Guideline for the Diagnosis and Clinical Management of Oral Submucous Fibrosis

Society of Oral Medicine, Chinese Stomatological Association

Oral submucous fibrosis (OSF) is a chronic, progressive and potentially malignant oral mucosal disease. Patients often have a habit of chewing betel nuts. Areca catechu has been listed as a Class 1 carcinogen by the International Agency for Research on Cancer (IARC), and its main active component, arecoline, is classified as a Group 2B carcinogen by the IARC. The World Health Organization (WHO) categorises OSF as an oral potentially malignant disorder (OPMD). The present guideline describes the risk factors, clinical symptoms and clinical signs of OSF. Clinical staging, auxiliary examination methods, basis for diagnosis and differential diagnosis and the need to improve bad lifestyle habits are proposed and addressed, and local treatment drugs, therapies, dosage and course of treatment, possible adverse reactions, and oral treatment drugs, dosage and course of treatment are proposed. The guideline also addresses the indications for surgical treatment, alternative non–drug treatment methods, selection of treatment plans for different clinical stages, criteria for efficacy evaluation, and preventive measures.

Key words: *carcinogenic, chewing betel nut, oral potentially malignant disorders, oral submucous fibrosis, risk factors*

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Preface

This document was prepared in accordance with the GB/T 1.1-2020 Structure and Drafting Rules for Standardisation Documents. It was proposed by the Chinese Society of Oral Medicine and is under the jurisdiction of the Chinese Stomatological Association.

Oral submucous fibrosis (OSF) is a chronic, progressive and potentially malignant oral mucosal disease. It is associated with various factors, and most patients who suffer from it have a habit of chewing betel nut, a chewing stimulant that is used widely in regions such as Hunan, Hainan and Taiwan in China, as well as in Southeast Asian countries like India, Pakistan and Vietnam. It has been classified as a Class 1 carcinogen by the International Agency for Research on Cancer (IARC), and its main active component, arecoline, is classified as a Group 2B carcinogen by the IARC. The World Health Organization (WHO) categorises OSF as an oral potentially malignant disorder (OPMD)[1].

The clinical manifestations of OSF mainly include burning pain when eating, formation of oral submucous fibrous cords and limited mouth opening. At present, no evidence-based guidelines relating to OSF have been published in the field of stomatology in China. To standardise the diagnosis and clinical management of OSF, an expert group and working group for the development of guidelines for the diagnosis and clinical management of OSF were established under the leadership of Peking University School and Hospital of Stomatology and Xiangya Hospital of Central South University in conjunction with 22 colleges and universities and units nationwide after the approval of the group standard development project of the Chinese Stomatological Association (CHSA approval number: T/CHSA 044-2022). The working group followed the methodological system design of the second edition of the WHO handbook for guideline development issued in 2014, conducted a comprehensive search and careful evaluation of the relevant literature on OSF at home and abroad based on the Grading of Recommendations

Corresponding authors: Dr Hong Wei LIU, Department of Oral Medicine, Peking University, School and Hospital of Stomatology, #22, Zhongguancun South Avenue, HaiDian District, Beijing 100081, P.R. China. Tel: 86-10-82195362. Email: hongweil2569@163.com.

Dr Xin Chun JIAN, Department of Oral and Maxillofacial Surgery, Xiangya Hospital, Central South University, #87 Xiangya Road, Changsha 410008, Hunan Province, P.R. China. Tel: 86-731-88908030. Email: drjianxinchun@163.com

Table 1 GRADE quality of evidence grading system description.

Level of evidence	Description
High (A)	Very confident, the observed value is close to the true value and further study will not change the credibility of the assessment results of this intervention.
Medium (B)	Moderate power for an observed value; the observed value is likely to be close to the true value but may vary widely; further research is likely to affect the credibility of the assessment results of this intervention and may alter them.
Low (C)	The power for an observation is limited and it is likely that the observation is very different from the true value; further research is very likely to affect the credibility of the assessment results of this intervention and is likely to change them.
Very low (D)	Little power is given to the observed value, which can be very different from the true value; any assessment is very uncertain.

Assessment, Development and Evaluation (GRADE) evidence quality grading system, and developed the exposure draft of the Guidelines for the Diagnosis and Clinical Management of OSF over 2 years. The guideline development process refers to the specifications of the Appraisal of Guidelines for Research and Evaluation (AGREE)-China quality evaluation standard system for clinical practice guidelines; the writing process refers to the requirements set out in the Reporting Items for Practice Guidelines in Health Care (RIGHT) guideline writing specifications to meet the trend of methodological development of current clinical practice guidelines.

The recommendations set out in the guidelines are divided into two major parts: the first concerns diagnosis of OSF, and the second part addresses its clinical management.

Scope

The target population of this guideline is patients in China who meet the diagnosis set out in the fifth edition of the 13th Five-Year Plan textbook "Oral Mucosal Diseases"[2]. The International Classification of Diseases (ICD) code for the disease is ICD-11 DA02.2.

