EVIDENCE BASED MANAGEMENT OF ORAL LESIONS

Abstract

Evidence based practice have been known since long times but have gained importance recently. Evidence based medicine is a vast phenomena used in various aspects of dentistry. This chapter aims to focus on the diagnosis and management of oral lesions commonly encountered in dental practice. The diagnosis and treatment of various oral lesions and conditions have always lacked proper clinical evidence and support and therefore needs a standard approach for their management. This chapter provides a brief description about evidence based practice, further it also brings out the various evidence based management strategies in the treatment of oral diseases. The methods discussed in this chapter can serve as a framework for further evaluation and treatment of these conditions.

Author

Dr Mehroz Amena
Senior Lecturer
Department of Oral Medicine and Radiology
Malla Reddy Dental College for Women
Hyderabad, Telanagana, India.
amena6844@gmail.com

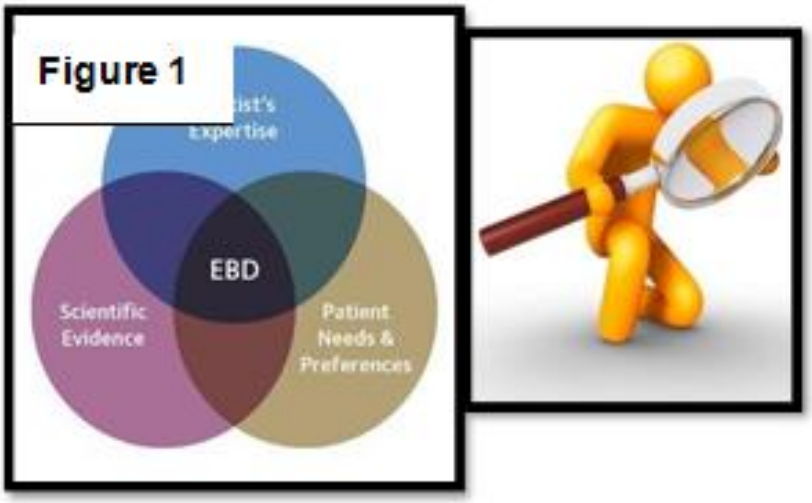
I. INTRODUCTION

Evidence-based medicine is not a new idea; it has gained recognition and respect over the years, especially in the last few decades. The phrase "evidence-based medicine" gained rapid traction once it was first used in publications, influencing reviews and Clinical Practice Guidelines that focused on using carefully gathered information to make recommendations. These initiatives have produced recommendations for and against drugs, surgeries, management strategies, and diagnostic testing methods. They have also drawn scientific attention to areas where there is insufficient data.[1]

Dental treatment that focuses on treating patients with complex medical conditions in their mouths is known as oral medicine. This includes the identification of medical problems affecting the oral and maxillofacial region, as well as their management, most of which are treated nonsurgically. Evidence-based medicine has been crucial in forming theoretical understanding and affecting clinical practice in each of these disciplines. The volume of research now in existence makes improved patient management possible. To continuously inform and direct our clinical practice, we must continuously assess new data as it becomes available.[1]

II. DEFINITION OF EVIDENCE BASED DENTISTRY (EBD)

The traditional definition of Evidence-Based Practice (EBP) originates from Dr. David Sackett. EBP is described as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research" [2]. The American Dental Association (ADA) characterizes Evidence-Based Dentistry (EBD) as an approach to oral healthcare that necessitates the careful integration of systematic assessments of clinically relevant scientific evidence concerning the patient's oral and medical condition and history with the clinical expertise of the dentist and the patient's treatment needs and preferences.[figure 1][2]



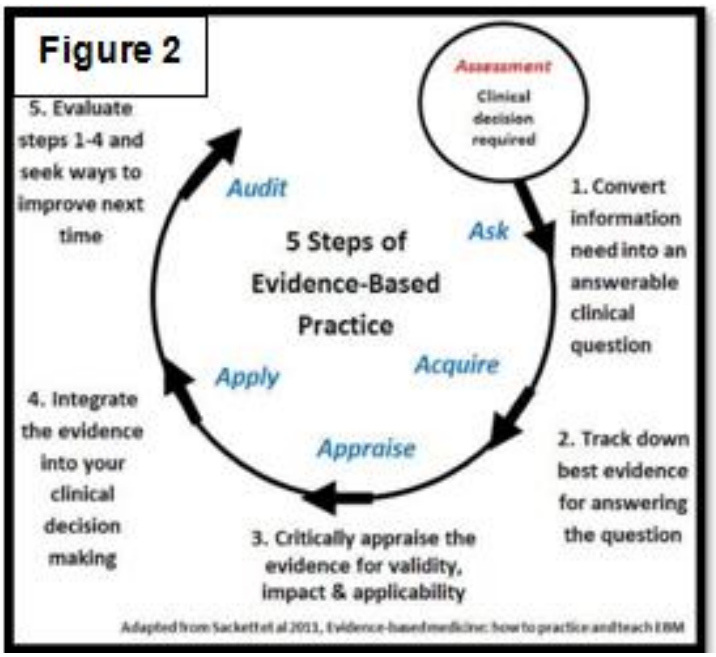
III. AIMS AND OBJECTIVES OF EVIDENCE BASED PRACTICE

1. The goal is to deliver the most efficient care currently available, with the objective of enhancing patient outcomes.

2. EBP also contributes to ensuring the prudent use of limited health resources and the incorporation of pertinent evidence in decision-making processes related to the allocation of funds for health services.

IV. PROCESS OF EVIDENCE BASED PRACTICE (EBP) (FIGURE 2)

The process of Evidence-Based Dentistry (EBD) involves "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based dentistry entails integrating individual clinical expertise with the best available external clinical evidence from systematic research."



The available evidence is dependent upon the particular healthcare issue and the level of urgency required; some clinical areas have little to no established body of evidence. Rapid reviews and traditional systematic reviews are the cornerstones of healthcare decision-making, regardless of whether they are pre-existing or specifically designed to inform new policies or clinical practice standards. A traditional systematic review identifies, picks, assesses, and extracts and analyzes data from relevant research using methodical and explicit techniques [3].

In order to provide information quickly, several steps of the systematic review process are streamlined or eliminated in a rapid review, which is a sort of knowledge synthesis. The importance of taking into account a wide range of study designs, contingent on the nature of the decision at hand, is highlighted by existing frameworks and criteria for evaluating the quality of evidence (i.e., the extent to which estimates from clinical studies substantiate a decision, recommendation, or policy) and policy recommendations. This methodology guarantees that relevant data from national or regional registries, economic assessments, and

governmental organizations is incorporated into the recommendation-making process [Figure 3]

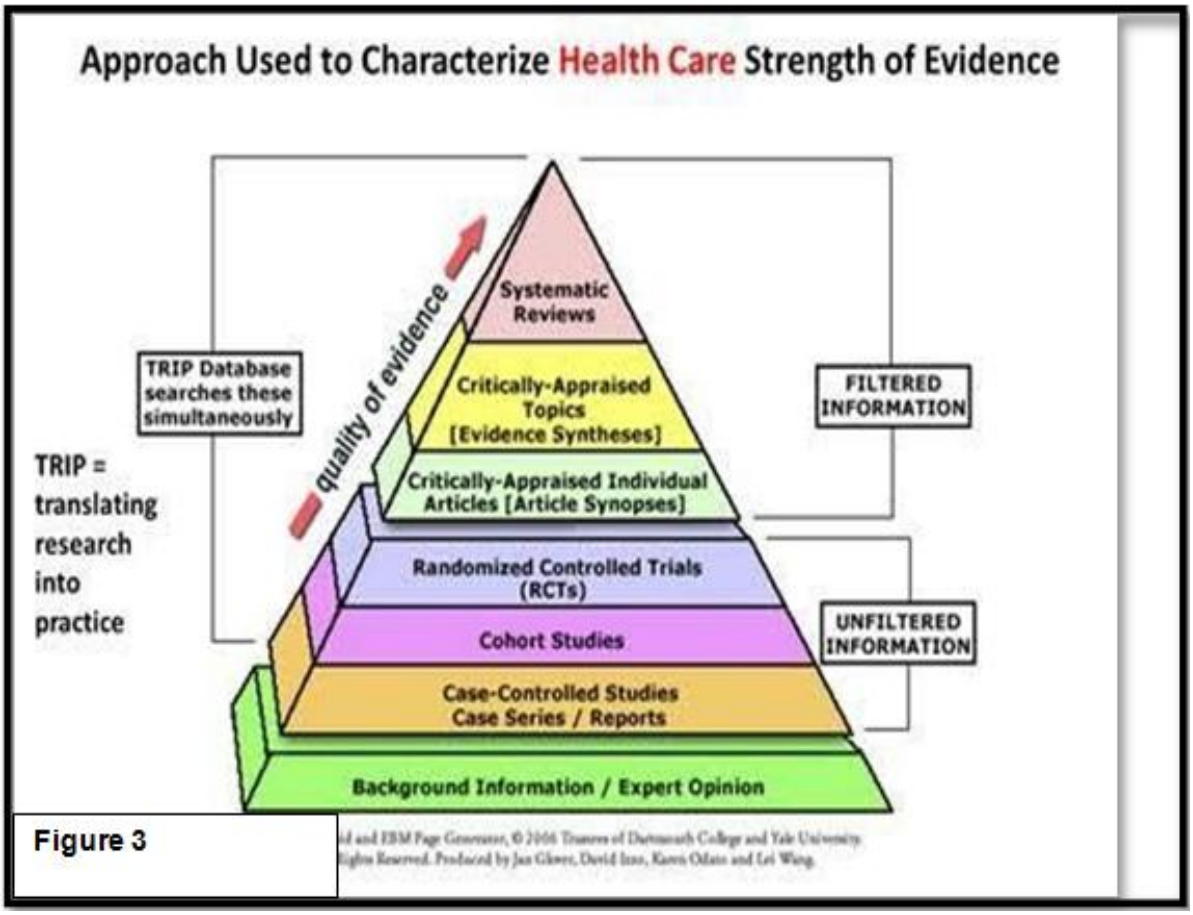


Figure 3

V. DRAWBACKS TO EVIDENCE BASED PRACTICE (EBP)

Barriers exist to the implementation of EBD in daily clinical practice. These barriers include

- a lack of an evidence base to certain clinical questions
- a lack of access to evidence-based information; and for clinical questions
- a lack of evaluation of evidence and development of evidence-based information in aconcise format that is useful to dentists.

