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Review

Ulcerative oral lesions: an overview of non-pharmacologic treatment options

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Abstract *Background and Objective:* Ulcerative diseases frequently affect the oral cavity and are disabling conditions. The management is challenging, and traditional treatments are associated with potential side effects. Alternative non-pharmacologic strategies have become available to effectively manage these conditions. This review aims at providing a synthesis of the most common erosive-ulcerative oral diseases and an updated overview of the main non-pharmacologic options for their management, such as laser therapy, ozone applications, and photodynamic therapy. *Methods:* A narrative review was conducted by searching PubMed/MEDLINE for the most recent relevant systematic reviews or, alternatively, clinical trials or case reports. *Results:* Laser photobiomodulation therapy (PBMT), ozone therapy and photodynamic therapy (PDT) generally resulted in rapid relief of painful symptoms, reduced healing time and improved oral functions and patients' quality of life. No major side-effects were reported. Regardless of the primary etiology, photodynamic therapy proved particularly effective in case of infections. Ozone was used in gaseous, ozonized water and oil formulations. The most used light sources were Nd:YAG, He:Ne, Er,Cr:YSGG, red and infrared diode lasers and LED for PBMT, while red diode lasers prevailed for PDT. The most common photosensitizers were methylene blue and toluidine blue O. *Conclusions:* There is growing evidence for an efficacy of PBMT, ozone and PDT for the treatment of ulcerative oral lesions, and therefore these approaches should be considered as valid non-pharmacologic strategies. However, due to the great heterogeneity of protocols, additional well-designed research to identify the best therapeutic protocols is needed. (www.actabiomedica.it)

Key words: laser, non-pharmacologic treatment, oral ulcers, ozone, photobiomodulation, photodynamic therapy

Introduction

Ulcerative lesions of the oral mucosa are a common and often debilitating clinical complaint. Patients of various age groups, including children, may be affected. The differential diagnosis is often challenging for the clinician, sometimes requiring combined clinical, histologic, and histochemical evaluation (1).

Erosive and ulcerative lesions can be classified on the basis of various parameters such as clinical presentation, microscopic features, and etiology. According to their etiology, ulcerative lesions can be considered as i) traumatic, ii) infectious, iii) immune-mediated, and iv) neoplastic. The clinical course of oral mucosal lesions can range from self-limiting to chronic to severe, ingravescent and sometimes life-threatening, mainly

depending on their pathogenesis. The prompt and correct diagnosis of oral ulcers, and consequently the identification of the underlying pathogenetic mechanism, is fundamental to establish the appropriate treatment and to effectively manage these diseases (2). These lesions are particularly debilitating in children and more prone to superinfection, negatively impacting daily activities such as eating, speaking, and sleeping (3,4). The control of clinical symptoms and the promotion of the healing process are thus of paramount importance.

Pharmacologic therapy, mainly antimicrobial agents and immunosuppressive drugs such as corticosteroids, plays an important role in the management of oral ulcerative diseases. However, these agents are associated to possible adverse effects and complications, especially for systemic, recurrent, and long-term treatments, including mucosal thinning, dysgeusia, tachyphylaxis, drug resistance, secondary infections, metabolic and immunologic side effects (1,5). The debilitating, chronic or recurrent nature of oral ulcerative diseases may require multiple cycles of therapy or maintenance treatments, and the possibility of using validated, effective, non-pharmacological therapeutic approaches without side effects, alone or in combination with other medications, should be considered as an important resource in the management of erosive-ulcerative oral pathologies of various etiology.

The aim of this narrative review is to provide a synthesis of the most common erosive and ulcerative oral diseases and an updated overview of the main non-pharmacological options available for their management, such as ozone applications, laser therapy, and photodynamic therapy, according to the most recent protocols reported in the literature.

Methods

This study was designed as a narrative review of the most recent summary evidence, such as systematic reviews and meta-analyses, and clinical studies concerning the management of ulcerative oral conditions using non-pharmacologic approaches. Due to the specific narrative design of this review, the protocol was not registered. We conducted the literature search using PubMed/MEDLINE database up to February 25, 2024.

