisposing factor for candidiasis has been reported previously by Laxmi *et al*., where 40% of patients were above 50 years of age. Aging appears to markedly influence the clinical manifestation of candidiasis.[14]

Chakrabarti *et al.* reported *C. tropicalis* as the most common culprit in systemic candidiasis, followed by *C. albicans* and *C. guilliermondii*. In our study too, *C. tropicalis* emerged as the major species isolated from urine, sputum, pus, ascitic fluid, and pleural fluid. Gradually, *C. tropicalis* and other *non-albicans Candida* are emerging on the scene as pathogens. Laxmi *et al.*, isolated 221 *Candida* species from various specimen, with *C. albicans* (37.1%) as the predominant species. Other cases of systemic infection with *C. tropicalis* have been reported by Conn *et al*. Nine cases of systemic candidiasis had been attributed to species other than *C. albicans*, by Toala *et al*.[10,11,14-16] *C. tropicalis* has been reported to be a common cause of septicemic candidiasis. In the present study, *C. tropicalis* was isolated from the blood of one suspected case of fungemia and from pus from a case of maxillary osteomyelitis, along with isolation from urine and sputum in large numbers of patients with underlying disease status. The mechanism of acquisition and risk factors appears to be similar to that of *C. albicans* as reported by Fridkin and Jarvis.[16-18] *C. pseudotropicalis* has been reported from feces of patients on cytotoxic therapy, with diarrhea. In our study, *C. pseudotropicalis* was isolated from two children aged 2 and 3 years, on antibiotic treatment for respiratory tract infection, with diarrhea. *C. albicans* was the predominant isolate in CSF, blood, throat swab, gastric-lavage, and skin-scraping. *C. stellatoidea* was isolated from urine and sputum.

Thirty-six patients on long-term broad-spectrum antibiotics had candidiasis in the present study. The treatment with antibiotics and cortisone destroys the primary microbial agents, and relatively, lower pathogens become virulent, causing the persistence and aggravation of the clinical condition. The granulocytopenia induced by these agents favors candidal colonization and growth of *Candida* may be stimulated by the antibiotic itself.[14,19]

Intravenous devices, tracheostomy tubes, and surgical procedures result in barrier break conditions and are associated with a high incidence of candidiasis as was seen in this study, where 17% of the patients were post-operative. In a study by Laxmi *et al*., post-operative conditions accounted for 34% of various underlying conditions. Transient candidaemia is a well-recognized complication associated with intravenous devices. This was seen in one patient, postoperatively in our study, who was on broad-spectrum antibiotics with an indwelling catheter too. The treatment with oral fluconazole along with catheter removal brought about a significant improvement in the patient's condition. It is important to treat candidaemia, even if transient, because, 15% of these patients may later develop localized candidiasis.[14]

In our study, pulmonary tuberculosis accounted for 33% of the total debilities, followed by post-operative condition, chronic obstructive pulmonary disease, diabetes mellitus, renal disease, and HIV infection. Pandalai and Kurup reported pulmonary tuberculosis in 56.52% of the disease conditions. In the presence of *Candida,* virulence of *Mycobacterium tuberculosis* is enhanced and its growth is promoted, even though it might have been inhibited in multiplication by exposure to streptomycin.[14,19]

Chronic obstructive pulmonary disease was seen in 15% of patients in our study, who were on steroids and antibiotics either alone or in combination. In a study in 1962, 49.54% of the underlying diseases comprised chronic obstructive pulmonary disease, promoting the resistant species to increase in their population, and overwhelm the host resistance. Disturbance in the normal flora due to antibiotic therapy upsets the mucosal integrity, leading to nutritional imbalances, paving the way for entry of *Candida.* A higher incidence of faucial colonization with *Candida* has been reported due to local impairment of the host's defense mechanisms during treatment with corticosteroids.[19,20]

Candida was isolated from CSF, pus, sputum, stool, and throat swabs of 16 HIV positive patients of whom four had HIV infection alone and 12 had pulmonary tuberculosis in addition. Two patients had oral candidiasis, an important predictor of HIV disease progression. Adherence to oral surface leads to colonization and infection, which might be associated with selection of *Candida* strains with altered virulence determinants, resulting in the replacement of original commensal strains.[21]

Diabetes mellitus accounted for 9% of the underlying debilities in the present study. In a study in 1993, 30% of the patients had diabetes mellitus. The normal flora carrier rate and colonization of *Candida* are high in diabetics. In the presence of increased tissue fluid glucose levels, the commensal *Candida* has an enhanced growth and accumulate sufficient enzymes for penetration of mucous membranes and become pathogenic.[12,14]

