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Original Article

Efficacy of oral nystatin treatment for patients with oral mucosal dysesthesia but without objective oral mucosal manifestations and necessity of *Candida* culture test before oral nystatin treatment

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KEYWORDS
Nystatin treatment;
Oral mucosal dysesthesia;
Candida culture;
Oral candidiasis;
Burning mouth syndrome

Abstract *Background/purpose:* Previous studies have shown that some of the patients with oral mucosal dysesthesia but without objective oral mucosal manifestations (so-called oral dysesthesia patients in this study) may have good responses to oral nystatin treatment. This study evaluated the efficacy of oral nystatin treatment for oral dysesthesia patients and the necessity of *Candida* culture test before oral nystatin treatment.
Materials and methods: The 147 oral dysesthesia patients were divided into 3 groups: *Candida* culture (+) group (n = 29), *Candida* culture (−) group (n = 34), and without *Candida* culture test group (n = 84), and treated with oral nystatin. The pain improvement was evaluated by the reduction of numeric pain rating scale (NRS) and global perceived effects (GPE). We defined the GPE score ≥4 points as a great improvement.
Results: We found that 44.8% of 29 patients in the *Candida* culture (+) group, 47.1% of 34 patients in the *Candida* culture (−) group, and 47.6% of 84 patients in the without *Candida* culture test group showed a significant reduction in the NRS score and achieved a great improvement after oral nystatin treatment for 1–4 weeks. Moreover, 72.4% of our 29 patients with *Candida* culture test achieved a great improvement within one week, and all the 29 patients achieved a great improvement within 4 weeks of oral nystatin treatment.
Conclusion: A portion of our oral dysesthesia patients are infected by *Candida* and it is beneficial to our patients to use oral nystatin treatment before the *Candida* culture test.

Introduction

In the oral medicine clinic, many patients with oral mucosal dysesthesia but without objective oral mucosal manifestations (so-called oral dysesthesia patients in this study) are encountered. The three most common symptoms for oral dysesthesia patients are burning, numbness, and tingling sensation on the tongue or hard palate mucosa. However, these oral dysesthesia patients are usually without visible or palpable oral mucosal manifestations or pain but are often diagnosed as having burning mouth syndrome (BMS).

The BMS is typically characterized by the burning and painful sensations on the oral mucosa which is normal in appearance.[1,2] BMS is more commonly found in women than in men,[3,4] particularly in women during or after menopause.[5–7] The etiology of BMS is multifactorial, and BMS can be classified as primary and secondary BMS, traditionally.[1–3] First, primary BMS is diagnosed by exclusion and the etiology of primary BMS is unknown. There are no organic local or systemic causes identified in patients with primary BMS. Some researchers consider the primary BMS to be a neuropathic disorder[1,8–12] or caused by psychological factors.[11–14] Thus, these patients with primary BMS are often treated with anticonvulsants or antidepressants.[1,13,15–17] Next, patients with secondary BMS are caused by local or systemic factors, such as oral candidiasis, hormonal imbalance, and/or nutrient deficiency.[3,11,18–20]

Oral candidiasis, an opportunistic infection, caused by *Candida* overgrowth, is a common cause of oral mucosal pain.[21] Clinically, oral candidiasis can be divided into pseudomembranous, erythematous, and hyperplastic types according to the different clinical manifestations.[22–24] In the past, the presence of *Candida* infection was preliminarily determined by whether obvious lesions were visible to the naked eyes. Recently, some research groups proposed the existence of a new type of oral candidiasis, that is, oral candidiasis with symptoms, usually oral mucosal pain, but without objective oral mucosal manifestations,[20,25–27] and Cho et al. named this type of oral candidiasis "morphologically normal symptomatic candidiasis".[28]

Various antifungal agents are used for the treatment of oral candidiasis, including topical and systemic agents.[22,29] Among them, topical antifungal agents are the main recommended treatment for uncomplicated oral candidiasis. Nystatin is one of the most commonly used topical antifungal drugs with high efficacy, low cost, and fewer side effects, due to no absorption from the gastrointestinal tract.[29–32] There are various available forms of nystatin, such as oral suspension, topical cream, and oral pastille.[24,31,33–37] Empirically, the treatment duration of nystatin can vary from 1 or 2–4 weeks.[24,31,32,37,38]

Clinically, the symptoms of morphologically normal symptomatic candidiasis are similar to the symptoms of BMS, and if the patients have no visible oral mucosal lesions, they are easy to be diagnosed as primary BMS and treated with antidepressants or anticonvulsants, such as clonazepam.[12,15,16] However, for part of these patients, the effect of antidepressant or anticonvulsant treatment is limited. Hence, some patients with morphologically normal symptomatic candidiasis are suffered from pain that lasted for a long time, and they usually consult a variety of departments for treatment.[4] Nevertheless, owing to the normal oral mucosal morphology, few physicians link this kind of oral mucosal pain to oral candidiasis. Based on our past clinical experience, we tried to treat oral dysesthesia patients with oral nystatin, and some of them improved greatly in a relatively short period of time. Therefore, this study tried to evaluate the efficacy of oral nystatin treatment for oral dysesthesia patients and the necessity of *Candida* culture test before oral nystatin treatment.

Materials and methods

Ethical approval

This study was approved by the Institutional Review Board and Medical Ethics Committee of Chang Gung Memorial Hospital (No. 202200307B0). This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study design

This study examined 252 patients who visited the oral mucosal disease clinic of Taipei Chang Gung Memorial Hospital (CGMH) between 2016 and 2021 with a chief complaint of oral mucosal pain or oral dysesthesia. The scheme of present study is shown in Fig. 1.