VI. MANAGEMENT OF POTENTIALLY MALIGNANT DISORDERS

The oral cavity serves as a precise reflection of the body, providing insights into the general health of an individual. The oral mucosa, a unique tissue, encompasses both keratinized and nonkeratinized stratified squamous epithelium, along with an underlying connective tissue referred to as the lamina propria. Subjected to constant exposure to various stressors such as chemicals, microorganisms, thermal fluctuations, and mechanical irritants like tobacco, areca nut, and alcohol, the oral mucosa undergoes acute and chronic reactive changes in both its epithelial and connective tissue components in response to these factors [4].

Clinical Pathway for the Evaluation of Potentially Malignant Disorders in the Oral Cavity- An evidence based approach – A REPORT BY American dental association (ADA)

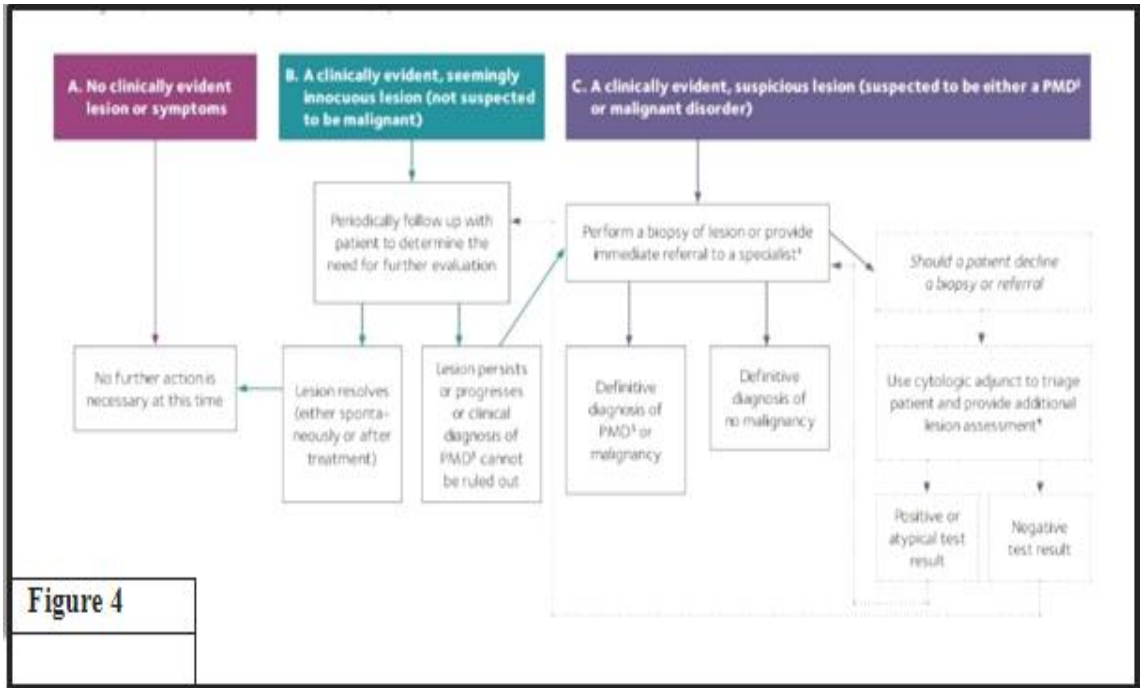


Figure 4

VII. MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis (OSMF) is a chronic, insidious, progressive, debilitating, scarring, irreversible, complex, and incapacitating disorder of the oral cavity. OSMF impacts the upper digestive tract, encompassing the oral cavity, oropharynx, and the upper third of the esophagus. It is characterized by a juxta-epithelial inflammatory reaction, succeeded by fibroelastic changes resulting from the gradual fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). This process leads to epithelial atrophy, causing stiffness and rigidity of the oral mucosa and eventually resulting in the inability to open the mouth.

The etiology of OSMF remains obscure, with various hypotheses suggesting multifactorial origins, including the predominant chewing of areca nut and its flavored formulations. Other contributing factors encompass chronic nutritional deficiencies, particularly in iron, Vitamin B complex, and protein, genetic predisposition, and autoimmunity. The excessive consumption of areca nut disrupts the hemostatic equilibrium between synthesis and degeneration. The copper ion in areca nut augments the activity of lysyl oxidase, leading to unregulated collagen production and subsequently resulting in oral fibrosis. Geographically, the sex distribution of OSMF exhibits variation. The buccal mucosa and retromolar region emerge as the most common oral sites for OSMF, followed by the soft palate, faucial pillars, floor of the mouth, tongue, labial mucosa, and gingiva [5] [Figure 5].

1. Staging of OSMF- BY KHANNA AND ANDRADE [Table 1]

Figure 1: Oral submucous fibrosis involving various areas of the oral cavity. (a and b) Significant blanching and presence of palpable, thick fibrous bands on the left and right buccal mucosa. Note the brownish-black pigmentation in the posterior vestibular region in b. (c and d) Blanching of the soft palate and faucial pillars. Note the shrunken uvula and its altered shape. (e) Blanching of the floor of mouth and loss of surface texture. (f-i) Blanching and palpable fibrous bands of the upper and lower labial mucosa. Note the stiff labial mucosa and presence of blanching of attached gingiva in f and g

2. **Proposed Stage Wise Evidence Based Treatment for OSMF:** Various therapeutic regimens are proposed to alleviate the signs and symptoms of OSMF. Despite seven decades having passed since its characterization as a precancerous condition, no substantial treatment has emerged due to its multifaceted pathogenesis [5]. Recently, diverse approaches, encompassing medicinal (allopathic, homeopathic, and Ayurvedic), surgical, and physiotherapeutic interventions, have been investigated either individually or in combination for managing OSMF. In advanced cases, surgical intervention stands out as the primary treatment modality, although relapse remains a significant challenge. Recommendations include discontinuation of harmful substances such as areca nut, tobacco, and alcohol, coupled with an increased intake of fresh red fruits, green leafy vegetables, and a mineral-rich diet [5].

Figure 2: Various fruits and vegetables having antioxidant properties

Stage 1 treatment [Table 2].

Table 3a: For Stage I OSMF

Stage	Treatment Regimen	Dosage and Duration
I	1. Tablet/Capsule - Vitamin A (50,000 IU) or β-carotene (10-20mg) or Vitamin E (400mg) or Lycopene (4mg) and micronutrients (either alone or in combination)	Once a day, for Six months to Twelve months
	2. Topical Corticosteroids	Thrice daily for One to Two months
	3. Tablet Curcumin (300 mg)	Once daily for a period of Six to Eight months

Stage 2 Treatments [Table 3]

Stage	Treatment Regimen	Dosage and Duration
II	1. Tablet/Capsule - Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400mg) or Lycopene (8mg) and micronutrients (either alone or in combination)	Once a day, for Six months to Twelve months.
	2. Topical Corticosteroids.	Thrice daily for One to Two months
	3. Tablet Ferrous Ascorbate (100 mg) + Folic acid (1.5mg)	Once daily for a period of Six to Eight months.
	4. Tablet Zinc Sulphate (220mg)	Twice a day, for Three to Six months

Stage 3 Treatments [Table 3]

Stage	Treatment Regimen	Dosage and Duration
III	1. Tablet/Capsule - Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400mg) or Lycopene (8mg) and micronutrients (either alone or in combination)	Twice a day, for Twelve to Twenty four months
	2. Topical Corticosteroids	Thrice daily for One to Two months
	3. Tablet Ferrous Ascorbate (100mg) + Folic acid (1.5mg)	Twice a day for Three to Four months
	4. Tablet Zinc Sulphate (220mg)	Twice a day, for Three to Six months
	5. Tablet Curcumin (300 mg)	Twice daily for a period of Six to Eight months.
	6. Tablet Pentoxifylline (400 mg) OR	Thrice daily for Four to Six months
	6. Tablet Isoxsuprine (10 mg)	Four times per day for Six to Eight weeks
	Intra-lesional/Submucosal Injection therapy. Any one	
	7. Mixture of Dexamethasone (4 mg) + Placental Extract (2 ml) + Chymotrypsin (5000 IU) OR	Two Injections per week for total Six to Eight weeks
	7. Mixture of Dexamethasone (4 mg) + Hyaluronidase (1500 IU)+ Chymotrypsin (5000 IU)	Two Injections per week for total Six to Eight weeks
	8. Tablet Levamisole (50mg)	Thrice daily for three consecutive days for Six to Eight weeks

Stage 4a Treatment [Table 4]

Stage	Treatment Regimen	Dosage and Duratio
IV A	1. Tablet/Capsule – Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400 mg) or Lycopene (8 mg) and micronutrients (either alone or in combination)	Once a day for Six months to Twelve months
	2. Topical Corticosteroids	Thrice daily for One to Two months
	3. Topical Antifungal – 2% Clotrimazole	Thrice daily for Two to Six months, on the other OPMD'S
	4. Tablet Ferrous Ascorbate (100mg) + Folic acid (1.5mg)	Twice a day for Three months
	5. Tablet Zinc Sulphate (220mg)	Twice a day, for Three to Six months
	6. Tablet Curcumin (300 mg)	Twice daily for a perio of Six to Eight months
	7. Tablet Pentoxifylline (400 mg) OR	Three times daily for Four months to Six months
	7. Tablet Isoxsuprine (10 mg)	Four times per day for Six weeks

Stage 4b Treatment [Table5]

Stage	Treatment Regimen	Dosage and Duration
IV B	1. Urgent Referral to Regional Cancer centre/Consultant Oncologist for treatment of Oral malignancy	-
	2. Tablet/Capsule - Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400mg) or Lycopene (8mg) and Micronutrients (either alone or in combination)	Once a day for Six to Twelve months
	3. Tablet Ferrous Ascorbate (100 mg) + Folic acid (1.5mg)	Once a day for Three months
	4. Tablet Zinc Sulphate (220mg)	Twice daily for Three to Six months
	5. Tablet Curcumin (300 mg)	Once daily for a period of Six to Eight months.