This guideline gives recommendations for the clinical diagnosis and treatment of OSF, and the user population comprises clinicians, dental practitioners, nursing staff, laboratory personnel, policy formulation and management personnel and other relevant professionals in various medical institutions at all levels in China.

Normative references

There are no normative references to this document.

Terms and definitions

The following terms and definitions are applicable to this document.

Abbreviation

OSF: this is a chronic, progressive oral mucosal disease with a tendency to become cancerous that is due to areca nut chewing, and is clinically characterised by burning pain in the oral mucosa, pain when eating irritating foods, loss of elasticity of the oral mucosa or formation of submucous fibrous cords, progressive limited mouth opening and dysphagia. The WHO lists OSF as a potential malignant disease of the oral cavity.

Coefficient of variation (CV)

The absolute value reflecting the degree of data dispersion; taking the coefficient of variation (CV) = standard deviation/mean value in this Delphi method, it is believed that CV > 0.3 indicates that there is disagreement in expert opinions.

Guideline recommendations

General

The literature was screened according to the inclusion and exclusion criteria and the GRADE system was used as the evaluation criteria. The quality of evidence is shown in Table 1, in which systematic reviews and randomised controlled trials were used as high-quality evidence (downgraded as appropriate); cohort studies were considered medium-quality evidence (upgraded or downgraded as appropriate); case-control studies and case series analyses were used as low-quality evidence; and individual case reports and expert opinions were listed as very low-quality evidence. This guideline did not use the results of animal and in vitro experiments as evidence.

The recommendations for intervention measures are based on the Evidence to Decision (EtD) framework

Table 2 Evidence to Recommendation (EtD) framework.

Content	Description
Prioritisation of issues	Prioritisation of issues
Benefit or risk	Degree of potential benefit (efficacy) to patients and the degree of possible risks (side effects, adverse reactions, etc.) to patients
Credibility of evidence	How credible the evidence population is
Importance of outcome measures	Whether there is significant uncertainty or variability in the judgment of primary outcome measures
Pros and cons balance	Judge whether the results tend to support the intervention or control from the perspective of the benefits and risks of the recommended intervention
Resource utilisation	How resource-intense an option is, if it is cost-effective and if there is incremental benefit. The more advantageous or clearly disadvantageous these resource implications are, the more likely is a strong recommendation
Equity	Impact on health-related equity
Acceptability	Whether the intervention is acceptable to stakeholders and meets the values or general wishes of the target population
Feasibility	Whether the intervention is possible to implement or whether the implementation process has the necessary prerequisites

Table 3 Recommendation strength description.

Recommended strength	Description
Strong	Clear support for the intervention, showing that the benefits outweigh the risks, and expert voting in Delphi, i.e., mean score > 7 and CV ≤ 0.3
Weak	The pros and cons of interventions are uncertain, or are comparable regardless of the quality of evidence, which may outweigh the pros and cons, with expert voting in Delphi averaging 5 to 7 and CV < 0.4
Good practice statement (GPS)	Recommendations based on non-direct evidence or expert opinion/experience, expert voting in Delphi, mean score 4 to 5 or CV > 0.4 with limited clinical reference

(Table 2), taking into account factors such as literature quality, socio-economic costs, values and willingness of users and target populations, feasibility and accessibility. Three rounds of Delphi questionnaire surveys, one face-to-face expert discussion and two online expert discussions were used to form recommendations. The recommendation strength of the intervention was based on the evaluation results of the body of evidence using the GRADE system and on the recommendations formed using the above EtD framework, referring to the mean score from the expert recommendation voting in the Delphi method questionnaire survey to form a graded recommendation intensity. (Table 3).

Guidelines for the diagnosis and treatment of OSF, part 1: Diagnosis

Risk factors for OSF

Recommendation

Areca nut chewing is a major risk factor for OSF (level of evidence, high; strength of recommendation, strong), and the occurrence of OSF may also be related to genetics, smoking and autoimmunity (level of evidence, very low; strength of recommendation, good practice statement [GPS]).

Evidence overview

Previous reviews[3-12] and results of four epidemiological surveys[13-16] showed that the prevalence of OSF in people who chew areca nut was higher than that in the normal population; from the above review, potential risk factors for OSF were selected and included in the two rounds of Delphi analysis by 52 experts.

Recommendation notes

The present recommendation is based on previous reviews, epidemiological surveys, and expert opinions and experience, because OSF mainly occurs in people with an areca nut chewing habit and in regions where this is common, and the incidence is higher in people who chew areca nut, so the history of this habit is one of the important foundations for the diagnosis of OSF.

Genetics, smoking, autoimmunity and other factors may also promote the occurrence of OSF.

Clinical symptoms of OSF

Recommendation

The clinical symptoms of OSF mainly include burning pain in the oral mucosa and when eating irritating food, inability to bulge the cheeks or whistle due to mucosal tightness (evidence level, very low; recommendation intensity, strong). Possible symptoms include limited tongue movement with dysphagia, dysphonia, dry mouth, hypogeusia and tongue numbness (evidence level, very low; recommendation intensity, weak).

