

# Treatment and Prevention of Oral Mucositis: A Literature Review

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## Abstract

Oral health is a cardinal element of nutritional as well as systemic well-being and plays a substantial part in sustaining optimum general health condition. Various factors influence oral health including metabolic diseases such as endocrine, hematological, gastrointestinal, cutaneous, and neurological diseases. The intent of this review is to highlight the treatment as well as prevention strategies for one of the most devastating repercussions of chemotherapy (CT) and radiotherapy (RT) on the oral cavity in the form of oral mucositis (OM). A review of literature was performed using relevant key words ("Mucositis" OR "Oral Mucositis" OR "Oral Stomatitis" AND "Treatment of Mucositis" OR "Treatment of Oral Mucositis" OR "Treatment of Oral Stomatitis" AND "Prevention of Mucositis" OR "Prevention of Oral Mucositis" OR "Prevention of Oral Stomatitis") in prominent journals pertaining to Oncology and Dentistry (*CA: A Cancer Journal for Clinicians*, *Cancer*, *Frontiers in Oncology*, *Journal of Clinical Oncology*, and *Oral Oncology*). It is basically sequelae of CT, RT, and radiochemotherapy in patients suffering from malignant diseases as well as those who require hematopoietic stem cell transplants. In addition to its negative effects on the oral cavity and consequently on the overall quality of life, OM may lead to delay in cancer treatment which incriminates in a poor prognosis of the disease.

**Keywords:** Oral mucositis, prevention, treatment

## INTRODUCTION

Mucositis (sometimes referred to as stomatitis) is a condition of inflammation and deterioration of the mucous membrane lining of the gastrointestinal tract and oral cavity.<sup>[1]</sup> It is almost an inevitable after the effect of high-dose radiation therapy. The major determining factor, whether oral mucosa or gastric mucosa will be affected, is the cancer treatment regimen that is being employed. Apart from being caused by chemotherapy (CT) and radiotherapy (RT), mucositis can also occur in people receiving bone marrow transplants (BMTs).<sup>[2]</sup>

## LITERATURE SEARCH METHODOLOGY

An electronic search was performed, from January 1990 to December 2018, to identify articles on the treatment and prevention protocols for CT- and RT-induced oral mucositis (OM). Related articles published in the English language and prominent oncology as well as dentistry journals were included.

- *CA: A Cancer Journal for Clinicians*
- *Cancer*
- *Frontiers in Oncology*

- *Journal of Clinical Oncology*
- *Oral Oncology*.

The keywords used for the search strategy are as follow:

- "Mucositis" OR "Oral Mucositis" OR "Oral Stomatitis"
- "Treatment of Mucositis" OR "Treatment of Oral Mucositis" OR "Treatment of Oral Stomatitis"
- "Prevention of Mucositis" OR "Prevention of Oral Mucositis" OR "Prevention of Oral Stomatitis."

## TREATMENT OF ORAL MUCOSITIS

Any single agent has not been recommended by the United States food and drug administration (US-FDA) to treat OM. Reduction of symptoms and prevention of complications, including pain control, combating secondary infections, nutritional support, and prophylaxis are regarded as

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**Table 1: Prevention and management options of oral mucositis**

Prevention	Management
Oral hygiene maintenance	Locally applied agents (glycyrrhetic acid/sodium hyaluronate gel)
Cryotherapy	L-glutamic acid
Keratinocyte growth factor	Manganese superoxide dismutase
Amifostine	Local anesthetics
Helium-neon laser	Oral and systemic anesthetics
IMRT	Antibacterials, antifungals, and antivirals
Miscellaneous protocols	Cellular therapies
IMRT – Intensity-modulated radiation therapy	

the cornerstone in the management of OM [Table 1].<sup>[3]</sup> According to recently updated evidence-based clinical and preclinical investigations, these agents are discussed as follow.<sup>[4]</sup>

### Locally applied agents

Glycyrrhetic acid/sodium hyaluronate gel has a mechanical effect in pain management associated with OM. It soothes oral lesions by adhering to the mucosal surface of the oral cavity. Nevertheless, there are controversies related to the preclinical studies, and only one clinical testing without any known result was carried out until now.<sup>[4]</sup>

### L-Glutamic acid

It is a nonessential amino acid that neutralizes RT-induced metabolic deficiencies.<sup>[5]</sup> Locally administered L-glutamine alleviated RT-induced OM in randomized clinical experiments.<sup>[6]</sup> Oral suspension of glutamine powder was approved for topical use by the US-FDA for management of CT-induced OM.<sup>[7]</sup>

### Manganese superoxide dismutase

It acts as a detoxifying agent and removes reactive oxygen species (ROS). It was believed of having radioprotective effects against RT-induced colitis, eye and intestinal injury, hepatic cells apoptosis, and esophagitis.<sup>[8]</sup> Phase 1 dose escalation research of GC4419 in conjunction with RT/CT for squamous cell carcinoma of head and neck has recently been finished awaiting release of results (NCT01921426).

