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Oral mucositis:

Supporting cancer therapy compliance with oral care

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Content

This document was developed in collaboration with

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Executive Summary

Patients undergoing cancer treatment, particularly those receiving a combination of radiotherapy and chemotherapy for the treatment of head and neck cancer, are at high risk of developing oral mucositis. Oral mucositis affects up to 90% of high-risk patients. Mucositis can be so debilitating that it prevents patients from eating and drinking. Some patients may be hospitalized and fed through a tube or intravenously. The adverse effects of mucositis often affect compliance to cancer therapies causing interruptions or discontinuation of treatment, thus reducing patient's chances of survival, and increasing costs to the healthcare system.

Preventing and managing oral mucositis is essential in the care of cancer patients. Oral mucositis requires an interdisciplinary approach with dentists, dental hygienists, nutritionists, oncologists and nurses working together to diagnose patients early and provide care to alleviate pain, keep patients nourished and manage the risk of secondary infections.

Definition

Oral mucositis is a condition that affects the mucosa of the mouth. It is **one of the most common and debilitating complication of cancer treatment.** It is frequently observed in patients being treated with chemotherapy and/or radiotherapy in the oral cavity or in the head and neck area. [1]

Mucositis lesions are present in the oral cavity when associated with local radiotherapy treatment of the head-neck area but may extend to the entire mucous membrane of the gastrointestinal tract when associated with systemic chemotherapy treatment. It typically presents itself as an **erythema of the mucous membrane and progresses to ulcerations and pseudomembranes** (Fig.1).

The adverse effects of mucositis can interfere with cancer therapies, reduce the effectiveness of radio and/or chemotherapy treatment [3] [5] and lead to hospitalization. Mucositis is associated with an increase in patient mortality in the first 100 days from the beginning of therapy. [4]

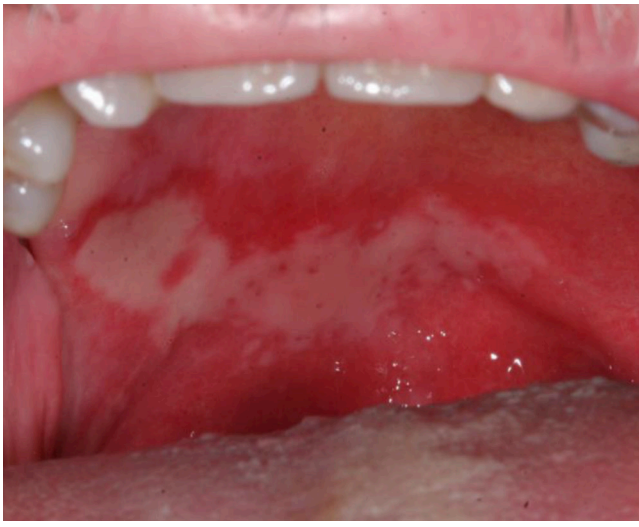


Fig. 1 – Oral mucositis - Courtesy of Prof. C. Lajolo

Mucositis symptoms:

The symptoms of mucositis include: [2] [3]

- Intense pain
- Dysgeusia
- Odynophagia
- Difficulty in feeding
- Important weight loss
- Difficulty in speaking

Epidemiology

Çakmak and Nural report that oral **mucositis develops in 51.7% of patients undergoing chemotherapy**[7] but the incidence and severity of mucositis vary greatly depending on the type of treatment, the number of cycles, the mode of administration, the dosages, the possible combination of different treatments and on the susceptibility of the patient.[6] [1] [8]

The percentage of patients treated with radiotherapy of the head-neck area who develops oral mucositis frameworks is very high, sometimes more than 90% of cases. **Patients undergoing a combination of radiotherapy and chemotherapy face the highest risk**, with studies demonstrating an increased incidence of severe mucositis among these patients (Grade 3 and 4 on the WHO scale). [9] [10] [11] [12] (Table 1)

Elting et al. conducted a study with patients treated with radiotherapy in the head-neck area and reported that **when combined with chemotherapy, more than half of patients (66%) developed severe mucositis** (Grade 3 and 4) and more than one third (37%) of this group were hospitalized.[10]

Patients undergoing chemotherapy and/or radiotherapy treatments prior to hematopoietic stem cell transplantation develop oral mucositis in more than **70% of cases.** [13]

Table 1: WHO classification (1979) of the grades of oral mucositis:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No symptoms of oral mucositis	Soreness in mouth, no ulcer; patient can eat a normal diet	Sore mouth with ulcers, patient is still able to eat a normal diet	Extreme sensitivity when swallowing solid food, patient needs to be on a liquid diet	Patient is not able to eat, drink or swallow, a parenteral nutrition or tube feeding is necessary

Incidence:

Up to 66% of head & neck cancer patients undergoing radio-chemo therapy are likely to develop severe mucositis, with up to 1/3 requiring hospitalization

Etiology

Main causes & risk factors of oral mucositis

Chemotherapy in general and radiotherapy to the head and neck region for the treatment of head and neck cancers are the main cause of oral mucositis.