Inclusion and exclusion criteria

The inclusion criteria for the patients in this study were described as follows: (1) those between 19 and 89 years old; (2) those with oral mucosal pain or oral mucosal dysesthesia; (3) those with other subjective symptoms, such as dry mouth, abnormal oral sensation, and taste dysfunctions; and (4) those without obvious oral mucosal lesions.

The exclusion criteria for the patients were described as follows: (1) those with obviously abnormal oral mucosa; (2) those with neurological disorders; (3) those with jawbone lesions; (4) those with dental problems; (5) those who received other treatments; (6) those who refused medication; and (7) those lost to the follow-up.

Diagnostic procedures and treatment

The clinical information including the age, gender, personal habit, systemic disease, all medications being taken, characteristics of oral mucosal dysesthesia, and nystatin treatment duration was collected from every oral dysesthesia patient. A single oral pathologist (M.L.C.) examined the oral cavities, prescribed the nystatin, and evaluated the oral nystatin treatment responses of all oral dysesthesia patients.

Laboratory blood tests, including complete blood counts, serum iron, ferritin, zinc, folic acid, vitamin B12, fasting blood glucose (FBG), and glycated hemoglobin (HbA1c) were routinely examined at their first visit and collected within 2 months from the hospital records. The purpose of the blood tests was to clarify the general condition of patients and investigate the potential causes to exclude all possible diseases and hematinic deficiencies. All the above blood tests were performed in the Department of Laboratory Medicine, CGMH.

The method of the *Candida* culture test was described as follows. The oral mucosal surface where experienced pain or dysesthesia was firmly swabbed 4—5 times with a COPAN eSwab (Copan Italia SpA, Brescia, Italy) or a simple cotton swab. The sample was then cultured on inhibitory mold agar (IMA), IMA plate with chloramphenicol and gentamicin (ICG), and brain heart infusion (BHIA) agar, with the streaking method. After 5 days, the colonies were counted

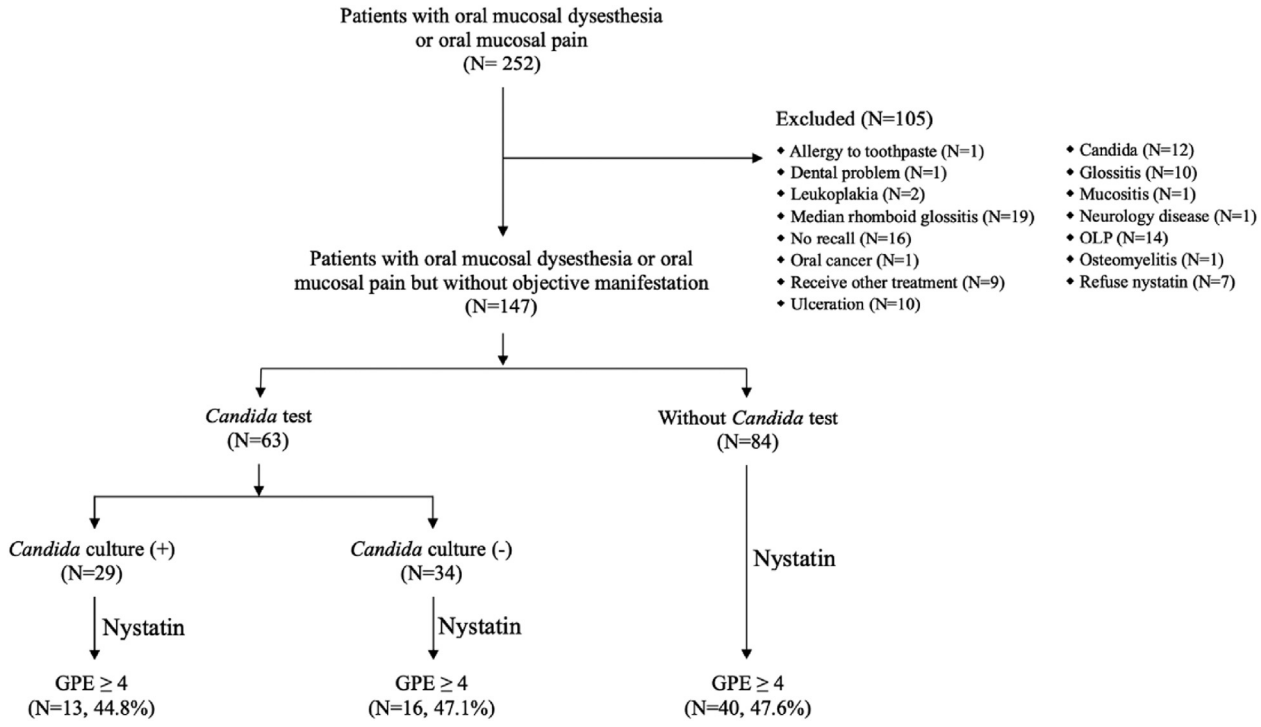

Fig. 1 Flow chart for analysis of patients with oral mucosal dysesthesia but without objective oral mucosal manifestations. OLP: oral lichen planus.

and sent into a matrix-assisted laser desorption/ionization-time of flight mass spectrometer (MALDI-TOF-MS) to execute bacteria or fungi identification. The *Candida* culture tests were performed in the Department of Laboratory Microbiology, CGMH.