Evidence overview

Clinical symptoms that may occur in OSF were screened from previous systematic reviews 3,12,17-20 and clinical physician recommendations. After two rounds of Delphi analysis by 52 experts, the above symptoms were included.

Recommendation notes

This recommendation is based mainly on the comments from the expert group involved in the development of previous reviews and guidelines. Patients with OSF may present with different clinical symptoms at different stages of the disease, which has certain value for diagnosis.

Clinical signs of OSF

Recommendation

Clinical signs of OSF mainly include pale mucosa, decreased mucosal elasticity and hardening, fibrous strip formation, reduced mouth opening, mucosal blister or ulcer formation, impaired secretion of minor salivary glands ("blisters" when eating irritating foods, which can gradually subside; mucocele formation in severe cases) (level of evidence, high; strength of recommendation, strong). Possible signs of OSF include atrophy of the lingual papillae, shortening of the lingual palatal arch/pharyngeal palatal arch, uvula shrinkage, lip tissue atrophy (lip redness thinning, scar contracture, mouth fissure narrowing), fibrosis of the soft palate and uvula (may be associated with velopharyngeal insufficiency, mild nasal sounds or language disorders), narrowing of the tongue morphology or atrophy of the lingual muscle (level of evidence, very low; strength of recommendation, weak).

Evidence overview

Clinical signs that may appear in OSF were selected from previous systematic reviews[3,12,17-20] and clinicians' recommendations and included in the aforementioned clinical signs by two rounds of Delphi analysis by 52 experts.

Recommendation notes

This recommendation is mainly based on the comments of the guideline development expert group. Patients with OSF with lesions at different stages may present with different clinical signs, which has certain value for diagnosis. When measuring mouth opening, it is advisable to use the distance between the incisal edges of the central incisors as the standard. The reference measurement method is to ask the patient to actively open their mouth as wide as possible and use a vernier caliper to measure the distance between the incisal edges of the maxillary and mandibular central incisors. If there is a dentition defect, measure the interdental distance closest to the middle and with the occlusal relationship.

Clinical staging of OSF

Recommendations

See Table 4 for details (level of evidence, high; strength of recommendation, strong).

Evidence overview

The clinical staging criteria refer to Professor Jian Xinchun's 2009 OSF diagnostic criteria published in 2009[21] and Khanna-Andrade[22] staging, from which several representative clinical symptoms or signs were selected and summarised into clinical stages with mouth opening as the main reference standard, which was statistically passed by Delphi method in two rounds by 52 experts.

Recommendation notes

The clinical staging of OSF has guiding significance for treatment. Defining the clinical stages of OSF can provide an objective reference standard for future clinical research and treatment.

Table 4 Clinical staging criteria for OSF.

Phase	Description
Phase I	When mouth opening is ≥ 30 mm, the oral mucosa shows local or scattered white changes; the texture is not changed or rough, and the elasticity is not significantly changed
Phase II	Mouth opening is 20 to 30 mm, the colour of mucosa shows a flaky white appearance or strip formation; the texture becomes hard and the elasticity decreases
Phase III	Mouth opening is 10 to 20 mm, the oral mucosa is widely white changed and stripes are formed; the texture becomes hard, with a plate- or leather-like appearance upon palpation, and poor elasticity
Stage IV	Mouth opening ≤ 10 mm, with leucoplakia or oral squamous cell carcinoma

Note: 1. The symptoms and signs that may occur in each phase include burning sensation, pain and ulceration (if there are no other symptoms or signs, it is classified as phase I). One of the manifestations listed in each stage can be classified as phase I.

2. Scope of lesions: The oral mucosa is divided into five regions: lip and perioral; buccal mucosa and transitional sulcus; tongue; floor of mouth; and soft palate, tongue and palate arch, and uvula. Stage I involves one to two regions; phase II involves three regions; and phase III involves four to five regions.

3. Patients with leucoplakia/oral squamous cell carcinoma, regardless of the above findings, are classified as phase IV.

4. If the clinical manifestations in different regions are in different phases, diagnose according to more advanced phases.

Auxiliary examination method for OSF

Recommendation

Histopathological examination is the gold standard for the diagnosis of OSF (level of evidence, high; strength of recommendation, strong). For patients with leucoplakia/epithelial dysplasia, histopathological examination is recommended. At the same time, the results of autofluorescence examination, toluidine blue staining, exfoliative cell smear and other precancerous lesion examinations can be referred to diagnosis of leucoplakia/epithelial dysplasia (level of evidence, high; strength of recommendation, weak).

Evidence overview

Auxiliary examination methods that may be used for OSF were selected from previous systematic reviews[22-26] and clinician recommendations and passed two rounds of Delphi analysis by 52 experts.

Recommended statement

Histopathological examination is the most reliable method for the diagnosis of OSF in clinical practice and has been widely used in previous randomised controlled trials, cohort studies and case-control studies. For patients with leucoplakia/epithelial dysplasia, histopathological examination is required to determine the progression status of the disease and the need for early surgical intervention.

