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Treatment Protocol for Secondary Burning Mouth Syndrome in *Candida albicans*- or Non-*albicans*-Positive Patients

Hye-Min Ju[1,2] | Sung-Hee Jeong[1,2] | Yong-Woo Ahn[1,2] | Hye-Mi Jeon[3] | Soo-Min Ok[1,2]

[1]Department of Oral Medicine, Institute of Translational Dental Sciences, Pusan National University, Yangsan, Korea
[2]Dental Research Institute, Pusan National University Dental Hospital, Yangsan, Korea
[3]Dental Clinic Center, Pusan National University Hospital, Busan, Korea

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Correspondence to:
Soo-Min Ok
Department of Oral Medicine, School of Dentistry, Pusan National University, 49 Busandaehak-ro, Mulgeum-eup, Yangsan 50612, Korea
Tel: +82-55-360-5243
Fax: +82-55-360-5234
E-mail: oksoomin@pusan.ac.kr
https://orcid.org/0000-0003-1776-371X

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Purpose: This study aimed to propose an efficient treatment approach for infection with different *candida* species.

Methods: Fifty-three patients who presented with a chief complaint of oral mucosal pain and exhibited positive *candida* culture findings were divided into two groups (*Candida albicans* and non-*albicans*). Pain, mucosal manifestations, salivary flow rates, durations of disease and treatment, and responses to treatment (nystatin and clonazepam) were investigated in both groups.

Results: Patients in the *C. albicans* group exhibited more prominent clinical characteristics (erythematous lesions, tongue coatings, and hyperalgesia) than those in the non-*albicans* group. In total, 70% of patients in the non-*albicans* group showed no abnormalities in the oral mucosa. Patients in the *C. albicans* group showed increased resistance to nystatin treatment compared to those in the non-*albicans* group, especially with longer disease durations. The patients resistant to nystatin treatment showed positive responses to clonazepam.

Conclusions: Patients with oral mucosal pain should be tested for the presence of *Candida*, even in the absence of mucosal abnormalities, especially those infected with non-*albicans* species. If no response to antifungal therapy is observed, treatment with clonazepam should be initiated, especially in patients infected with *C. albicans*.

Keywords: Burning mouth syndrome; *Candida albicans*; *Candidiasis*; Non-*albicans* Candida infection

INTRODUCTION

Burning mouth syndrome (BMS), also known as oral dysesthesia, is a chronic orofacial condition associated with moderate-to-severe pain of burning (or similar) nature that affects the oral mucosa [1,2]. Depending on the etiology, BMS is categorized into two forms as follows: "primary or idiopathic BMS" whose causes cannot be identified and "secondary BMS" resulting from local factors or systemic conditions [3]. Local factors that could lead to secondary BMS include poorly-fitting prostheses, parafunctional habits, dental anomalies, allergic reactions, infection, chemical factors, galvanism, dysgeusia, and xerostomia [4].

Oral infections by various microorganisms such as *Enterobacter*, *Klebsiella*, *Fusobacterium*, *Staphylococcus aureus*, and *Helicobacter pylori* have been frequently associated with BMS. In particular, *Candida* species have been considered one of the most frequent microorganisms associated

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with the development of secondary BMS [4].

Infection by *Candida* species continues to be cited as a possible cause of BMS; however, there is a paucity of documented studies to support the theory [5-7]. The inconsistency in the results could be attributed to the fact that these studies primarily analyzed the relationship between the increase in the number of *Candida* species and burning sensations and did not consider the fact that clinical symptoms may differ according to the different levels of toxicity of each species of *Candida* [8].

Candida albicans is the most-prominent opportunistic fungal pathogen causing oral candidiasis. The second-most common pathogen associated with oral candidiasis is *Candida glabrata*, which is a non-*albicans* species of *Candida*. Other non-*albicans* spp., such as *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*, have also been suggested as oral pathogens [9-13]. The virulence factors of *candida* species include the ability to avoid host defenses, biofilm production, adherence to mucosal epithelium, hemolytic activity, and invasion via the production of enzymes such as proteinases, phospholipases, and esterases [14]. Each *candida* species has varying degrees of virulence factors [8]. Clinical symptoms may vary according to these virulence factors; however, few studies have documented the risk factors for clinical symptoms and the severity of burning sensations according to the *candida* species.