All oral dysesthesia patients were treated with an antifungal drug, nystatin oral suspension (MYCOSTATIN™ Oral Suspension, Genovate, Biotechnology Co., Ltd., Hsinchu, Taiwan; 100,000 U/mL; 4–6 mL; four times a day). Patients were instructed to gargle the nystatin oral suspension and maintain the solution contacting all the oral mucosa, especially the symptomatic oral mucosa for at least 10 min, and then spat it out. All oral dysesthesia patients were instructed and reviewed their nystatin usage methods at the next week recall.

Assessment of the effectiveness of oral nystatin treatment

After oral nystatin treatment, improvement of oral mucosal pain or dysesthesia was evaluated with the reduction of numeric pain rating scale (NRS) and global perceived effects (GPE). NRS is one of the most commonly used pain scales in medicine, with the pain scale ranging from 0 to 10 (no pain to the most severe pain, respectively).[39–41] GPE is an effectiveness assessment tool that measures a change in the patient's chief complaint. In this study, GPE was adapted from Cavalcanti et al.,[42–44] and it was scored by the patient (self-reported description) on a 5-point scale, ranging from: 1 = deterioration; 2 = no difference; 3 = mild improvement; 4 = much improvement; 5 = entirely improvement. We defined the GPE score $\geq$4 points as a great improvement of symptoms after oral nystatin treatment.

The scheme of the follow-up assessment and treatment protocol is shown in Fig. 2. Patients reporting the GPE score $\leq$2 points were regarded as insusceptibility to nystatin, resulting in diagnosis of BMS and termination of oral nystatin treatment after 1 week. Patients reporting the GPE score = 5 points were continually treated with oral nystatin for one more week and then discontinued. Patients reporting the GPE score = 3 or 4 points were constantly treated with oral nystatin and regularly followed up on the efficacy until they felt entirely improvement (the GPE score = 5 points) or stopped feeling improvement (after reporting several times of the GPE score = 4 points) but were satisfied with the treatment. On the other hand, patients repeatedly reporting the GPE score = 3 points or unsatisfied with solely oral nystatin treatment, even with the GPE score = 4 points, were diagnosed as having BMS, perhaps with oral candidiasis simultaneously, and arranged for additional treatments.

Statistical analysis

Statistical analyses were performed with SPSS software (SPSS version 28.0.1; IBM, Chicago, IL, USA). The differences in age, NRS, and blood test results among groups were analyzed by two-tail *t*-test or analysis of variance (ANOVA), where appropriate. The differences between the initial NRS and final NRS in each group were analyzed by paired samples and two-tail *t*-test. The differences in gender, personal history, systemic disease, insomnia, taking hypnotics, dry mouth symptom, taste disturbance, types of oral mucosal dysesthesia, and the proportion of the GPE score $\geq$4 points were analyzed by chi-square test. In ANOVA test, the homogeneity of variance was analyzed by Levene's test at first. If the variance was homogeneous, LSD test would be conducted as the post hoc test of ANOVA. Otherwise, Games–Howell test would be conducted as the post hoc test of ANOVA in which the variance was heterogeneous. The result was considered to be significant if the *P*-value was less than 0.05.

Results

Of the 252 patients reviewed, 70 were excluded from the study because they did not meet the diagnostic criteria, one had the neurologic disease, two had dental problems, 16 were dropped, 7 were opposed to taking oral nystatin, and 9 received other treatments. Therefore, 147 (25 men and 122 women, age range 19–89 years, mean age 58.0 $\pm$ 14.1 years) oral dysesthesia patients were further analyzed in this study. Among the 147 oral dysesthesia patients, 63 were examined with *Candida* culture test; of them, 29 were positive and 34 were negative. The other 84 patients did not receive *Candida* culture test. Therefore, these 147 oral dysesthesia patients were divided into three groups: the *Candida* culture-positive [*Candida* culture (+)] group (n = 29), the *Candida* culture-negative [*Candida* culture (−)] group (n = 34), and the without *Candida* culture test group (n = 84) (Fig. 1).

Clinical characteristics and laboratory data

The demographic and clinical characteristics of the 147 oral dysesthesia patients are shown in Table 1. The age distribution, gender distribution, and medical history showed no significant differences among the three groups. The medical history here included patients with systemic disease, insomnia, or taking hypnotics. Less than 10% of patients had alcohol, betel nut, and cigarette consumption. Moreover, 78.2% of patients complained of dry mouth and 37.4% complained of taste disturbances (Table 1). Most of the taste disturbance patients had hypergeusia and/or phantogeusia, only a few patients felt hypogeusia. Hypergeusia patients felt very sensitive to spicy or salty food, and phantogeusia patients could feel salty, sweet, or bitter sensations even without eating any food.

Because men tended to have higher blood hemoglobin, serum iron, and ferritin levels than women, these three mean levels were calculated separately for men and women (Table 2). There were no significant differences in laboratory blood data among the three groups, except that the ferritin level of female patients in the *Candida* culture (+) group was nearly twice as high as that in the *Candida* culture (−) group. The HbA1C values in all three groups were slightly above the normal upper limit (5.6%) (Table 2).

