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Review Article

A Comprehensive Review of Oral Mucositis and its Management

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Abstract: Haematopoietic stem cell transplantation, chemotherapy, and radiation therapy are frequently linked to the crippling condition known as oral mucositis (OM). It can seriously impair quality of life and possibly interfere with cancer treatment plans. It manifests as painful ulceration, erythema, and oedema. Microbiota dysbiosis, oxidative stress, and inflammatory pathways are all intricate components of the pathophysiology of OM. Its severity is influenced by several risk factors, such as chemotherapy, radiation dosage, genetic predisposition, and oral hygiene. There is still no ideal gold-standard treatment for it, despite its high prevalence. Pharmacological interventions like cytoprotective agents, anti-inflammatory medications, growth factors, biological response modifiers, and antimicrobial agents are all part of the multimodal approach used in current management strategies. Low-level laser therapy (LLLT), cryotherapy, and dental hygiene practices are examples of non-pharmacological methods that have demonstrated promise in reducing symptoms and enhancing patient outcomes. Recent developments in OM pathophysiology and treatment approaches are compiled in this review, which highlights the importance of tailored, evidence-based treatment plans. To improve patient care and reduce OM-related morbidity, more research is necessary to create innovative, affordable, and widely recognized treatments.

Keywords: Oral mucositis, chemotherapy, radiotherapy, pathophysiology, inflammatory pathways, low-level laser therapy (LLLT), cryotherapy, biological response modifiers.

INTRODUCTION

A specialized mucous membrane called the oral mucosa lines the structures of the oral cavity. It extends from the labial mucosa and vermilion edge of the lips in the front to the palatopharyngeal folds in the back. This soft, wet membrane acts as a barrier against biological, chemical, and mechanical stresses, and it is essential to preserving the integrity of the oral environment. The submucosa, lamina propria, and oral epithelium are the three layers that make up the oral mucosa histologically. A stratified squamous epithelial layer, the oral epithelium varies in thickness and degree of keratinization according to its function and location. (Groege S *et al*., 2019). The layer of connective tissue beneath it, known as the lamina propria, contains blood arteries, neurons, and immune cells in addition to providing structural support. In some places, the submucosa— which is made up of dense, irregular connective tissue—is located beneath the lamina propria, but it is not present in places like the hard palate and gingiva where the lamina propria directly clings to bone or muscle. (Wang SS *et al*., 2019; AlJulaih GH *et al*., 2023).

The three different forms of oral mucosa—lining mucosa, masticatory mucosa, and specialized mucosa—each have their own structural and functional traits. It performs a number of critical roles, such as shielding the underlying tissues from damaging stimuli, secreting chemicals necessary for preserving oral homeostasis, and permitting the senses of touch, taste, pain, and temperature (Laugerette F *et al*., 2007). Oral mucositis, which is characterized by ulcerations, edema, and erythema, is one of the most incapacitating disorders that affect the oral mucosa. It is a common and serious side effect of radiation therapy, hematopoietic stem cell transplantation, chemotherapy, and chemoradiotherapy that targets the head and neck area (Beech N *et al*., 2014). Patients may need parenteral nutrition in extreme circumstances, as the accompanying pain frequently interferes with oral intake. Furthermore, the mucosal barrier is compromised by the ulcerative lesions, making the patient more vulnerable to systemic and local infections.(Elad S *et al*., 2020; Sonis ST *et al*., 2004;

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Lalla RV *et al*., 2008).According to recent research, an inflammatory cascade mediated by reactive oxygen species (ROS) and innate immune responses is primarily responsible for the pathophysiology of oral mucositis brought on by chemotherapy and radiation therapy (Iglesias-Bartolome *et al*., 2012)The NLRP3 inflammasome is triggered by the generation of ROS in mitochondria in response to bacterial infections and tissue injury(Yoshino *et al*., 2013). Research has demonstrated that radiation-induced oral mucositis can be avoided by inhibiting the mitochondrial ROS/NLRP3 axis, underscoring its significance in the development of the disease (Mariathasan and Monack 2007; Ortiz *et al.*, 2015). The nuclear factor κB (NF-κB) pathway is another important molecular pathway linked to the pathophysiology of oral mucositis. It triggers downstream pattern-recognition receptors like nucleotide-binding oligomerization domain (NOD)-like receptors and Toll-like receptors (TLRs). This pathway contributes to an increased inflammatory response by reacting to both endogenous cell injury and external microbial components (Lotze *et al.,* 2007; Han *et al*., 2013; Luo *et al*., 2019). The complicated pathobiology of oral mucositis in patients receiving chemoradiotherapy is driven by the interaction of several important inflammatory pathways, which creates a complex regulatory network (Maria *et al*., 2017).