Differential diagnosis of OSF

Recommendation

OSF needs to be differentiated from leucoplakia of oral mucosa (level of evidence, low; strength of recommendation, weak), lichen planus (level of evidence, low; strength of recommendation, weak), keratosis alba (level of evidence, low; strength of recommendation, weak) and white oedema (level of evidence, low; strength of recommendation, GPS).

Evidence overview

Diseases that may require differential diagnosis with OSF were selected from previous systematic reviews[22-26] and clinician recommendations and passed two rounds of Delphi analysis by 52 experts.

Recommendation notes

This recommendation is based on previous reviews3,12,17-20 and the comments from the expert group that developed the guideline. The main diseases that need to be differentiated from OSF are those characterised primarily by white lesions.

Diagnosis basis of OSF

Recommendation

The diagnosis of OSF should be based on the following criteria:

- history of areca nut chewing (level of evidence, high; strength of recommendation: strong);
- typical clinical symptoms or signs (level of evidence, high; strength of recommendation, strong);
- histopathological findings (level of evidence, high; strength of recommendation: strong);
- auxiliary examinations suggestive of carcinogenesis: autofluorescence examination, toluidine blue staining, exfoliated cell smear (level of evidence, low; strength of recommendation, weak).

Evidence overview

Taking into account aforementioned the risk factors, clinical symptoms, clinical signs, and auxiliary examination methods for OSF, the items that may be used as the basis for the diagnosis of OSF were selected and 52 experts conducted and passed two rounds of Delphi analysis.

Recommendation notes

This recommendation is based on the opinion of the guideline development panel. A diagnosis of OSF can be made mainly with reference to the patient's history of areca nut chewing, typical clinical symptoms or signs and histopathological examination results.

Part 2: Clinical management

Patients with OSF need to improve their bad lifestyle habits

Recommendations

Patients need to abstain from areca nut chewing (level of evidence, high; strength of recommendation, strong), stop smoking (level of evidence, moderate; strength of recommendation, strong) and abstain from alcohol prior to treatment (level of evidence, moderate; strength of recommendation, weak). Stopping consuming betel nuts, smoking and drinking alcohol and reducing intake of spicy, irritating and rough foods are effective preventive measures against OSF (level of evidence, moderate; strength of recommendation, weak).

Evidence overview

Based on the above-mentioned risk factors for OSF combined with clinicians' suggestions, the measures that may be taken for the management of patients with OSF were selected and 52 experts conducted and passed two rounds of Delphi analysis.

Recommendation notes

This recommendation is based primarily on the opinion of the Expert Group on Epidemiological Surveys, Cohort Studies and Guideline Development. OSF is one of the potential malignant diseases of the oral cavity, and bad habits that are not conducive to treatment such as areca nut chewing, smoking and alcohol consumption can be first corrected in patients prior to treatment. Abstaining from these and reducing intake of spicy, irritating and rough foods are effective preventive measures for OSF.

Drugs and therapies, dose and course of treatment available for local treatment of OSF

Recommendations

- Local injection of triamcinolone acetonide + lidocaine (10 mg/ml triamcinolone acetonide suspension 2 to 3 ml + 1 ml lidocaine, bilateral submucosal multi-point injection) (level of evidence, high; strength of recommendation, strong);
- Local injection of triamcinolone acetonide + lidocaine + salvia miltiorrhiza or tanshinone (50 mg triamcinolone acetonide + 2 ml lidocaine, 4 ml after shaking, 2 ml bilateral submucosal multi-point injection, followed by 2 mg salvia miltiorrhiza or tanshinone solution on each side) (level of evidence, high; strength of recommendation, strong);
- Local injection of triamcinolone acetonide (2 to 40 mg, bilateral submucosal multi-point injection) (level of evidence, high; strength of recommendation, weak);
- Hyaluronidase + triamcinolone acetonide injection (topical injection of 1500 IU hyaluronidase every 1 to 2 weeks, mixed with 10 mg triamcinolone acetonide) (level of evidence, high; strength of recommendation, weak).

Local injection treatment should be administered once every 1 to 2 weeks, with a treatment course lasting 4 to 10 weeks. The specific dosage and number of courses of treatment should be determined based on the individual patient's condition. There should be an interval of 1 to 2 months between each treatment course (level of evidence, high; strength of recommendation, strong).

Evidence overview

Two meta-analyses[27,28] and 14 randomised controlled studies[29-42] showed that Danshen injection combined with steroid therapy could increase maximum mouth opening significantly and reduce the burning sensation of the oral mucosa in patients and reduce the area of oral mucosal lesions without increasing adverse reactions. According to the aforementioned literature and based on clinical experience, the local injection drugs and treatment courses that may be used for OSF were selected and passed by Delphi method in two rounds by 52 experts.

