Disease-a-Month 68 (2022) 101300

Contents lists available at ScienceDirect

Disease-a-Month

journal homepage: www.elsevier.com/locate/disamonth

Oral mucositis: Current knowledge and future directions

Sameep S. Shetty, BDS, MDS[a], Meghana Maruthi, MDS[b], Vasantha Dhara, MDS[c], José Alcides Almeida de Arruda, DDS, MSc[d,*], Lucas Guimarães Abreu, DDS, PhD[e], Ricardo Alves Mesquita, DDS, PhD[f], Antonio Lucio Teixeira, MD, PhD[g], Tarcília Aparecida Silva, DDS, PhD[h,1,*], Yash Merchant, MDS[i,1]

[a] *Department of Oral and Maxillofacial Surgery, Manipal College of Dental Sciences, Mangalore, Manipal Academy of Higher Education, A Constituent of MAHE, Manipal 576104, India*
[b] *Department of Dental Rehabilitative Oncology, HealthCare Global Enterprises Ltd., Bangalore, India*
[c] *Consultant Maxillofacial Surgeon, Hyderabad, Telangana, India*
[d] *Department of Oral Surgery, Pathology and Clinical Dentistry, School of Dentistry, Universidade Federal de Minas Gerais, Av. Pres. Antônio Carlos, 6627, room 3202 D, CEP: 31.270-910, Belo Horizonte, Minas Gerais, Brazil*
[e] *Department of Child's and Adolescent's Oral Health, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*
[f] *Department of Oral Surgery, Pathology and Clinical Dentistry, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*
[g] *Faculdade Santa Casa BH, Belo Horizonte, Brazil. Neuropsychiatry Program, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, Texas, USA*
[h] *Department of Oral Surgery, Pathology and Clinical Dentistry, School of Dentistry, Universidade Federal de Minas Gerais, Av. Pres. Antônio Carlos, 6627, room 3204, CEP: 31.270-910, Belo Horizonte, Minas Gerais, Brazil*
[i] *Consultant Maxilofacial Surgeon, Pune, Maharashtra, India*

ARTICLE INFO

Keywords:
Chemotherapy
Differential diagnosis
Head and neck cancer radiation
Management
Oral mucositis
Oral oncology
Salivary glands

ABSTRACT

Oral mucositis secondary to head and neck chemoradiation displays a complex molecular pathogenesis involving epithelial and microvascular injury, release of pro-inflammatory cytokines, and host-microbiome communications. These processes lead to oxidative stress and the release of reactive oxygen species that stifle the structural integrity of the oral mucosa, with emergence of erosions and ulcers. The consequences are malnutrition, psychological/psychiatric symp-

* Corresponding authors.
E-mail addresses: sameep.shetty@manipal.edu (S.S. Shetty), meghana11191@gmail.com (M. Maruthi), dg91dan@gmail.com (V. Dhara), alcidesalmeida@ufmg.br, alcides_almeida@hotmail.com (J.A.A. de Arruda), lucasgabreu01@gmail.com (L.G. Abreu), ramesquita@ufmg.br (R.A. Mesquita), altexr@gmail.com (A.L. Teixeira), tarcilia@ufmg.br, silva.tarcilia@gmail.com (T.A. Silva), merchantyash@gmail.com (Y. Merchant).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.disamonth.2021.101300

toms, poor quality of life, and occurrence of opportunistic infections. The latter pose a major challenge due to the risk of interruption of anti-neoplastic therapy, tumour recurrence and, ultimately, death. This article aims to present the clinical characteristics, molecular pathogenesis, and an overview of the predisposing factors and current management of oral mucositis. It is anticipated that the future direction of the management of oral mucositis will focus on evidence-based prehabilitation and pre- and per-chemoradiation therapy monitoring.

Introduction

Mucositis is an inflammatory process that involves the mucous membranes of the alimentary tract (i.e., oesophagus, stomach, and intestine). Oral mucositis is the most common side effect of radiotherapy and/or chemotherapy. Quality of life has been known to be drastically affected, even compromising the administration of the anti-cancer regimen itself, leading to morbidity and mortality.[1] The frequency of oral mucositis differs among populations worldwide and is often underreported due to the heterogeneity of the studies and multiple scoring criteria for diagnosis.[2,3]

Clinicians have realized that oral mucositis is no longer an individual problem, but a national healthcare obligation, particularly in low/middle income countries.[4,5] A recent systematic review revealed that oral mucositis is associated with increased use of resources, additional consultations, and prolonged hospitalizations, resulting in a substantial increment of spending, plus economic pressure on the patient and the health insurance system during the treatment period.[3] The distressing physical, psychological, economic, and systemic burden due to the spectrum of mucositis has required effective solutions to mitigate this condition.

Understanding the economic burden

Treatment costs per head and neck cancer patient increase by up to USD $1,700 for individuals with oral mucositis grade <3 and up to USD $3,600 for those with oral mucositis grade ≥ 3.[6] The budget allocated to the management of individuals with oral mucositis usually includes spending on prolonged hospitalization, emergency departments visits, hospital admission, number of clinic visits, nutritional consultations, total parenteral nutrition, use of a feeding tube or gastrostomy tube, use of analgesics and opioids, and use of oral or intravenous antibiotics. Murphy et al.[7] observed that, among individuals with head and neck cancer, 85% needed opioids, 51% required a feeding tube, and 30% were hospitalized due to mucositis, with a mean time of hospitalization of 4.9 days. A study showed that the incremental cost of oral mucositis was approximately $5,000 to $30,000 among patients who received radiation therapy and $3,700 per cycle among patients who received chemotherapy.[8] Furthermore, the Ontario Case Costing Initiative provided data on the total cost for the management of oral mucositis and stomatitis in clinically homogeneous groups, ranging from $2,957 to $4,966.[9]

Clinical considerations

Integrity of the oral mucosa protects the underlying tissues from environmental threats.[10,11] Oral mucositis can manifest as oral mucosal atrophy, erythema, erosion, and ulceration or as a combination of these manifestations (**Fig. 1**). It is exacerbated by injuries caused by sharpened teeth, bruxism, food scraps, foreign substances, and microorganisms.[12] The clinical manifestations of oral mucositis commonly observed in non-keratinized tissues begin as painful erythema

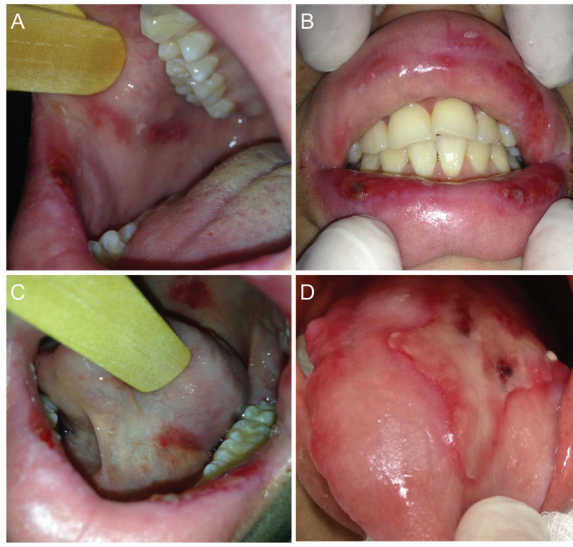

Fig. 1. Clinical aspects of chemotherapy-induced oral mucositis. **(A)** Multiple ulcers in the right buccal mucosa with areas of necrosis in the lower lip mucosa. **(B)** Upper and lower lip exhibiting epithelial necrosis and ulcerations. **(C)** Multiple ulcerations in the soft palate, ventral surface of the tongue and lower lip mucosa. **(D)** Extensive ulcer with areas of necrosis and pseudomembrane covering the dorsum of the tongue.

and inflammation of the affected mucosa. Thus, subsequent ulcerations become a free entryway for microorganisms.

Dysphagia caused by oral mucositis can further worsen the severity of the oral lesions and aggravate systemic symptoms such as fatigue and anorexia, alongside psychological symptoms. It is estimated that about half the patients with oral mucositis have meaningful anxiety and depressive symptoms.[13] These symptoms can affect patients' perception of their quality of life and might influence treatment outcomes according to adherence to therapeutic regimen, among other mechanisms.[14] Despite this reality, there is a dearth of studies investigating psychiatric symptoms and disorders within the context of cancer-related oral mucositis. Of note, radiotherapy strongly contributes to the burden of oral mucositis among head and neck cancer patients. Even with a dose of 50 Gy given during head and neck cancer therapies, there are sequelae such as dysphagia with xerostomia and changes in taste leading to anorexia.[15] In this context, the approach to these symptoms requires a comprehensive assessment prioritizing treatment of the underlying causes and addressing psychosocial distress with a multidisciplinary oncology team.[16]

Given the relevance of the topic, our aim is to discuss the pathophysiology and management of oral mucositis in individuals with chemo-radiated oral cancer. The influence of antineoplastic treatment on the interruption of oral mucosa homeostasis is also explored.

Pathophysiology of oral mucositis

The epithelial cells of the oral mucosa have a rapid renewal cycle of seven to 14 days. The pathophysiology of oral mucositis starts with the initiation phase which involves injury to the cells, upregulation of inflammatory cytokines, a primary damage response, plus signalling and amplification of the inflammatory cascade, followed by ulceration and healing of the mucosa by epithelial proliferation.[17] In contrast to what is observed in self-limited oral ulcers, the pathology

of oral mucositis is not restricted to the mucosal epithelial layer, but also covers the deepest submucosal tissues involving multiple signalling pathways (**Fig. 2**).