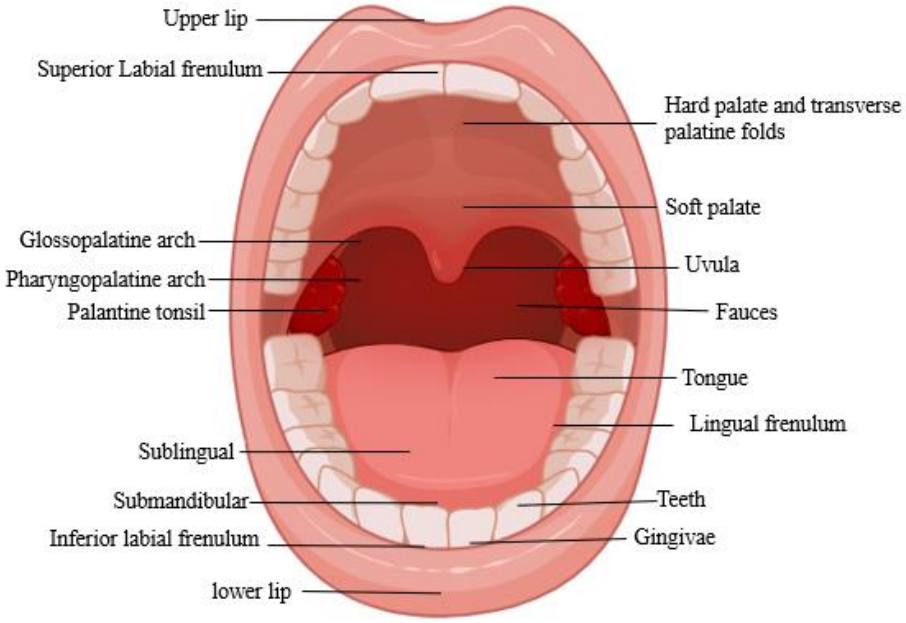

Figure 1: Structure of oral cavity

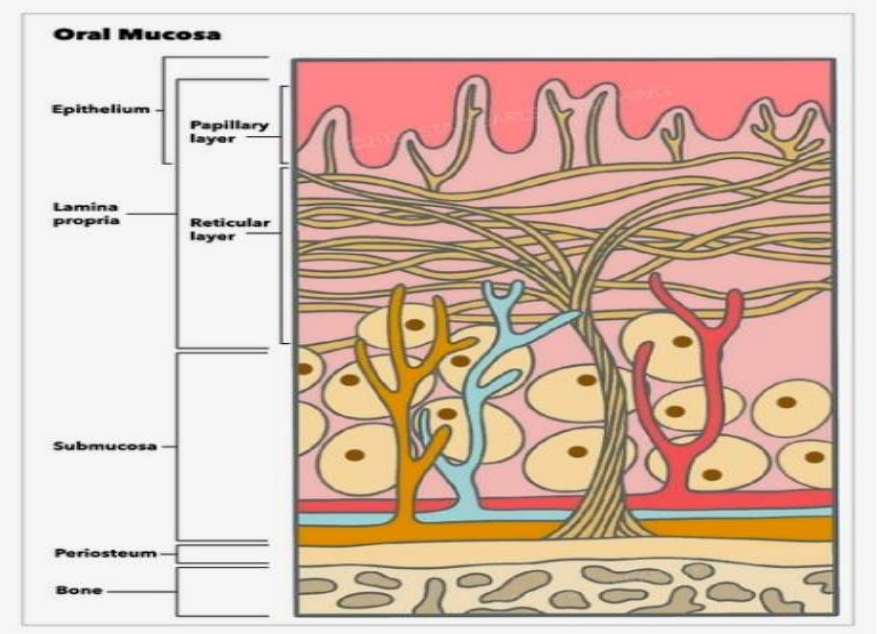

Figure 2: Layers of Oral Mucosa (Melina Brizuela *et al*., 2023)

Immune homeostasis and tissue integrity depend on the host-microbe interaction at the mucosal barriers. One of the most intricate and abundant ecosystems is formed by tooth-adherent biofilms, which are part of the oral cavity's diverse microbial community (Moutsopoulos and Konkel 2018). There is growing evidence that the etiology and severity of oral mucositis caused by chemotherapy and radiation therapy may be influenced by dysbiotic changes in the oral microbiome. Antimicrobial tactics that modify the oral microbiota are therefore becoming more and more popular as possible treatment measures (Vasconcelos *et al*., 2016). Understanding the pathobiology of oral mucositis and creating innovative treatments to lessen its effects on patients with head and neck cancer are the main goals of research efforts. Patients' quality of life is greatly reduced by the severe morbidity linked to oral mucositis, which can even interfere with the delivery of cancer medicines that could save lives (Hong *et al*., 2019). Due to differences in study designs and diagnostic scoring standards, the worldwide prevalence of oral mucositis is still underreported despite its clinical importance. By addressing these issues with tailored therapy approaches and standardized assessment instruments, cancer therapies may become more effective and patient outcomes may be improved (Subramaniam and Muthukrishnan 2019; Vesty *et al*., 2019).

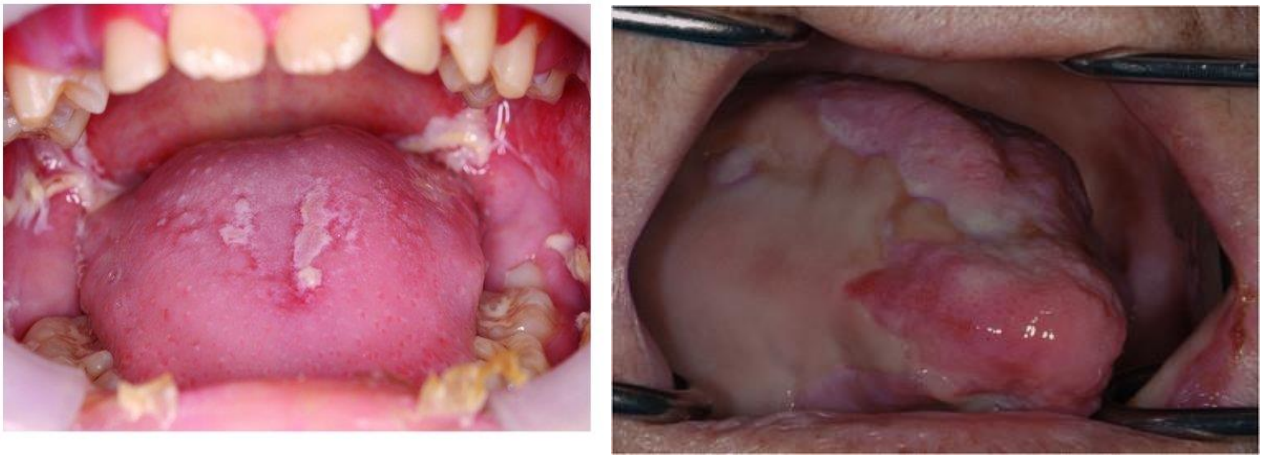

Figure 3: Clinical appearance of Acute and chronic oral mucositis, persistent form (Hai Ming Wong *et al*., 2014) (Sharon *et al*., 2016)

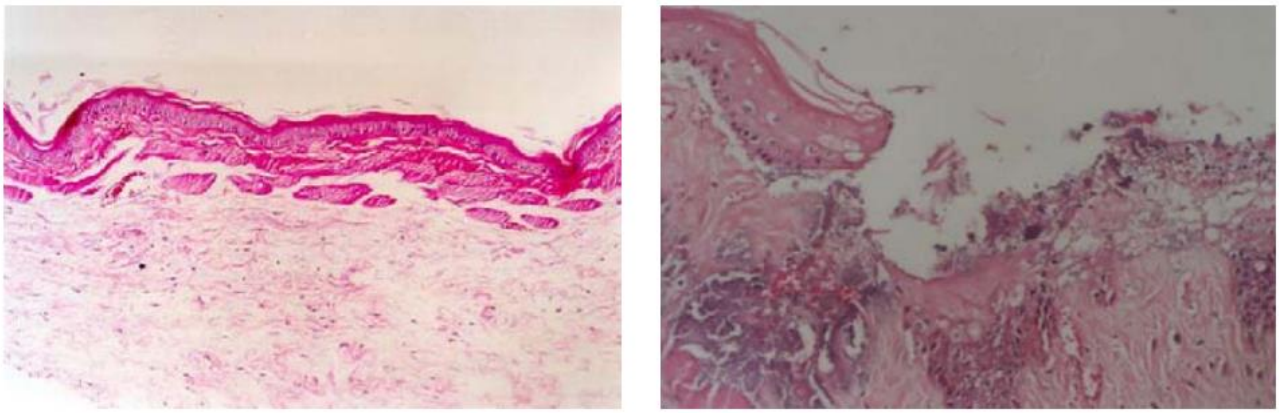

Figure 4: Histological appearance of oral mucosa: (a) Intact healthy mucosa; (b) ulceration and bacterial colonization on the surface of the mucosa (Pelin Aksungur *et al*., 2004)

CLINICAL SIGNIFICANCE OF ORAL MUCOSITIS

Oral mucositis can range in severity from mild erythema with burning and mucosal discomfort to large, deeply eroded ulcers that require high dosages of opioids to treat. All bacteria, viruses, and fungi have been found to thrive in the oral cavity. Mucositis is therefore recognized as a contributing factor to sepsis and bacteremia. Following a cumulative radiation dose, patients receiving chemotherapy and radiation therapy for head and neck cancers exhibit mucosal changes. By the end of the third week, when nearly 30 Gy of radiation is administered, ulcerative lesions start to appear. Mucositis brought on by chemotherapy usually starts 4–5 days after the infusion and peaks 5 days later. Lesions typically only affect non-keratinized surfaces, such as the soft palate, buccal mucosa, and the lateral and ventral surfaces of the tongue. Oral mucositis is more common and more severe when certain substances, such as alkylating agents and antimetabolites, are used.