Risk factors play an important role in the etiology of mucositis as patients suffering from the same neoplasms and undergoing similar treatments can often display varying degrees of incidence and severity.[15] [30] Pico et al. propose two predictive indices: **1 Treatment related risk factors, 2 Patient associated risk factors** [31]

1 Treatment-related risk factors

Treatment-related risk factors:

- Drug used
- Dosage and therapeutic protocol
- Method of administration and formulation
- Concomitent therapies
- Time of administration of therapy

Drugs used in chemotherapy

Pharmacological agents most commonly associated with the onset of oral mucositis include cytarabine, alkylating agents, methotrexate and 5-fluorouracil used at high doses.

Conditioning protocols used before a hematopoietic stem cell transplant, such as total body irradiation or the use of doxorubicin or melphalan, are among those most associated with the onset of oral mucositis. [8] [35] [36]

The association between chemo and radiotherapy, particularly when cisplatin and cetuximab are used, also exposes the patient to an increased risk of developing the complication. [34]

Etiology

Main causes & risk factors of oral mucositis

2 Patient-related risk factors

Patient-related risk factors are often conflicting but they do demonstrate a **positive association between smoking and oral mucositis.** [35] **Data on age, BMI and gender is less clear** - a precise definition of patient-related risk based on these factors is not possible. [39] [35] [40] [36] Some studies report an association between the incidence of mucositis following chemotherapy and the female gender [41] [42] [43], while other studies demonstrate an association between the incidence of mucositis following chemotherapy for head-neck neoplasms and the male gender. [34]

Studies also suggest a **possible correlation between genetic characteristics and the risk of severe events**, identifying the presence of polymorphisms and mutations related to drug metabolization pathways, DNA repair mechanisms, genes, cell proliferation and immune and inflammatory responses as possible causes of adverse events. [44] [45] [46] [47] [48] [49] [50] [35]

Finally, some studies have highlighted an increased incidence of severe mucositis in patients performing radiotherapy sessions in the afternoon and have hypothesized that **the circadian rhythm may also affect the severity of the side effects of radiotherapy.** [37] [38]

Although current knowledge on patient-related risk factors is still limited, the aim of future research will be to sharpen the value of predictive indices at the individual level so as to enable the delivery of personalized support therapies before severe mucositis symptoms arise. [35] [15]

Patient-related risk factors:

- Age
- Body mass index (bmi)
- Sex
- Smoke
- Genetic factors
- Previous infections with herpes simplex (HSV) and papilloma virus (HPV)
- Microbiome
- Tumor characteristics (localization, size, stage)
- Renal and liver function
- Oral status
- Laboratory parameters before treatment (neutropenia, lymphopenia, thrombocytopenia, ALT (>16U/L), urea, hemoglobin)
- Comorbidities
- Hyposalivation [32] [33] [34] [35]

Risk factors

Treatment-related risk factors have shown the strongest predictive value while patient-related risk factors need further research. The future holds opportunities for more personalized support therapies.