Initiation phase

Chemoradiation-induced DNA cleavage causes damage to the basal epithelium and submucosa. Subsequently, lipid peroxidation and the generation of reactive oxygen species (ROS) trigger a series of molecular reactions in the connective tissue before clinically manifesting on the epithelium.[18]

Upregulation and message generation/primary damage response

Mucosal damage occurs as a consequence of a multifaceted series of molecular events after the initiation phase. DNA cleavage activates transcription factors such as p53 and nuclear factor κB (NF-κB). In addition, cell membrane-bound molecules upregulate genes encoding the c-Jun N-terminal kinases (JNK) which, in turn, will upregulate nuclear factor erythroid 2-related factor 2 (NRF2).[19]

NF-κB can run a gamut of 200 genes involved in pro- and anti-apoptotic functions. Activation of NF-κB, the central mediator of pro-inflammatory gene induction, leads to the production of inflammatory cytokines, chemokines, and adhesion molecules. Among these are death agonists which instigate cell death (e.g., BAK, BIK, BAX, and BID), manifesting clinically as an injury to the mucosa. The activation of transcription factors influences the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which initiate ectomesenchymal signalling that reduces epithelial oxygenation, exacerbating the damage to the basal epithelial cells, connective tissue, and the endothelium.[20] Non-DNA damage by radiation occurs by means of the activation of an enzyme called sphingomyelinase (or ceramide synthase) which hydrolyses the lipid sphingomyelin from the cell membrane and initiates the apoptotic pathway. This intracellular sphingolipid mediator, ceramide, modulates a transduction signal inducing apoptosis through key transcription factor activator protein (AP-1) activation. AP-1 causes the secretion of matrix metalloproteinase (MMP), affecting the subepithelial collagen matrix (MMP1) and the epithelial membrane (MMP3).[10] All of these enzymes result in injury within the tissue of the submucosa and disrupt the integrity of the interface between the epithelium and submucosa at the basement membrane level.

Signal amplification

Signals are amplified due to tissue damage, apoptosis, vascular permeability, and activation of enzymes (e.g., cyclooxygenase-2). Pro-inflammatory cytokines provide a positive feedback loop, intensifying the response to primary damage. TNF-α is an efficient activator of NF-κB and also initiates the signalling of the mitogen-activated protein kinase (MAPK), leading to the activation of JNK which, in turn, regulates the transcriptional activity of AP1.[21] This complex pathway ultimately results in activation of caspase 3 and cell death.

Ulceration

The tissue lesion is clinically manifested as a sloughed/denuded epithelium, with inflammation of the mucosa and ulceration. The neutropenia associated with chemoradiation disrupts the function of immune cells and the peeled epithelium.[22] Ulceration is a gateway for microorganisms to penetrate deep into the connective tissue, causing an additional release of pro-

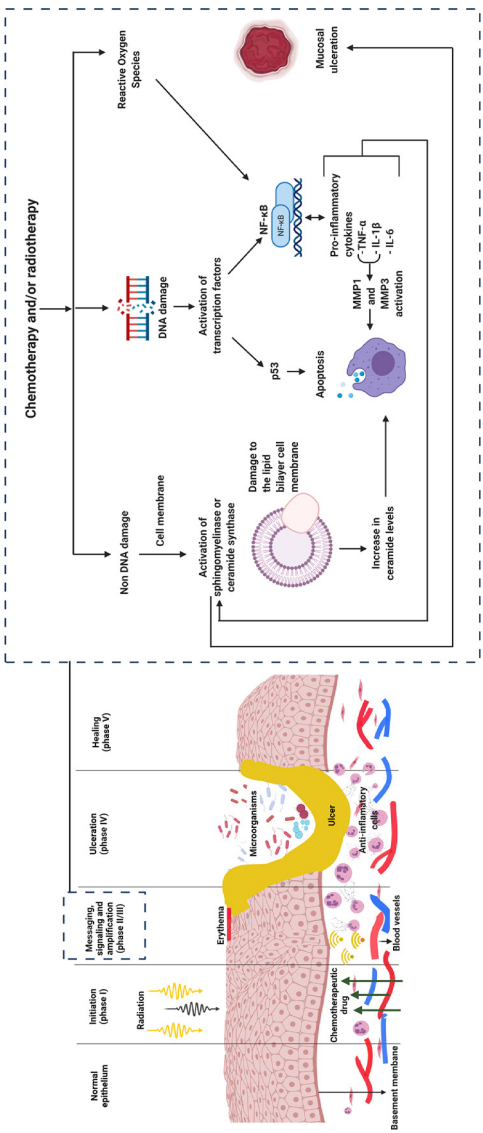

Fig. 2. Pathophysiology of oral mucositis showing phase I (0-2 days), phase II (2-3 days), phase III (2-10 days), phase IV (10 -15 days), and phase V (15-21 days).

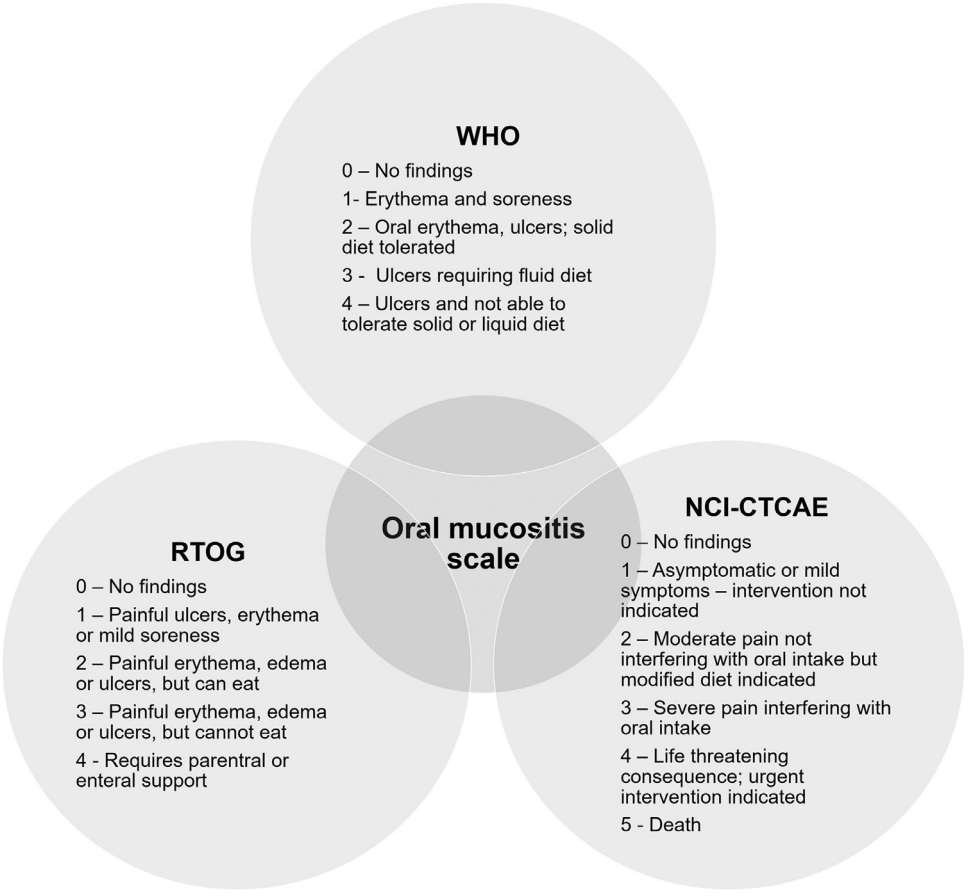

Fig. 3. Common oral mucositis scales depicting grades. Note: NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; and WHO, World Health Organization.

inflammatory cytokines, which perpetuate the cascade.[23] The invasion by microorganisms also increases the risk of secondary infection and, as a consequence, of bacteraemia and sepsis.[24]

Healing

The healing of these confluent mucosal ulcers depends on several host factors such as systemic diseases (including baseline disease), host immunity, or presence of opportunistic infections. The signals of the submucosal and mesenchymal extracellular matrix influence the rate of migration, proliferation, and differentiation of epithelial cells and the consequent healing.[25]

Grades of oral mucositis

Various scales are available in the literature for the assessment of the severity of mucositis (**Fig. 3**). The most common scales that provide the grade of oral mucositis in an objective way are the tools of the World Health Organization (WHO), the Radiation Therapy Oncology Group (RTOG), and the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse

Events (CTCAE).[26] The WHO and RTOG tools are less complicated than the CTCAE scale; however, the CTCAE is known to incorporate both objective and subjective interpretations of the symptoms, which make it more significant. An increase of one point in the score for oral mucositis is indicative of more prolonged hospitalization, higher odds of having fever, secondary infection, dependence on total parenteral nutrition, and use of intravenous opioid analgesics.[27]

Differential diagnosis of oral mucositis

The differential diagnosis of oral mucositis includes multiple conditions such as traumatic ulcers, erosive lichen planus, aphthous ulcers, herpetiform ulcers, erythematous candidiasis, vesiculobullous lesions, and malignancies **(Fig. 4)**.