Recommendation description

This recommendation is mainly based on meta-analysis, randomised controlled trials and the opinions of expert groups in guideline development. The above operation mode and dose are only used as references, and the clinical operation should be adjusted according to patients' specific circumstances. In addition to the above recommendations, the local therapeutic drugs recommended by experts for OSF include compound Danshen tablets made into sublingual paste, topical application of epidermal growth factor, topical application of triamcinolone acetonide oral ointment and other doses for treatment. Due to insufficient evidence or a lack of consensus among experts, they are not included in this guideline.

Possible adverse reactions to drugs for topical treatment of OSF

Recommendations

Possible adverse reactions to tanshinone injection include allergy (shock, laryngeal oedema, dyspnoea, palpitation), transient elevated blood pressure, local pain and headache (level of evidence, high; strength of recommendation, weak). Potential reactions to triamcinolone acetonide include glucocorticoid-related adverse reactions (Cushing syndrome, calcium and potassium loss, induced or aggravated infection, or neurological symptoms such as agitation, insomnia and seizures) (level of evidence, high; strength of recommendation, weak).

Evidence overview

The adverse reactions that may occur in the use of related drugs were summarised from the drug instructions and expert experience, which were passed by Delphi method in 2 rounds by 52 experts.

Recommendation notes

This recommendation is based mainly on the comments from the expert group for the development of drug instructions and guidelines. Adverse reactions shall be based on those indicated in the package insert. The possible adverse reactions should be explained to patients prior to local treatment. Patients' medical history should be taken before treatment to determine whether they have any systemic diseases or general conditions that may affect treatment or lead to an intolerance to treatment. For patients with poor control of hypertension and diabetes, glucocorticoids can be used with caution.

Drugs, dosage and course available for oral treatment of OSF

Recommendations

Danshen dripping pills can be used for systemic treatment of OSF. The recommended dose is 540 mg daily for 12 weeks (level of evidence, high; strength of recommendation, strong), and lycopene can be employed at a recommended dose of 6 to 24 mg daily for 3 to 6 months (level of evidence, high; strength of recommendation, weak).

Traditional Chinese medicine (TCM) can be used to treat OSF, which is differentiated according to individual conditions (level of evidence, moderate; strength of recommendation, weak). Vitamins and trace elements can be used for adjuvant treatment of OSF, and the recommended dose is vitamin A (25,000 IU once daily) combined with zinc agents (such as zinc gluconate, used with reference to the instructions) for 4 months (level of evidence, moderate; strength of recommendation, weak).

Evidence overview

A randomised controlled trial found that multi-point injection of triamcinolone acetonide acetate along with use of sublingual compound Danshen dripping pills was more effective than local injection of hormones only[43]. Combined with the above literature, relevant reviews[44-57] and clinicians' suggestions, the drugs that may be used for oral treatment of OSF were selected and passed by Delphi method in two rounds by 52 experts.

Recommended instructions

This recommendation is based mainly on randomised controlled clinical studies and was formed in combination with the comments of an expert group. In the aforementioned studies, oral drugs except TCM were used in combination with local injection drugs, and few clinical studies used oral drugs alone, suggesting that the treatment of OSF can focus mainly on local treatment at present and be supplemented by oral medication. Vitamins and trace elements may be used as adjunctive therapeutic agents.

Indications for surgical treatment of OSF

Recommendations

Indications include pooled heterogeneous leucoplakia (level of evidence, moderate; strength of recommendation, strong) and other symptoms that seriously affect patients' quality of life (such as pharyngeal arch adhesion affecting eating) (level of evidence, moderate; strength of recommendation, strong).

Histopathological examination revealed epithelial dysplasia (level of evidence, moderate; strength of recommendation, strong). This was combined with impacted third molars, recurrent ulcers and a wound surface higher than the mucosal surface (level of evidence, moderate; strength of recommendation, strong).

Limited mouth opening affects oral therapy (e.g., extraction of impacted the third molar, implant restorations) (level of evidence, moderate; strength of recommendation, weak). Mouth opening is less than 10 mm (level of evidence, medium; strength of recommendation, weak). Patients needed rapid improvement in mouth opening limitation (level of evidence, moderate; strength of recommendation: weak) and requested surgery and signed an informed consent (level of evidence, moderate; strength of recommendation, weak).

Evidence overview

Seven case reports[58-63] and six reviews[64-69] showed that surgical treatment improved mouth opening significantly and rapidly in patients with OSF.

Recommendation description

This recommendation is mainly based on case reports and expert opinions. Surgical treatment is an effective means to relieve the limitation of mouth opening in patients with OSF, but because it was reported at the end of the last century that patients with OSF had limited mouth opening again after surgical treatment due to scar contracture, implantation of artificial skin materials and other reasons, the exploration of surgical treatment of OSF gradually slowed down. In recent years, due to the development of surgical techniques and artificial skin materials, the incidence of postoperative recurrence of limited mouth opening has been reduced compared with in the past. After expert discussion, it is believed that patients with heterogeneous leucoplakia, severely impacted quality of life, epithelial dysplasia and third molar impaction are recommended for surgical treatment, and patients with limited mouth opening affecting oral treatment, mouth opening < 10 mm, and who need rapid improvement of mouth opening undergo surgical treatment as appropriate. An informed consent form was required before surgery, and the risk of recurrence of limited mouth opening was explained to the patient.