### Local anesthetics

For the purpose of short-term pain relief associated with OM, local anesthetics such as lidocaine, diphenhydramine, xylocaine, and dyclonine hydrochloride are used, despite the fact that they may meddle with sensation of taste leading to hypoalimentation.<sup>[9]</sup>

The magic mouthwash, benzocaine-containing lozenges, and morphine mouthwashes are preferably being used for lessening oral pain associated with OM.<sup>[10]</sup>

Promising results are shown by the application of corticosteroid mouthwashes, but there is a gap related to its large-scale data availability that should be connected by relevant clinical trials.<sup>[11]</sup>

In mild cases of Radiation-induced oral mucositis (RIOM), artificial saliva spray is frequently used to reduce mucosal dryness.<sup>[12]</sup>

Chamomile has antiseptic, antibacterial, anti-inflammatory, and anti-spasmodic effects. In CT-induced mucositis, it has investigated as an emulsion therapy with encouraging result.<sup>[13]</sup> However, studies are required for its use in RIOM for determining its efficacy.<sup>[4]</sup>

Honey has a mucoprotective effect. It has been investigated in several preclinical trials that is reduces the severity and incidence of RIOM.<sup>[14,15]</sup> However, when Manuka honey was used, the available clinical trial contradicted the preclinical studies' results.<sup>[16]</sup> More research is needed to ensure honey's therapeutic potential in RIOM.<sup>[4]</sup>

Vitamin A (retinol) and its derivatives have epithelial proliferative and anti-inflammatory effect.<sup>[17]</sup> During BMT, topical tretinoin has shown to alleviate oral complications.<sup>[18]</sup>

Tocopherol (Vitamin E) reduces the oxidative injury of the oral mucosa and lessens the risk of symptomatic RT-induced OM in head-and-neck carcinoma patients in randomized, double-blind clinical experiments.<sup>[19]</sup>

A randomized clinical trial showed that sodium alginate mitigates severity and pain of RIOM.<sup>[20]</sup>

Povidone-iodine, an antifungal, antiviral, and antibacterial agent, curtails the duration, incidence, and severity of concurrent chemoradiotherapy (CCRT)-induced OM. Furthermore, it is economical and easily applied.<sup>[21]</sup>

Capsaicin, a neutrophilic inhibitor, diminishes pain sensation. One clinical study showed that oral capsaicin temporarily relieved pain associated with mucositis caused by RT and CT.<sup>[22]</sup> However, further research is required to enhance its analgesic effect.<sup>[4]</sup>

### Oral and systemic analgesics

Cyclooxygenase-2 (COX-2) inhibitors, having a different mechanism of action, were practiced in the management of RIOM. They suppress nuclear factor-kappaB (NF-κB), inhibit angiogenesis, and tapper off cytokine generation.<sup>[23]</sup> A randomized placebo-controlled experiment demonstrated that indomethacin, a COX-2 inhibitor, significantly abated the severity and deferred the onset of RIOM.<sup>[4]</sup>

Moreover, prostaglandin E1 and E2 demonstrated improvement in CT/RT-induced OM in some studies, but there are still controversies associated with their application.<sup>[24]</sup>

N-acetylcysteine, an antioxidant that suppresses activation of NF-κB,<sup>[25]</sup> has a radioprotective function in RT-induced liver toxicity, dermatitis, intestinal injury, and bone injury,<sup>[26]</sup> and hence, it was recommended as a nominee for a trial in RIOM. In a placebo-controlled Phase 2 experiment done on patients suffering from head-and-neck carcinoma, N-acetylcysteine significantly mitigated the severity of RIOM.<sup>[27]</sup>

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and CSF recruit neutrophils to the site of tissue injury when administered systemically.<sup>[28]</sup> In several studies, when GM-CSF mouthwash is applied locally, it remarkably relieved RIOM.<sup>[29]</sup> However, some other studies did not demonstrate the same result.<sup>[4]</sup> Controversies surround the therapeutic potential of GM-CSF when applied systemically and necessitates further research.<sup>[4]</sup>

Transforming growth factor- $\beta$ 3, inhibitor of oral basal cell proliferation, mitigates the risk of CT-induced OM.<sup>[30]</sup> However, a valid clinical trial is necessarily required to evaluate its therapeutic potential in RT.<sup>[4]</sup>