The clinical manifestations of individuals with fungal or viral infections, and graft-versus-host disease (GVHD) may be misdiagnosed as oral mucositis. In neutropenic individuals, whose condition poses a dilemma for the clinician in deciding whether the lesion is oral mucositis or the result of viral infection, exfoliative cytology and/or culture are mandatory to confirm the diagnosis. Herpetic ulcers usually involve the keratinized mucosa, whereas oral mucositis affects the non-keratinized mucosa. Moreover, oral mucositis may be concomitant with chronic GVHD commonly observed in individuals who have received allogeneic haematopoietic stem cell transplantation. However, the differential diagnosis of these conditions is not straightforward and requires the analysis of other clinical parameters such as medical history, use of immunomodulating therapeutics, nutritional status, and others.[28,29]

Recent studies have pointed out that therapies including monoclonal antibodies that block immune checkpoints have led to the development of lichenoid reactions, oral lichen planus, and mucositis.[30–33] For example, Schaberg et al.[31] documented five cases of lichenoid eruption, including one case of lichenoid mucositis, associated with anti-PD-L1 and anti-PD-1 therapy. Shazib et al.[33] demonstrated that 10 of 13 individuals who were treated with nivolumab or pembrolizumab (PD-1 inhibitor) suffered immune-related adverse oral events, including lichenoid lesions, erythema multiforme, and acute GVHD reactivation. Likewise, a multicentre study demonstrated that three of 33 individuals with recurrent or metastatic head and neck squamous cell carcinoma undergoing therapy with pembrolizumab and cetuximab (EGFR inhibitor) had oral mucositis as a treatment-related adverse event.[34]

Oral mucositis due to head and neck cancer therapy

Oral mucositis is inescapably observed among individuals undergoing conventional anticancer therapies for head and neck cancer. The frequency of severe cases has also increased at an alarming rate, affecting up to 66% to 85% of individuals treated for head and neck cancer.[35] The prolonged course of the lesions and their variable severity are a challenge for the treatment of oral mucositis. Therefore, the natural history of the disease may be influenced by factors associated with the host, tumour, and treatment, as detailed below:

Host factors

Although some host factors seem to predict the risk of oral mucositis, robust evidence is limited.[36] These factors could be non-modifiable, such as sex, age, chronic systemic comorbidities, and genetic make-up, or modifiable, including diet and oral hygiene. Nonetheless, the severity of oral mucositis can depend on sex (women are at increased risk), age (young adults have a higher cell turnover than older adults, who, in turn, have increased mucosal damage and reduced reparative ability), chronic systemic diseases, host microbiome cross-talk, epigenetic and genetic susceptibilities (more evidence required for the association of the *TNKS, ERCC1, XRCC1*,

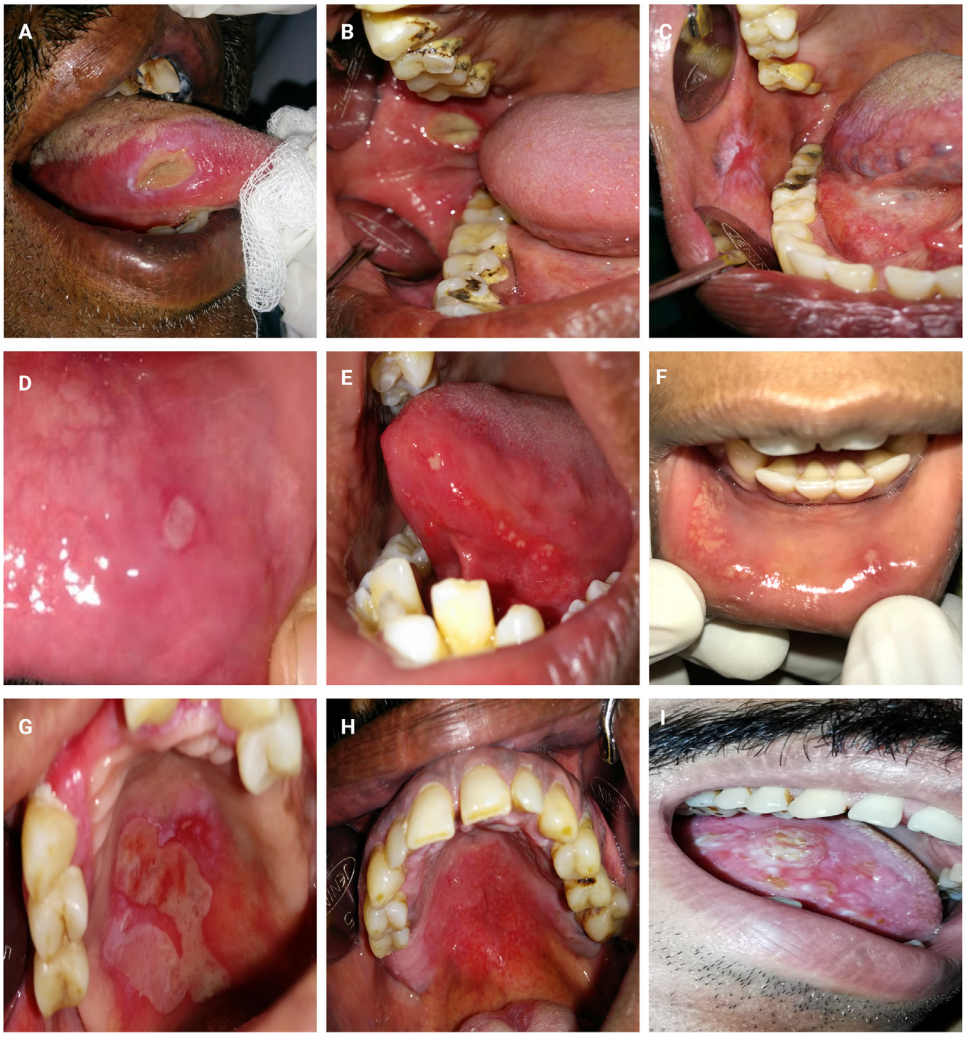

Fig. 4. Differential diagnosis of oral mucositis. **(A)** Traumatic ulcer showing a solitary irregularly shaped ulcer, raised margins and keratotic border. **(B)** Traumatic ulcer with stromal eosinophilia. Same as traumatic ulcer, long standing with/without indurated base. **(C)** Ulcerative lichen planus showing multiple shallow ulcers with Wickham's striae. **(D-F)** Aphthous ulcer exhibiting a shallow circular shape with an erythematous halo. **(G-H)** Vesiculobullous ulcerative lesion showing an irregular painful ulcer with epithelial tags preceded by vesicles/bulla. **(I)** Malignant non-healing indurated ulcer with everted edges and rolled out borders.

and *MTHFR* genes), impaired liver and renal function (increased mucotoxicity is linked to elevated serum creatinine levels), and a prior history of cancer treatment.[37,38] Likewise, oral hygiene, high levels of salivary TNF-α, comorbidities, and anxiety and/or depression[13] have been documented as predictors of oral mucositis.

Tumour factor

The presence of mucositis is more frequent in advanced stage tumours, tumours of the oral cavity and neighbouring regions, proximity to the radiation site, and tumours with positive mar-

gins.[39] The presence of extranodal extension (advanced tumour) requires the need for concomitant chemoradiation after surgery, which is remarkably mucotoxic with the use of increased doses.[40] However, in selected cases with a very poor prognosis, palliative support with lower doses is considered to be less mucotoxic for the affected individuals.[39]

Treatment modalities

The intensity of oral mucositis depends on cumulative radiation dose, volume, fields/portal of radiation, fractional doses, type of ionizing radiation, concurrent chemoradiation/neoadjuvant chemotherapy, and any targeted therapy given.

Anticancer therapies such as chemoradiation are delivered with the purpose of halting the exponential growth of tumour cells.[41] The oral mucosal cells have high mitotic activity and are shed within the site of radiation. The shed mucosal cells are feeble and break down, resulting in ulcers, erosions, and opportunistic infections. The non-keratinized tissues of the oral mucosa lack the protective keratin coating and are often affected by radiation. The course of oral mucositis differs depending on its aetiology and the anti-neoplastic treatment employed (chemotherapy *vs.* radiation or concomitant chemoradiation therapy).[7,42,43]

Radiation and oral mucositis

Given the anatomical location and the relatively high radiosensitivity of head and neck cancers, radiation is usually the treatment of choice.[41] Radiation increases local cure and survival rate by strongly striking the tumour. However, irradiation of the adjacent normal tissues is a side effect that may lead to late toxicity involving laryngeal and pharyngeal functioning.[5]

Despite the use of a fractional amount of radiation at lower doses, the first symptoms of oral mucositis are observed at the beginning of the first and second weeks of radiotherapy with a cumulative dose of 10–15 Gy.[44] The symptoms of oral mucositis worsen in severity during radiation. Deep confluent ulcers in the mucosa of the tongue, gingiva, and palate develop with a cumulative dose of 30 Gy (week 3) and are extremely painful. Other consequences of oral mucositis include disabling pain, dysphagia, odynophagia, dehydration, anorexia, weight loss, electrolyte imbalances, and a tendency to secondary systemic infections. Moreover, dysgeusia, hypogeusia, and ageusia can cause food aversion, nutritional deficit, cachexia, and greater predisposition to infections. Pain and discomfort during speech and swallowing may force the oncologist to indicate the placement of a feeding tube, i.e., Ryles nasogastric tube and a percutaneous endoscopic gastrostomy tube for nutritional support.

Finally, a few studies have shown the bidirectional association between oral mucositis and psychiatric symptoms, such as anxiety and depression. Patients with oral mucositis are at increased risk of developing anxiety and depressive symptoms,[13] while these symptoms, especially anxiety, have been associated with a higher probability of incidence and greater severity of oral mucositis.[45] Given their impact on quality of life, greater attention should be paid to these symptoms. Importantly, more research is warranted in this area in order to explore this bidirectional association (both in the short- and long-terms) and the potential of specific therapeutic interventions delivers better clinical outcomes.

Effect of radiation on the salivary glands

Oral cancers treated with intensity-modulated radiation therapy (IMRT) may have the same risk for the development of oral mucositis, with their safety feature of homogeneous radiation distribution being offset compared to those treated with conventional radiation.[46] The salivary glands are close to the target volume of head and neck cancers and are inevitably irradiated.