Other non-pharmacological treatments for OSF

Recommendations

Other treatments for OSF include mouth opening training (level of evidence, high; strength of recommendation, strong), hyperbaric oxygen therapy (level of evidence, low; strength of recommendation, weak), photodynamic therapy (level of evidence, very low; strength of recommendation, weak) and laser therapy (level of evidence, very low; strength of recommendation, weak).

Evidence overview

One case observation71 and one systematic review72 showed that mouth opening training has an effect on improving mouth opening and maintaining therapeutic effects in patients with OSF. (numbers in superscript) Five case observations showed an effect of hyperbaric oxygen therapy helps to improve symptoms of OSF[72-76]. It was passed by Delphi method by 52 experts.

Recommendation notes

This recommendation is mainly based on the opinions of randomised controlled studies, case observations and consensus of expert groups. Mouth opening training is an effective way to improve mouth opening in patients with OSF and has a significant effect on the maintenance of therapeutic effects. Hyperbaric oxygen therapy,

photodynamic therapy and laser therapy play a role in relieving the symptoms of OSF and can be used as an adjunct to treatment.

Selection of treatment plans for different clinical stages of OSF

Recommendations

- Phase I: observation after education, local injection drug therapy, oral drug therapy (combined with local injection or used alone) and other therapies (such as hyperbaric oxygen therapy);
- Phase II: education, local injection drug therapy (can be combined with oral drug therapy) and other therapies (photodynamic therapy, hyperbaric oxygen therapy, mouth opening training, laser therapy, etc.);
- Phase III: education, local injection drug therapy (can be combined with oral drug therapy), other therapies (photodynamic therapy, hyperbaric oxygen therapy, mouth opening training, laser therapy, etc.), surgery as appropriate;
- Phase IV: education, surgical treatment, local injection drug therapy (can be combined with oral drug therapy) and other treatments (photodynamic therapy, hyperbaric oxygen therapy, mouth opening training, laser therapy, etc.).

Evidence overview

Referring to the above clinical symptoms, signs, staging and treatment options for OSF combined with clinician recommendations, 52 experts passed two rounds of Delphi method analysis.

Recommended instructions

The treatment options for patients with different stages of OSF may vary. Clinicians need to select the treatment that is appropriate to patients' specific circumstances. Some experts believe that patients without obvious symptoms in the first stage can only be educated, and if the lesion progresses, further treatment with medication, surgery and so on can be performed.

Efficacy criteria for the treatment of patients with OSF

Recommendations

- Recovered: mouth opening returned to > 30 mm or normal, oral mucosal elasticity recovered, pale mucosa disappeared, oral submucosal fibrous cords disappeared, burning pain in general and when eating disappeared, symptoms of mucosal "tightness" disappeared (bulging cheeks or whistling were possible) (level of evidence, high; strength of recommendation, strong);
- Significantly effective (or significantly improved): partial recovery of mouth opening (amount recovered > 20 mm or recovered to > 25 mm), increased elasticity of oral mucosa, reduction/disappearance of mucosal pallor, reduction/disappearance of oral submucosal fibrous cords, reduction/disappearance of burning pain in general and when eating, reduction/disappearance of symptoms of mucosal "tightness" (level of evidence, high; strength of recommendation, strong);
- Improvement: minimal recovery of mouth opening (recovery > 10 mm or to > 20 mm), increased elasticity of oral mucosa, decreased paleness of mucosa, decreased fibrous cords in oral submucosa, reduced burning pain in general and when eating, reduced symptoms of mucosal "tightness" (level of evidence, high; strength of recommendation, strong);
- Ineffective: no improvement in limitation of mouth opening (amount recovered < 10 mm or recovered to < 15 mm), carcinogenesis, no improvement in oral mucosal elasticity, no improvement in the degree of mucosal pallor, no reduction in oral submucosal fibrous cords, no relief of burning pain in general and when eating, and no improvement in symptoms of mucosal "tightness" (level of evidence, high; strength of recommendation, strong).

Evidence overview

Referring to the above clinical symptoms, signs and staging of OSF combined with clinicians' suggestions, four criteria for the efficacy of treatment of OSF were proposed and passed by Delphi method in two rounds by 52 experts.

Recommendation notes

This recommendation is mainly based on the comments from the guideline development expert group. The objective evaluation of the therapeutic effect takes the degree of mouth opening as the main standard, which referred to other indicators. If the items are in different classifications, the grade with the best efficacy should prevail (if there are both recovered and significantly effective items, the final treatment efficacy is recovered).

Prevention of OSF

Suggestions for stopping areca nut chewing

Recommendations

Suggestions for stopping areca nut chewing for the public include:

- Strengthening popular science and education: publicising the harm that areca nut chewing can cause and resisting the transmission of areca nut;
- Controlling the placement of betel nuts: prohibiting placing them in easily accessible locations and advertising them;
- Not adding opioids, nicotine, ephedra and other addictive substances to areca nut;
- Placing a warning on products regarding the consumption of areca nut (for example, warning: chewing areca nut may cause oral cancer).