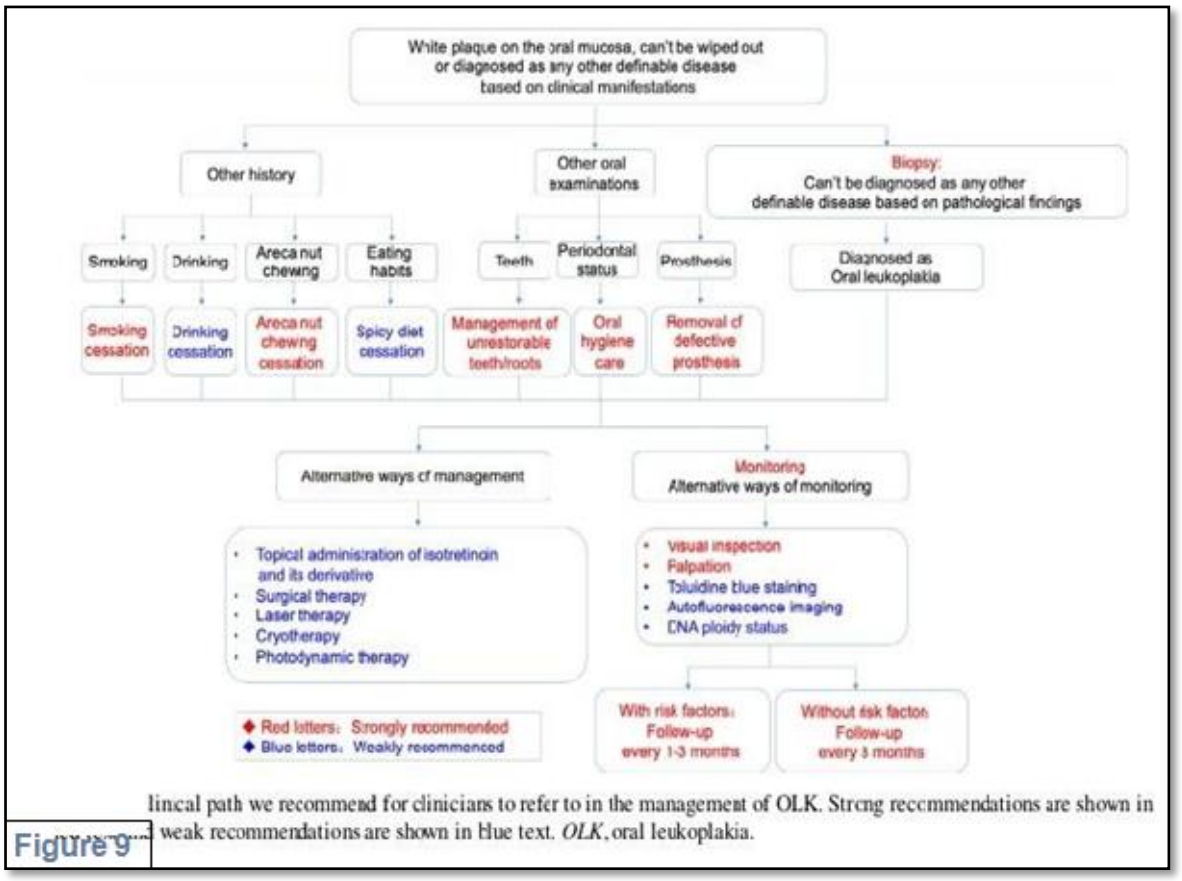
VIII. MANAGEMENT OF ORAL LEUKOPLAKIA

Oral leukoplakia (OLK) is identified by its predominantly white patch or plaque on the oral mucosa, which is non-removable and lacks clinical or histological characteristics defining any other specific disorder. It is recognized as a potentially malignant disorder (PMD) with a notable risk of malignant transformation, affecting the physical and mental well-being of patients to varying degrees [6]. Based on clinical manifestations, OLK can be classified into two types with significant differences in the rate of malignant transformation: homogeneous and nonhomogeneous. The homogeneous type typically appears as a thin, flat, and uniformly white plaque, with at least one area that is well-demarcated, accompanied by or without fissuring

(Figure 7).

Nonhomogeneous leukoplakia is characterized by the presence of speckled and nodular orverrucous areas.[figure 8]

Currently, there are many treatmentoptions for OLK, including drug therapy, surgery, andlaser ablation. However, none are curative. The goal ofdisease management is to relieve symptoms, improvequality of life, prevent malignant transformation, andgradually extend the interval between follow-up until theneed for



linical path we recommend for clinicians to refer to in the management of OLK. Strong recommendations are shown in weak recommendations are shown in blue text. *OLK*, oral leukoplakia.

Figure 9

8 monitoring is eliminated.[6][Figure 9]

3. **Evidence-based guidelines for the clinical management of OLK:** OLK carries a specific risk of malignant transformation. Irrespective of the occurrence of malignant transformation, certain management measures should be implemented based on characteristics such as health education, control of local stimulating factors, initiation of drug therapy, lesion removal therapy, and regular follow-ups [7].

4. **Control of Local Stimulating Factors**

- **Smoking cessation: Strongly recommended:** Findings from a case-control study suggested that smoking stands as an independent risk factor for OLK.16 Outcomes from a prospective cohort study demonstrated a notable reduction in the incidence of OLK following smoking cessation. Several studies indicated that the malignant transformation rate of OLK among smokers remained constant, while others observed a lower malignant transformation rate in smokers compared to nonsmokers.

- **Areca Nut Chewing Cessation:** Strongly recommended

  Two case-control studies have indicated that the act of chewing areca nut independently constitutes a risk factor for potentially malignant disorders (PMDs) affecting the oral mucosa, and a dose–effect relationship has been established between

chewing areca nut and the occurrence of PMDs in the oral mucosa.

- **Oral hygiene care:** Strongly recommended

In a case-control study24, patients with OLK exhibited more pronounced bleeding on probing and attachment loss in comparison to the control group. Both bleeding on probing and attachment loss were identified as risk factors for OLK. The risk of OLK escalated with the increased severity of periodontitis. It's essential to note that the included study has substantial limitations, and the level of evidence is notably low [7].

5. Non surgical treatment of OLK / Drug therapy

- **Beta-Carotene:** Functioning as a precursor to vitamin A, beta-carotene is recommended for the prevention of OL and potentially oral cancer. Its potential benefits and protective effects against cancer are likely associated with its antioxidizing action. This role is fulfilled by beta-carotene binding with oxygen, an unstable reactive molecule, thereby mitigating the detrimental impacts of free radicals.

In a study involving twenty-four patients with OL, beta-carotene was administered at a dose of 30 mg/day for six months. Only 2 patients (8.3%) exhibited a complete clinical response, and 15 patients (62.5%) showed a partial clinical response.

Garewal et al. assessed 50 patients with OL treated with beta-carotene at a dose of 60 mg/day for six months. Only 2 patients (4%) demonstrated a complete clinical response, with relapses observed in 4 patients. A second biopsy was obtained after 6 months of therapy in 23 patients.[7].

- **Lycopene:** Lycopene, a carotenoid lacking provitamin A activity, is a fat-soluble red pigment found in certain fruits and vegetables. Tomatoes, commonly used in culinary practices, stand out as the primary source of lycopene. An distinguishing feature of lycopene is its ability to bind to oxygen-reactive chemical species, rendering it an exceptionally potent biological antioxidant. In addition to its antioxidative role, lycopene has the capability to modify intercellular exchange junctions, constituting an anticancer mechanism. In a study conducted by Singh et al. [48], the efficacy of lycopene was assessed in 58 cases of OL. The patients were divided into three groups and received daily doses of 8 mg, 4 mg, and a placebo over a three-month period. Lycopene supplementation (8 mg/day and 4 mg/day) exhibited comparable efficacy in reducing hyperkeratosis (clinically assessed by the lesion size) in 80% of cases. The complete clinical response rates were 55% for patients receiving 8 mg/day and 25% for those receiving 4 mg/day [6,7].

- **L-Ascorbic Acid (Vitamin C):** L-ascorbic acid (L-AA), commonly referred to as vitamin C, is found in citrus fruits such as kiwi, strawberries, papaya, and mango. L-AA possesses antioxidative properties and interacts with superoxide generated during normal cellular metabolic processes. This inactivation of superoxide impedes the formation of nitrosamines during protein digestion, thereby preventing damage to

DNA and cellular proteins. In a study, 24 patients with OL underwent treatment with a combination of beta-carotene, vitamin E, and L-AA, leading to an observed increase in the reversal of oral mucosa dysplasia. Antioxidant combinations resulted in a reduction of dysplasias in 97.5% of patients.

- **Alpha-Tocoferol (Vitamin E):** Alpha-Tocopherol (AT) is the most prevalent and potent form of vitamin E, commonly found in plant oils, margarine, and green leaves. AT functions as an effective antioxidant in high-oxygen environments, protecting cellular membranes against lipid peroxidation. Benner et al. conducted an evaluation of the toxicity and efficacy of AT in 43 patients with OL, administering 400 IU twice daily for 24 weeks. Follow-up assessments at 6, 12, and 24 weeks after initiating treatment were carried out to evaluate toxicity, clinical response, and serum AT levels. The results indicated that 10 patients (23%) achieved complete clinical remission of lesions, and 10 patients (23%) showed a partial clinical response. Moreover, nine patients (21%) exhibited histologic responses, including the complete reversal of dysplasia to normal epithelium.

- **Retinoic Acid (Vitamin A)-** The present definition of retinoid encompasses both natural and synthetic compounds exhibiting activity akin to Vitamin A. Retinoic acid is derived from carotene and animal products such as meat, milk, and eggs. In the intestine, these substances undergo conversion into retinal and retinol, respectively.

- Topical application of isotretinoin and its derivative: Weakly recommended - 13-cRA stands out as the recommended retinoid for OL treatment, and its efficacy in resolving OL has been well-established [33, 34]. Nevertheless, the limiting factors of high recurrence rates after brief discontinuation periods and associated side effects need consideration. In a study involving 45 registered patients, 7 (15.5%) had OL, and they were administered a fixed dose of 13-cRA (10 mg/day) alongside an escalating dose (initiating at 800 IU/day and progressing to 2000 IU/day) for 4 months. A notable 71% of OL patients achieved complete clinical responses [71]. Another study employing retinoic supplementation (300,000 IU retinol acetate) for OL treatment displayed complete resolution in 52% of patients. An RCT demonstrated that the topical administration of 0.1% 13-cis-retinoic acid (isotretinoin) gel reduced the lesion area. Furthermore, another case series study (n = 26)26 indicated that the topical administration of 0.05% vitamin A acid (tretinoin) gel induced complete clinical remission in a few OLK lesions [6,7].

6. **Lesion-Removing Therapy- Surgical Therapy:** Weak recommendation - A meta-analysis comprising 5 observational studies focused on surgical therapy for OLK revealed that, following the complete surgical removal of OLK lesions, the overall recurrence rate was 25%. Clinicians should undertake a comprehensive consideration of the following factors when opting for surgical therapy in OLK treatment: the extent of epithelial dysplasia, clinical type of lesion, lesion location, lesion size, concomitant Candida infection, concomitant papillomavirus infection, patient's age and sex, and the presence of other systemic diseases.