Morphological and functional changes such as loss of parenchyma, acinar atrophy and interstitial fibrosis, duct proliferation, dilation of intercalated striated ducts, loss of secretory granules in acinar cells, and infiltration of inflammatory cells such as lymphocytes and plasma cells in the salivary glands after radiotherapy can trigger hyposalivation/xerostomia (**Fig. 5**). Moreover, the reduced salivary flow may be irreversible if the mean dose exceeds the threshold safety dose. Of note, there is a discrepancy in the limit dose ranging from 20 to 60 Gy, as discussed in the literature.[47]

The cumulative effect of radiation on the salivary glands depends on the irradiated gland and the technique deployed. The initial radiation dose of 10 to 20 Gy causes hyperkeratosis of the oral mucosa, which is often unnoticed. On the other hand, at a dose of 20 Gy, erythema is the first clinical sign of oral mucositis.[48] With an accumulated total dose of 30 Gy administered after the third week of treatment, ulceration may be observed, occasionally leading to colonization by opportunistic microorganisms.[49] The use of multiple fractions per day resulting in a cumulative mean radiation dose of >65 Gy rapidly disrupts dividing tumour cells in the presence of toxic mucosal reactions compared to conventional fractionation, which is less effective and more toxic.[49,50] The Asian expert panel guidelines have recommended the use of midline radiation blocks and three-dimensional radiation treatment delimiting/demarcating the contours of the tumour by radiation, while obscuring the contiguous normal mucosa to minimize the severity of mucositis.[51] Once the radiotherapy treatment is complete, mucositis will spontaneously subside within two to six weeks. Furthermore, key histo-biochemical changes in the salivary glands include mast cell congregation in response to radiation-induced inflammatory cytokines that play a role in later-occurring damage and increased deposition of hyaluronic acid (produced in large quantities by activated fibroblasts), which at a later stage is indicative of pronounced tissue damage.[52,53]

Notably, the loss of parenchyma observed in the parotid glands is much greater than the loss occurring in irradiated submandibular glands since the parotid glands contain more acini formed by serous cells. The saliva produced and excreted by these damaged irradiated glands has inadequate volume, flow, and composition, which, in turn, affect the digestive and protective processes of the oral cavity.[54] The submandibular glands, for example, secrete unstimulated saliva and support the maximum impact since they are located inside the radiation portals. Also, the lymph nodes in the vicinity of the submandibular glands are considered to be one of the echelon nodes of cancers of the oral cavity. Thus, the constant flow of unstimulated saliva is essential for lubricating the oral cavity and maintaining the integrity of the oral mucosa.[55]

Effect of chemotherapy and oral mucositis

Depending on the type of drug administered and its mechanism of action, other sites of the alimentary tract, including the oropharynx, oesophagus, stomach, and intestine, can be affected, causing dysphagia, gastritis, and diarrhoea.[56] Multi-drug therapies (e.g., a combination of 5-fluorouracil, cyclophosphamide, methotrexate, and epirubicin) are known to decrease salivary flow and modify the salivary composition of individuals with cancer. Hyposalivation can increase the risk of oral mucositis, dysphagia and odynophagia, and adversely affect the patient's quality of life.[56]

Previous animal studies have demonstrated that the use of 5-fluorouracil reduces the weight of the salivary glands, causes oxidative stress, apoptosis in the submandibular and parotid gland acinar cells due to the periductal oedema, cell vacuolization, and increased influx of inflammatory cells and cytokines.[57] As a consequence, the risk of oral mucositis increases, and its severity is further augmented with the associated leukopenia. Furthermore, the atrophy of the salivary glands weakens the protective salivary function known for its protective action against oral mucositis. Hyposalivation caused by these toxic drugs slows the healing of confluent mucous ulcers, probably due to loss of salivary clearance and antimicrobial function.[57]

Ulcers and erythema in the oral cavity induced by chemotherapy are more diffuse and widespread and appear within two weeks after the onset of chemotherapy, in contrast to ra-

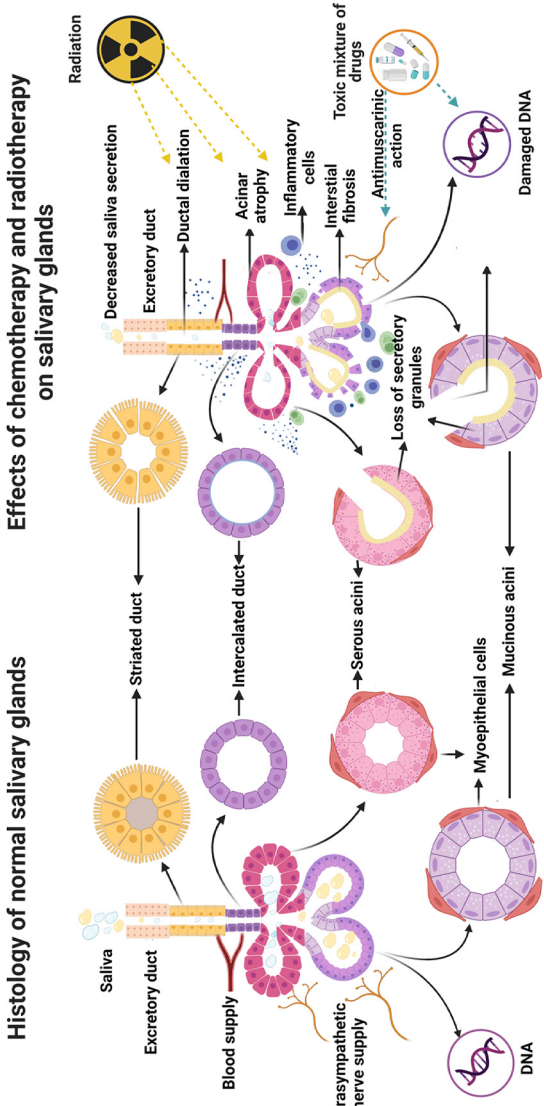

Fig. 5. Effects of chemo-radiation therapy on salivary glands.

Table 1
Summary of level I evidence on oral mucositis in head and neck cancer provided by articles retrieved in PubMed/MEDLINE

Authors (year of publication)	No. of studies	Summary of recommendations and conclusions
Bjordal et al. [58]	11	Red and infrared photobiomodulation therapy may partly prevent the development of cancer therapy-induced oral mucositis
Jensen et al. [59]	32	Pilocarpine and pentoxifylline were determined to be ineffective
Yarom et al. [60]	49	Suggestion in favour of zinc and a recommendation against glutamine
Nicolatou-Galitis et al. [61]	41	Recommendation for benzydamine. Use of other anti-inflammatories needs more evidence
McGuire et al. [62]	52	Does not support chlorhexidine. Additional well-designed research is needed for other interventions
Leung & Chan [63]	5	Glutamine effective in chemo-radiated oral mucosa
Co et al. [64]	8	Honey is beneficial; however, no definite reduction in peak mucositis score
Peng et al. [65]	57	Photobiomodulation therapy in addition to standard oral care may be a more effective prophylactic treatment
Carneiro-Neto et al. [66]	60	MuGard - mucoadhesive hydrogel; PerioAid Tratamiento® antiseptic mouthrinse with chlorhexidine and cetylpyridinium chloride; Episil® plus benzydamine - bioadhesive oromucosal gel; 0.03% Triclosan mouthwash Colgate Plax; and photobiomodulation therapy are safe
Daugėlaitė et al. [67]	55	Individual oral hygiene does not prevent oral mucositis; professional oral hygiene is required. Palifermin, chlorhexidine, Smecta, Actovegin, Kangfuxin, L. Brevis lotion, royal jelly, benzydamine, and zinc supplement are effective. Photobiomodulation therapy and cryotherapy showed efficacy
Münstedt et al. [68]	17	Honey is likely to be effective for prophylaxis and treatment
Christoforou et al. [69]	6	Non-opioid interventions, including topical doxepin, amitriptyline, diclofenac and benzydamine, were found to provide relief of pain due to mucositis
De Sanctis et al. [70]	10	Precise dose-volume parameters, as well as a definition of oral mucositis anatomic boundaries should be paramount in order to reduce the subsequent incidence of oral mucositis in head and neck cancer
Hong et al. [71]	17	Multi-agent combination oral care protocols are beneficial. However, chlorhexidine is not used to prevent oral mucositis in individuals undergoing head and neck cancer radiotherapy
Campos et al. [72]	19	Photobiomodulation therapy for oral mucositis in individuals receiving head and neck cancer treatment was clinically effective and cost-effective
Saunders et al. [73]	71	Efficacy of a morphine-doxepin mouth rinse is suggested. Recommendations against chlorhexidine mouthwash, sucralfate, and antimicrobial lozenges

diation, which causes ulcers limited to tissues in the radiation field.[57] Chemotherapy-induced oral mucositis can affect the area targeted by radiation, including the keratinized regions of the oral cavity; however, the gingiva and hard palate appear to be less prone to the effects of the toxic components of chemotherapy.[57]

Therapeutic approaches for oral mucositis

The symptomatic control of pain and of hyposalivation/xerostomia, nutritional support and oral decontamination accelerate the healing of the mucosa and the attainment of the basic goals of the treatment of oral mucositis. A summary of recommendations is displayed in Table 1.[58–73]

Prehabilitation

The rationale for prehabilitation is based on the pathogenesis of oral mucositis. Complications related to compound treatment trigger a sequence of biological events that lead to tissue damage and prehabilitation may minimize the action of the initial triggering factors.[74] Ideally, prehabilitation should begin at the time of cancer diagnosis, with frequent surveillance of oral lesions during adjuvant therapy.

The appearance of multiple painful oral ulcers during treatment impairs the individual's ability to maintain oral hygiene. Accordingly, the guidelines of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) recommend a tailored approach and the use of a standardized oral health care protocol, including brushing with a soft brush, dental floss, and the use of non-medicated rinses such as saline.[75] Thus, adequate hygiene of the oral cavity can prevent or minimize the occurrence and severity of complications by interrupting the onset of bacteraemia induced by opportunistic pathogens.