The clinician should be completely aware of the outcome predictors of the disease to help in the selection of the most appropriate treatment modality for each individual patient. This study aimed to identify predictors of the outcome of treatment in patients with secondary BMS caused by infection with *candida* species.

MATERIALS AND METHODS

1. Subjects

The 423 subjects enrolled in the study were patients at the department of oral medicine, Pusan National Dental Hospital, who presented with a chief complaint of oral mucosal pain between January 2014 and December 2017. All the experiments were undertaken with the understanding and written consent of each subject, and the study was conducted per the principles of the Declaration of Helsinki. For each patient, the following data were obtained: age at presentation, sex, duration of the symptom (oral mucosal pain), complete medical history, and prior treatments or medications received for the symptom. Intraoral examinations were performed by skilled dentists specialized in oral medicine. To diagnose secondary BMS, in addition to candida swab & culture, laboratory tests, including mycological examinations, complete blood counts, and measurements of the levels of hemoglobin, iron, folic acid, and vitamin B12, were performed for all patients. Patients with xerostomia were treated with artificial salivary agents. We also educated patients to reduce parafunctional habits and corrected contributing factors through general behavioral control therapy such as nonirritant diets and the use of nonirritant kinds of toothpaste. Three hundred and sixty-one patients who were diagnosed with specific diseases such as lichen planus, recurrent aphthous ulcers, and mucous membrane pemphigoid, and nine patients who were *candida* culture-negative (n=7) or positive (n=2) but with the coexistence of *albicans* and non-*albicans* were excluded from the study to specifically define the clinical characteristics. Fifty-three patients who presented with a chief complaint of oral mucosal pain and were *candida* culture-positive were divided into two groups (culture-positive with *C. albicans* and with non-*albicans*) (Fig. 1).

The study protocol was approved by the Institutional Review Board of Pusan National University Dental Hospital

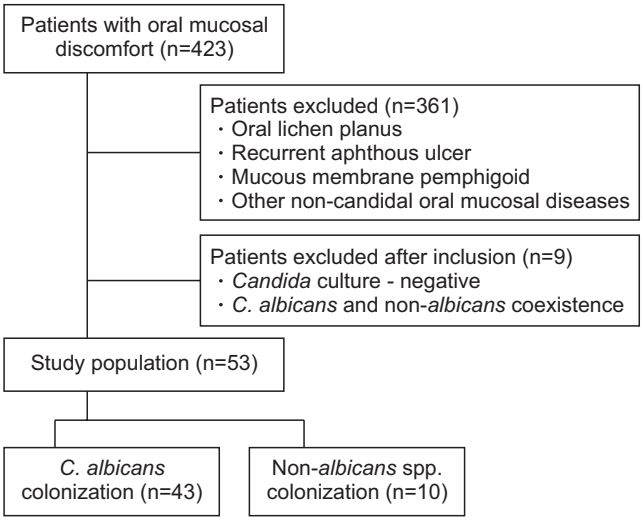

Fig. 1. Flow chart of the study population. *C. albicans*, *Candida albicans*.

(PNUDH-2018-004) and written informed consent was obtained from all patients at the initial visit.

2. Salivary Flow Rates

The resting whole-mouth salivary flow rate (RSFR) and stimulated whole-mouth salivary flow rate (SSFR) were measured for 5 minutes [15]. During the measurements of the SSFR, the participants were asked to chew unflavored gum for 5 minutes. An RSFR of >0.1 mL/min was considered normal, and hyposalivation was defined as an RSFR of ≤0.1 mL/min. An SSFR of >0.7 mL/min was considered normal, and hyposalivation was defined as an SSFR of ≤0.7 mL/min [16,17].

3. Identification of *Candida* Species

Samples for mycological examination were collected by firm swabbing of the surface of the site associated with the chief complaint. The cultures were obtained from Sabouraud's agar medium at 35°C for 3 days. Candida species were identified by skilled pathologists via a combination of phenotypic tests that assess morphological characteristics and carbohydrate assimilation and fermentation patterns.