Auto-immune diseases, requiring administration of anti-malignancy drugs like methotrexate, induce granulocytopenia and favor colonization by *Candida.* In the present study, 3% of the patients had auto-immune disease like rheumatoid arthritis and 1% was post-renal transplant cases. In a study by Laxmi *et al*., 6% of patients had autoimmune diseases and 4% were post-renal transplant cases. Rifkind *et al*. had also reported bronchopulmonary candidiasis in post-renal transplant cases. Cerebrovascular accident as an underlying condition for repeated isolation of *Candida* has been reported by Laxmi et al. in 11% of patients. In our study, CVA was seen in only 1% of patients.[14,22]

About 77.14% *Candida* were isolated from urine in our study. About 19.3% of positive cultures in urine have been reported by Toala *et al*. This can be attributed to iatrogenic factor, indwelling urinary catheters for more than 1 week, along with the administration of antibiotics, steroids, anti-malignancy drugs, and underlying disease conditions, like diabetes mellitus. Most

common isolate in urine was *C. tropicalis* (68.5%), followed by *C. albicans* (27.77%), *C. stellatoidea* (1.85%), and *C. pseudotropicalis* (1.85%). Urinary tract candidiasis responds to antifungal therapy and supports the fact that urinary candidiasis is a definite entity.[11,14,23]

In sputum, the isolation rate was 69.11%, of which *C. tropicalis* (53.19%) was the commonest species, followed by *C. albicans* (44.68%) and *C. stellatoidea* (2.12%). *C. tropicalis* has been reported in bronchopulmonary involvement by Pandalai and Kurup, who isolated *Candida* from 52% of the sputum samples. Chakrabarti *et al.* had also established that sputum shows more *Candida* in patients with bronchopulmonary diseases compared to the normal population.[13,15,19]

Thrush, caused by *C. albicans,* is a disease of infancy, regarded as benign. In our study, a child of 2 months was being bottle-fed and had dysphagia due to severe stomatitis. Thrush was suspected due to granular coating of the tongue. Candid mouth paint, that is, clotrimazole twice daily and crushed capsule forcan, 500 mg cured the lesions which if missed on routine examination, could have extended into the esophagus causing esophageal thrush. Ludlum and Henderson showed an increase in incidence of thrush in bottle-fed infants.[24]

Of eight gastric lavage samples, 6(75%) yielded *Candida* spp., of which four were *C. albicans* and two were *C. tropicalis*. One was post-operative case of resected gastric ulcer on broad-spectrum antibiotics, in which *C. albicans* was isolated. Katzenstein and Maksen have reported candidal infection in 33% of the 72 resected gastric ulcers. The other post-operative patient was also culture positive for *C. albicans* and was on broad-spectrum antibiotics and intravenous fluids with an indwelling urinary catheter. Remaining four isolates were from children in age group of 3 months to 5½ years, with pulmonary tuberculosis with protein-energy malnutrition, miliary Koch's, bronchopneumonia, cough with dyspnea, and refusal to feed.[25]

Stool showed 40% culture positivity rate with isolation of *C. albicans* in two patients and *C. pseudotropicalis* in two patients. *C. pseudotropicalis* has been reported by Laxmi *et al*. from the feces of patients on cytotoxic therapy with diarrhea. The presence of *Candida* in stools does not necessarily indicate its role, since it may be found in the normal stools of 9.20% of healthy people. However, in digestive disorders and sprue, its proliferation is well recognized. Browne have reported the appearance of *Candida* in stools, along with clinical manifestations of mycotic infections of the respiratory tract and peri-anal signs. In prolonged antibiotic therapy, colicin is not formed due to destruction of *E. coli* and consequent super-infection by *Candida* spp.[14,26]

Candida isolates from blood or fluids from closed spaces are suggestive of systemic infection and should be aggressively treated. *Candida* grows within tissues in both yeast and pseudo-hyphal forms. In our study, out of six ascitic fluid samples, five were culture positive for *C. tropicalis* and all of them had predisposing factors such as an indwelling catheter, acute renal failure on chronic proliferative glomerulonephritis, post-operative hydropneumothorax with intercostal drainage, and Koch's abdomen with intestinal perforation. All four pleural fluid samples showed isolates of *Candida*, with three of *C. tropicalis,* and one of *C. albicans*. Tuberculosis and post-operative complications were underlying predisposing factors. Burnie *et al.* have reported *C. albicans* from a pleural aspirate of a patient suspected of systemic candidiasis. Three of the eighteen blood cultures grew *Candida* spp., of which two were *C. albicans* and one was *C. tropicalis*. Predisposing factors included post-operative condition with a central venous catheter, diabetic ketoacidosis with tubercular pneumothorax, and anemia. The passage of yeast from the small intestine into the bloodstream by a perception mechanism is an important route of entry for systemic yeast infection. Application of antibiotic ointments to the site of indwelling intravenous catheters favors local colonization with *Candida* and a longer duration of candidaemia is associated with a higher mortality rate. Hence, amphotericin B was started in all three patients with successful recovery.[27,28]