The salivary glands, oral mucosa, skin, and bones are susceptible to systemic complications such as dehydration, malnutrition, and infections. The stages of mucositis are co-dependent, mediated by cytokines, epithelial damage, opportunistic infections, altered microbiome, and bone marrow status. In this respect, prehabilitation can interrupt this inflammatory process and its further progression. Prehabilitation must focus on improving oral health by removing potential focal points of inflammation/infection, thus expanding the therapeutic window of the toxic chemoradiation protocols **(Fig. 6)**.

(a) Tobacco cessation

Smoking cessation by means of pharmacological (nicotine replacement therapy and cysteine) and nonpharmacological aids (counselling) is strongly recommended during prehabilitation.[76,77]

(b) Prehabilitation of the oral mucosa

The replacement of cells in the oral epithelium is impaired, with consequent atrophy and ulceration of the mucosa. Plaque control with daily topical application of 1% neutral sodium fluoride gel and a non-cariogenic diet may reduce the occurrence of infections during the course of treatment. Mouthwashes with antiseptic analgesics and oral prophylaxis may minimize the rapid decalcification of tooth enamel caused by the action of radiation (radiation caries). Moreover, administration of medications that induce xerostomia/hyposalivation (e.g., anorectic agents, antiemetics, or antihistamines) should be carefully considered.[42]

(c) Stents

Intraoral stents are beneficial during radiotherapy. They extend the distance between the maxilla and mandible, restrict mandibular motion, directing the radiation beams precisely to the target area and preventing irradiation of the contiguous normal mucosa. This can minimize the hostile effects of radiation, including the appearance of oral mucositis, osteoradionecrosis, and xerostomia/hyposalivation. Custom-made intraoral stents are comfortable to wear, protect the tongue, floor of the mouth, and mandible from radiation during open-mouth treatment, and allow repeated insertion and periodic examination.[78]

Management of oral mucositis

The treatment of oral mucositis is performed at its best through prophylactic measures that guarantee the anticipated identification of the cause and subsequent prevention. Multiple studies and clinical trials with palliative drugs have been performed in an attempt to prevent and control oral mucositis **(Table 1)**.[58–73] However, high level evidence of a single target therapeutic drug for curing oral mucositis is lacking. It was only in recent years that keratinocyte growth factor was approved by the Food and Drug Administration (**FDA**) for its promising action on

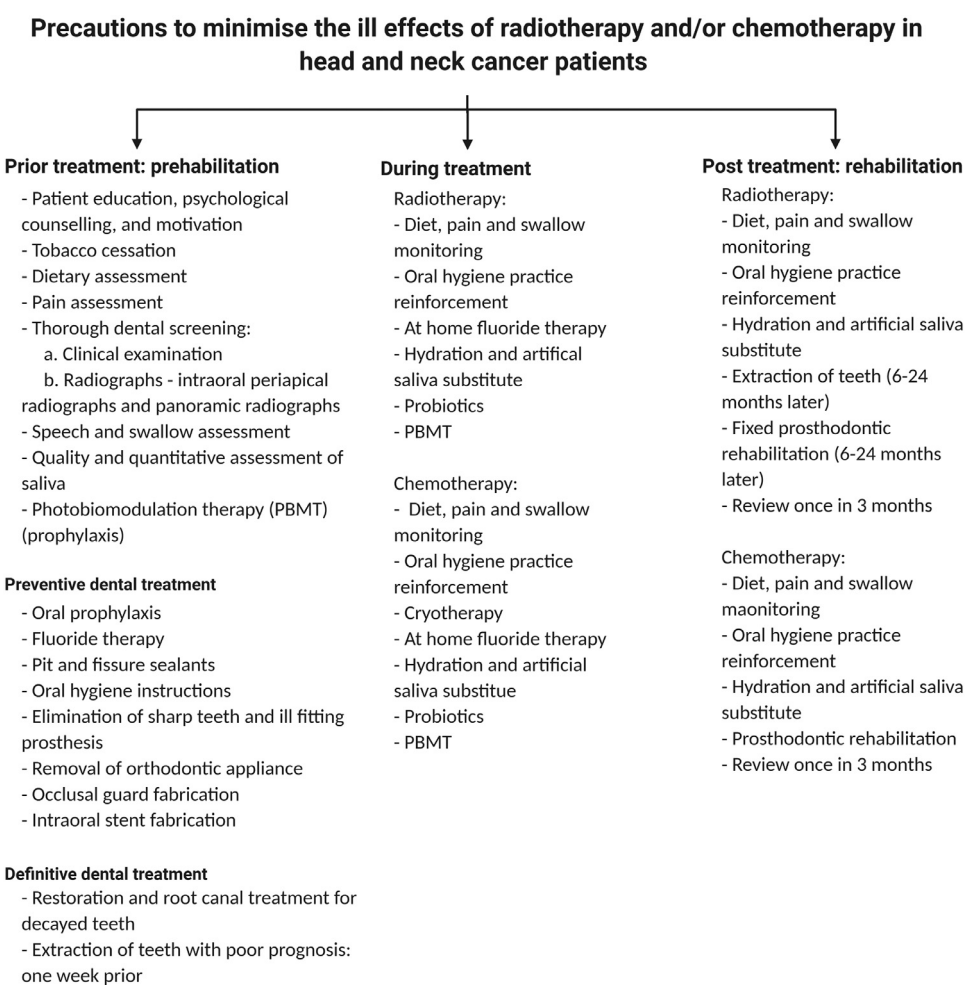

Fig. 6. Prehab-rehab flowchart showing how to minimize the effects of radiotherapy and/or chemotherapy on the oral cavity.

the reduction of mucositis. In addition, the management of oral mucositis aims to provide nutrition, rejuvenation of the dry mouth, management of oral bleeding due to chemotherapy-induced thrombocytopenia, pain relief with anaesthetic mouthwashes, bioadhesive topical agents for the mucosa, and management of the condition with therapeutic interventions.

(a) Mouthwashes

Anti-inflammatories such as benzydamine hydrochloride inhibit pro-inflammatory cytokines, including TNF-α, and can reduce the severity of oral mucositis, as demonstrated in a phase III clinical trial by Epstein et al. [79] An anti-inflammatory oral rinse has shown effectiveness in relieving post-radiation oral mucositis, but it had no effect on lesions associated with concomitant chemoradiation regimens.

According to the latest MASCC/ISOO clinical practice guidelines, it is recommended to rinse with benzydamine the mouth of individuals with head and neck cancer receiving a moderate dose of radiotherapy or chemoradiotherapy for the prevention of oral mucositis.[75] In addition, a 0.2% morphine mouthwash has been indicated for the treatment of pain associated with oral

mucositis. By contrast, treatment with combined topical and systemic sucralfate is not recommended for the prevention of pain associated with oral mucositis in individuals with head and neck cancer.[75]

It is noteworthy that chlorhexidine bisguanidine is not recommended by the MASCC/ISOO guidelines, despite its broad spectrum antibacterial and antimycotic action.[65] Chlorhexidine containing alcohol works as a divalent cation and binds to negatively charged salivary mucins or glycoproteins rather than directly to the epithelial tissues. Post-chemoradiation-induced xerostomia eliminates the protective lubricating coating of oral epithelial tissues and mitigates the effect of chlorhexidine.[66]

Among the different types of mouthwashes with biologically natural ingredients available on the market, those containing chamomile, honey, and curcumin have been used, but the level of evidence about their effectiveness is low.[80] Of note, medicinal plant extracts of *Isatis indigótica, Olea europaea, Calendula officinalis, A. digitatae*, and *M. sylvestris* are of proven clinical benefit by reducing the severity and incidence of lesions, with improvement of pain symptomatology.[80] A former study explored the efficacy of a mouthwash with doxepin or diphenhydramine-lidocaine-antacid and observed a significant reduction in pain from oral mucositis during the first four hours after administration.[81] Nonetheless, the long-term efficacy and safety of both types of mouthwashes has not yet been validated. In contrast to other topical analgesic agents with limited local properties, doxepin is an antidepressant with sedative properties. Although the doxepin-mediated pain relief mechanism is not completely clear, its analgesic effects are certainly related to the blocking of sodium channels, which limits the transmission of harmful stimuli to mucosal nociceptors.