IV

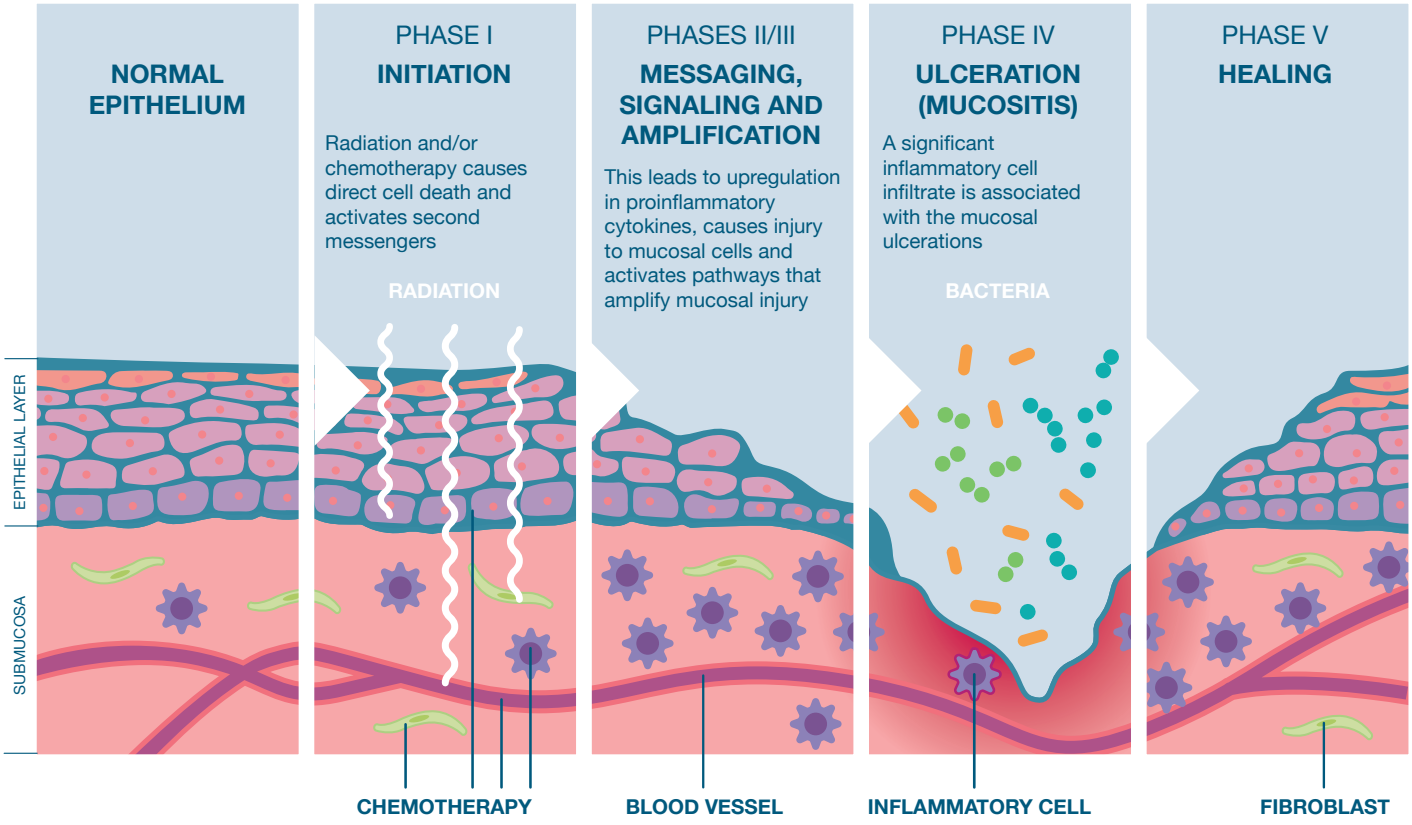
Pathogenesis

Our understanding of the pathogenesis of mucositis is based almost exclusively on *in vitro* and animal models. The models have helped us understand the multifactorial nature of this condition and the complex mechanisms that determine its onset [15] [16].

The model proposed by Sonis (see Fig.2) highlights the importance of endothelial damage [17], pro-inflammatory cytokines [18] [19] [20] [21], extracellular matrix [22], [23], [24] and microbiome [15].

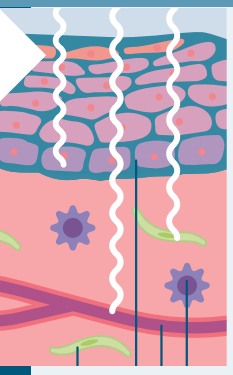
Sonis's model portrays the biological events underlying mucositis in the light of a **five-step process: initiation, initial damage response, signal amplification, ulceration, and healing**. Although this subdivision helps understand the complexity of disease progression, it is important to keep in mind that the development of mucositis is a dynamic process that can be triggered either by a single very intense event (such as chemotherapy treatment for patients waiting for transplantation of hematopoietic stem cells) or by repeated lower intensity stress (as is the case with fractional therapeutic regimens). A standard head-neck area radiotherapy treatment for example, involves a dose of 70 Grays divided into 7 weeks (2 Grays per day) meaning the phases of the model proposed by Sonis overlap, since the damage is divided into small and numerous daily doses. [14]

Fig. 2: Adaptation of the model of the pathogenesis of oral mucositis by Sonis [14]



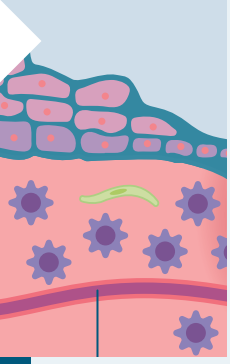
IV Pathogenesis

PHASE I: **INITIATION**



Radiotherapy and chemotherapy can cause very early **direct and non-direct DNA and cell damage** regulated by different mechanisms, including the **production of reactive oxygen species (ROS)**. Direct damage to DNA may cause the death of certain cells of the basal layer and those present in the submucosa, but the extent of this phenomenon is not such as to determine the appearance of mucositis; without the contribution of non-direct damage to DNA, the complex processes leading to mucous damage would not be triggered. ROS are compounds with high oxidizing capacity potentially capable of damaging any macromolecule and determining cell death if not adequately counteracted by antioxidant substances. During this phase the mucous membrane does not present any alteration, but the cascade of events triggered in the submucosa will progressively lead to its destruction. [14]

PHASE II/III: **MESSAGING, SIGNALING AND AMPLIFICATION**



DNA-induced damage and ROS activation lead to an initial response to damage through three main routes: the production of ceramide, the increase in the activity of matrix metalloproteinases (MMP) and the activation of transcription factors.