7. **Laser Therapy:** Weakly recommended- In a meta-analysis involving 27 observational studies with a total of 4292 participants, focused on laser management for OLK32, it was determined that following the complete remission of OLK lesions through laser therapy, the overall recurrence rate was 24% (95% CI, 13%-43%), and the total malignant transformation rate was 4.9% (95% CI, 3.2%-7.3%) over an average follow-up period of 58.2 months.

8. **Cryotherapy:** Weakly recommended- A meta-analysis involving 5 studies and a total of 330 participants, focusing on cryotherapy for OLK, revealed that following cryotherapy, the overall recurrence rate was 16% (95% CI, 10%-25%) over an average follow-up period of 23 months [7].

9. **Photodynamic therapy:** Photodynamic therapy (PDT) represents a noninvasive approach for the treatment of premalignant lesions and head and neck cancers [90, 91]. The fundamental principle of PDT involves a nonthermal photochemical reaction, requiring the concurrent presence of a photosensitizing drug (photosensitizer), oxygen, and visible light. Typically, the light source involves a portable diode laser, and the light is conveyed to or into the tumor through laser fibers. Exposure of the tumor to light at the activating wavelength leads to cell destruction through a nonfree radical oxidative process. These reactive oxygen species possess the potential to harm essential cell components, including structural proteins, enzymes, DNA, and phospholipids. Over time, various photosensitizers have been developed, with haematoporphyrin and its derivatives being among the initial ones. Currently, four photosensitizers have obtained approval.

    - Photofrin has received approval in numerous countries for the treatment of esophagus cancer and lung cancer.
    - 5-Aminolaevulinic acid (ALA) has also obtained approval in several countries for the treatment of skin cancer.
    - Verteporfin is approved for the treatment of macular degeneration.
    - Foscan is the sole photosensitizer that gained approval for the treatment of advanced squamous cell carcinoma of the head and neck in Europe in the year 2001.

    ALA is a naturally occurring compound in the haem biosynthetic pathway, undergoing metabolism to produce the photosensitive product protoporphyrin IX (PpIX). The primary advantage of ALA, when compared to synthetic photosensitizers, lies in its rapid metabolism, leading to a significant reduction in the duration of cutaneous photosensitivity. In most cases within head and neck surgery, the photosensitizer is administered systemically via intravenous injection. However, for very superficial skin lesions or premalignant lesions of the oral mucosa, ALA can be applied topically [7]. Chen et al. [97] treated 24 patients with OL using 20% ALA-PDT once a week, while another 24 patients underwent 20% ALA-PDT twice a week. In the latter group, 8 patients exhibited complete responses to the treatment, 16 showed partial responses, and 9 did not respond. Significantly, all patients in the twice-a-week group demonstrated superior responses compared to those treated only once a week.

    A meta-analysis involving 5 studies and 182 participants, focused on photodynamic therapy for OLK, indicated that following photodynamic therapy, the overall recurrence rate was 25% (95% CI, 19%-32%). In an observational study43 with

147 participants, it was revealed that after photodynamic therapy, the recurrence rate of oral epithelial dysplasia was 11.6%, and the malignant transformation rate was 7.5% during an average follow-up period of 87.6 months [6,7].

Follow-up of all patients with OLK: Strongly recommended- Upon the diagnosis of OLK, consistent follow-ups are highly recommended, irrespective of whether patients exhibit risk factors for malignant transformation or the chosen treatment modality. It is strongly advised that OLK patients without specific risk factors undergo follow-up every 3 months, while OLK patients with high-risk factors (such as advanced age, female sex, leukoplakia exceeding 200 mm2, nonhomogeneous type, and higher grades of dysplasia) should be monitored every 1 to 3 months [7].

IX. MANAGEMENT OF ORAL LICHEN PLANUS (OLP)

Lichen planus (LP) is a chronic inflammatory condition that can affect the skin, mucous membranes, and skin appendages. LP can occur at any age, without displaying gender or racial preferences. Mucosal LP (MLP) has a prevalence of 0.89% and is more commonly observed in the female population. Oral LP (OLP) is the most common subtype of MLP and can be diagnosed either as an isolated condition or in association with cutaneous, scalp, nail, or mucosal manifestations, including the genital, gastrointestinal, and ocular mucosa.

Various clinical subtypes of OLP have been identified, including reticular, plaque-like, papular, erosive, ulcerative, atrophic, and bullous OLP (Figure 10). Oral involvement has been observed in up to 90% of patients with cutaneous LP. Reticular OLP, characterized by white streaks surrounded by well-defined erythematous borders, is typically asymptomatic. In contrast, erosive OLP exhibits ulcerations and erosions surrounded by erythematous mucosa. While reticular OLP is generally manageable, erosive OLP is highly painful and resistant to therapies, thereby significantly impacting the patients' quality of life [8]. 12

Figure 10

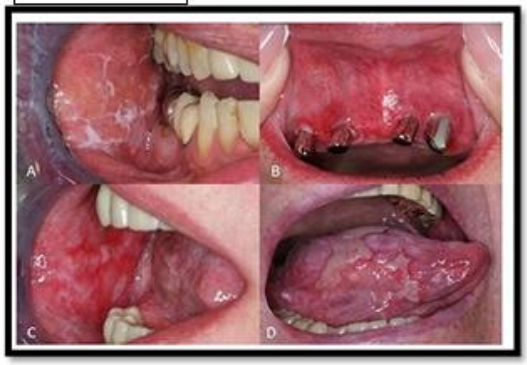


Figure 10: Clinical manifestation of oral lichen planus (OLP). **(A)** Reticular OLP with characteristic Wickham's striae **(B)** Erythema in a female patient with OLP **(C)** Multiple erosions on the left buccal mucosa in a patient with erosive OLP **(D)** Extreme painful ulcerations of the tongue in a patient with ulcerative OLP.

Regular screening for oral cancer is recommended in OLP. Several risk factors associated with malignant transformations in OLP have been identified, including an erosive clinical phenotype, tongue involvement, female gender, and advanced age. In this context, Fitzpatrick et al. found that out of 7806 OLP patients, 85 (1.09%) and out of 125 patients with oral lichenoid lesions, 4 (3.2%) developed oral squamous cell carcinoma.

Both antigen-specific and non-specific mechanisms play a role in the pathogenesis of OLP. On one hand, the activation of CD4+ helper and CD8+ cytotoxic T lymphocytes is initiated by antigen presentation through keratinocytes and Langerhans cells. Activated helper T cells generate IL-2 and interferon (IFN)-gamma, resulting in the proliferation and activation of cytotoxic T lymphocytes. These cytotoxic T lymphocytes subsequently trigger the apoptosis of basal keratinocytes and the degeneration of basal epithelial cells, as typically observed in OLP lesions.

The diagnosis of OLP is based on clinical and histological characteristics. Clinical features are frequently adequate for confirming a diagnosis, particularly when patients display typical skin lesions such as Wickham's striae and symmetric, purplish, flat, polygonal, pruritic papules on the extremities. However, a biopsy of oral lesions is advisable to validate the clinical diagnosis and exclude the possibility of malignancy [8].

Therapies for Managing OLP [Table 6]

Leading clinical phenotype	Topical therapy	Systemic therapy		
Non-erosive OLP	- Topical corticosteroids - Intralesional corticosteroids - Tacrolimus 0.1%*	Usually not necessary		
		First line	**Second line***	**Compassionate use***
Erosive OLP	- Topical corticosteroids - Tacrolimus 0.1%* - PDT*	- Oral corticosteroids - Corticosteroids i.v. - Alitretinoin*	- Hydroxychloroquine - Methotrexate - Apremilast - Azathioprine	- Sekukinumab - Guselkumab - JAKI

JAKI, Janus-Kinase inhibitors; OLP, oral lichen planus; PDT, photodynamic therapy.
*Off-label in Germany.
†The therapies are listed in order of recommendation according to the experience of the authors.

1. **Corticosteroids:** Topical corticosteroids (CS) represent the primary therapeutic approach in OLP, with clobetasol propionate 0.05% commonly used as the initial treatment. Various other corticosteroids, including triamcinolone, betamethasone, fluocinonide, fluticasone, dexamethasone, and prednisolone, delivered through different topical forms such as ointment, oral suspension, aqueous solution, mouthwash, and adhesive paste, have demonstrated efficacy and safety. In a recent phase II randomized controlled trial (RCT), a novel mucoadhesive clobetasol patch (Rivelin®-CLO) was tested on patients with erosive OLP, with the verum group (25/32) reporting an improvement in OLP symptoms compared to the placebo group (11/30).

Intralesional injection of CS, including triamcinolone acetonide, hydrocortisone, dexamethasone, and methylprednisolone, has proven effective in erosive OLP. However, this approach is notably painful for the patient, and only a limited number of erosions can be addressed in each session. Oral CS, such as dexamethasone or prednisone, are commonly prescribed for recalcitrant OLP. Typically, a regimen of oral prednisone (0.5 mg/kg) for 4–6 weeks is employed. Prolonged use of oral CS may lead to severe side effects, including muscle weakness, sleep disturbances, weight gain, pathologic fractures, anemia, acne, striae rubrae, and menstrual irregularities. To mitigate these side effects, a novel concept of oral mini-pulse therapy has been proposed. Malhotra et al. conducted a comparison between a mini-pulse therapy regimen (5 mg betamethasone orally on two consecutive days per week) and triamcinolone acetonide 0.1% paste in OLP patients. The authors reported that both groups exhibited a similar clinical response, but patients on oral betamethasone showed an earlier improvement, and the side effects (e.g., facial edema, headache, and muscular weakness) were mild, transient, and reversible [8].

2. **Cyclosporine:** Cyclosporine (CsA), a calcineurin inhibitor employed as an immunosuppressive medication, has been noted for its systemic use in OLP, as evidenced in several case reports. However, systemic CsA is not recommended as routine therapy for OLP due to its adverse effects, including hypertension, dysregulation of renal function, and gingival hyperplasia. In a randomized, comparative, double-blind study involving 40 patients, topical clobetasol demonstrated superior efficacy compared to topical CsA in inducing clinical improvement. Additionally, the cost of therapy with topical CsA is five times higher than that with clobetasol.