(b) Palifermin (recombinant human keratinocyte growth factor-1)

Palifermin, Kepivance/KGF1, has demonstrated a substantial effect in reducing severe oral mucositis associated with cycled chemotherapy. The stimulation of NRF2 and IL-13 minimizes ROS damage and prevents the cleavage of DNA strands by their activation of DNA polymerases. It also activates antiapoptotic factors such as Bcl-2, Bax, and p53 and increases epithelial regeneration.[82] An overall favourable economic profile has been shown for this agent in the anti-cancer arsenal, despite its higher costs. A study showed that the average cost of hospitalization for patients with autologous hematopoietic stem cell transplantation ranges from $2,834 to $4,663. Of note, reductions in adverse outcomes and their associated hospital stay offset the acquisition price of palifermin.[83]

(c) Vitamins

Topical application of vitamins A and E has an anti-inflammatory and epithelial proliferative effect and can minimize the oxidative damage to the oral mucosa.[84] Also, salivary and systemic levels of immunoglobulins decrease in individuals receiving antineoplastic therapy. Intravenous or intramuscular immunoglobulins have immunomodulatory and anti-inflammatory properties and can be used as prophylactic and therapeutic options for radiation-induced oral mucositis.[73]

(d) Superoxide mimetics

GC4419, a superoxide dismutase mimetic, has been successfully evaluated in a study by Anderson et al. [85] It impedes the initial stage of mucositis in which ROS, including superoxide, are generated and activate a cascade of biological events that culminate in tissue damage. In a phase Ib/IIa trial in patients receiving standard concomitant cisplatin and IMRT for head and neck cancer, the incidence of mucositis, its duration and severity seemed to be improved compared to historical data when GC4419 was administered at doses of 30 or 90 mg before each IMRT fraction. Indeed, GC4419 has been associated with a decreased need for narcotic use with reduced normal tissue toxicity, while maintaining anticancer efficacy. A nitric oxide potentiating effect of GC4419 was seen in 0.09% of candidates who showed a dose-dependent increase in low-grade hypotension, without frank syncope or perioral tingling.[85]

(e) Cryotherapy

Oral cryotherapy causes local vasoconstriction, which may minimize the absorption of chemotherapeutic drugs with a short half-life inside the mucous cells, reducing the severity of mucosal ulcers.[86] A systematic review recommended the use of oral cryotherapy for the prevention of oral mucositis for patients undergoing autologous hematopoietic stem cell transplant with high-dose melphalan conditioning protocols or for patients receiving bolus 5-fluorouracil chemotherapy.[86]

(f) Granulocyte stimulating factors

Significant neutropenia during chemotherapy can accelerate the onset of ulceration. Clinical studies have shown that the systemic use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) can activate neutrophil migration, promote their proliferation and differentiation, and cause chemotaxis and phagocytosis. Also, G-/GM-CSF may trigger the proliferation of mucosal epithelial cells through the paracrine mechanisms of fibroblasts.[87,88]

(g) Probiotics

The gut microbiota is known to play an important regulatory role in host immunity.[89] It has been suggested that gut microbiota such as probiotics could modulate the anti-cancer immune response and mitigate cancer treatment-related toxic side effects.[90] Probiotics such as *Lactococcus lactis* and *Bifidobacterium longum* initiate T and B cell memory and activate the immune system by stimulating the production of salivary glycoproteins and antimicrobial peptides, protecting the oral mucosa from damage.[91] Thus, probiotic-based therapeutic interventions have been shown to be beneficial for chemotherapy- or radiotherapy-induced mucositis, possibly by regulating the microbiome and inhibiting pro-inflammatory cytokines.[92]

(h) Photobiomodulation therapy (PBMT)

Laser provides a “coating for the fibroblast” inducing rapid regeneration and growth factors.[93] PBMT exploits the effect of light energy on living cells and is absorbed by cytochromes and porphyrins in the mitochondria. This triggers numerous pathways that stimulate cell proliferation and differentiation and the regeneration process, and modulates the inflammatory mediators. Overall, PBMT rejuvenates wound injury, stimulates wound regeneration, and decreases the pain induced by chemotherapy in oral mucositis.[75,94] A previous study demonstrated that individuals with head and neck cancer who underwent concomitant chemoradiation and PBMT showed a trend toward better overall and disease-free survival when compared to the placebo arm.[95]

The low fluency of light modulates the release of inflammatory cytokines (TNF-α and NF-κB), produces a scanty amount of nitric oxide, and decreases the inflammation.[93] Targeted therapeutic interventions include the administration of recombinant human keratinocyte growth factor-1, cryotherapy, and PBMT, thus possibly reducing the levels of ROS and/or pro-inflammatory cytokines that trigger mucositis.[96] This is due to the fact that epidermal growth factor and keratinocyte growth factor stimulate cell growth, differentiation and proliferation and accelerate the healing of oral mucositis.[97]

Conclusion

Oral mucositis is linked to debilitating pain as well as impaired speech, swallowing, sleep, and feeding. Prolonged hospitalization and interruption of antineoplastic therapy may be necessary to mitigate the symptoms of oral mucositis, with a consequent increase in total treatment time affecting tumour control, polypharmacy, and parenteral nutrition, with higher care costs. It is essential to adopt preventive protocols for oral mucositis and to reinforce the daily need for active surveillance of the oral cavity, as soon as toxic chemoradiation therapy has started. The oral cavity is the primary target of mucotoxicity in view of the therapeutic challenge caused by

a mixture of toxic therapies that cannot differentiate between normal and malignant cells. The accessibility and the uniqueness of the oral cavity make it a “window” of potential mucotoxicity.

There has been a substantial effort in the field of oral medicine to propose strategies to alleviate the symptoms of oral mucositis since its ramifications have a significant clinical and economic impact. Despite the understanding of its etiopathogenesis, treatment of oral mucositis is still challenging and should focus on preventive measures. Thus, emphasis on the best measures of supportive care, restoration of salivary flow during and after radiation, circumvention of neutropenia, and administration of chemo-radioprotectors to minimize the debilitating effect of oral mucositis should be encouraged. Further progress in diagnostic tools for predicting the risk of oral mucositis and expand evidence-based interventions aiming to boost the clinical management of this biologically intricate toxicity is the need of the hour.

Consider summarizing the gaps in the literature (e.g., psychiatric impact of mucositis) and strategies to move the field forward, including studies to be done.

Declaration of Competing Interest

None.

Acknowledgements

This study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Finance Code 001), Brazil. J.A.A.A. is the recipient of a fellowship. We also thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (#305493/2018-3; #435644/2018-1; #404710/2018-2; #310797/2019-5; #302157/2017-4). L.G.A., R.A.M., and T.A.S. are research fellows of CNPq. Mrs. E. Greene provided English editing of the manuscript.

Source of Funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (#305493/2018-3; #435644/2018-1; #404710/2018-2; #310797/2019-5; #302157/2017-4).

References

1. Barkokebas A, Silva IH, de Andrade SC, et al. Impact of oral mucositis on oral-health-related quality of life of patients diagnosed with cancer. *J Oral Pathol Med*. 2015;44(9):746–751 https://doi.org/.1111/jop.12282.
2. Gutiérrez-Vargas R, Díaz-García ML, Villasís-Keever MÁ, Portilla-Robertson J, Zapata-Tárres M. Instruments to measure the quality of life in patients with oral mucositis undergoing oncological treatment: a systematic review of the literature. *Bol Méd del Hosp Infant M*. 2016;73(6):457–466. doi:10.1016/j.bmhimx.2016.10.007.
3. Rodrigues-Oliveira L, Kowalski LP, Santos M, et al. Direct costs associated with the management of mucositis: a systematic review. *Oral Oncology*. 2021;118:105296. doi:10.1016/j.oraloncology.2021.105296.
4. Joshi P, Dutta S, Chaturvedi P, Nair S. Head and neck cancers in developing countries. *Rambam Maimonides Med J*. 2014;5(2):e0009. doi:10.5041/RMMJ.10143.
5. Berger K, Schopohl D, Bollig A, et al. Burden of oral mucositis: a systematic review and implications for future research. *Oncol Res Treat*. 2018;41(6):399–405. doi:10.1159/000487085.
6. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. *Int J Radiat Oncol Biol Phys*. 2007;68(4):1110–1120. doi:10.1016/j.ijrobp.2007.01.053.
7. Murphy BA, Beaumont JL, Isitt J, et al. Mucositis-related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. *J Pain Symptom Manag*. 2009;38(4):522–532. doi:10.1016/j.jpainsymman.2008.12.004.
8. Elting LS, Chang YC. Costs of oral complications of cancer therapies: estimates and a blueprint for future study. *J Nat Cancer Inst*. 2019;2019(53):lgz010. doi:10.1093/jncimonographs/lgz010.
9. Ontario Case Costing Initiative (OCCI), Costing analysis (CAT) tool. https://data.ontario.ca/dataset/ontario-case-costing-initiative-occi. Accessed 21 June 2021.
10. Bowen J, Al-Dasooqi N, Bossi P, Wardill H, Van Sebille Y, Al-Azri A. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). The pathogenesis of mucositis: updated perspectives and emerging targets. *Supp Care Cancer*. 2019;27(10):4023–4033 10.1007/s00520-019-04893-z.
11. Wang SS, Tang YL, Pang X, Zheng M, Tang YJ, Liang XH. The maintenance of an oral epithelial barrier. *Life Sci*. 2019;227:129–136. doi:10.1016/j.lfs.2019.04.029.