The *Candida* species in the 29 patients in the *Candida* culture (+) group are shown in Table 3. Of the 29 patients with the *Candida* culture (+), 22 (75.9%) were infected with

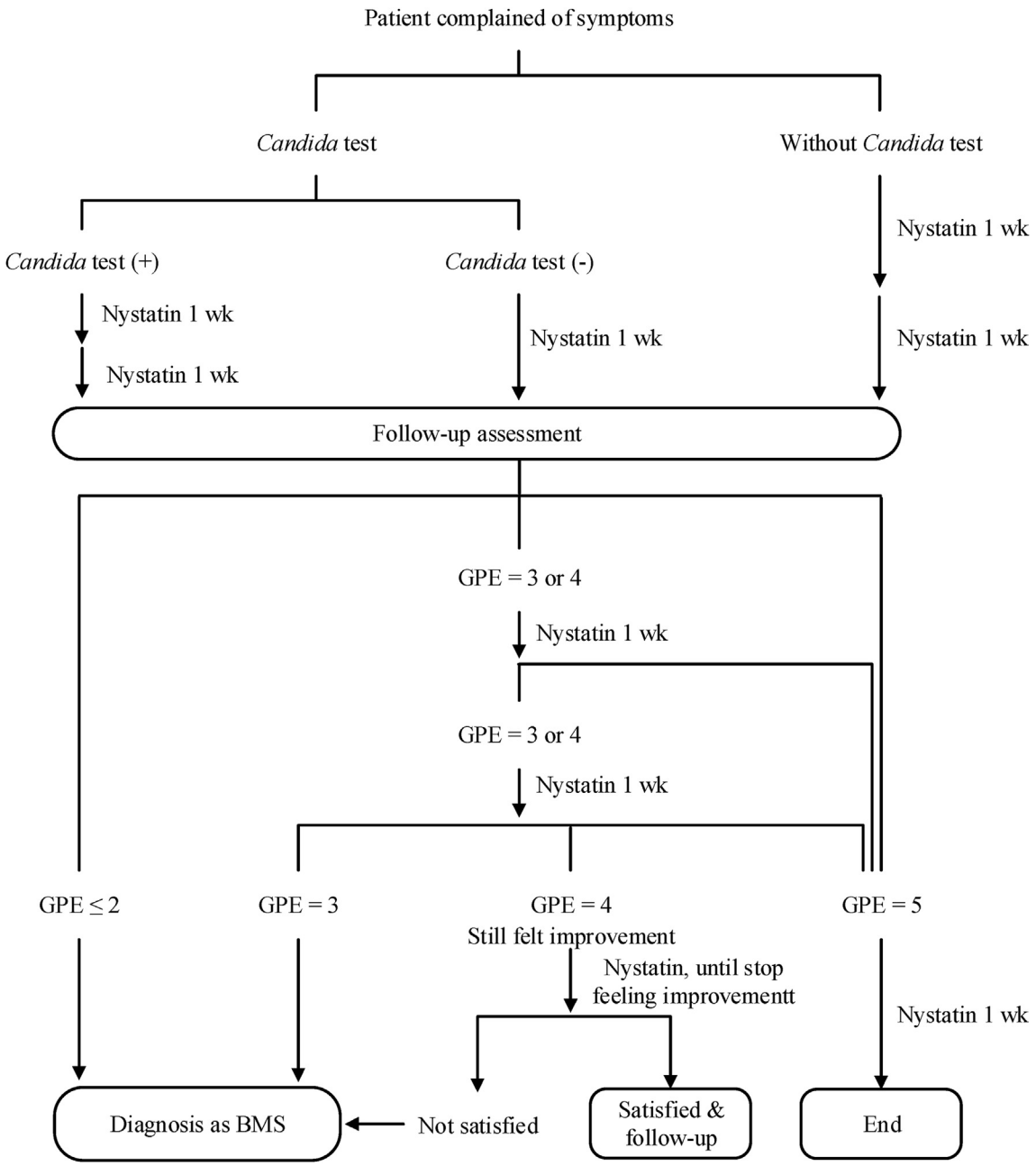

Fig. 2 Flow chart of oral nystatin treatment and assessment of efficacy of oral nystatin treatment.

Candida albicans and the other 7 (24.1%) were infected with other *Candida* species (Table 3).

Outcome of oral nystatin treatment

After oral nystatin treatment, 69 (46.9%) of the 147 patients felt much improvement or entirely improvement (defined as the GPE score $\geq$4 points). Of the 69 patients with the GPE score $\geq$4 points, 13 (44.8% of 29 patients) were in the *Candida* culture (+) group, 16 (47.1% of 34 patients) were in the *Candida* culture (−) group, and 40 (47.6% of 84 patients) were in the without *Candida* culture test group (Fig. 1). There was no significant difference in the level of symptom improvement among the three different groups ($P > 0.05$).

A comparison of the changes of NRS score in the three groups with the GPE score $\geq$4 points before and after oral nystatin treatment is shown in Table 4. All three groups showed a significant pain reduction (all three *P*-value $\leq$0.003) after oral nystatin treatment. However, there were no statistically significant differences in the initial or final NRS scores among the three groups (both *P*-values $>$ 0.05) (Table 4).

We also found that of the 29 patients with *Candida* culture test and the GPE score $\geq$4 points, 10 *Candida* culture (+) and 11 *Candida* culture (−) patients achieved a GPE score $\geq$4 points after the first week of oral nystatin

Table 1 Demographic and clinical characteristics of patients with oral mucosal dysesthesia but without objective oral mucosal manifestations.