3. **Apremilast:** Apremilast, an oral phosphodiesterase type 4 inhibitor, has been granted approval for the management of psoriasis and psoriatic arthritis. Its mechanism of action involves reducing the production of TNF-alpha, IFN-gamma, IL-2, IL-5, IL-8, and IL-12, all of which contribute to the pathogenesis of OLP. In a multicentric, retrospective study comprising 11 OLP patients (8 of whom had concurrent cutaneous LP), the authors noted that 55% of the patients exhibited an amelioration of their symptoms. by week 12.

4. **Azathioprine:** Azathioprine (AZA) has been employed in various skin disorders, such as pemphigus vulgaris, bullous pemphigoid, and pyoderma gangrenosum. Its effectiveness as a steroid-sparing therapy has been observed in a limited number of patients with erosive OLP. Verma et al. reported positive outcomes in four patients with exclusive erosive OLP and in two patients with diffuse skin LP and OLP when AZA was administered at 50 mg orally twice daily (approximately 2 mg/kg per day) for durations ranging from three to seven months. Therefore, the off-label use of AZA in OLP may be considered as a therapeutic option.

5. **Biologics:** Several biologic therapies have been used in patients with refractory OLP, including anti- CD2, anti-TNF-alpha, anti-IL2, anti-IL17, anti-IL12/23, and anti-IL23 drugs.[8][Table 7]

Table 7

	Number of patients	Treatment period	Observation period	Comment
Adalimumab (29)	1	50 weeks	50 weeks	Clinical improvement
Adalimumab (30)	1	12 weeks	12 weeks	Complete healing
Alefacept (34)	2	12 weeks	32 weeks	Clinical improvement
Alefacept (33)	2	12 weeks	12 weeks	Clinical improvement
Etanercept (28)	1	10 weeks	17 weeks	Clinical improvement and pain relief after etanercept; disease recurrence after agent discontinuation
Guselkumab (15)	1	30 weeks	30 weeks	Complete healing
Infliximab (27)	1	6 months	6 months	Clinical improvement
Rituximab (37)	1	4 weeks	10 months	Clinical improvement; relapse after 10 months
Rituximab (35)	2	14 months	14 months	Remission lasted until 8 months
Rituximab (38)	5	4 months	9 months	Clinical improvement
Secukinumab (15)	3	12–48 weeks	12–48 weeks	Complete healing
Tildrakizumab (16)	1	28 weeks	28 weeks	Complete healing
Ustekinumab (15)	1	48 weeks	48 weeks	Complete healing

6. **Calcineurin Inhibitors:** The use of topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, is widespread in clinical practice for OLP. However, there is a need for a greater number of placebo-controlled, randomized studies to assess the effectiveness and safety of topical calcineurin inhibitors in comparison to topical corticosteroids. In a recent meta-analysis, Sun et al. concluded that, among topical calcineurin inhibitors, topical tacrolimus 0.1% should be the preferred choice for the short-term treatment of refractory OLP. Volz et al. documented a significant reduction in oral erosions with topical pimecrolimus 1% compared to placebo in a prospective randomized double-blind vehicle-controlled study.

7. **Janus Kinases Inhibitors:** JAK inhibitors (JAKI) are emerging as a novel category of drugs applicable to various dermatological conditions, such as atopic dermatitis and alopecia areata. However, in the case of OLP, the utilization of JAK inhibitors is currently constrained to anecdotal reports. Notably, three OLP patients achieved successful treatment outcomes with JAK inhibitors—specifically, one with baricitinib and two with upadacitinib [8].

8. Hydroxychloroquine- HCQ is a widely used anti-malarial agent globally. Due to its immunomodulatory properties, HCQ is extensively utilized in dermatology for treating various conditions, including systemic lupus erythematosus, polymorphous light eruption, and dermatomyositis. In a recent prospective clinical trial involving 45 patients with erosive OLP, the effectiveness and safety of HCQ were demonstrated at a dosage of 200 mg orally twice daily as monotherapy. Additionally, Yeshurun et al. observed a

moderate to marked improvement in 57% and complete remission in 24% of patients with erosive OLP who received HCQ at a dose of 400 mg/day orally as monotherapy.

9. Lasers-Lasers represent a non-pharmacological and non-invasive alternative option for the treatment of OLP.

Photobiomodulation(PBM)or low-level laser therapy (LLLT) as effective alternative- Low-level laser therapy (LLLT) is recognized for its biostimulatory, anti-infective, and anti-ablation effects, presenting itself as a potential alternative treatment. Photobiomodulation therapy (PBM) administered twice a

10. Methotrexate: Methotrexate (MTX) is a folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication. MTX can be administered either orally or subcutaneously and proves effective in various inflammatory dermatoses, including psoriasis and bullous pemphigoid. An open prospective trial employed oral MTX in patients with unresponsive OLP, revealing a partial response in 83.3% of the patients. In a recent prospective observational study, the combination of oral MTX with triamcinolone 0.1% oral paste was reported to be more effective compared to oral MTX or triamcinolone 0.1% oral paste alone in patients with severe OLP.

week for one month (8 sessions) using a laser with a wavelength of 660+/-10nm, power of 100mW, radiant energy of 177J/cm2, 5-second exposure time per point, and 0.5 J of energy per point has demonstrated effectiveness comparable to corticoid therapy in the management of oral lichen planus. The number of treatment points varies based on the size of the lesion. Erosive lichen planus is primarily addressed with a 630 nm low-level laser, applied for 10 sessions per month with a power of 1.5 J/cm2. Photobiomodulation therapy utilizing red diode lasers contributes to an analgesic effect in patients without significant side effects [12]. This approach involves an infrared diode laser. Low-level laser (LLL) encompasses various light sources, such as helium-neon (633 nm), ruby (694 nm), and argon (488 and 514 nm). In a randomized controlled trial (RCT), LLL and CO2 laser were compared, both proving effective in OLP treatment, but LLL exhibited a quicker lesion improvement compared to CO2 lasers. The efficacy of CO2 laser treatment was also confirmed by Van der Hem et al. and Dalirsani et al. [13].

11. Photodynamic Therapy: Photodynamic therapy (PDT) entails the application of a photosensitive agent combined with a harmless light source of specific wavelength. Traditionally applied in the treatment of non-melanoma skin cancers, PDT has recently emerged as a non-invasive therapeutic option for OLP. Additionally, PDT can be administered as monotherapy or in conjunction with other treatment modalities. In a cohort of 20 patients with longstanding OLP, PDT utilizing 5% methylene blue as a photosensitizer demonstrated effectiveness. Notably, the efficacy of PDT is influenced by lesion localization and is notably reduced in the proximity of the masticatory oral mucosa. A study involving 45 OLP patients indicated that PDT was more efficacious than low-level laser (LLL) therapy and was linked to a reduction in CD4+, CD8+, and IL-17+ cells in the oral mucosa affected by OLP [8].

12. **Alternative Medicines in the Management of OLP** Various alternatives to steroid therapy have been investigated in the treatment of OLP. Curcuminoids, derived from turmeric, have been extensively studied for their effectiveness in OLP management. Additionally, Aloe vera, lycopene, hyaluronic acid, and BCG-PSN have been assessed for their efficacy in OLP management. Propolis, a beeswax derivative, purslane (a herb), ignatia (a homeopathic medication), and quercetin have shown promise in the management of OLP.

- **Curcumin** has exhibited antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic properties. Owing to its diverse benefits in lichen planus treatment in comparison to steroids, numerous studies have been undertaken in the past. Case-control studies have indicated that topical curcumin treatment can enhance lesions and diminish pain severity, yielding effects similar to those of triamcinolone cream.

  Curcumin faces challenges in water solubility and bioavailability due to its hydrophobic nature, hindering its practical clinical application as a therapeutic agent. Nanoparticles enhance the dissolution rate of hydrophobic agents by providing a large surface-to-volume ratio. Several studies have shown that the recovery rate of oral lesions in patients with oral lichen planus (OLP) treated with Prednisone and Curcumin was higher than those who received Prednisone alone. Further research indicates that the group receiving Curcumin in three doses of 2000 mg per day for 14 days exhibited a noticeable improvement in clinical signs and symptoms compared to the control group.

  In the study conducted by Thomas et al., the effectiveness of Curcumin 1% gel administered three times a day and Curcumin 1% gel six times a day was compared to that of Triamcinolone cream. All groups underwent a 3-month treatment period, during which a reduction in burning sensation, redness, and ulceration was observed.[9]. In a recent investigation, Nano-Curcumin, administered at a dosage of 80 mg, was utilized, a significantly lower dose compared to other studies employing non-nanosilic forms. An in vivo study demonstrated that low-dose (20 mg/kg) Nano-Curcumin exhibited an equivalent therapeutic effect to high-dose (400 mg/kg) pure Curcumin. These research findings suggest that oral Nano-Curcumin could serve as an alternative treatment for OLP lesions in individuals who cannot take oral corticosteroids or in patients who need to approach corticosteroid use cautiously. Additionally, oral Curcumin might be utilized to prevent the recurrence of OLP lesions post-treatment and initial control. Further studies are recommended to explore this aspect in more detail.[9]

- **Aloevera** demonstrates anti-inflammatory effects by inhibiting the cyclo-oxygenase pathway, leading to a reduced production of prostaglandin E2. It also hinders the release of histamine and leukotriene from mast cells, a process triggered by antigen-antibody reactions and deemed crucial in the pathogenesis of OLP. Nevertheless, the available data are insufficient to draw a definitive conclusion regarding the substitution of aloe vera for conventional OLP treatment.

- A**mlexanox** utilized as a 5% oral paste, serves as a topical anti-inflammatory agent for treating recurrent aphthous stomatitis. Its mechanism involves inhibiting the

synthesis and release of histamine, leukotrienes, and TNF alpha from mast cells, mononuclear cells, and neutrophils. A randomized clinical trial showcased similar therapeutic efficacy between the 5% amlexanox paste and the 0.043% dexamethasone paste in OLP.

- **Hyaluronic acid (HA)** plays a pivotal role in various biological processes, encompassing cell signaling, cell proliferation, regulation of gene expression, morphogenesis, matrix organization, lubrication, tissue hydration, and wound healing. One of the notable advantages of hyaluronic acid is its favorable safety profile, allowing for its secure use in all patients, including infants and pregnant females. Furthermore, it proves effective across all grades of oral ulceration. A study conducted by Yousef et al. concluded that the application of topical HA (0.2%) exhibited superior efficacy in alleviating OLP symptoms compared to topical corticosteroids.