Summary of evidence

Based on expert opinions and referring to relevant policies and measures for stopping smoking, the evidence was discussed and adopted by Delphi method.

Recommendation notes

This recommendation is mainly based on the comments from the guideline development expert group. Experts believe that areca nut can cause substance dependence, but there is still disagreement regarding whether it is a psychoactive substance. The State Radio and Television Administration of China issued a notice in September 2021 to stop radio and television and online audiovisual programmes being used to publicise and promote areca nut and its products. Experts did not achieve a consensus on whether increasing the price of areca nut products helps individuals to stop consuming them.

Measures for stopping areca nut chewing

Recommendations

The measures to quit areca nut that can be used for individuals are as follows:

- Identifying the hazards of areca nut chewing: recognising that areca nut chewing may lead to OSF and/or oral cancer;
- Stopping chewing areca nut and using chewing substitutes, such as gum and liquorice;
- Diverting attention, exercising when wanting to chew areca nut, etc.;
- Being supervised by relatives and friends: asking family members, relatives and friends to offer supervision and dissuade from chewing areca nut.

Summary of evidence

Based on expert opinion, relevant policies and measures for stopping smoking were discussed and evidence was adopted by Delphi method.

Recommendation notes

This recommendation is mainly based on the comments from the guideline development expert group. The above measures can be used as a reference for people who need to stop chewing areca nut. In addition, with regard to the possible reactions during withdrawal from chewing areca nut, the large differences between individuals mean that more clinical observation is required. There are also significant differences in expert opinions, which are not included in this guideline for the time being.

Advantages and disadvantages of guideline implementation

Favourable factors

Further attention will be paid to the standardised diagnosis and treatment of OSF; medical institutions at all levels in all regions can select a reasonable clinical management plan according to their own actual situation and patients' wishes, values and preferences.

Adverse factors

As a chronic progressive disease, OSF may have a carcinogenic outcome, and this guideline does not discuss the relevant parts of malignancy. There are relatively few references in some parts of this guideline, and recommendations are formed based on the opinions of the expert group.

Limitations and deficiencies of the guideline

This guideline is intended for the Chinese population, but does not distinguish the ethnic characteristics of the population. There may be some deviations in the application process for the guideline of different ethnic groups. The clinical data derived from the Chinese population are concentrated in Hunan and Taiwan, and

there may be some deviations in the application process in other regions.

Appendix

Specific method for preparing the guidelines: Guideline development methodology

This guideline was prepared by referring to the relevant methodological standards in the WHO handbook for guideline development issued in 2015, as well as the contents of the guideline for developing the Report Checklist of AGREE-China, and according to the RIGHT Items statement.

Composition of the working group on guidelines

A guideline development expert group and working group were formed in April 2019. The working group is composed of young and middle-aged physicians engaged in the clinical diagnosis and treatment of oral mucosal diseases in Hunan, Hainan, Beijing and other regions who are especially familiar with the diagnosis and treatment of OSF, and the group leader is Professor Wu Yingfang. The expert group is composed of the members superior to the standing committee level of the Specialised Committee of Oral Mucosal Diseases, Chinese Stomatological Association and senior experts familiar with the diagnosis and treatment of OSF in China. The members specialise in oral mucosal diseases, oral and maxillofacial surgery and TCM, and the leader is Professor Liu Hongwei. Patients' values and wishes (for example, acceptance of invasive testing methods) were considered in the development of clinical questions and recommendations.

Collection and selection of clinical questions

Through systematic inquiry into published literature and systematic reviews on OSF, based on the population, intervention, control and outcome (PICO) principle of clinical study and combined with interviews with intended users of guidelines such as clinicians, this working group preliminarily drafted a list of clinical problems of interest and created a list of clinical problems in this guideline through analysis, classification and combination, with a total of seven diagnostic problems and ten clinical management problems.

Evidence retrieval, synthesis and evaluation

This guideline deconstructs the clinical questions and outcome measures included according to the PICO principles, develops inclusion and exclusion criteria and conducts the relevant literature search.

Inclusion and exclusion criteria

The inclusion criteria were as follows:

- Study subjects: patients with OSF or OSF accompanied by oral leucoplakia and/or oral squamous cell carcinoma;
- Interventions and comparative measures: not limited;
- Outcome measures: not limited;
- Type of study: retrieval of case reports, observational studies, clinical studies, systematic reviews, meta-analyses and consensus or guidelines related to OSF.

The exclusion criteria were duplicate publications and proposals.

Data sources

The data sources were Chinese databases (CNKI, Wanfang Database, Chinese Biomedical Literature Database and VIP Database), English databases (PubMed, Cochrane Library and EMBASE) and data resources related to guidelines (American Clinical Guideline Center, National Institute for Health and Clinical Excellence, Scottish Intercollegiate Guideline Network and Yimaitong), and supplementary searching was performed using Baidu Scholar, Google Scholar, etc. The search period spanned from 1968 to 2021.