- **The complex mechanisms triggered by these three pathways increase tissue damage and stimulate apoptosis.** [25] [14] Radiotherapy and chemotherapy can activate certain enzymes dedicated to the hydrolysis of cell membrane components, sphingomyelinases, which determine the production of ceramide and the consequent stimulation of cellular apoptosis.
- Instead, the damage of fibroblasts seems to be mainly due to the activation of activator protein 1 (AP1) which leads to an increase in the secretion of MMP, proteins capable of causing the destruction of the extracellular matrix and basal membrane; this phenomenon leads to an increase in apoptosis both directly and indirectly. [14] [22] [23]
- **Transcription factors most involved in the initial damage response phase include nuclear factor kB (NF-kB), p53 and erythroid-2 nuclear transcription factor (NRF2)**; the link between these proteins and DNA is fundamental for the regulation of multiple genes, including those related to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules. [18] [19] [20] [21]

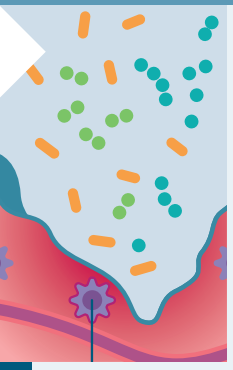
Cells are then stimulated to **increase the secretion of pro-inflammatory cytokines**, such as tumor necrosis factor alpha (TNF-α), interleukin 1-beta (IL-1β), interleukin 6 (IL-6) and prostaglandins (PGs), a set of molecules that increase the damage produced in the initiation phase: they **reduce the oxygenation** of epithelial cells and further feed the mechanisms underlying cell damage induced by radiotherapy and/or chemotherapy. [15] [14] [26]

The signals induced by the initial response to the damage are further amplified by establishing a **cascade of events that stimulates tissue damage again**. All these changes involve not only epithelial cells but all the cells that make up the mucous membrane. [14]

Due to the multiple mechanisms that cause direct and indirect damage induced by radiation and chemotherapy drugs, the **epithelium loses its normal ability to renew itself** and the first signs and symptoms of mucositis begin to appear. [9] [14]

IV Pathogenesis

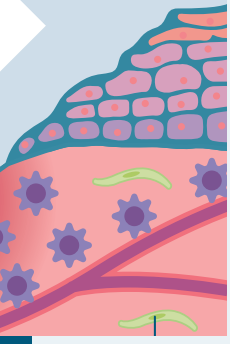
PHASE IV: **ULCERATION (MUCOSITIS)**



All the mechanisms described above are part of a dynamic process that continues to damage the mucous membrane, sometimes until it results in loss of integrity. **At this stage, macroscopic alterations of the oral mucosa become evident, extremely painful ulcers appear, poorly defined and often widespread. The pain associated with the ulcerative phase is so intense because tissue damage is such as to cause the loss of the myelinic sheath of the nerve endings present in the mucosa**. Mucositis ulcerations are an important problem not only for the symptoms they entail, but also because the **loss of integrity of the mucous membrane predisposes patients, especially if suffering from neutropenia, to infections that can lead to bacteremia and sepsis.** [14]

In addition, the products of the cell wall of bacteria manage to penetrate the submucosa by stimulating the further production of pro-inflammatory cytokines and the consequent activity of other inflammatory cells; all this contributes to tissue damage [14] and probably indirectly promotes the expression of pro-apoptotic genes. [27]

PHASE V: **HEALING**



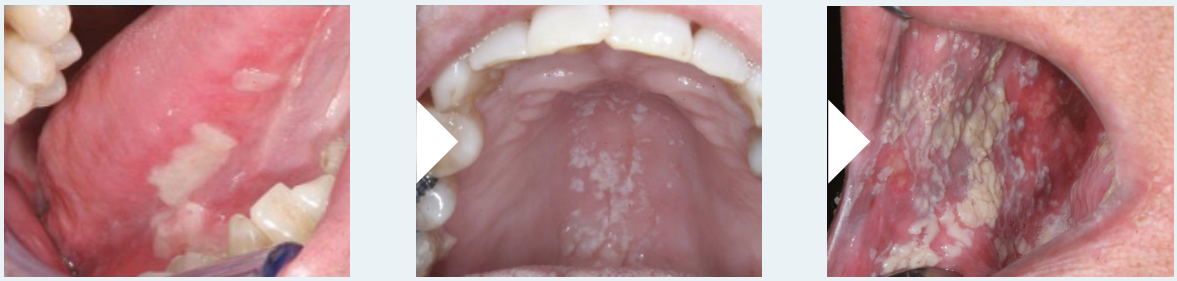
In most cases, **mucositis is an acute phenomenon that tends to resolve once cancer therapy is over; healing times may vary depending on the type of treatment, its duration and the dosages used.** [14]