4. Antifungal Treatments and Treatment Outcome Assessments

The degree of pain was analyzed using the numeric rating scale (NRS). The outcomes of all treatments were evaluated as the amount of change in NRS.

All patients received an antifungal agent (nystatin suspension, 5 mL; four times a day). Patients were instructed to place a drop of the gel on the tongue, spread it over the oral mucosa, hold it as long as possible, and swallow it. This antifungal treatment was continued for at least 2 weeks [18] and was stopped if no response to the antifungal therapy was observed. After the completion of treatment, the degree of symptom alleviation was determined. If the symptom (oral mucosal pain) improved by more than 50% (as determined by the NRS at the first visit), the treatment was considered effective; on the other hand, less than 50% improvement was regarded as treatment inefficacy or nonresponse to treatment. The total period of treatment with the antifungal agent was defined as the treatment period.

5. Clonazepam Application

Patients with residual symptoms such as hyperalgesia due to irritant foods after antifungal treatment were prescribed 0.5 mg of clonazepam three times daily. Patients were asked to dissolve the tablet in the saliva in their oral cavities for three minutes before swallowing [19,20]. This modality of treatment with clonazepam was continued for at least 2 weeks and was discontinued if no response to clonazepam therapy was observed. After treatment, the degree of symptom alleviation was determined.

6. Statistical Analysis

The Shapiro–Wilk test was used to evaluate the normality of data distribution. The Mann–Whitney U test and Pearson's chi-square test were used to compare the differences between the *albicans* and non-*albicans* groups. If the frequency of observations was small, Fisher's exact test was used. The data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Co., Armonk, NY, USA). A p-value of ≤0.05 was considered statistically significant.

RESULTS

1. Baseline Characteristics

The numbers of patients with cultures positive with specific species of *Candida* in the two groups were as follows: *C. albicans* group, n=43; non-*albicans* group, n=10 [*C. glabrata*, n=8 (80.0%); *C. parapsilosis*, n=1 (10.0%); and *C. krusei*, n=1 (10.0%)]. Patients' basic clinical characteristics were analyzed, and no significant differences in age, sex (Table 1; p>0.05), wearing dentures, ill-fitting dentures, underlying conditions, predisposing factors, and history of medications for tongue pain (Supplementary Table 1; available online only) were observed between the two groups. These findings imply that certain systemic diseases, such as hypertension and diabetes mellitus, have no preference for a specific species of *candida*.

2. Differences in Clinical Characteristics

When the clinical characteristics of oral lesions in *candida* culture-positive patients were investigated, patients in the *C. albicans* group showed higher proportions of tongue coatings and erythematous lesions, which are a prerequisite

for the diagnosis of oral candidiasis, compared to those in the non-*albicans* group (Fig. 2A, B; p<0.05). Though these lesions are known to be characteristic of *candida* infection, most patients infected with non-*albicans* species did not display any distinct lesions. The numbers of patients without erythema and tongue coating were 1 (2.3%) in the *C. albicans* group and 7 (70.0%) in the non-*albicans* group.

When the salivary flow rates of *candida* culture-positive patients were compared, both RSFR and SSFR were lower than those in normal individuals, which is consistent with the findings reported in numerous studies [21-23]. SSFR values of patients in the non-*albicans* group were significantly higher than those of patients in the *C. albicans* group. RSFR was also higher in patients in the non-*albicans* group; however, the differences were not statistically significant (Fig. 2C).

The NRS score did not differ significantly between the *C. albicans* and non-*albicans* groups (Fig. 3A; p>0.05). In contrast, the proportion of patients who complained of hyperalgesia during the intake of irritant foods, such as hard or spicy foods, was significantly higher in the *C. albicans* group than in the non-*albicans* group (Fig. 3B; p<0.05).

The duration of the disease (the time from the onset of the disease to the hospital visit) was significantly shorter in patients in the *C. albicans* group than in those in the non-*albicans* group (Fig. 3C, p<0.05). This relatively early visit (shorter disease duration) could be related to the hyperalgesia caused by irritant foods, as well as the tongue erythema and coating induced by *C. albicans*.