Because oral mucositis has such severe side effects, patients choose to stop receiving their treatments, which disrupts the oncologist's prescribed regimen. Additionally, there is subpar cancer treatment because of improper management. Days after the infusion and peaks 5 days later. Lesions typically only affect non-keratinized surfaces, such as the soft palate, buccal mucosa, and the lateral and ventral surfaces of the tongue. Oral mucositis is more common and more severe when certain substances, such as alkylating agents and antimetabolites, are used. Because oral mucositis has such severe side effects, patients choose to stop receiving their treatments, which disrupts the oncologist's prescribed regimen. Additionally, there is subpar cancer treatment because of improper management days after the infusion and peaks 5 days later. Lesions typically only affect non-keratinized surfaces, such as the soft palate, buccal mucosa, and the lateral and ventral surfaces of the tongue. Oral mucositis is more common and more severe when certain substances, such as alkylating agents and antimetabolites, are used. Because oral mucositis has such severe side effects, patients choose to stop receiving their treatments, which disrupts the oncologist's prescribed regimen. Additionally, there is subpar cancer treatment because of improper management (Sonal *et al*., 2010).

ETIOLOGY

Oral mucositis is a common and crippling side effect in patients undergoing high dose myeloablative chemotherapy prior to haematopoietic cell transplantation, chemotherapy for solid tumors or lymphoma, and radiation therapy to the head and neck. The type of chemotherapeutic drug employed affects the incidence and severity of oral mucositis(Sonis ST *et al*., 2004). Drugs including 5-fluorouracil, methotrexate, and cytarabine that disrupt DNA synthesis during the S-phase of the cell cycle are known to dramatically raise the risk of mucositis(Naidu MU *et al*., 2004). Patients receiving anthracycline, mTOR inhibitor, alkylating agent, or antimetabolite treatment are also at a higher risk (Valer JB *et al.*, 2004) (Barasch A *et al.*, 2003).

The basal epithelial layer of the oral mucosa is especially vulnerable to radiation-induced damage because of its high rate of cellular turnover. Cell loss and tissue collapse result from the epithelium's incapacity to heal itself when radiation therapy or chemotherapy interferes with normal cell division and regeneration. Oral mucositis consequently causes excruciating ulceration, erythema, and oedema, which severely impair a patient's capacity to speak, eat, and practice good oral hygiene. Additionally, illness may weaken the mucosal barrier, raising the possibility of infections and systemic problems. Oral mucositis has a significant effect on cancer patients receiving therapy; it frequently necessitates dose reductions or treatment delays, which can affect the overall effectiveness of the treatment and patient outcomes (Beech N *et al*., 2014).

PATHOPHYSIOLOGY

According to the five-phase model, tissue damage is the first step in the complicated Pathophysiology of oral mucositis brought on by radiation therapy, chemotherapy, or both (Sonis ST 2007).

The development of oral mucositis progresses through five sequential stages: initiation, signaling, amplification, ulceration, and healing, triggered by radiation and chemotherapy.

1. Tissue injury initiation: Chemotherapy and/or radiation cause cell damage, which kills basal epithelial cells. Furthermore, the production of reactive oxygen species, or free radicals, by radiation or chemotherapy is thought to contribute to the development of mucosal injury. As byproducts of oxygen metabolism, these tiny, extremely reactive chemicals have the capacity to seriously harm cells.
2. Upregulation of inflammation through messenger signal generation: Free radicals not only directly kill cells but also trigger the production of second messengers, which carry messages from cell surface receptors inside the cell. This results in tissue damage, cell death, and an increase in pro-inflammatory cytokines.
3. Signalling and amplification: Proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), which are mostly produced by macrophages, are upregulated, which damages mucosal cells and triggers molecular pathways that intensify mucosal damage.
4. Ulceration and inflammation: There is noticeable inflammatory cell infiltration connected to the mucosal ulceration, partly because of metabolic byproducts of the colonizing oral microbiota. Pro-inflammatory cytokine production is further elevated by this secondary infection (Sonis *et al*., 2000).
5. Healing: This stage restores the integrity of the epithelium and is marked by tissue and cellular differentiation in addition to epithelial proliferation (Dorr *et al*., 1994).

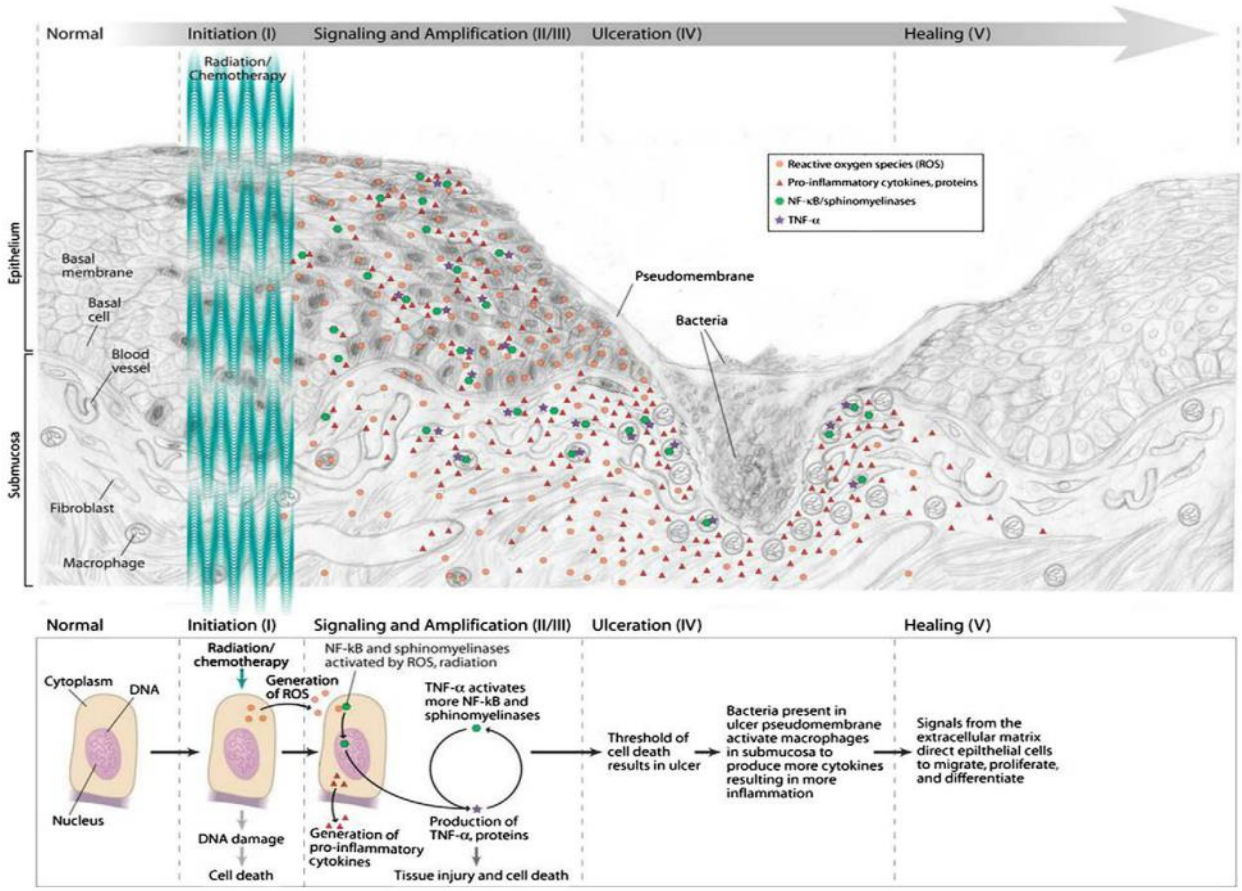

Figure 5: The pathobiology of mucositis as a five-stage process (Sonis, S.T *et al.*, 2009)