- A potential alternative for treating OLP involves platelet-rich plasma (PRP), denoting concentrates of human platelets derived from the patient's blood (autologous). PRP contains 3- to 5-times more platelets than the normal concentration in whole blood, along with bioactive molecules such as growth factors, cytokines, and cell adhesion molecules. The rationale behind using PRP in regenerative medicine lies in platelet degranulation, facilitating the release of growth factors, modifying the inflammatory response, and fostering cell proliferation and differentiation within the target tissue. The therapeutic efficacy of autologous platelet concentrates has been documented in various autoimmune diseases in the published literature.

  PRP also encompasses various growth factors, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), epithelial growth factor (EGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), fibronectin, serotonin, dopamine, histamine, adenosine, and calcium. Each of these factors plays distinct roles in promoting cell differentiation, proliferation, and regeneration. PDGF and TGF-β, in particular, have demonstrated the ability to stimulate fibroblast proliferation and increase collagen production. TGF-α and EGF can effectively regulate the propagation and migration of keratinocytes, leading to an augmentation in epidermal thickness. Furthermore, PRP enhances the expression of matrix metalloproteinases (MMPs), pivotal in the regulation of remodeling. Hence, the anti-inflammatory, antioxidant, and immunomodulatory properties of PRP position it as a promising therapy for OLP patients.[10]

X. MANAGEMENT OF ORAL ULCERS

Oral ulceration is a prevalent mucosal condition that can arise from factors such as physical or chemical trauma, viral, fungal, or bacterial infections, allergies, malignancies, or as a manifestation of systemic diseases. The occurrence of oral ulceration involves a disruption in the oral epithelium, exposing nerve endings in the underlying lamina propria, leading to pain or soreness, particularly aggravated by the consumption of spicy foods or citrus fruits [2]. Given that most ulcers necessitate addressing the root cause, accurate diagnosis is pivotal for the effective treatment and prevention of such lesions. [11]

1. **Management of Recurrent Aphthous Stomatitis:** Recurrent aphthous stomatitis (RAS) is acknowledged as the most prevalent oral mucosal lesion, characterized by the recurrence of multiple small or ovoid ulcers with yellow floors, encircled by erythematous haloes. These ulcers typically manifest initially during childhood or adolescence. The etiology of aphthous ulcers remains elusive, with various factors implicated in the disease, including hormonal changes, trauma, drugs, food hypersensitivity, nutritional deficiency, stress, and tobacco. [11]

2. **Classification and clinical presentation of RAS[**12]**[Table 8 &9]**

Recurrent oral ulceration
• Recurrent aphthous stomatitis
Minor
Major
Herpetiform
• Recurrent aphthous ulcers with Behçet's disease
• Smoking-related aphthous ulcers
• Recurrent erythema multiforme
• Atypical recurrent oral ulceration
Persistent oral ulceration
• Secondary to hematological deficiency state/anaemia
• Secondary to a gastrointestinal enteropathy
• Secondary to a dermatological condition
• Secondary to connective tissue disease

Character	Type of RAS		
	Minor	Major	Herpetiform
Peak age of onest (decade)	Second	First and second	Third
Number of ulcers	1-5	1-3	5-20 (up to 100)
Size of ulcers (mm)	<10	>10	1-2
Duration	7-14 days	2 weeks-3 months	7-14 days
Heal with scarring	No	Yes	No
Site	Non-keratinized mucosa especially labial/buccal mucosa. Dorsum and lateral borders of the tongue	Keratinized and non-keratinized mucosa, particularly soft palate	Non-keratinized mucosa but particularly floor of the mouth and ventral surface of the tongue

RAS: Recurrent aphthous stomatitis

3. **Treatment therapies of RAS- evidence based:** The cause of RAS remains uncertain, and consensus on its treatment is lacking. Consequently, numerous therapies have been explored, with only a limited number subjected to double-blind randomized controlled trials. The primary objectives of treating RAS are symptom reduction, minimizing the number and size of ulcers, and extending disease-free intervals. The choice of treatment strategy should be guided by factors such as disease severity (especially pain), the patient's medical history, the frequency of flare-ups, and the patient's tolerance for the prescribed medication

Despite recurrent aphthous stomatitis (RAS) being a prevalent oral disorder, there are no universally accepted guidelines for its treatment. The main therapeutic objectives, aside from pain relief, include (a) promoting the healing of existing ulcers and (b) preventing the onset of new ulcerations. Various topical preparations aim to facilitate the healing process, with many claiming efficacy, while systemic medications are typically employed to prevent the occurrence of new episodes[12].

4. **Topical Agents:** Various pastes and gels are available for coating the surface of ulcers, creating a protective barrier against secondary infection and additional mechanical irritation. Topical agents represent the primary treatment option for recurrent aphthous stomatitis (RAS). Patients are advised to apply a small amount of gel or cream after rinsing and to refrain from eating or drinking for 30 minutes. This application can be repeated 3 or 4 times daily.

5. **Mouthwashes:** Topical tetracycline mouthwash, whether used independently or in conjunction with liquid antifungals or topical steroids, has been particularly employed in treating Herpetiform recurrent aphthous stomatitis (RAS) and remains the preferred treatment for this steroid-resistant variant. Its efficacy lies in diminishing ulcer size, duration, and pain, attributed to its capacity to impede collagenase activity. In major and minor RAS cases, the use of topical tetracycline or minocycline mouthwashes as local antibacterials is anticipated to mitigate the severity of ulcerations and associated pain, although recurrence prevention is not guaranteed..[12]

6. **Topical gels, creams, and ointments** Topical medications washes away from the target area; therefore, it is better to use different kinds of adhesive vehicles in combination with the drug.

7. **Topical corticosteroids** have the potential to mitigate the inflammatory processes associated with aphthae formation. These medications exert their influence on lymphocytes, altering the response of effector cells to triggers of immunopathogenesis, such as trauma and food allergies. The use of steroid tablets as a mouthwash represents one of the most prevalent treatments in specialized clinics. Despite limited clinical evidence supporting its efficacy, it is a recognized therapy for recurrent aphthous stomatitis (RAS) and generally acknowledged as effective in managing this common oral condition [54]. Al Na'mah et al. [36] have determined that the novel dexamucobase is equally effective in treating oral aphthous ulceration, offering some advantages over the widely used Kenalog in Orabase preparation. Application of dexamethasone ointment three times a day for 5 days demonstrates the potential to reduce ulcer size and pain, accompanied by an improvement in healing time.

8. **Betnesol** mouthwash consists of a 500 mcg betamethasone sodium phosphate tablet dissolved in 10 ml of water and used as a mouthwash for 3 minutes before being discarded. It is administered four times a day (QID) when ulcers are present and twice a day (BID) in between ulcer attacks. In a 3-month study conducted by Tappuni et al., betnesol mouthwash (four times a day) was compared with a combination of betnesol mouthwash and colchicine tablets (0.5 mg a day). Utilizing an ulcer severity scoring (USS) system, the authors demonstrated a significant improvement in USS for most patients in the betnesol group, as well as in the combined treatment of colchicine plus betnesol.

9. **Amlexanox,** with its anti-inflammatory, anti-allergic, and immunomodulatory properties (currently unavailable in the USA), has shown effectiveness in treating recurrent aphthous stomatitis (RAS). Two adequately sized double-blind trials involving 100–200 RAS patients demonstrated that Amlexanox oral adhesive tablets, applied four times a day for five days, effectively promoted healing and reduced pain. Meng et al. have suggested that amlexanox oral adhesive pellicles exhibit comparable efficacy and safety to amlexanox

oral adhesive tablets in treating minor RAS in this Chinese cohort. However, pellicles are deemed more user-friendly compared to tablet forms, making amlexanox oral adhesive pellicles a potentially better choice for RAS patients in clinical practice. Some topical glucocorticoids, such as fluocinonide and clobetasol, may also be preferable when used alone or mixed with orabase. [12]

10. Recommended Treatment For Different Types of RAS[12] **[Table 10 and 11]**

Other alternative therapies for treating RAS

Treatment	Results
Levamisole 50 mg/TDS	Reduction in ulcers in up to 66 %
Infliximab, Adalimumab, Golimumab	Complete remission in up to 89 %
Dapsone 50–125 mg	Improvement in 60 %
Colchicine 500 µg/day	Effective in over 70 %
Prednisolone 25 mg/day	Pain, ulcer number and duration reduced
Azathioprine 25 mg/day	Reduction of RAS in Behcets (see Table 1)
Thalidomide 50 mg/day	Complete remission in 85 %. Beware side effects of neuropathy
Tetracycline mouthwash four times daily	Remission in majority but not all
Pentoxifylline 400 mg/TDS	Ulcer pain, size, number reduced. ulcer free period increased
TPMT Thiopurine methyltransferase	

	First line treatment	Second line treatment	Maintenance treatment
Minor RAS	For 3 months local steroid mouthwash four times a day when ulcers present, twice daily when not	Colchicine 500–1000 µg/day for 3 to 6 months	Local steroid mouthwash four times a day when ulcers present
Major RAS	Colchicine 500–1000 µg/day for 6 months. Short course of systemic steroids may precede	Azathioprine 50–100 mg/day	Local steroid mouthwash four times a day when ulcers present
Herpetiform RAS	Tetracycline mouthwashes four times a day when ulcers	Colchicine 500–1000 µg/day for 3–6 months	Tetracycline mouthwashes four times a day in prodrome
RAS in children	Hydrocortisone hemisuccinate pellets 2.5 mg four times daily	Local steroid mouthwash four times a day when ulcers present	Continue for 3 months, twice daily if no ulcers

Various topical herbal treatments have demonstrated effectiveness as alternative therapies, including aloe vera gel, berberine gelatine, Yunnan baiyao, Myrtus communis, and citrus oil with magnesium salts. All these topical herbal therapies have been applied in the treatment of minor recurrent aphthous stomatitis (RAS). In a randomized, placebo-controlled, double-masked, parallel-arm clinical trial, Lalla et al. found that daily multivitamin supplements did not enhance the number or duration of RAS episodes in 160 subjects. [12]

11. Photobiomodulation or Low level laser therapy(LLLT): LASER (light amplification by stimulated emission of radiation) was initially discovered by Theodore H. Maiman in 1960. The term photo biostimulation was introduced by Endre Mester after he observed the effects of low-dose laser treatments in stimulating wound healing. Subsequently, it was observed that, in addition to stimulation, light therapy could also modify certain detrimental processes, such as inflammation or pain. Thus, the term "photobiomodulation" (PBM) was coined. Currently, PBM encompasses a wide range of nonionizing light sources, including lasers, Light-Emitting Diodes (LEDs), and broadband visible light in the visible and near-infrared spectrum, administered at very low, non-thermal doses. PBM stimulates both positive tissue processes, such as wound healing, regeneration, and immune responses, and negative tissue processes, including inflammation, pain, and aberrant immune responses[.13]