Table 1. Demographic characteristics of patients in the *C. albicans* and non-*albicans* groups

Variable	*C. albicans* (n=43)	Non-*albicans* (n=10)	p-value
Age (y)	69±9 (49-85)	69±11 (47-84)	0.665
Male	14 (32.6)	2 (20.0)	0.374
Female	29 (67.4)	8 (80.0)	

C. albicans, *Candida albicans*.
Values are presented as mean±standard deviation (range) or number (%).

3. Resistance to Nystatin Treatment

Antifungal therapy showed a significant effect in resolving oral mucosal pain. Especially, all patients in the non-*albicans* group responded to therapy; i.e., the response to antifungal treatment was significantly better in the non-*albicans* group than in the *C. albicans* group (Fig. 4A).

Antifungal treatment was only discontinued when the discomfort in the oral mucosa did not show any further improvement. Some patients infected with *C. albicans* displayed an early response to nystatin treatment compared to

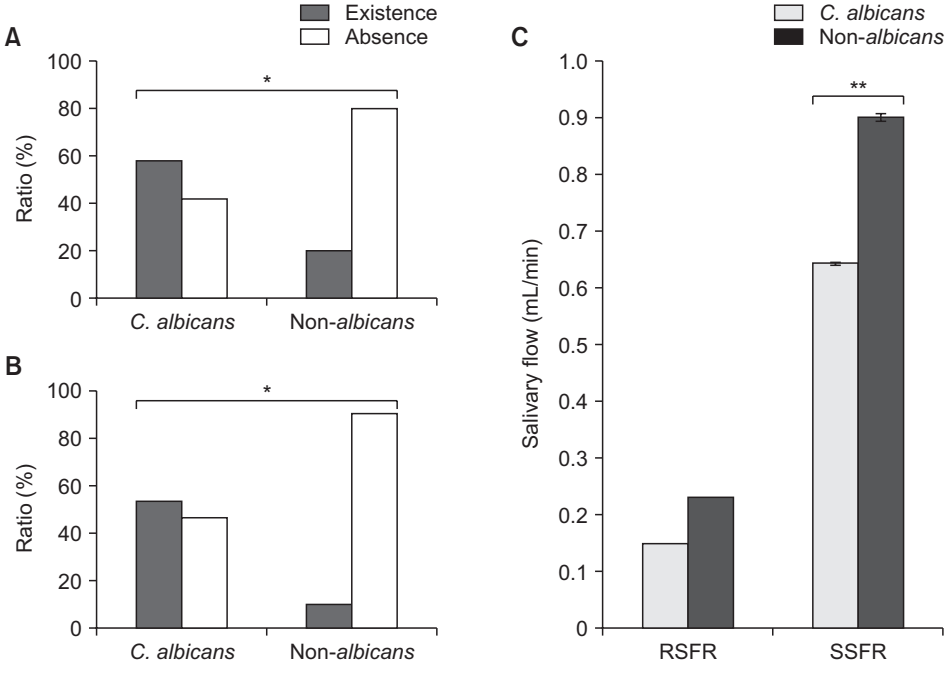

Fig. 2. Clinical characteristics of patients in the *C. albicans* and non-*albicans* groups. (A) Tongue erythema at the first visit. (B) Tongue coating at the first visit. (C) Sialometry findings for patients with oral *C. albicans* infection and those with non-*albicans Candida* infection. RSFR, resting whole-mouth salivary flow rate; SSFR, stimulated whole-mouth salivary flow rate; *C. albicans*, *Candida albicans*. *p<0.05 (Pearson's chi-square test), **p<0.05 (Mann – Whitney U test).