Table 1: Pathophysiology of Oral Mucositis

Phase	Description
Initiation	Chemotherapy/radiotherapy causes cell damage, leading to the generation of reactive oxygen species (ROS) and free radicals.
Signalling	ROS triggers secondary messengers that activate pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6).
Amplification	Increased inflammatory response due to NF-κB and NLRP3 inflammasome activation, worsening mucosal injury.
Ulceration	Extensive tissue breakdown, severe pain, and secondary infection due to microbial colonization of ulcers
Healing	Tissue regeneration, epithelial proliferation, and restoration of mucosal integrity.

RISK FACTORS

Mucositis development is impacted by several factors pertaining to patient characteristics and treatment. Certain risk factors have been discovered, but others are still unknown (Barasch *et al*., 2003). The kind, dosage, and timing of systemic cytotoxic medications, radiation dose, field, and the co-administration of chemotherapy and radiation are all treatment-related variables. These variables affect how severe mucositis is; people receiving high-dose chemotherapy or treatment for head and neck tumors frequently develop severe versions of the ailment (Logan RM *et al*., 2009) (Sonis ST *et al*., 2010), While preliminary studies indicate that mucositis may be less severe after reduced-intensity hematopoietic stem cell transplantation, most patients undergoing aggressive cancer treatments remain at high risk (Takahashi *et al*., 2010). Although its prevalence in some solid tumor regimens may be as low as 10%, a number that may be underreported, mucositis affects about 40% of individuals with malignancies other than head and neck cancers. Although its prevalence in some solid tumor regimens may be as low as 10% (Barasch *et al*., 2003), a number that may be underreported, mucositis affects about 40% of individuals with malignancies other than head and neck cancers. The risk of mucositis is also significantly influenced by patient-associated variables (Sonis ST *et al*., 2010), Key contributing factors include age, body mass index, gender, changes in salivary output, poor dental health, and mucosal damage. Furthermore, pre-existing diseases including Addison's disease, diabetes mellitus, and compromised renal function may make a person more

vulnerable (Robien K, *et al*., 2004),. Mucositis risk can also be influenced by the tumor itself, making it more difficult to predict when it will arise in each patient. With studies indicating that genes controlling the metabolism of chemotherapeutic medicines contribute to toxicity risk, genetic variables have drawn more attention (Bogunia-Kubik *et al*., 2003). For example, differences in the enzymes that metabolize folate may be useful in identifying those who are more susceptible to methotrexate-induced mucositis. Although enzyme shortages are not common, mucositis in patients receiving Allogeneic stem cell transplantation has been associated with genetic variants that impact the production of inflammatory mediators such as TNF-alpha (Blijlevens *et al*., 2008).

Table 2: Risk Factors for Oral Mucositis

Category	Specific Factors
Treatment-Related	High-dose chemotherapy, radiation dose >5000 cGy, concurrent chemo-radiotherapy, fractionation schedules.
Patient-Related	Age (elderly at higher risk), genetic predisposition, poor oral hygiene, malnutrition.
Medical Conditions	Diabetes, renal impairment, Addison's disease, low salivary flow (xerostomia).
Tumor-Related	Tumors in the oral cavity, nasopharynx, and oropharynx are associated with a higher risk of mucositis.
Microbial Factors	Dysbiosis of oral microbiota, bacterial colonization of ulcerated mucosa, secondary infections.

Bacterial colonization of ulcerated mucosal surfaces can worsen inflammation and delay healing, making the significance of oral microbiota in the pathophysiology of mucositis another area of consideration. Although neutrophil engraftment has been linked to the length of mucositis in patients after myeloablative cell transplantation, it is still unknown how exactly innate and adaptive immunity contributes to the development of mucositis. Immune responses, genetic predisposition, and microbial effects interact in a complicated way, highlighting the multifaceted character of mucositis and the difficulties in diagnosing and treating it in cancer patients (Blijlevens *et al*., 2008).

CURRENT GLOBAL EPIDEMOLOGY

Usually, for five to fourteen days following treatment, 20% to 40% of individuals with solid tumors receiving chemotherapy develop mucositis (Brown *et al*., 2020). A daily dose of roughly 200 cGy is administered five days a week for five to seven weeks to patients receiving radiation therapy for head and neck cancer. Most of these individuals have some degree of oral mucositis between 29% and 66% of patients have severe cases (Brown *et al*., 2020). Severe mucositis is more likely to occur in:

- Individuals who get more than 5000 cGy of radiation overall.
- Individuals undergo chemotherapy at the same time.
- Individuals with primary tumors in the nasopharynx, oropharynx, or oral cavity.
- Patients receive several daily treatments under modified fractionation radiation schedules. The patient's capacity to eat, drink, and speak may be severely impacted by these conditions, which may aggravate mucosal damage and the severity of mucositis (Elting *et al*., 2007).

EVALUATION

The results of the physical examination and clinical history are utilized to evaluate for oral mucositis. The lab and radiography are less helpful. If ulcers are discovered on the hard palate, connected gingiva, or dorsum of the tongue, cultures should be taken to rule out a fungal or viral cause (Lalla *et al*., 2008).

The severity of mucositis is measured using a well-defined scale, and several scales have been developed.

Criteria for Common Terminology in Adverse Events (CTCAE) The CTAE was developed by the National Cancer Institute (NCI) and uses a 1–5 scoring system. This scale consists of two parts: a clinical exam and a functional/symptoms-based assessment.

Functional/Symptoms-Based Exam

- **Grade 1:** The patient continues to eat regularly, the symptoms are minimal or nonexistent, and no action is necessary.
- **Grade 2:** Moderate discomfort or an ulcer that necessitates a changed diet but does not impair swallowing.
- **Grade 3:** Excruciating pain that hinders oral intake and necessitates medical care.
- **Grade 4:** Mucositis that is life-threatening and needs to be treated right away. Death is grade five.

Clinical Assessment

- **Grade 1:** Mucosal erythema, or redness, without obvious ulceration.
- **Grade 2:** Patchy ulceration or pseudomembranes are present.
- **Grade 3:** Minor wounds that result in bleeding, confluent ulcers, or pseudomembranes.
- **Grade 4:** Life-threatening circumstances involving tissue necrosis or spontaneous bleeding;
- **Grade 5:** Death

WHO Scale of the World Health Organization
The WHO scale evaluates oral mucositis using both objective and subjective metrics:

- **Grade 1:** Soreness and erythema (grade 0 means there is no mucositis).
- **Grade 2:** The patient has ulcers but is still able to eat solid food.
- **Grade 3:** Ulcers that need to be fed just liquids.
- **Grade 4:** Severe ulcers that make eating impossible.