Search keywords

The search keywords included oral submucosal fibrosis, diagnosis, treatment or management. Foreign language databases searched the MeSH vocabulary for relevant topics, listing the following subject headings/keywords and their combined forms: oral submucous fibrosis, oral; oral submucous fibrosis; disease management; management; therapeutic; therapy; clinic; treatment; treatments; examinations; examinations; diagnosis, diagnosis; diagnosis.

Quality assessment

This guideline uses A Measurement Tool to Assess Systematic Reviews (AMSTAR)[77], Cochrane Risk of Bias (ROB)[78] and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)[79] to evaluate the methodological quality of the included systematic reviews/meta-analyses, randomised controlled trials, diagnostic studies

and observational studies. The evaluation process was completed independently by two individuals, and any disagreements were resolved through discussion or consultation with a third party. Evidence and recommendations were graded using the GRADE Quality of Evidence Evaluation System[80-82] (Tables 1 and 3).

Form recommendation

Based on the evidence bodies related to various clinical problems, and with reference to relevant guideline evidence and expert opinions for some problems, the guideline working group also considered the diagnosis and treatment wishes of the Chinese patient population, human and economic costs, and the actual situation of medical institutions at all levels in all regions, focused on the risks/benefits of intervention measures, universal accessibility and feasibility in China, and formulated 17 recommendation opinions. The recommendations of this guideline were finally formed after three rounds of a Delphi questionnaire, one face-to-face expert discussion and two expert discussions.

Dissemination and implementation

The exposure draft of the guidelines was improved and revised, and then submitted to the expert steering committee for review. After further review and approval by the relevant administrative authorities of the Chinese Society of Stomatology, the formal release version will be created and released to the public. After the issuance of the formal version, the sponsor of these guidelines will disseminate and promote them in the following ways:

- By introducing and interpreting the guidelines at relevant academic conferences;
- By published the guidelines in professional academic journals and guideline databases;
- By disseminating the guidelines through the official publicity platform of each initiator (such as public number);
- By publicising the guidelines in all types of continuing education training at all levels so they can be interpreted by dental practitioners nationwide.

Update of guidelines

The guideline working group plans to update these guidelines 3 to 5 years after they are issued, or based on actual clinical needs and major research progress in this field at home and abroad. The updated method is performed according to the updated process of the guidelines.

Author contribution

This document was drafted by experts from Peking University School and Hospital of Stomatology; Xiangya Hospital of Central South University; Beijing Hospital; Changsha Stomatological Hospital; Hospital of Stomatology, Guangxi Medical University; Affiliated Stomatological Hospital of Guizhou Medical University; Haikou People's Hospital; Hainan General Hospital; The Second Affiliated Hospital of Hainan Medical University; The First Affiliated Hospital of Hainan Medical University; School of Stomatology of Hainan Medical University; Stomatological Hospital of Hebei Medical University; The First Hospital of Hunan University of Chinese Medicine; The Third Affiliated Hospital of Air Force Military Medical University; Affiliated Stomatological Hospital of Kunming Medical University; Affiliated Stomatological Hospital of Nanchang University; Qingdao Stomatological Hospital; Affiliated Stomatological Hospital of Nanjing University School of Medicine; Sanya People's Hospital; Sanya Central Hospital; Shanxi Medical University Stomatological Hospital; The Ninth People's Hospital of Shanghai Jiaotong University School of Medicine; Shanghai Tongji University Stomatological Hospital; Capital Medical University Beijing Stomatological Hospital; West China Stomatological Hospital of Sichuan University; Affiliated Stomatological Hospital of Tongji University; Stomatological Hospital of Wuhan University; Affiliated Stomatological Hospital of Southwest Medical University; Xiangtan Stomatological Hospital; The Second Affiliated Hospital of Zhejiang University School of Medicine; Stomatology Hospital, Zhejiang University School of Medicine; Affiliated Stomatological Hospital of China Medical University; Xiangya Stomatological Hospital of Central South University; The Second Xiangya Hospital of Central South University; Affiliated Stomatological Hospital of Sun Yat-sen University.

The main drafters of this document were Drs Wu Yingfang*, Wang Yutian*, Huang Guodong, Liu Zijian, Jian Xinchun and Liu Hongwei.

The individuals involved in the formulation/drafting of this document, listed in alphabetical order based on the first letter of their pinyin names, were as follows: Cai Yang, Zeng Xin, Chen Chen, Chen Jun, Chen Qianming, Chen Lizhong, Cheng Bin, Dan Hongxia, Du Yongxiu, Fang Changyun, Feng Hui, Fu Qiya, Gao Xing, Gao Yijun, Guan Xiaobing, Han Ying, He Shengteng, He Yuan, Hong Yun, Hu Yanjia, Huang Xieshan, Jiang Lu, Jiang Canhua, Jiang Weiwen, Li Chuanzhen, Li Ming, Li Ning,

* Drs Wu Yingfang and Wang Yutian contributed equally to the drafting of this document.

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