During this phase, the extracellular matrix plays a fundamental role in stimulating the proliferation, migration, and differentiation of epithelial cells [24], but it is possible that there are many other mechanisms that can influence tissue healing. Some *in vitro* studies of oral keratinocytes have shown how much the presence of bacteria influences this phase. [28] [29] Changes in the oral and gastrointestinal microbiome induced by cancer therapies most likely play a key role at all stages of mucositis pathogenesis, but current knowledge, especially on the relationship between oral dysbiosis and mucositis, is still very limited. [26]

Clinical characteristics and diagnosis

Initially, oral mucositis presents itself as an **erythema of the oral mucosa** that tends to progress with the formation of **very painful and extensive ulcers**, characterized by strongly erythematous areas and areas covered with pseudo membrane consisting of fibrin, cellular debris and bacteria (Fig.3).

Fig.3 : Various clinical appearances of oral mucositis - Courtesy of Prof. C. Lajolo



The grading system proposed by the WHO (see Table 1 p.5) is often used to define the severity of mucositis and incorporates clinical appearance, symptoms and functional status. (11)

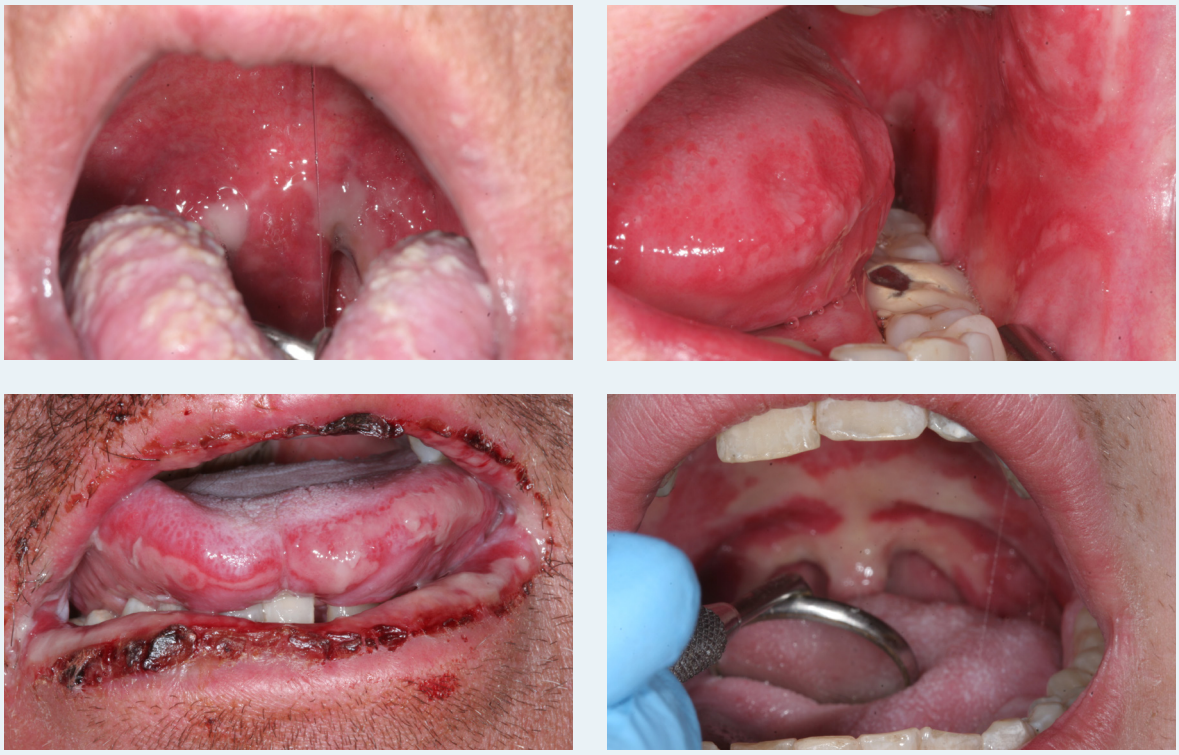
Patients with a grade 1 or 2 mucositis (Fig.4) usually manage to feed despite the morbidity of such a condition.