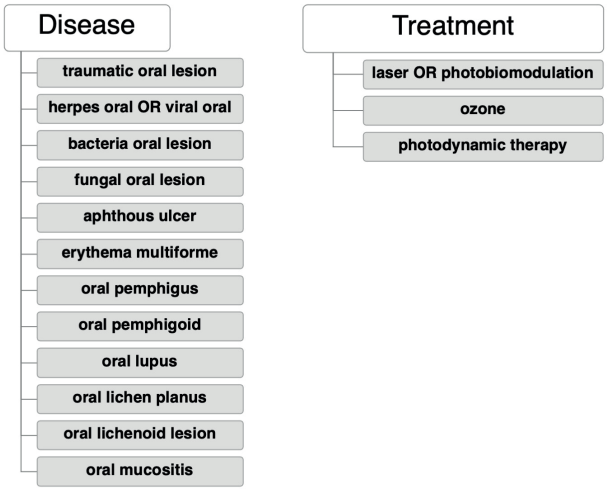

Figure 1. Schematic presentation of the search strategy used for the literature screening. For example, the entry terms for traumatic oral lesion and laser photobiomodulation were "traumatic oral lesion AND (laser OR photobiomodulation)".

We performed the online literature search using terms related to the non-pharmacologic treatments (i.e. laser photobiomodulation, ozone, and photodynamic therapy) combined with terms related to all possible oral ulcerative diseases. A schematic presentation of the search strategy is provided in Figure 1. We considered papers published in English in the recent 15 years (2010-2024). We focused on the most recent relevant systematic reviews or, alternatively, on the most recent relevant clinical trials available for each domain. When neither systematic reviews nor clinical trials were available, relevant case reports were considered.

Overview of common ulcerative oral lesions

A list of the most common erosive and ulcerative oral diseases classified by etiology is presented in Table 1.

Traumatic ulcerative lesions

Mechanical, thermal or chemical traumas are a frequent cause of acute or chronic ulcerative lesions, sometimes resembling ulcers of neoplastic origin, presenting with bleeding, granulation tissue or fibrosis (6). A thorough clinical examination and history of the

Table 1. Common oral diseases manifesting as erosive-ulcerative lesions.

Trauma
Thermal / electrical
Chemical
Mechanical
Infections
Viral
Human simplex virus type 1 (HSV-1)
Varicella-zoster virus (VZV)
Cytomegalovirus (CMV)
Coxsackievirus
Bacterial
Syphilis
Tuberculosis
Necrotizing ulcerative gingivitis (NUG) / stomatitis (NUS)
Fungal
Aspergillosis
Mucormycosis
Histoplasmosis
Cryptococcosis
Blastomycosis
Coccidioidomycosis
Immune-based
Recurrent aphthous stomatitis (RAS)
Erythema multiforme (EM)
Pemphigus vulgaris (PV)
Mucous membrane pemphigoid (MMP)
Systemic (SLE) and discoid lupus erythematosus (DLE)
Oral lichen planus (OLP)
Oral lichenoid lesions (OLL)
Neoplastic
Oral squamous cell carcinoma
Hematologic malignancies (Leukemia, T-cell or B-cell lymphomas)
Metastatic malignancies
Cancer therapy-induced oral mucositis

patient will often reveal the presence of a sharply fractured tooth, a poorly fitting denture, or a recent burn from a hot meal or local contact with acidic medications such as aspirin.

Causal treatment consists of identification and removal of the traumatic agent. Consequently, spontaneous and uneventful resolution of the lesion should be achieved in approximately two weeks (7). Symptomatic management may benefit from topical application of antiseptics, coating gels that promote tissue regeneration.

Infectious ulcerative lesions

Infectious ulcerative lesions are commonly caused by viral agents and are usually preceded by blisters or vesicles, otherwise they are more likely to be of fungal or bacterial origin.

Primary herpetic gingivostomatitis (PHGS), caused by *Herpes simplex* virus type 1 (HSV-1), is the most frequent viral infection of the oral cavity. Up to 90% of the world population is estimated to be seropositive for HSV-1 by the age of 40 years (8). PHGS mostly affects children either presenting as asymptomatic or with multiple vesicles that disrupts into painful ulcerations both of the keratinized and non-keratinized mucosa (9). Conversely, adults with primary infection usually suffer from the symptomatic form associated with herpetic pharyngotonsillitis. Accompanying symptoms may include fever, headache, and cervical lymphadenopathy. Primary infection is usually self-limiting, but initiation of systemic acyclovir suspension within 72 hours of onset helps reduce symptoms, with shorter duration of lesions and decreased viral shedding. Recurrent forms have a milder course, often present as self-limiting herpes labialis, and are frequently triggered by various factors, including UV exposure, stress, or dental anesthesia. *Varicella zoster* virus (VZV / HHV-3) can also cause oral manifestations as self-limiting ulcerating papules. *Coxsackievirus* is another common virus that affects the oral mucosa, causing Herpangina or Hand-Foot-Mouth Disease. Clinical presentation includes hyperemic red macules followed by self-limiting ulcerations diffusely involving the tonsillar pillars and soft palate, often associated with fever, sore throat, and headache. Although often asymptomatic, *Cytomegalovirus* (CMV) infection can also cause oral ulcers with pseudomembranes, predominantly involving the hard and soft palate (10). Other viruses may less commonly involve the

oral mucosa, presenting with nonspecific erythematous and ulcerative lesions (11).