12. Mechanism of action [13]

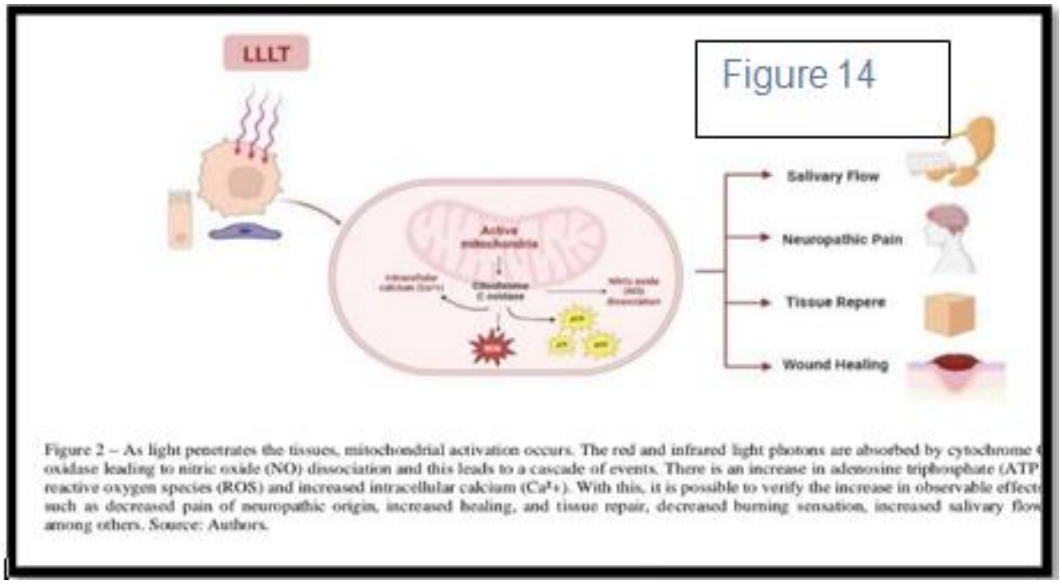


Figure 2 – As light penetrates the tissues, mitochondrial activation occurs. The red and infrared light photons are absorbed by cytochrome c oxidase leading to nitric oxide (NO) dissociation and this leads to a cascade of events. There is an increase in adenosine triphosphate (ATP) reactive oxygen species (ROS) and increased intracellular calcium (Ca^{2+}). With this, it is possible to verify the increase in observable effects such as decreased pain of neuropathic origin, increased healing, and tissue repair, decreased burning sensation, increased salivary flow among others. Source: Authors.

PBMT is effective in the pain relief and healing of these lesions when used with a diode laser of 645 nm wavelength, power 100mw onto the lesion of spot size 1cm2for a duration of 30sec per cm2 and energy density 10J/cm2 used in continuous mode for 3 consecutive days. PBMT with a diode laser of 940nmused in noncontact mode for 30-45 seconds with a pause for 10-20 seconds and a total of 2 minutes in a single session has shown faster reduction of pain and healing of ulcers.

13. Aphthous stomatitis stands out as one of the most prevalent oral cavity pathologies, characterized as a multifactorial condition that presents with painful necrotizing ulcers persisting for up to two weeks. These ulcers significantly impact the patient's eating, hygiene, and communication practices. Leveraging its analgesic, anti-inflammatory, and regenerative efficacy, photobiomodulation (PBM) has proven to be a valuable therapeutic approach for aphthous stomatitis. In a recently published case report, the authors detailed a patient who underwent PBM with a wavelength of 808 nm applied directly to the lesion site, as well as on the submandibular and cervical lymph nodes for lymphatic drainage on the lesion's side.

The patient reported an absence of recurrences for approximately two years, underscoring the effectiveness of PBM in facilitating tissue repair, providing analgesia, and preventing the swift, painless, and reliable recurrence of lesions.[13]

XI. MANAGEMENT OF ORAL CANCER OR MALIGNANCY

Oral cancer ranks as the eighth and 13th most prevalent malignancy globally among males and females, respectively. The majority of these cases, up to 80%, are reported in Asia. Precancerous and cancerous oral lesions have the potential to resemble various benign oral conditions, leading to instances where investigation and treatment are deferred until the conditions have progressed significantly.

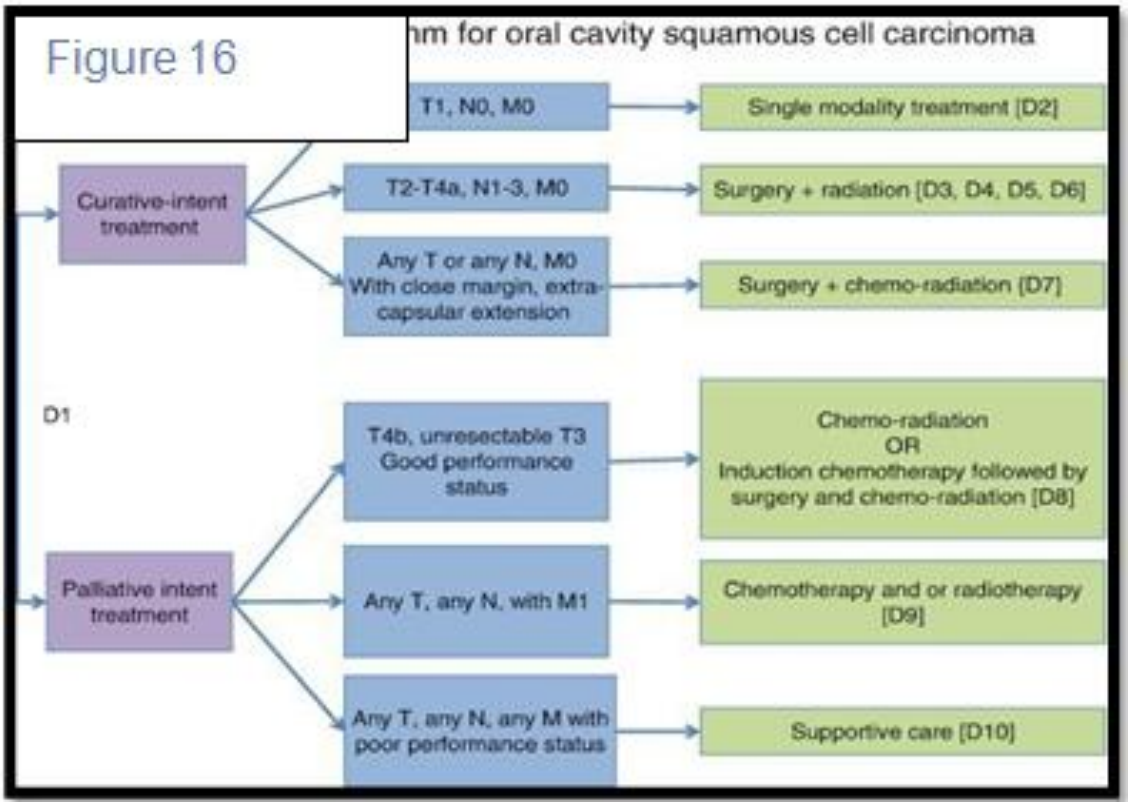
Oral squamous cell carcinoma (OSCC) is the 16th most common neoplasm worldwide, with almost 355,000 newly diagnosed cases and over 177,000 deaths estimated in 2018. The incidence of oral squamous cell carcinoma predominantly includes tongue, gum, floor of mouth and oropharynx, excluding lip.

Multiple established risk factors contribute to the onset of oral cancer, with the most extensively researched and recognized factor being tobacco use. There is a growing body of evidence highlighting the impact of alcohol consumption on the development of oral cancer. Dentists play a crucial role in enhancing survival rates and reducing the morbidity associated with oral cancer treatment by detecting lesions at an early stage. Ideally, the discovery, diagnosis, treatment, and monitoring of precursor lesions for malignant progression are essential steps in this process.[14]

1. **Diagnosis and management of OSCC:** Efficient and timely diagnosis remains vulnerability in the management of OSCC. Tumors are frequently referred to specialists with substantial delays, often reaching advanced stages, significantly impacting prognosis and constituting the initial variable in need of optimization. Bioendoscopic filters, such as Narrow Band Imaging (NBI), have the potential to enhance the diagnostic capabilities of conventional oral examinations. However, these techniques come with a notable learning curve and are susceptible to subjectivity in interpretation. The study conducted by Paderno et al. presents, for the first time, the feasibility of employing fully convolutional neural networks on NBI endoscopic frames of oral lesions to automatically identify tumors and outline their margins. This initial report underscores the potential of the emerging field of "Videomics" for the diagnosis and comprehensive characterization of OSCC.

   A notable advancement in the diagnostic, therapeutic, and rehabilitative strategy for OSCC (and head and neck cancers in general) has been the widespread acknowledgment of the crucial role played by multidisciplinary teams. This notion is substantiated by the recent assessment conducted by Shang et al., demonstrating that patients undergoing effective multidisciplinary management exhibited a significantly elevated survival rate.

The treatment of patients with oral cancers through a multidisciplinary approach has exhibited no substantial improvement over the past few decades, with poorer survival linked to advanced age and disease in advanced stages. A multimodal strategy involving surgery followed by postoperative radiotherapy or chemotherapy appears to outperform non-surgical treatment protocols. Recurrences and the emergence of new cancers in the region of the excised lesion after surgery have been documented to range from 10% to 20% and 3% to 9%, respectively.[14]



When contemplating the treatment of oral squamous cell carcinoma (OSCC), surgery continues to be the primary approach, possibly complemented by adjuvant therapies. However, surgery is a dynamic field, and methodologies should be enhanced and adapted based on emerging evidence and technologies. Over recent years, the notion of compartmental surgery for OSCC has garnered considerable attention. In this context, Carta et al. and Grammatica et al. have, respectively, conducted a retrospective analysis affirming the favorable oncologic outcomes achievable through compartmental tongue resections and have provided a step-by-step guide outlining such a surgical technique.