Fig.4 : Clinical appearance of oral mucositis Grade 1 and 2 - Courtesy of Prof. C. Lajolo

Clinical characteristics and diagnosis

If the mucositis progresses towards grade 3 (Fig.5), a liquid diet becomes necessary with hydration also becoming a challenge. At stage 4 oral nutrition and hydration are no longer possible.

Fig.5 : Clinical appearance of oral mucositis Grade 3 and 4 - Courtesy of Prof. C. Lajolo



Mucositis can lead to **significant functional impairment**, causing **malnutrition, dehydration, weight loss, need for parenteral feeding and hospitalization.** In addition, the loss of integrity of the mucous layer represents a clinically significant **risk factor for bacteremia, fungemia and sepsis.** (3) (5) (51)

Oral mucositis has an important **economic impact** – resources need to be allocated to the management of the patient's symptoms, the management of **secondary infections**, the delivery of **adequate nutritional support and in severe cases,** hospitalization. (4) (54)

Symptoms and complications associated with oral mucositis can also **indirectly impair or reduce the success of antineoplastic treatment, limiting the patient's ability to tolerate therapy itself.** (52) The search for mucositis control therapies is essential because **interruptions in radiant or chemotherapy treatments** favor the repopulation of neoplastic cells, **resulting in a reduction in tumor control.** (53)

To ensure compliance with oncological treatment and avoid potentially lethal complications, it is necessary to support the patient in nutrition and hydration, manage painful symptoms and infections. (11) (35)

Despite the strong impact on the quality of life of patients, mucositis tends to resolve spontaneously between the second and fourth weeks after the end of radiotherapy. In patients undergoing radio-chemotherapy treatments, the complication may arise earlier, take a more severe clinical course, and persist longer. In severe cases, it may be necessary to put patients in intensive care. (55) (56) (9)

VI

Prevention and management

Patients who could suffer from oral mucositis must be managed by a multidisciplinary team. Good communication between all members of the team is essential – dentists, oral-maxillofacial surgeons, dental hygienists, general practitioners, oncologists and nutritionists.

Dentists play an active role in the management of oral mucositis– they help prevent the onset of the disease, manage disease progression, alleviate symptoms and avoid secondary infections. Their role helps support cancer therapy compliance and the maintenance of good oral health. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) has issued clinical practice guidelines for the management of mucositis secondary to cancer therapy. The new guidelines are based on an extensive systematic review of the literature and provide professionals an evidence-based tool to help with the management of mucositis. They cover the following interventions from **basic oral care** to **specific therapies** like laser or cryotherapy. (Table 2) [57] [58].

Basic Oral care

The ISOO guidelines suggest different oral care recommendations in function of the treatment pathway - before, during or after the chemotherapy or radiotherapy [61].

Overall, basic oral care includes all routine actions performed by the patient or care provider to reduce the bacterial load in the oral cavity, prevent infections, and provide comfort.

Basic oral care includes all routine actions performed by the patient or care provider to reduce the bacterial load in the oral cavity, prevent infections, and provide comfort. Included are:

Mechanical cleaning (tooth brushing, interdental cleaning)

Rinsing with mild mouthwashes, without chlorhexidine (CHX), to reduce bacterial build-up

Application of moisturizing agents for hydration of the oral mucosal surfaces. [60]

VI

Prevention and management

1) Mechanical cleaning:

- Interdental cleaning: at least once a day if the patient is able.
- Brushing with a soft toothbrush and fluoride toothpaste to avoid tooth decay - if possible, twice a day after meals and before bed.
- A clean moist gauze or foam swab soaked in mouthrinse can be used to clear the mouth.
- If the patient cannot bear toothpaste, she/he can use a bland mouth rinse. Even if sore, the mouth will benefit from daily oral care.

2) Rinsing with a mild mouthwash after brushing, flossing and eating or every 1-2 hours while awake, or even more if the mucus is thick. The ISOO guidelines suggest a recipe for a bland mouthrinse based on baking soda. The data in the literature on the use of saline-based rinses or baking soda is limited but experts agree that they can support oral hygiene and give patients a feeling of relief, also reducing xerostomia.

The ISOO recommends as mouthrinse a bland recipe [61]**:**

- 1 level teaspoon (5 mL) of salt
- 1 level teaspoon (5 mL) of baking soda
- 4 cups (1 L) of water

The mix is kept at room temperature in a closed container and renewed every day.