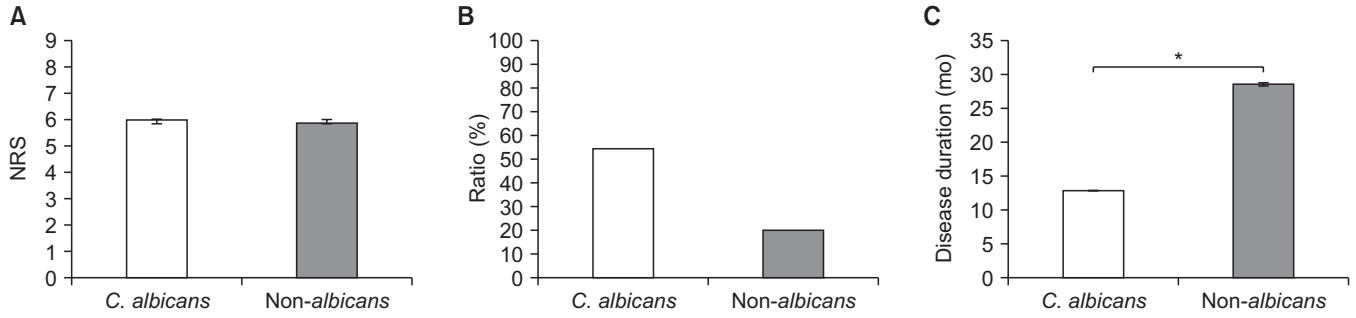

Fig. 3. Clinical characteristics of patients in the *C. albicans* and non-*albicans* groups. (A) The NRS assesses the degree of pain at the first visit between patients infected with *C. albicans* and patients infected with non-*albicans candida*. (B) Number of patients with hyperalgesia during the intake of irritating foods among patients in the *C. albicans* and non-*albicans* groups. (C) Disease durations among patients in the *C. albicans* and non-*albicans* groups. NRS, numerical rating scale; *C. albicans*, *Candida albicans*; Disease duration, the time from the onset of the disease to the hospital visit. *p<0.05, p-values were obtained by independent t-test, Pearson's chi-square test and Mann-Whitney U test.

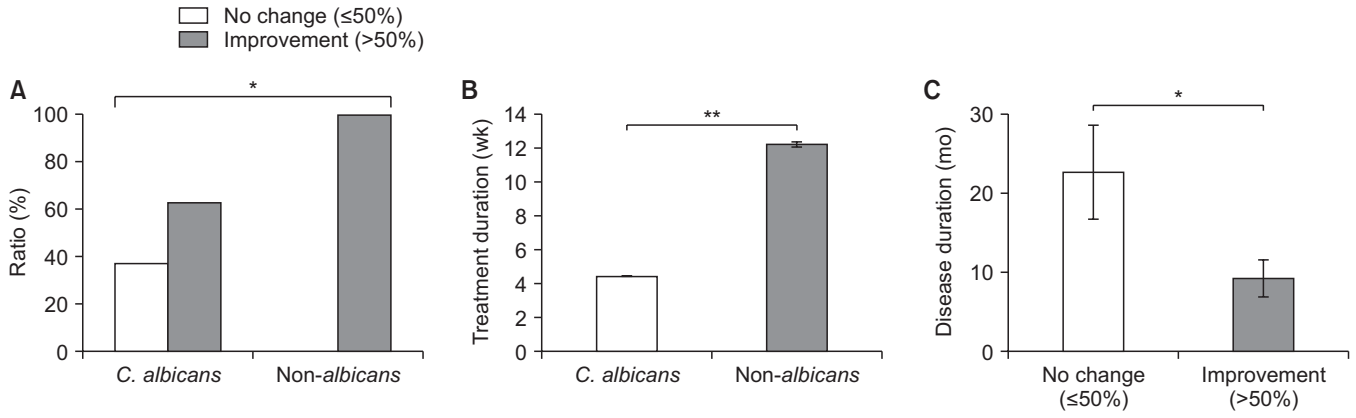

Fig. 4. Characteristics of antifungal treatment outcomes in patients in the *C. albicans* and non-*albicans* groups. (A) Outcomes of antifungal treatment (percentage of patients showing more than 50% improvement in pain as determined by the NRS at the first visit). (B) Duration of treatment with antifungal agents in patients in the *C. albicans* and non-*albicans* groups. (C) Disease duration according to antifungal treatment outcomes in the *C. albicans* group. NRS, numerical rating scale; *C. albicans*, *Candida albicans*. *p<0.05, **p<0.01, p-values were obtained by Pearson's chi-square test and Mann-Whitney U test.

those infected with non-*albicans* and responded to antifungal treatment even after 2 weeks. Interestingly, one-third of the patients infected with *C. albicans* did not show any response to antifungal treatment. Mucosal lesions improved; however, the severity of pain was not affected. Conversely, in all patients in the non-*albicans* group, oral mucosal discomfort was resolved by the antifungal therapy; the treatment period was almost three times longer than that in the *albicans* group, suggesting that patients infected with non-*albicans* species required longer durations of antifungal treatment (Fig. 4B).