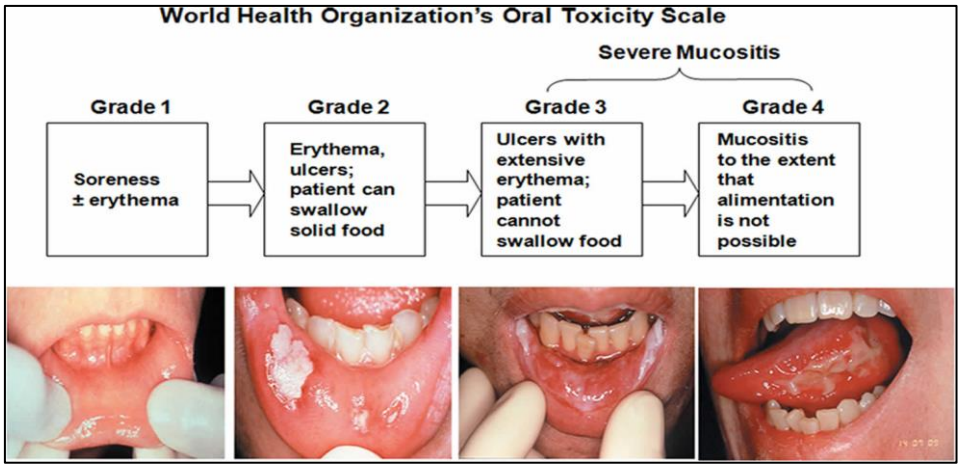

Figure 6: Visual Representation of WHO grading for Oral Toxicity Severity Levels (Maria *et al*., 2017)

TREATMENT

For the treatment of oral mucositis (OM), the US Food and Drug Administration (US-FDA) has not suggested a single all-purpose medication. Rather, its management emphasizes a multimodal strategy to prevent complications and lessen symptoms. Pain management, preventing secondary infections, providing proper nutritional support, and putting preventative measures in place to lessen the intensity and duration of symptoms are all essential components of effective OM treatment (Ahmad *et al*., 2019). Numerous treatment options, including pharmacological and non-pharmacological interventions, have been strongly supported by recent clinical and preclinical studies. These studies highlight the value of individualized treatment plans that consider the severity of OM, the underlying cause, and patient-specific risk factors. Research developments keep improving treatment plans and providing better ways to enhance patient outcomes. (Rodríguez-Caballero *et al*., 2012).

The following are the primary methods and medications that have been documented in the literature during the past ten years to prevent and/or treat OM brought on by chemotherapy:

Oral hygiene protocols in addition to being essential for preserving general oral health, oral hygiene practices can also greatly aid in the treatment of oral mucositis (OM). Frequent dental care reduces the risk of secondary infections, minimizes pain and bleeding, and helps lessen the presence of harmful microbial flora. Preventing dental complications, which can worsen the condition and slow healing, is another reason to maintain good oral health. Although maintaining good dental hygiene is generally advised as a supportive measure in the management of OM, its ability to either prevent the onset of the condition or significantly lessen its severity is still up for debate. Routine dental care may help reduce the frequency and severity of OM, according to some research, but other studies show little to no benefit. These disparities could result from differences in patient demographics, underlying medical conditions, treatment plans (like chemotherapy or radiation therapy), and the oral hygiene procedures used. Maintaining proper oral hygiene is still crucial to comprehensive OM care, even considering the contradicting data. To increase patient comfort and promote healing, it is frequently recommended to employ techniques like frequent use of a soft-bristled toothbrush, mouthwashes without alcohol, drinking enough water, and avoiding irritants like alcohol or tobacco. To develop standardized oral hygiene practices that are most successful in managing and preventing OM in various patient groups, more research is required (Miller *et al*., 2012).

Antimicrobial agents' efficacy in treating oral mucositis (OM) is still ongoing, with conflicting results. A popular antiseptic mouthwash, chlorhexidine, has been extensively researched for its ability to prevent and lessen the severity of OM, especially in patients receiving radiation and chemotherapy. Chlorhexidine can help lower the incidence and severity of mucositis, according to some studies that have shown a significant preventive effect. These results are contradicted by other research, which indicates that chlorhexidine does not significantly outperform other rinses like saline solution or bicarbonate rinses, which are frequently more affordable and better tolerated by patients. Chlorhexidine has not been shown to significantly improve the severity of mucositis when compared to other mouthwashes like physiological saline solution or sterile water in thorough reviews. da Cruz (Campos *et al*., 2014). On the other hand, research suggests that povidone-iodine rinses can

reduce mucositis severity by 30% when compared to sterile water rinses. For some patient groups, povidone-iodine is the preferred option because it doesn't harm the oral mucosa as much as some other antiseptics do.

Iseganan hydrochloride is another antimicrobial agent that has been studied, but no discernible protective effects against mucositis have been shown. The wider role of antimicrobial agents in the treatment of mucositis has also been studied; however, some reviews have concluded that routine use of these agents for prevention is not warranted. According to these results, patients with late-stage ulcerative mucositis, where the risk of secondary bacterial infections is considerably higher, may be the only ones who benefit from antimicrobial therapy. Overall, even though antimicrobial mouthwashes are still an essential part of oral hygiene for people with OM, their use should be carefully evaluated depending on the severity of the condition, cost-effectiveness, and the needs of each patient. To create clear guidelines for their use in managing and preventing mucositis, more research is required (Alterio *et al*., 2007).

Cytoprotective agents are used to shield the mucosal lining from harm brought on by radiation and chemotherapy. The main ways in which these substances function is by scavenging reactive oxygen species (ROS), lowering inflammation, and encouraging tissue repair.

Clinical research has produced conflicting findings about the efficacy of certain cytoprotective medications, even though they have demonstrated potential advantages. (Ahmad *et al*., 2019).

Amifostine

During cancer treatment, amifostine (Ethyol®), an organic thiophosphate, is thought to act as a ROS scavenger, lowering oxidative stress and safeguarding healthy tissues. Amifostine was studied for its possible protective effects because ROS are important in the development of OM. Only one randomized, controlled clinical trial (RCCT) assessing amifostine's effectiveness in patients receiving chemotherapy and radiation therapy was discovered during a review of clinical trials conducted in the last ten years, and it came to the conclusion that amifostine did not significantly improve OM prevention.

Sucralfate

A cytoprotective medication called sucralfate is frequently used to treat peptic ulcers by creating a barrier that shields the ulcerated area. Numerous studies have examined its possible role in managing OM, especially in patients undergoing radiation therapy. But the results have been very mixed, with some studies showing no discernible benefit and others reporting positive effects. Less research has been done on sucralfate in chemotherapy-induced OM. Over the past ten years, only one clinical trial has looked at its effectiveness in chemotherapy patients receiving 5-fluorouracil (5-FU), and it concluded that sucralfate was ineffective at preventing OM.