12. Raber-Durlacher JE, Elad S, Barasch A. Oral mucositis. *Oral Oncol*. 2010;46(6):452–456. doi:10.1016/j.oraloncology.2010.03.012.
13. Chaitanya NC, Garlapati K, Priyanka DR, Soma S, Suskandla U, Boinepally NH. Assessment of anxiety and depression in oral mucositis patients undergoing cancer chemoradiotherapy: a randomized cross-sectional study. *Indian J Palliat Care*. 2016;22(4):446–454. doi:10.4103/0973-1075.191797.
14. Housman B, Flores R, Lee DS. Narrative review of anxiety and depression in patients with esophageal cancer: underappreciated and undertreated. *J Thor Dis*. 2021;13(5):3160–3170. doi:10.21037/jtd-20-3529.
15. Bressan V, Stevanin S, Bianchi M, Aleo G, Bagnasco A, Sasso L. The effects of swallowing disorders, dysgeusia, oral mucositis and xerostomia on nutritional status, oral intake and weight loss in head and neck cancer patients: a systematic review. *Cancer Treat Rev*. 2016;45:105–119. doi:10.1016/j.ctrv.2016.03.006.
16. Dy SM, Apostol CC. Evidence-based approaches to other symptoms in advanced cancer. *Cancer J*. 2010;16(5):507–513. doi:10.1097/PPO.0b013e3181f45877.
17. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4(4):277–284. doi:10.1038/nrc1318.
18. Epstein JB, Schubert MM. Oropharyngeal mucositis in cancer therapy. Review of pathogenesis, diagnosis, and management. *Oncology*. 2003;17(12):1767–1779 (Williston Park)discussion 1779-1782, 1791-1792.
19. Sonis ST. Pathobiology of oral mucositis: novel insights and opportunities. *J Supp Oncol*. 2007;5(9 Suppl 4):3–11.
20. Zelová H, Hošek J. TNF-α signalling and inflammation: interactions between old acquaintances. *Inflamm Res*. 2013;62(7):641–651. doi:10.1007/s00011-013-0633-0.
21. Curra M, Pellicioli AC, Filho NA, et al. Photobiomodulation reduces oral mucositis by modulating NF-kB. *J Biomed Opt*. 2015;20(12):125008. doi:10.1117/1.JBO.20.12.125008.
22. Akpek G, Knight RD, Wright DG. Use of oral mucosal neutrophil counts to detect the onset and resolution of profound neutropenia following high-dose myelosuppressive chemotherapy. *Am J Hematol*. 2003;72(1):13–19. doi:10.1002/ajh.10250.
23. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. *Front Oncol*. 2017;7:89. doi:10.3389/fonc.2017.00089.
24. Christaki E, Giamarellos-Bourboulis EJ. The complex pathogenesis of bacteremia: from antimicrobial clearance mechanisms to the genetic background of the host. *Virulence*. 2014;5(1):57–65. doi:10.4161/viru.26514.
25. Sonis ST. A hypothesis for the pathogenesis of radiation-induced oral mucositis: when biological challenges exceed physiologic protective mechanisms. Implications for pharmacological prevention and treatment. *Supp Care Cancer*. 2021. doi:10.1007/s00520-021-06108-w.
26. Villa A, Vollemans M, De Moraes A, Sonis S. Concordance of the WHO, RTOG, and CTCAE v4.0 grading scales for the evaluation of oral mucositis associated with chemoradiation therapy for the treatment of oral and oropharyngeal cancers. *Supp Care Cancer*. 2021. doi:10.1007/s00520-021-06177-x.
27. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M. Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 Suppl):1995–2025. doi:10.1002/cncr.20162.
28. Woo SB, Lee SJ, Schubert MM. Graft-vs.-host disease. *Crit Rev Oral Biol Med*. 1997;8(2):201–216. doi:10.1177/10454411970080020701.
29. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy. Part 2: diagnosis and management of mucositis. *Head Neck*. 2004;26(1):77–84. doi:10.1002/hed.10326.
30. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:190–209. doi:10.1016/j.ejca.2016.02.025.
31. Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. *J Cutan Pathol*. 2016;43(4):339–346. doi:10.1111/cup.12666.
32. Wakade DV, Carlos G, Hwang SJ, Chou S, Hui R, Fernandez-Peñas P. PD-1 inhibitors induced bullous lichen planus-like reactions: a rare presentation and report of three cases. *Melanoma Res*. 2016;26(4):421–424. doi:10.1097/CMR.0000000000000263.
33. Shazib MA, Woo SB, Sroussi H, et al. Oral immune-related adverse events associated with PD-1 inhibitor therapy: a case series. *Oral Dis*. 2020;26(2):325–333. doi:10.1111/odi.13218.
34. Sacco AG, Chen R, Worden FP, et al. Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: an open-label, multi-arm, non-randomised, multicentre, phase 2 trial. *Lancet Oncol*. 2021;22(6):883–892. doi:10.1016/S1470-2045(21)00136-4.
35. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent Clin North Ame*. 2008;52(1):61–77 viii. doi:10.1016/j.cden.2007.10.002.
36. Wardill HR, Sonis ST, Blijlevens NMA, Van Sebille YZA, Ciorba MA, Loeffen EAH. Mucositis study group of the multinational association of supportive care in cancer/international society of oral oncology (MASCC/ISOO). Prediction of mucositis risk secondary to cancer therapy: a systematic review of current evidence and call to action. *Supp Care Cancer*. 2020;28(11):5059–5073. doi:10.1007/s00520-020-05579-7.
37. Reyes-Gibby CC, Melkonian SC, Wang J, et al. Identifying novel genes and biological processes relevant to the development of cancer therapy-induced mucositis: An informative gene network analysis. *Plos One*. 2017;12(7):e0180396. doi:10.1371/journal.pone.0180396.
38. Yang DW, Wang TM, Zhang JB, et al. Genome-wide association study identifies genetic susceptibility loci and pathways of radiation-induced acute oral mucositis. *J Transl Med*. 2020;18(1):224. doi:10.1186/s12967-020-02390-0.
39. Pulito C, Cristaudo A, Porta C, et al. Oral mucositis: the hidden side of cancer therapy. *J Exp Clin Cancer Res*. 2020;39(1):210. doi:10.1186/s13046-020-01715-7.
40. Barasch A, Peterson DE. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. *Oral Oncol*. 2003;39(2):91–100. doi:10.1016/s1368-8375(02)00033-7.

41. Huang SH, O'Sullivan B. Oral cancer: Current role of radiotherapy and chemotherapy. *Med Oral Patol Oral y Cirugia Bucal*. 2013;18(2):e233–e240. doi:10.4317/medoral.18772.
42. Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis–complicating the treatment of cancer. *Neoplasia*. 2004;6(5):423–431. doi:10.1593/neo.04169.
43. Lalla RV, Brennan MT, Gordon SM, Sonis ST, Rosenthal DI, Keefe DM. Oral mucositis due to high-dose chemotherapy and/or head and neck Radiation therapy. *J Nat Cancer Inst*. 2019;2019(53):lgz011. doi:10.1093/jncimonographs/lgz011.
44. Barnett GC, West CM, Dunning AM, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nat Rev Cancer*. 2009;9(2):134–142. doi:10.1038/nrc2587.
45. Cheng KK, Lee V, Li CH, et al. Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. *Oral Oncol*. 2011;47(3):153–162. doi:10.1016/j.oraloncology.2010.11.019.
46. Li K, Yang L, Xin P, et al. Impact of dose volume parameters and clinical factors on acute radiation oral mucositis for locally advanced nasopharyngeal carcinoma patients treated with concurrent intensity-modulated radiation therapy and chemoradiotherapy. *Oral Oncol*. 2017;72:32–37. doi:10.1016/j.oraloncology.2017.06.026.
47. Brodin NP, Tomé WA. Revisiting the dose constraints for head and neck OARs in the current era of IMRT. *Oral Oncol*. 2018;86:8–18. doi:10.1016/j.oraloncology.2018.08.018.
48. Liu S, Zhao Q, Zheng Z, et al. Status of treatment and prophylaxis for radiation-induced oral mucositis in patients with head and neck cancer. *Front Oncol*. 2021;11:642575. doi:10.3389/fonc.2021.642575.
49. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol*. 2003;66(3):253–262. doi:10.1016/s0167-8140(02)00404-8.
50. Zackrisson B, Mercke C, Strander H, Wennerberg J, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in head and neck cancer. *Acta Oncol*. 2003;42(5-6):443–461. doi:10.1080/02841860310014886.
51. Zhu G, Lin JC, Kim SB, et al. Asian expert recommendation on management of skin and mucosal effects of radiation, with or without the addition of cetuximab or chemotherapy, in treatment of head and neck squamous cell carcinoma. *BMC Cancer [Electron Resour]*. 2016;16:42. doi:10.1186/s12885-016-2073-z.
52. Henriksson R, Fröjd O, Gustafsson H, et al. Increase in mast cells and hyaluronic acid correlates to radiation-induced damage and loss of serous acinar cells in salivary glands: the parotid and submandibular glands differ in radiation sensitivity. *Br J Cancer*. 1994;69(2):320–326. doi:10.1038/bjc.1994.58.
53. Castelli J, Simon A, Louvel G, et al. Impact of head and neck cancer adaptive radiotherapy to spare the parotid glands and decrease the risk of xerostomia. *Radiat Oncol*. 2015;10:6. doi:10.1186/s13014-014-0318-z.
54. Wu V, Leung KY. A review on the assessment of radiation induced salivary gland damage after radiotherapy. *Front Oncol*. 2019;9:1090. doi:10.3389/fonc.2019.01090.
55. Jasmer KJ, Gilman KE, Muñoz Forti K, Weisman GA, Limesand KH. Radiation-induced salivary gland dysfunction: mechanisms, therapeutics and future directions. *J Clin Med*. 2020;9(12):4095. doi:10.3390/jcm9124095.
56. Cheng KK, Leung SF, Liang RH, Tai JW, Yeung RM, Thompson DR. Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life. *Supp Care Cancer*. 2010;18(11):1477–1485. doi:10.1007/s00520-009-0771-7.
57. Lalla RV, Peterson DE. Oral mucositis. *Dent Clin N Am*. 2005;49(1):167–184 ix. doi:10.1016/j.cden.2004.07.009.
58. Bjordal JM, Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Supp Care Cancer*. 2011;19(8):1069–1077. doi:10.1007/s00520-011-1202-0.
59. Jensen SB, Jarvis V, Zadik Y, Barasch A, Ariyawardana A, Hovan A. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of miscellaneous agents for the management of oral mucositis in cancer patients. *Supp Care Cancer*. 2013;21(11):3223–3232. doi:10.1007/s00520-013-1884-6.
60. Yarom N, Ariyawardana A, Hovan A, Barasch A, Jarvis V, Jensen SB. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of natural agents for the management of oral mucositis in cancer patients. *Supp Care Cancer*. 2013;21(11):3209–3221. doi:10.1007/s00520-013-1869-5.
61. Nicolatou-Galitis O, Sarri T, Bowen J, Di Palma M, Kouloulias VE, Niscola P. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients. *Supp Care Cancer*. 2013;21(11):3179–3189. doi:10.1007/s00520-013-1847-y.
62. McGuire DB, Fulton JS, Park J, Brown CG, Correa ME, Eilers J. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Supp Care Cancer*. 2013;21(11):3165–3177. doi:10.1007/s00520-013-1942-0.
63. Leung HW, Chan AL. Glutamine in alleviation of radiation-induced severe oral mucositis: a meta-analysis. *Nutr Cancer*. 2016;68(5):734–742. doi:10.1080/01635581.2016.1159700.
64. Co JL, Mejia MB, Que JC, Dizon JM. Effectiveness of honey on radiation-induced oral mucositis, time to mucositis, weight loss, and treatment interruptions among patients with head and neck malignancies: A meta-analysis and systematic review of literature. *Head Neck*. 2016;38(7):1119–1128. doi:10.1002/hed.24431.
65. Peng H, Chen BB, Chen L, et al. A network meta-analysis in comparing prophylactic treatments of radiotherapy-induced oral mucositis for patients with head and neck cancers receiving radiotherapy. *Oral Oncol*. 2017;75:89–94. doi:10.1016/j.oraloncology.2017.11.001.
66. Carneiro-Neto JN, de-Menezes JD, Moura LB, Massucato EM, de-Andrade CR. Protocols for management of oral complications of chemotherapy and/or radiotherapy for oral cancer: Systematic review and meta-analysis current. *Med Oral Patol Oral Cirugia Bucal,*. 2017;22(1):e15–e23. doi:10.4317/medoral.21314.
67. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, Filipauskas A. Prevention and treatment of chemotherapy and radiotherapy induced oral mucositis. *Medicina*. 2019;55(2):25 (Kaunas, Lithuania). doi:10.3390/medicina55020025.