Considering the factors and clinical characteristics that determine response to antifungal therapy in patients in the *albicans* group, it was found that response to therapy was dependent on the duration of the disease. Patients whose conditions did not improve with nystatin treatment reported a significantly longer disease duration than those whose symptoms were resolved, implying that the factor most closely related to symptom improvement by antifungal treatment was the disease duration (the time from the onset of the disease to the hospital visit) (Fig. 4C).

4. Clonazepam as Adjuvant Therapy

Thirteen patients infected with *C. albicans* who were resistant to antifungal treatment were additionally treated with clonazepam for 4-6 weeks, and the NRS scores of 11 patients (84.6%) showed significant improvement (Fig. 5A). The 11 *C. albicans* patients with symptom improvement (>50%) reported a shorter disease duration than those with no symptom improvement (<50%) and revealed a

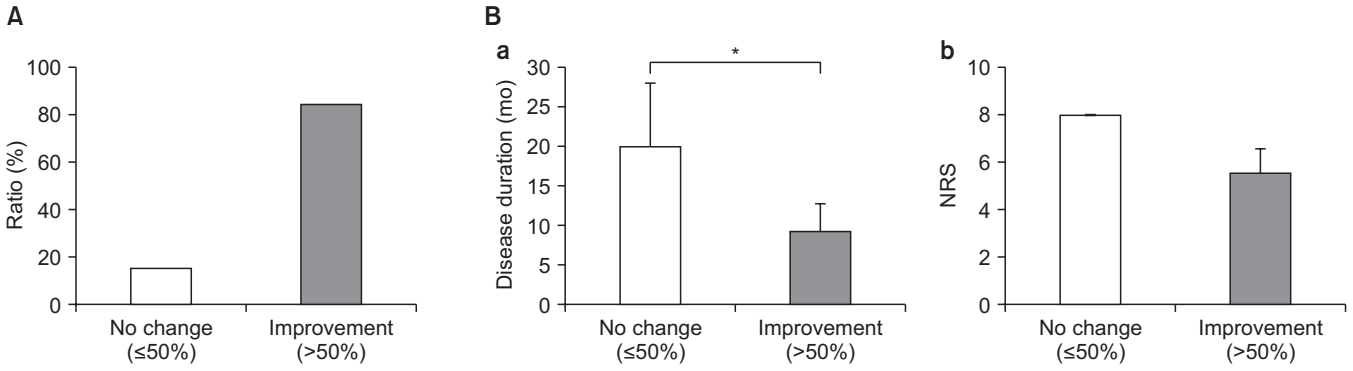

Fig. 5. Characteristics of clonazepam treatment outcomes in *C. albicans*-infected patients showing resistance to antifungal treatment. (A) Clonazepam treatment outcome. (B) Disease durations and NRS scores (degree of chief complaints at first visit) according to clonazepam treatment outcomes. NRS, numerical rating scale; *C. albicans*, *Candida albicans*. (a) Disease duration, (b) NRS. *p<0.05, p-values were obtained by Mann-Whitney U test.

lower NRS score than those with no symptom improvement (<50%).

Four patients who were infected with non-*albicans* species of *candida* that required additional treatment with clonazepam for the residual nonpainful mild discomfort showed improvement (3 patients with 100% cure, data not shown). One patient who complained of persistent, nonpainful mild discomfort even after clonazepam treatment suffered from zinc deficiency and used antipsychotic medications for anxiety symptoms.

DISCUSSION

Many patients present to a hospital with complaints of burning and tingling sensations and discomfort in the oral mucosa. However, most of them have minor erythematous lesions in the oral cavity or slight tongue coatings while some have no definite lesions or no lesions at all. In this study, among the 53 *candida* culture-positive patients, 8 (1 (2.3%) with *C. albicans*, 7 (70.0%) with non-*albicans*) did not show any signs of oral mucosal lesions and their symptoms improved after antifungal therapy. Even in cases of patients without any specific mucosal abnormalities, if a patient complains of pain in the oral mucosa, possibility of candidiasis exists, especially of infection with a non-*albicans* species. Therefore, it is important to confirm the presence of *candida* infection and the *candida* species by culture.