Glutamine

One of the most prevalent amino acids in the human body, glutamine is essential for immune system function, tissue repair, and cell proliferation. Because of its role in controlling the redox potential and lowering the production of proinflammatory cytokines, it has been studied for its possible advantages in the prevention and treatment of OM. Although there is conflicting evidence, some studies have suggested that taking glutamine supplements lessens the severity of OM. Over the last ten years, three RCCTs have assessed glutamine's effects in chemotherapy patients; two of these studies have found that glutamine can help lessen the severity of OM. (Lionel *et al*., 2006).

Nevertheless, the sample sizes in these studies were rather small. However, another study discovered that glutamine not only did not prevent OM but also raised the possibility of tumor recurrence and worsening mucositis.

Anti-inflammatory agents; because they can lessen inflammation, ease pain, and encourage healing, anti-inflammatory drugs have been investigated for the prevention and treatment of oral mucositis (OM). These medications function by regulating the body's inflammatory response, which is crucial to the emergence of OM, especially in patients receiving radiation and chemotherapy. Although some anti-inflammatory medications have demonstrated promise, conflicting findings from clinical trials have cast doubt on their broad use in the treatment of OM. (Wilkes, 1998).

Benzidamine

Benzidamine is an analgesic, anesthetic, and antimicrobial nonsteroidal anti-inflammatory drug (NSAID). It has been extensively utilized as an oral rinse and for the prevention and treatment of OM. Benzidamine's anti-inflammatory properties aid in lowering oral mucosal pain, swelling, and irritation. There are conflicting findings regarding its overall effectiveness, though, as some studies have shown promising results while others have not produced any appreciable advantages.

Misoprostol

The potential of misoprostol, a synthetic prostaglandin analogue, to stop mucosal damage in OM caused by chemotherapy has been investigated. It has undergone testing in several formulations, such as mouthwash and oral tablets. Misoprostol, however, may not be useful in lessening the severity of OM, according to research (Saadeh *et al.*, 2005). Indeed, research comparing Misoprostol tablets to placebo groups has

revealed that, rather than preventing mucositis, it may even make it more common and severe. Similarly, small patient trials have not shown any discernible improvement in OM symptoms, and misoprostol rinses (prepared as a solution) have not shown any notable clinical benefits.

Immunoglobulins, histamine, and additional anti-inflammatory substances

The efficacy of additional anti-inflammatory therapies, such as gel-based histamine and intravenous or intramuscular immunoglobulin administration, in the treatment of OM has been assessed. Although there is currently insufficient evidence to support the benefits of these therapies, it is thought that they control the immune response and lower inflammation. To ascertain their role in the prevention and treatment of mucositis, more carefully planned clinical trials are needed.

Mesalazine and Diphenhydramine

Mesalazine gels and diphenhydramine rinses have also been studied as possible anti-inflammatory therapies for OM. When used as an oral rinse, diphenhydramine, also referred to as an antihistamine, may help lessen pain and irritation, especially when combined with other supportive therapies. The anti-inflammatory medication mesalazine, which is mostly used to treat gastrointestinal disorders, has been investigated for direct application to oral lesions in gel form. More thorough clinical trials are required to confirm both agents'. Therapeutic value in the management of OM, even though preliminary studies indicate that they may be somewhat effective (Lionel *et al*., 2006).

Biological response modifiers, particularly growth factors, play a vital role in alleviating oral mucositis (OM) effects. These medications primarily aim to reduce the duration of neutropenia in patients with non-myeloid cancers and promotes myeloid recovery in patients who have undergone bone marrow transplants. Granulocyte colony-stimulating factor (G- CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) are key growth factors used for these purposes. They help stimulate the production of white blood cells, which accelerates recovery and reduces mucosal damage in affected patients (Ahmad *et al*., 2019). Are two of the biological response modifiers that have been studied the most commonly. White blood cell production is known to be stimulated by these growth factors, improving immune function and decreasing vulnerability to inflammation and infections. Clinical research has assessed how well G-CSF and GM-CSF rinses work to lessen the intensity and duration of OM. Results indicate that subcutaneous administration of G-CSF may reduce the incidence of OM in cancer patients undergoing chemotherapy regimens containing doxorubicin, etoposide, and cyclophosphamide. Oral rinses containing G-CSF have also shown some promise in minimizing mucosal damage. Its effectiveness hasn't been substantiated by all research, though, as some clinical trials revealed no appreciable advantage in preventing mucositis. Like G-CSF, GM-CSF has been researched for topical and systemic use. Systemic GM- CSF administration has been shown to lessen the severity and duration of OM in patients with head and neck cancer receiving chemotherapy. Furthermore, in patients with chemotherapy-induced mucositis, GM-CSF rinses have been linked to decreased morbidity and quicker mucosal healing. Results haven't always been favorable, though, as some research found that using GM-CSF rinses in breast cancer patients undergoing chemotherapy did not significantly lessen the severity of OM (da Cruz Campos *et al*., 2014).

The Function of Palifermin in the Prevention of OM

Palifermin, a recombinant form of keratinocyte growth factor (KGF) made with recombinant DNA technology, is another significant biological response modifier. Patients with haematological malignancies undergoing myeloablative therapy—a treatment known to have a high incidence of severe OM—are specifically prescribed palifermin. Palifermin's main purpose is to promote the growth of epithelial cells and increase the thickness of the oral and gastrointestinal mucosa's non-keratinized layers. This encourages mucosal regeneration, which lowers the incidence, severity, and duration of OM. Palifermin is typically administered intravenously at a dose of 60 µg/kg/day for three days in a row, prior to and following myelosuppressive therapy, for a total of six doses. 24–48 hours prior to bone marrow suppression, the last pre-treatment dose is given. (Alterio *et al*., 2007).

According to research, palifermin can effectively lower the incidence and severity of OM when taken at doses ranging from 1 to 180 µg/kg/day. Nevertheless, there are some negative effects linked to its use, which mostly impact the skin and oral mucosa. Discoloration of the oral mucosa, tingling sensations (paraesthesia), oral mucosal hypertrophy, and taste disturbances (dysgeusia) are some of the most frequently reported adverse effects. There have also been reports of additional skin-related side effects, including rash, erythema, hyperpigmentation, and pruritus (itching). (Daugėlaitė *et al*., 2019). In certain instances, there have also been reports of joint pain (arthralgia), rhinitis, and cough. Thankfully, most of these side effects are mild to moderate in severity and usually manifest near the end of treatment. Many times, these adverse effects don't require stopping treatment, so patients can keep taking advantage of palifermin's protective benefits.

Physical treatments like low-power laser therapy and cryotherapy have drawn interest as possible in preventative and therapeutic approaches for oral mucositis (OM), especially in patients receiving chemotherapy. By using localized cooling or phototherapy, these non- pharmacological methods seek to lessen mucosal damage, ease pain, and encourage

tissue healing. The overall effectiveness of these treatments can vary based on the type of chemotherapeutic agent used, the patient's condition, and treatment protocols, even though some studies have shown positive effects. (Saadeh, 2005).

Cryotherapy and Its Role in Mucositis Prevention

Although the precise mechanism underlying cryotherapy's protective effects is still unknown, it is thought to work by causing local vasoconstriction, which lowers blood flow to the oral tissues. This limits the mucosa's exposure to cytotoxic agents, thereby reducing the direct toxic effects of chemotherapy on oral tissues. Cryotherapy is the topical application of ice to the oral mucosa, which has been found to be beneficial in preventing OM in certain chemotherapy patients.