Of the 39 pus samples, seven grew *Candida*, of which two were *C. albicans* and five were *C. tropicalis*. Underlying disease states were present, such as diabetic mellitus with maxillary osteomyelitis, sub-mandibular abscess with rheumatoid arthritis on treatment with methotrexate and NSAIDs, pulmonary tuberculosis with malaria with chronic meningitis and HIV infection, diabetes mellitus with trauma and post-operative condition with intercostal drainage, and ventilator and burns. Osteomyelitis is a well-documented manifestation of disseminated candidiasis. Intravenous amphotericin-B was the treatment of choice in these patients, all of whom recovered, except two. Recovery was not seen in a child with pyogenic meningitis who suffered from burns in the NICU incubator and was put on broad-spectrum antibiotics. *C. albicans* isolated from the case was resistant to both amphotericin-B and fluconazole *in vitro*. Another patient with PTB and HIV infection succumbed, despite treatment with amphotericin-B.

Throat swab yielded *C. albicans* in four patients with underlying disease such as tuberculosis, HIV, anemia, renal transplant (with pneumonitis and septicemia), diabetes mellitus (with cellulitis), and anemia (in a 2-month-old bottle-fed child). Bronchopulmonary candidiasis in renal transplant cases has been reported, as was seen in our study, where one patient with renal transplant had pneumonitis, with throat swab showing growth of *C. albicans*.[22]

Of the six vaginal swabs received, two yielded *C. albicans*. Both patients were on oral contraceptives with pruritus, discharge, and dysuria. Corbishley had reported *C. albicans* to be more common in women <25 years, which was also the case in the present study. Heavy curdy vaginal discharge, vulval itch, and use of oral contraceptive pills should be correlated with the isolation of *C. albicans*.[29]

Of the five skin scrapings, 4 (80%) were culture positive for *C. albicans*. These skin scrapings were obtained from patients in children <1 year of age with cutaneous candidiasis presenting as red, macerated intertriginous areas. Jacob *et al*. isolated *C. albicans*, *C. stellatoidea,* and *C. guilliermondii* from patients suffering from superficial skin infections.[30]

Despite treatment with amphotericin-B, mortality is as high as 70%, as reported by Gold *et al*. In our study, four out of six patients (66.66%) died despite amphotericin-B therapy, with one isolate of *C. albicans* from a pediatric burns patient resistant to both amphotericin-B and fluconazole.[31]

About 100% recovery rate was seen with clotrimazole therapy, using candid paint for local application, because resistance to clotrimazole is rare in cutaneous candidiasis. Amphotericin-B due to its potential nephrotoxicity and nystatin, due to its inefficacy in crusted skin lesions was not administered. In mucosal candidiasis, sensitivity to clotrimazole was the highest (70.58%), followed by nystatin (64.1%) and amphotericin-B (58.9%) with a cure rate of 100%. In vulvovaginal candidiasis, the cure rate is above 80% and in oral and pharyngeal candidiasis, as high as 100%. About

72% sensitivity to amphotericin-B and 61.67% to fluconazole was seen in systemic candidiasis. Dupont-Drouhet and Kauffman *et al.* reported 100% therapeutic success with fluconazole in systemic candidiasis, while Anaissie *et al*. reported 88% response to fluconazole in chronic disseminated candidiasis. In the present study, 75% therapeutic response to fluconazole was seen and was less effective in a patient taking rifampicin, isoniazid, and ethambutol for pulmonary tuberculosis. Rifampicin decreases fluconazole levels by about 25%, leading to failure in fluconazole therapy, correlating with *in vitro* resistance to fluconazole.[18,32-35]

Conclusion

To conclude, advances in health-care facilities have revolutionized medical care and have provided the gift of life to many. This has also led to an increase in the numbers of severely ill, immunocompromised, hospitalized patient population, and susceptible to fungal infections which are rapidly progressive and difficult to diagnose or treat, making it imperative to strengthen mycological diagnostic methods.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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