Demographic and clinical characteristics	*Candida* culture (+)	*Candida* culture (−)	Without *Candida* culture test	Total
	(n = 29)	(n = 34)	(n = 84)	(n = 147)
Age (y)				
Mean ± SD	60.1 ± 13.7	54.4 ± 16.8	58.7 ± 12.9	58.0 ± 14.1
Range	33–85	20–88	19–89	19–89
Gender				
Female	22 (75.9)	25 (75.8)	75 (89.3)	122 (83.0)
Male	7 (24.1)	8 (24.2)	9 (10.7)	25 (17.0)
Personal history				
Alcohol drinking	0 (0.0)	0 (0.0)	3 (3.6)	3 (2.0)
Betel nut chewing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cigarette smoking	4 (13.8)	0 (0.0)	5 (6.0)	9 (6.1)
Systemic disease	23 (79.3)	21 (61.8)	62 (73.8)	106 (72.1)
≥ 2 diseases	20 (69.0)	14 (41.2)	38 (45.2)	72 (49.0)
Insomnia	21 (72.4)	22 (64.7)	54 (64.3)	97 (66.0)
Taking hypnotics	16 (55.2)	19 (55.9)	34 (40.5)	68 (46.3)
Dry mouth	26 (89.7)	25 (73.5)	64 (76.2)	115 (78.2)
Taste disturbance	11 (37.9)	15 (44.1)	29 (34.5)	55 (37.4)

Abbreviations: "+", presence of *Candida*; "−", absence of *Candida*.
The data are presented as the patient number (%).

treatment. Moreover, all 29 patients with *Candida* culture test achieved a GPE score ≥4 points within 4 weeks of oral nystatin treatment (Table 5). Of the 13 *Candida* culture (+) patients with the GPE score ≥4 points, 2 achieved a GPE score = 5 points after 3 or 4 weeks of oral nystatin treatment. Of the 16 *Candida* culture (−) patients with the GPE score ≥4 points, 2 achieved a GPE score = 5 points after 1 week of oral nystatin treatment (Table 5).

Characteristics and types of oral mucosal dysesthesia

Oral dysesthesia patients complained of more than 10 different types of oral mucosal dysesthesia. One or more types of oral mucosal dysesthesia might present in the same patient. The different types of oral mucosal dysesthesia in 69 patients with the GPE score ≥4 points in the three

Table 2 Laboratory data of patients with oral mucosal dysesthesia but without objective oral mucosal manifestations.

Parameters	*Candida* culture (+)	*Candida* culture (−)	Without *Candida* culture test	*P*-value	Normal range
	(n = 29)	(n = 34)	(n = 84)		
FBG (mg/dL)	99.6 ± 30.2	97.4 ± 18.6	101.9 ± 27.5	0.749	70–100
HbA1c (%)	5.9 ± 0.9	5.9 ± 0.4	6.1 ± 1.7	0.834	4.6–5.6
Hb (g/dL)	13.3 ± 1.3	13.7 ± 1.4	13.1 ± 1.3	0.112	12–17.5
Female	13.0 ± 0.7	13.1 ± 1.0	12.9 ± 1.3	0.722	12–16
Male	14.1 ± 2.2	15.2 ± 0.9	14.7 ± 0.5	0.297	13.5–17.5
Iron (μg/dL)	93.3 ± 31.0	107.9 ± 51.9	97.0 ± 37.1	0.331	40–160
Female	87.7 ± 24.9	102.1 ± 44.8	95.9 ± 37.8	0.448	40–150
Male	113.0 ± 43.6	123.8 ± 69.0	106.5 ± 30.4	0.794	50–160
Ferritin (ng/mL)	236.9 ± 189.3	150.1 ±186.0	143.5 ± 123.7	0.027[a]	10–322
Female	217.0 ± 166.4[a]	98.7 ± 89.1[a]	131.1 ± 113.7	0.005[a]	10–291
Male	303.3 ± 258.8	291.5 ± 233.7	247.5 ± 161.1	0.900	22–322
Vitamin B_{12} (pg/mL)	978.6 ± 474.9	1002.6 ± 786.3	894.7 ± 432.1	0.585	197–771
Folic acid (ng/mL)	13.8 ± 5.7	14.0 ± 6.9	13.9 ± 8.5	0.996	4.6–18.7
Homocysteine (μM)	8.9 ± 2.0	10.1 ± 4.3	9.8 ± 2.6	0.282	<12
Zinc (μg/dL)	81.7 ± 11.7	85.8 ± 11.4	81.3 ± 10.6	0.150	70–120

ANOVA, significant difference between the groups, $P < 0.05$.
[a] Games–Howell post hoc test among groups. Abbreviations: "+", presence of *Candida*; "−", absence of *Candida*; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin.

Table 3 *Candida* species in the 29 patients in the *Candida* culture (+) group.

Candida species	n	%
Candida albicans	22	75.9
Candida guilliermondii	1	3.4
Candida parapsilosis	4	13.8
Candida parapsilosis complex	1	3.4
Candida (unrecognized)	1	3.4
Total	29	100.0

different groups of patients are summarized in Table 6. Burning (87.0%), numbness (53.6%), and tingling pain (46.4%) were the three most frequently complained types of oral mucosal dysesthesia. Of the 69 patients with the GPE score $\geq$4 points, 63 (91.3%) had more than one type of oral mucosal dysesthesia simultaneously and 8 (11.6%) had up to 5 types of oral mucosal dysesthesia (Table 6).

Analysis of 29 oral dysesthesia patients with *Candida* culture test and the GPE score $\geq$4 points, there was no statistically significant difference in the proportion of all the various oral mucosal dysesthesia between the 13 patients in the *Candida* culture (+) group and the 16 patients in the *Candida* culture (−) group. However, patients in the *Candida* culture (+) group reported a higher frequency of intense oral pain, such as sharp pain, while the patients in the *Candida* culture (−) group reported a higher frequency of mild oral pain, such as dull or itching pain (Fig. 3).