Less frequent manifestations include bacterial infections, such as syphilis caused by *Treponema pallidum* or tuberculosis caused by *Mycobacterium tuberculosis*, that can manifest as single asymptomatic or multiple painful oral ulcers, respectively (12). A rare oral pathology sustained by a variety of spirochete and fusiform bacteria and often associated with malnutrition and debilitation is acute necrotizing ulcerative gingivitis (NUG)/stomatitis (NUS), which presents with extremely painful and locally destructive ulcers (13).

Lastly, fungal infections, such as aspergillosis and mucormycosis can be considered relatively uncommon causes of deep ulceration and locally invasive oral necrosis, that predominantly affect immunocompromised patients (14,15).

Medical management of ulcers of infectious origin generally aims to eradicate the causative agent with appropriate systemic antibacterial or antifungal therapy. Pain control with anti-inflammatory or analgesic agents and antiseptic mouthrinses (e.g., chlorhexidine, iodopovidone), along with coating gels, may help relieve symptoms and accelerate healing of lesions (16,17)

Immune-mediated ulcerative lesions

Recurrent aphthous stomatitis (RAS) is the most common oral ulcerative disorder in healthy individuals (18). It is characterized by painful, recurrent single or multiple small round ulcerations with well-defined margins, surrounded by erythematous haloes. It tends to occur in young patients, but both children and adults can be affected. Based on the size, number and duration of the lesions, it can be classified into three types: minor RAS, major RAS, and herpetiform ulcers. Minor RAS, which accounts for more than 80%–90% of RAS cases, typically presents with lesions of less than 1 cm in diameter and heals within 7–14 days without scarring. Major RAS lesions are larger than 1 cm in diameter and heal within 20–30 days with scarring. Herpetiform ulcers are characterized by 1–3 mm, multiple and clustered lesions, that may coalesce into larger ulcers and take up to 15 days to heal (19). The etiology of RAS is multifactorial, and includes stress, immune system dysfunction, genetic factors, nutritional deficiencies, food allergens, celiac disease, local trauma, endocrine alterations, hormonal changes, chemical products, and microbial agents (19,20). Although the ulcers are usually self-limiting, these lesions are particularly debilitating and thus often require support therapy. A variety of treatments have been proposed in recent years, such as topical analgesics, antiseptics, steroids, immunomodulating drugs, mucosal barrier gel, sucralfate, and herbal remedies (18).

Erythema multiforme (EM) is a type IV cytotoxic immune reaction mediated by T-cells in response to various antigens such as viruses, bacteria, drugs, or chemicals, resulting in apoptotic epithelial cell death (21). Occasional triggers include microorganisms such as *Herpes simplex* type 1 and 2, and *Mycoplasma pneumonia* (22). Particularly severe cases, characterized by progressive involvement of the skin and mucosal tissues, are referred to as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and are mainly associated with medications such as nonsteroidal anti-inflammatories and anti-rheumatics, anticonvulsants, and antibiotics, especially penicillins and sulfonamides (23,24). Pathognomonic skin lesions of EM consist of target-shaped round, edematous, erythematous papules with well-defined borders and a central whitish vesicle. Oral lesions can indicate the beginning of further mucocutaneous involvement or can be isolated. Typically, these lesions present with swollen, cracked, bleeding, and crusted lips, occasionally with blistering and ulcerations on the mucosa. Prompt diagnosis, removal of the causal agent and corticosteroid treatment are essential to limit disease severity and achieve rapid relief and resolution (25).

Several immune-mediated dermatological conditions can involve oral mucosa, either associated with skin lesions, as the initial presentation or occasionally as the only clinical presentation (4). These mucocutaneous disease include oral lichen planus (OLP), pemphigus vulgaris (PV), mucous membrane pemphigoid (MMP) and systemic lupus erythematosus (SLE/DLE).

Pemphigus vulgaris (PV) is mediated by autoantibodies directed against keratinocyte adhesion proteins (desmosomes), causing acantholysis. PV typically affects patients of 40-60 years of age, that present with

thin-roofed, intra-epithelial bullae that rupture rapidly after onset, resulting in large, irregular areas of painful oral mucosal ulceration (26).