According to studies, cryotherapy works especially well for patients undergoing chemotherapy who are taking medications with short half-lives, like 5-fluorouracil (5-FU). For cryotherapy application, the recommended protocol is to begin 5–10 minutes prior to the administration of chemotherapy, (Rodríguez-Caballero *et al.,* 2012).continue for 15–35 minutes during the drug infusion, and continue for up to 30 minutes following the infusion. The incidence and severity of mucositis have significantly decreased in patients who adhered to this protocol. Patients receiving high-dose melphalan as part of their conditioning treatment for haematopoietic stem cell transplantation have also shown benefits from cryotherapy in addition to 5-FU. However, there is still conflicting evidence regarding the effects of other chemotherapy drugs, including methotrexate, etoposide, cisplatin, mitomycin, edatrexate, and vinblastine, with some studies finding no discernible change. Cryotherapy is not advised for patients undergoing oxaliplatin-based chemotherapy, despite its possible advantages, because it can cause acute neurological side effects such as mandibular stiffness and (Miller *et al.,* 2012). laryngopharyngeal dysesthesia, which is a burning or tingling sensation in the jaw and throat. Cryotherapy should therefore be avoided by patients receiving cold-sensitive chemotherapy regimens because of the possibility of side effects.

Low-Power Laser Treatment for the Treatment of Mucositis

Photobiomodulation therapy (PBM), another name for low-power laser therapy, has been investigated as a treatment and prevention strategy for chemotherapy-induced OM. It is thought that laser therapy reduces inflammation, pain, and the degree of mucosal damage by speeding up tissue regeneration and healing. Low-power laser therapy has been shown in studies to dramatically reduce the incidence and severity of OM, especially in patients receiving high-dose chemotherapy with or without total body irradiation and those undergoing haematopoietic stem cell transplantation. The treatment entails applying particular laser light wavelengths to the oral mucosa, which promotes quicker healing by improving circulation and activating cellular repair mechanism (Saadeh, 2005).Even though several studies have produced encouraging results, there is ongoing discussion regarding the overall efficacy of laser therapy because results vary depending on the patient group. For instance, although certain research has demonstrated a definite protective effect, other studies—including those involving pediatric patients—have not demonstrated any appreciable advantage. Variability in patient conditions, treatment protocols, and laser parameters (wavelength, intensity, and duration of application) could all contribute to the inconsistent outcomes.

A thorough and multimodal approach combining pharmaceutical, non-pharmacological, and preventive measures is needed to manage oral mucositis (OM), a crippling side effect of cancer treatment. Significant advancements have been made in understanding and mitigation of OM despite the lack of a single, all-encompassing treatment. These advancements have included the use of biological response modifiers, antimicrobial agents, cytoprotective medications, anti-inflammatory therapies, oral hygiene practices, and physical interventions such as laser and cryotherapy (Ahmad *et al*., 2019).

Although their efficacy is still debatable, cytoprotective drugs like glutamine, amifostine, and sucralfate have been investigated for their potential to shield mucosal tissues among pharmacological interventions. In a similar vein, anti-inflammatory medications such as mesalazine, misoprostol, and benzidamine have shown differing degrees of efficacy in promoting healing and lowering inflammation. Although side effects and patient-specific factors need to be carefully considered, the role of biological response modifiers—in particular, granulocyte colony-stimulating factors (G-CSF, GM-CSF) and palifermin—has demonstrated encouraging results in speeding tissue regeneration and lowering the severity of OM. (Lionel *et al*., 2006).

Physical therapies, such as low-power laser therapy and cryotherapy, have become popular non-invasive and well-tolerated methods of managing OM. Laser therapy has demonstrated promise in lowering inflammation and hastening mucosal healing, while cryotherapy has demonstrated significant advantages in chemotherapy regimens containing short half-lives. To standardize procedures and maximize treatment effectiveness, more research is necessary because patient responses differ. Although OM management has advanced, no single intervention offers a comprehensive solution; instead, treatment should be customized to meet the needs of each patient, the severity of the disease, and the prescribed course of action. The prevention and treatment of OM will be further improved by ongoing clinical research and technological advancements in

biomedicine and drug formulation. Future OM management may also be significant. This is impacted by the combination of personalized medicine and cutting-edge 3D printing technologies, which could provide tailored therapeutic solutions with better patient outcomes and quality of life. (Rodríguez-Caballero *et al.*, 2012).

Strategies in Management of Oral Mucositis

There are many treatment protocols available to prevent and/or reduce the severity of oral mucositis, but there is not enough evidence to support any one approach as the gold standard. Oral mucositis can be managed with two types of procedures: the first group addresses pain management, nutritional support, oral hygiene, palliative treatment for xerostomia, and oral bleeding control; the second group focusses on therapeutic interventions. (Ahmad *et al*., 2019)

Management of Symptoms and Palliative Care

Severe cases of oral mucositis (OM), which is still a major side effect of cancer treatment, result in more hospital stays, serious complications, and higher medical expenses. Palliative measures and analgesics might not be enough when OM reaches advanced stages (Grades III and IV). Depending on the severity of mucositis, treatment may need to be stopped for up to a week. To prevent and treat OM, strict oral hygiene is necessary because it lowers the number of harmful bacteria. A standardized oral hygiene regimen, which includes routine dental care prior to chemotherapy and radiation therapy, should be followed by patients receiving cancer treatment. Regular oral examinations are highly advised, especially for patients who are at high risk.(Rodríguez-Caballero *et al.*, 2012).

Dental Hygiene and Proactive Steps

Maintaining proper oral hygiene lowers the chance of dental problems while minimizing discomfort, bleeding, and infections. Every chemotherapy cycle, patients should replace their toothbrushes and brush their teeth at least twice a day. It's also recommended to use dental floss every day and rinse with sodium bicarbonate, saline solution, or clean water. Alcohol, tobacco, spicy foods, and mouthwashes with alcohol in them should all be avoided, and Proper hydration should always be maintained (Miller *et al*., 2012).A soft, liquid diet is advised for patients with mucositis because it is more tolerable. Refined carbs give you energy, but cancer treatments often change how you taste things, so you eat less sugar. Foods that worsen diarrhea should be avoided, and eating more protein-rich foods like meat, fish, and eggs is recommended.

Analgesics and Pain Management

A vital component of OM care is pain management, especially for patients receiving radiation therapy for head and neck cancers. Analgesics, mouthwashes, lubricants, ulcer remedies, and dietary changes are examples of common self-care practices. While systemic opioid Analgesics like intravenous morphine may be necessary for severe pain. Paracetamol with codeine is commonly used for pain relief. Under close supervision, a patient-controlled analgesia system can be used to administer morphine. Adjunctive therapies, including NSAIDs, gabapentin, cannabinoid receptor agonists, clonidine, nicotine, lidocaine, and ketamine, may be used to enhance pain relief. Furthermore, it has been proposed that ranitidine and omeprazole can prevent epigastric pain after chemotherapy (da Cruz Campos *et al.*, 2014).