Discussion

In this study, we evaluated the efficacy of oral nystatin treatment for oral dysesthesia patients and the necessity of *Candida* culture before oral nystatin treatment. The 147 oral dysesthesia patients were divided into 3 groups: 29 in the *Candida* culture (+) group, 34 in the *Candida* culture (−) group, and 84 in the without *Candida* culture test group. All of the 147 oral dysesthesia patients were given the oral nystatin treatment. Of 29 patients in the *Candida* culture (+) group, 44.8% of them reported a significant improvement in their symptoms after oral nystatin treatment. Additionally, 47.1% of the 34 patients in the *Candida* culture (−) group demonstrated a significant improvement in oral mucosal pain after oral nystatin treatment, and the improvement rate was even slightly higher than that of patients in the *Candida* culture (+) group, although the difference was not statistically significant. Besides, the patients in the *Candida* culture (−) group got the best NRS reduction and took less time to achieve a GPE score $\geq$4 points. This surprising result was beyond our original inference that the oral nystatin treatment might have little effect on patients in the *Candida* culture (−) group. Consequently, from this evidence, we suggest that the oral mucosal pain in some oral dysesthesia patients in the *Candida* culture (−) group may result from oral candidiasis but the *Candida* infection is so mild that results in the inability to cultivate sufficient quantities of *Candida* for obtaining a positive culture result in the microbiology laboratory. Moreover, 47.6% of 84 patients in the without culture test group achieved a great improvement in oral mucosal pain after oral nystatin treatment, despite that we could not ensure whether they were infected by *Candida* or not at the beginning of oral nystatin treatment. This particular finding indicates that oral nystatin treatment may be the first-line treatment of choice for oral dysesthesia patients before we start other kinds of specific therapy for oral dysesthesia patients. There is no need to do the *Candida* culture test before the oral nystatin treatment.

At the early stage in our oral mucosal disease clinic, we used simple cotton swabs to get the samples for *Candida* culture test. Although the *Candida* culture results were nearly all negative, approximately half of the oral dysesthesia patients reported excellent responses to oral nystatin treatment. This particular phenomenon made us ponder the possibility of sampling variation using simple cotton swabs for sampling and the necessity of sampling for *Candida* culture test before the start of oral nystatin treatment. Hence, some oral dysesthesia patients were directly treated with oral nystatin without doing the *Candida* culture tests. The strategy has changed to arrange a regular *Candida* culture test after the hospital replaced simple cotton swabs with the eSwabs, which were reported to have better sampling performance for *Candida* culture tests.[45]

Although these patients' oral mucosae were morphologically normal clinically, positive cultures for *Candida* were observed in 46.03% (29/63) of the patients in our study, which was similar to 45.16% (14/31) of *Candida* culture positive rate for Brazilian BMS patients,[46] although the sampling methods were different. Many previous studies

Table 4 Changes of the numeric pain rating scale (NRS) score in patients with the global perceived effects (GPE) score $\geq$4 points before and after oral nystatin treatment in the three different groups of oral dysesthesia patients.

NRS score	*Candida* culture (+)	*Candida* culture (−)	Without *Candida* culture test	
	(n = 13)	(n = 16)	(n = 40)	
Initial NRS score	4.0 ± 2.5	5.9 ± 2.9	4.4 ± 2.1	$P = 0.058$[b]
Final NRS score	1.8 ± 1.3	2.1 ± 1.5	1.5 ± 1.5	$P = 0.300$[b]
	$P = 0.003$[a]	$P < 0.001$[a]	$P < 0.001$[a]	

[a] Paired samples and two-tailed Student *t*-test between the initial and final NRS scores in each group.
[b] Analysis of variance (ANOVA) among the three different groups.

Table 5 The oral nystatin treatment period required for the patient to feel much improvement or entirely improvement (defined as the global perceived effects (GPE) score ≥4 points).

Treatment periods (weeks)	*Candida* culture (+) (n = 13)		*Candida* culture (−) (n = 16)	
	GPE = 4	GPE = 5	GPE = 4	GPE = 5
1	10	0	9	2
2	11	0	12	2
3	11	1	14	2
4	12	1		

Abbreviations: "+", presence of *Candida*; "−", absence of *Candida*.

assessed the relationship between *Candida* and oral mucosal dysesthesia/BMS,[47] and all of them tried to clarify the association of the proposed causative/precipitating factors for oral mucosal dysesthesia/BMS. However, the conclusion shows no significant association of oral mucosal dysesthesia with the presence or the load of oral *Candida*.[46−49] Based on the above results and the concept that oral *Candida* is a common oral flora, most scientists still think that oral candidiasis is just a coincidence in BMS patients.[46,49]

Approximately 45%−48% of the oral dysesthesia patients in our study showed pain relief after oral nystatin treatment, irrespective of their culture results. Moreover, for the evaluation of NRS reduction after oral nystatin treatment, oral dysesthesia patients in the three different groups all presented a significant reduction in the oral pain level after oral nystatin treatment. Therefore, we aroused an idea that if antifungal treatment eliminates the burning or various kinds of abnormal oral sensations in patients with normal-looking oral mucosa, it may be explained that our oral dysesthesia patients still had some kind of mild but invisible oral candidiasis. This kind of oral candidiasis is not classified but was once mentioned by Cho et al. as morphologically normal symptomatic candidiasis.[28] However, we may need further researches, especially the molecular biological and genetic studies, to prove that some oral dysesthesia patients do still have candidiasis even if the *Candida* culture is negative.

Indeed, there were still half of the oral dysesthesia patients in all three different groups who did not achieve a GPE score ≥4 points after oral nystatin treatment, and part of the patients were not satisfied with the improvement, even though they had achieved a GPE score ≥4 points. These oral dysesthesia patients might have primary BMS or

Table 6 The different types of oral mucosal dysesthesia in patients with the global perceived effects (GPE) score ≥4 points in the three different groups.