Mucous membrane pemphigoid (MMP) is a common systemic autoimmune blistering disease that predominantly involves mucosal tissues. Antibodies are directed against the proteins of keratinocyte-connective tissue adhesion (hemi-desmosomes), causing subepithelial detachment and resulting in thick roofed vesicles that may still be intact on examination. The rupture of the vesicles results in ulcerative lesions (26). Desquamative gingivitis (erythematous and friable gingiva with epithelial disruption) is also a common finding (27).

Systemic (SLE) and discoid lupus erythematosus (DLE) can also involve the lips and the oral mucosa, presenting with an ulcerative pattern (28).

Oral lichen planus (OLP) is a relatively common, chronic inflammatory disorder typically affecting middle-aged females. Various subsets of t-lymphocytes and mast cells appear to play a role in the basal membrane damage, but the pathogenesis is still unclear (2). The disease can present with a diverse clinical pattern, including atrophic, erosive, ulcerative and less commonly, bullous variants (29). Treatment is mainly aimed at regression of atrophic and ulcerative lesions and symptomatic control only (30).

In addition, hypersensitivity reactions may cause oral mucosal ulcerations, which are less common than cutaneous ulcerations due to the possible dilution of the allergen and the continuous rinsing effects of normal salivary flow (31). A temporal or spatial association with an offending agent can usually be identified. These reactions are due to either a systemic drug or direct contact with an offending agent. The resulting erosive lesions have clinical and histologic features similar to lichen planus and are therefore referred to as oral lichenoid lesions (OLL) (32).

The treatment of immune-mediated oral ulcers generally relies on the use of topical or systemic corticosteroids and other immunosuppressive agents. Topical corticosteroids are considered first-line therapy for mild to moderate disease, while systemic therapy is recommended for severe and multifocal disease (5). Topical corticosteroids are typically used for short-term therapy or as part of a maintenance regimen and include triamcinolone acetonide, fluocinonide, and clobetasol propionate (33). The most commonly used systemic corticosteroids are prednisone and prednisolone. Long-term treatment with systemic corticosteroids leads to suppression of the hypothalamic-pituitary axis, resulting in significant adverse effects. However, short-term and topical use has also been associated with side effects, including hyperglycemia and an increased risk of infection (34). Severe, diffuse, and recalcitrant lesions often require combination or elective treatment with other systemic immunosuppressive agents, including mycophenolate mofetil (MMF), azathioprine, cyclophosphamide, methotrexate, and dapsone (35). Additional use of NSAIDs, systemic analgesics or topical rinses, or barrier gel applications may help limit the severity and control the symptoms (5,30,36).

Ulcerative lesions related to neoplasia

The oral mucosa can be affected by both primary and metastatic malignancies, all of which can present as non-specific ulcers. Oral squamous cell carcinoma (OSCC) is the most common, often manifesting as ulceration with clinical induration, fixation to underlying tissue, rolled exophytic margins, and symptoms of pain and/or numbness. Neoplastic lesions of the oral cavity require a comprehensive diagnostic approach and, in most cases, a multimodal treatment (37).

In addition, anticancer treatments can cause a variety of side effects affecting the oral cavity, including taste dysfunctions, xerostomia, and radio- and chemotherapy induced mucositis (38–40). Oral mucositis (OM) is one of the most common debilitating complications in patients receiving cancer therapy. OM can present as erythema, edema, or painful ulceration with significant pain, dysgeusia, and malnutrition, all of which can have a negative impact on the patient's prognosis and quality of life (41,42).

Evidence based guidelines for the management of cancer therapy induced oral mucositis include oral cryotherapy, oral rinses with benzydamine hydrochloride, topical anesthetics, glutamine and palifermin, but the results are not satisfactory and the preventive and therapeutic management of OM remains a challenge (42–44).

Alternative non-pharmacologic treatment options

The literature search yielded the following results: 1275 possibly relevant records were retrieved for laser photobiomodulation, 64 for ozone therapy, and 397 for photodynamic therapy. Among these, for each disease we focused on the most recent and relevant systematic review when available (n=10) or, alternatively, on the most recent and relevant clinical trial (n=10). If neither type of study was available, case reports were also considered (n=6) Overall, the key references reviewed for alternative treatment options are listed in Table 2.

Laser photobiomodulation

Applications of laser in oral medicine are multiple and have demonstrated to ensure several advantages, with a minimally invasive technique (71,72). Different laser technologies with different wavelengths and settings are able to perform either

Table 2. Key references concerning non-pharmacologic treatments of ulcerative oral lesions considered in this review, ordered by publication date.