In a randomized clinical experiment, antioxidative effect of beta-carotene<sup>[31]</sup> was implemented and it showed a significant alleviation in the risk of OM in CCRT.<sup>[32]</sup>

Analgesics are a substantial contender for pain relief associated with RIOM.<sup>[33]</sup>

Azelastine, a potent histamine antagonist, anti-inflammatory, and antioxidant have been demonstrated as a reliable agent in lessening the severity and risk of OM with CCRT.<sup>[4]</sup>

Immunoglobulins, which act as immune modulators and anti-inflammatory agents, are administered intramuscularly or intravenously as a therapeutic and prophylactic option for RT-induced OM.<sup>[4]</sup>

## Agents for alleviating oral microbial burden

### Antimicrobial agents

A fast track designation has been granted for brilacidin-OM (an oral rinse) by FDA. To assess its efficacy and safety, there is a Phase 2 clinical trial being carried out (NCT02324335).

### Antifungal agents

Although they do not contribute directly in development of RIOM, yet they can complicate the condition, especially in patients who are immunocompromised. Fluconazole, clotrimazole, and amphotericin B play a handful role in reducing the severity of RIOM.<sup>[4,29,34]</sup> However, carrier allergy of amphotericin B limits its application.<sup>[35]</sup>

### Antibacterial agents

The main culprits in the generation of secondary infection stage in RIOM are aerobic species (e.g., *Staphylococcus epidermidis* and *Pseudomonas* spp.), endotoxins of aerobic Gram-negative bacilli, and anaerobic bacteria (e.g., *Veillonella* spp., and *Bacteroides* spp.).<sup>[29]</sup> Mouthwashes containing ciprofloxacin, ampicillin, and tobramycin have demonstrated symptoms relieving effects in RIOM.<sup>[4,36-38]</sup>

### Antiviral agents

Herpes simplex virus type-1 and varicella-zoster virus are most frequently seen viral infections in individuals who are myelosuppressed and seropositive.<sup>[39]</sup> A marked diminishing of the oral herpetic infections was noted when acyclovir was administered topically and systemically. However, no prophylactic role was evident against OM itself.<sup>[40]</sup>

## Cellular therapies

Bone marrow-derived mesenchymal stromal cells (BM-MSCs) therapy has been employed in fractionated RT-induced OM, where the application systemic single dose of 6 million mesenchymal stromal cells (MSCs) resulted in a compelling reduction in ED50 (the RT dose that formed ulcer in half of the irradiated mice).<sup>[41]</sup> The first ever MSCs therapy was performed in 2014.<sup>[41]</sup> They reckoned that transplantation of bone marrow or BM-MSCs s could regulate RIOM in fractionated RT, depending on transplantation time.<sup>[41]</sup> Nonetheless, in another research, the researchers came to a conclusion that there are no therapeutic advantages of BM-MSCs on RIOM in single-dose RT as compared to the therapeutic impact of the operation of endogenous bone marrow stem cells.<sup>[42]</sup> On the bedrock of initial studies, more research is required in this area.<sup>[4]</sup>

## PREVENTION OF ORAL MUCOSITIS

Along with curtailing the progression of OM, its risk can also be prevented by maintaining good oral hygiene. We will review contemporary measures and agents for preventing OM<sup>[4,43]</sup> [Table 1].

### Good oral hygiene

It has been proved as one of the most efficient methods to lessen the risk of OM and attenuate its advancement. Pre-existing oral pathology, for instance, xerostomia, dental caries, pulpal disease, and periodontal lesions are associated with escalated bacterial colonization and severe OM. Before initiating any mucotoxic therapy for cancer, it is recommended to have an early oral inspection. To alleviate the adverse effects of anticancer therapy on the oral cavity, it is proposed to eradicate any preexisting oral pathology before commencing RT. This may be attained by executing early serological, histological, microbiological, and cytological examinations.<sup>[29]</sup>

The International Society of Oral Oncology (ISOO) and Multinational Association of Supportive Care in Cancer (MASCC) guidelines suggest the application of standardized oral care protocol, for example, flossing, use of toothbrush having soft bristles, and utilization of nonmedicated rinses (NaHCO<sub>3</sub> and saline).<sup>[3,4]</sup> It is summarized as follows:

- Daily brush with an ultrasoft toothbrush with fluoride toothpaste
- Scaling
- Rinse by using nonirritating solution, that is, saline to enhance the quality of saliva
- Soft diet having low sugar content
- Non-acidic drinks and food
- Flossing is not advised as platelet count is low
- Minimum use of denture
- No smoking or alcohol
- Other preventive methods such as reducing the microbial load and patient education on good oral hygiene.