Types of oral mucosal dysesthesia	*Candida* culture (+) (n = 13)	*Candida* culture (−) (n = 16)	Without *Candida* culture test (n = 40)	Total (n = 69)
Burning	11 (84.6)	15 (93.8)	34 (85.0)	60 (87.0)
Numbness	8 (61.5)	13 (81.3)	16 (40.0)	37 (53.6)
Tingling pain	7 (53.8)	8 (50.0)	17 (42.5)	32 (46.4)
Fullness pain	3 (23.1)	5 (31.3)	10 (25.0)	18 (26.1)
Sharp pain	5 (38.5)	1 (6.3)	6 (15.0)	12 (17.4)
Others	2 (15.4)	3 (18.8)	2 (5.0)	7 (10.1)
Itching	0 (0.0)	3 (18.8)	4 (10.0)	7 (10.1)
Dull pain	0 (0.0)	2 (12.5)	3 (7.5)	5 (7.2)
Cutting pain	1 (7.7)	1 (6.3)	2 (5.0)	4 (5.8)
Sore pain	0 (0.0)	1 (6.3)	2 (5.0)	3 (4.3)
Throbbing pain	1 (7.7)	0 (0.0)	0 (0.0)	1 (1.4)
Compression pain	1 (7.7)	0 (0.0)	0 (0.0)	1 (1.4)
Simultaneous presence of types of oral mucosal dysesthesia in patients				
1 type	0 (0.0)	0 (0.0)	6 (15.0)	6 (8.7)
2 types	7 (53.8)	6 (37.5)	12 (30.0)	25 (36.2)
3 types	2 (15.4)	5 (31.3)	13 (32.5)	20 (29.0)
4 types	1 (7.7)	1 (6.3)	8 (20.0)	10 (14.5)
5 types	3 (23.1)	4 (25.0)	1 (2.5)	8 (11.6)
≥ 1 type	13 (100.0)	16 (100.0)	34 (85.0)	63 (91.3)

"Others" represented the discomfort or pain that differed from the types of pain listed above, including but not limited to roughness and foreign body sensation.
Abbreviations: "+", presence of *Candida*; "−", absence of *Candida*.
The data are presented as the patient number (%).

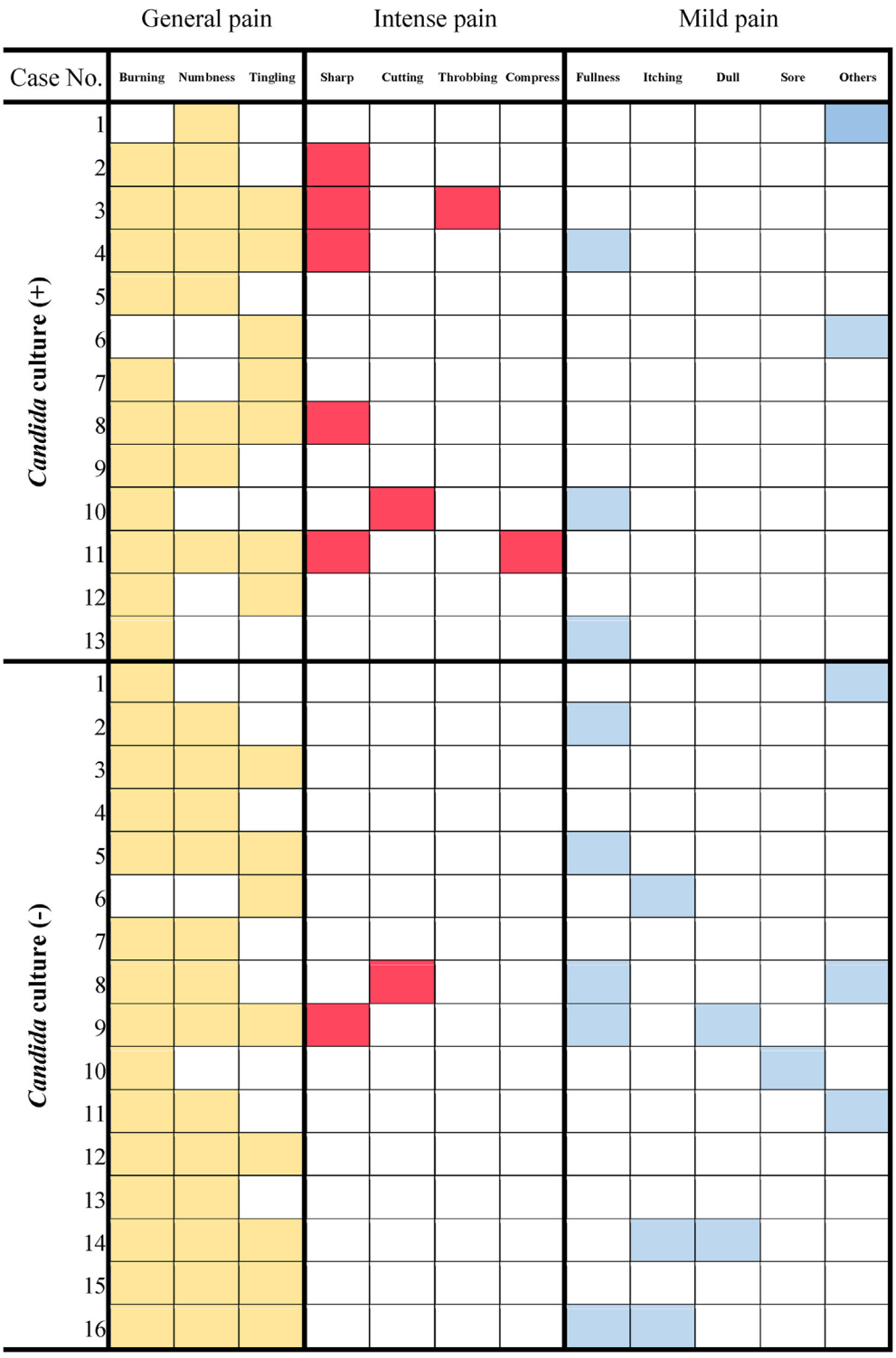

Fig. 3 Heat map of pain type distribution in 29 patients with the *Candida* culture test and the global perceived effects (GPE) score $\geq$4 points.