First author	Year	Topic
Simões A (45)	2011	PBMT; Stevens-Johnson Syndrome (CR)
Cafaro A (46)	2012	PBMT; Pemphigoid (CT)
Thongprasom K (47)	2014	PBMT (CO_2 laser); Oral Lichenoid Lesions (CR)
Kazancioglu HO (48)	2015	PBMT; Ozone Therapy; Oral Lichen Planus (CT)
Kurtulmus-Yilmaz S (49)	2015	PBMT, (Er,Cr:YSGG laser); Denture trauma (RCT)
Al-Omiri MK (50)	2016	Ozone Therapy; Recurrent Aphthous Stomatitis (CT)
Kumar T (51)	2016	Ozonized olive oil; oral lesions of various etiology (CT)
Casu C (52)	2017	PDT; Afta Major (CR)
Dos Santos LFM (53)	2017	PDT; Oral Paracoccidiodomycosis (CT)
Zand N (54)	2017	PBMT, (CO_2 laser); Pemphigus Vulgaris (CT)
Rocha AL (55)	2019	PBMT; Oral Toxic Epidermal Necrolysis (CR)
Khaleel Ahmed M (56)	2020	PBMT; Aphthous Ulcers (SR)
Veneri F (57)	2020	Ozonized water; Oral Lichen Planus (RCT)
de Oliveira AB (58)	2021	PDT; Oral mucositis (SR and MA)
Amadori F (59)	2022	PBMT; Pemphigus Vulgaris (RCT)
Barros AWP (60)	2022	PBMT; Herpes Labialis (SR and MA)
Khalil M (61)	2022	PBMT; PDT; Herpes Labialis (SR)
Pan D (62)	2022	PDT; Oral Lichenoid Lesion (CR)
Raffaele RM (63)	2022	PBMT; PDT; Erythema Multiforme (CR)
Ruiz Roca JA (64)	2022	PBMT; Oral Lichen Planus (SR)
Vellappally S (65)	2022	PDT; Herpetic Gingivostomatitis (RCT)
Gulzar MA (66)	2023	PDT; Oral Lichen Planus (SR)
Nagi R (67)	2023	PDT; Oral Lichen Planus (SR)
Cruz AR (68)	2024	PBMT; Oral Mucositis (SR and MA)
Mahuli SA (69)	2024	PBMT; Oral Lichen Planus (SR and MA)
Shen B (70)	2024	PBMT; Oral Mucositis (SR and MA)

Abbreviations: PBMT: laser photobiomodulation therapy; PDT: photodynamic therapy; CT: clinical trial; CR: case report; MA: meta-analysis; RCT: randomized controlled trial; SR: systematic review.

surgical and non-surgical (biostimulation, decontamination, hemostasis) interventions on both soft and hard tissues (73–75).

The use of laser with biostimulatory function, known as photobiomodulation therapy (PBMT) or low-level laser therapy (LLLT), which is obtained with low-energy settings, has proved effective in several fields of medicine for the treatment of acute or chronic painful conditions due to its anti-inflammatory and analgesic effects. In fact, the application of light (usually delivered via a low power laser or light-emitting diode-LED) is able to promote re-epithelialization, fibroblastic proliferation, collagen synthesis, increases vascularization, and reduces alterations in nerve impulse conduction (76).

The mechanisms explaining the molecular and cellular effects of PBMT are numerous and extremely complex, and although extensively studied, are still not fully understood. Overall, they are related to laser light exerting a photochemical effect by stimulating mitochondrial cytochrome c oxidase, one of the major natural chromophores. The leading hypothesis is that the photons dissociate inhibitory nitric oxide from the enzyme, leading to an increase in electron transport, mitochondrial membrane potential and ATP production (77). Another hypothesis involves light-sensitive ion channels that can be activated to allow calcium entry into the cell. After the initial photon absorption events, numerous signaling pathways are activated via reactive oxygen species, cyclic AMP, NO, and Ca^{2+}, leading to activation of transcription factors and resulting in increased expression of genes involved in protein synthesis, cell migration and proliferation, anti-inflammatory signaling, anti-apoptotic proteins, and antioxidant enzymes (78,79).