A summary of diet and habits that are acceptable as well as nonadmissible during OM is given in Table 2.

**Table 2: Recommended diet in patients with oral mucositis**

Admissible diet	Nonadmissible diet	Nonadmissible habits
Eggs	Salty food	Tobacco smoking
Cheese	Acidic fruits (lemon, orange, etc.)	Alcohol consumption
Fresh juices	Spicy food	Betel quid chewing
Ice	Junk food	Cheek biting
Nonacidic fruits (mango, banana, etc.)		

### Cryotherapy

Cryotherapy has been proposed for CT-induced OM, but no establish role in RIOM inadequate evidence.<sup>[4]</sup> Recent studies have proven the use of cryotherapy for preventing OM in patients who received 5-fluorouracil. Cryotherapy is also suggested in individuals who will experience high doses of melphalan for BMT.<sup>[44]</sup>

### Keratinocyte growth factor

An epithelial mitogen, that is, keratinocyte growth factor (KGF) plays a vital role in the reduction of ROS by activation of Nuclear factor (erythroid-derived 2)-like 2 and had been utilized in radiation-induced OM with promising results.<sup>[45]</sup> It seems to be one of the most auspicious preventions and treatment options for radiation-induced OM that has been examined in clinical trials.<sup>[4]</sup> Palifermin (IV recombinant human KGF-1) had been recommended by US-Food and Drug Authority (FDA) for reducing the risk of OM in patients with hematological malignancies who are receiving myelotoxic therapies and need hematopoietic cell support post reliable results in lessening WHO Grade 3 and 4 OM in such patients. Palifermin is delivered intravenously 3 days before RT/CT and for 3 days after CT. Palifermin should not be administered on the same day of CT/RT.<sup>[27]</sup>

### Amifostine

Amifostine has three distinct properties, i.e., cytoprotective agent, free-radical scavenger, and antioxidant. It is conventionally administered intravenously before RT or CT. It is recommended by the US-FDA to alleviate the cumulative renal toxicity related with frequent administration of cisplatin with individuals having advanced ovarian carcinoma. Moreover, it is also approved in alleviating the risk of mild-to-severe xerostomia in individuals who are undergoing postoperative RT for head and neck cancer.<sup>[46]</sup> For mild-to-severe RT-induced xerostomia, its approved dose is 200 mg/m<sup>2</sup> QD over 3 min intravenously, initiating 15–30 min before standard fraction RT (1.8–2.0 Gy). Monitoring of blood pressure is imperative before, during, and after intravenous infusion. Oral administration of 5-HT<sub>3</sub> receptor antagonists is suggested before amifostine therapy.<sup>[47]</sup>

### Helium–neon laser

Low-energy helium–neon laser exercised before RT showed a substantial decline in duration and intensity of radiation-induced RT in head and neck cancer patients.

The MASCC/ISOO guidelines propose the utilization of low-level laser technique in CT-induced OM at institutions that can administer the essential technology as well as training.<sup>[4]</sup>

### Miscellaneous protocols

Intraoral appliances (radiation shields), 3D and RT field design, removal of prosthetics, midline mucosa-sparing blocks, and intensity-modulated radiation therapy are proven in preclinical research to lessen the radiation scatter and radiation-induced OM injury.<sup>[27]</sup>

### Future prospects

Given the magnitude of the problem, oral repercussions of RT/CT are a grave concern for the public health all over the world. Their effect on individuals as well as communities due to suffering and pain, alleviated quality of life, and inability to function properly they inflict, is substantial. An extensive and exhaustive research is being done on this very topic of concern worldwide as some influential breakthroughs have been made, but there is a dire need to transform these researches into practical and clinical application.

In the contemporary era of innovation, much emphasis is being laid on the formulation of novel and offbeat techniques. Recently, there has been the development of anti-interleukin (IL)-6 antibodies and fragments having binding precision of IL-6 for prevention and treatment of OM. Likewise, tumor necrosis factor (TNF)-specific antibody is also being assessed for early interception and treatment of OM. It is believed that the inflammatory response will be shut down by the anti-TNF antibody. However, there is a set of clinical trials waiting for these novel agents.

### CONCLUSION

The oral cavity is one of the major sites of the human body, where RT and CT can wreak havoc. OM is almost an inevitable negative repercussion of CT, RT, and radiochemotherapy. Oral complications of RT/CT, that is, mucositis is almost imminent, but their incidence and severity can be lessened by regularly visiting physician and dentist. The role of a dentist should never be underestimated or ignored in such instances as he/she plays a crucial role in preventing as well as management of oral disorders associated with RT/CT. Proper prophylaxis and management may prevent the intensity of OM and eventually leads to a better disease control.

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