C. albicans can produce proteinases in higher amounts than non-*albicans* species, which enables them to easily break epithelial adhesions. This ability of *C. albicans* is related to the severity of erythematous *candida* lesions [24,25]. In general, the mucosal infiltration ability and the induction of host inflammation are weaker in the non-*albicans* species of *candida* than in *C. albicans*. Blastophores of non-*albicans* species of *candida*, such as *C. glabrata*, are phagocytosed by macrophages as well as by *C. albicans*. In contrast to *C. glabrata*, *C. albicans* can form hyphae that can kill macrophages during internalization [26]. Non-*albicans* species of *candida*, which usually possess more hydrophobic properties than *C. albicans*, can attach to the surfaces of dentures and prostheses [11]. In the absence of these mediators, non-*albicans* species rarely cause infections. Therefore, mucosal symptoms due to infection with *C. albicans* are worse than those due to infection with non-*albicans* species (Fig. 2, 3A, B). It is believed that the severity of these symptoms can lead patients infected with *C. albicans* to visit a hospital earlier than those infected with non-*albicans* species (Fig. 3C).

Depending on the fungal species, the response to antifungal therapy is different. The number of patients infected with *C. albicans* who were resistant to nystatin treatment was significantly higher than the number of those infected with non-*albicans* species. The principal factors that affect the therapeutic efficacy in patients infected with *C. albicans* are the duration of the disease and the severity of pain at the first visit. As mentioned earlier, *C. albicans* is known to be more virulent than non-*albicans* species of *candida*

and can characteristically produce more proteases and form hyphae better than non-*albicans* species of *candida*; thus, it can deeply penetrate the epithelium and cause inflammation around the peripheral nerves [26]. In this process, various proinflammatory cytokines secreted as a part of the immune response include interleukin-1β, interleukin-6, and tumor necrosis factor-α. These cytokines are known to cause inflammatory hyperalgesia [27,28]. Another hypothesis states that the ability of *C. albicans* to penetrate the epithelium and cause inflammation around the chorda tympani nerves of the taste buds could lead to the denervation of the nerves and alternative trigeminal nerve innervation. This could result in pain and sensitivity during the consumption of hot foods [29]. The response to antifungal agents could be affected due to the associated hyperalgesia. A longer duration of symptoms before treatment could increase the possibility of neurosensitization. Non-*albicans* species of *candida* possess decreased ability to infiltrate deeper tissues; thus, they reside in the surface layer or under the denture and have less interaction with the host [30,31], suggesting that intractable neurosensitization will be less frequent even with a longer disease duration. This is thought to be the reason for the lower nystatin resistance. However, because of the increased denture adhesiveness of non-*albicans* species of *candida*, if the appropriate and complete antifungal treatment is not provided, the recurrence rate would be high and the treatment period could be longer (Fig. 4B) [11,32].

In 54.3% of patients infected with *C. albicans*, symptoms of neurosensitization, such as hyperalgesia, were evident. In such cases, no response to antifungal agents was observed. *Candida*-induced hyperalgesia can be regarded as secondary BMS. The treatment of BMS is generally focused on symptomatic relief, just for other neuropathic pain diseases [33]. Clonazepam modulates pain by enhancing the neural inhibition mediated by gamma-aminobutyric acid [34]. Clonazepam therapy is the most widely accepted treatment modality among other pharmacologic options, including tricyclic antidepressants, benzodiazepines, anticonvulsants, alpha-lipoic acid, and capsaicin [4]. Therefore, clonazepam was used as a treatment modality for BMS.