The choice of appropriate settings (energy, power and application time) has a paramount importance on the effectiveness of the treatment (78). PBMT protocols typically use low irradiance or power density, between 5 mW/cm^2 to 5 W/cm^2, and the output power can vary widely from 1 mW up to 500 mW, usually between 100 and 200mW, for single application time between 30-60 seconds per point, up to a few minutes per area/lesion (80,81). The irradiation can be delivered through a continuous wave or a pulsed light consisting of a relatively low-density beam, typically 0.04 to 50 J/cm^2 (81). The most used laser types for PBMT include Nd:Yag, He:Ne, AlGaIP, GaAlAs, and GaAs lasers, and other diode lasers and LED (68,76). Wavelengths in the red (600 to 700 nm) or near-infrared (780 to 1100 nm) range are usually preferred because of the low scatter and absorption by tissue chromophores, resulting in deeper tissue penetration. Conversely, light in the 700-780 nm range is avoided because it is almost completely absorbed by cytochrome c oxidase (79).

Current evidence report beneficial effects of PBMT for the treatment of many ulcerative oral diseases (3,55,59,76). According to clinical evidence, ulcers induced by denture trauma showed significant improvements following a single session of PBMT using Er,Cr:YSGG, (λ 2790 nm; 0.25 W, 5 J/cm^2, 20s per point) as compared to controls where no PBMT was applied (49). Laser PBMT has also shown to considerably decrease symptoms, healing time and recurrence rate of herpes labialis, especially when associated to antimicrobial photodynamic therapy (aPDT) (60,61). According to a recent systematic review, PBMT resulted more effective than topical treatments in the management of recurrent aphthous stomatitis, without side-effects, regardless of the protocols used. All wavelengths used were reported to be successful, i.e. Nd:YAG laser (1064 nm), InGaA1P diode laser (670 nm), other diode lasers (810 nm, 970 nm, 658 nm) (56). With regards to the management of Erythema multiforme, only case reports of PBMT were retrieved, that reported immediate symptoms relief and remarkably rapid clinical improvement of severe clinical presentations of EM, SJS and TEN in children, poorly responsive to other treatments (45,55,63). PBMT was performed with a diode laser (λ 660 nm; 100 mW) in all reports, and associated to antimicrobial photodynamic therapy in the case of EM secondary to viral infection (63). PBMT with diode laser (λ 645 nm; 100 mW; 3 J/cm^2) was also reported to effectively decrease pain more rapidly in patients with oral Pemphigus Vulgaris undergoing systemic corticosteroids therapy (59). Interestingly, also CO_2 laser (λ 10 600 nm; 1W) can be used in non-ablative, non-thermal mode, achieving an immediate and perduring pain relief after a single session of PBMT in PV patients (54). Additionally, Pemphigoid oral lesions have shown considerable improvements of symptoms and clinical signs after three

sessions of PBMT (980-nm GaAIAs diode laser; 300 mW, 4 J/cm^2), performed twice a week as only treatment, and long-term, complete resolution within 10 sessions (46). According to a recent systematic review, erosive Oral Lichen Planus has also been successfully managed using PBMT as an alternative or complementary therapy to corticosteroids, with different types of lasers (Nd:YAG, He-Ne, diode lasers; 25 mW to 3W) (64). Interestingly, a recent meta-analysis also found evidence of an enhanced reduction of OLP-related pain for PBMT compared to corticosteroid therapy (69). However, despite the considerable body of literature on the subject, standardized protocols have not yet been established. A case-report on lichenoid reactions showed a remarkable improvement of oral lesions after two sessions of local PBMT (5W; 2 minutes) using non-ablative CO_2 laser (47). Additionally, cancer-therapy-induced oral mucositis can be successfully controlled with PBMT, as indicated by current evidence and reported by Multinational Association of Supportive Care in Cancer (MASCC) guidelines (42,68). According to recent summary evidence, high quality studies report that regardless of the laser type, PBMT (λ 632 nm to 970 nm; 2-5 J/cm^2; 125-145s) is effective in reducing the mean duration of severe OM, mean pain scores and subsequently in improving patients' quality of life (68,82). Additionally, InGaAIP or He-Ne lasers with a power range of 10–25 mW appears to be particularly beneficial for the prevention and treatment of OM (70).

The therapeutic mechanism of photobiomodulation makes it an important tool for the management of erosive and ulcerative lesions, regardless of their pathogenesis. Additionally, no side-effects or contraindications are reported for this treatment, making it a valid choice either as a standalone intervention, for example as maintenance treatment, or in association with other pharmacologic treatments, ensuring a faster relief of symptoms, wound healing and tissue regeneration.