Simultaneously, the increasing recognition of sentinel lymph node biopsy in oral oncology could bring about enhancements in the preventive management of contralateral neck metastases. According to Mahieu et al., elective neck dissection typically does not address the contralateral neck in early-stage OSCC not involving the midline, whereas sentinel lymph node biopsy has the potential to stage both the ipsilateral and contralateral neck. Notably, the authors observed a higher incidence of contralateral regional recurrence in patients undergoing elective neck dissection compared to those who underwent sentinel lymph node biopsy. This outcome underscores the effectiveness of such a procedure in identifying unexpected contralateral nodal spread, potentially paving

the way for new avenues. applications for this technique in the setting of minimally invasive contralateral neck staging.[14]

Additionally, non-surgical treatments have undergone evaluation due to advancements in radiation techniques and chemotherapy regimens. Kim et al. conducted a comparison between postoperative chemoradiation and radiotherapy alone, utilizing new-generation techniques. The results were found to be comparable, except for tumors with extranodal extension. Various schedules of induction chemotherapy have been proposed, with evidence supporting the superior tolerability of weekly induction taxane–platinum–fluorouracil compared to a 3-week schedule, as reported by Tousif et al.

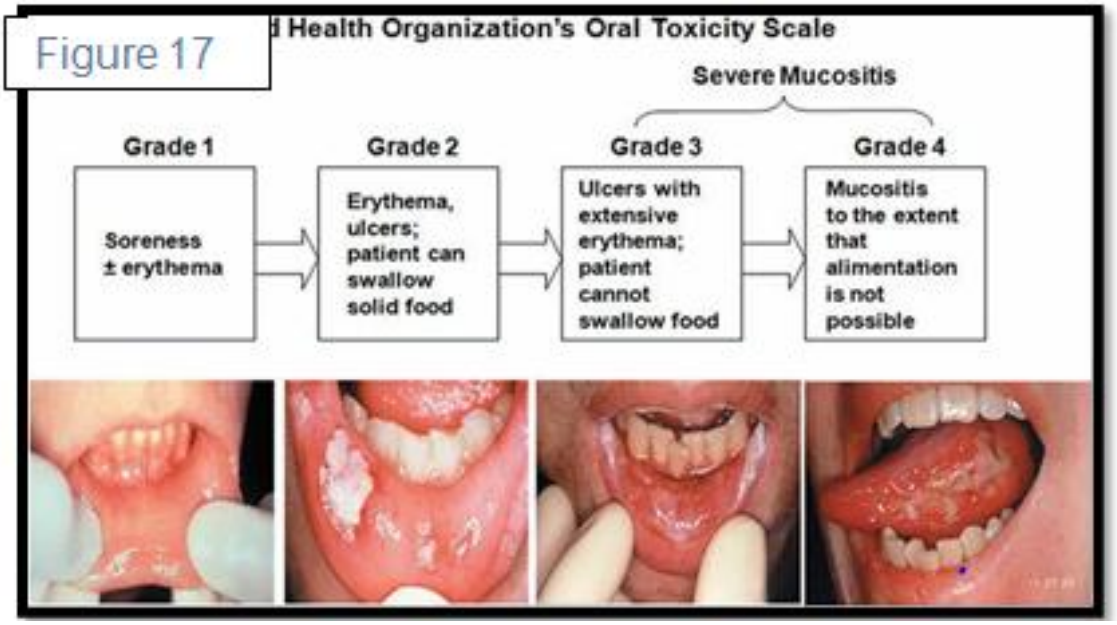
Looking to drug repurposing, a potential synergic effect has been found when low molecular weight heparin is added to cisplatin (Camacho-Alonso et al.). Still, drug discovery may conceivably offer novel tools for treatment of OSCC. In this regard, melatonin can exert anti-proliferative, anti-invasive, and anti- migrative effects on OSCC via the miR-25-5p/NEDD9 pathway, thus warranting further assessment of its potential.

Lambert et al. reported a single-center experience on the use of photodynamic therapy as an alternative treatment tool in inoperable oral and oropharyngeal cancer. While limited to highly selected patients, functional and oncologic outcomes were satisfying considering the specific setting. Swallowing and airway patency were preserved in 77% and 96% of patients, respectively, and the recurrence-free rate at two years was 32%.

The management of OSCC has significant room for improvement, and this should be primarily obtained by optimizing current strategies. Indeed, many factors that decrease survival are related to late diagnosis or inadequate treatment and could be addressed by prompt referral to leading oncologic centers. Once this issue has been solved, the introduction of molecular analyses and artificial intelligence tools have the potential to further improve treatment personalization and outcomes.[14]

XII. EVIDENCE BASED MANAGEMENT OF ORAL MUCOSITIS

Oral mucositis is a prevalent side effect of cancer therapy, bringing about morbidity characterized by pain, compromised nutrition, and an elevated risk of infection. These consequences may lead to interruptions or dose reductions in cancer therapy. Traditionally, the primary focus of management centered on pain relief and nutritional assistance. Nevertheless, there has been a recent update in evidence-based clinical practice guidelines for oral and gastrointestinal mucositis. These guidelines are formulated by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology.[15]



1. **For oral mucositis in patients receiving systemic chemotherapy, the guidelines include**

   - Recommendations for oral cryotherapy in patientsreceiving bolus fluorouracil and high-dose melphalan
   - A recommendation for intravenous keratinocytegrowth factor-1 in patients with hematologic cancerreceiving high-dose chemotherapy for autologoushematopoietic stem-cell transplantation (HSCT).
   - A recommendation for intra-oral low-level laser therapy in patients receiving high-dose chemotherapy for HSCT.

2. **For oral mucositis in patients receiving head and neckradiation therapy (H&N RT), the guidelines include:**

   - Recommendations for intra-oral low-level lasertherapy in patients receiving H&N RT with orwithout concurrent chemotherapy
   - A suggestion for benzydamine mouthwash in patients receiving H&N RT with concurrent chemotherapy6
   - A recommendation for benzydamine mouthwashin patients receiving moderate-dose H&N RT
   - A suggestion for oral glutamine in patients receiving H&N RT with concurrent chemotherapy.

3. **Mucositis Management**

   - **Bland Rinses**
     - 0.9% saline solution.
     - Sodium bicarbonate solution.
     - 0.9% saline/sodium bicarbonate solution.

- **Topical Anesthetics**
  - Lidocaine: viscous, ointments, sprays.
  - Benzocaine: sprays, gels.
  - 0.5% or 1.0% dyclonine hydrochloride (HCl).
  - Diphenhydramine solution.

- **Mucosal Coating Agents**
  - Amphojel.
  - Kaopectate.
  - Hydroxypropyl methylcellulose film-forming agents (e.g., Zilactin).
  - Gelclair (approved by the U.S. Food and Drug Administration [FDA] as a device).

- **Analgesics**
  - BenzydamineHCl topical rinse (not approved in the United States).
  - Opioid drugs: oral, intravenous (e.g., bolus, continuous infusion, patient-controlled analgesia [PCA]), patches, transmucosal.

- **Growth factor (keratinocyte growth factor-1)**
  - Palifermin (approved by the FDA in December 2004 to decrease the incidence and duration of severe oral mucositis in patients undergoing high-dose chemotherapy with or without radiation therapy followed by bone marrow transplant for hematologic cancers).[15]

ABBREVIATIONS

[1] EBD- Evidence based dentistry
[2] OSMF- Oral submucous fibrosis
[3] OLK- Oral leukoplakia
[4] OLP- Oral lichen planus
[5] RAS- Recurrent aphthous stomatitis
[6] PDT- photodynamic therapy
[7] LLLT- low level laser therapy
[8] PBM- Photobiomodulation
[9] CS- corticosteroid
[10] CsA- cyclosporine
[11] AZA- Azathioprine

REFERENCES

[1] K France, T.P.Sollecito. How Evidence-Based Dentistry Has Shaped the Practice of Oral Medicine. Dent Clin N Am 63 (2019) 83–95.
[2] Evidence-based Dentistry (EBD) Published on FDI World Dental Federation (https://www.fdiworlddental.org)
[3] Dhar V. Evidence-based dentistry: An overview. ContempClin Dent 2016;7:293-4.
[4] Evidence-Based Clinical Practice Guideline for the Evaluation of Potentially Malignant Disorders in the Oral Cavity: A Report of the American Dental Association. JADA.ADA.org/article/S0002-8177(17)30701-8/fulltext.
[5] More CB, Gavli N, Chen Y, Rao NR. A novel clinical protocol for therapeutic intervention in oral submucous fibrosis: An evidence based approach. J Oral MaxillofacPathol. 2018 Sep-Dec; 22(3): 382–

391.
[6] Chen Q, DanH,Pan W, Lu Jiang, Yu Zhou, Xiaobo Luo, Xin Zeng. Management of oral leukoplakia: a position paper of theSociety of Oral Medicine, Chinese StomatologicalAssociation. and may require further modification as new evidence is produced.Oral SurgOral Med Oral Pathol Oral Radiol 2021;132:3243.
[7] Ribeiro AS, PR Salles, TAparecida da Silva,RAMesquita. A Review of the Nonsurgical Treatment of Oral Leukoplakia. International journal of dentistry. Jan 2010.
[8] Didona D, Caposiena Caro RD,Sequeira Santos AM, Solimani F andHertl M (2022) Therapeutic strategiesfor oral lichen planus: State of the artand new insights.Front. Med. 9:997190.
[9] Vadivel JK, Ezhilarasan D, Govindarajan M, Somasundaram E. Therapeutic effectiveness of alternative medications in oral lichen planus: Asystematic review. J Oral MaxillofacPathol 2020;24:344-51.
[10] Sriram, S.; Hasan, S.; Alqarni, A.; Alam, T.; Kaleem, S.M.; Aziz, S.; Durrani, H.K.; Ajmal, M.;Dawasaz, A.A.; Saeed, S. Efficacy of Platelet-Rich Plasma Therapy in Oral Lichen Planus: A Systematic Review. Medicina 2023, 59, 746.
[11] Sh.A. Ali, H.I. Saudi. An expert system for the diagnosis and management of oral ulcers. Tanta dental journal 11; 2014: 42-46.
[12] Stephen J. C, SurabAlsahaf, Anwar Tappuni. Recurrent Aphthous Stomatitis: TowardsEvidence- Based Treatment?Curr Oral Health Rep (2015) 2:158–167
[13] Cassia Alves de et al. Photobiomodulation in the treatment of oral diseases. Research, Society and Development, 12, 3, e9512338070, 2023.
[14] Paderno A, Bossi P and Piazza C (2021) Editorial: Advances in the Multidisciplinary Management of Oral Cancer. Front. Oncol. 11:817756.
[15] Rajesh V L. Evidence based management of oral mucositis. Journal of oncology practice, 16;3, 2023