Antiseptics and Topical Anesthetics

Local pain relief can be achieved with topical anesthetics, such as 2% viscous lidocaine mixed with other substances like diphenhydramine, kaolin, milk of magnesia, or chlorhexidine. These anesthetics, however, have the potential to change swallowing reflexes and taste perception. Because of its possible adverse effects, which include inflammation, oral discomfort, dysgeusia, and dental pigmentation, chlorhexidine—which is frequently used for its Antimicrobial and antifungal qualities—is not advised for the prevention of mucositis. As an alternative, benzidamine, a non-steroidal anti-inflammatory drug (NSAID) with analgesic, cytoprotective, and antimicrobial qualities, has demonstrated promise in easing pain and lowering the use of opioids. Substance P, a crucial component in nociceptor activation during inflammation, has been inhibited by other substances like doxepin, morphine, and capsaicin. (Miller *et al.*, 2012).

Handling Ulcer Bleeding and Xerostomia

Chemotherapy frequently causes xerostomia, or dry mouth, by affecting salivary gland function. Artificial saliva, frequent water consumption, mouthwashes containing sodium Bicarbonate, and sugar-free chewing gum are examples of palliative measures that increase saliva production. Avoid using sympathomimetic or anticholinergic medications as they further decrease salivary flow. Topical hemostatic agents, such as fibrin glue, can help control bleeding related to ulcers.(Rodríguez-Caballero *et al*., 2012). Patients with platelet counts below 20,000/mm³ may not be candidates for blood transfusions because of the possibility of internal bleeding.

Regenerative Therapies and Growth Factors

Growth factors as well as regenerative therapies Because of their anti-inflammatory properties and capacity to stimulate fibroblast proliferation and vascular regeneration, biological materials such as amniotic membranes have been demonstrated in recent research to hasten the healing process in ulcerated mucosal surfaces. The potential of growth factors such as transforming growth factor-beta 3 (TGF-β3), G-CSF, and GM-CSF to reduce pain and promote mucosal repair has been studied, but their high-cost limits widespread use. Recombinant human keratinocyte growth factor palifermin promotes the growth of epithelial cells and

inhibits cell death. Palifermin, which has been approved for use in the US, is especially helpful for patients receiving bone marrow transplants or high- dose chemotherapy. Although it is useful in lessening the intensity and length of mucositis, ulceration, itching, erythema, paranesthesia, and dysgeusia are possible side effects (Lionel *et al.*, 2006).

Cryotherapy and Photobiomodulation Therapy

Particularly in patients receiving high-dose chemotherapy or radiochemotherapy prior to bone marrow transplantation, low-energy laser radiation (photobiomodulation therapy) has shown promise in lowering the degree of mucositis, its associated pain, and its functional impairment. This treatment reduces pain and promotes healing without being toxic, but it needs costly equipment (Wilkes, 1998).By causing transient vasoconstriction, cryotherapy lowers blood flow and restricts the exposure of chemotherapy agents to the oral mucosa, especially in patients undergoing 5- fluorouracil (5-FU) chemotherapy. An affordable, non-toxic, and efficient substitute is ice chips, which are used for 30 minutes prior to and during chemotherapy.

Supplemental Foods and Protective Gels

The potential of glutamine, an essential amino acid, to prevent mucositis by lowering the production of pro-inflammatory cytokines has been investigated. Furthermore, a protective layer over ulcerations is provided by Gelclair®, a hyaluronic acid-based gel that lessens pain and discomfort while eating. Parenterally administered amifostine has demonstrated efficacy in lowering pro-inflammatory cytokine levels, which in turn reduces the severity of mucositis. However, side effects like nausea, vomiting, hypotension, allergic reactions, and hypocalcaemia limit its use.

Natural and Herbal Treatments

Numerous natural products and medicinal herbs have been investigated for the treatment of mucositis. Because of its bacteriostatic qualities, pure natural honey has been shown to speed up epithelial repair and lower the incidence of severe mucositis (Grades III and IV) when applied topically. Furthermore, the Protium kleinii plant's alpha and beta-amyrin pentacyclic triterpenes have demonstrated analgesic and anti-inflammatory qualities, which may alleviate the symptoms of mucositis (Ahmad *et al*., 2019).

Table 3: Management Strategies for Oral Mucositis

Approach	Examples
Pharmacological	- Cytoprotective agents: Amifostine, Sucralfate, Glutamine - Anti-inflammatory drugs: Benzidamine, Misoprostol, Mesalazine - Biological response modifiers: G-CSF, GM-CSF, Palifermin
Non-Pharmacological	- Oral hygiene: Regular brushing, alcohol-free mouthwash - Physical therapies: Low-Level Laser Therapy(LLLT), Cryotherapy
Pain Management	- Systemic opioids (Morphine), NSAIDs, Benzidamine, Lidocaine mouthwash
Supportive Care	- Nutritional support: Soft/liquid diet, protein-rich food - Hydration and avoidance of irritants (alcohol, tobacco, spicy food)
Emerging Therapies	- AI-based predictive models, nanomedicine, probiotics, regenerative medicine (stem cells, growth factors)

FUTURE SCOPE

Advanced biotechnological interventions, novel drug formulations, and personalized Medicine are key to the management of oral mucositis in the future. Mucosal damage may be avoided by investigating oxidative stress and inflammatory mediator inhibitors, such as NF- κB and NLRP3 inflammasome blockers, while mucoadhesive hydrogel formulations and Drug carriers based on nanotechnology may enhance targeted drug delivery. Tissue repair may be possible with regenerative medicine, which includes enhanced keratinocyte growth factors and stem cell therapy. Antimicrobial peptides could be used as substitutes for traditional antiseptics, and probiotics and microbiota-targeted treatments are viable methods for re-establishing the balance of oral microbes. Machine learning models and artificial intelligence (AI) may be able to predict a patient's vulnerability to OM and help tailor treatment regimens.

Additional research is necessary to standardize procedures and optimize the effectiveness of non-invasive physical therapies such as cryotherapy and low-level laser therapy (LLLT).

Large-scale clinical trials should also be conducted to investigate herbal and natural therapies like honey, aloe vera, curcumin, and bioactive derived from plants. By combining these developments with precision medicine and biomedical breakthroughs, more accessible, focused, and efficient management techniques will be developed, ultimately leading to better patient outcomes and quality of life.

CONCLUSION

In oncology, oral mucositis is still a significant problem that affects patients receiving radiation and chemotherapy. There is still no widely recognized gold-standard treatment for it, despite tremendous progress in our understanding of its pathophysiology. The focus of current management approaches is on multimodal

interventions, which include non- pharmacological therapies like LLLT and cryotherapy, antimicrobial tactics, and pharmacological agents (growth factors, cytoprotective agents, and anti-inflammatory drugs). Although the efficacy of these tactics has varied, individualized treatment plans based on each patient's risk factors and reactions are essential. More focused, efficient, and minimally invasive treatments may be possible thanks to new research in nanomedicine, regenerative therapies, AI-driven predictive models, and microbiota modulation. To enhance patient care and treatment adherence, future initiatives should concentrate on improving new therapies, enhancing treatment guidelines, and guaranteeing accessibility. The burden of oral mucositis can be greatly decreased by sustained innovation and interdisciplinary cooperation, improving patient quality of life and therapeutic efficacy.

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