The results of this study showed that treatment with clonazepam showed a positive response in patients with *Candida* who were resistant to nystatin (Fig. 5). Nonresponders had longer disease duration (late visit to the hospital) than responders to clonazepam treatment and more intense pain at the first visit. Similar studies conducted on neuropathic pain have shown similar results to our findings. A poor

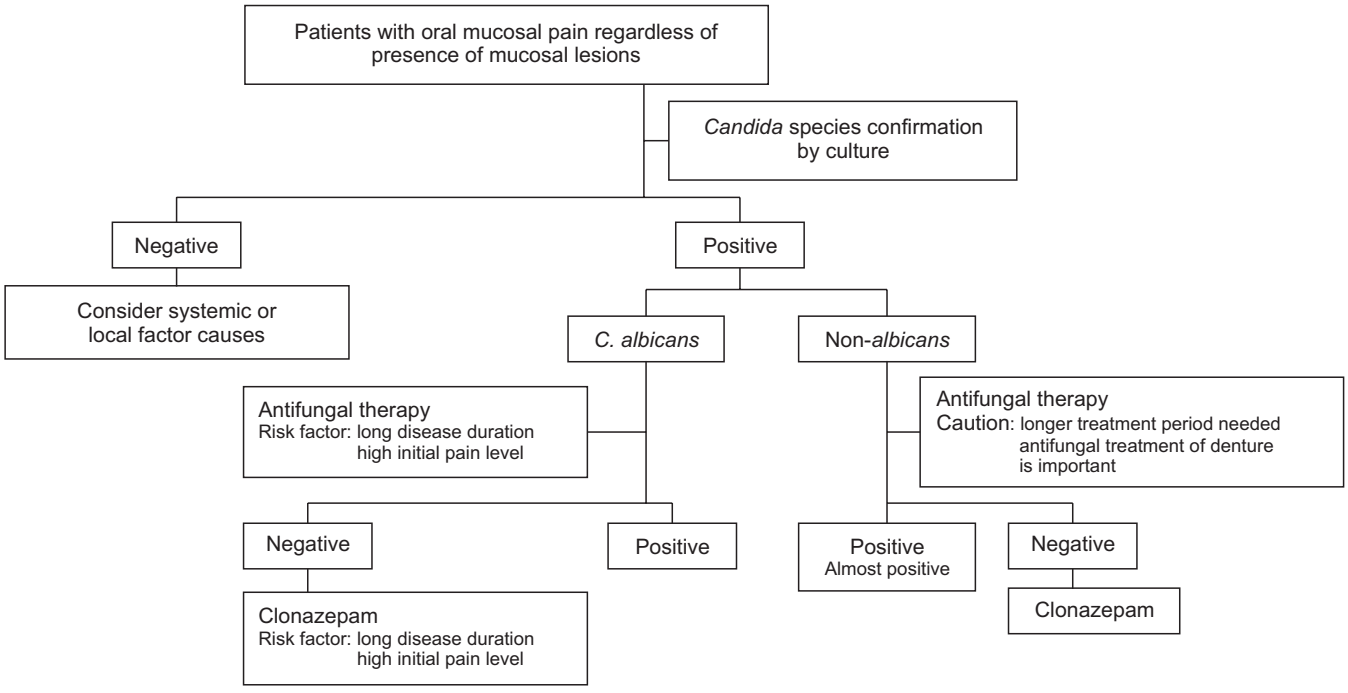

Fig. 6. Suggested treatments and associated risk factors. *C. albicans*, *Candida albicans*.

prognosis and low treatment efficacy are associated with severe initial symptoms [33] and longer disease durations [35-37].

The present study was conducted to investigate the clinical characteristics of *candida* infections and treatment methods against *Candida* strains by analyzing the clinical symptoms and response to treatment according to the species of *Candida*. Further long-term studies evaluating the characteristics and therapeutic efficacy of mixed infections with *candida* species will be required to expand the applicability of our findings in the future.

Based on the results of this study, the authors suggest that samples obtained from a person with oral mucosal pain should first be cultured for the detection of *candida* and determination of its species. Second, the patient (especially patients infected with non-*albicans* species) should receive standard antifungal therapy according to the culture results, even if mucosal lesions are not evident. If no response to antifungal therapy is evident, clonazepam can be used as the primary treatment modality for pain relief, especially in patients infected with *C. albicans*. In addition, the sooner patients visit the hospital, the higher the probability of successful treatment. Adequate patient education is required to promote early seeking of medical care for such lesions (Fig. 6).

CONFLICT OF INTEREST

Soo-Min Ok serves as an editor at the Journal of Oral Medicine and Pain; however, she has no role in the decision to publish this article. There are no other potential conflicts of interest relevant to this article.

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