Ozone therapy

Ozone (O_3) is a naturally occurring compound, composed of three oxygen atoms resulting from conversion by ultraviolet radiation. Although not a radical molecule, at low medical concentrations ozone is a powerful oxidizing agent. It has broad-spectrum antimicrobial properties, as well as the ability to promote healing and to modulate inflammation, through the activation of protective antioxidant pathways, thereby exerting therapeutic effects in many diseases (83–89). Due to its strong oxidizing activity, ozone has been widely used as a disinfectant and germicidal agent, for industrial and medical purposes, with a variety of applications as a sterilizing agent for closed environments, dental settings and medical equipment (90–92). Anti-microbial action is explained by ozone-induced oxidation, that damages the cell wall and cytoplasmic membrane of microbial cells, increasing their permeability to ozone molecules and leading to cell lysis and death (93,94).

Additionally, ozone by-products are able to exert a pharmacological immunomodulating activity, by inducing a mild reactive oxygen species (ROS) signaling or mitochondrial stress that triggers an antioxidant response through the activation of the Nrf2 (nuclear factor erythroid 2-related factor)-mediated system and inhibition of NF-κB pathway, switching immunity toward anti-inflammatory mechanisms (95,96). Finally, topical application of ozone improves the reological properties of blood by activating glycolysis at the erythrocyte level and improving peripheral perfusion of oxygen (97).

Ozone has been used in dentistry since the early 1900s. However, due to the risk of inhalation toxicity and the difficulty in obtaining optimal gas concentrations without dispersion, its use was abandoned for some time. With modern technologies and appropriate delivery and application techniques, these issues have been addressed (98).

Except for the inhalation route, which should be avoided because of broncho-pulmonary toxicity, many parenteral and topical routes are used to administer ozone without toxic effects (97). Gas, ozonized water, ozonized oil are the most used formulations used for oral cavity.

The recommended concentration for medical oxygen-ozone mixture ranges from 5 to 50 micrograms of ozone per 1 cc (mL) of oxygen (97). According to the guidelines and good clinical care practices in oxygen-ozone therapy, for applications of ozonized products by intralesional injections or by irrigation it is

recommended an ozone concentration of 5-10 μg/mL in order to achieve a therapeutic effect, without toxicity risks even in the case of possible ingestion of the mixture (99,100). By carefully using available technologies according to the manufacturers' indications, ozone therapy is neither toxic nor harmful to the human body and is free of side effects (99).

Clinical human evidence on this topic is still relatively limited when compared to the literature on PBMT. However, ozone therapy has shown to be particularly promising in treating erosive or ulcerative lesions of the oral cavity, whether of traumatic, infectious, inflammatory origin, or induced by cancer therapies (50,57,101). A clinical study by Kumar et al. showed that topical applications of ozonized oil exerted a therapeutic effect on a variety of oral lesions (e.g. aphthous ulcers, herpes labialis, oral candidiasis, angular cheilitis, and oral lichen planus) leading to a rapid resolution of the lesions and of the painful symptoms associated (51). Ozone in gaseous form (2350 ppm) applied for 60s has shown remarkable effectiveness in reducing pain, ulcer duration and size, as compared to placebo, in the management of aphthous stomatitis (50). Similarly, gaseous ozone (10~100 μg/mL; 10s) was successfully used to treat oral lichen planus, with signs and symptoms score significantly better for ozone and corticosteroids groups, as compared to PBMT with 808 nm wavelength (48). Ozonized water (0.06 mg/L; 1 minute) was also effectively used in rinses, in combination with topical corticosteroids, to improve clinical sign and pain scores in erosive OLP (57).

Standardized protocols for ozone applications for the management of oral mucosa diseases have not yet been established, and further well-designed clinical studies are required to tackle this knowledge gap.

Photodynamic therapy

Photodynamic therapy (PDT) is a medical treatment that uses light to activate a photosensitizing agent (photosensitizer) in the presence of oxygen. Exposure of the photosensitizer (PS) to light results in the formation of oxygen species, such as singlet oxygen and free radicals, that cause localized photodamage and cell death (102). Most photosensitizers are effectively activated by red light between 630 and 700 nm, corresponding to a light penetration depth from 0.5 to 1.5 cm (103). This limits the depth and defines the therapeutic window.