68. Münstedt K, Momm F, Hübner J. Honey in the management of side effects of radiotherapy- or radio/chemotherapy-induced oral mucositis. A systematic review. *Complement Ther Clin Pract*. 2019;34:145–152. doi:10.1016/j.ctcp.2018.11.016.
69. Christoforou J, Karasneh J, Manfredi M, et al. World workshop on oral medicine VII: non-opioid pain management of head and neck chemo/radiation-induced mucositis: a systematic review. *Oral Dis*. 2019;25(Suppl 1):182–192. doi:10.1111/odi.13074.
70. De Sanctis V, Merlotti A, De Felice F, et al. Intensity modulated radiation therapy and oral mucosa sparing in head and neck cancer patients: a systematic review on behalf of italian association of radiation oncology - head and neck working group. *Crit Rev Oncol/Hematol*. 2019;139:24–30. doi:10.1016/j.critrevonc.2019.04.022.
71. Hong CHL, Gueiros LA, Fulton JS, Cheng KKF, Kandwal A, Galiti D. Mucositis study group of the multinational association of supportive care in cancer/international society for oral oncology (MASCC/ISOO). Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supp Care Cancer*. 2019;27(10):3949–3967. doi:10.1007/s00520-019-04848-4.
72. Campos TM, do Prado Tavares Silva CA, Sobral APT, et al. Photobiomodulation in oral mucositis in patients with head and neck cancer: a systematic review and meta-analysis followed by a cost-effectiveness analysis. *Supp Care Cancer*. 2020;28(12):5649–5659. doi:10.1007/s00520-020-05613-8.
73. Saunders DP, Rouleau T, Cheng K, Yarom N, Kandwal A, Joy J. Mucositis study group of the multinational association of supportive care in cancer/international society of oral oncology (MASCC/ISOO). Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supp Care Cancer*. 2020;28(5):2473–2484. doi:10.1007/s00520-019-05181-6.
74. Cinausero M, Aprile G, Ermacora P, et al. New frontiers in the pathobiology and treatment of cancer regimen-related mucosal injury. *Front Pharmacol*. 2017;8:354. doi:10.3389/fphar.2017.00354.
75. Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM. Mucositis guidelines leadership group of the multinational association of supportive care in cancer and international society of oral oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer,*. 2020;126(19):4423–4431. doi:10.1002/cncr.33100.
76. Saito N, Imai Y, Muto T, Sairenchi T. Low body mass index as a risk factor of moderate to severe oral mucositis in oral cancer patients with radiotherapy. *Supp Care Cancer*. 2012;20(12):3373–3377. doi:10.1007/s00520-012-1620-7.
77. Szeszko B, Osowiecka K, Rucińska M, Wasilewska-Teśluk E, Gliński K, Kępka L. Smoking during radiotherapy for head and neck cancer and acute mucosal reaction. *Rep Pract Oncol Radiother*. 2015;20(4):299–304. doi:10.1016/j.rpor.2015.04.001.
78. Inoue Y, Yamagata K, Nakamura M, Ohnishi K, Tabuchi K, Bukawa H. Are intraoral stents effective for reducing the severity of oral mucositis during radiotherapy for maxillary and nasal cavity cancer? *J Oral Maxillofac Surg*. 2020;78(7):1214 e1-1214.e8. doi:10.1016/j.joms.2020.02.009.
79. Epstein JB, Silverman S, Paggiarino DA, et al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Cancer*. 2001;92(4):875–885. doi:10.1002/1097-0142(20010815)92:4⟨875::aid-cncr1396⟩3.0.co;2-1.
80. Eubank PLC, Abreu LG, Violante IP, Volpato LER. Medicinal plants used for the treatment of mucositis induced by oncotherapy: a systematic review. *Supp Care Cancer*. 2021. doi:10.1007/s00520-021-06247-0.
81. Sio TT, Le-Rademacher JG, Leenstra JL, et al. Effect of doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash vs placebo on radiotherapy-related oral mucositis pain: the alliance A221304 randomized clinical trial. *J Am Med Assoc*. 2019;321(15):1481–1490. doi:10.1001/jama.2019.3504.
82. Mazhari F, Shirazi AS, Shabzendehdar M. Management of oral mucositis in pediatric patients receiving cancer therapy: a systematic review and meta-analysis. *Pediat Blood Cancer*. 2019;66(3):e27403. doi:10.1002/pbc.27403.
83. Elting LS, Shih YC, Stiff PJ, et al. Economic impact of palifermin on the costs of hospitalization for autologous hematopoietic stem-cell transplant: analysis of phase 3 trial results. *Biol Blood Marrow Transpl*. 2007;13(7):806–813. doi:10.1016/j.bbmt.2007.03.004.
84. Ferreira PR, Fleck JF, Diehl A, et al. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. *Head Neck*. 2004;26(4):313–321. doi:10.1002/hed.10382.
85. Anderson CM, Sonis ST, Lee CM, et al. Phase 1b/2a trial of the superoxide dismutase mimetic GC4419 to reduce chemoradiotherapy-induced oral mucositis in patients with oral cavity or oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;100(2):427–435. doi:10.1016/j.ijrobp.2017.10.019.
86. Correa MEP, Cheng KKF, Chiang K, et al. Systematic review of oral cryotherapy for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supp Care Cancer*. 2020;28(5):2449–2456. doi:10.1007/s00520-019-05217-x.
87. Wang L, Huang XE, Ji ZQ, Liu MY, Qian T, Li L. Safety and efficacy of a mouth-rinse with granulocyte colony stimulating factor in patients with chemotherapy-induced oral mucositis. *Asian Pac J Cancer Prev*. 2016;17(1):413–418. doi:10.7314/apjcp.2016.17.1.413.
88. Liang G, Du W, Ke Q, Huang B, Yang J. The effects of recombinant human granulocyte colony-stimulating factor mouthwash on radiotherapy-induced oral mucositis in locally advanced nasopharyngeal carcinoma patients. *Adv Clin Exp Med*. 2017;26(3):409–413. doi:10.17219/acem/61913.
89. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016;16(6):341–352. doi:10.1038/nri.2016.42.
90. Xia C, Jiang C, Li W, et al. A phase II randomized clinical trial and mechanistic studies using improved probiotics to prevent oral mucositis induced by concurrent radiotherapy and chemotherapy in nasopharyngeal carcinoma. *Front Immunol*. 2021;12:618150. doi:10.3389/fimmu.2021.618150.
91. Cereda E, Caraccia M, Caccialanza R. Probiotics and mucositis. *Curr Opin Clin Nutr Metab Care*. 2018;21(5):399–404. doi:10.1097/MCO.0000000000000487.

92. Prisciandaro LD, Geier MS, Butler RN, Cummins AG, Howarth GS. Evidence supporting the use of probiotics for the prevention and treatment of chemotherapy-induced intestinal mucositis. *Crit Rev Food Sci Nutr*. 2011;51(3):239–247. doi:10.1080/10408390903551747.
93. Spanemberg JC, Figueiredo MA, Cherubini K, Salum FG. Low-level laser therapy: a review of its applications in the management of oral mucosal disorders. *Altern Ther Health Med*. 2016;22(6):24–31.
94. Nunes LFM, de Arruda JAA, et al. Prophylactic photobiomodulation therapy using 660 nm diode laser for oral mucositis in paediatric patients under chemotherapy: 5-year experience from a Brazilian referral service. *Lasers Med Sci*. 2020;35(8):1857–1866. doi:10.1007/s10103-020-03060-9.
95. Antunes HS, Schluckebier LF, Herchenhorn D, et al. Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. *Oral Oncol*. 2016;52:85–90. doi:10.1016/j.oraloncology.2015.10.022.
96. Hanna R, Dalvi S, Benedicenti S, et al. Photobiomodulation therapy in oral mucositis and potentially malignant oral lesions: a therapy towards the future. *Cancers*. 2020;12(7):1949 (Basel). doi:10.3390/cancers12071949.
97. Riley P, Glenny AM, Worthington HV, et al. Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. *Cochrane Database Syst Rev*. 2017;11(11):CD011990. doi:10.1002/14651858.CD011990.pub2.