they might be infected by other pathogens, resulting in poor efficacy of oral nystatin treatment. Nonetheless, in this group of patients insusceptible to oral nystatin, the physicians could search for other possible causes for BMS such as iron, vitamin B12, and folic acid deficiencies to test whether the iron, vitamin B12, and folic acid supplement therapy can achieve the symptom or pain relief in BMS patients.[19,50–63]

Nystatin is a widely-used and long-established antifungal drug. Its various advantages, such as fewer adverse effects, inexpensive price, and effectiveness on oral candidiasis in a short period of time make it a first-line drug of choice for

the treatment of oral candidiasis.[29–32] In this study, when assessing the patients who achieved a GPE score ≥4 points in both the *Candida* culture (+) and *Candida* culture (−) groups, 72.4% (21/29) of patients showed good responses to oral nystatin treatment within one week, and 100% of these 29 patients demonstrated either much improvement or entirely improvement within 4 weeks (Table 5). Additionally, it usually took at least a week or up to 4 weeks to obtain the result of the *Candida* culture test. Therefore, it would exist a gap for weeks before the patients received oral nystatin treatment. If the nystatin treatment should begin following the positive *Candida* culture results, it might render the treatment less effective due to the late intervention.

In the present study, burning pain, numbness, and tingling pain were the three predominant types of oral mucosal dysesthesia in our patients, which highly overlapped with the typical pain types in primary BMS, resulting in difficulty in the differential diagnosis between oral mucosal dysesthesia and primary BMS clinically. Besides, we noticed a slightly higher tendency to have the intense pain in patients in the *Candida* culture (+) group, whereas the mean NRS score was slightly lower in patients in the *Candida* culture (+) group (4.0 ± 2.5) than in patients in the *Candida* culture (−) group (5.9 ± 2.9) (Table 4). Moreover, the Vitkov's study pointed out the association of pre-DM or DM with oral candidiasis.[64] In this study, we found a slightly higher frequency of pre-DM or DM in patients with the GPE score ≥4 points than in patients with the GPE score <4 points, although there was no statistically significant difference. In this regard, further follow-up studies with large sample size of oral dysesthesia patients are needed to confirm the relationship between the pain performance and the relatively higher blood glucose level in oral dysesthesia patients as well as between the oral candidiasis and the relatively higher blood glucose level in oral dysesthesia patients.

Finally, we propose that oral dysesthesia patients may have the morphologically normal symptomatic candidiasis, thus the oral nystatin treatment can be immediately given to the patients for up to 4 weeks, even before obtaining the fungal culture test result. Furthermore, the early use of nystatin treatment can help physicians to differentiate between primary BMS and oral candidiasis and reduce the chance of misdiagnosis, because the patients with primary BMS are often treated with the antidepressants or anticonvulsants that are expected to produce more adverse effects than the oral nystatin treatment.

Undeniably, our study exists some limitations. First, it was not a randomized controlled clinical trial. In addition, the precision of oral mucosal sampling might be affected by the inconsistent use of the swabs, which were changed from simple cotton swabs to the COPAN eSwabs after 2020. Last, we didn't have sufficient information on comorbidities and duration of symptoms to analyze their effect on the severity of disease and the assessment of clinical outcome of oral nystatin treatment. Thus, in the future, it is necessary to design a randomized controlled study to test the influence of comorbidities and duration of symptoms on the clinical outcomes of oral nystatin treatment for oral dysesthesia patients and the use of polymerase chain reaction (PCR) to precisely confirm whether the oral dysesthesia patients have the *Candida* infection or not.

In this study, 147 oral dysesthesia patients were treated with oral nystatin (4–6 cc, four times a day) for 1–4 weeks. We found that 44.8% of the 29 patients in the *Candida* culture (+) group, 47.1% of the 34 patients in the *Candida* culture (−) group, and 47.6% of the 84 patients in the without *Candida* culture test group showed a significant reduction in the NRS score and achieved a great improvement after oral nystatin treatment for 1–4 weeks. Moreover, 72.4% of our 29 oral dysesthesia patients with the *Candida* culture test achieved a great improvement within one week, and all the 29 oral dysesthesia patients achieved a great improvement within 4 weeks of oral nystatin treatment. This finding indicates that approximately 45%–48% of our oral dysesthesia patients can be effectively treated with oral nystatin and obtain a significant improvement of oral symptoms, regardless of whether the patients receive the *Candida* culture test before the start of oral nystatin treatment or not. Among the patients in three different groups, they had the nearly identical NRS score reduction and the similar proportions of patients with the GPE score ≥4 points after oral nystatin treatment. Therefore, we conclude that part of our oral dysesthesia patients are infected by *Candida* and it is beneficial to our oral dysesthesia patients to use oral nystatin treatment before the *Candida* culture test.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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