PDT is a minimally invasive treatment that is clinically used in the treatment of several oncologic human diseases, however PDT also has several non-oncologic applications, including the vascular malformations, dermatologic and oral diseases (104). A specific application of PDT consists of the inactivation of microorganisms, including bacteria, yeasts, and fungi, and is known as antimicrobial photodynamic therapy (aPDT). Antimicrobial PDT works in three ways: by directly killing the microbes, by interfering with the pathogenicity of the microbes, and by enhancing an immune response to antagonize the microbes (105,106). Changes in microbial morphology can be induced by PDT that disrupt structural integrity, thus compromising microorganism survival. Additionally, PDT can cause functional damage by inactivation of essential enzymes and suppression of metabolic processes, also resulting in direct DNA damage (107). PDT has also shown to hamper the formation and functionality of microbial structures involved in adhesion capacity and pathogenicity, such as bacterial biofilm and fungal hyphae (102). Finally, PDT exerts an immune-modulating effect, by significantly enhancing the innate and adaptive immunity, increasing neutrophils migration and activating T lymphocyte-mediated immune responses (102,108). A key advantage of aPDT consists of its nonselective microbicidal effect, also able to disrupt several complex processes associated with multidrug resistance (109). Therefore, aPDT can be used as an alternative to antibiotics and antiviral drugs that usually cause resistance.

Photosensitizers can be applied topically, intravenously or ingested, depending on the desired therapeutic effect. In oral medicine they are mainly used in topical applications and most common PSs for non-oncologic purposes include 5-aminollevulinic acid (ALA), methylene blue (MB) and toluidine blue O (TBO) (110). Light sources such as Nd:yag, KTP lasers were more commonly used in the past, while more recently, less expensive, cost-effective and portable diode lasers and LED are preferred (104,110).

The main side effect associated with intravenous photosensitizers is photosensitivity, thus exposure

to bright light or direct sunlight must be carefully avoided until the drug is cleared, which may take several hours to weeks. PDT itself is usually not painful, but most patients experience severe pain several hours after treatment. Therefore, pain medication should be prescribed during or before the laser treatment. Such side effects are extremely limited for topical application of PSs, consisting of occasional burning sensation during irradiation (110).

Thanks to its antimicrobial and immune-stimulating properties, PDT can have therapeutic effects in many oral infectious and non-infectious diseases, such as biofilm-related pathologies, viral, bacterial and fungal infections, as well as immune-mediated conditions. Interestingly, it has also been suggested for decontamination in periodontal patients, and against biofilm in patients with high caries risk, such as ECC and enamel defects (111–113).

Current clinical evidence on PDT applications in oral ulcerative lesions is encouraging. PDT with methylene blue as photosensitizer (diode laser λ 640 nm; 150 mW; 30-40s, 300 J/cm^2), was used in combination to topical antiviral therapy, for the treatment of herpetic gingivostomatitis in children, and showed a better performance in reducing pain scores, virus quantification and pro-inflammatory cytokine levels, compared to the respective treatments alone (65). Similarly, TBO-aPDT (660 nm wavelength, 40 mW, 90 J/cm^2; 90s) was successfully used to treat oral paracoccidiodomycosis-related ulcers, inducing immediate relief of pain and almost instantaneous improvement of swallowing and mouth opening, and complete healing within 2-3 applications (53). A case report on the management of a long-lasting, atypical *afta major* through PDT using toluidine blue and LED light source (630 nm; 2-3W/cm^2; 30s) indicated a considerable relief of symptoms after few hours from the application and complete resolution within one week (52). Evidence on the use of PDT for the management of oral lichen planus is more abundant and two recent systematic reviews support its use as an alternative to corticosteroids (66,67). Toluidine blue and methylene blue were the most used photosensitizers, combined with red LED or diode lasers (630 to 660 nm wavelength; 25 to 250 mW) (67). PDT was effective in significantly reducing symptoms and improving oral functions, but a great heterogeneity in protocols was highlighted (66). Also, a case of resolution of a lichenoid lesion of the lip was reported, using 5-ALA as photosensitizer and a 9-minute total session of irradiation with a 400 nm LED (100 J/cm^2), once a month for three consecutive months (62). Lastly, a meta-analysis on the use of PDT for the treatment of oral mucositis have reported similar therapeutic effects as PBMT, with symptoms relief and faster clinical resolution, with an expected better performance for PDT in presence of infection (58). Different protocols have been successfully used, with methylene blue and curcumin as photosensitizers, and light sources as red light-emitting diodes (λ 660–810 nm), blue-light emitting diodes (λ 400–470 nm), for 30s to 10 min irradiation times (58).

Conclusion

Current body of evidence shows promising results. However, these treatments should be kept under investigation. The great heterogeneity of protocols, devices and settings, prompts the necessity for additional well-designed longitudinal and randomized clinical studies. Nevertheless, clinicians treating patients with these frequent and debilitating conditions should be aware of the opportunity to use minimally invasive, safe, and effective strategies.

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