3) Moisturizing:

- Nasal passages can be moisturized through the night with a steam vaporizer in the room.
- Oral moisturizing can be achieved with a mouth rinse and water-based lubricants.
- Lip Care can be done with water-soluble, wax-based, or oil-based lubricants

4) Patient education

The ISOO guidelines also underline the importance of patient education in supporting compliance with recommended oral care during cancer therapy. Although the data in the literature on the role of professional dental hygiene in the prevention of oral mucositis is not sufficient to define a specific guideline, experts agree that the support of a dentist is indicated to prevent the risk of local or systemic infections caused by oral infections. [57]

VI

Prevention and management

Topical Soothing agents

The ISOO guidelines suggest some analgesics and natural agents. (Table 2) [57] [58]

- **Analgesics:** new evidence supports the suggestion in favor of topical morphine.
- **Natural and Miscellaneous Agents:** Honey is suggested for the prevention of oral mucositis in patients with head and neck cancer who receive treatment with either radiotherapy or radiotherapy - chemotherapy
- **Chewing gum is not suggested** for the prevention of oral mucositis in pediatric patients with hematological or solid cancer who receive chemotherapy.

Aside from these suggestions from the ISOO, there are also other topical agents that can help soothe and protect the mucosa.

- **Protective mucosal agents:** drug-free topical agents that deploy their action mainly by forming **a protective barrier over the intact mucosa to protect it** during radiation therapy and over the breached mucosa after outburst of oral mucositis. These topical agents have been reported to provide a safe and gentle approach to reduce oral mucositis and its associated symptoms.

Other interventions

- **Anti-inflammatory agents:** Benzydamine mouthwash is suggested for the prevention of oral mucositis in patients with head and neck cancer receiving a moderate dose of radiotherapy or radiotherapy – chemotherapy [57].
- **Photobiomodulation:** Low-laser therapy is used to modulate tissue response, inhibiting mechanisms such as tissue healing, inflammatory responses, and pain [59]. While this is a rapidly growing field, research indicates that this technology is only able to prevent the onset of oral mucositis in specific patient populations and only if protocols are followed with extreme precision [57].
- **Cryotherapy:** Cryotherapy is based on the application of ice cubes or cold water on the oral mucosa, to obtain a vasoconstriction of the superficial blood vessels, thereby limiting the spread and concentration of cytotoxic drugs in the cooling area; because cooling and vasoconstriction are temporary, this treatment option is only useful if the drug is administered in a short period of time or if it has a short half-life. [57] [60]
- **Growth Factors and Cytokines:** New evidence was identified for the keratinocyte growth factor-1.

MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy

Treatment	Level of Evidence	Guidelines and recommendations
Basic Oral Care		
Oral hygiene	III	Suggested
Chlorhexidine Rinse	III	Not recommended
Anti-inflammatory agents		
Benzidamine	II	Recommended
Photobiomodulation		
Low Level Laser Therapy	I/II	Recommended
Cryotherapy	II	Recommended in patients subjected to conditioning with high doses of melphalan and/or F-5U
Analgesics		
Morphine 0.2%	III	Suggested for pain treatment
Growth factors and cytokines		
KGF-1	I	Recommended
Natural agents		
Glutamine	II	Can be used with caution in patients with T-C neoplasms undergoing RT-CT treatments (high mortality observed in patients treated with TCSE undergoing parenteral administration of glutamine)
Honey	II	Advised
Chewing-gum	III	Not recommended

Table 2: Therapeutic and preventive options to counteract oral mucositis – Adapted from Elad et al [57]
F-5U, 5-fluorouracyl; CT, chemotherapy; KGF-1, keratinocyte growth factor-1; RT, radiation therapy; T-C, head-neck; TCSE, hematopoietic stem cell transplantation; Level of Evidence (I, higher; II, medium; III, lower).

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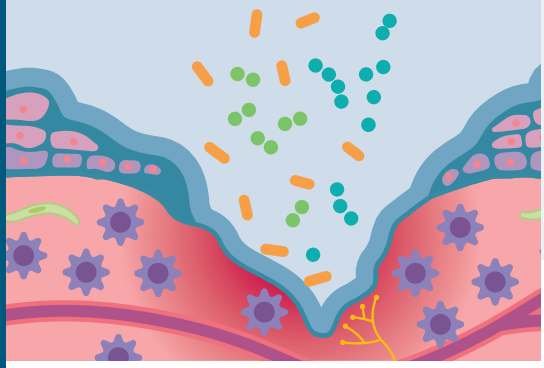
Colita et al, Single-center, retrospective study on 149 patients: "A retrospective study to evaluate the effects of gelX Oral Spray in the management of chemotherapy and radiation therapy induced oral mucositis"

The gelX® formulation relieves pain



Biomechanical benefits:

- Provides a bioadhesive barrier for durable protection
- Coats oral lesions to soothe and relieve pain
- Promotes healing of lesions
- Protects ulcerated tissue from further insult and bacterial colonization
- Alcohol free

1) Dragomir M., GelX Oral Spray in prevention and treatment of chemotherapy - induced oral mucositis in children with cancer - Institute of Oncology, Bucharest, Romania: ECCO Vienna 2015 poster presentation.
2) Dragomir et al, Single center, open-label safety and efficacy. "The efficacy of PVP – zinc gluconate and taurine gel (GelX) in prophylaxis and treatment of oral Mucositis in children treated with chemotherapy" - Poster at EHA June 2015, Vienna.
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5) Cozzi C., Della Torre S., Zannier F., Rota S., Final Study report: Study to evaluate the effects of 3 products in the prevention and treatment of chemotherapy and radiation therapy-induced oral mucositis
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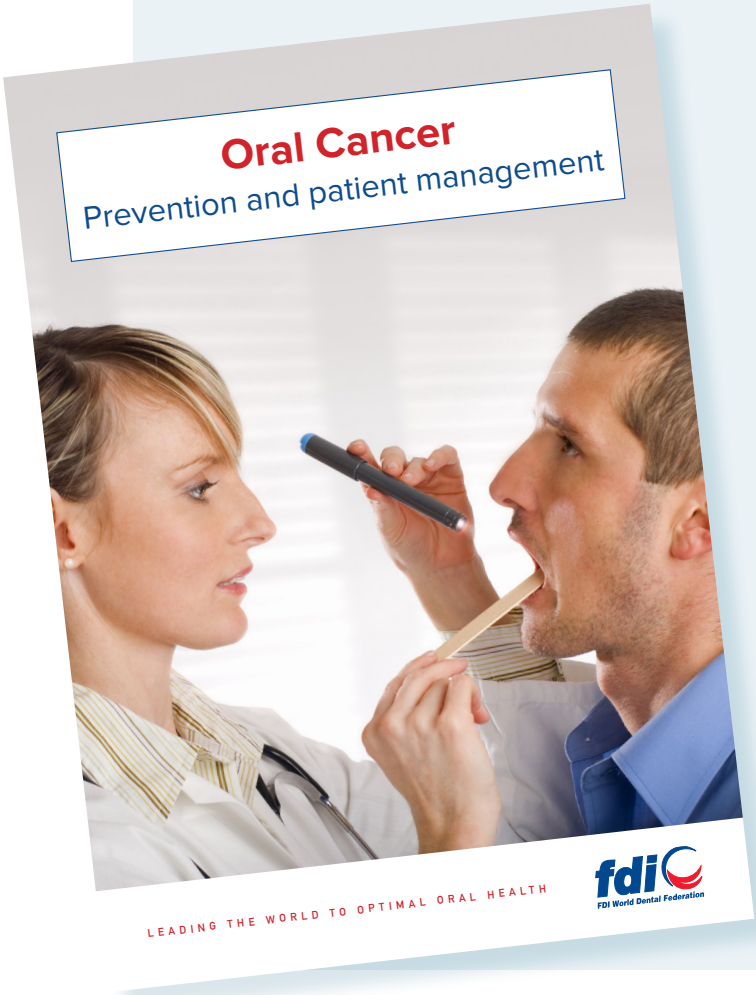
Annex : FDI/Sunstar guidelines on oral cancer

In 2018, Sunstar and FDI World Dental Federation launched **Oral Cancer: Prevention and patient management**, a toolkit for oral health professionals that aims to mitigate the effects of oral cancer by **promoting comprehensive oral cancer screenings as an integral part of routine dental check-ups**. It highlights the most common risk factors for oral cancer and underlines the **importance of early diagnosis and treatment** by providing practical solutions for the care pathway.

The chairside guide provides information about oral cancer prevention, risk factors and management, and also helps them navigate the clinical examination and diagnosis through a decision tree. It focuses on the most common sites of oral cancer: the tongue, the insides of the cheeks, and the floor of the mouth.



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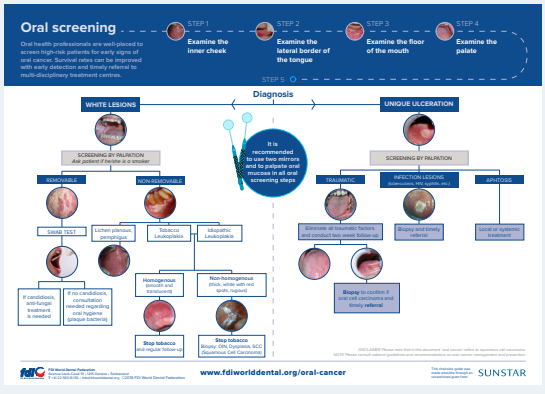

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